The 5-Minute Urology Consult

3RD EDITION

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Third Edition

9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data
The 5-minute urology consult / editor-in-chief, Leonard G. Gomella ; associate editors, Gerald Andriole [and six others]. – Third edition.
p. ; cm.
Five minute urology consult
Includes bibliographical references and index.
ISBN 978-1-4511-8998-8 (alk. paper)
I. Gomella, Leonard G., editor. II. Title: Five minute urology consult.
[DNLM: 1. Urologic Diseases–Handbooks. WJ 39]
RC872.9
616.6–dc23

2014037959

To Tricia, Leonard, Patrick, Andrew, and Michael, for their understanding and encouragement, and with appreciation for their individual accomplishments.

“En tierra de los ciegos el tuerto es rey."

SPANISH PROVERB

PREFACE

I am very pleased to present the third edition of *The 5-Minute Urology Consult*. The first edition was released almost 15 years ago, with the second edition published in 2010. The continuing advances in urology lead to this much-needed 2015 update. The goal of this book is to provide the reader with useful information in a quick reference format to help with the everyday care of patients with urologic problems. This third edition has undergone extensive editing and updating to reflect the most current data possible at the time of publication.

Urologic diseases and conditions are common problems seen by all health care providers. Almost one-third of all congenital disorders involve the genitourinary system, and the urinary tract accounts for almost 25% of all solid tumors in adults. While this book is written primarily for urologists, any health care practitioner who deals with urologic complaints and conditions should find the book a useful resource. Students of urology, residents and fellows preparing for oral and written in-service examination, and practicing urologists preparing for certification examinations will find the book a useful study aid. While primarily written for practitioners in the United States, the table of contents has been reviewed by our international editorial board, which represent more than three dozen countries, in an attempt to capture as many diseases and conditions as possible for international readers.

The broad array of topics addressed in this book is based on reviews of published literature, major textbooks, grand rounds case presentations, validated Internet resources, and actual patient consultations. Topics are meant to represent "real-world" clinical questions from very broad to very specific topics. Some of the topics may appear redundant, such as Section I topics "Scrotum and testicle, mass" and "Testis, tumor and mass, adult, general considerations." There is a deliberate reason for this, namely, to frame the thought process to differentiate scrotal masses from testicular masses when the presenting problem is not clear. If it is clearly a testicular mass, then the one topic deals effectively with that setting. If it is not a clear mass in the testicle, the reader can approach the problem more broadly in terms of a mass within the scrotum that may or may not involve the testicle. Coverage includes adult and pediatric urology, as well as subspecialty areas of urology such as urologic oncology, endourology, female urology, neurourology, andrology, infectious diseases, and renal transplantation. It represents a core of essential "must-know" and practical information specifically written for the field of urology. While some surgical techniques are discussed, this is not meant to be a comprehensive urologic surgical text. Numerous high-quality publications address the finer points of urologic surgery. This book addresses pre and post operative care as well as some intra-operative techniques; however the focus is on more global patient management issues.

I am often surprised when asked why medical books such as this are even necessary as a reference in the modern world because there is so much information readily available on devices such as smartphones via the Internet. While the reality is that virtually any topic can be searched for on the Internet, the ability to sort through the information presented, confirm the validity, and rapidly find the specific information needed is often very time-consuming and can be prone to error. Multiple studies have shown that many websites can contain erroneous, misleading, or out-of-date information. Readers of this book can be assured that

the information presented is held to the highest standards possible, as it is written, reviewed, and further edited primarily by academic urologists and other academic specialists. Every effort is made to present the most up-to-date standards of care at the time of publication.

This book, a member of the popular "5-Minute Consult" series published by Wolters Kluwer Health, generally follows the organizational formatting of the other books in the series. However, there are notable exceptions, as this book is focused on a primarily surgical subspecialty. **Section I: Urologic Diseases and Conditions** provides information on more than 300 major topics in the field of urology. The style of this section, while similar to the other books in the series, focuses more attention on the surgical management, where appropriate. Furthermore, evidence-based medicine references, standard fare in the "*5-Minute Consult*" series, are included in this urology edition. This is representative of the trend in the field of medicine to assign "levels of evidence" to treatment recommendations (see page ix for a further discussion). A challenge with any surgical discipline is that, when reviewing published literature, this type of information is not as well represented as in other medical disciplines. The reader will note that in this edition, the use of evidence-based medicine is identified in chapters as appropriate. Many topics are further supported by algorithms and the enhnaced image library available in the ebook version provided along with the print version. Both *ICD-9* and preliminary high level *ICD-10* codes have been incorporated in preparation for the rollout of *ICD-10* in late 2015.

Section II: Short Topics: A to Z consists of more than 1,300 diseases, conditions, presenting complaints, or key concepts in the field that the practitioner must be aware of but may not be worthy of a complete 2-page chapter. **Section III** has been greatly expanded and now features nearly 90 visual algorithms to enhance many more clinically relevant topics. **Section IV** is dedicated exclusively to a core discipline in our field, **Urinalysis and Urine Studies. Section V: Alternative and Complementary Urologic Therapies** is a focused review that is of interest to both patients and caregivers alike. **Section VI: Urologic Drug Reference** is a very unique collection of information on hundreds of drugs used in urologic practice in the United States as well as some traditionally nonurologic medications that are clinically significant to the urologic practitioner. Additional urologic applications not often found on the package insert for "off-label" use in daily care are included for many medications. These "off-label" applications are noted on the basis of published literature with additional input and the personal observations of the authors and editors. Finally, **Section VII: Reference Tables** is a collection of useful reference information and forms. A media and image collection is available in the ebook version of this book. Please see information inside front cover on how to access this content.

In any project of this magnitude, there are numerous individuals responsible for its success. I would like to thank the following individuals who provided the initial guidance in 1996 to develop the first urology version of the 5-Minute Consult: Lippincott Williams & Wilkins editors Carroll Cann and Craig Percy, and an early pioneer of the 5-Minute Consult concept, Dr. Mark Dambro. Thanks to my administrative assistants Denise Tropea and Barbara Devine, who provided key support to keep the contributors and this edition organized. A special thanks to the more than 370 authors and editors who took the time to contribute to this edition and the numerous contributors to the previous editions that laid a strong foundation for this third update. To my colleagues who served as Associate, Consulting, Specialty and

International Editors, my most sincere gratitude and appreciation for the time you took to recruit authors, create and review content. It is also with great sadness that one of our international editors and an icon in the field of Urology, Professor John Fitzpatrick passed away during the completion of this book. He will be missed by all but his numerous contributions to our field will live on.

Residents from the Department of Urology of Thomas Jefferson University and from the University of West Virginia deserve special acknowledgement. They supported the content of both Section II “Short Topics" and Section III “Algorithms." Their names appear in the contributor listing as having been authors but are not specifically recognized for their work in these sections. Now however, they are.

The editorial and production staff at Wolters Kluwer Health have distinguished themselves as the best publishing team I have had the opportunity to work with. My personal interactions with the company and their willingness to discuss any and all issues relating to the book are testimony to their corporate philosophy in respecting the authors’ opinions to develop the best educational products possible in the field of medicine. Brian Brown, Keith Donnellan, and Brendan Huffman are the best partners a medical author could hope to work with. In the final production stages, David Saltzberg and Harish Kumar kept everything moving to stay on schedule. Special thanks to Philadelphia-based friend and professional photographer Robert Neroni, who captured the spirit of urology in our cover photo.

Our children, Leonard, Patrick, Andrew, and Michael, deserve credit for their encouragement and patience over the many years of my time spent working on this project. In this edition, i am very proud that a few of the boys were actually able to make tangible professional contributions.

Most importantly, I would like to thank my wife, Tricia, with the usual and customary accolades that authors share about their spouses in acknowledging the love and support provided. However, her attention to detail as a behind-the-scenes editorial partner and skilled reviewer for final content of this book added a degree of accuracy that I could never have accomplished alone.

Please contact me if you have corrections or suggestions on ways to improve future editions of the book. I hope that *The 5-Minute Urology Consult* will provide useful information to allow all of us to care for our urology patients in the best way possible.

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EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) is generally defined as the use of current best medical evidence to aid in making decisions about the care of an individual patient. While the ultimate decision-making process for or against a given treatment must be made between the patient and the health care provider, EBM seeks to assess the quality of evidence that a specific course of action is based on. The underlying principle is the evaluation of medical interventions and the literature that supports these interventions in a systematic and organized fashion. Since its introduction as a concept in the modern medicine over 30 years ago, there has been increased emphasis on this concept in daily patient care. While there are currently many different systems of EBM, we have adopted the *5-Minute Clinical Consult* standard of the "SORT Taxonomy" from the American Academy of Family Physicians. The key components are summarized later. A full review of this article can be viewed at http://www.aafp.org/afp/20040201/548.html. Throughout this edition of *The 5-Minute Urology Consult*, these evidence-based recommendations can be found. However, we recognize that in a primarily surgical-based specialty such as urology, this area is not yet as well defined as in more general areas of medical practice. As an illustrative example in a chapter on hypertension, the EBM recommendation might read:

> "Use thiazide diuretics as a first-line agent for the treatment of essential hypertension, as it has the greatest efficacy in preventing the vascular complications of hypertension (5)[A]."

The A designation, as noted in the algorithm later, implies this recommendation is based on the highest-quality, patient-oriented evidence, and should be followed. The number 5 refers to the source, which would be listed under the "References" heading as reference #5. Recommendations that are level A evidence are shaded blue in the text.

Strength of recommendation	Definition
A	**Recommendation based on consistent and good-quality patient-oriented evidence.** • Highest-quality resource, such as a systematic review. This is a summary of the medical literature on a given topic that uses strict, explicit methods to perform a thorough search of the literature and then provides a critical appraisal of the individual studies concluding in a recommendation. The Cochrane reviews are considered by many to be the most prestigious collection of systematic reviews (www.cochrane.org).
B	**Recommendation based on inconsistent or limited-quality patient-oriented evidence.** • This implies that the data referenced are derived from high-quality randomized controlled trials that were performed to minimize bias in their outcome. Bias is anything that may interfere with the truth; in the medical literature, it is often unintentional but is more common than we appreciate. In short, always assume that some degree of bias exists in any research endeavor.
C	**Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.** • This implies that the reference used does not meet het "A" or "B" requirements; these are often treatments recommended by consensus groups (such as the American Cancer Society). In some cases, they may be the standard of care. But implicit in a group's recommendations is the bias of the group or author that supports the reference.

Modified from Domino FJ, ed. *The 5-Minute Clinical Consult 2010*. Philadelphia: Lippincott Williams & Wilkins; 2009.

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SECTION I

Urologic Diseases and Conditions

Section Editor: Leonard G. Gomella, MD, FACS

ABDOMINAL MASS, ADULT, UROLOGIC CONSIDERATIONS

Brian M. Benway, MD
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BASICS

DESCRIPTION

- Urologic masses are usually retroperitoneal in adults
  - May arise from several sites
    - Renal (malignant and benign)
    - Adrenal
    - Germ cell (retroperitoneal lymphadenopathy)
    - Metastatic
    - Other (retroperitoneal fibrosis [RPF], hematoma, abscess, lymphocele, lymphoma, urinary retention)

EPIDEMIOLOGY

Incidence

- Renal cell carcinoma: 55,000 new cases per year. Incidence is rising (1)
- Testis cancer: 8,000 new cases per year

Prevalence

Varies with disease type

RISK FACTORS

- Cancer (renal, adrenal, testis)
- Prior surgery (lymphocele)
- Infection (abscess, RPF)
- Trauma (hematoma, urinoma)
- Urinary retention

Genetics

- Renal lesions have some known genetic alterations:
  - von Hipple Lindau (VHL)
  - Hereditary papillary renal cell
  - Birt–Hogg–Dubé
  - Hereditary leiomyomatosis
  - Tuberous sclerosis

PATHOPHYSIOLOGY

- Various urologic pathologic conditions may present with a mass:
- Primary renal neoplasms:
  - Malignant: Renal cell carcinoma (RCC), renal sarcoma, adult Wilms tumor, urothelial carcinoma, lymphoma
  - Benign: Renal cortical adenoma, renal oncocytoma, renal hamartoma (angiomyolipoma) fibroma

- Primary adrenal neoplasms: Adrenal cortical carcinoma, pheochromocytoma, adrenal adenoma, paraganglioma
- Hydronephrosis
- Primary and metastatic germ cell tumor (GCT): Are composed of seminoma, embryonal cell carcinoma, yolk sac tumor, teratoma, and choriocarcinoma
- Primary extragonadal GCTs can occur intraperitoneally
  – Metastatic GCTs are associated with retroperitoneal lymphadenopathy
- Renal abscesses: Usually follow insufficient treatment of lobar nephronia; needle aspiration may be needed to make a diagnosis
- TB can cause cold abscess formation. Pus developing from a renal source may track alongside psoas muscle and appears in the groin, where it must be distinguished from hernia.
- Perinephric abscess: Usually arises as a result of pre-existing renal factors such as renal calculi, ureteral calculi, hydronephrotic changes, renal cystic disease, or infected carcinoma
- Hematomas: May be caused by a ruptured kidney or ureteral avulsion. Blood in the retroperitoneal space may track to the corresponding iliac fossa
- Renal cysts
- Bladder-related: Retention, tumors and urachal abnormality, or cancer
- Metastatic tumors to the adrenal glands and kidney

ASSOCIATED CONDITIONS
- Hydronephrosis, renal insufficiency (malignant obstruction)
- Aortitis, aortic aneurysm (RPF)
- Stauffer syndrome (RCC)

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Weight loss, cachexia, night sweats (malignancy or chronic septic disease)
- Spiking fevers, flank pain (infectious)
- Recent trauma with or without hematuria
- History of testis mass
- Classic triad for renal cell carcinoma (hematuria, flank pain, palpable mass) is relatively uncommon in modern era

PHYSICAL EXAM
- Abdominal wall masses such as lipomas, hematomas, lymph nodes, and hernias can be readily determined by physical exam
- Palpable abdominal mass
  – Location, tenderness
- Any mucoid drainage from the umbilicus
- Hypertension
- Lymphadenopathy
- Lower extremity edema

- Lower extremity pulses
- Varicocele (more common on right)
  – Left side consider renal mass with occlusion of renal vein
- Scrotal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC, complete metabolic panel
- Urinalysis and culture
- Adrenal metabolic workup if adrenal mass is suspected – see Section I "Adrenal Adenoma"
- Tumor markers
  – Testis – AFP, β-HCG, LDH
    ◦ AFP – may be elevated in embryonal, teratocarcinoma, yolk sac, but never in pure choriocarcinoma or pure seminoma
    ◦ LDH may indicate retroperitoneal involvement, but not specific to testis
- Pregnancy testing where appropriate

Imaging

- Ultrasound
  – Good for detecting cystic lesions, but not optimum for calcified masses or smaller stones. Quality is operator-dependent.
- Computed tomography (CT)
  – Good for detecting solid abdominal masses, metastatic lesions, and stone.
  – CT angiography can evaluate renal vasculature.
  – PET-CT approved for diagnosis of RCC metastases.
- Magnetic resonance imaging (MRI)
  – Good for evaluating adrenal masses and indeterminate renal lesions.
  – Can be used in patients with iodine allergies and renal insufficiency, though caution should be exercised in the latter.
- ^{131}I-metaiodobenzylguanidine (MIBG)
  – Only role for evaluating pheochromocytoma.
- Intravenous pyelogram/excretory urogram
  – Largely historical, replaced by CT or MR urography.

Diagnostic Procedures/Surgery

- Fine-needle aspiration or core biopsy of mass
  – Renal biopsy sensitivity enhanced by use of coaxial core biopsy techniques (2)

Pathologic Findings

Varies depending upon type and location of mass

DIFFERENTIAL DIAGNOSIS

- Adrenal mass: See Section I "Adrenal Mass"
- Distended bladder
- GI tract:
  – Hepatomegaly, splenomegaly, pancreatitis, pancreatic mass, tumors, volvulus, constipation

- Gynecologic:
  - Pregnancy, uterine fibroids, ovarian cysts, malignancy
  - Hydronephrosis
- Other: Intra-abdominal abscess, ascites
- Renal mass: See Section I "Renal Mass"
- Retroperitoneal mass: See Section I "Retroperitoneal Masses, Fluid, and Cysts"
- Ruptured abdominal aortic aneurysm
- Urachal abnormality

TREATMENT

GENERAL MEASURES

- Varies by underlying ailment
  - Renal malignancy – radical or partial nephrectomy, ablation, observation (3)
  - Adrenal malignancy – adrenalectomy
  - Adrenal adenoma – excision or observation
  - Testis cancer – retroperitoneal lymph node dissection, chemotherapy, radiation
  - Renal abscess, xanthogranulomatous pyelonephritis – antibiotics, drainage, nephrectomy
  - Cysts – observation, decortication, drainage and sclerosis
  - Retention – placement of Foley catheter
  - Hydronephrosis – double-J stent placement or percutaneous nephrostomy tube placement

MEDICATION

First Line

- Antibiotics for abscess or obstruction
- Corticosteroids, tamoxifen for RPF

Second Line

Mycophenolate mofetil, azathioprine for RPF

SURGERY/OTHER PROCEDURES

Depends upon clinical diagnosis

ADDITIONAL TREATMENT

Radiation Therapy

- Limited utility for renal cell carcinoma
- Used for seminomatous germ cell tumors

Additional Therapies

Depends upon clinical diagnosis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Prognosis depends upon clinical diagnosis and staging

COMPLICATIONS

See associated chapters regarding disease-specific interventions

FOLLOW-UP

Patient Monitoring

Depends upon clinical diagnosis and management. See associated chapters regarding specific disease processes.

Patient Resources

N/A

REFERENCES

1. Chow WH, Devesa SS, Warren JL, et al. Rising incidence of renal cell carcinoma in the United States. *JAMA*. 1999;281:1628–1631.
2. Maturen KE, Nghiem HV, Caoili EM. Renal mass core biopsy: Accuracy and impact on clinical management. *AJR AM J Roentgenol.* 2007;188:563–570.
3. Kunkle DA, Kutikov A, Uzzo RG. Management of small renal masses. *Semin Ultrasound CT MR.* 2009;30:352–358.

ADDITIONAL READING

- Glockner JF, Vrtiska TJ. Renal MR and CT angiography: Current concepts. *Abdom Imaging.* 2007;32:407–420.
- Hussain HK, Korobkin M. MR imaging of the adrenal glands. *Magn Reson Imaging Clin N Am.* 2004;12:515–544, vii.
- Johns Putra L, Lawrentschuk N, Ballok Z. et al. 18F-fluorodeoxyglucose positron emission tomography in evaluation of germ cell tumor after chemotherapy. *Urology*. 2004;64:1202–1207.
- Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. *Semin Nucl Med.* 2004;34:274–292.

See Also (Topic, Algorithm, Media)

- Abdominal Mass, Adult, Urologic Considerations Image
- Abdominal Mass, Newborn, Child, Urologic Considerations
- Hydronephrosis
- Renal Masses
- Renal Cell Carcinoma
- Retroperitoneal Masses, Fluid, and Cysts
- Retroperitoneal Fibrosis
- Testis Cancer

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 194.0 Malignant neoplasm of adrenal gland
- 789.30 Abdominal or pelvic swelling, mass, or lump, unspecified site

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- C74.90 Malignant neoplasm of unsp part of unspecified adrenal gland
- R19.00 Intra-abd and pelvic swelling, mass and lump, unsp site

CLINICAL/SURGICAL PEARLS

- Abdominal masses in the adult can arise from several different processes.
- Radiographic information is often essential to diagnosis.
- Management varies upon disease type.

ABDOMINAL MASS, NEWBORN/CHILD, UROLOGIC CONSIDERATIONS

Yong Seung Lee, MD
Sang Won Han, MD

BASICS

DESCRIPTION

- Traditional presentation was palpable mass in the newborn/child abdomen
- Current presentation is usually by prenatal ultrasound
- Most masses are nonsurgical; 87% of surgical lesions are benign
- Almost 2/3 of infantile abdominal masses arise from kidneys, followed by GI tract (12%), female genital system (10%), retroperitoneum (9%)

EPIDEMIOLOGY

Incidence

Abdominal mass in 1 per 1,000 live births

Prevalence

Varies with disease type

RISK FACTORS

Genetics

- Disease specific
- Neuroblastoma
  - Chromosome 1p deletion
  - Allelic loss of 11q
  - Gain of copies of 17q correlate with more aggressive tumor
  - N-*MYC* oncogene amplification
- Polycystic kidney disease, autosomal recessive (ARPKD)
  - Gene locus at chromosome 6p21
- Rhabdomyosarcoma (RMS)
  - Mutation of TP53 gene found in tumors of patients with Li–Fraumeni syndrome
  - Alveolar RMS is associated with translocation between chromosomes 1 or 2 and 13
  - Embryonal RMS demonstrates LOH on chromosome 11p15.5
- Wilms tumor
  - WT1 (11p13): Denys–Drash and WAGR (Wilms tumor, aniridia, genitourinary problems, retardation)
  - WT2 (11p15): Beckwith–Wiedemann
  - *WTX* (Xq11.1): Inactivated in up to 1/3 of Wilms tumors
  - FWT1 (17q), FWT2 (19q): Familial
  - LOH at 1p and 16q is associated with an increased risk of tumor relapse and death

PATHOPHYSIOLOGY

Disease specific, related to organ of origin

ASSOCIATED CONDITIONS
Disease specific

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Prenatal ultrasound (1)
  - Oligohydramnios: Associated with PUV, bilateral UPJ, urethral atresia, polycystic or multicystic dysplastic kidneys, renal agenesis
  - Polyhydramnios: Associated with high GI obstructions
- Postnatal history
  - Initial discovery
  - Duration from detection of mass
  - Rapidity of growth
  - Constitutional symptoms: Fever, pain, weight loss, UTI, dysuria, hematuria, melena, anorexia, bilious vomiting

PHYSICAL EXAM
- Perform thorough abdominal exam (2):
  - Size and location
  - Solid or cystic
  - Tender or nontender
  - Smooth, irregular, indurated, or soft
  - Fixed or mobile
  - Auscultation, percussion, and transillumination
- Additional exam:
  - Nasogastric tube for intestinal decompression
  - Foley catheter for urinary decompression
  - Rectal/introital exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Labs should be tailored to clinical suspicion
- CBC:
  - Anemia, neutropenia, thrombocytopenia may suggest bone marrow involvement
  - Leukocytosis suggests possible infection/ obstruction
- BUN/creatinine/electrolytes
  - Elevated BUN/creatinine suggests renal compromise, dehydration
- Urinalysis:
  - Hematuria seen in Wilms tumor, renal vein thrombosis, UPJ obstruction after trauma
- 24-hr urine
  - Elevated homovanillic acid and vanillylmandelic acid seen in neuroblastoma or pheochromocytoma
- Serum β-hCG and α-fetoprotein:

– Used in tumors such as teratoma, liver, and germ-cell tumors

Imaging

- Plain abdominal x-rays:
  – Check for obstruction/ileus; air–fluid levels on upright and lateral; absence of air in rectum
  – Calcifications can suggest neuroblastoma, teratoma, hepatoblastoma, meconium peritonitis, urinary, or biliary stones
- Abdominal US:
  – Primarily evaluation modality
  – Used to establish location, size, organ of origin, internal architecture, and vascular supply
  – Can determine cystic vs. solid
  – Inexpensive and noninvasive; rarely requires sedation
- CT:
  – Used to enhance findings on US or solid mass on US
  – Good anatomic detail
  – Useful in older children and suspected malignancies
  – Limitation: High sensitivity of pediatric patients to radiation exposure, may require sedation
- MRI:
  – Good for vascular involvement, adrenal origin
  – Good anatomic detail
  – May gather functional and quantitative information
  – Limitation: May require sedation/anesthesia
- Radionuclide scans:
  – Renal scans: Used to determine renal function, scarring, infection, and obstruction
  – Biliary scans: Evaluate for choledochal cysts
  – Liver–spleen scans: Used for diagnosis of liver tumors or splenic enlargement
- VCUG:
  – Used to rule out lower urinary tract pathology

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

Disease specific

DIFFERENTIAL DIAGNOSIS

- Hydronephrosis: Most common cause of neonatal abdominal mass (1):
  – UPJ obstruction: Most common cause of hydronephrotic abdominal mass
  – Other causes: UVJ obstruction, PUV, VUR, megaureter, and ureteroceles
  – $<$15% of neonates present with mass
  – Later presentation: UTI, flank pain, hematuria after trauma
- Multicystic dysplastic kidney:
  – 2nd most common cause; together with UPJ constitute 40% of all neonatal abdominal masses
  – Unilateral flank mass; more common on left, and in boys

  - US shows multiple noncommunicating cysts of various sizes; nuclear scan shows nonfunction on affected side
- Multilocular cystic nephroma:
  - Spectrum from benign cyst to cystic Wilms tumor
  - Present in males <5 yr and females >30 yr
  - Diagnosis by surgical excision
- Renal vein thrombosis:
  - Most common cause of neonatal hematuria; 65% occur in neonatal period, 30% after age 1; male predominance
  - Classic features: Flank mass, hematuria, thrombocytopenia
  - Occurs in conditions associated with dehydration, maternal diabetes, sepsis, diarrhea, or sickle cell disease
- Polycystic kidney disease:
  - Autosomal recessive; diagnosed in neonatal period; 50% die in 1st few hours or days usually from respiratory failure; of survivors, 86% alive at 1 yr and 67% at 15 yr
- Congenital mesoblastic nephroma:
  - Most common renal tumor diagnosed on antenatal US
  - Most common renal neoplasm of infancy
  - Mean age 3.5 mo
  - Surgery is usually curative
- Wilms tumor:
  - Most common childhood abdominal malignancy; most common malignant renal neoplasm in children
  - Usually presents as smooth, nontender, unilateral abdominal mass
  - Rare >10 yr and <6 mo; median age 3.5 yr
  - 80% of cases occur in age <5 yr
  - Increased frequency in WAGR, Beckwith–Wiedemann, and Denys–Drash syndromes
  - Combination surgery, chemotherapy, and radiation yields success rates >90% in favorable histology; lower in unfavorable histology
- Neuroblastoma:
  - Most common solid neonatal abdominal mass
  - Most common malignancy of newborn
  - 50% of all malignant tumors in children; 50% before age 2
  - Fixed, painful, irregular mass that often crosses midline
  - Fever, malaise, weight loss; ill-appearing compared to Wilms tumor
  - 90% have catecholamine excess
- Adrenal hemorrhage:
  - 1–2% of healthy infants
  - Predisposing factors: Birth trauma, large birth weight, perinatal asphyxia, sepsis, and coagulopathy
  - Supportive care, rare intervention
- Genital mass – Hydrocolpos and hydrometrocolpos (3):
  - Hydrocolpos: Gross distension of the vagina
  - Hydrometrocolpos: Gross distension of the vaginal and uterus

  - Due to obstruction from vaginal atresia or stenosis, imperforate hymen, or cloacal anomaly
  - Pelvic midline mass; US shows fluid-filled mass between bladder and rectum
- Genital mass – Ovarian cyst:
  - 1:3,000 girls
  - Most common cause of abdominal cystic tumor in female fetus
  - Presents as large mobile midabdominal mass
  - Cysts and tumors: 17% neonatal to age 4; 28% from 5–9 yr; 55% 9–18 yr
  - Prepuberty 50% are malignant, teratoma most common
- Genital mass – RMS:
  - 15–20% arise from genitourinary system: Prostate, bladder, paratesticular, vulvar/vaginal, uterine
  - 2 major subtypes: Embryonal (most common), alveolar (worse prognosis)
- GI masses:
  - 12% of neonatal abdominal masses
  - Intestinal duplication:
    - Common; congenital cystic abnormalities, with ileum most common, followed by esophagus, duodenum
  - Hypertrophic pyloric stenosis
  - Intestinal cysts: Meconium, omental, duplication, mesenteric
- Hepatobiliary masses:
  - Primary liver tumors are 3rd most common solid abdominal mass in childhood (15% total)
  - Benign lesions: 1/3 (hemangioendothelioma, mesenchymal hamartoma, adenoma, focal nodular hyperplasia, congenital cysts)
  - Malignant: 2/3 (hepatoblastoma most common <5 yr; hepatocellular carcinoma present ages 12–15)
- Splenic masses:
  - Congenital splenic cysts
  - Congenital hemolytic anemias: Hemoglobinopathies, thalassemias, hereditary spherocytosis
- Lymphoma: Common in boys >5 yr
  - 60% non-Hodgkin; 1/3 involve abdomen; can present as intussusception

TREATMENT

GENERAL MEASURES

Stabilize patient as necessary. Treatment is based on diagnosis.

MEDICATION

First Line

- Neuroblastoma
  - Chemotherapy is a part of a multidisciplinary approach including surgery, and bone or stem cell transplantation
  - Treatment schema based on INSS stage, age, N-*MYC* amplification, DNA ploidy, and

Shimada histopathology
- RMS
  – Chemotherapy is 1st line prior to radiation or surgical resection in all cases except those amenable to immediate partial cystectomy
- Wilms tumor
  – Adjuvant chemotherapy is based on NWTSG recommendations
  – SIOP studies favor preop chemotherapy

Second Line
N/A

SURGERY/OTHER PROCEDURES
Surgery is specific to disease process. In general, tumors, obstructive/infection problems will need surgery.

ADDITIONAL TREATMENT
Radiation Therapy
- RMS: Part of a multidisciplinary approach to curative therapy including surgical excision and chemotherapy
- Wilms tumor: For higher stage favorable histology, or for patients with focal or diffuse anaplasia

Additional Therapies
Neuroblastoma: Multidisciplinary approach may include bone or stem cell transplantation

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Disease specific

COMPLICATIONS
Treatment specific

FOLLOW-UP
Patient Monitoring
Disease specific

Patient Resources
N/A

REFERENCES

1. Becker AM. Postnatal evaluation of infants with an abnormal antenatal renal sonogram. *Curr Opin Pediatr.* 2009;21:207–213.
2. Golden CB, Feusner JH. Malignant abdominal masses in children: Quick guide to evaluation and diagnosis. *Pediatr Clin N Am.* 2002;49:1369–1392.
3. Miller RJ, Breech LL. Surgical correction of vaginal anomalies. *Clin Obstet Gynecol.* 2008;51:223–236.

ADDITIONAL READING

Isaacs H. Fet al and neonatal hepatic tumors. *J Pediatr Surg.* 2007;42:1797–1803.

See Also (Topic, Algorithm, Media)

- Abdominal Mass, Newborn, Child, Urologic Considerations Image
- Hydrocolpos and Hydrometrocolpos
- Hydronephrosis/hydroureteronephrosis
- Multicystic Dysplastic Kidney
- Neuroblastoma
- Polycystic Kidney Disease
- Rhabdomyosarcoma, Pediatric
- Ureteropelvic Junction Obstruction
- Wilms Tumor (Nephroblastoma)

CODES

ICD9

- 753.14 Polycystic kidney, autosomal recessive
- 789.3 Abdominal or pelvic swelling, mass, or lump
- 789.30 Abdominal or pelvic swelling, mass, or lump, unspecified site

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- C74.90 Malignant neoplasm of unsp part of unspecified adrenal gland
- Q61.19 Other polycystic kidney, infantile type

CLINICAL/SURGICAL PEARLS

- Determining the age (neonates vs. children) can differentiate between likely etiologies. In general, older children are more at risk of developing malignant masses compared with neonates and young children.
- Two most common entities causing neonatal abdominal mass (UPJ obstruction and MCDK), can be differentiated by renal scan. The renal scan usually shows some function in the hydronephrotic kidney and nonfunction MCDK.
- Concerning malignant masses, neuroblastoma, and hepatoblastoma are more likely in children <2; older children are more susceptible to Wilms, hepatocellular carcinoma, genitourinary tract tumors, and germ-line tumor.

ACUTE KIDNEY INJURY, ADULT (RENAL FAILURE, ACUTE)

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BASICS

DESCRIPTION

- The term acute kidney injury (AKI) has replaced the older descriptor of acute renal failure (ARF)
  - Rapid decline in renal function characterized by progressive azotemia, with or without oliguria (< 500 mL/d)
  - Decreased glomerular filtration rate
- Attempts to standardize the definition of AKI have been proposed by different groups as noted below. However, their utility in daily clinical care has not been confirmed (1)
  - Acute dialysis quality initiative (ADQI) group RIFLE criteria
  - Acute kidney injury network (AKIN)
  - Kidney Disease/Improving Global Outcomes (KDIGO) Clinical Practice Guidelines

EPIDEMIOLOGY

Incidence

- 5% of hospital admissions
- 30% of ICU admissions
- 25% of hospital patients develop AKI
  - 50% are iatrogenic

RISK FACTORS

- Preoperative risk factors for development of AKI:
  - Age > 56
  - Male
  - Emergency surgery
  - Intraperitoneal surgery
  - Diabetes mellitus
  - Active CHF
  - Ascites
  - Hypertension
  - Preoperative renal insufficiency

Genetics

No genetic association

PATHOPHYSIOLOGY

- Pre-renal
  - Transient renal hypoperfusion (reversible)
  - Stimulation of sympathetic nervous system and RAS causing renal vasoconstriction and sodium reabsorption; stimulation of antidiuretic hormone

  - Water reabsorption, low urine output, concentrated urine
- Intrarenal
  - Acute tubular necrosis (ATN)
    - Renal ischemia
    - Depletion of ATP
    - Dysfunction of plasma membrane
    - Reperfusion injury
    - Oxidative stress leading to tubular cell damage
    - Rhabdomyolysis and hemolysis
- Postrenal (obstruction)
  - Intrinsic obstruction
  - Extrinsic compression
- Iatrogenic (urinary extravasation, fistula)
  - Reabsorption of BUN, Cr

ASSOCIATED CONDITIONS
- Dehydration
- Trauma
- Burns
- Sepsis
- Urinary tract infection
- Chronic renal insufficiency
- Hypertension
- Congestive heart failure
- Liver disease, cirrhosis
- Nephrolithiasis
- BPH
- Advanced prostate or bladder cancer, malignancy
- Malignant hypertension

GENERAL PREVENTION
- Hydration
- Proper renal dosing of medication; daily dosing of aminoglycosides
- Avoidance of nephrotoxic agents
- Adequate voiding (timed, double voiding)
- Risk of contrast-induced AKI may be reduced by N-acetylcysteine 600 mg PO BID on day prior to and day of contrast and isotonic $NaHCO_3$ 3 mL/kg/h × 1 hr before and 1 mL/kg/h × 6 hr after contrast administration

ALERT
Determine if the patient is on any nephrotoxic medication? Has there been recent contrast injection? Is the foley draining?

DIAGNOSIS

- **HISTORY**

  - Urination history—frequency, urgency, strength of stream, hematuria
  - Fever, chills
  - Nausea, vomiting, diarrhea
  - Flank or abdominal pain
  - Recent strenuous activity
  - Review medications—nephrotoxic agents, diuretics
  - Comorbidities
    - Renal disease
    - Diabetes
    - Hypertension
    - Liver disease
  - Infections
  - Nephrolithiasis
  - BPH
  - Malignancies, metastatic disease
  - Previous abdominal or pelvic surgeries
  - Radiation
  - Chemotherapy
  - Prior ureteroscopy or endoscopy
- ***Social History***
  - Smoking
  - Alcohol
  - Drug use

PHYSICAL EXAM

- Vital signs: Blood pressure, heart rate, orthostatic changes
- Volume status, body weight
- Urinary output, drain output
- Neck vein distention, lung rales
- Abdominal exam
  - Bruits
  - Palpable mass
  - Distention, palpable bladder
  - Costovertebral angle tenderness
- Digital rectal exam—prostate size/nodularity
- Patency of urinary catheters, stents
- Peripheral edema, rash

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC, BUN, creatinine, electrolytes (including Ca/Mg/Phos), consider arterial blood gases (ABGs)
- AKI
  - Rise in serum creatinine (SCr) of at least 0.3 mg/dL over a 48-hr period
  - Over 1.5 times the baseline SCr value within the 7 previous days
- Common lab abnormalities in AKI:

  - Increased: K+, phosphate, Mg, uric acid
  - Decreased: Hematocrit (Hct), Na, Ca
- NephroCheck™ detects the presence of insulin-like growth-factor binding protein 7 (IGFBP7) and tissue inhibitor of met alloproteinases (TIMP-2) in the urine (both AKI associated); the test provides a risk score of developing AKI within 12 hrs
- Creatinine kinase (rhabdomyolysis)
- Immune antibodies (vasculitis)
- Urine
  - Urinalysis: Blood, protein, cells, casts, crystals
    - Transparent hyaline casts—prerenal etiology; pigmented granular/muddy brown casts—ATN; WBC casts—acute interstitial nephritis; RBC casts—glomerulonephritis
  - Urine eosinophils: ≥1% eosinophils by Hansel's stain suggestive of acute interstitial nephritis (sensitivity, 67%; specificity, 83%)
  - Urine electrolytes (Urine Na; U_{Na})
  - Urine osmolality (U_{osm})
  - Fractional excretion of sodium (FENA)
- Prerenal
  - FENA <1%; BUN/Cr >20
  - U_{Na} <10; U_{osm} >500
- Intrarenal
  - FENA >2%; BUN/Cr <15
  - U_{Na} >20; U_{osm} <350
- Postrenal
  - FENA >4%; BUN/Cr >15
  - U_{Na} >40; U_{osm} <350

Imaging

- Renal/bladder ultrasound
  - Hydronephrosis
  - Stones
  - Bladder volume, post void residual
  - Prostatic size
  - Bladder masses causing obstruction
  - Ureteral jets, resistive indices
- Abdominal x-ray (KUB)
  - Calcifications
  - Stent location
- CT abdomen/pelvis
  - Obstructing stones
  - Obstructing masses
- Renal scan
  - Obstruction
  - Kidney function

Diagnostic Procedures/Surgery
- Cystoscopy with retrograde pyelography
- Renal biopsy (acute glomerular nephritis)

Pathologic Findings
- Acute interstitial nephritis
  - Interstitial edema, marked interstitial infiltrate of T cells and monocytes
  - Eosinophilic plasma cells
  - PMN cells
  - Granulomata

DIFFERENTIAL DIAGNOSIS (4)
- Prerenal (~55%): Hypotension; volume depletion (GI losses, excessive sweating, dehydration, hemorrhage); renal artery stenosis/embolism; burns; heart failure; liver failure
- Intrarenal (~40%): ATN (from prolonged prerenal insufficiency, radiographic contrast material, aminoglycosides, NSAIDs, or other nephrotoxic substances); glomerulonephritis; acute interstitial nephritis (drug-induced); arteriolar insults; vasculitis; accelerated hypertension; cholesterol embolization (common after arterial procedures); intrarenal deposition/sludging (uric acid nephropathy and multiple myeloma [Bence Jones proteins])
- Postrenal (~5%): Extrinsic compression (eg, BPH, carcinoma, pregnancy); intrinsic obstruction (eg, calculus, tumor, clot, stricture, sloughed papillae); decreased function (eg, neurogenic bladder)
- Pseudo-AKI: Endogenous chromogens (eg, bilirubin, ascorbic acid, uric acid) and exogenous chromogens (eg, cephalosporins, trimethoprim, cimetidine) may interfere with the creatinine assay and cause falsely elevated results

TREATMENT

GENERAL MEASURES
- AKI requires close management of fluid, acid–base, and electrolyte balance and the removal of uremic toxins
- Fenoldopam, a dopamine agonist, may decrease dialysis and mortality in AKI (4)
- Furosemide is ineffective in preventing and treating AKI
- Prerenal
  - Restoration of renal perfusion; isotonic fluid
- Intrarenal
  - Cessation of nephrotoxic drugs
  - Renal dosing of medications
- Postrenal
  - Foley or suprapubic tube drainage
  - Ensure patency of drains
    - Ensure proper placement within bladder
    - Rule out catheter obstruction (mucus, clot)
  - Percutaneous nephrostomy tube
- Treatment of hyperkalemia (3)
  - Monitor EKG when K^+ >6 mmol/L

    - IV calcium
    - Sodium bicarbonate (if acidotic)
    - Insulin and glucose
    - Kayexalate
    - Hemodialysis for severe hyperkalemia or refractory to treatment
- Control of urinary extravasation
- Dietary considerations
  – Maintain carbohydrate and protein intake
  – Restrict: Phosphorus, potassium, sodium

MEDICATION

First Line

See above

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Postrenal
  – If cannot drain bladder per urethra, consider suprapubic tube
  – Ureteral stent
  – Percutaneous nephrostomy
  – If clot retention, removal of clots. May require cystoscopy, clot evacuation
  – If BPH, consideration for outpatient TURP
- Indications for dialysis (called renal replacement therapy can be hemo or peritoneal dialysis: For these urgent and potentially life-threatening indications:
  – Metabolic disturbances refractory to medical management such as hyperkalemia, metabolic acidosis, hypo/hypercalcemia, hyperphosphatemia
  – Pericarditis or pleuritis
  – Uremic encephalopathy
  – Uremia-related bleeding diathesis
  – Volume overload refractory to diuretics
  – Severe refractory hypertension

ONGOING CARE

PROGNOSIS

- Prerenal
  – Good if renal function improvement within 24–72 hr after fluid repletion
- ATN
  – Mortality rate of ATN generally 50%
  – Mortality rate of ATN in ICU 75%
  – Of those who survive ATN, 50% have complete resolution of renal function
  – 5% of AKI patients will require chronic renal replacement therapy
- Postrenal
  – Great recovery once obstruction and insult are resolved

COMPLICATIONS

- Postobstructive diuresis
- Sepsis post relief of obstruction with instrumentation
- Stent inflammation, crusting, and pain
- Chronic renal failure

FOLLOW-UP

Patient Monitoring

- Blood pressure control
- Monitoring of creatinine, potassium, calcium, and phosphorus
- Repeat imaging (US) to re-evaluate hydronephrosis
- If question of stent migration, obtain KUB or US
- Ureteral stents will need to eventually be exchanged or removed
- Consideration of internalization of percutaneous nephrostomy tubes

Patient Resources

National Kidney Foundation: www.kidney.org

REFERENCES

1. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet*. 2005;365:417–430.
2. Pannu N, Klarenbach S, Wiebe N, et al. Renal replacement therapy in patients with acute renal failure: A systematic review. *JAMA*. 2008;299:793–805.
3. Weisberg LS. Management of severe hyperkalemia. *Crit Care Med*. 2008;36:3246–3251
4. White HF, Kurland JM. Acute kidney injury. In: Domino FJ, ed. *The Five Minute Clinical Consult*. Philadelphia, PA: Wolters Kluwer; 2014.

ADDITIONAL READING

- Duty BD, Kavoussi LR. Assessment and Management of Incidentally Detected Unilateral Hydronephrosis in Adults. *AUA Update Series*. 2012;31:30.
- Van Wert R, Friedrich JO, Scales DC, et al. High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis. *Crit Care Med*. 2010;38:1360–1369.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Pediatric (Renal Failure, Acute)
- Acute Glomerulonephritis
- Acute Tubular Necrosis
- Contrast-Induced Nephropathy (CIN)
- Postobstructive Diuresis

CODES

ICD9

- 584.5 Acute kidney failure with lesion of tubular necrosis
- 584.9 Acute kidney failure, unspecified
- 593.81 Vascular disorders of kidney

ICD10

- N17.0 Acute kidney failure with tubular necrosis
- N17.9 Acute kidney failure, unspecified
- N28.0 Ischemia and infarction of kidney

CLINICAL/SURGICAL PEARLS

- Maximize urinary drainage.
- Avoid nephrotoxic agents.
- Upper tract obstructive uropathy should be acutely managed by stent vs. percutaneous nephrostomy.

ACUTE KIDNEY INJURY, PEDIATRIC (RENAL FAILURE, ACUTE)

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BASICS

DESCRIPTION

- A sudden or recently acquired functional impairment of the kidney relative to physiologic demands with or without actual kidney injury (1)
- Causes mild to potentially life-threatening alterations in fluid, electrolyte, acid–base and hormonal homeostasis
- Terminology evolving from acute tubular necrosis (ATN) to acute renal failure (ARF) to acute kidney injury (AKI) of varying grades to standardize reporting, clinical care, and research
- Diagnosed by the Pediatric Modified Risk Injury Failure Loss End Stage Renal Disease (pRIFLE) criteria based on the estimated creatinine clearance (eCCl, based on Schwartz formula) and urine output (UOP) (2)
  - Risk: eCCl decrease by 25% and/or UOP <0.5 mL/kg/h for 8 hr
  - Injury: eCCl decrease by 50% and/or UOP <0.5 mL/kg/h for 16 hr
  - Failure: eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2 and/or UOP <0.3 mL/kg/h for 24 hr or anuric for 12 hr
  - Loss: Persistent failure >4 wk
  - End stage renal disease (ESRD): Persistent failure >3 mo
- No standardized definition for neonatal AKI

EPIDEMIOLOGY

Incidence

- A difficult assessment since, until recently, there was no unifying criteria to make the diagnosis
  - Recent meta-analysis showed reported incidences in hospitalized pediatric population from 1–82% (3)

Prevalence

Unknown

RISK FACTORS

- Chronic kidney disease (CKD) increases the risk for AKI
- Hospitalization, especially in the ICU
- Exposure to potentially nephrotoxic agents, such as nonsteroidal anti-inflammatories (NSAIDs), contrast, aminoglycosides
- Recent surgery, solid organ or marrow transplant, cardiopulmonary bypass

Genetics

- If recurrent rhabdomyolysis, consider an underlying defect in muscle metabolism

- If recurrent hemolytic uremic syndrome (HUS) consider a defect in the complement cascade
- If AKI in the presence of CKD then consider inherited forms of ESRD, such as autosomal recessive polycystic kidney disease

PATHOPHYSIOLOGY

- Prerenal and intrinsic renal injury disrupt the regional perfusion of, and subsequent oxygen delivery to, the kidney (3)
  - The natural arterial gradient of oxygen tension from cortex to medulla makes the kidney highly susceptible to hypoxic and oxidative injury during ischemia and reperfusion
  - Poorly perfused glomerular endothelial cells release vasoactive substances, proteases, reactive oxygen species, and nitric oxide and activate the coagulation cascade and complement pathways
  - Even well-perfused kidneys can develop AKI during sepsis from circulating cytokines, lymphocytes, T cells, and other factors
  - When found in the presence of cardiac, pulmonary, or hepatic failure it is likely due to endothelial activation and circulatory aberrations
  - Nephrotoxic agents each have their own mechanism of damage, eg, by forming crystals in the microstructures of the kidney
  - Rhabdomyolysis causes intrarenal vasoconstriction, direct ischemic tubule injury, and tubular obstruction in acidic urine
- Postrenal injury is due to antegrade urine flow disruption from the kidney
  - Must be bilateral to cause pRIFLE findings but can be unilateral if only one kidney is present due to congenital absence, prior nephrectomy, or kidney transplant
- Etiology may be multifactorial, especially in the ICU setting

ASSOCIATED CONDITIONS

CKD increases the risk for AKI

GENERAL PREVENTION

- Prerenal
  - Prevent volume depletion (1)[B]
  - Maintain cardiac output and oxygenation with vasopressors and blood transfusions as needed (1)[C]
- Intrinsic renal
  - Careful dosing and therapeutic drug level monitoring of aminoglycosides or avoidance altogether
  - Use lipid formulation of amphotericin B or another antifungal alternative
  - Contrast-induced AKI
    - Avoid the use of contrast
    - Use either iso- or low-osmolar iodinated contrast media
    - Intravenous fluid expansion for those patients at risk
  - Avoid NSAIDs
  - Animal models have shown the potential benefit of vasodilators, growth factors, antioxidants, and anti-inflammatory drugs in preventing AKI
- A single dose of theophylline given to neonates with severe perinatal asphyxia has been shown to significantly reduce the risk of AKI

DIAGNOSIS

HISTORY

- Evaluate for shock, sepsis, bleeding, dehydration, gastrointestinal losses
- Assess recent medication exposure, including natural products
- History of urologic surgery, anatomic problems, or kidney transplantation
- Family history of ESRD, HUS
- Recent trauma, crush injury
- Seek signs of CKD, such as growth delay
- Review recent blood tests to determine baseline serum creatinine (SCr) and onset of AKI

PHYSICAL EXAM

- Assess hydration status, blood pressure, heart rate, and temperature
- Lungs for rales
- Abdomen for masses

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- SCr and blood urea nitrogen will be elevated
- May have hyperkalemia, acidosis
- Hemoglobin will be low if bleeding
- HUS causes thrombocytopenia, increased lactate dehydrogenase
- When muscular damage is the cause creatinine kinase will be elevated and urinary myoglobin will be positive
- Urinalysis to detect red blood cells, proteinuria
- Urine eosinophils indicate interstitial nephritis
- Strict UOP monitoring to assess AKI stage and progression
- Atypical-AKI
  - Clinical AKI fails to meet the definition
    - SCr falsely lowered by dilution due to large volume fluid resuscitation or transfusions, thereby reflecting the blood donors' kidney function
    - SCr falsely lowered by muscle wasting or reduced muscle mass due to quadriplegia, cerebral palsy, or other neuromuscular disorders
    - SCr falsely lowered during sepsis by decreased muscle perfusion
- Real-time markers of AKI are being sought
  - Candidates include serum cystatin C, kidney injury molecule-1, interleukin-18, liver fatty acid–binding protein, neutrophil gelatinase-associated lipocalin

Imaging

- Renal ultrasound with Doppler analysis of the renal artery and veins
  - Hydronephrosis indicates obstruction
  - Increased echogenicity consistent with medical renal disease
  - Thrombosis of renal artery or vein
  - Small echogenic kidneys, cystic kidneys indicate CKD
- Bladder ultrasound
  - Trabeculated, thick-walled bladder may indicate lower urinary tract abnormality such as a neurogenic bladder or obstruction

- Technetium-99m MAG3 renal scan can be used in prolonged AKI to differentiate prolonged ATN from permanent cortical necrosis

Diagnostic Procedures/Surgery

Kidney biopsy rarely necessary but may be indicated to diagnosis prolonged AKI without a clear etiology

Pathologic Findings

Kidney biopsy may reveal ATN, interstitial disease, thrombotic microangiopathy, medication-induced crystal formation, glomerulonephritis

DIFFERENTIAL DIAGNOSIS

- Prerenal
  - Intravascular volume depletion
    - Dehydration, hemorrhage, gastrointestinal losses, burns, pancreatitis, peritonitis
    - Congestive heart failure, sequestration in interstitial spaces, shock, anaphylaxis
- Intrinsic renal
  - ATN, hypoxic/ischemic insults, sepsis/toxin mediated, multiple organ dysfunction syndrome, interstitial nephritis, tumor lysis syndrome, glomerulonephritis, vascular thrombosis, cortical necrosis, HUS, cortical dysplasia or hypoplasia, rhabdomyolysis
  - Potentially nephrotoxic agents such as aminoglycoside antibiotics, NSAIDs, radio-opaque contrast, antivirals, antifungals, chemotherapeutic agents
  - Chinese herb nephropathy is an acute to chronic interstitial fibrosis caused by Aristolochia fangchi, an herb still available in natural products ordered online
- Postrenal
  - Obstruction in the ureter(s) or urethra
  - Bilateral nephrolithiasis due to cystinuria has been reported as a cause of pediatric AKI
- Pseudo-AKI
  - Always interpret lab data in clinical context to avoid overdiagnosis of AKI
    - Endogenous chromogens (eg, bilirubin, ascorbic acid, uric acid) and exogenous chromogens (eg, cephalosporins, trimethoprim, cimetidine) may interfere with the creatinine assay and cause falsely elevated results
    - Weight-based determination of UOP may falsely cause the obese patient to fulfill the criteria without actual AKI

TREATMENT

GENERAL MEASURES

- Reduce risk of dehydration or fluid overload by only replacing calculated insensible fluid losses and measured UOP
  - Intravenous fluid should have no potassium
- Maintain renal perfusion and oxygenation (1)[C]
  - Renal dilators (dopamine, fenoldopam) have not been shown to improve pediatric AKI
  - No studies relating fluid type used in pediatric resuscitation on AKI incidence or outcome
- Continuous renal replacement therapy (CRRT) has not been shown to improve kidney function or mortality, although there is controversy about the timing of initiation, dose,

route, and duration (1)[C]
- Hemodialysis or peritoneal dialysis may play a role in supportive care of the patient with AKI
- Discontinue potentially nephrotoxic drugs
- Medications with renal clearance require dosing/timing adjustments/drug level monitoring, when available, to reduce the risk of toxicity
- Nutritional research is limited to observational studies
  – Critically ill children should receive 100–130% of their basal energy needs

MEDICATION

First Line

- Diuretics to convert oliguric AKI to nonoliguric AKI have not been shown to affect outcomes (1)[C]
- IV sodium bicarbonate has been administered to correct the acidosis of AKI but has not been studied with randomized controlled trials
- Emerging treatments include apoptosis inhibitors, iron chelators, anti-inflammatory agents, repair agents (eg, stem cells)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Central venous access may be needed for renal replacement therapy (CRRT or hemodialysis)
- Postrenal AKI may require decompression surgery, nephrostomy tube, or ureteral stent
- Nephrolithiasis may respond to extracorporeal shock wave lithotripsy, endoscopic surgery, or surgery (open, laparoscopic, robotically assisted)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- With multisystem organ failure the addition of AKI increases mortality from 10–57%
- A 3–5-yr follow-up study after resolution of AKI showed that 40–50% of pediatric patients showed signs of CKD (3)

COMPLICATIONS

- Hyperkalemia, fluid overload, pulmonary edema, hypertension, acidosis, reduced drug excretion, and uremic symptoms
  – Overcorrection of any of the above
- Nephrogenic systemic fibrosis (NSF) is a rare but potentially lethal fibrosing disorder of the

skin, liver, heart, lungs, diaphragm, and skelet al muscle observed in patients with AKI or CKD who were exposed to gadolinium used in MRI (4)
  – 335 cases in the NSF International Registry at the time of writing; some were children
  – Gadolinium should be avoided in AKI
- Patients exposed to the Aristolochia fangchi herb are at increased risk for urothelial malignancies

FOLLOW-UP

Patient Monitoring

Monitor SCr, blood pressure, somatic growth, urinalysis for signs of CKD after resolution of AKI

Patient Resources

- American Society of Pediatric Nephrology
  – www.aspneph.com/parentpatient.asp
- Kidney & Urology Foundation of America
  – www.kidneyurology.org/
- National Kidney Foundation
  – www.kidney.org/patients/index.cfm

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Inter., Suppl. 2012;2:1–138.
2. Akcan-Arikan A, Zappitelli M, Loftis LL, et al. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Inter.* 2007;71:1028–1035.
3. Basu RK, Devarajan P, Wong H, et al. An update and review of acute kidney injury in pediatrics. *Pediatr Crit Care Med.* 2011;12:339–347.
4. Perazella M. Nephrogenic Systemic Fibrosis, kidney disease, and gadolinium: Is there a link? *Clin J Am Soc Nephrol.* 2007;2:200–202.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Chronic Kidney Disease, Pediatric (Renal Failure, Chronic)
- Pediatric Modified Risk Injury Failure Loss End Stage Renal Disease (pRIFLE)

CODES

ICD9

- 584.5 Acute kidney failure with lesion of tubular necrosis
- 584.9 Acute kidney failure, unspecified
- 728.88 Rhabdomyolysis

ICD10

- M62.82 Rhabdomyolysis
- N17.0 Acute kidney failure with tubular necrosis
- N17.9 Acute kidney failure, unspecified

CLINICAL/SURGICAL PEARLS

- AKI is often multifactorial.
- Seek prerenal, intrinsic renal, and postrenal causes of the AKI.
- Stage AKI with pRIFLE criteria.
- Avoid potentially nephrotoxic drugs and gadolinium during AKI.

ACUTE SCROTUM

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BASICS

DESCRIPTION

- Acute pain and swelling in the scrotum is typically related to testicular pathology and is usually referred to as "acute scrotum" in the absence of obvious trauma.
- Occasionally pain from ureteral colic can be referred to the testicle but swelling is usually absent.
- Chronic testicular pain is referred to orchalgia.
- Testicular torsion is a major cause of the acute scrotum particularly in children and requires timely diagnosis and treatment to avoid testicular loss.
- In adults acute epididymo-orchitis is the most common cause of an acute scrotum.
- In children torsion of a testicular appendix or testicle are most common causes.

EPIDEMIOLOGY

Incidence

- Testicular torsion occurs most commonly in neonates and postpubertal boys and is more common on the left
  - However in 1 series 39% of patients were reported to be in men >21 yr of age (1)
- Torsion of an appendix more common in prepubertal boys
- Approximately 600,000 cases of epididymitis/yr in US

Prevalence

Testicular torsion: 1:4,000 males <25 yr old

RISK FACTORS

- Testicular torsion
  - Cryptorchidism
  - Bell clapper deformity
- Epididymitis
  - Unprotected sex in younger men
  - Prostate disorders in older men
  - Urinary tract instrumentation
  - Anal insertive intercourse

Genetics

Testicular torsion reported in 10% of family members; may be autosomal or X-linked recessive; no specific genetic defects identified

PATHOPHYSIOLOGY

- Testicular torsion can be either intravaginal or extravaginal
  - Intravaginal testicular torsion is twisting of the spermatic cord *within* the tunica vaginalis
    - Usually due to a so-called "bell clapper deformity": A failure of normal posterior

anchoring of the gubernaculum, epididymis and testis. Leaves the testis free to rotate within the tunica vaginalis of the scrotum much like the clapper inside of a bell (present in 12% of males)
  - Extravaginal testicular torsion is twisting of both the spermatic cord *and* tunica vaginalis
- Perinatal: Extravaginal testicular torsion is usually the cause
- Appendix torsion is a result of vascular compromise may be related to pedunculated anatomy of the appendage
  - Appendix testis 95% of appendix torsions
  - Appendix epididymis torsion is less common
- Epididymitis
  - Can present as acute or chronic epididymitis
    - Acute: Severe swelling, tenderness, rigors, high fevers
  - Infectious causes
    - In men >35 yr of age, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (sexually transmitted infections) are the most common pathogens
    - In men >35 yr of age coliforms most common
    - Less common pathogens: Ureaplasma, TB, Brucella species; with HIV infection, Cytomegalovirus and Cryptococcus
  - Less frequent causes include autoimmune diseases, vasculitis, trauma
  - In a prepubertal boy epididymitis is almost always associated with a urinary tract anomaly

ASSOCIATED CONDITIONS

- Torsion
  - Bell clapper deformity: 10–15% of males
  - Cryptorchidism
- Epididymitis
  - Other sexually transmitted infections
  - Prostatic hypertrophy

GENERAL PREVENTION

- Torsion: Reduce testicular loss risk by
  - Early diagnosis and treatment
  - Community awareness about testis pain
  - Elective bilateral orchidopexy for intermittent pain or contralateral orchidopexy at surgery for an episode of acute torsion
- Epididymitis
  - Safe sex practices

DIAGNOSIS

HISTORY

- Rule out any traumatic insult to the groin area
  - Some patients report minor trauma before presentation of torsion
- Sexual practice history
- Recent urinary tract instrumentation
- Testicular torsion

- The classic presentation is sudden hemiscrotal pain often awakening the patient from sleep
- Pain can radiate to the groin
- Nausea and/or vomiting can be present
- Movement tends to worsen the pain
- A history of intermittent testicular discomfort may be present suggesting past torsion and detorsion

• Appendix torsion
- Symptoms are similar to testicular torsion but not as severe

• Epididymitis
- Can present with acute: Fever, chills, rigors, or as chronic testicular/scrotal discomfort
- More likely to be associated with voiding complaints than torsion

PHYSICAL EXAM

• General
- Vital signs; low-grade fever with torsion, fever with UTI
- Presence of inguinal hernia
- Abdominal and flank tenderness

• GU exam
- Assess cremasteric reflex (2):
  - Stroke or pinch the skin of the upper thigh
  - Normal reflex is contraction of the cremaster muscle with elevation of the testis.
  - Absent reflex may aid in distinguishing testicular torsion from epididymitis/other causes of an acute scrotum where reflex is present
  - Phren sign (pain relief with elevation of testicle) is no longer considered accurate for diagnosis of torsion

• Testicular torsion
- Testicle may be high riding
- Very tender and may assume a transverse lie due to twisting of the cord
- The spermatic cord will not usually be palpable
- May be scrotal wall erythema and swelling
- Cremasteric reflex often absent

• Torsion appendix
- Pain may be localized to upper pole of testicle
- Cremasteric reflex usually present
- Blue dot sign: Rare, more likely in prepubertal boys;
  - Tender nodule with blue discoloration on the upper pole of the testis and more easily seen in light-skinned individuals
- In late findings scrotal swelling and reactive hydrocele may be present

• Epididymitis
- Cremasteric reflex usually present
- Acute epididymitis may have significant swelling and tenderness; with chronic epididymitis there is tenderness but usually no scrotal swelling

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - White cells and positive leukocyte esterase
    - Suspect epididymitis or UTI
  - Red blood cells suggest renal or ureteral source of pain (eg, stone)
  - In cases of torsion UA usually negative
- Urine culture if epididymitis or UTI suspected
- Consider urethral swab if urethral discharge present: Culture and nucleic acid amplification testing for chlamydia and gonorrhea

Imaging

- Scrotal US with Doppler
  - Intravaginal testicular torsion findings
  - Usually shows decreased or absent arterial flow but may be normal
- Appendix torsion findings
  - Normal exam most common
  - Supratesticular complex mass without vascular flow may be present
- Epididymitis
  - Enlarged epididymis reported as “epididymitis” often present
  - Doppler flow normal or increased

Diagnostic Procedures/Surgery

In cases of testicular torsion, surgical exploration is usually diagnostic and therapeutic

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Abscess or other infection such as Fournier gangrene
- Appendix torsion (appendix testis or epididymis testis)
  - Most commonly seen in prepubertal boys
  - Most common cause of acute scrotum in this age group
- Epididymitis due to UTI or STD: Rare or uncommon in pediatric age group; more likely in adult
- Fat necrosis of scrotal wall
- Henoch–Schönlein purpura
  - Rash usually present
- Incarcerated inguinal hernia
- Orchitis: With the exception of mumps orchitis, isolated orchitis without epididymitis in adults is rare
- Referred pain: Urolithiasis or intra-abdominal process such as appendicitis
- Testicular infarction due to spermatic cord injury or thrombosis
- Testicular torsion: Most common in peripubertal boys but can occur at any age; less common than appendix torsion
- Testicular tumor: Usually painless but may have tenderness with trauma
- Trauma and possible testicular rupture: History suggestive; hematocele usually present
- Orchalgia; consider voiding dysfunction

TREATMENT

ALERT
Testicular torsion is a surgical emergency because the likelihood of testicular salvage diminishes with the duration of torsion.

GENERAL MEASURES

- Clinical history, exam, and diagnostic studies (urinalysis, Color Doppler Ultrasound) have a high degree of accuracy in making the diagnosis
- Emergent exploration indicated if evaluation suggests intravaginal testicular torsion or diagnosis is equivocal
- If torsion is present and surgery cannot be performed in a reasonable amount of time, manual detorsion should be considered
- Most cases of epididymitis can be treated on an outpatient basis

MEDICATION

First Line

- Epididymitis: Acute
  - Ice, scrotal elevation, and NSAIDs with antipyretic for high temperature
  - Younger male: Ceftriaxone (250 mg IM) with doxycycline (100 mg PO BID × 10 days).
  - Older males: Ceftriaxone (250 mg IM) along with a 10-day course of fluoroquinolone for enteric organisms (ofloxacin 300 mg PO BID or levofloxacin (500 mg PO BID)
- Epididymitis: Chronic
  - Scrotal elevation, avoid sexual and athletic activity, warm baths, and NSAIDs
- Appendix torsion: Ibuprofen to reduce inflammation and discomfort
- Testis torsion: Pain control may require opioids

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Urgent scrotal exploration, bilateral fixation for extravaginal testicular torsion to avoid asynchronous contralateral torsion
- Manual detorsion: Use only if surgery is delayed >2 hr
  - Testicle most often rotates medially during torsion
  - Manual detorsion is accomplished by attempting to rotate the testicle laterally toward the thigh
  - The twisting can range from 180–720 degrees such that multiple detorsion twists may be required
  - However in up to 1/3 of cases, the torsion rotation can be lateral
  - Successful detorsion still requires operative intervention and orchidopexy
  - Hallmarks of successful manual detorsion include pain relief, testicle assuming a lower position in the scrotum, reorientation of the testicle from transverse lie to vertical positioning, restoration of Doppler blood flow

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- In cases of testicular torsion 12 hr is considered the point at which the testis suffers irreversible damage
- Torsion surgery outcomes appear better in children than in adults
  - Salvage rates in males <21 yr was 70% vs. those >21 yr who had a salvage rate of 41% (3)
    - Potential explanations: Time to presentation impacted salvage and patients over 21 yr of age had a greater degree of cord twisting than the younger patients

COMPLICATIONS
- Testicular torsion
  - Testicular loss and or atrophy
  - Infertility
- Appendix testis/epididymis torsion
  - Usually none long term
- Epididymitis
  - Scrotal abscess
  - Urosepsis
  - Chronic orchalgia

FOLLOW-UP
Patient Monitoring
Epididymitis due to culture-proven *C. trachomatis* or *N. gonorrhoeae*: refer sex partners for evaluation and treatment disease

Patient Resources
MedlinePlus: Testicular torsion
http://www.nlm.nih.gov/medlineplus/ency/article/000517.htm

REFERENCES
1. Cummings JM, Boullier JA, Sekhon D, et al. Adult testicular torsion. *J Urol*. 2002;167(5):2109–2110.
2. Rabinowitz R. The importance of the cremasteric reflex in acute scrotal swelling in children. *J Urol*. 1984;132(1):89–90.

ADDITIONAL READING
Yu KJ, Wang TM, Chen HW, et al. The dilemma in the diagnosis of acute scrotum: Clinical clues for differentiating between testicular torsion and epididymo-orchitis. *Chang Gung Med J*.

2012;35(1):38–45.

See Also (Topic, Algorithm, Media)

- Acute Scrotum Algorithm
- Acute Scrotum Image
- Appendix Testis and Appendix Epididymis, Torsion
- Epididymitis
- Torsion, Testis, or Testicular/Epididymal Appendages

CODES

ICD9

- 604.90 Orchitis and epididymitis, unspecified
- 608.9 Unspecified disorder of male genital organs
- 608.20 Torsion of testis, unspecified

ICD10

- N44.00 Torsion of testis, unspecified
- N45.3 Epididymo-orchitis
- N50.9 Disorder of male genital organs, unspecified

CLINICAL/SURGICAL PEARLS

- Color Doppler ultrasonography is the preferred imaging technique for evaluating the acute scrotum.
- Cremasteric reflex is usually absent in testicular torsion.

ACUTE TUBULAR NECROSIS

Costas D. Lallas, MD, FACS

BASICS

DESCRIPTION

- Acute tubular necrosis is the most common type of intrarenal acute renal injury (AKI)
  - Usually due to prolonged ischemia or administration of nephrotoxins
- A syndrome of intrinsic renal failure secondary to ischemic or toxic insults
- Histopathologic findings of ATN variable
- Decreased urine output:
  - Can be nonoliguric, oliguric >500 mL/d, or anuric. Mortality increases from 20–60% to 80% if the patient is oliguric or anuric.
- Signs of underlying disorder:
  - Signs of sepsis or of hypotensive events secondary to trauma, cardiac disease, surgery with excessive blood loss, or interruption of blood supply to kidneys

EPIDEMIOLOGY

Incidence

- ARF is present in 209 per million population.
- ARF may affect 2–5% of patients in a tertiary care hospital, and the incidence of ARF in the surgical or medical ICU may exceed 20–30%
- Breakdown of ARF: ATN, 45%; prerenal causes, 21%; acute or chronic renal failure, 13%; urinary tract obstruction, 10%; glomerulonephritis or vasculitis, 4%; acute interstitial nephritis, 2%; atheroembolism, 1%

RISK FACTORS

- Decreased renal perfusion from:
  - Prolonged hypotension, surgical interruption of blood flow, NSAIDs, ACE inhibitors, cyclosporine
- Nephrotoxic agents:
  - Radiocontrast media (low osmolality is possibly safer), aminoglycosides, cisplatin, amphotericin, drug intoxications with acetaminophen or ethylene glycol
  - The most commonly seen nephrotoxins in the hospitalized patient include radiographic contrast material, antibiotics (especially aminoglycosides and amphotericin B), chemotherapeutic agents, NSAIDs, and ACE inhibitors

Genetics

N/A

PATHOPHYSIOLOGY (1)

- Acute tubular injury
- Renal hypoperfusion and renal ischemia are the most common causes of ATN
- The ischemic form is due to the reductions in glomerular filtration rate (GFR) are secondary to vascular and tubular factors

  - Ischemia from reductions in GFR from decreased renal plasma flow or dilatation of the efferent arteriole. After return of normal blood flow, ATN persists secondary to tubular changes
  - In addition, both exogenous and endogenous nephrotoxic compounds exist.
- Tubular factors: Backleak and tubular obstruction. Tubular obstruction secondary to a sloughed brush border, cellular debris, Tamm–Horsfall protein, and decreased filtration pressure contribute to obstruction and maintenance of ATN

ASSOCIATED CONDITIONS
- Sepsis
- Hemorrhage (operative, obstetric, trauma)
- Pre-existing renal insufficiency (diabetes, hypertension)
- Edematous states such as CHF

GENERAL PREVENTION
- Avoid prolonged renal ischemia by timely management of hemorrhage, dehydration and other causes of renal hypoperfusion
- Avoidance of contrast agents in the setting of renal insufficiency (contrast-induced nephropathy)
- Appropriate management of potentially nephrotoxic medications

DIAGNOSIS
HISTORY
- Specific attention to:
  - Hypotensive episodes, blood transfusions, intravenous contrast exposure
- Meticulous listing of medications to include dosage to assure appropriate dosing for level of renal function
- Make sure other medications which depend on renal metabolism are also given at appropriate doses to avoid side effects

PHYSICAL EXAM
- Vital signs and hemodynamic parameters should be critically assessed.
- A patient's weight is helpful information, and its daily measurement is important in the diagnosis and management of ARF.
- Evaluate the volume status of the patient.
- Evaluate neck veins and auscultation of heart and lungs; assess extremities and the presacral area for edema.
- General exam
- Evaluate for bladder distention and assess for signs of vasculitis or cutaneous rashes.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum tests (2)
  - BUN/plasma creatinine ratio: The ratio is normal at 10 to 15:1 in ATN, but >20:1 in prerenal disease due to the increase in passive reabsorption of urea, the ratio may also be increased with GI bleed, muscle breakdown, and administration of corticosteroids or

tetracycline
  - Rate of rise of plasma creatinine: Rise of >0.3–0.5 mg/dL in ATN vs. slower rise with fluctuations with prerenal disease
- Urine tests
  - Urinalysis: Muddy brown granular and epithelial cell casts and free epithelial cells secondary to sloughing of the tubular epithelium vs. near-normal in prerenal disease
  - The classic sediment of ATN includes pigmented (muddy brown) granular casts and renal tubular epithelial cells, which may be seen in nearly 80% of cases of oliguric ARF
  - Urine sodium concentration: High >40 mEq/L due to tubular injury vs. <20 mEq/L in prerenal disease in an attempt to conserve sodium
  - Fractional excretion of sodium (FENa): Above 2% in ATN while <1% in prerenal disease, measured as urine Na divided by plasma Na times plasma CR divided by urine CR, although causes of ATN associated with a low FENa are that due to intravenous contrast material, rhabdomyolysis, sepsis, and multisystem organ failure
  - Urine osmolality: Urine osmolality <450 mOsm/kg in ATN secondary to loss of concentrating ability; >500 mOsm/kg in prerenal disease
- Urine creatinine concentration divided by plasma creatinine concentration: Ratio is <20 in ATN while >40 in prerenal disease, reflecting loss of tubular water reabsorption

Imaging
- Renal ultrasonography
  - Sensitive test to determine obstruction. Doppler can detect gross blood flow in renal vein and artery
- Plain abdominal film
  - Identifies the presence or location of renal calculi and is particularly helpful to discern the proper position of stents and drains
- Functional studies
  - Nuclear scans can determine perfusion or tubular secretion; MRI can give some functional information while providing anatomic information

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
- Tubule cell injury (2):
  - Tubular epithelial cells are particularly sensitive to ischemia and are also vulnerable to toxins. The structural changes include those of reversible injury (such as cellular swelling, loss of brush border and polarity, blebbing, and cell detachment) and those associated with lethal injury (necrosis and apoptosis)
- Disturbances in blood flow:
  - Intrarenal vasoconstriction results in both reduced glomerular blood flow and reduced oxygen delivery to the functionally important tubules in the outer medulla (thick ascending limb and straight segment of the proximal tubule)

DIFFERENTIAL DIAGNOSIS
- Prerenal azotemia
- Postrenal azotemia

- Other forms of renal azotemia
- Glomerulonephritis, disseminated intravascular coagulopathy, arterial or venous obstruction, intrarenal precipitation

TREATMENT

GENERAL MEASURES

- Define and treat the underlying cause.
- Discontinue any nephrotoxic agents.
- Prophylaxis and treatment of complications of ARF.
- Early nephrology consultation.
- Management of fluid disturbances.
- Maintain a euvolemic state by restricting total fluids to no more than urine output plus insensible losses.

MEDICATION

First Line

- High-dose loop diuretics (1–3 g/d) may convert oliguric to nonoliguric ATN in some patients; it has not been determined that this conversion decreases the duration of ATN or mortality. Dopamine may increase urine output, but its benefit is in question.
  - Studies suggest that patients who respond to mannitol, furosemide, or dopamine with an increased urine output have better outcomes than nonresponders.
- Management of electrolyte disturbances
  - Electrolyte disturbances can be minimized by prophylactic institution of a low-potassium, low-protein diet accompanied by fluid restriction and oral phosphate binders.
- Hyperkalemia is the most common and most dangerous abnormality and should be treated aggressively with calcium supplementation until potassium levels can be reduced with combinations of insulin and glucose or potassium-binding resins.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Hemodialysis (HD), peritoneal dialysis (PD), and continuous arteriovenous hemofiltration (CAVH)
  - CAVH: Need ICU, limited mobility, need anticoagulation, removes fluid well but slow correction of electrolyte abnormalities
  - PD: No anticoagulation needed but slower correction of electrolyte abnormalities
  - HD: Expensive, anticoagulation necessary, vascular access necessary but allow rapid correction of fluid and electrolyte abnormalities

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Slight improvements in survival in those patients with ATN requiring dialysis in an ICU setting
  - The Mayo Clinic compared 1977–1979 with 1991–1992 showed high survival both in hospital (52% vs. 32%) and at 1 yr (30% vs. 21%)
  - Higher mortality rates are seen in elderly patients and in patients with respiratory failure, multiple organ failure, pre-existing chronic diseases, and systemic hypotension
- Major causes of death are infection and underlying disease, not renal failure
  - Patients at risk are generally very ill, with evidence of multiple organ dysfunction
- Of patients who survive ATN, nearly half will have a complete recovery of renal function and a majority of the remainder have an incomplete recovery. Only about 5% of all ARF patients require chronic maintenance dialysis

COMPLICATIONS
- Fluid overload, electrolyte disturbances, metabolic acidosis
  - Hypertension, edema, acute pulmonary edema, hyponatremia, hyperkalemia, hypermagnesemia, hypercalcemia, hyperphosphatemia, hyperuricemia
  - Uremic signs and symptoms
- GI: Nausea, vomiting, GI bleed; neurologic: Encephalopathy, coma, seizures, peripheral neuropathy; cardiac: Pericarditis uremic pneumonitis; hematologic: Bleeding, anemia; immunologic: Impaired granulocyte/lymphocyte function

FOLLOW-UP
Patient Monitoring
- Duration
  - Renal failure phase usually lasts 7–21 days if the primary insult (ischemia, nephrotoxin) can be corrected. Recovery is usually heralded by a progressive increase in urine output and a return of BUN and CR to the previous baseline.
- Recovery of renal function
  - Irreversible loss of renal function can occur if the combination of pre-existing renal disease and prolonged ARF secondary to repeat ischemic insults and/or nephrotoxin administration
  - If the patient survives, baseline CR is usually only 1–2 mg/dL above baseline.
- Those patients that need dialysis and have bioincompatibility with the dialysis membrane or have repeat episodes of hypotension have a worse prognosis.

Patient Resources
N/A

REFERENCES
1. Goldfarb DA, Poggio ED. Etiology, pathogenesis, and management of renal failure. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology*, 10th ed.

Philadelphia, PA: WB Saunders, 2012.
2. Erdbruegger U, Okusa, MD. Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury (acute renal failure). *UpToDate.* Accessed August 4, 2014

ADDITIONAL READING

Belcher JM, Parikh CR. Is it time to evolve past the prerenal azotemia versus acute tubular necrosis classification? *Clin J Am Soc Nephrol.* 2011;6:2332–2334.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Acute Kidney Injury, Pediatric (Renal Failure, Acute)
- Contrast Induced Nephropathy (CIN)

CODES

ICD9

584.5 Acute kidney failure with lesion of tubular necrosis

ICD10

N17.0 Acute kidney failure with tubular necrosis

CLINICAL/SURGICAL PEARLS

- High-dose loop diuretics (1–3 g/d) may convert oliguric to nonoliguric ATN in some patients; it has not been determined that this conversion decreases the duration of ATN or mortality.
- Of patients who survive ATN, nearly half will have a complete recovery of renal function and a majority of the remainder have an incomplete recovery. Only about 5% of all ARF patients require chronic maintenance dialysis.
- A patient's weight is helpful information, and its daily measurement is important in the diagnosis and management of ARF.

ADDISON DISEASE

Shaun G.S. Grewal, MD
Gerald L. Andriole, MD, FACS

BASICS

DESCRIPTION

- Primary adrenal insufficiency
- Inadequate production of glucocorticoid and mineralocorticoid
  - Differentiated from secondary (pituitary) and tertiary (hypothalamic) causes of adrenal causes of adrenocorticoid insufficiency in which mineralocorticoids are normally spared

ALERT

Acute adrenal insufficiency (Addisonian crisis):

- Life-threatening hypotensive shock.
- Most common cause is acute withdrawal of chronic steroid.
- Acute stress (ie, surgery) without an adequate stress dose of steroids.

EPIDEMIOLOGY

Incidence

- 4.7–6.2 per million in Western populations (1)
- Females more frequently affected than males
  - TB most common cause in underdeveloped nations
  - Autoimmune disorders most common cause in developed nations (90%)

Prevalence

- 93–140 per million (1)
  - Mortality 0.3 per 100,000

RISK FACTORS

- Tuberculosis
- Autoimmune disease
- AIDS
- Immunosuppression
- Bilateral adrenal hemorrhage
- Bilateral adrenalectomy
- Drug induced
  - Mitotane, aminoglutethimide, etomidate, ketoconazole, suramin, mifepristone

Genetics

- 40% of patients with a 1st-/2nd-degree relative with an associated disorder
- Isolated autoimmune adrenalitis
  - HLA-DR3, CTLA 4
- APS type 1
  - Adrenal insufficiency, hypoparathyroidism, chronic mucocutaneous candidiasis
  - AIRE gene (21q22)

- APS type 2
  - Adrenal insufficiency, Thyroid disease, Type I DM
  - HLA-DR3, CTLA-4
- APS type 4
  - Other autoimmune diseases
- Congenital adrenal hyperplasia
  - 21β-hydroxylase (CYP21 mutation)
  - 11β-hydroxylase (CYP 11B1 mutation)
  - 17∂-hydroxylase (CYP17 mutation)
- Adrenoleukodystrophy (ALD)
  - Demyelination of CNS
- Triple A syndrome (Allgrove)
  - Alacrima, achalasia, neurologic impairment

PATHOPHYSIOLOGY

- Autoimmune disorders are the most common cause in developed nations (80–90%)
- Partial or complete T-cell mediated destruction of adrenal cells
  - 90% of adrenal gland must be destroyed to cause insufficiency
  - Decreased production of cortisol, aldosterone, and adrenal androgens
  - Hypovolemia and prerenal azotemia cause orthostatic hypotension, dizziness, and lethargy
  - Adrenal crisis mostly attributable to mineralocorticoid deficiency
  - Pituitary compensation with increased ACTH
  - ACTH and proopiomelanocortin-related peptides stimulate melanocytes causing hyperpigmentation
- Adrenal dysgenesis or hypoplasia
  - AHC or Triple A syndrome
- Adrenal destruction
  - APS1, APS2, APS4, ALD
  - Infectious
    - TB, HIV, CMV, histoplasmosis, cryptococcus, coccidioidomycosis
  - Adrenal hemorrhage
    - Sepsis
    - Disseminated intravascular coagulation
    - Anticoagulant therapy
  - Bilateral adrenalectomy
- Adrenal infiltration
  - Adrenal metastasis, primary adrenallymphoma, sarcoidosis, amyloidosis, hemochromatosis
- CAH (see Genetics)

ASSOCIATED CONDITIONS

- Autoimmune endocrine disorders
- Thyroid disorder (17%)
- Diabetes mellitus (12%)
- Gonadal dysfunction (12%)

GENERAL PREVENTION

No general prevention guidelines exist for prevention of primary hypoaldosteronism.

DIAGNOSIS

HISTORY

- Vague symptoms; requires high index of suspicion
  - Fatigue, weight loss, anorexia, vomiting, GI complaints, abdominal pain, diarrhea, muscle aches, salt craving, hypotension, behavioral changes, headaches, sweating, depression, decreased libido, lethargy
  - Acute adrenal insufficiency: Life-threatening hypotension, acute abdominal pain, vomiting, fevers

PHYSICAL EXAM

- Vitals: Orthostatic hypotension
- Weight loss
- Hyperpigmentation
- Pigmented buccal mucosa and nail beds
- Loss of axillary and pubic hair
- Vitiligo
- Goiter

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Electrolyte disturbances
  - Classic triad: Hyponatremia, hyperkalemia, azotemia
  - Hypercalcemia
  - Lymphocytosis
  - Hypoglycemia
  - Metabolic acidosis
- Screening test
  - Measure cortisol, ACTH
    - Low cortisol (< 165 nmol/L)
    - Elevated ACTH (> 45 pmol/L)
- Confirmation of abnormal screening test
  - Short corticotropin test
    - 250 μg ACTH
    - Serum cortisol at 0, 30, and 60 min
    - Peak cortisol < 550 nmol/L diagnostic (2)

Imaging

- Routine imaging not recommended in cases of definite autoimmune adrenalitis
- CT or MRI in cases of suspected infection, malignancy, infiltration, hemorrhage
- Calcifications present in up to 50% with TB

Diagnostic Procedures/Surgery

No specific diagnostic procedures

Pathologic Findings

Atrophic adrenals in autoimmune adrenalitis

DIFFERENTIAL DIAGNOSIS
- Primary adrenal insufficiency (Addison disease)
- Secondary adrenal insufficiency (pituitary failure)
  - No hyperpigmentation (lack of ACTH elevation)
  - Etiologies include chronic steroids, panhypopituitarism, Sheehan syndrome (postpartum necrosis), brain trauma, pituitary apoplexy, pituitary surgery
- Tertiary adrenocortical insufficiency

TREATMENT

GENERAL MEASURES
- Acute adrenal insufficiency (addisonian crisis)
  - 5 S's:
    - Salt
    - Sugar
    - Steroids
    - Support
    - Search for precipitating cause

MEDICATION
First Line
- Corticosteroid replacement:
  - Hydrocortisone 15–25 mg/d
    - BID dosing: 20 mg, 10 mg
    - TID dosing: 10 mg, 5 mg, 5 mg
    - Monitor body weight and signs/symptoms of over/under replacement
- Mineralocorticoid replacement:
  - Fludrocortisone 0.05–0.20 mg/d
  - Monitor blood pressure, peripheral edema, serum sodium, and potassium
- Major stress: Surgery, trauma, sepsis:
  - IV hydrocortisone 100–300 mg/d (TID dosing) then taper
- Minor stress
  - Increase steroid dose 2–3-fold then taper over several days

Second Line
- Dehydroepiandrosterone (DHEA) replacement
  - 25–50 mg/d
  - Impacts mood/feeling of well-being (3)

SURGERY/OTHER PROCEDURES
Stress dose steroids: 25–150 mg hydrocortisone or 5–30 mg methylprednisolone IV day of the procedure in addition to maintenance therapy; taper to the usual dose over 1–2 days.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies

- Salt loading prior to major stress recommended by some
- Future advances using long-acting hydrocortisone preparations to better mimic physiologic state

Complementary & Alternative Therapies

No established alternative therapies

ONGOING CARE

PROGNOSIS

- Adrenal crisis may be lethal.
- Recommended dosages for glucocorticoid and mineralocorticoid replacement rarely cause significant side effects; close monitoring is essential to prevent excess treatment.

COMPLICATIONS

- Side effects of excess steroid replacement:
  - Weight gain, high BP, hyperglycemia, growth retardation, bruising, cardiovascular risks, gastric ulcers, poor wound healing, skin striae, osteoporosis
- Side effects of excess mineralocorticoid:
  - Hypertension, bradycardia, hypernatremia, congestive heart failure, suppressed renin levels, growth retardation
- Acute withdrawal of chronic steroid replacement may precipitate acute adrenal crisis
- Must rule out or treat glucocorticoid deficiency prior to initiation of thyroxine for hypothyroidism, as this may precipitate adrenal crisis.

FOLLOW-UP

Patient Monitoring

- Medic-alert bracelet to be worn at all times
- Instruct patients on proper use of emergency hydrocortisone injections
- Monitor for signs of appropriate glucocorticoid and mineralocorticoid replacement

Patient Resources

- www.addisonsdisease.net
- www.addisonssupport.com

REFERENCES

1. Arlt W, Allolio B. Adrenal Insufficiency. *Lancet.* 2003;361:1881–1893.
2. Lvås K, Husebye E. Addison's disease. *Lancet.* 2005;365:2058–2061.
3. Reisch N. Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin North Am.* 2009;38:407–418.

ADDITIONAL READING

Chakera AJ. Addison disease in adults: Diagnosis and management. *Am J Med.* 2010;123:409–413.

See Also (Topic, Algorithm, Media)

- Addison Disease (Adrenocortical Insufficiency) Algorithm

• Waterhouse–Friderichsen Syndrome

CODES

ICD9

255.41 Glucocorticoid deficiency

ICD10

E27.1 Primary adrenocortical insufficiency

CLINICAL/SURGICAL PEARLS

• Addisonian crisis: Is acute, life-threatening shock.
• 5 S's for treatment of addisonian crisis
  – Salt; Sugar; Steroids; Support; Search for precipitating cause.
• Classic triad: Hyponatremia, Hyperkalemia, Azotemia.
• Use "stress dose" steroids for patients with Addison disease undergoing surgical procedures.

ADENOMATOID TUMORS, TESTICULAR AND PARATESTICULAR

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BASICS

DESCRIPTION
- Adenomatoid tumors are benign lesions of the male testicular adnexa.
- Usually ~1 cm in size (range 0.5–7.5 cm) (1)[C]
- Most often asymptomatic
- Mesenchymal origin (2)[C]

EPIDEMIOLOGY
Incidence
- The majority of patients present within the 3rd–5th decades of life (3)[C].
- Adenomatoid tumors are the most common neoplastic processes involving the testicular adnexal and spermatic cord structures (3)[C].
- Adenomatoid tumors in females occur in uterus > fallopian tubes > ovary (1)[C].

Prevalence
Not well defined

RISK FACTORS
None described

Genetics
N/A

PATHOPHYSIOLOGY
- Mesothelial origin is most accepted theory (3)[C]
- Benign with no reported cases of metastasis
- Capable of local invasion
- Epididymis, tunica vaginalis, spermatic cord are most common sites

ASSOCIATED CONDITIONS
N/A

GENERAL PREVENTION
- Routine self-exam for identification of scrotal content masses
- Routine genital exam by physician

DIAGNOSIS

HISTORY
- Duration of lesion and size
- Interval growth

- Associated pain, dysuria, tenderness – epididymitis
- Prior malignancy or scrotal pathology
- Exposure to tuberculosis (TB)
- History of sarcoidosis, histoplasmosis
- History of urinary tract infection or sexually transmitted infection
- Recent GU manipulation – bacillus Calmette–Guérin (BCG) instillation

PHYSICAL EXAM

- Scrotal exam
  - Identify location of mass – single or multiple
  - Evaluate for varicocele or hydrocele
  - Compare with contralateral scrotal contents
  - Evaluate if fixed, mobile, indurated, or encroaching on other structures
  - Evaluate for spermatic cord involvement
  - Transillumination – to identify if fluid filled (spermatocele, hydrocele)
- Inguinal exam
  - Evaluate for lymphadenopathy
  - Hernia

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Tumor markers if concern for testicular mass – α-fetoprotein (AFP),
- β-human chorionic gonadotropin (β-HCG)
- Lactate dehydrogenase (LDH)
  - Purified protein derivative (PPD) if TB suspected
  - No specific labs to diagnose adenomatoid tumors

Imaging

- Scrotal ultrasound
  - Solid vs. cystic
  - Location – testicular or paratesticular
    - If located in the tunica albuginea can grow into the testicular parenchyma and resemble a testicular malignancy
  - Vascular or avascular

Diagnostic Procedures/Surgery

- Excision via inguinal approach
- Frozen section for pathology – proceed to orchiectomy with high cord ligation if malignant

Pathologic Findings

- Gross
  - Small (1 cm), well circumscribed without fibrous capsule
  - Tan-white, homogeneous
- Microscopic
  - Adenomatoid cells within fibrous stroma
  - Occasional cystic dilation
  - Irregular, somewhat branched-appearing tubular structures appear within the tumor, a

coalescence of the cellular vacuoles, which form a false lumen (4)[C]

DIFFERENTIAL DIAGNOSIS

- Benign tumors of epididymis:
  - Leiomyoma
  - Papillary cystadenoma (associated with von Hippel–Lindau syndrome)
  - Lipomas
  - Hamartomas
  - Adrenal cortical adenomas
- Malignant tumors of the epididymis:
  - Sarcoma (rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, liposarcoma)
  - Melanotic neuroectodermal tumor of the epididymis
- Extension of primary testicular tumor
- Metastatic tumor to epididymis:
  - Urologic (prostate, kidney)
  - GI (stomach, colon, carcinoid, pancreas)
- Other lesions of the epididymis
  - Granuloma (sperm, TB, sarcoidosis)
  - Spermatocele
  - Epididymitis
  - Epidermoid inclusion cyst
  - Epididymal abscess

TREATMENT

GENERAL MEASURES

- Excision via inguinal approach – for benign lesions
- Epididymitis – consider sexually transmitted infection as source in young men and treat accordingly (see Sexually Transmitted Infections section)

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Excision of suspicious lesion via inguinal approach with proximal vascular control
- Frozen section
- If positive for malignancy, radical orchiectomy
- Further surgical therapy guided by pathology but may include retroperitoneal lymph node dissection if rhabdomyosarcoma

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Adenomatoid tumors are uniformly benign with no well-documented cases of true invasion, metastasis, or recurrence after excision (3)[C]

COMPLICATIONS
Scrotal hematoma, pain, infection

FOLLOW-UP
Patient Monitoring
- Oncologic follow-up if malignant disease
- Patient testicular self-exam

Patient Resources
http://www.aafp.org/afp/1998/0215/p685.html

REFERENCES

1. Wachter DL, Wünsch PH, Hartmann A, et al. Adenomatoid tumors of the female and male genital tract. A comparative clinicopathologic and immunohistochemical analysis of 47 cases emphasizing their site-specific morphologic diversity. *Virchows Arch.* 2011;458(5):593–602.
2. Delahunt B, Eble JN, King D, et al. Immunohistochemical evidence for mesothelial origin of paratesticular adenomatoid tumor. *Histopathology.* 2000;36:109–115.
3. Montgomery JS, Blood DA. The diagnosis and management of scrotal masses. *Med Clin North Am.* 2011;95(1):235–244.
4. Amin MB. Selected other problematic testicular and paratesticular lesions: Rete testis neoplasms and pseudotumors, mesothelial lesions and secondary tumors. *Mod Path.* 2005;18:S131–S145.

ADDITIONAL READING

- Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010;59 (No. RR-12)
- Montgomery JS, Blood DA. The diagnosis and management of scrotal masses. *Med Clin North Am.* 2011;95(1):235–244.
- Rubenstein RA, Dogra VS, Seftel AD, et al. Benign intrascrotal lesions. *J Urol.* 2004;171:1765–1772.

See Also (Topic, Algorithm, Media)
- Adenomatoid Tumors, Testicular and Paratesticular Image
- Epididymis, Cystadenoma
- Epididymis, Metastasis to

- Epididymitis
- Paratesticular Tumors, General
- Sexually Transmitted Infections
- Spermatocele
- Testis, Tumor and Mass, Adult, General
- Testis, Tumor and Mass, Pediatric, General Considerations
- Von Hippel–Lindau Disease

CODES

ICD9

- 222.0 Benign neoplasm of testis
- 222.3 Benign neoplasm of epididymis
- 222.8 Benign neoplasm of other specified sites of male genital organs

ICD10

- D29.8 Benign neoplasm of other specified male genital organs
- D29.20 Benign neoplasm of unspecified testis
- D29.30 Benign neoplasm of unspecified epididymis

CLINICAL/SURGICAL PEARLS

- Adenomatoid tumors are benign with no reported metastasis.
- Excision via inguinal approach with proximal vascular control preferred.
- Treatment for epididymitis is guided by risk of sexually transmitted infections as a source.
- Ultrasound is important to delineate a testicular vs. paratesticular origin of the mass.

ADRENAL ADENOMA

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BASICS

DESCRIPTION

- Adrenal adenoma is a benign cortical neoplasm that may or may not have endocrine activity (functioning)
- Up to 80% are nonfunctioning and benign; the other 20% need further evaluation
  - Generally <4 cm and discovered incidentally

EPIDEMIOLOGY

Incidence

$\sim$1% if <30 yr old and 7% if >70 yr old

Prevalence

- Found in 1.8–8.7% of autopsies
- Incidental adrenal masses found on 0.5–5% of abdominal CTs (82% nonfunctional, 5% Cushing, 5% pheochromocytoma, 1% Conn)
  - Usually between 20 and 60 yr old

RISK FACTORS

Slightly more common in females

Genetics

More common in multiple endocrine neoplasia (MEN) type I, Beckwith–Wiedemann syndrome, and the Carney complex

PATHOPHYSIOLOGY

- Primary hyperaldosteronism (Conn syndrome)
  - Excess production of aldosterone (Zona Glomerulosa): Hypokalemia, Alkalosis, HTN
- Cushing syndrome
  - Excess production of cortisol (Zona Fasciculata): Suppresses ACTH from pituitary

ASSOCIATED CONDITIONS

- Hypertension
- Glucose intolerance
- MEN1 syndrome
- Subclinical Cushing syndrome (SCS) (obesity, hypertension, type 2 diabetes, hypercholesterolemia)

DIAGNOSIS

HISTORY

- Determine history of hypertension, obesity, and glucose intolerance
  - Suggestive of Cushing syndrome or adrenocortical carcinoma

- Hypertension and history of hypokalemia
  - Aldosterone-producing adenoma
- History of malignancy
- Patient medications ("polypharmacy" for hypertension)
- Family history

PHYSICAL EXAM

- Blood pressure and heart rate
- Look for stigmata of Cushing syndrome
  - Hirsutism, oligomenorrhea, easy bruising, excessive acne, muscle weakness, truncal obesity, buffalo hump, purple striae

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Extent of endocrine evaluation in patients with adrenal adenoma is controversial. Basic screening evaluation consists of:
  - Basic metabolic panel (BMP)
    - If elevated K^+ and patient also hypertensive may be aldosterone-secreting lesion
  - Plasma metanephrines: Most sensitive test for pheochromocytoma
  - 24-hr urine cortisol
  - Low-dose dexamethasone suppression test to R/O SCS if suspected clinically
- Complete endocrine evaluation should be performed if findings on examination and history suggest excess of specific hormone or if positive findings found on screening examination
- Primary hyperaldosteronism (Conn syndrome)
  - Basic metabolic profile
    - Hypokalemia, alkalosis, HTN
  - Aldosterone: Renin ratio
    - Values that define a positive screen subject to lab variability but >30 suggested by NIH as cutoff for positive aldosterone to renin ratio and indicates need for confirmatory testing
  - Confirmatory testing for hyperaldosteronism
    - 3-day oral sodium-loading test—high sodium diet for 3 days followed by 24-hr urine measurements of aldosterone, sodium, and creatinine
    - + test = 24-hr aldosterone > 12 mg/d
    - Captopril suppression test may be used for patients with cardiac and renal disease which prohibit sodium loading
- Cushing syndrome
  - 24-hr urine cortisol >100 mg
  - If equivocal, perform low-dose dexamethasone suppression test
    - 1 mg dexamethasone at 11 PM
    - Plasma cortisol between 8 AM and 9 AM
    - Normal: Cortisol <5 ng/mL
    - Cushing syndrome: Inability to suppress cortisol production
  - Rule out ACTH-dependent cause (ectopic or pituitary hypersecretion of ACTH)
  - Measure late-afternoon ACTH

- – >15 pg/mL – ACTH dependent
- – <15 pg/mL – ACTH independent (adrenal)
- – Adrenal venous sampling may be indicated if bilateral adrenal lesions present to establish lateralization of aldosterone secretion in surgical candidates

ALERT

Subclinical Cushing syndrome (SCS can occur where abnormalities of the hypothalamic–pituitary–adrenal axis exists in the absence of overt signs and symptoms of Cushing syndrome.

- May occur in 5–24% of patients with incidentally discovered adrenal tumors.
- May not be clinically evident following standard screening for cortisol hypersecretion.
- 1 mg overnight dexamethasone suppression test most sensitive for SCS.
- Should be performed in ALL patients with adrenal mass and metabolic syndrome.
- SCS is an indication for adrenalectomy.
- Patients are at risk for postoperative adrenal insufficiency (AI).
- Pheochromocytoma:
  - – If screening: Stop tricyclic antidepressants, phenoxybenzamine before testing
  - – Screening tests
  - – Plasma-free metanephrines
    - Stop acetaminophen 5 days prior
    - Draw sample in supine position
  - – 24-hr fractionated urinary metanephrines
    - Verify normal renal function before testing
- See pheochromocytoma section for details.

Imaging

- Adrenal adenoma: Small, well defined, homogeneous
- Size criteria important
  - – ≤5 cm usually benign
  - – ≥6 cm – 25% malignant
- May see atrophy of contralateral adrenal
- CT (triphasic adrenal scan)
  - – CT Adenoma characteristics: Sharp margin, smooth and homogeneous, lipid rich, <10 HU density on noncontrasted images, density reduces by 60% on initial contrast density at scan delayed 15 min
  - – <10 HU on noncontrast CT
    - 71% sensitive, 98% specific for adenoma
  - – >60% washout at 15 min
    - 100% sensitive/100%specific for adenoma
  - – Adrenal myelolipoma – low HU, but never below 20 HU
- MRI
  - – Both carcinoma and pheochromocytomas are hyperintense on T2 images (ie, they “light up” as they go from T1 to T2)
  - – Signal from cortical adenomas drops out in opposed phase
    - Loss of signal between in- and out-of-phase images (microscopic fat-sensitive sequence)

suggest adenoma
  - MRI T2 intensity < 0.8 compared to liver
  - 80% sensitive/80% specific for adenoma

Diagnostic Procedures/Surgery
- Adrenal biopsy or fine needle aspiration may be performed in select cases
  – Reserved for differentiation of metastatic disease and benign lesion
  – May not be able to differentiate between benign from malignant adrenocortical tumor
- Rule out pheochromocytoma with plasma metanephrine screening before performing biopsy on an adrenal mass

Pathologic Findings
- Aldosterone-producing adenoma
  – Spironolactone bodies – eosinophilic laminated cytoplasmic inclusions
    - Found after treatment with spironolactone
  – Cortisol-producing adenoma
  – Vacuolated neoplastic cells
  – Intracytoplasmic lipid
- Bilateral adrenal adenomas
  – Fungal, TB, histoplasmosis

DIFFERENTIAL DIAGNOSIS
- Adrenal cortical carcinoma (up to 80% functional)
- Adrenal hemorrhage
  – Bilateral lesions
- Adrenal hyperplasia (pituitary hypersecretion of ACTH)
- Adrenal myelolipoma
- Lymphoma
- Metastatic lesion
  – Melanoma, lung, breast, kidney
- Neuroblastoma
- Nonfunctioning adenoma
- Pheochromocytoma
- TB, or other infectious cause

TREATMENT

GENERAL MEASURES
- Based on functional status and size of lesion
- Correct hypertension and electrolyte abnormalities.

MEDICATION

First Line
- For hormonally active adenomas in patients who refuse surgery or have contraindications to surgery
- Conn syndrome
  – Spironolactone, eplerenone

- Aldosterone receptor antagonists in the distal convoluted tubule (DCT).
- 2nd line – Amiloride, triamterene
  - Inhibitors of DCT aldosterone sensitive sodium channels
- Cushing syndrome
- Aminoglutethimide
  - Blocks the 1st step in cortisol synthesis (cholesterol to pregnenolone)
- Metapyrone
  - Blocks the final step in cortisol synthesis (11-deoxycortisol to cortisol)
- Ketoconazole
  - Inhibits 1st step and to a lesser extent the last step in cortisol synthesis

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgical indications
  - Hormonally active masses
  - Any masses ≥5 cm (25% of masses >6 cm are assumed to be adrenal cortical carcinomas)
  - Masses with suspicious imaging characteristics of carcinoma
    - Homogeneous, irregular borders, HU >20
- Laparoscopic and robotic approaches described, but may have limitations with larger lesions
- Retroperitoneal approach possible for both open and laparoscopic surgery; may reduce ileus
- Perioperative stress dose steroids indicated during unilateral adrenalectomy for cortisol-producing adenomas and may be indicated for patients with SCS
- Preoperatively: 50 mg hydrocortisone IV q8h postop day 1
- Steroid supplementation will be needed after adrenalectomy for cortisol-producing tumors until suppressed HPA recovers (median of 15 mo)
  - Postoperatively (POD 2): Hydrocortisone 20 mg PO qAM, 10 mg qPM
  - Hydrocortisone slowly tapered over 3 mo to 10 mg daily
  - AM cortisol should be measured and repeated until >10 ng/dL
  - Confirm recovery of HPA with cosyntropin test
- Monitor for electrolyte disturbances with BMP and postoperative AI in patients with hormonally active tumors and/or SCS
- Acute AI (addisonian state)

ALERT

This is a life-threating condition often preceded by hypotension unresponsive to fluid resuscitation.

- May occur in the postoperative state in the setting of cortisol-secreting lesion with downregulated contralateral adrenal function, and in patients with previous contralateral adrenal resection or due to concurrent illness or infection.
- Other nonspecific symptoms may include abdominal pain, salt craving, nausea, vomiting, fatigue, and fever.
- Electrolyte abnormalities such as hypernatremia or hyperkalemia and other laboratory anomalies such as anemia, lymphocytosis, or eosinophilia may also be found.

- Prolonged use of etomidate may increase risk of postoperative adrenal insufficiency.
- May begin steroid replacement if high clinical index of suspicion.
- Diagnosis Obtain AM serum cortisol and ACTH level:
  - Normal >10 ng/dL, low–normal (3.4–10 ng/dL), AI <3.4 ng/dL
  - Confirmatory testing with evaluation of response to ACTH stimulation (cosyntropin test)
    - Measure serum cortisol at baseline
    - Give cosyntropin 0.25 mg IV × 1
    - Measure serum cortisol 60 min after dose
    - Adequate response: Cortisol >18 μg/dL
- If acute AI is highly suspected, don't wait for result before treating:
  - Give 2–3 L D5 NS quickly and 4 mg dexamethasone IV
  - Use dexamethasone because IV cortisol will interfere with the diagnosis later during hospitalization
- Maintenance therapy:
  - Hydrocortisone 30 mg/d
  - Fluorohydrocortisone 0.05–0.1 μg/d

ONGOING CARE

PROGNOSIS

- Untreated Cushing syndrome can be fatal due to cardiovascular, thromboembolic, or hypertensive complications or infection
- Surgical removal of hormonally active adenomas is usually *curative*

COMPLICATIONS

- Hypertension
- Diabetes mellitus
- Atherosclerosis
- Poor wound healing
- Nephrolithiasis
  - 15% of patients with Cushing syndrome – due to hypercalciuria
- Adrenal insufficiency (Addison disease)

FOLLOW-UP

Patient Monitoring

- Nonfunctioning benign adrenal mass can be followed with physical and radiologic examinations
  - 5–20% show enlargement >1 cm
  - No guideline on growth velocity on surgical treatment

REFERENCES

1. Kapoor A, Morris T, Rebello R. Guidelines for the management of the incidentally discovered adrenal mass. *Can Urol Assoc J.* 2011;5(4):241–247.
2. Gill IS. The case for laparoscopic adrenalectomy. *J Urol.* 2001;166:429–436.
3. Bittner JG, Brunt LM. Evaluation and management of adrenal incidentaloma. *J Surg Onc.* 2012;106:557–564.

4. Mandevillle J, Moinzadeh A. Adrenal incidentalomas: *AUA Update Series.* 2010;29:33–39.

See Also (Topic, Algorithm, Media)

- Adrenal Adenoma Image
- Adrenal Cortical Carcinoma
- Adrenal Cysts and Pseudocysts
- Adrenal Hemorrhage
- Adrenal Incidentaloma
- Adrenal Mass
- Adrenal Mass, Algorithm
- Adrenal Mass Image
- Adrenal Metastasis
- Adrenal Myelolipoma
- Adrenal Myelolipoma (Adrenal Myolipoma)

CODES

ICD9

- 227.0 Benign neoplasm of adrenal gland
- 255.0 Cushing's syndrome
- 255.12 Conn's syndrome

ICD10

- D35.00 Benign neoplasm of unspecified adrenal gland
- E24.0 Pituitary-dependent Cushing's disease
- E26.01 Conn's syndrome

CLINICAL/SURGICAL PEARLS

- Adrenal lesions should be surgically treated if ≥5 cm or if functional/active.
- No guideline on normal growth velocity for adrenal lesions.
- Melanoma, lung, breast, colon, and renal cell cancers have metastatic predilection to adrenal gland.

ADRENAL CORTICAL CARCINOMA

John M. Lacy, MD, FACS
Stephen E. Strup, MD, FACS

BASICS

DESCRIPTION

Adrenal cortical carcinoma is a primary malignancy arising in the adrenal cortex

EPIDEMIOLOGY

Incidence

- Rare: 0.5–2 cases per million people per year
- Bimodal occurrence:
  - Initial peak in children <5 yr old;
  - 2nd peak in adults in 4th and 5th decades of life
- Female:male ratio ~1.5:1
- ~80–130 cases in USA annually
- <5% of all adrenal incidentalomas, with correlation between size of tumor and likelihood of ACC
  - 2% of lesions <4 cm
  - 6% of lesions 4–6 cm
  - 25% of lesions >6 cm

Prevalence

Mirrors incidence, as prognosis is poor

RISK FACTORS

Genetic associations (see below)

Genetics

- Sporadic cases
  - Inactivation of p53 on 17q13
  - Alterations at 11p15 locus, site of IGF-2
  - Activation of β-catenin gene
- Familial syndromes
  - Li–Fraumeni syndrome
  - Beckwith–Wiedemann syndrome
  - Multiple endocrine neoplasia (MEN) 1
  - Congenital adrenal hyperplasia
  - Adenomatous polyposis coli

PATHOPHYSIOLOGY

- Difficult to distinguish benign from malignant adrenal tumors in absence of metastatic disease.
- Pathologic features such as mitotic activity, grade, vascular invasion, various architectural features, and tumor size have not consistently correlated with prognosis.

• Most (60–70%) ACCs are functioning, although this is related to the extent of workup.

ASSOCIATED CONDITIONS
• Cushing's syndrome secondary to functional tumors
• Familial syndromes (see above)

GENERAL PREVENTION
No recommendations

DIAGNOSIS
HISTORY
• Most common symptoms are related to excess cortisol production (Cushing's syndrome) in 50–60%, then virilization (20%), or mixed syndromes (20–30%)
• History of onset of symptoms < 12 mo is suspicious for ACC
• Constitutional symptoms:
  – Weight loss, malaise, weakness, nausea, or vomiting usually associated with poor prognosis
• In children, suggested by generalized weight gain and delayed linear growth
• Nonfunctional tumors may be larger and present with mass effect
  – Painful or palpable mass
  – Lower extremity edema
  – Urinary obstruction
  – Budd–Chiari syndrome
  – GI symptoms
• Hyperaldosteronism (rare):
  – Hypertension
  – Hypokalemic alkalosis
• Feminization (rare)
• Incidental finding during imaging workup for other morbidities

PHYSICAL EXAM
• Palpable abdominal mass
• Signs of Cushing's syndrome (functional ACCs): Violaceous striae, moon facies, truncal obesity, buffalo hump, glucose intolerance, hyperpigmentation
• Signs of virilization (oligomenorrhea, hirsutism, cystic acne, excessive muscle mass, voice deepening, temporal balding, clitoromegaly)
• Gynecomastia

DIAGNOSTIC TESTS & INTERPRETATION
Lab
• Tests for glucocorticoid excess (minimum 3 out of 4 tests)
  – Dexamethasone suppression test
  – 24-hr urinary free cortisol
  – Basal cortisol (serum)
  – Basal ACTH (plasma)
• Sexual steroids and steroid precursors

- DHEA-S (serum)
- 17-OH-progesterone (serum)
- Testosterone (serum)
- 17-β-estradiol
- 24-hr urine steroid metabolite exam

• Mineralocorticoid excess
- Potassium (serum)
- Aldosterone/renin ratio
  - Only used in patients with arterial hypertension and/or hypokalemia

• Catecholamine excess to exclude pheochromocytoma
- Meta- and normetanephrines (plasma)
- Catecholamines or metanephrine excretion (24-hr urine)

Imaging

• CT of abdomen is preferred initial study in patients adrenal lesion:
- Benign tumors
  - Homogeneous appearance with well-delineated margins
  - Generally <4–6 cm, smooth and round or oval contour
  - <10 HFU or rapid washout of contrast <15 min
- Primary ACCs:
  - Nonhomogeneous internal architecture
  - Irregular contour, invasion of surrounding structures
  - >10 HFU or delayed washout of contrast >15 min

• MRI not proven to be more sensitive in differentiating malignant from benign tumors:
- Preferred imaging modality for evaluation of vena caval involvement
- ACCs generally isodense to the liver on T1-weighted images; intermediate to high signal intensity (brighter white) on T2-weighted images (less bright than pheochromocytoma).

• FDG-PET potentially useful in radiologically indeterminate lesions.

• Bone scan if suspicious of skelet al metastases.

Diagnostic Procedures/Surgery

• Role of percutaneous biopsy limited
- Difficult to distinguish between benign and malignant tissue
- Concern for seeding biopsy tract

Pathologic Findings

• Macroscopic:
- Lobulated, orange tumor with necrotic areas, calcifications, intratumoral hemorrhages

• Microscopic:
- Weiss criteria for malignancy includes ≥ 3 of the following:
  - High nuclear grade
  - Mitotic rate $>$ 5/50/hpf
  - Atypical mitotic fevers
  - Eosinophilic tumor cell cytoplasm
  - Diffuse architecture in $>33\%$ of tumor
  - Necrosis

    - Vascular invasion
    - Sinusoidal invasion
    - Capsular invasion
- Antigen Ki-67 is a promising new immunohistochemical marker
  – Marker of proliferative activity
  – Low-risk ACC – expressed in $<10\%$ of cells
  – High-risk ACC – expressed in $>10\%$ of cells

DIFFERENTIAL DIAGNOSIS
- Functioning adrenal masses:
  – Adenoma, aldosteronoma, pheochromocytoma
- Nonfunctioning adrenal masses:
  – Hemorrhage, cyst, metastatic tumor, neuroblastoma
- Other: Renal cell carcinoma

TREATMENT

GENERAL MEASURES
Complete surgical excision is treatment of choice in resectable stage I or II tumors and children

MEDICATION
First Line
- Mitotane is the treatment of choice for metastatic ACC
  – Objective regression in tumor size in 35%
  – Dosage escalated to tolerance, which is limited
  – Significant toxicity – GI, CNS, endocrine
  – Must monitor serum levels closely
  – Strong inhibitor of steroidogenesis
    - Both glucocorticoid and mineralocorticoid replacement necessary
- Mitotane monotherapy may be used in patients with low tumor burden or indolent disease
- Polychemotherapy indicated with high tumor burden or rapidly progressive disease
  – Cytotoxic chemotherapy under investigation
    - Etoposide, doxorubicin, cisplatin, and mitotane
    - Streptozotocin and mitotane

Second Line
- If failed mitotane monotherapy, add cytotoxic chemotherapy
- If failed initial polychemotherapy regimen, may try whichever regimen was not used
- Clinical trials underway for targeted therapies
  – IGF-1 receptor inhibitors
  – Multi-tyrosine-kinase inhibitors

SURGERY/OTHER PROCEDURES
- Indications for surgery (1)
  – Hormonally active mass
  – Size >5–6 cm

- Open approaches
  - Anterior approach (chevron or subcostal incision) for the rare low-stage ACC
  - For more advanced ACCs, a thoracoabdominal incision provides optimal exposure
  - Avoid risk of port side seeding associated with laparoscopy
- Laparoscopy
  - Feasible in stage I and stage II tumors <10 cm in size
  - Many studies report equivalent oncologic outcomes (1)
  - Postoperative advantages
    - Less analgesic requirement
    - Lower blood loss
    - Shorter postop fasting period
    - Reduced length of hospital stay
- Advanced local disease may require resection of adjacent visceral organs, portions of vena cava and/or tumor thrombus
- Surgery may also play a role in the setting of metastatic disease
  - Primary tumor represents the bulk of disease
  - Complete resection is feasible
  - Tumor objectively responds to medical treatment or stabilizes over period of 6 mo
- Lymphadenectomy provides improved staging and may lead to favorable oncologic outcomes (2)

ADDITIONAL TREATMENT

Radiation Therapy

- ACCs formerly considered radioresistant
- Now radiation used in 2 scenarios:
  - Adjuvant therapy in patients with high risk for recurrence
  - Palliative control of local symptomatic metastases to bone, brain, or vena cava obstruction (3)

Additional Therapies

- Inhibitors of steroid synthesis may be useful in controlling symptoms of glucocorticoid excess
  - Metyrapone
  - Aminoglutethimide
  - Ketoconazole
  - Etomidate

ALERT
Hydrocortisone must be administered during surgery and postoperatively if patients with glucocorticoid excess.

Complementary & Alternative Therapies

- Locoregional therapy may be indicated in cases of progression despite mitotane
  - Arterial chemoembolization
  - Radiofrequency ablation

ONGOING CARE

PROGNOSIS

- Overall prognosis is poor, with overall 5-yr survival ranging from 15–60% based on stage
- Overall recurrence rate 17–85%
  - 23% in R0 patients
  - 51% for R1 and R2 patients
- Stage at diagnosis is the most important prognostic variable
- ~70% of patients present with advanced disease (stage III or IV)

COMPLICATIONS

- Fever due to tumor necrosis
- Anemia from hemorrhage into the tumor
- Adrenal crisis in patients who undergo surgery for functioning tumors without adequate steroid prep

FOLLOW-UP

Patient Monitoring

- Close follow-up is critical
- Abdominal CT or MRI and chest CT recommended every 3 mo for a minimum of 2 yr
- Serum and urinary steroid levels should also be monitored, though they are less sensitive for detection of recurrence than imaging
- Follow-up should be long-term, since late recurrence of ACC (after ≥10 yr) is not uncommon

Patient Resources

- www.adrenalcancerhope.org
- www.adrenocorticalcarcinoma.org

REFERENCES

1. Carnaille B. Adrenocortical Carcinoma: Which surgical approach? *Langenbecks Arch Surg*. 2012;397(2):195–199.
2. Reibenantz J, Jurowich C, Erdogan I, et al. Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. *Ann Surg*. 2012;255:363–369.
3. Polat B, Fassnacht M, Pfreunder L, et al. Radiotherapy in adrenocortical carcinoma. *Cancer*. 2009;115:2816–2823.

ADDITIONAL READING

- Baudin E, Leboulleux S, Al Ghuzlan A, et al. Therapeutic Management of advanced adrenocortical carcinoma: What do we know in 2011? *Horm Cancer*. 2011;6:363–371.
- Berruti A, Baudin E, Gelderblom H, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii131–8.
- Carnaille B. Adrenocortical carcinoma: Which surgical approach? *Langenbecks Arch Surg*. 2012;397(2):195–199.

See Also (Topic, Algorithm, Media)

- Adrenal Adenoma

- Adrenal Cortical Carcinoma Image
- Adrenal Mass
- Adrenal Mass Algorithm

CODES

ICD9

- 194.0 Malignant neoplasm of adrenal gland
- V84.09 Genetic susceptibility to other malignant neoplasm

ICD10

- C74.00 Malignant neoplasm of cortex of unspecified adrenal gland
- C74.02 Malignant neoplasm of cortex of left adrenal gland
- Z15.09 Genetic susceptibility to other malignant neoplasm

CLINICAL/SURGICAL PEARLS

- Rapid development of symptoms is key to distinguishing ACC from Cushing's syndrome.
- Lymphadenectomy provides improved staging and may lead to favorable oncologic outcomes.
- Radiation therapy useful as adjuvant therapy in high-risk patients and for local palliation.
- Laparoscopic adrenalectomy feasible in experienced surgeon's hands if mass $<$8–10 cm.
- Close follow-up is critical, as late recurrence is reported.

ADRENAL INSUFFICIENCY, ACUTE (ADRENAL CRISIS)

Debasish Sundi, MD
Misop Han, MD

BASICS

DESCRIPTION

- Acute adrenal insufficiency (Sometimes called Addisonian crisis) symptoms are attributable to mineralocorticoid deficiency—there are many etiologies (1)[A].
- Adrenal crisis is a subtype of acute adrenal insufficiency; it is a rapid and intensive process triggered by a stressor such as surgery or sepsis.
- Symptoms of the Addison disease (chronic adrenal insufficiency) are difficult to recognize; often the diagnosis of Addison disease is made when patients present with an acute crisis.
- Patient may present in hemodynamic compromise secondary to sodium and plasma volume depletion.
- Addisonian crisis should be treated immediately; treatment should not be delayed pending diagnostic test results.
- The disease usually results from bilateral adrenal cortex destruction: Destruction of the adrenal cortex causes a combined deficiency of glucocorticoids, mineralocorticoids, and adrenal androgens.

ALERT
Hypotension and shock refractory to resuscitation with fluids and vasopressors should be considered Addisonian crisis and treated with intravenous steroids.

EPIDEMIOLOGY

Incidence

- Addison disease incidence: 0.6/100,000 per year
- Up to 0.7% of patients undergoing major surgery may experience adrenal insufficiency

Prevalence

- Addison disease prevalence: 4–11/100,000
- >75% of patients with septic shock manifest adrenal insufficiency

RISK FACTORS

- Neonates: Bilateral adrenal hemorrhage from birth trauma
- Children: Pseudomonal or meningococcal septicemia leading to acute hemorrhagic destruction of both adrenal glands (Waterhouse–Friderichsen syndrome)
- Adults: Adrenal crisis after surgical or septic stress; bilateral adrenal hemorrhage from systemic anticoagulation or coagulation disorder
- Special at-risk populations: Pregnant women, patients with idiopathic adrenal vein thrombosis, patients who have undergone venography or vascular embolization of adrenal adenoma
- Most common cause: Rapid withdrawal of steroids from patients with adrenal atrophy secondary to chronic steroid use

- Medications: Ketoconazole, aminoglutethimide, dronabinol, mitotane, phenytoin, rifampin

Genetics

- Hereditary factors may influence development of autoimmune adrenal insufficiency.
- Familial glucocorticoid insufficiency may be associated with a recessive gene pattern.
- Addison disease has been associated with a variety of autoimmune diseases.

PATHOPHYSIOLOGY

- The adrenal cortex produces 3 classes of steroid hormones: Mineralocorticoids (aldosterone), glucocorticoids (cortisol), and androgens.
- Cortisol deficiency is primarily responsible for the manifestations of the crisis.
- Primary adrenal insufficiency is due to failure of the adrenal cortex.
- Secondary adrenal insufficiency is caused by failure of ACTH stimulation of the adrenal cortex.
- Chronic steroid administrations result in suppression of ACTH production via feedback inhibition

ASSOCIATED CONDITIONS

Nearly 50% of patients with adrenalitis have some form of autoimmune disease: Hypoparathyroidism, gonadal collapse, diabetes mellitus type I, hypothyroidism (Hashimoto thyroiditis), or hyperthyroidism (Grave disease).

GENERAL PREVENTION

- Perioperative stress dose steroid replacement when indicated (3)[B].
- Low threshold to intervene with IV glucocorticoid replacement at early signs of fluid refractory hypotension

DIAGNOSIS

HISTORY

- Prior steroid use:
  - Risk increases with minimum 20 mg/d prednisone or equivalent for at least 5 days within the past 12 mo
  - Patients receiving normal physiologic levels require about 1 mo to recover normal adrenal function.
  - Extensive topical use of high-potency steroids or high-dose inhaled steroids over prolonged periods can also be a factor
- Lapse in steroid therapy in a patient on chronic therapy
- Severe physiologic stress such as burn, surgery, or severe bacterial infection
- Bleeding diathesis or anticoagulant use
- Worsening or possibly intractable nausea, vomiting, and abdominal pain
- Fever may be severe or completely absent
- Primary or secondary adrenal insufficiency usually present insidiously with nonspecific symptoms of chronic fatigue, weakness and lethargy, anorexia, weight loss, postural hypotension, and somnolence
- Acute adrenal crisis usually presents acutely with hypotension or hypotensive shock:
  - Clinical picture is more complex as a result of a mixture of preceding slow-onset

symptoms and signs including abdominal pain, sepsis, pituitary or adrenal hemorrhage, surgery, or trauma
  - Acute adrenal insufficiency should be considered in patients presenting in the emergency room with abdominal pain, nausea, diarrhea, hypotension, and fever
  - The etiology of hypotension is profound hypovolemia
  - Hypotension may be one of the last signs (preterminal) because mineralocorticoid secretion is usually somewhat preserved in patients on chronic glucocorticoid replacement.

PHYSICAL EXAM

- Check blood pressure: Extreme hypotension and/or shock refractory to fluids and vasopressors suggests acute adrenal crisis.
- Vitiligo often coexists with Addison disease: Hyperpigmentation along palmar creases, buccal mucosa, pressure points, perianal mucosa, and nipple areolas.
- Check for signs of generalized weakness and specifically muscle weakness.
- Check for loss of axillary hair in females.
- In adrenal crisis, patients may be hyper- or hypothermic.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Plasma cortisol: Early AM levels < 3 μg/dL (80 nmol/L) suggests diagnosis
- Serum ACTH:
  - If low in the setting of low cortisol, patient has pituitary/hypothalamic disease
  - If high in the setting of low cortisol, primary adrenal insufficiency exists
- Electrolyte abnormalities: Decreased sodium and chloride levels, increased potassium levels and an increased BUN/Cr ratio (reflecting hypovolemia)
- Hypercalcemia may be seen during adrenal crisis
- Hypocalcemia may be seen with associated polyglandular failure and hypoparathyroidism
- Excess proopiomelanocortin and melanocyte-stimulating hormone levels may be found

ALERT

Labs are used only in the setting of nonemergent adrenal insufficiency and have no role in the acute management of adrenal crisis.

Imaging

- Abdominal x-rays may show adrenal calcifications if adrenocortical insufficiency is secondary to fungal or TB infection.
- Abdominal CT may show enlarged adrenal glands with TB infection or malignant mass.
- Adrenals may be small secondary to idiopathic atrophy, autoimmune adrenalitis, or advanced TB.
- Adrenal gland hemorrhage or thrombosis may be seen.

Diagnostic Procedures/Surgery

- Rapid ACTH stimulation (cosyntropin, a synthetic derivative of ACTH) test:
  - Following collection of baseline serum cortisol, 250 μg of synthetic ACTH is administered IM or IV.
  - Plasma cortisol response is reassessed at 60 min.

– Those with no response have primary adrenal failure; if the cortisol levels increase following synthetic ACTH injection, the adrenal insufficiency is secondary to pituitary dysfunction.

Pathologic Findings

- Autoimmune adrenal cortical infiltrate
- Adrenal cortical infarction/necrosis, with or without hemorrhage
- Metastatic carcinoma in adrenal gland
- Tuberculous granuloma of adrenal
- Radiation effect

DIFFERENTIAL DIAGNOSIS

- Acute insufficiency (addisonian crisis) (1)[A]
  – Shock (septic, cardiogenic, or hemorrhagic)
  – Acute abdomen
- Chronic insufficiency (Addison disease)
  – Secondary adrenocortical insufficiency
  – Celiac disease
  – Syndrome of inappropriate ADH secretion
  – Lead exposure
  – Severe nutritional deficiencies
  – Neurofibromatosis
  – Peutz–Jeghers syndrome
  – Porphyria cutanea tarda
  – Salt-depletion nephritis
  – Bronchogenic carcinoma
  – Anorexia nervosa, depression

TREATMENT

GENERAL MEASURES

- In critically ill and decompensating patients, maintain airway, and ensure adequate ventilation.
- Treatment instituted with IV fluid and dexamethasone or hydrocortisone should not be delayed in suspected adrenal crisis. Start treatment and perform more extensive tests once patient is stabilized.

MEDICATION

First Line

- IV fluids: 0.9% NS or 5% dextrose in NS
- Hydrocortisone: 100 mg IV bolus immediately; followed by either 100 mg q6h or 10 mg/h continuous infusion for 2–3 days (2)[A].
- Dexamethasone: 2–8 mg as a single dose; this may be repeated as necessary

Second Line

- Pediatric considerations
  – Hydrocortisone: 1–2 mg/kg/dose bolus immediately; followed by 25–150 mg/d given in

divided doses q6–8h (infants and young children)
- Geriatric considerations
  - Start dosage on the low end of the dosing range due to greater frequency of impaired cardiac and renal function
  - Increased susceptibility to adverse effects such as glaucoma, diabetes, and osteoporosis with long-term therapy
- Pregnancy considerations
  - During labor and delivery, IV normal saline 0.9% and 25 mg of IV hydrocortisone should be given q8h with quick tapering after delivery
  - Considered compatible with lactation: Infant must be monitored for adverse effects including hypoadrenalism

SURGERY/OTHER PROCEDURES
- Perioperative management during routine urologic surgery
  - Consultation with the preoperative physician for medical clearance and the procedural anesthesiologist is advised.
  - Many patients taking low-dose prednisone (such as for autoimmune inflammatory disorder) are able to undergo major surgery without any endocrine morbidity even without administration of intraoperative stress-dose steroids (3)[B]. Incident fluid-refractory hypotension in this group should be promptly treated with IV hydrocortisone.
  - Patients with chronic adrenal failure and complete physiologic steroid replacement do generally require procedural stress-dose steroids.
  - Individualization of stress-doses and postoperative taper regimens is recommended.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Maintenance doses of steroids:
  - Hydrocortisone (oral): 15–20 mg qAM and 5–10 mg qPM
  - Prednisone (oral): 5 mg AM and 2.5 mg PM
  - Fludrocortisone (oral): 0.05–0.2 mg/d

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- There is a high risk of morbidity and mortality associated with unrecognized acute crisis. May result in cardiovascular collapse if not recognized.
- Excellent long-term prognosis following immediate management of acute crisis and long-term maintenance therapy.

COMPLICATIONS
- Abdominal distention, peptic ulcer

- Edema, glaucoma, increased intraocular pressure
- Hyperglycemia, hypertension
- Immunosuppression
- Mood changes, weight gain, hirsutism

FOLLOW-UP

Patient Monitoring

- Consider increase in steroid dosing when the patient has an episode of minor fever, infection, trauma, or physical stress.
- Monitor blood pressure, weight, serum electrolytes, and blood glucose levels.
- Monitor growth in pediatric patients.
- Bone density, ophthalmologic exams.

Patient Resources

National Library of Medicine:
http://www.nlm.nih.gov/medlineplus/ency/article/000378.htm

REFERENCES

1. Oelkers W. Adrenal insufficiency. *N Engl J Med*. 1996;335:1206–1212.
2. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862–871.
3. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids. *Arch Surg*. 2008;143(12):1222–1226.

ADDITIONAL READING

Williams GH, Dluhy RG. Disorders of the Adrenal Cortex. In: *Harrison's Principles of Internal Medicine*, 16th ed. New York, NY: McGraw-Hill, 2004.

See Also (Topic, Algorithm, Media)

- Adrenal Calcifications
- Addison Disease
- Addison Disease (Adrenocortical Insufficiency Algorithm ↕)
- Adrenal Hemorrhage
- Adrenal Hypoplasia

CODES

ICD9

255.41 Glucocorticoid deficiency

ICD10

- E27.2 Addisonian crisis
- E27.40 Unspecified adrenocortical insufficiency

CLINICAL/SURGICAL PEARLS

Preoperative anesthesia consultation for perioperative stress dose steroid replacement is

recommended for any patient on steroid therapy.

ADRENAL MASS

Kyle A. Richards, MD

BASICS

DESCRIPTION

- An adrenal mass is generally considered to be an adrenal lesion >1 cm
- Often found after abdominal imaging and often termed "adrenal incidentaloma"
- Rarely presents with acute or chronic symptoms

EPIDEMIOLOGY

Incidence

- Incidental adrenal mass (1,2)[A]
  - Peak incidence at age 50–70
  - 50–60% right side, 30–40% left side, 10–15% bilateral
- Female:Male 1.2–1.5:1
- Nonsecretory adenoma 75%
- Cortisol-producing 8%
- Pheochromocytoma 5%
- Adrenocortical carcinoma 5% (3)[A]
  - Bimodal age distribution: Age <5 and 40–50
  - 1–2 per million persons per year
  - 2–6% bilateral
  - Slightly higher incidence on left side
- Metastases 2%
- Aldosteronoma 1%

Prevalence

- 4% in patients undergoing CT scan
- 6% in autopsy series
- Increases with age (2)[A]
  - 0.2% age 20–29; 7% age ≥70

RISK FACTORS

- Sex (1)[A]
  - Malignant adrenal mass: Male > female (2:1)
  - Benign adrenal mass: Female > male (1.7:1)
- Aging
- Prior history of cancer especially melanoma, lung, breast, or kidney
  - 50% of these adrenal masses are metastases

Genetics

- Rare genetic syndromes may predispose to adrenal masses (1,4)[B]
  - Beckwith–Wiedemann

- Overexpression of insulin-like growth factor II gene
- Adrenocortical carcinoma

– Li–Fraumeni
- Mutations in p53 tumor suppressor gene
- 10–20% have adrenocortical carcinoma

– Multiple endocrine neoplasia 1
- 40% have adrenal masses
- Adenoma and adrenocortical carcinoma

– Multiple endocrine neoplasia 2
- RET-2 proto-oncogene abnormalities associated with pheochromocytoma
- 40–50% have adrenal masses

– Carney complex
- 30% have adrenal hypercortisolism

– McCune–Albright syndromes
- Associated with adrenal hypercortisolism

– Von Hippel–Lindau disease
- 10–20% have pheochromocytoma

– Neurofibromatosis type 1
- Up to 5% have pheochromocytoma

PATHOPHYSIOLOGY

- Adrenal glands consist of an outer cortex and inner medulla and are part of endocrine system
- Aberrant secretion of hormones = symptoms
- Adrenal cortex
  – Zona glomerulosa
    - Produces mineralocorticoid aldosterone
    - Regulates sodium and fluid homeostasis
    - Promotes exchange of potassium for sodium in distal tubule of nephron
    - Excess aldosterone = Conn's syndrome
  – Zona fasciculata
    - Produces glucocorticoid cortisol
    - Regulates cellular and glucose metabolism, immune processes, and other regulatory functions
    - Excess cortisol = Cushing's syndrome
  – Zona reticularis
    - Produces adrenal androgens
    - Excess androgens = virilization
- Adrenal medulla
  – Produces catecholamines
  – Excess catecholamines = pheochromocytoma
- Addison's disease = adrenal insufficiency
  – Usually not caused by adrenal masses

ASSOCIATED CONDITIONS

- See "Genetics"

- Hypertension (paroxysmal or sustained)
- Osteoporosis/osteopenia (cortisol excess)
- Diabetes mellitus (cortisol excess)
- Hypokalemia (aldosterone excess)
- Hyperlipidemia (cortisol excess)
- Pheochromocytomas
  - Multiple endocrine neoplasia IIa or IIb
  - Neurofibromatosis type 1
  - Von Hippel–Lindau syndrome
  - Tuberous sclerosis
  - Sturge–Weber syndrome
  - Carney triad
- Adrenocortical carcinoma
  - Multiple endocrine neoplasia 1
  - Li–Fraumeni syndrome
  - Carney complex
  - Beckwith–Wiedemann

GENERAL PREVENTION

None

DIAGNOSIS

HISTORY

- Focus on symptoms suggestive of adrenal hyperfunction or malignant disease
  - Cushing's syndrome
    - Weight gain
    - Easy bruising
    - Poor wound healing
    - Proximal muscle weakness
    - Emotional and cognitive changes
    - Opportunistic and fungal infections
    - Altered reproductive function
  - Pheochromocytoma
    - Episodic symptoms
    - Forceful heartbeat, pallor, tremor, headache, and diaphoresis
    - Spontaneous or precipitated by postural change, anxiety, meds, and Valsalva
  - Primary hyperaldosteronism
    - Nocturia/polyuria (due to hypokalemia)
    - Muscle cramps and palpitations
  - Adrenocortical carcinoma
    - Abdominal/back pain
    - Cushing's syndrome (see above)
    - Altered reproductive or sexual function
    - Hyperaldosteronism (see above)
  - Sex steroid-secreting tumor

- Altered reproductive or sexual function
  - Metastatic cancer
    - History of extra-adrenal cancer
- Medical history
  - Malignancy or syndromes
- Medications such as exogenous steroids
- Family history: See “Genetics”

PHYSICAL EXAM

- Blood pressure and heart rate
- Focus on signs suggestive of adrenal hyperfunction or malignant disease
  - Cushing’s syndrome
    - Hypertension
    - Central adiposity
    - Facial rounding and plethora
    - Supraclavicular and upper back fat pads
    - Thin skin, purple striae, and acne
    - Hirsutism
  - Pheochromocytoma
    - Hypertension, orthostasis, tachycardia
    - Fever, pallor, tremor
    - Retinopathy
  - Primary hyperaldosteronism
    - Edema, paresthesias, weakness, tremors
  - Adrenocortical carcinoma
    - Abdominal mass
    - Cushing’s syndrome signs (see above)
    - Gynecomastia
  - Sex steroid-secreting tumor
    - Gynecomastia or testicular atrophy

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Assess all for biochemical function (2)[A]
- Cushing’s syndrome
  - Hyperkalemic, hyperglycemic
  - 24-hr urinary free cortisol (5)[A]
    - <80 μg/24 h excludes diagnosis
  - Cortisol suppression testing
    - 1 mg dexamethasone at 11 PM and measure serum cortisol at 8 AM next day
    - Serum cortisol $>$ 5 μg/dL is diagnostic
    - 97% specificity
- Pheochromocytoma
  - Plasma metanephrines
    - 96–100% sensitivity, 85–89% specificity

- 24-hr urine fractionated metanephrines
  - 91–98% sensitivity and specificity
- Primary hyperaldosteronism
  - Hypokalemia, mild hypernatremia, alkalosis
  - 40% normokalemic
  - Aldosterone-to-renin ratio (morning)
    - Patients must stop spironolactone, eplerenone, or amiloride
    - Cutoff for + result is lab dependent
  - Confirmatory testing
    - Saline infusion test
    - 24-hr urinary aldosterone excretion test while patient maintains high sodium diet
- Adrenocortical carcinoma (3)[A]
  - Most commonly cortisol secreting
  - Serum dehydroepiandrosterone (DHEA)
- Sex steroid-secreting tumor
  - Serum testosterone and 17β-estradiol in women with virilization or men with feminization

Imaging

- CT scan (2)[A]
  - Benign adrenal adenoma
    - Usually <3 cm and homogeneous
    - Density <10 HU with >50% washout of contrast at 10 min
  - Adrenocortical carcinoma or adrenal mets
    - Usually >4 cm, heterogeneous, calcifications, necrosis
    - Density >25 HU and <50% washout of contrast at 10 min
- MRI
  - Benign adrenal adenoma
    - Rapid contrast washout and high lipid content; isointense with liver on T2
  - Adrenocortical carcinoma or adrenal mets
    - Hyperintense with liver on T2 imaging
  - Pheochromocytoma
    - "Light bulb" sign: see very high signal intensity on T2-weighted imaging
- Metaiodobenzylguanidine (MIBG) scan
  - Useful for extra-adrenal pheochromocytoma

Diagnostic Procedures/Surgery

- Primary hyperaldosteronism
  - Adrenal vein sampling for lateralization of aldosterone production, if unclear by imaging
- Biopsy
  - Rule out pheochromocytoma prior to biopsy
  - Helpful if concern for metastases or infection

Pathologic Findings

See "Differential Diagnosis"

DIFFERENTIAL DIAGNOSIS

- Adrenal cortical tumors (4)[A]
  - Adenoma
  - Carcinoma
  - Nodular hyperplasia
- Adrenal medullary tumors
  - Pheochromocytoma
  - Ganglioneuroma/neuroblastoma
- Other adrenal tumors
  - Myelolipoma, lipoma, hemangioma
  - Metastases
  - Hamartoma, teratoma
- Infectious or inflammatory
  - Abscess or fungal infection
  - Amyloidosis, sarcoidosis
  - Cytomegalovirus
  - Cysts (pseudocysts, parasitic, epithelial- and endothelial-lined cysts)
- Congenital adrenal hyperplasia
- Hemorrhage
- Pseudoadrenal masses
  - Splenic, pancreatic, renal lesions
  - Vascular lesions or technical artifacts

TREATMENT

GENERAL MEASURES

- Observation, resection, or medical therapy
- Depends on size of lesion, functionality, malignant potential, and overall health of patient

MEDICATION

First Line

- Cushing's syndrome (5)[C]
  - Aminoglutethimide, metyrapone, ketoconazole
- Pheochromocytoma
  - Phenoxybenzamine, propranolol
- Primary hyperaldosteronism: Spironolactone
- Adrenocortical carcinoma: Mitotane

Second Line

- Adrenocortical carcinoma
  - Cisplatin, etoposide, 5-flurouracil, doxorubicin, vincristine

SURGERY/OTHER PROCEDURES

- Should remove all functional adrenal masses
- Open surgery if large or locally advanced; evaluate for vein thrombus or adjacent organ invasion
- Minimally invasive surgery is now accepted

- Remove masses >5 cm; high malignancy risk
- Consider partial adrenalectomy for solitary adrenals, bilateral disease, familial syndromes

ADDITIONAL TREATMENT

Radiation Therapy

Only for palliation of bone metastases from adrenal cortical carcinoma

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Adrenalectomy cures hypertension in 33–72% of patients with primary hyperaldosteronism (5)[B]
- 10–15% recurrence rate after resection of pheochromocytoma
- Adrenocortical carcinoma has poor prognosis
  - Mean survival 18 mo (4)[B]
  - 5-yr survival 15–47%

COMPLICATIONS

- Adrenal insufficiency post adrenalectomy
- Unrecognized malignancy/pheochromocytoma

FOLLOW-UP

Patient Monitoring

- Conservative management principles (2)[B]
  - Repeat imaging at 6, 12, and 24 mo
  - Repeat hormonal testing annually for 4 yr
  - If growth ≥1 cm or autonomous hormonal secretion, consider surgery

Patient Resources

- www.pheochromocytoma.org
- www.cancer.gov/cancertopics/types/adrenocortical

REFERENCES

1. Barzon L, Sonino N, Fallo F, et al. Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol*. 2003;149:273–285.
2. Young WF. The incidentally discovered adrenal mass. *N Engl J Med*. 2007;356:601–610.
3. Ng L, Libertino JM. Adrenocortical carcinoma: Diagnosis, evaluation, and treatment. *J Urol*. 2003;169:5–11.
4. Aron D, Terzolo M, Cawood TJ. Adrenal incidentalomas. *Best Pract Res Clin Endocrinol Metab*. 2012;26:69–82.
5. Mandeville J, Moinzadeh A. Adrenal incidentaloma. *AUA Update Series*. 2010;29:34–39.

ADDITIONAL READING

Taffel M, Haji-Momenian S, Nikolaidis P, et al. Adrenal imaging: A comprehensive review. *Radiol Clin N Am.* 2012;50:219–243.

See Also (Topic, Algorithm, Media)

- Addison Disease
- Adrenal Adenoma and Cortical Carcinoma
- Adrenal Angiomyelolipoma
- Adrenal Calcifications
- Adrenal Cysts and Pseudocysts
- Adrenal Hemorrhage
- Adrenal Incidentaloma
- Adrenal Mass Algorithm
- Adrenal Mass Image
- Adrenal Metastasis
- Adrenal Myelolipoma
- Adrenal Oncocytoma
- Cushing's Disease and Syndrome
- Pheochromocytoma

CODES

ICD9

- 194.0 Malignant neoplasm of adrenal gland
- 227.0 Benign neoplasm of adrenal gland
- 255.9 Unspecified disorder of adrenal glands

ICD10

- C74.90 Malignant neoplasm of unsp part of unspecified adrenal gland
- D35.00 Benign neoplasm of unspecified adrenal gland
- E27.9 Disorder of adrenal gland, unspecified

CLINICAL/SURGICAL PEARLS

- Assess all for biochemical function.
- Remove all adrenal masses >5 cm.
- Do not biopsy pheochromocytoma.

AMYLOIDOSIS, GENITOURINARY

Christopher Wright, MD
Mark L. Jordan, MD, FACS

BASICS

DESCRIPTION

- Heterogeneous group of disorders with extracellular deposition of protein in abnormal fibrillar form:
  - Can involve any organ system
  - Kidney, ureters, seminal vesicles, prostate, penis, and testis can be involved
  - >50% of genitourinary (GU) tract cases involve the bladder
  - Commonly forms "pseudotumors" in bladder, ureter, or renal pelvis
- 25 structurally unrelated proteins known to cause amyloidosis
- May be primary, secondary, or hereditary
- May be organ limited or systemic

EPIDEMIOLOGY

Incidence

- Uncommon disorder and exact worldwide incidence is unknown
  - In the United States appears to be stable at 6–10 cases per million person-years
- Age-specific incidence rates increase in each decade over age 40
  - Median age at diagnosis is 64 yr and <5% of patients are under age 40 (1)

RISK FACTORS

- Chronic and recurrent mucosal and submucosal inflammation
- Hemodialysis patients develop deposits in kidneys
- Chronic inflammatory disorders

Genetics

- Familial or hereditary amyloidosis exists
- Dozens of specific variations described
- Familial forms often do not present until adulthood
- Patients with immunoglobulin light chain (AL) amyloidosis frequently have chromosomal abnormalities but there is no single chromosome change that is diagnostic

PATHOPHYSIOLOGY

- More than 20 distinct low–molecular-weight proteins are recognized to form amyloid fibrils, the 2 most common being (2):
  - AL, formerly referred to as primary amyloidosis
    - Fibrils composed of fragments of monoclonal light chains
    - Affected patients may have amyloidosis alone or in association with other plasma cell dyscrasias (eg, multiple myeloma)
  - AA amyloidosis
    - Fibrils composed of fragments of the acute phase reactant serum amyloid A

    - Typically reactive (secondary) to chronic inflammation
- Thought to be a misfolding event; misfolded variants are prone to self-aggregation
  – These become insoluble complexes that accumulate in tissues
- Renal amyloid is often a glomerular deposition leading to proteinuria

ASSOCIATED CONDITIONS
- End-stage renal disease (ESRD) requiring dialysis
- Nephrotic syndrome
- Diabetes
- Multiple myeloma
- Familial Mediterranean fever (FMF)
  – Hereditary inflammatory disorder characterized by severe attacks of abdominal pain in 95% of patients
  – AA amyloidosis with renal failure is common complication

GENERAL PREVENTION
N/A

DIAGNOSIS
- Clinical presentation depends on the number and nature of the organs affected
- Even in patients with multiple-organ involvement, it is usually possible to identify 1 organ as the “dominant” site of involvement

HISTORY
- Nonspecific symptoms such as fatigue and weight loss are common
- Patient on dialysis
- Family history of amyloidosis
- Chronic disease or inflammation
- Cardiac:
  – 60% of patients
  – Signs/symptoms of heart failure
- Neurologic:
  – 20% with mixed sensory and peripheral neuropathy
  – Carpal tunnel syndrome
- Liver:
  – 70% will have hepatomegaly
- Bladder:
  – Painless hematuria in 75%
  – Irritative symptoms (urgency, frequency)
  – Clinically similar to bladder cancer
- Ureter:
  – Flank pain if obstruction
  – Anuria if bilateral amyloidosis
  – Hematuria
- Prostate:
  – Hematuria

- Bladder outlet obstruction may be present

PHYSICAL EXAM

- Peripheral edema (nephritic syndrome)
- Hepatosplenomegaly
- Generally no specific physical exam findings

DIAGNOSTIC TESTS & INTERPRETATION

- Proteinuria in 50–80%
- Renal failure in 50%
- Elevated liver function tests (cholestatic pattern)
- Diagnosis of AL amyloidosis requires evidence of a monoclonal proliferative disorder
  - Serum or urine monoclonal (M) protein can be detected

Imaging

- CT or ultrasound (US) may demonstrate hydronephrosis secondary to obstruction (ureteral amyloid)
- Magnetic resonance imaging (MRI):
  - T2-weighted images are suggestive of amyloid deposition. Can be confused with prostate cancer invading into seminal vesicles on MRI for prostate

Diagnostic Procedures/Surgery

- Cystoscopy for hematuria
  - Lesions are difficult to distinguish from transitional cell carcinoma (TCC) without biopsy or resection
- Ureteroscopy or retrograde pyelogram for ureteral involvement
- Biopsy
  - Abdominal fat pad aspirate or bone marrow biopsy have high success rates and are preferred sites of biopsy
  - Renal biopsy performed if former is negative with high suspicion
    - Will be positive in >90% of cases

Pathologic Findings

- Diagnosis requires histologic demonstration of amyloid deposits:
  - Congo red stain
    - Orange under light microscope
    - Green birefringence under polarized light
  - Electron microscopy can be used to identify microfibrils
  - Immunohistochemical analysis assists in typing:
    - Diagnosis of transthyretin-type amyloidosis limits need for further evaluation as it identifies the amyloidosis as inherited
- Seminal vesicle amyloidosis can be seen in radical prostatectomy specimens but the significance is unknown

DIFFERENTIAL DIAGNOSIS

- Bladder
  - Difficult to distinguish from TCC without biopsy
- Ureter

– May be confused with stones or other causes of obstruction (eg, strictures)
• Nephrotic syndrome and glomerulonephritis

TREATMENT

GENERAL MEASURES

• In AL amyloidosis treatment is aimed at reducing the production of monoclonal light chain precursor with chemotherapy or, occasional, radiotherapy or surgery of a localized amyloidogenic plasmacytoma
• In AA amyloidosis treatment is generally supportive with therapy directed at primary cause if identified

MEDICATION

First Line

• High-dose melphalan chemotherapy followed by autologous blood stem cell transplantation (2)
– 25–67% complete hematologic response seen in single and multicenter trials
– Response far exceeds cyclic oral melphalan and prednisone (see 2nd line)
• Colchicine can be used in FMF to prevent proteinuria

Second Line

• Low-dose oral melphalan with prednisone in a cyclical fashion
– Rarely results in complete hematologic response or reversal of amyloid-related organ dysfunction

SURGERY/OTHER PROCEDURES

• Renal transplant
– Graft survival similar to matched controls without amyloidosis
– Recurs in graft in 20–33% due to continued activity of underlying disease
• TUR of bladder lesion with fulguration
– Adjuvant intravesical DMSO has shown success in preventing recurrence (3)

ADDITIONAL TREATMENT

Radiation Therapy

Only rarely used for localized amyloidogenic plasmacytoma

Additional Therapies

• Supportive care
– Management of heart failure
– Salt restriction, diuretics, and treatment of secondary hyperlipidemia for nephrotic syndrome
– Analgesics for neuropathic pain

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Single institution experience of 421 patients who received high-dose melphalan with stem cell transplant shows event-free survival and overall survival of 2.6 and 6.3 yr, respectively (4)
- Long-term survival in those who develop renal failure remains poor
  – Ranges from 12–24 mo
- AA amyloidosis has better prognosis

COMPLICATIONS

See above

FOLLOW-UP

Patient Monitoring

- Bladder or urethra
  – Repeat periodic surveillance cystoscopies
  – Recurrence rates >50%
- Ureters
  – US or CT to monitor hydronephrosis

Patient Resources

Amyloidosis foundation (www.amyloidosis.org)

REFERENCES

1. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989 [see comments]. *Blood.* 1992;79:1817–1822.
2. Sanchorawala V, Jacobson DR, Seldin JC, Buxbaum JN. The Amyloidoses. In: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, eds. *Williams Hematology*, 8th ed. New York, NY: McGraw-Hill; 2010.
3. McCammon KA, Lentzner AN, Moriarty RP, et al. Intravesical dimethyl sulfoxide for primary amyloidosis of the bladder. *Urology.* 1998;52:1136–1138.
4. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: Long-term results in a series of 421 patients. *Blood.* 2011;118:4346–4352.

ADDITIONAL READING

- Javed A, Canales BK, Maclennan GT. Bladder amyloidosis. *J Urol.* 2010;183:2388–2389.
- Mangera A, Linton KD, Fernando M, et al. What is the evidence for the management of urethral amyloidosis? A systematic review of the literature. *BJU Int.* 2012;109:1858–1861.

See Also (Topic, Algorithm, Media)

- Amyloidosis Image ☼
- Bladder Tumors, Benign and Malignant, General Considerations
- Bladder Mass, Differential Diagnosis
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)

CODES

ICD9

- 277.30 Amyloidosis, unspecified
- 277.39 Other amyloidosis
- 583.81 Nephritis and nephropathy, not specified as acute or chronic, in diseases classified elsewhere

ICD10

- E85.3 Secondary systemic amyloidosis
- E85.8 Other amyloidosis
- N08 Glomerular disorders in diseases classified elsewhere

CLINICAL/SURGICAL PEARLS

- Both surgically and radiologically, genitourinary amyloidosis may mimic TCC in GU tract, therefore biopsy is needed.
- Abdominal fat pad aspirate is preferred location to obtain biopsy, followed by bone marrow and finally kidney.

ANDROPAUSE (LATE-ONSET HYPOGONADISM)

Katie S. Murray, DO
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BASICS

DESCRIPTION

- Hypogonadism is a reduction in serum testosterone and other circulating androgens
  - Primary hypogonadism: Arises directly from testicular causes
  - Secondary hypogonadism is where changes occur in hypothalamic–pituitary–testicular axis
  - Late-onset hypogonadism is a gradual reduction in serum testosterone levels in elderly men; often referred to as "andropause."

EPIDEMIOLOGY

- Estimates suggest more than 4.5 million elderly American men may be affected
- 80% of men report moderate or severe scores consistent with hypogonadism on surveys (1) [B]
- Thought to be underreported and underdiagnosed in elderly males

RISK FACTORS

Decreases in serum testosterone occur naturally as part of the aging process

Genetics

- Attenuated action of androgen receptor (AR) may contribute
- Those with longer AR CAG repeat polymorphism are at higher risk of andropausal symptoms (2)[B]

PATHOPHYSIOLOGY

- Testosterone age-related declines vary by reported study:
  - Testosterone declined approximately 100 ng/dL (3.5 nmol/L) from age 20–80 yr
  - European Male Aging Study (EMAS) total testosterone (TT) fell 0.4% a year and the free testosterone fell 1.3% from age 40–79 yr
- As age increases, there is:
  - Decreased number of Leydig cells within the testicle (site of testosterone production)
  - Decreased testicular responsiveness to LH
  - Dampening in the amplitude of circadian release of T
  - Increased serum sex hormone binding globulin (SHBG)
    - binds T, therefore less bioavailable (functionally active) T
- Relationship with cardiovascular (CV) disease is thought to be multifactorial
  - Nitric oxide (NO) is an important mediator in both CV health and erectile function

ASSOCIATED CONDITIONS

- Metabolic syndrome
- Diabetes mellitus

- Hypertension
- Tobacco abuse
- Sleep apnea
- Psychological disorders
- Social stress

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Patients often complain of:
  - Frailty-decreased grip strength, diminished gait speed, easy fatigue and exhaustion, unintentional weight loss, and low levels for physical activity
  - Decreased energy
  - Decreased mentation
  - Diminution in muscle mass and strength
  - Decreased libido
  - Erectile dysfunction
  - Loss of morning erections
  - Increased visceral fat
  - Decrease in bone mineral density (osteoporosis and osteopenia)
  - Sleep disturbances
  - Depression
  - Metabolic syndrome
  - Poor glycemic control and diabetes mellitus
  - Coronary/CV disease

PHYSICAL EXAM
- Overall energy, muscle mass, and disposition
- Psychological evaluation
  - Screen for clinical depression
- Include complete GU exam
  - Testis (size, consistency), digital rectal exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- TT: Diurnal variations so most accurate specimens are obtained in the morning (prior to 10:00 AM)
  - General accepted values although there is no clear lab definition of hypogonadism
  - < 300 ng/dL with symptoms
  - < 200 ng/dL without symptoms
  - FDA research trial definition: < 300 ng/dL
- Free testosterone
  - < 50 pg/mL
- SHBG (sex hormone binding globulin)

  – Increases with aging, which leaves a greater percentage of protein-bound testosterone and lower levels of circulating free testosterone
- Estradiol: Increased aromatization of testosterone to estradiol in adipose tissue
- If abnormal TT levels, then check LH and prolactin
- Blood glucose to screen for diabetes mellitus
- PSA for prostate cancer screening
- Monitoring while on testosterone replacement therapy (TRT)
  – CBC to monitor hematocrit (risk of polycythemia)
  – PSA
  – Liver function tests

Imaging

Bone density scan to evaluate for osteopenia or osteoporosis

Diagnostic Procedures/Surgery

Prostate biopsy if PSA and DRE are suspicious for prostate cancer

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Acute critical illness (surgery, head trauma)
- Age-related decline ("Andropause")
- Alcoholism
- Chronic illness (liver failure, chronic renal failure, hypertension, hypothyroidism, diabetes, sleep apnea, obesity, anorexia nervosa, depression, HIV)
- Hematologic (sickle cell disease, thalassemia)
- Hemochromatosis of the pituitary, Leydig cells
- Hypopituitarism (hypothalamic/pituitary)
- Kallmann syndrome (congenital absence of GnRH)
- Klinefelter syndrome
- Medications: LHRH analogs/antagonists, glucocorticoids, androgens, estrogens, progestins (eg, megestrol), chronic opioids, marijuana (controversial)
- Noonan syndrome
- Pituitary infections, infiltration, trauma, radiation (decreased LH/FSH production)
- Pituitary tumors, macroadenomas, hyperprolactinemia
- Prader–Willi syndrome
- Sertoli-cell-only syndrome
- Testicular failure (primary): Congenital or acquired anorchia, cryptorchidism, mumps orchitis, radiation therapy, chemotherapy
- Testicular tumors

TREATMENT

GENERAL MEASURES

- Can treat ED with phosphodiesterase-5 inhibitors if no contraindications
  – Avanafil

- Sildenafil
- Tadalafil
- Vardenafil
- Start at lowest dose and titrate up for efficacy

MEDICATION

First Line

- TRT (3)[B]
  - Intramuscular, transdermal (patches and gels), and buccal preparations. See Section I "Testosterone Replacement Therapy, General Principles" for specifics on TRT agents
  - Selection is dependent on patient/physician preference and feasibility
  - Considerations in the older male: The American Geriatrics Society (AGS) lists testosterone in the Beers Criteria as a medication to generally avoid in older adults because of potential for cardiac problems and men with personal history of prostate cancer (4)[A]
  - The choice of TRT should be individualized on specific clinical needs
  - Absolute contraindications: Personal history of breast cancer or untreated prostate cancer
  - Relative contraindications: Polycythemia, BPH causing urinary retention, treated prostate cancer

Second Line

N/A

SURGERY/OTHER PROCEDURES

Men with primary erectile dysfunction complaints can discuss surgical placement of penile prostheses, use of vacuum erection devices, or vasoactive intracavernosal injection therapy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Increased weight-bearing exercise
- Diet and exercise
- Weight loss
- Phytotherapies: Limited research on safety and efficacy of herbal medications
  - Limited data on ability of any OTC supplement to influence T levels

ONGOING CARE

PROGNOSIS

- TRT is associated with improved responses in many areas
  - Quality of life
  - Mood and affect
  - Sexual function and libido
  - Cognitive function

– Glycemic control

COMPLICATIONS

- Prostate cancer diagnosis or progression of disease
- Polycythemia
  – Potential for cardiac and cerebral vascular events

FOLLOW-UP

Patient Monitoring

- Hemoglobin and hematocrit
- Bone mineral density
- DRE and PSA for prostate cancer screening
- Continued monitoring of testosterone levels
- Overall men's health issues
  – Blood glucose
  – Serum lipids
  – Overall cardiovascular health

Patient Resources

Urology Care Foundation AUA www.urologyhealth.org/urology/index.cfm?article=132

REFERENCES

1. Trinick TR, Feneley MR, Welford, et al. International web survey shows high prevalence of symptomatic testosterone deficiency in men. *Aging Male*. 2011;14:10–15.
2. Liu CC, Lee YC, Wang CJ, et al. The impact of androgen receptor CAG repeat polymorphism on andropausal symptoms in different serum testosterone levels. *J Sex Med.* 2012;9:2429–2437
3. Bhattacharya RK, Khera M, Blick G, et al. Testosterone replacement therapy among elderly males: The Testim Registry in the US (TRiUS). *Clin Interv Aging*. 2012;7:321–330.
4. American Geriatric Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;15:22–27.

ADDITIONAL READING

- Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metabol.* 2010;95:2536–2539.
- Petak SM, Nankin HR, Spark RF, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients–2002 Update. *Endocr Pract.* 2002;8:440–456.

See Also (Topic, Algorithm, Media)

- Beers Criterion
- Erectile Dysfunction/Impotence, General Considerations
- Hypogonadism, Society Definitions
- Testis, Normal Size
- Testosterone (Free and Total) Lab Testing

- Testosterone Replacement Following Localized Prostate Cancer Therapy
- Testosterone Replacement Therapy, General Principles
- Testosterone, Decreased (Hypogonadism)

CODES

ICD9

- 253.4 Other anterior pituitary disorders
- 257.2 Other testicular hypofunction

ICD10

- E23.0 Hypopituitarism
- E29.1 Testicular hypofunction

CLINICAL/SURGICAL PEARLS

Treatment is based upon symptomatology more than lab values.

ANORECTAL MALFORMATIONS: IMPERFORATE ANUS, CLOACA, AND UROGENITAL SINUS ANOMALIES

Youngjae Im, MD
Sang Won Han, MD

BASICS

DESCRIPTION

- Anorectal malformations (ARMs) are a spectrum of congenital anomalies involving the anorectal and urogenital systems, such that the anus and distal rectum are often absent
  - Imperforate anus: Absence of an anus, typically with a fistula between rectum and lower urinary tract
  - Persistent urogenital sinus (UGS) is seen in 4 entities (1):
    - Genital ambiguity state: Most common being congenital adrenal hyperplasia (CAH)
    - Pure UGS: With normal external genitalia
    - Cloaca: In females, a common channel between lower urinary tract, vagina, and rectum
    - Female exstrophy

EPIDEMIOLOGY

Incidence

- ARM: 1 in 4,000–5,000 live births:
- Cloaca: 1 in 40,000–50,000 live births
- UGS: 1 in 500 live births
- Incidence of ARM in the setting of genetic disease is about 5–10%

Prevalence

N/A

RISK FACTORS

- Proposed association with in utero vascular accidents, maternal diabetes and obesity, maternal ingestion of thalidomide, phenytoin, and trimethadione and maternal exposure to smoking and caffeine
- Some degree of heritability, as incidence of subsequent children having ARM is 1%

Genetics

- ARM found in certain congenital syndromes with associated genetic abnormalities (2)
  - Trisomy 21: Imperforate anus without fistula
  - Microdeletion of chromosome 22q11.2
  - Familial inheritance pattern: ARM with a rectovestibular or rectoperineal fistula, almost 15% had a positive family history for an ARM
  - Currarino triad: ARM, sacral agenesis, presacral mass (or meningocele); autosomal dominant
  - Townes–Brocks syndrome: ARM, external ear abnormalities, hearing loss, polydactyly, renal anomalies; autosomal dominant
  - Cat eye syndrome: ARM, coloboma, preauricular tag, heart defect, urinary tract

abnormalities, mental retardation

PATHOPHYSIOLOGY

- Classic theory: The urorectal septum (mesoderm), fails to grow caudally to meet the lateral Rathke folds to divide the cloacal membrane (endoderm and ectoderm) into the anterior urogenital membrane and the posterior anal membrane.
- Alternative theory: A mesenchymal mass displaces the dorsal cloacal membrane anteriorly, preventing its joining with the hind gut.

ASSOCIATED CONDITIONS

- About 50–67% of all ARM are associated with other anomalies
  - In general, the higher the ARM, the more likely there are associated abnormalities
- Can occur as an isolated abnormality or as part of a syndrome:
  - VACTERL: Vertebral, anorectal, cardiac, tracheoesophageal fistula, renal, limb abnormalities
- Spinal and bony abnormalities are present in 33–50% of ARM:
  - Tethered cord in 20–30%
  - Sacral agenesis, the most common vertebral anomaly
- Genitourinary abnormalities ranges from 33% to almost 50% of ARM:
  - VUR present in 14–56% of ARM
  - Renal agenesis: 12–30%
  - Neurogenic bladder: 4–25%
  - Renal anomalies: Horseshoe kidney, ectopic kidney, multicystic dysplastic kidney 4–12%
  - Cryptorchidism/hypospadias: 4–6%
- Gynecologic problems are common in ARM, but most may not be diagnosed until puberty or adulthood
  - Duplicated vaginas with septum
  - Absent vagina; vaginal atresia
  - Bicornuate uterus
  - Clitoromegaly in UGS associated with CAH
- Cardiovascular abnormalities are present in 10–30% of ARM:
  - Atrial septal defects and ventricular septal defects are most common
- Tracheoesophageal fistula (TEF) and esophageal atresia (EA) occur in 5–10% with ARM

GENERAL PREVENTION

International Consortium on Anorectal Malformations aims to identify genetic and environmental risk factors in ARM. No prevention reduction strategies are currently available.

DIAGNOSIS

HISTORY

- Prenatal diagnosis: Low sensitivity/specificity
  - Dilated colon, oligohydramnios, and distended vagina on prenatal US may be signs of ARM
  - Antenatal findings suggestive of cloacal anomaly:
    - Transient fet al ascites with bilobed or trilobed pelvic cystic structures
    - Bilateral hydronephrosis or oligohydramnios

- Lower-level ARM and UGS may go undiagnosed in newborn until later symptoms develop:
  - Constipation, abdominal distension in rectal atresia, anorectal stenosis
  - Urinary incontinence and/or retention in UGS
  - Amenorrhea and abdominal distension due to hydrometrocolpos or hematocolpos at puberty in UGS

PHYSICAL EXAM

- Thoroughly examine the perineum to determine number and position of orifices:
  - Perineum flattened in higher-level ARM
- Inspect the genitalia: Rule out hypospadias, cryptorchidism, clitoromegaly
- Assess vertebrae: Look for sacral abnormalities
- Palpate for an abdominal mass that may represent a distended bladder or hydrometrocolpos
- Rule out associated pathologies:
  - Cardiac auscultation for murmur
  - Insert nasogastric tube for tracheoesophageal fistula
  - Skelet al/limb assessment
- Once the diagnosis of an imperforate anus is made, assess for the presence of a fistula
  - It may take up to 24 hr for signs of fistula to be evident

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Renal profile
- Urinalysis: Abnormal if fistula to urinary tract
- 17-hydroxy-progesterone in UGS with virilization to rule out CAH
- Karyotype if ambiguous genitalia

Imaging

- Studies to determine level of ARM:
  - Prone, cross-table lateral plain film
    - Should be performed at 24 hr after birth to allow enteric gas to reach the most distal area of the colon
    - Distance between rectal gas shadow and perineal opening measured
- Abdominal US: Evaluate bilateral kidneys, bladder, ± müllerian structures
- Voiding cystourethrogram (VCUG)/cloaca gram/genitogram: Evaluate presence of VUR as well as relation of urinary tract to rectum (and to müllerian structures)
- Colostogram: Distal to mucous fistula and proximal to colostomy to evaluate colon and its relation to other pelvic structures prior to definitive surgery
- Spinal imaging:
  - Spinal US prior to 6 mo of age
  - Spinal MRI after 6 mo of age

Diagnostic Procedures/Surgery

- Echocardiogram and ECG: Rule out cardiac anomalies
- Urodynamic study : Especially in cases of UTI, VUR, urinary incontinence, spinal anomalies
  - The most common finding on UDS is an upper motor neuron lesion with an overactive detrusor and/or detrusor sphincter dyssynergia (DSD)
- Exam under anesthesia/endoscopy: Helps delineate relationships between structures and

measure length of common channel and proximity of fistula/confluence to bladder neck

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Classification systems for ARM (3)
  - Wingspread classification: Traditional "low," "intermediate," or "high" ARM
  - Pena classification: Based on the presence and position of the fistula
  - Krickenbeck anatomic classification: An anatomic description of ARM, type of surgical procedure performed, and postop assessment of bowel movements, constipation, and soiling
- Lesions in the male: Classifying patients (ie, into low-lying or higher lesions) have important clinical implications with regard to their treatment and prognosis
  - Imperforate anus without fistula, rectal atresia, rectoperineal fistula
  - Recto bulbar urethral fistula
  - Recto posterior urethral fistula
  - Rectovesical fistula
- Lesions in the female:
  - Imperforate anus without fistula, rectal atresia, rectoperineal fistua
  - Rectovestibular fistula: Most common defect
  - Cloaca: Further subdivided into length of common channels:
    - Short (<3 cm): Good prognosis
    - Long (>3 cm): More complicated and worse prognosis
  - UGS:
    - Some associated with virilization, as in CAH
    - Some not associated with virilization
    - Can be result of congenital cloaca following isolated repair of the rectum

TREATMENT

GENERAL MEASURES

- Newborn should not be given any enteric intake and should have nasogastric suction
- Hydrometrocolpos (present in 50% of cloaca) and urinary retention in newborn period managed with catheter drainage until operative intervention

MEDICATION

First Line

- IV antibiotics neonatally and perioperatively
- Prophylactic antibiotics continued at least until VUR is ruled out
- Eventual fecal incontinence may be treated with combination of enemas and antimotility agents
- Eventual constipation may be treated with combination of enemas and laxatives
- Anticholinergics may be necessary for neurogenic bladder

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Newborn:
  - Diverting colostomy with mucous fistula needed in all but the lowest of ARM:
    - Level of colostomy should be distal on descending colon; distance between stomas should be wide to minimize the length of bowel that could potentially be in contact with urine in cases of fistula
  - Neonatal posterior sagittal anorectoplasty (PSARP) in low ARM
  - In cases of hydrometrocolpos, vaginotomy may be necessary as newborn
  - In cases of urinary retention, cutaneous vesicostomy may be necessary as newborn
- Definitive surgery at age 2–24 mo:
  - Lower lesions: Approached through a PSARP
  - Higher lesions: Laparotomy as well as PSARP
  - In cloaca with a long common channel, when vagina will not reach perineum, can interpose a section of bowel between vagina and perineum
  - Genitoplasty in cases of virilized genitalia
- Colostomy take-down a few months after definitive reconstruction, once anal dilations satisfactory
- Further urologic surgery later as indicated (ureteral reimplantation for VUR, bladder neck reconstruction for incontinence, augmentation for small capacity, poorly compliant bladder)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Clean intermittent catheterization may be necessary in cases of neurogenic bladder

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Bowel function (4):
  - Voluntary bowel movements in 75% of ARM after definitive repair
  - Fecal soiling occurs in about half of patients with voluntary bowel movements
  - Total fecal continence (voluntary bowel movements, no soiling) in 37% of ARM; the lower the ARM, the chance of fecal continence
  - Constipation in 48% of ARM; the lower the ARM, the more likely to have constipation
- Positive prognostic factors for fecal continence: Good perineal raphe, well-defined anal dimple, normal spine, brisk muscle reflex
- Urinary incontinence (4):
  - Present overall in 9% of ARM
  - Highest probability in cloaca (19% if common channel <3 cm, 69% if >3 cm)
- Renal failure (CKD): 1–6% (5)

COMPLICATIONS

- Ongoing problems usually due to underlying congenital abnormality, not iatrogenic causes
- NGB in many ARM, but rarely due to surgery

FOLLOW-UP

Patient Monitoring

- Close follow-up needed to manage long-term problems like fecal and urinary incontinence and associated urologic abnormalities
- Should follow through puberty and child-bearing age due to potential for hydrometrocolpos/ hematocolpos, infertility, ectopic pregnancy, delivery issues

Patient Resources

http://www.pullthrough.org/anorectal-malformation-treatment/

REFERENCES

1. Rink RC, Kaefer M. Surgical management of disorders of sexual differentiation, cloacal malformation, and other abnormalities of the genitalia in girls. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2012.
2. Marcelis C, de Blaauw I, Brunner H. Chromosomal anomalies in the etiology of anorectal malformations: A review. *Am J Med Genet A*. 2011;155:2692–2704.
3. Nah SA, Ong CC, Lakshmi NK, et al. Anomalies associated with anorectal malformations according to the Krickenbeck anatomic classification. *J Ped Surg*. 2012;47:2273–2278.
4. Peña A, Hong A. Advances in the management of anorectal malformations. *Am J Surg*. 2000;180:370–376.
5. Ganesan I, Rajah S. Urological anomalies and chronic kidney disease in children with anorectal malformations. *Pediatr Nephrol*. 2012;27:1125–1130.

ADDITIONAL READING

- Grano C, Aminoff D, Lucidi F, et al. Long-term disease-specific quality of life in children and adolescent patients with ARM. *J Ped Surg*. 2012;47:1317–1322.
- Herman RS, Teitelbaum DH. Anorectal malformations. *Clin Perinatol*. 2012;39:403–422.

See Also (Topic, Algorithm, Media)

- Anorectal Malformations: Imperforate Anus, Cloaca and Urogenital Sinus Anomalies Images
- Disorders of Sexual Differentiation
- Exstrophy, Cloacal

CODES

ICD9

- 255.2 Adrenogenital disorders
- 751.2 Atresia and stenosis of large intestine, rectum, and anal canal
- 751.5 Other anomalies of intestine

ICD10

- E25.0 Congenital adrenogenital disorders assoc w enzyme deficiency
- Q42.3 Congenital absence, atresia and stenosis of anus without fistula
- Q43.9 Congenital malformation of intestine, unspecified

CLINICAL/SURGICAL PEARLS

ARM usually requires neonatal surgical interventions and follow-up to obtain and maintain fecal and urinary continence.

ANORGASMIA, MALE

Robert L. Segal, MD, FRCS(C)
Arthur L. Burnett, II, MD, MBA, FACS

BASICS

DESCRIPTION

- Anorgasmia is defined as the complete inability to achieve an orgasm (the physical and emotional sensation experienced at the peak of sexual excitation) (1)
  - In males, orgasm is typically associated with ejaculation (antegrade semen passage through the urethra)
  - There is more robust literature in the female population with anorgasmia
  - Also described in some references as orgasmic disorder, orgasmic dysfunction, or orgasmic inhibition
- Anorgasmia is often associated with delayed/inhibited ejaculation or anejaculation, although orgasm and ejaculation are separate phenomena
  - Orgasm is a cerebrally mediated event, whereas ejaculation is localized to the genitourinary tract
- Must result in personal distress or interpersonal difficulty according to definitions by the DSM-IV-TR and the World Health Organization Second Consultation on Sexual Dysfunction (2)
- May be lifelong or acquired; may be global (every sexual encounter), intermittent or situational (in a certain environment, with a particular partner)

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Difficult to clearly report, as there is no clear definition of normal ejaculatory latency time
- In general, DE is reported at low rates in the literature, rarely exceeding 3% (3,4), but has been reported in up to 25% of clinical cohorts (2)

RISK FACTORS

- Advancing age
- Endocrinopathies (hypothyroidism, hypogonadism)
- Pelvic trauma/surgery (radical prostatectomy, proctocolectomy, bilateral sympathectomy)
- Pelvic radiation therapy
- Neuropathy (multiple sclerosis, diabetes mellitus, spinal cord injury)
- Secondary to medication (thiazide diuretics, tricyclic and selective serotonin reuptake inhibitor [SSRI] antidepressants, alcohol, gabapentin)

Genetics

N/A

PATHOPHYSIOLOGY

- Unless a specific organic cause is noted (see Risk Factors), anorgasmia is associated with underlying psychological factors
  - Fear, anxiety, hostility, and relationship difficulties
  - It has been suggested to relate to orthodoxy of religious belief (ie, it is sinful to experience orgasm/sexual pleasure)
  - "Performance anxiety" may be a common cause
- May relate to men deriving greater arousal/enjoyment from masturbation than intercourse (2)
  - Masturbatory frequency/style may be predisposing factors, as men with coital anorgasmia may report high levels of masturbation (2)
- Alcohol may transiently cause anorgasmia

ASSOCIATED CONDITIONS
- Anejaculation
- Delayed/inhibited ejaculation
- Depression
- Infertility

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Is the problem lifelong or acquired?
- Sexual history
  - Establish the conditions (if any) where the patient is able to experience orgasm
- Assess the presence of life stressors or other psychological factors, the quality of the patient's nonsexual relationship with the partner
- Medication use
  - SSRIs and gabapentin have been implicated

PHYSICAL EXAM
- Genital exam to verify the presence and normalcy of testicles and epididymides bilaterally
- Secondary sexual characteristics and hair distribution
- Neurologic exam to assess genital sensation
- May not be contributory

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum morning testosterone level
- As indicated
  - Semen analysis
  - Semen culture
  - Urine culture
  - Urine cytology
  - Thyroid screen

Imaging
Scrotal/transrectal ultrasound if indicated

Diagnostic Procedures/Surgery
None

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Psychiatric distress (anxiety, depression)
- Retrograde ejaculation
- Anejaculation
- Delayed ejaculation
- Reduced ejaculation
- Penile hypnoanesthesia

TREATMENT

GENERAL MEASURES
- Treatment should be etiology specific
- May include patient/couple psychoeducation and/or psychosexual therapy [C]
- Pharmacologic treatment has met limited success (2)

MEDICATION
First Line
None currently FDA approved

Second Line
- No drugs are specifically approved for treatment of anorgasmia, so any treatment is off-label (2)
  - Cyproheptadine (increases cerebral serotonin levels)
  - Amantadine (stimulant of dopaminergic nerves)
  - Bupropion, buspirone, and yohimbine have been anecdotally employed to reverse SSRI-induced anorgasmia

SURGERY/OTHER PROCEDURES
None

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Psychotherapy
- Masturbation retraining
- Education on revised sexual techniques which maximize arousal

Complementary & Alternative Therapies
Yohimbine has utility in anecdotal reports

ONGOING CARE

PROGNOSIS

- Continued support/psychotherapy may be required
- Anorgasmia related to trauma/surgery, radiation therapy, and neuropathies may not be reversible

COMPLICATIONS

None

FOLLOW-UP

Patient Monitoring

N/A

Patient Resources

N/A

REFERENCES

1. Mulhall JP, Nelson CJ. Male orgasmic disorder: What do we know? *Contemp Urol*. 2007;Feb 1.
2. McMahon CG, Jannini E, Waldinger M, et al. Standard operating procedures in the disorders of orgasm and ejaculation. *J Sex Med*. 2013;10:204–229.
3. Rowland D, McMahon CG, Abdo C, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2010;7(4 Pt 2):1668–1686.
4. McMahon CG, Abdo C, Incrocci L, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2004;1:58–65.

ADDITIONAL READING

- Perloff MD, Thaler DE, Otis JA. Anorgasmia with gabapentinxs may be common in older patients. *Am J Geriatr Pharmacother*. 2011;9(3):199–203.
- Segraves RT. Considerations for a better definition of male orgasmic disorder in DSM V. *J Sex Med*. 2010;7(2 Pt 1):690–695.

See Also (Topic, Algorithm, Media)

- Ejaculatory Disturbances (Delayed, Decreased, or Absent)
- Erectile Dysfunction, Following Pelvic Surgery or Radiation

CODES

ICD9

- 302.74 Male orgasmic disorder
- 608.89 Other specified disorders of male genital organs

ICD10

- F52.32 Male orgasmic disorder
- N53.11 Retarded ejaculation

CLINICAL/SURGICAL PEARLS

- Anorgasmia is often associated with ejaculatory disorders.
- Unless a specific organic cause is noted, anorgasmia is associated with underlying psychological factors.
- Anorgasmia related to trauma/surgery, radiation therapy, and neuropathies may not be reversible.
- There are no approved pharmacologic treatments for anorgasmia.

ANURIA AND OLIGURIA, ADULT

Won K. Han, MD

BASICS

DESCRIPTION

- Anuria: No urine output or <50 mL/d
- Oliguria: Urine output of 500 mL/d or <0.5 mL/kg/h
- Often the earliest sign of impaired renal function
- Associated with a severe decrease in the glomerular filtration rate (GFR) compromising kidney's main functions
  - Maintenance of body composition (such as fluid, acid–base, electrolyte content, and concentration)
  - Excretion of metabolic end products and foreign substances (urea, toxins, and drugs)

EPIDEMIOLOGY

Incidence

- Frequency depends on various clinical settings:
  - 1% at admission
  - 2–5% during hospitalization
  - 4–15% after cardiopulmonary bypass

Prevalence

N/A

RISK FACTORS

- Chronic kidney disease
- Congestive heart failure
- Diabetes mellitus
- Hypertension
- Myeloma
- Nephrotoxic medications

Genetics

N/A

PATHOPHYSIOLOGY

- Oligoanuria may result from 3 broad pathophysiologic processes: Prerenal, intrarenal, and postrenal causes
- Prerenal:
  - Physiologic responses that lead to decreased GFR
  - Maintain GFR by afferent arterial dilatation and efferent arteriolar constriction (mediated by angiotensin II)
  - Enhanced tubular reabsorption of salt and water
  - Prolonged renal hypoperfusion can lead to acute tubular injury
    - True volume depletion: Hemorrhage, gastrointestinal loss (vomiting, diarrhea, bleeding),

renal loss (diuretics, osmotic diuresis), skin or respiratory loss (insensible loses, burns), 3rd spacing (pancreatitis, crush injury, or skelet al fracture)
    - Decrease in effective circulating blood volume: Sepsis, heart failure, hepatic failure, nephrotic syndrome, anaphylaxis
    - Drugs affecting glomerular hemodynamics: Afferent arteriolar dilatation (nonsteroidal anti-inflammatory drugs [NSAIDs] or calcineurin inhibitors [CNIs]), efferent arteriolar constriction (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs])
- Intrarenal:
  - Associated with structural renal damage
    - Vascular (renal infarction, renal artery stenosis, renal vein thrombosis, etc.)
    - Tubular (ischemia, nephrotoxin)
    - Glomerular (acute glomerulonephritis, vasculitis, thrombotic microangiopathy)
    - Interstitium (interstitial nephritis, tumor infiltration)
- Postrenal (obstructive uropathy):
  - Mechanical or functional obstruction of the flow of urine
    - Intraureteral obstruction (stones, crystals, clots, tumor)
    - Extraureteral obstruction (tumor, retroperitoneal fibrosis)
    - Prostatic hypertrophy
    - Neurogenic bladder

ASSOCIATED CONDITIONS
- Chronic kidney disease
- Nephrolithiasis
- Diabetes mellitus
- Peripheral vascular disease
- Bladder outlet obstruction
- Pelvic and abdominal tumors

GENERAL PREVENTION
- Avoid nephrotoxic medications (NSAIDs, ARBs (angiotensin receptor blockers), ACEIs (angiotensin-converting-enzyme inhibitors), radiographic contrast) especially in the setting of impaired renal function
- Avoid hypotension (keep mean arterial pressure [MAP] >60 mmHg)
- Adequate hydration

DIAGNOSIS
HISTORY
- Age, gender
- Duration of symptoms
- Chronic kidney disease
- Diabetes mellitus
- Hypertension
- Cardiac disease
- Liver disease

- Organ transplantation
- Episode of hypotension (MAP <60 mmHg)
- Fluid losses
  - Vomiting, diarrhea
  - Diuretics
  - Burns, trauma, surgery
- Exposure to nephrotoxic medications
  - ACEIs, ARBs, NSAIDs
  - CNIs (cyclosporine, tacrolimus)
  - Aminoglycosides, cephalosporins amphotericin B, radiographic contrast
  - Acyclovir, sulfonamides, indinavir (can precipitate within the tubular lumen)
  - Anticholinergics
  - Chemo agents (cisplatin, methotrexate, 5-fluorouracil, interleukin-2, etc.)
- Symptoms of urinary tract obstruction
  - Anuria or oliguria
  - Urinary urgency, hesitancy
  - Intermittent polyuria
  - History of kidney stones
  - Gross hematuria

PHYSICAL EXAM

- Signs of intravascular depletion
  - Orthostatic hypotension
  - Tachycardia
  - Decreased skin turgor
  - Dry mucous membrane
- Signs of heart failure
  - Jugular venous distension
  - Rales or crackles in lung exam
  - Dyspnea, orthopnea
  - Gallop rhythm
- Signs of volume overload
  - Generalized edema
  - Ascites
  - Dyspnea
  - Paroxysmal nocturnal dyspnea
- Signs of abdominal compartment syndrome
  - Abdominal distension
  - Abdominal tenderness
- Signs of postrenal obstruction
  - Bladder distention
  - Enlarged prostate on rectal exam
  - Signs of urethral trauma
  - Pelvic mass
  - Patients with indwelling catheters should be irrigated to rule out blockage

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum electrolytes
  - Acute kidney injury (AKI)
    - Rise in serum creatinine (SCr) of at least 0.3 mg/dL over a 48-hr period
    - Over 1.5 times the baseline SCr value within the 7 previous days
  - Electrolyte and acid–base disorders
    - Metabolic acidosis
    - Hyponatremia
    - Hyperkalemia
    - Hyperphosphatemia
- Urinalysis with microscopic exam
  - Prerenal: High specific gravity, normal, or hyaline casts
  - Intrarenal:
    - Acute tubular necrosis (ATN): Low specific gravity, granular casts, muddy brown cast, tubular epithelial cells
    - Glomerulonephritis: Proteinuria, hematuria, red blood cell casts
    - Interstitial nephritis: White blood cells (WBCs), WBC casts, eosinophils, hematuria
    - Vascular disorders: Normal or hematuria
  - Postrenal: Normal or hematuria. WBCs, occasional granular casts
- Urine indices
  - Prerenal: Fractional excretion of sodium (FeNa) $<1\%$, serum Bun/Cr ratio $>20:1$
  - Intrarenal: FeNa $>1\%$, serum Bun/Cr ratio $<20:1$
  - Postrenal: FeNa variable, serum Bun/Cr ratio $>20:1$

Imaging

- Renal/bladder ultrasonography: 1st line in imaging, noninvasive, no radiation exposure
  - Hydronephrosis and hydroureter
  - Kidney stones
  - Pelvic/retroperitoneal masses
- Duplex Doppler ultrasound: To evaluate the patency of renal artery and vein
- Voiding cystourethrogram: To evaluate vesicoureteral reflux
- Nuclear renal scans (such as technetium 99 m mercaptoacetyltriglycine [MAC3]): To assess the adequacy of renal perfusion and obstructive uropathy
- Intravenous urography or intravascular contrast dye generally does not indicate as it may exacerbate renal injury

Diagnostic Procedures/Surgery

- Foley catheter placement: To rule out lower urinary tract obstruction
- Retrograde pyelography with cystoscopy: To define the site and cause of obstruction
- Urodynamic study: To evaluate functional abnormality of the bladder (neurogenic bladder)
- Renal biopsy: To determine intrarenal etiology

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Prerenal causes of AKI
  - Gastrointestinal loss
  - Renal loss
  - Heart failure
  - Hepatic failure
  - Nephrotic syndrome
  - Medications affecting renal hemodynamics
- Intrarenal causes of AKI
  - Renal ischemia
  - Nephrotoxins
  - Acute glomerulonephritis
  - Interstitial nephritis
  - Vascular complication
- Postrenal causes of AKI
  - Intraureteral obstruction
  - Extraureteral obstruction
  - Bladder outlet obstruction

TREATMENT

GENERAL MEASURES

- Prompt diagnosis of cause for oliguria/anuria to guide treatment
- All patients with oliguria/anuria should have a Foley catheter placed to monitor accurate urine output and eliminate lower urinary tract obstruction causes
- Appropriate medical managements for acid–base disorder, fluid imbalance, electrolyte imbalance (such as hyperkalemia, hyperphosphatemia, hypocalcemia)
- Renal replacement therapy: If supportive medical managements are not successful
  - Refractory hyperkalemia
  - Refractory volume overload
  - Refractory acidosis
  - Uremic pericarditis

MEDICATION

First Line

- Prerenal causes: Usually rapidly reversed following restoring renal perfusion
  - Replace fluid with intravenous hydration or blood product transfusion
  - Discontinue the nephrotoxic medications (NSAIDs, ARBs, ACEIs)
  - Optimize cardiac output and volume status
- Intrarenal causes: ATN is the most common cause
  - There is no single or sequence of interventions that will significantly improve renal function after onset of ATN (1)[A]
  - Use of diuretics and low-dose dopamine
    - Increasing urine output does not shorten the duration of renal failure, decrease the requirement for dialysis or improve survival in patients with established oliguric AKI (2,3)[A]

- Diuretics may be given for a short length of time for volume control
- Low-dose dopamine (1–3 μg/kg/min, intravenously) does not reduce mortality or promote the recovery of renal function (4)[A]

SURGERY/OTHER PROCEDURES

- Obstructive uropathy: Usually responds to release of the obstruction and type of procedure is depending on level of obstruction
  - Nephrostomy tube
  - Ureteral stent
  - Foley catheter
- Thrombotic microangiopathies and dysproteinemias (intrarenal causes)
  - Plasmapheresis/or plasma exchange

ONGOING CARE

PROGNOSIS

- Mortality rate depends on the underlying cause and associated medical condition
- In most clinical situations, acute oliguria is reversible and does not result in permanent renal impairment
- Identification and timely treatment of reversible causes are crucial because the therapeutic window may be small

COMPLICATIONS

- Inability to manage electrolytes and fluid balance resulting in various complications
  - Cardiovascular
    - Arrhythmias
    - Congestive heart failure
  - Gastrointestinal
    - Nausea and vomiting
    - Ileus
    - Bleeding
  - Neurologic
    - Confusion
    - Asterixis
    - Seizures
  - Infection
- Requirement of renal replacement therapy

FOLLOW-UP

Patient Monitoring

- Serial renal function testing for resolution
- Subsequent renal imaging study to confirm the resolution of postrenal obstruction

REFERENCES

1. Han WK. Biomarkers for early detection of acute kidney injury. *Current Biomarker Findings*. 2012;2:77–85.
2. Metha RL, Pascual MT, Soroko S, et al. Diuretics, mortality, and nonrecovery of renal

function in acute renal failure. *JAMA*. 2002;288:2547–2553.
3. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. *Anaesthesia*. 2010;65:283–293.
4. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet*. 2005;365:417–430.

ADDITIONAL READING

• Devarajan P. Oliguria. Medscape 2014: http://emedicine.medscape.com/article/983156-overview; Accessed July 28, 2014.
• Klahr S, Miller SB. Acute oliguria. *N Engl J Med*. 1998;338:671–675.

See Also (Topic, Algorithm, Media)

• Acute Kidney Injury, Adult (Renal Failure, Acute)
• Acute Kidney Injury, Pediatric (Renal Failure, Acute)
• Acute Tubular Necrosis (ATN)
• Anuria or Oliguria Algorithm ‡

CODES

ICD9

• 593.9 Unspecified disorder of kidney and ureter
• 599.60 Urinary obstruction, unspecified
• 788.5 Oliguria and anuria

ICD10

• N13.9 Obstructive and reflux uropathy, unspecified
• N28.9 Disorder of kidney and ureter, unspecified
• R34 Anuria and oliguria

CLINICAL/SURGICAL PEARLS

• Oliguria is often the earliest sign of impaired renal function.
• Prompt diagnosis and timely treatment of reversible causes are crucial because the therapeutic window may be small.
• Diuretics and low-dose dopamine do not reduce mortality or promote the recovery of renal function.

ANURIA AND OLIGURIA, PEDIATRIC

Jennifer A. Hagerty, DO

BASICS

DESCRIPTION

- Typically 1st sign of impaired renal function
- Anuria: No urine output
- Oliguria: Significantly reduced urine volume
  - < 1 mL/kg/h in infants
  - < 0.5 mL/kg/h in children

EPIDEMIOLOGY

Incidence

- 10% of newborns in the NICU (1)[C]
- 2–5% of children in the ICU (1)[C]
- 10–30% of children undergoing cardiac surgery (1)[C]

Prevalence

N/A

RISK FACTORS

- Hypovolemia
- Intrinsic renal disease
- Urinary tract obstruction
- Glomerulonephritis
- Nephrotoxic medications

Genetics

Dependent on diagnosis

PATHOPHYSIOLOGY

- Prerenal failure
  - Most common cause of oliguria
  - Hypoperfusion in otherwise normal kidneys
  - Administration of nephrotoxic agents can precipitate oliguria when reduced renal perfusion is present
- Intrinsic renal failure
  - Associated with structural kidney damage including acute tubular necrosis (ischemia, drugs, or toxins), primary glomerular diseases, or vascular lesions
  - Altered tubule cell metabolism leads to ischemia, then altered metabolism and subsequently cell death
- Postrenal failure
  - Obstructive uropathy
  - Usually reversible with relief of the obstruction

ASSOCIATED CONDITIONS
- Pre-existing renal disease
- Obstructive uropathy

GENERAL PREVENTION
- Maintain adequate hydration
- Avoid nephrotoxic agents in children with underlying renal disease

DIAGNOSIS
HISTORY
- Age, sex
- Duration of symptoms
- Pre-existing renal disease
- Medications
- Symptoms of urinary tract obstruction
- Antenatal history
- Family history

PHYSICAL EXAM
- Signs of hypovolemia
  - Tachycardia
  - Hypotension
  - Decreased skin turgor
  - Dry mucous membranes
- Signs of hypervolemia
  - Edema
- Signs of obstructive uropathy
  - Palpable bladder or kidney
  - Meatal stenosis

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
  - Protein, red cells, casts: Possible glomerulonephritis
  - Low specific gravity: Possible acute interstitial nephritis or intrinsic renal disease
  - High specific gravity: Possible prerenal cause
  - Nitrate: Suggests infection
- Basic metabolic panel
  - BUN/Cr ratio: >20 suggests prerenal cause
  - Evaluate renal function and electrolyte balance

Imaging
- Renal and bladder ultrasound for hydronephrosis and bladder distention and thickening of the wall
- VCUG for suspected bladder outlet obstruction
- Nuclear renal scan for function, dysplasia, and drainage

Diagnostic Procedures/Surgery
Placement of a urethral catheter

Pathologic Findings
Dependent on diagnosis

DIFFERENTIAL DIAGNOSIS
- Prerenal
  - Burns
  - Dehydration
  - Drugs
  - GI losses
  - Heart disease
  - Hemorrhage
  - Respiratory distress syndrome
  - Shock/sepsis
- Intrinsic renal disease
  - Acute tubular necrosis
  - Exposure to nephrotoxins (drugs, myoglobin, uric acid)
  - Congenital kidney disease
  - Renal vascular abnormalities
  - Glomerulonephritis
- Urinary tract obstruction
  - Neurogenic bladder
  - Posterior urethral valves
  - Meatal stenosis
  - Bilateral UPJ or ureteral obstruction or unilateral in a solitary kidney
  - Bilateral obstructing calculi

TREATMENT

GENERAL MEASURES
- Treatment of the underlying cause
- Appropriate medical managements for acid–base disorder, fluid imbalance, electrolyte imbalance (such as hyperkalemia, hyperphosphatemia, hypocalcemia)
- Strict volume monitoring of input and output
- Avoidance of nephrotoxic agents (NSAIDs, ARBs (angiotensin receptor blockers), ACEIs (angiotensin-converting-enzyme inhibitors))

MEDICATION
First Line
Hydration to optimize cardiac output and volume status

Second Line
- Diuretics considered if adequate intravascular volume status and patient remains oliguric
- Hemodialysis or peritoneal dialysis to be considered if severe electrolyte abnormalities or volume overload

SURGERY/OTHER PROCEDURES
Relief of obstruction with urethral catheter, ureteral stenting, or nephrostomy tube

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
None

ONGOING CARE
PROGNOSIS
- Acute oliguria is often completely reversible if recognized and treated promptly
- Small increases in serum creatinine can be indicative of worsening outcome (2)[C]

COMPLICATIONS
- Progression to permanent renal injury
- Infections secondary to uremia leading to impaired defenses
- Cardiovascular complications secondary to fluid overload and electrolyte abnormalities
- Neurologic changes: Confusion, lethargy, and seizures
- Gastrointestinal effects: Anorexia, nausea, and vomiting

FOLLOW-UP
Patient Monitoring
- Serial renal function testing until resolution of anuria/oliguria
- Imaging based on diagnosis
  – Monitor renal/bladder ultrasound for obstructive uropathy

Patient Resources
- American Society of Pediatric Nephrology: www.aspneph.com
- National Kidney Foundation: www.kidney.org

REFERENCES

1. Schneider J, Khemani R, Grushkin C, et al. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. *Crit Care Med*. 2010;38:933–939.
2. Askenazi DJ, Feig DI, Graham NM, et al. 3–5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int*. 2006;69:184–189.

ADDITIONAL READING

- Daniels RC, Bunchman TE. Renal Complications and therapy in the PICU: Hypertension, CKD, AKI, and RRT. *Crit Care Clin*. 2013;29:279–299.
- Fortenberry JD, Paden ML, Goldstein SL. Acute Kidney Injury in Children. *Pediatr Clin North Am*. 2013;60:669–688.

See Also (Topic, Algorithm, Media)
- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Acute Kidney Injury, Pediatric
- Acute Tubular Necrosis
- Anuria and Oliguria, Adult
- Chronic Kidney Disease, Pediatric
- Posterior Urethral Valves
- Ureteropelvic Junction Obstruction
- Urinary Retention, Pediatric

CODES

ICD9
- 276.52 Hypovolemia
- 599.60 Urinary obstruction, unspecified
- 788.5 Oliguria and anuria

ICD10
- E86.1 Hypovolemia
- N13.9 Obstructive and reflux uropathy, unspecified
- R34 Anuria and oliguria

CLINICAL/SURGICAL PEARLS
- Prerenal oliguria is typically reversible with complete return of renal function within 24–72 hr.
- Avoid nephrotoxic agents in patients with underlying intrinsic renal failure.

AUTONOMIC DYSREFLEXIA

Michael J. Amirian, MD
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BASICS

DESCRIPTION

- Autonomic dysreflexia (AD) occurs in patients with spinal cord lesions at and above the 6th thoracic level (T6)
- Potentially life-threatening condition in response to noxious stimuli
  - Genitourinary cause is the most common trigger for AD
  - Bladder distention, instrumentation of the urinary tract, and UTI are the most common causes to trigger AD
- Rapid, extreme BP elevation, bradycardia, headache, diaphoresis, sweating, nausea, and piloerection

EPIDEMIOLOGY

Incidence

Unknown

Prevalence

- ~85% of quadriplegic and high paraplegic individuals prone to AD in response to noxious stimuli
- More common in men than women
  - Due to increased bladder outlet resistance

RISK FACTORS

- Male
- High spinal cord injury (SCI)

Genetics

None

PATHOPHYSIOLOGY

- Activation of sympathetic neurons in lateral horn of spinal cord causing unopposed reflex sympathetic activity
  - Stimuli (bladder or bowel distention and pain) cause activation
- Vasoconstriction and subsequent hypertension (HTN)
  - In response, vagal nerve triggers bradycardia
- Vagal nerve is able to vasodilate above injury (flushing in face), but vessels below injury remain vasoconstricted
- Other symptoms of sympathetic activation
  - Diaphoresis and piloerection

ASSOCIATED CONDITIONS

SCI

GENERAL PREVENTION
- Avoid rapid or prolonged bladder distention
- Maintain regular schedule of bowel emptying
- Monitor for pressure sores

DIAGNOSIS
HISTORY
- SCI or transverse myelitis at T6 or above
- Screen for urologic causes
  - Bladder distention
  - Recent instrumentation
  - Indwelling urethral or suprapubic tube
  - Urinary tract infection
  - Renal, ureteral, or bladder calculi
  - Epididymitis or orchitis
  - Ejaculation
  - Urodynamic testing
- Nonurologic causes
  - Bowel distention
  - Pressure sores
  - Tight clothing
  - Ingrown toenails
  - Sexual intercourse
  - Pregnancy and labor
- Symptoms may include blurred vision, nasal congestion, anxiety

PHYSICAL EXAM
- BP often severely elevated and often accompanied by bradycardia
  - Consider that the resting BP is decreased after SCI (ie, 90/60)
  - A normal BP of 120/80 may actually represent HTN in this patient population
  - A BP 20–40 mmHg above the patients baseline may be a sign of AD
- Flushing and profuse sweating above level of injury
- Piloerection (“goose bumps” with cold or clammy skin below the level of the SCI)
- Evaluate for noxious stimuli below level of SCI
  - Skin
    - Infection, pressure sores
    - Ingrown nails
    - Burns
    - Tight-fitting clothing

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis and urine culture
  - Evaluate for infection
  - UTI can be a trigger for AD

Imaging
- CT of abdomen and pelvis
  - Evaluate for urolithiasis if cause not apparent

Diagnostic Procedures/Surgery
- Urodynamic tests to:
  - Evaluate bladder compliance
  - Rule out persistently elevated bladder pressures

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Brain stem tumors
- Paroxysmal HTN
- Pheochromocytoma
- Preeclampsia

TREATMENT

GENERAL MEASURES
- Removal of triggering stimulus is the 1st step
  - Minimize noxious stimuli below level of injury
  - Bladder drainage or bowel decompression
  - If present, consider gentle Foley catheter irrigation with no more than 10–20 mL saline to make sure that the catheter is patent
- Monitor BP closely during acute episodes
  - BP >150 mmHg requires urgent management to avoid severe complications
- Sitting the patient upright might reduce BP

ALERT
Left untreated consequences of autonomic dysreflexia can cause seizures, intracranial bleeds, hypertensive encephalopathy, and death.

MEDICATION
First Line
- Acute episodes managed with nitrates or arterial dilators under closely monitored conditions
  - Nitrates: Sub lingual nitroglycerine, apply 1”, 2% nitro paste
    - Nitrates should be avoided in patients who may be using PDE-5 inhibitors (sildenafil vardenafil, tadalafil) for erectile dysfunction
  - Nifedipine 10 mg PO immediate release form
    - “Bite and swallow” technique
  - Captopril 25 mg SL
  - Hydralazine or labet alol 10 mg IV
- Chronic treatment with α-blockers may improve some symptoms of AD (1)[B]
  - Doxazosin 2–8 mg PO QD
  - Terazosin 2–5 mg PO QD-BID

– Tamsulosin 0.4 mg PO QD
– Alfuzosin 10 mg PO QD

- Appropriate antibiotics if UTI suspected

Second Line

- Phenoxybenzamine 10 mg PO BID
- Botulinum toxin injection into the detrusor
  – For patients on intermittent catheterization to decrease bladder pressure
- Botulinum toxin injection into external sphincter
  – For patients who void reflexively to decrease voiding pressures

SURGERY/OTHER PROCEDURES

- Sphincterotomy or sphincter stent prosthesis
  – Allows reflex voiding with low-pressure bladder emptying into a condom catheter (2)[A].
- Bladder augmentation
  – Only in patients with ability to catheterize
- Sacral rhizotomy
  – For severe cases (3)[B]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Managed effectively will have little impact on patient

COMPLICATIONS

Intracerebral and subarachnoid hemorrhage

FOLLOW-UP

Patient Monitoring

- Clean intermittent catheterization
  – Frequent (at least 4 times daily)
- Regular bowel program
- Assess AD symptoms and BP at every appointment
- Teach SCI patients significance of AD
  – Symptoms should prompt patients to empty bladder and bowel

Patient Resources

Christopher & Dana Reeve Foundation Paralysis Resource Center. Autonomic Dysreflexia.http://www.paralysis.org/site/c.erJMJUOxFmH/b.1338071/k.5E45/Autonomic_D

REFERENCES

1. Vaidyanathan S, Soni BM, Sett P, et al. Pathophysiology of autonomic dysreflexia: Long-term treatment with terazosin in adult and pediatric spinal cord injury patients manifesting recurrent dysreflexic episodes. *Spinal Cord.* 1998;36:761–770.
2. Chancellor M, Gajewski J, Ackmain CF, et al. Long-term follow-up of the North American Multicenter UroLume Trial for the treatment of external detrusor-sphincter dyssynergia. *J Urol.* 1999;161:1545–1550.
3. Hohenfellner M, Pannek J, Bötel U, et al. Sacral bladder denervation for treatment of detrusor hyperreflexia and autonomic dysreflexia. *Urology.* 2001;58:28–32.

ADDITIONAL READING

Consortium for Spinal Cord Medicine. *Acute management of autonomic dysreflexia: Individuals with spinal cord injury presenting to health-care facilities*, 2nd ed. Available at http://www.pva.org/site/c.ajIRK9NJLcJ2E/b.6305831/k.986B/Guidelines_and_Publications.ht Accessed April 8, 2013.

See Also (Topic, Algorithm, Media)

- Autonomic Dysreflexia Image
- Detrusor-Sphincter Dyssynergia
- Spinal Cord Injury

CODES

ICD9

- 337.3 Autonomic dysreflexia
- 596.89 Other specified disorders of bladder
- 599.0 Urinary tract infection, site not specified

ICD10

- G90.4 Autonomic dysreflexia
- N32.89 Other specified disorders of bladder
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- Most common triggers are from the genitourinary system such as bladder distention or instrumentation.
- AD occurs at and above level of T6.
- Chronic treatment with α-blockers may improve some symptoms of AD.
- Sphincterotomy or sphincter stent prosthesis allows reflex voiding with low-pressure bladder emptying into a condom catheter.

BACTERIURIA AND PYURIA

Mary K. Powers, MD
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BASICS

DESCRIPTION

- Urinary tract infection (UTI) is an inflammatory response of urothelium to bacterial invasion that is usually associated with bacteria and pyuria.
- Bacteriuria: Presence of bacteria in the urine, which is normally bacteria free
- Bacteriuria = valid indicator of bacterial infection or colonization
  - Can be either symptomatic or asymptomatic
  - Significant bacteriuria: Quantitative count $>1 \times 10^5$ colony forming units (CFL/mL) in 2 consecutive specimens
  - Majority of individuals with significant bacteria have significant pyuria
  - Usually 1 organism
  - >1 organism: Either contamination or polymicrobial infection
- Pyuria: Presence of WBC in the urine:
  - Generally implies an inflammatory response or infection
  - Significant pyuria: >10 WBCs/HPF centrifuged
  - Close association between pyuria and bacteriuria; 96% of patients who are symptomatic and bacteriuric have >10 WBCs/HPF
- Sterile pyuria: Presence of WBCs in the urine in the absence of bacteriuria:
  - Contamination: Vaginal or prepuce secretions
  - Infections: Treated UTI, mycobacterial, TB, chlamydial, gonococcal, fungal (GU or systemic), viral, haemophilus, bilharzia
  - Other infections: Appendicitis, diverticulitis, prostatitis
  - Noninfectious: Nephritis, stones, foreign bodies, transplant rejection, trauma, malignancy, chemotherapy, nephrotoxic substances, drug-induced interstitial nephritis
- Cystitis: Clinical syndrome of dysuria, frequency, urgency occasionally with suprapubic pain
  - Usually indicative of bacterial cystitis but can be associated with infections of the urethra or vagina or noninfections process such as interstitial cystitis, bladder carcinoma, or calculi

EPIDEMIOLOGY

Incidence (1)

- 0.3–0.5 episodes of bacteriuria per person per year among asymptomatic females aged 18–40
- Newborns:
  - Males: 1.5–3.6%; females: 0.4–1.0%
- 1–5 yr:
  - Males: 0.0–0.4%; females: 0.7–2.7%
- School-age:

  – Males: 0.04–0.2%; females 0.7–2.3%
- Adult (middle-age):
  – Males <1%; females 4–6%
- Older adults:
  – Males 11–13%; females 6–33%
- Almost 100% prevalence of bacteriuria in individuals with long-term, indwelling catheters

Prevalence

- Pregnancy: 2–7% of all pregnant females (2)
- Elderly: 20% of females, 10% of males
  – 24% of nursing home residents vs. 12% of healthy domiciliary elderly (3)

RISK FACTORS

Age, diabetes mellitus, sexual intercourse, use of diaphragm or spermatocide, delayed postcoital micturition, history of recent infection, immunosuppression, long-term indwelling catheters, pregnancy, neurologic disorders, foreign bodies, stones, obstructive uropathy, vesicoureteral reflux.

Genetics

Certain populations may be more susceptible to bacteriuria and recurrent UTIs due to distinct molecular defects causing impaired host responses. Certain receptor sites on epithelial cells may predispose some women to UTIs.

PATHOPHYSIOLOGY

- Urinary tract is normally sterile.
- Bacteriuria usually ascends up the urinary tract from colonizing flora of the gut, vagina, or distal urethra.
- Bacteriuria can also invade the urinary tract hematogenously or through direct transfer after instrumentation.
- Bacteria colonize the urinary tract and then multiply, causing inflammation with pyuria.
- Bacterial factors:
  – Certain bacteria are more efficient at adhering to mucosal cells than others due to fimbria.
  – Virulence factors: Hemolysis, adhesions, colicin, metabolic properties, etc.
- Host factors:
  – Cystitis prone: Certain patients are more prone to bacteriuria (transitional cell bacterial receptor sites).
  – Menstrual cycle: Bacteriuria may be influenced by hormones.
  – Postmenopausal: Increasing incidence of bacteriuria
  – Vaginal pH: Normally acidic pH; colonization with uropathogens may occur as vaginal pH rises
  – Competitive organisms: Normal vaginal flora discourages uropathogenic colonization
  – Buccal and vaginal cells: More receptive to uropathogens' adherence in cystitis-prone patients
  – Local production of IgA, IgG may play defense role.
  – Production of mucous protective layer as a local bladder defense
  – Blood group antigen (secretors) saturate or block bacterial adherence.

ASSOCIATED CONDITIONS
Diabetes mellitus, pregnancy, immunosuppression, structural urinary tract abnormalities, indwelling catheters

GENERAL PREVENTION
- Screening and treatment of asymptomatic bacteriuria in at-risk populations such as pregnant patients or prior to urologic intervention can prevent subsequent morbidity of UTIs.
- Screening of asymptomatic spinal cord injury patients or those with indwelling Foley catheter is not recommended.
- Bacteriuria and pyuria from an incompletely treated UTI may be avoided with the appropriate use of antibiotic class with sufficient duration; patient compliance should be encouraged.

DIAGNOSIS
HISTORY
- Dysuria, frequency, urgency, malaise, rarely low-grade fever, malodorous urine
- Occasionally hematuria (gross): Especially in the female patient; uncommon in children and men
- Fever and flank pain with upper tract origin: Pyelonephritis
- Asymptomatic or atypical symptoms: Young and old patients
- Young patients: Abdominal discomfort, failure to thrive, fever, vomiting, jaundice
- Older patients: May be asymptomatic or have incontinence, fevers, frequency, and urgency
- Varied symptoms with sterile pyuria associated with differeing conditions
- History of childhood fevers: May imply UTIs and associated congenital abnormalities
- Problems with toilet training, urgency, incontinence
- UTI family history: Mothers, daughters, sisters
- History of a risk factor for bacteriuria

PHYSICAL EXAM
- Suprapubic tenderness: Cystitis
- Flank tenderness: Pyelonephritis
- Fever: Usually with upper tract infection
- Children may have abdominal discomfort, tenderness, or distention.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Indications for screening:
  - Symptomatic patients
  - Pregnant women
  - Prior to genitourinary procedures
- Urine dipstick: Best for screening:
  - Leukocyte esterase test:
    - Detects enzyme release by WBCs
    - Sensitivity 90%, specificity 95% for UTI
  - Conversion of nitrate to nitrite (Griess test): 70–80% sensitivity for UTI
  - Catalase test: Cannot differentiate infection from inflammation

- Microscopy:
  - Rapid in-office test: 80% accurate; usually fresh unspun
  - Centrifugation: Increases finding 10-fold
  - Difficult to see bacteria if $<1 \times 10^5$ CFU/mL
  - Vaginal organisms may be misread as uropathogens: Lactobacilli and Corynebacterium
- Gram stain: Increases identification of bacteria with sensitivity and specificity of 96.2% and 93.0%, respectively
- Urine culture:
  - Clean-catch midstream urine: Commonly used
  - Catheterized urine: May be necessary to assure diagnosis or in special situations (ie, children, patients unable to void, the debilitated, the obese)
  - Segmented urine specimen, initial 10 mL, midstream, post exam: For localization of bacteria or WBCs
  - Quantitative counts in UTI are usually $>1 \times 10^5$ CFU/mL with a uropathogen
    - Range 1×10^2 to 1×10^6
    - $<10^5$ per milliliter in 47% of patients
    - $<10^4$ per milliliter in 30% of patients
    - $>10^2$ per milliliter: Uropathogen; suspect UTI
- Conditions causing variation: Hydration, bacterial growth rate, urinary pH, pyelonephritis, catheterized specimen:
  - Multiple organisms usually indicate contamination or polymicrobial infection
- Uncomplicated infections: *Escherichia coli*, other Enterobacteriaceae, *Staphylococcus saprophyticus*, enterococci
- Complicated infections: *E. coli*, other Enterobacteriaceae, *Pseudomonas*, *S. aureus*, coagulase negative staph, enterococci
- Contaminants: Lactobacilli, streptococci, diphtheroids, *Gardnerella, Mycoplasma*, coagulation-negative staph

Imaging

- Bacteriuria:
  - Childhood: US, VCUG, radionuclide cystogram, IV pyelogram
  - Adult: Only indicated if suspicious of pathology or childhood history, obstruction, stone disease, hematuria, febrile infections, failure to respond to therapy, recurrent UTIs
  - Imaging in routine UTIs involving normal adult females: Very low yield of pathology
- Pyuria:
  - Associated with infection and bacteriuria: Same indications
  - Sterile pyuria evaluation for other causes
  - Isotopic function studies and cystogram
  - CT: Localization of nidus or abnormality responsible for bacteriuria/pyuria (ie, abscess)

Diagnostic Procedures/Surgery

Localization of bacteria: Segmented urine, ureteral catheterization, immunologic antibody studies

DIFFERENTIAL DIAGNOSIS

- Cystitis: Pyuria, positive culture, abrupt onset
- Urethritis: Pyuria, negative urine culture, gradual onset
- Vaginitis: No pyuria, vaginal discharge, pruritus
- Pyelonephritis
- Noninfectious causes
  - Interstitial cystitis
  - Nonuropathogenic cause, as in sterile pyuria
- Contamination with vaginal/skin flora

TREATMENT

GENERAL MEASURES

- Obtain urine culture:
  - Indwelling catheters should be used as infrequently as possible
  - In patients with indwelling catheter, urine specimen for culture should be obtained at the time catheter is changed under sterile conditions from newly placed catheter

MEDICATION

- Asymptomatic bacteriuria is treated as a UTI in childhood, prior to urologic surgery, and in pregnancy.
  - Persistent or recurrent bacteriuria may need treatment for more prolonged periods followed by chronic low-dose medication.
    - TMP-SMX (Trimethoprim-sulfamethoxazole) 40/200 mg daily
    - Nitrofurantoin 50–100 mg daily
    - Cephalexin 250 mg daily
  - Postmenopausal: Treated only if symptomatic or associated with complicating factors:
  - Diabetes, obstruction, immunosuppression (14–21 days of therapy)
    - Norfloxacin 400 mg PO BID
    - Ciprofloxacin 500 mg PO BID
    - Gentamicin 1–1.7 mg/kg IV Q8h
    - Ceftriaxone 1–2 mg IV/Q 24 h
  - Catheter-associated bacteriuria, if asymptomatic, should not be treated (may be due to colonization).
- Bacteriuria in pregnancy should be treated, as untreated bacteriuria is linked with prematurity, IUGR, low birth weight, and neonatal death.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Cranberry juice may decrease frequency of bacteriuria and pyuria in selected populations.

ONGOING CARE

PROGNOSIS

Variable severity ranging from asymptomatic bacteriuria to severe UTI with urosepsis and secondary organ failure

COMPLICATIONS

20–40% of untreated bacteriuria in pregnancy leads to pyelonephritis

FOLLOW-UP

Patient Monitoring

- Repeat exam: 2 wk posttreatment, not necessary in young women who are asymptomatic after therapy
  - Microscopic urinalysis and culture
- Periodic office visits to verify sterile urine
- 2008 USPSTF guidelines:
  - In pregnant women, high certainty exists that net benefit of screening for asymptomatic bacteriuria is substantial (1)[A].
  - In men and nonpregnant women, there is moderate certainty that the harms of screening for asymptomatic bacteriuria outweigh the benefits. (1)[D]
  - Adults with diabetes were included in this recommendation, for the general adult population, the USPSTF did not consider evidence for screening specific patient groups at high risk for severe UTIs, including transplant recipients, patients with sickle cell disease, and those with recurrent UTIs.

Patient Resources

http://patienteducationcenter.org/articles/asymptomatic-bacteriuria/

REFERENCES

1. Screening for asymptomatic bacteriuria in adults: US Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2008;149:43–47.
2. Genao L, Buhr GT. Urinary tract infections in older adults residing in long-term care facilities. *Ann Longterm Care.* 2012;20(4):33–38.
3. Imade PE, et al. Asymptomatic bacteriuria among pregnant women. *N Am J Med Sci.* 2010;2(6):263–266.

ADDITIONAL READING

- D'Hondt F, Everaert K. Urinary tract infections in patients with spinal cord injuries. *Curr Infect Dis Rep.* 2011;13(6):544.
- Siddiq DM, Darouiche RO. New strategies to prevent catheter-associated urinary tract infections. *Nat Rev Urol.* 2012;9(6):305.

See Also (Topic, Algorithm, Media)

- Bacteruria and Pyuria Image
- Cystitis, General Considerations
- Pyuria Algorithm
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Catheter-related

• Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

• 590.80 Pyelonephritis, unspecified
• 595.9 Cystitis, unspecified
• 599.0 Urinary tract infection, site not specified

ICD10

• N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
• N30.90 Cystitis, unspecified without hematuria
• N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

Screening of asymptomatic spinal cord injury patients or those with indwelling Foley catheter is not recommended.

BALANITIS AND BALANOPOSTHITIS

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BASICS

DESCRIPTION

- Balanitis: Inflammation of the glans penis.
- Balanoposthitis: Inflammation of the foreskin and glans penis (affects uncircumcised men).

EPIDEMIOLOGY

Incidence

- Can occur at any age.
- No incidence studies of balanoposthitis have been reported in US.
  - 1.5% of uncircumcised boys ages 0–15 were affected in a Japanese cohort.

Prevalence

- Common, the exact prevalence is unknown.
  - Balanitis affects 11% of adult men and 3% of boys seen in urology clinics.

RISK FACTORS (1)

- Presence of a foreskin (uncircumcised)
- Tight foreskin (phimosis)
- Poor genital hygiene
- Intertrigo (see below)
- Sexual contact (with or without infection)
- Poorly controlled diabetes mellitus
- Immunocompromised host
- Coexisting penile cancer

Genetics

N/A

PATHOPHYSIOLOGY (2)

- The pathophysiology is usually different in young boys compared to adult men:
  - Boys: From bacterial invasion of tissue
  - Men: Combination of poor genital hygiene, intertrigo, irritant dermatitis, maceration injury, and bacterial, or candidal overgrowth
  - Candida is the most common infectious cause
- Intertrigo refers to a condition in which damp, moist body areas are predisposed to inflammation:
  - Involves genitals, inner thighs, underbelly
  - Risk factors: Grossly overweight, diabetes, bed rest, diaper use, poor personal hygiene
  - Skin dampness predisposes to secondary opportunistic bacterial or fungal overgrowth
- Balanitis xerotica obliterans (BXO) is a specific form of balanitis:
  - Chronic, progressive, fibrotic disease (a form of lichen sclerosis isolated to the penis)

  - Elastin is replaced by collagen
  - The skin around the meatus becomes white, featureless, contracted, causing meatal stricture
  - BXO may spread to the foreskin and coronal sulcus. In extreme cases, the entire end of the penis is replaced by fibrotic tissue, becomes thickened and nonretractile, causing sexual and voiding issues (eg, weak stream, obstruction)

ASSOCIATED CONDITIONS
Diabetes mellitus

GENERAL PREVENTION
- Maintain good genital hygiene
- Retraction of foreskin to clean the glans
- Keep the glans and foreskin dry
- Circumcision
- Safe sexual contact
- Manage risk factors (eg, glycemic control)

DIAGNOSIS

HISTORY
- Symptoms may include: Pain, discharge, irritation, voiding symptom (dysuria, weak stream)
- Prior episodes and treatment
- Uncircumcised
- Foreskin retractability
- Genital hygiene habits
- Sexual contacts, sexually transmitted diseases
- Other systemic risk factors (eg, diabetes)

PHYSICAL EXAM
- Inspection (ulcers, mass, genital pus, edema)
- Palpation (tenderness, induration, mass)
- Inguinal lymph nodes should be nonpalpable

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Swab of glans/foreskin for viral, bacterial, and fungal culture

Imaging
N/A

Diagnostic Procedures/Surgery
- Potassium hydroxide and Tzanck preparation for men
  - Potassium hydroxide smear evaluates for fungus
  - Tzanck preparation for herpes virus

Pathologic Findings
- Biopsy is indicated for:
  - Balanitis that persists and in which the cause remains unclear warrants biopsy to rule out

coexisting neoplasm or premalignant lesions
– For definitive diagnosis of BXO

DIFFERENTIAL DIAGNOSIS
- Fixed drug eruption (allergy)
- Contact dermatitis
- Squamous cell carcinoma of the penis
- Carcinoma in situ of the penis
- Zoon (plasma cell) balanitis
- Psoriasis
- Reiter syndrome (Reactive arthritis/reactive arthritis triad) (with circinate balanitis)
- Human papilloma virus

TREATMENT

GENERAL MEASURES
- Meticulous genital hygiene
- Keep the glans and foreskin clean and dry
- Expose the glans to air as often as possible
- Avoid excessive dampness in the genitals
- Avoid soaps while inflammation is present
- Cleaning with soap and water routinely
- Manage risk factors (eg, glycemic control)

MEDICATION
Treatment depends on the underlying cause (infectious vs. inflammatory) and organisms

First Line
- Candidal infection: The most common cause of infectious balanitis
  – Clotrimazole cream 1%
  – Miconazole cream 2%
  – Apply BID until symptoms resolve
  – Oral fluconazole if symptoms are severe
  – Nystatin cream if allergic to imidazole
  – Imidazole with hydrocortisone if inflammation
- Anaerobic infection:
  – Metronidazole 400 BID for 1 wk
  – Optimal dosage schedule is unknown
  – Alternatively, amoxicillin/clavulanic acid PO or clindamycin topically
- Aerobic infection:
  – Group A streptococci, *Staphylococcus aureus*, *Gardnerella vaginalis* are all reported cases of balanitis.
  – Treatment based on sensitivity of the culture (topical antibiotics, occasionally oral antibiotics)
- BXO:
  – Topical steroids (clobetasol propionate or betamethasone valerate) offers limited efficacy

- Zoon (plasma cell) balanitis:
  – Topical steroids with or without antibacterial cream
- Circinate balanitis (Reiter syndrome):
  – Hydrocortisone cream 1% apply BID
  – Treatment of associated infection
- Irritant, allergic balanitis:
  – Avoid exposure to irritants especially soaps
  – Emollients aqueous cream: Apply PRN and used as a soap substitute while inflammation is present
  – Hydrocortisone 1% apply QD or BID until symptoms resolve

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Circumcision is reserved for recurrent balanitis, balanoposthitis, or phimosis that have failed conservative treatments.
- Occasionally dorsal slit may be performed.
- For BXO that does not respond to steroid:
  – Periodical self-dilation with tapered dilators
  – Dilation by urologists
  – Formal surgical reconstructive repair

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Can be recurrent or persistent
- 10% recurrence rate
- Some patients may require circumcision to prevent recurrence and ensure resolution.

COMPLICATIONS

- Abscess formation
- Penile cellulitis
- Progression to Fournier gangrene
- Scarring and subsequent phimosis

FOLLOW-UP

Patient Monitoring

- After an acute episode and treatment is implemented, patients should be seen again to

ensure resolution of symptoms and infection.
– Progression to cellulitis or gangrene may occur in diabetic patients with genital infection.
• Follow closely with genital dysplasia among those men with condyloma with a history of balanoposthitis than those with no such history.

Patient Resources
N/A

REFERENCES
1. Vohra S, Badlani G. Balanitis and balanoposthitis. *Urol Clin North Am.* 1992;19(1):143–147.
2. Edwards S. Balanitis and balanoposthitis: A review. *Genitourin Med.* 1996;72(3):155–159.

ADDITIONAL READING
Wikström A, Hedblad MA, Syrjänen S. Human papillomavirus-associated balanoposthitis–a marker for penile intraepithelial neoplasia? *Int J STD AIDS*. 2013;24(12):938–943.

See Also (Topic, Algorithm, Media)
• Balanitis and balanoposthitis Image
• Balanitis Xerotica Obliterans
• Balanitis, Zoon (Plasma Cell Balanitis)
• Lichen Sclerosis Et Atrophicus
• Penis, Lesion

CODES

ICD9
• 605 Redundant prepuce and phimosis
• 607.1 Balanoposthitis
• 607.81 Balanitis xerotica obliterans

ICD10
• N47.1 Phimosis
• N47.6 Balanoposthitis
• N48.1 Balanitis

CLINICAL/SURGICAL PEARLS
• Maintaining good genital hygiene is a key preventive strategy (keep the foreskin and glans clean and dry).
• Underlying risk factors should also be managed (eg, glycemic control in diabetes).
• Treatment depends on the underlying cause (infectious vs. inflammatory) and organisms.
• Circumcision is reserved for recurrent balanitis, balanoposthitis, or phimosis that have failed conservative treatments.
• Balanitis that persists and if the cause remains unclear warrants biopsy to rule out coexisting neoplasm or premalignant lesions.

BCG SEPSIS/BCG-OSIS

John B. Eifler, MD
Michael S. Cookson, MD

BASICS

DESCRIPTION

- BCG sepsis: Potentially life-threatening event secondary to intravasation of intravesical BCG resulting in cardiovascular collapse and acute respiratory distress
  - Possible etiologies include hypersensitivity reaction and bacterial sepsis
- "BCG-osis" is a term used to refer to disseminated disease in patients treated with BCG
  - The lungs and liver are typically involved
  - Patients are usually hemodynamically stable

EPIDEMIOLOGY

Incidence

- >95% of patients treated with BCG have no significant morbidity (1).
- 1 in 15,000 patients treated with intravesical BCG will develop BCG sepsis (2).
- 10 reported deaths due to BCG sepsis (3).

Prevalence

N/A

RISK FACTORS

- Inadequate delay after transurethral instrumentation (TURBT or bladder biopsy)
- Traumatic catheterization or gross hematuria at time of intravesical instillation

Genetics

N/A

PATHOPHYSIOLOGY

- BCG is live attenuated *Mycobacterium bovis*
- Intravasation of BCG through damaged urothelium with subsequent systemic response
- Symptoms may be related to mycobacterial infection and/or hypersensitivity reaction

ASSOCIATED CONDITIONS

- Recent transurethral instrumentation
- Traumatic catheterization
- Concomitant UTI
- Age >70

GENERAL PREVENTION

- The following will minimize the risk of BCG sepsis; however, no strategy has been shown to be effective at eliminating the risk (2,4)
  - Defer installation of BCG at least 2 wk after instrumentation
  - Abort instillation if hematuria or traumatic Foley catheter placement
  - Do not treat with active UTI

– Avoid BCG in immunocompromised host
– BCG cystitis (see below): Delay future instillations until complete resolution of symptoms
– BCG sepsis: Avoid any future BCG instillation

DIAGNOSIS

HISTORY

- BCG cystitis: Dysuria, frequency 2–4 hr after installation +/– low-grade fever, malaise, hematuria
  – Typically resolves within 48 hr
- Regional infection is common though often asymptomatic (eg, 75% develop granulomatous prostatitis) and distant infection (hepatitis, osteomyelitis, pneumonitis) may occur
- Symptoms often occur within 2 hr of instillation but may occur years after therapy
- Symptoms of systemic infection: Intermittent fever >39°C (102.2°F) with drenching night sweats lasting >48 hr
- BCG sepsis: Fever, rigors, progressing to vascular collapse and respiratory distress
  – Often occurs within hours of instillation

PHYSICAL EXAM

- BCG sepsis
  – High fevers (>38.5°C/101.3°F) within 2 hr of treatment, resembling gram-negative sepsis
  – Hypotension/shock physiology
- BCG cystitis
  – Suprapubic tenderness to palpation
  – Hematuria
  – Low-grade fevers

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Mild/moderate symptoms
  – Urine culture
- Severe symptoms (Sepsis, severe cystitis symptoms >48 hr)
  – Urine, blood cultures
  – Liver function tests to assess for hepatitis
  – CXR to assess for pneumonitis
  – Acid-fast testing of urine
  – Consider PCR testing for mycobacterial DNA if disseminated BCG suspected
- Coagulation studies: PT/PTT/fibrinogen if DIC suspected

Imaging

See “Lab”

Diagnostic Procedures/Surgery

See “Lab”

Pathologic Findings

- Noncaseating granulomas
  – May be found in lung, liver, bone, prostate, kidney, epididymis

DIFFERENTIAL DIAGNOSIS

- Post-BCG bacterial cystitis
- BCG cystitis (cytokine release without intravasation of BCG)
- Gram-negative sepsis

TREATMENT

GENERAL MEASURES

- Consultation with infectious disease specialist is recommended for septic patients (2,4)
- If antitubercular therapy required, intravesical BCG should be discontinued (2)

MEDICATION

First Line

- Mild/moderate symptoms including low-grade fevers < 48 hr (BCG cystitis) (2,4,5)
  - Analgesics
  - NSAIDs
  - +/– Fluoroquinolone
    - Such as levofloxacin 500 mg/d
    - Helpful for bacterial cystitis and has mild antitubercular activity
- Antitubercular medications should be initiated for signs of sepsis or severe cystitis symptoms > 48 hr (2 – 5)
  - Typically isoniazid 300 mg/d and rifampin 600 mg/d for 3–6 mo
  - For solid organ involvement, ethambutol 15 mg/kg/d added
  - BCG resistant to cycloserine and pyrazinamide
  - Prednisone 40 mg/d recommended for septic shock or if hypersensitivity reaction suspected

Second Line

N/A

SURGERY/OTHER PROCEDURES

Not indicated; supportive care only

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Good if treatment initiated in timely manner

COMPLICATIONS

Solid organ involvement

FOLLOW-UP

Patient Monitoring

ICU admission with invasive monitoring for BCG sepsis

Patient Resources

N/A

REFERENCES

1. Lamm DL. Efficacy and safety of bacille calmette-guerin immunotherapy in superficial bladder cancer. *Clin Infect Dis.* 2000;31(suppl 3):S86.
2. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol.* 1992;147:596–600.
3. Rawls WH, Lamm DL, Lowe BA, et al. Fatal sepsis following intravesical bacillus Calmette-Guérin administration for bladder cancer. *J Urol.* 1990;144:1328–1330.
4. Jones JS, Larchian WA. Non-muscle-invasive bladder cancer (Ta, T1, and CIS). In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology*. Vol. 3. Philadelphia, PA: Elsevier; 2011:2343–2346.
5. Durek C, Rüsch-Gerdes S, Jocham D, et al. Sensitivity of BCG to modern antibiotics. *Eur Urol.* 2000;37(suppl 1):21–25.

ADDITIONAL READING

- Gonzalez OY, Musher DM, Brar I, et al. Spectrum of bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. *Clin Infect Dis*. 2003;36:140.
- Mehta AR, Mehta PR, Mehta RL. A cough conundrum in a patient with a previous history of BCG immunotherapy for bladder cancer. *BMJ Case Rep*. 2012;2012.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General
- Bladder Cancer, Nonmuscle-Invasive Bladder Cancer (Ta, T1).
- Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC)
- Urosepsis

CODES

ICD9

- 038.8 Other specified septicemias
- 995.91 Sepsis
- 999.39 Infection following other infusion, injection, transfusion, or vaccination

ICD10

- A41.89 Other specified sepsis
- T80.29XA Infct fol oth infusion, transfuse and theraputc inject, init

CLINICAL/SURGICAL PEARLS

- Patients undergoing intravesical BCG therapy who have traumatic catheterization or gross hematuria should delay therapy until symptoms resolve.
- Patients with high fever (>38.5°C/101.3°F) or severe cystitis symptoms lasting >48 hr should be hospitalized and undergo additional testing.

BLADDER AREFLEXIA (DETRUSOR AREFLEXIA)

H. Henry Lai, MD, FACS
Gerald L. Andriole, MD, FACS

BASICS

DESCRIPTION

- Bladder areflexia (detrusor areflexia) is the inability of the bladder to contract to empty.
- Requires urodynamics study for diagnosis.
- Presentation may include urinary retention, incomplete emptying, and overflow incontinence.

EPIDEMIOLOGY

Incidence

No incidence study has been reported. The risk of urinary retention may increase with aging.

Prevalence

- No prevalence study has been reported in US.
  - 40% of men and 13% of women over the age of 65 have detrusor underactivity during urodynamics in a Korean cohort (1,179 patients).
  - 48% of men and 12% of women over the age of 70 have underactivity in a study from Israel.

RISK FACTORS

- Diabetes mellitus
- Longstanding bladder outlet obstruction
- Neurologic diseases
- Recent radical pelvic surgery

Genetics

- Genetic diseases predisposing to bladder dysfunction include:
  - Muscular dystrophy
  - Neurofibromatosis

PATHOPHYSIOLOGY

- May result from primary detrusor muscle failure (myogenic causes) and/or neurologic causes (eg, from lower motor neuron lesions, injury to sacral spinal cord, multiple sclerosis).
- Patients often attempt to void by valsalva.
- Success of emptying depends on resistance of smooth and striated sphincter mechanisms.
- Continence depends on sphincter competence.

ASSOCIATED CONDITIONS

- Cauda equina syndrome
- Diabetes mellitus
- Fowler syndrome (“nonneurogenic, neurogenic bladder”)
- Intervertebral disc diseases

- Longstanding bladder outlet obstruction with detrusor decompensation (myogenic failure)
- Lumbosacral spinal surgery
- Lyme disease
- Multiple sclerosis
- Myelodysplasia, spina bifida
- Radical pelvic surgery
- Recent spinal or brain trauma ("spinal shock")
- Sacral spinal cord injury

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Symptoms may include: Incomplete bladder emptying, frequency, urgency, incontinence (urge or stress), weak urine stream, straining to empty.
- History of any risk factors listed in the section entitled "Associated Conditions."
- Medication: Recent use of anticholinergic medications or over-the-counter cold medicine.
- Recurrent bladder infections.

PHYSICAL EXAM

- Palpable suprapubic mass (distended bladder)
- Stress incontinence on pelvic exam (overflow)
- High post-void residual volumes
- Abnormal neurologic exam:
  - Perianal and perineal sensation
  - Anal sphincter tone
  - Bulbocavernous reflex
- Enlarged prostate on rectal exam
- Sacral abnormalities:
  - Sacral dimple
  - Tuft of hair
  - Sacral agenesis
  - Spinal surgical scar

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Blood: Creatinine to assess renal function.
- Urine: Urinalysis to assess urinary infection.

Imaging

Renal and bladder ultrasound (to assess renal stones, bladder stones, hydronephrosis).

Diagnostic Procedures/Surgery

- Bladder scanner
  - High post-void residuals may be identified to support the diagnosis
- Multi-channel urodynamics study:

- No or minimal detrusor contraction (P_{det} line)
- Urodynamics criteria:
  - Bladder contractility index (BCI) <100
  - Maximal flow rate (Q_{max}) <12 mL/s
  - Detrusor pressure P_{det} at Q_{max} <10 cm water
- To distinguish detrusor areflexia from bladder outlet obstruction (benign prostatic hyperplasia).
- To assess detrusor compliance and storage pressure. Detrusor leak point pressure >40 cm of water poses risk to the upper urinary tract.
- To identify the etiology of incontinence.
- To guide rational, safe management strategy.

Pathologic Findings

Bladder wall thickening and fibrosis may be found in decompensated bladder from obstruction.

DIFFERENTIAL DIAGNOSIS

- Bladder outlet obstruction causing retention:
  - Benign prostatic hyperplasia
  - Urethral stricture disease
- Functional outlet obstruction (eg, detrusor external sphincter dyssynergia)
- Potential reversible causes of areflexia:
  - Recent spinal shock or stroke
  - Recent radical pelvic surgery
  - Medication use (eg, anticholinergics)
  - Fowler syndrome

TREATMENT

GENERAL MEASURES

- Intermittent catheterization is preferred over chronic indwelling catheters (Foley or suprapubic catheter) to reduce the risks of infection and stones.
- Sacral neuromodulation (InterStim) may be considered for nonobstructive urinary retention (eg, good results in Fowler syndrome).

MEDICATION

First Line

- Bethanechol was ineffective in reducing residual volumes in a randomized, placebo trial (1) [C].
  - Bethanechol may decrease the duration of transient urinary retention in patients who underwent radical hysterectomy or anorectal surgery in randomized, controlled trials (1) [C].
  - Typical dosage: 10–50 mg PO BID–TID.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Sacral neuromodulation (InterStim) in selected patients who do not have contraindications.
  - Effective in restoring voiding in patients with Fowler syndrome (1)[C].
  - May be selectively considered in patients with nonobstructive urinary retention (2)[C].
- Bladder augmentation may be considered in patients with poor detrusor compliance, and high detrusor leak point pressure and storage pressure.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most cases are irreversible, except the few circumstances described in "Differential Diagnosis"
- However with proper urologic management, secondary complications may be minimized.

COMPLICATIONS

- Bladder neoplasm from indwelling catheter
- Hydronephrosis and hydroureters
- Recurrent urinary tract infections
- Renal and bladder stones
- Renal insufficiency, failure, and dialysis
- Urethral erosion from chronic Foley catheter
- Urinary incontinence
- Urosepsis and death

FOLLOW-UP

Patient Monitoring

- Patients with poor detrusor compliance need periodic urodynamics studies, upper tract imaging, and creatinine lab work to minimize complications.
- Patients who refuse to catheterize should be monitored closely.
- Patients with chronic indwelling catheter should undergo cystoscopy periodically due to the increased risk of bladder neoplasm.

Patient Resources

N/A

REFERENCES

1. Kessler TM, Fowler CJ. Sacral neuromodulation for urinary retention. *Nat Clin Pract Urol.* 2008;5(12):657–666.
2. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral

neuromodulation therapy for urinary voiding dysfunction: Outcomes of a prospective, worldwide clinical study. *J Urol*. 2007;178(5):2029–2034.

ADDITIONAL READING

Cruz CD, Cruz F. Spinal cord injury and bladder dysfunction: New ideas about an old problem. *Scientific World J*. 2011;11:214–234.

See Also (Topic, Algorithm, Media)

- Bladder Areflexia (Detrusor Areflexia) Image
- Neurogenic Bladder, General Considerations
- Sacral Neuromodulation
- Spinal Cord Injury, Urologic Considerations
- Urodynamics, Indications, and Normal Values

CODES

ICD9

- 596.55 Detrusor sphincter dyssynergia
- 788.29 Other specified retention of urine
- 788.38 Overflow incontinence

ICD10

- R33.8 Other retention of urine
- N36.44 Muscular disorders of urethra
- N39.490 Overflow incontinence

CLINICAL/SURGICAL PEARLS

- Detrusor areflexia requires urodynamics for diagnosis.
- Urodynamics can distinguish detrusor areflexia from bladder outlet obstruction.
- Intermittent catheterization is preferred over chronic indwelling catheters.
- Sacral neuromodulation (InterStim) may be selectively considered in patients with nonobstructive urinary retention or Fowler syndrome.
- Patients with chronic indwelling catheter should undergo cystoscopy and urine cytology periodically due to the increased risk of bladder neoplasm.

BLADDER CALCULI (VESICAL CALCULI)

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BASICS

DESCRIPTION

- Bladder calculi (also called bladder stones) are calcified material that are present in the bladder.
- It can originate primarily in the bladder.
- It can be a secondary renal stone that formed in the kidney and passed into the bladder.
- Often associated with bladder outlet obstruction in the US.
- Historically the removal of bladder calculus was performed via an incision in the perineum with the patient in a supine position and the legs elevated (the origin of the term "lithotomy position").

EPIDEMIOLOGY

Incidence

- The incidence of bladder calculi in the Western world has significantly dropped as a result of improved diet, nutrition, and infection control
- Bladder calculi are endemic in Thailand, Burma, Indonesia, Middle east, and north Africa
- Mostly in middle age men
- In catheterized patients the incidence of developing bladder calculi is 25% in 5 yr
- The incidence in children has declined significantly however in the developing countries they are common in boys younger than 11 yr
- Vaginal prolapse and urethral surgery are common causes in women

Prevalence

- Bladder calculi constitute 10–15% of the stone burden in adult and 15–30% in children
- Data on the world wide incidence are not available

RISK FACTORS

- Urinary stasis
  - Bladder outlet obstruction
    - Benign prostatic hyperplasia
    - Urethral stricture
    - Bladder neck contracture
  - Neurogenic bladder
- Foreign body such as urethral catheter and ureteric stent that act as nidus for stone formation
- Urinary tract infection
- Urinary diversion and bladder substitution
  - Secondary to foreign body, infection, and systemic acidosis
  - Rarely patients may place foreign bodies in bladder that become calcified

Genetics
N/A

PATHOPHYSIOLOGY
- Bladder calculi are primarily formed in the bladder, rarely can be a secondary renal stone that has formed in the kidney and passed into the bladder
  - Foreign bodies, retained catheter balloon fragments
  - Patients on chronic intermittent catheterization may force pubic hair into the bladder that can become calcified over time
- Stone analysis frequently reveals uric acid stone in 50% of the cases
- Other constituents are ammonium urate, calcium oxalate, and calcium phosphate
- In infected urine, struvite stones are the most common
- In patients with spinal cord injuries (SCIs), bladder stones are often composed of struvite or calcium phosphate
- In endemic areas, low phosphate diet results in increased ammonium excretion in the urine
- Low intake of animal protein contributes to high urinary oxalate and low urinary citrate levels with increased risk of stone formation
- Solitary stone are present in 75% of cases

ASSOCIATED CONDITIONS
- Foreign bodies in the bladder
- Intermittent catheterization
- Low phosphate diet
- Low protein diet
- Urinary stasis (prostatic hypertrophy, stricture, congenital abnormalities [ureterocele], diverticulum, cystocele)
- Urinary tract infection

GENERAL PREVENTION
- Adequate hydration
- Treatment of bladder outlet obstruction
- Prevention of urinary tract infection
- Prevention of urololithiasis as appropriate
  - Allopurinol for uric acid stones
  - Reduce oxalate intake
  - Increase urinary citrate
  - Low sodium low diet

DIAGNOSIS
HISTORY
- Patients with SCI, neurogenic bladder may be at increased risk
- Bladder calculi may be asymptomatic and may be incidental finding on imaging (plain x-ray, renal ultrasound, CT, or flexible cystoscopy)
- Patients commonly presents with
  - Suprapubic or perineal pain
  - Irritative urinary symptoms

  - Intermittent urinary stream
  - Hematuria, gross, and microscopic
  - Recurrent urinary tract infection

PHYSICAL EXAM

- Examine the abdomen for palpable bladder or suprapubic tenderness
- Examine the external genitalia for any abnormalities (meatal stenosis) that may contribute to outlet obstruction
- Digital rectal exam to assess for BPH and prostate cancer

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis: Hematuria, leukocytes, and crystalluria may be present
- Urine culture and sensitivity in case of suspected infection
- Urine cytology in the presence of calculi is nonspecific
- Serum creatinine
- Stone analysis should be considered when removed

Imaging

- Calcified stones can be visible on plain x-ray (KUB)
  - Stones may be densely radiopaque.
  - Occasionally laminations may be visible on plain x-ray
- Uric acid and ammonium acid urate stones are radiolucent but will be seen on ultrasounds or CT scan.
- Bladder calculi may not be visible on MRI
- CT without contrast is highly sensitive and specific to detect calculi, however it is rarely used to diagnose bladder stones

Diagnostic Procedures/Surgery

- Cystoscopy to visualize the stone and guide subsequent removal of the stone
  - Allows evaluation of bladder outlet obstruction or other abnormality such as bladder diverticulum

Pathologic Findings

- Acute and chronic inflammation
- Squamous metaplasia and squamous cell carcinoma can result from chronic vesical calculus irritation

DIFFERENTIAL DIAGNOSIS

- Bladder diverticulum
- Bladder malignancy with or without calcification
  - Urothelial carcinoma
  - Other bladder malignancies
- Chronic pelvic pain syndrome
- Fungal bezoar or blood clot
- Interstitial cystitis
- Lower urinary tract symptoms due to bladder outlet obstruction
- Overactive bladder

- Urinary tract infection
- Ureteral urolithiasis
  – Distal ureteral stone can cause significant vesical irritation

TREATMENT

GENERAL MEASURES

- Surgical removal is the mainstay treatment
- Determining and correcting the cause (ie, bladder outlet obstruction) should be a priority

MEDICATION

First Line

- Medical therapy is used to treat associated urinary tract infection
- Bladder outlet obstruction is treated with alpha blockers such as tamsulosin 0.4 mg QD and 5 alpha reductase inhibitors such as dutasteride 0.5 mg QD

Second Line

- Alkalinization of urine to a PH of 6.5 in case of uric acid stones
  – Use potassium citrate 60 mEq/d PO

SURGERY/OTHER PROCEDURES

- Endoscopic cystolitholapaxy using stone fragmenting forceps
- Electrohydraulic, ultrasonic, laser, and pneumatic lithotrites are used for larger or harder stones
- Large stones can be removed through small abdominal incision (open cystolitholapaxy)
- Cystolitholapaxy can be safely combined with procedures such as TURP or TUIP for bladder outlet obstruction

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- ESWL has a limited role in treating bladder calculi
- Bladder outlet procedure may be necessary if urinary stasis is causing vesical calculus to improve bladder emptying
- Consideration to repair of bladder diverticulum or other anatomic abnormality if contributory

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent with complete stone removal and associated bladder outlet obstruction are treated
- Metabolic stone evaluation may be considered if appropriate (ie, multiple upper tract calculi, recurrent bladder calculi, etc.)

COMPLICATIONS

- Recurrent urinary tract infection
- Squamous metaplasia
- Chronic irritation may result in secondary malignancy (ie, squamous cell carcinoma)

FOLLOW-UP

Patient Monitoring

- Urine analysis
- Flowmetry and postvoid residual
- Renal ultrasound scan to screen for upper tract urolithiasis

Patient Resources

PubMed Health: Bladder Stones http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002254/

REFERENCES

1. Huffman JL, Ginsberg DA. Calculi in the bladder and urinary diversions. In: Coe FL, Favus MJ, Pak CY, Parks JH, Preminger GM, eds. *Kidney Stones: Medical and Surgical Management.* Philadelphia, PA: Lippincott-Raven; 1996:1025–1034.
2. Douenias R, Rich M, Badlani G, et al. Predisposing factors in bladder calculi. Review of 100 cases. *Urology*. 1991;37(3):240–243.
3. Paez E, Reay E, Murthy LN, et al. Percutaneous treatment of calculi in reconstructed bladder. *J Endourol*. 2007;21(3):334–336.

ADDITIONAL READING

Preminger GM, Tiselius HG, Assimos DG, et al; EAU/AUA Nephrolithiasis Guideline Panel. 2007 guideline for the management of ureteral calculi. *J Urol.* 2007;178(6):2418–2434.

See Also (Topic, Algorithm, Media)

- Bladder Calculi (Vesical Calculi) Image
- Bladder Diverticulum
- Bladder Filling Defect
- Bladder Wall Calcification, Differential Diagnosis
- Fungal Infections, Genitourinary
- Urolithiasis, Adult, General Considerations

CODES

ICD9

- 594.0 Calculus in diverticulum of bladder
- 594.1 Other calculus in bladder
- 596.0 Bladder neck obstruction

ICD10

- N21.0 Calculus in bladder
- N32.0 Bladder-neck obstruction

CLINICAL/SURGICAL PEARLS

If an otherwise healthy person is found to have a bladder calculus, a complete evaluation is warranted to evaluate for causes such as urinary stasis.

BLADDER CANCER, ADENOCARCINOMA

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Sandip M. Prasad, MD, MPhil

BASICS

DESCRIPTION

- Adenocarcinoma of the bladder is an uncommon and frequently aggressive nonurothelial cancer.
- It is frequently muscle-invasive or metastatic at the time of diagnosis and therefore carries a poor prognosis.
- A common site is the urachus.

EPIDEMIOLOGY

- 0.5–2.0% of all primary bladder malignancies, making it the 3rd most common epithelial tumor of the bladder
- Can arise from the urachus or nonurachal epithelium, or in association with exstrophy of the bladder
- Most common tumor arising in the bladder of exstrophy patients, who have a 4% lifetime risk
- A majority of nonurachal, nonexstrophy-associated adenocarcinomas occur in men and are frequently associated with long-term inflammation or infection
- Occurs more frequently in areas where Schistosoma is endemic
- Urachal cancer: $<1\%$ of primary bladder cancer; 1/3 of bladder adenocarcinomas

RISK FACTORS

In tissue recombinant studies, adenocarcinoma can be produced from bladder urothelium under the appropriate hormonal and mesenchymal stimuli.

Genetics

Associated with gain of function in regions 20q and 8q, or loss of function at regions 5q and 8p (1)

PATHOPHYSIOLOGY

- Classification: Three groups related to site of tumor origin (2,3)
  - Primary adenocarcinoma of bladder
  - Urachal adenocarcinoma
  - Extravesical adenocarcinoma (metastatic)
- Primary vesical adenocarcinoma: Can occur anywhere in the bladder, but the dome and the trigone of the bladder are common
  - Most common type of cancer in bladder exstrophy
  - All histologic variants of enteric carcinoma may occur in the bladder
  - Papillary or solid; most are mucin-producing
  - Most are poorly differentiated and invasive at the time of diagnosis
  - Poor response to radiotherapy and chemotherapy

- Urachal carcinoma
  - For classification as a urachal carcinoma, there must be:
    - Presence of a urachal remnant
    - Clear demarcation between the tumor and adjacent bladder mucosa
    - Predominant invasion of the muscularis propria or deeper structures of the bladder or extension to the space of Retzius, anterior abdominal wall, or umbilicus
    - Possible production of mucoid drainage from the umbilicus
- M.D. Anderson Cancer Center Diagnostic Criteria for Urachal Carcinoma
  - Location in bladder dome or elsewhere in the midline of the bladder
  - Sharp demarcation between tumor and normal surface epithelium
  - Supportive criteria
    - Enteric-type histology
    - Absence of urothelial dysplasia
    - Absence of cystitis cystica or cystitis glandularis transitioning to the tumor
    - Absence of primary adenocarcinoma of another organ
- May produce stippled calcifications on plain films
- Prognosis is worse for urachal carcinoma than for primary adenocarcinoma of the bladder
- Urachal carcinoma demonstrates more extensive infiltration of the bladder wall, and for this reason, radical cystectomy is preferred over partial cystectomy, although the latter is still an option
- Urachal carcinomas are not always adenocarcinomas (most common type); others include transitional cell carcinoma, squamous cell carcinoma, and rarely sarcoma
- Metastatic lesions are very rare
  - Adenocarcinomas from the colon, stomach, breast, ovary, endometrium, and prostate can metastasize to the bladder
  - Local invasion of a colonic primary tumor is more common than metastasis
  - Bladder adenocarcinoma is histologically indistinguishable from adenocarcinoma of the colon
- Sheldon Staging System for Urachal Carcinoma
  - Stage I: No invasion beyond the urachal mucosa
  - Stage II: Invasion confined to the urachus
  - Stage III: Local extension into the
    - bladder (IIIA)
    - abdominal wall (IIIB)
    - peritoneum (IIIC)
    - viscera other than bladder (IIID)
  - Stage IV: Metastases to the
    - regional lymph nodes (IVA)
    - distant site (IVB)

ASSOCIATED CONDITIONS
- Bladder exstrophy
- Schistosomiasis

GENERAL PREVENTION
Elimination of factors leading to chronic bladder inflammation

DIAGNOSIS

HISTORY

- Hematuria, mucosuria (uncommon)
  - Usually painless
- Irritative voiding symptoms (frequency, urgency, dysuria)
- Foreign travel: Schistosomiasis
- Weight loss, flank pain, umbilical discharge (rare)
- Chronic infection
- History of exstrophy or other bladder pathology
- History of colon cancer or other malignancy; risk of metastatic lesion

PHYSICAL EXAM

- Pelvic mass by bimanual/rectal exam
- Bloody or mucoid umbilical discharge or umbilical mass
- Digital rectal exam; presence of blood in stool

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine studies: Urinalysis, culture and sensitivity, urine cytology
- Serum electrolytes: BUN/Creatinine, liver function tests
- Carcinoembryonic antigen (CEA), CA125, and CA 19-9 may be elevated in 40–60% of patients presenting with peritoneal carcinomatosis

Imaging

- Urachal cancers may show stippled calcifications on plain x-ray films
- 60% of bladder tumors are detected with IVP, which has been largely replaced with the CT scan
- CT scan: Imaging method of choice for staging of bladder tumors; useful for detecting presence of pelvic lymphadenopathy and extravesical tumor extension
  - Sensitivity: 64–94%, specificity: 62–100%
- Other investigations: CXR (staging), bone scan (staging, if bone pain is present), GI endoscopy, and breast exam (to exclude primary tumor) if clinically indicated

Diagnostic Procedures/Surgery

- Diagnostic cystoscopy and biopsy
  - Essential for definitive diagnosis
  - Bloody efflux from ureteral orifices suspicious for upper tract pathology

Pathologic Findings

- All histologic variants of enteric carcinoma may occur in the bladder
- Adenocarcinoma can have glandular, mucinous, or signet ring patterns
- Most produce mucin
- Primary adenocarcinoma of the bladder is associated with cystitis glandularis and is thought to arise from glandular metaplasia of the urothelium. These tumors can be papillary or solid
- Signet ring tumors produce linitis plastica of the bladder. They are aggressive and radical surgical excision should be considered

DIFFERENTIAL DIAGNOSIS

- Metastasis from colon, prostate, or other adenocarcinoma
- Benign or malignant urothelial tumors

TREATMENT

GENERAL MEASURES

- Site of origin and tumor behavior are factors important in determining treatment
- Adenocarcinoma of the bladder is generally unresponsive to radiation and chemotherapy.
  - Radical cystectomy is treatment of choice.
  - Excision of the urachus and umbilicus is usually required if a urachal primary is suspected
- Adjuvant chemotherapy or radiotherapy may be used, but surgery remains the most consistently effective treatment (4,5,6)

MEDICATION

First Line

- Generally unresponsive to radiation and cytotoxic chemotherapy (7)
- Some response to standard regimens such as combination methotrexate, vinblastine, adriamycin, cisplatin (MVAC)
- Recently, 5-FU and cisplatin-based chemotherapy have demonstrated a modest response rate
- A clinical trial at M.D. Anderson using gemcitabine, 5-FU, leucovorin, and cisplatin (Gem-FLP) reported a clinical response rate in 30–40% of patients
- Currently there is no role for neoadjuvant chemotherapy for clinically node-negative resectable disease

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical cystectomy with pelvic lymph node dissection remains the gold standard
- Adjuvant chemotherapy or radiotherapy has not improved survival significantly
- Partial cystectomy (with bladder mucosal sampling) with en bloc removal of the urachus and umbilicus is an option for low-volume, low-stage urachal carcinoma

ADDITIONAL TREATMENT

Radiation Therapy

Urachal adenocarcinoma is radio resistant

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Signet cell variant has a 50% mortality at 1 yr
- Urachal adenocarcinoma: Overall 11–55% 5-yr survival, but early-stage disease may have up to 93% 5-yr survival

- Nonurachal adenocarcinoma: 27–61% 5-yr survival
- Recurrence risk for urachal carcinoma
  - Positive margin
  - Umbilicus sparing resections are associated with a higher risk of relapse
  - Tumor involving the peritoneal surfaces or the abdominal wall
  - Occult lymph node metastases

COMPLICATIONS
- Ureteral obstruction from local spread of tumor
- Metastasis to pelvic lymph nodes, liver, lung, mediastinum, and bone
- Surgical complications: Bleeding, infection, rectal injury

FOLLOW-UP

Patient Monitoring
- Abdominal imaging (CT)
- Metastatic workup if suspected

Patient Resources
- American Cancer Society:
  - www.cancer.org
- National Cancer Institute
  - www.nci.nih.gov
- United Ostomy Association:
  - www.uoa.org

REFERENCES

1. Vauhkonen H, Böhling T, Eissa S, et al. Can bladder adenocarcinomas be distinguished from schistosomiasis-associated bladder cancers by using array comparative genomic hybridization analysis? *Cancer Genet Cytogenet.* 2007;177(2):153–157.
2. El-Mekresh MM, el-Baz MA, Abol-Enein H, et al. Primary adenocarcinoma of the urinary bladder: A report of 185 cases. *Br J Urol.* 1998;82(2):206–212.
3. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: A review. *Eur Urol.* 2003;44:672–681.
4. Siefker-Radtke AO, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: The MD Anderson Cancer Center experience. *J Urol.* 2003;169:1295–1298.
5. Herr HW, Bochner BH, Sharp D, et al. Urachal carcinoma: Contemporary surgical outcomes. *J Urol.* 2007;178:74–78.
6. Siefker-Radtke A. Urachal Adenocarcinoma: A Clinician's Guide for Treatment. *Sem Oncol.* 2012;39(5):619–624.
7. Siefker-Radtke A. Systemic chemotherapy options for metastatic bladder cancer. *Expert Rev Anticancer Ther.* 2006;6:877–885.

ADDITIONAL READING

Zhong M, Gersbach E, Rohan SM, et al. Primary adenocarcinoma of the urinary bladder: Differential diagnosis and clinical relevance. *Arch Pathol Lab Med.* 2013;137(3):371–381.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, Adenocarcinoma Image
- Bladder Cancer, General
- Urachal Carcinoma

CODES

ICD9

- 188.1 Malignant neoplasm of dome of urinary bladder
- 188.7 Malignant neoplasm of urachus
- 188.9 Malignant neoplasm of bladder, part unspecified

ICD10

- C67.1 Malignant neoplasm of dome of bladder
- C67.7 Malignant neoplasm of urachus
- C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

- Umbilicus may be involved in up to 7% of patients with adenocarcinoma of the bladder.
- Most common tumor arising in the bladder of exstrophy patients, who have a 4% lifetime risk.
- Adenocarcinoma of the bladder is generally unresponsive to radiation and chemotherapy.

BLADDER CANCER, GENERAL

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BASICS

DESCRIPTION

- Bladder cancer is the most common site of malignancy in the urinary system
- Includes multiple histologic types:
  - Urothelial cell carcinoma (formerly transitional cell carcinoma) is most common
  - Other: Adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma
  - TNM staging: Initially based on clinical findings (bladder biopsy) (See Section VII: "Reference tables: TNM Classification: Urinary Bladder cancer.")
  - T staging: Primary tumor
    - Ta/Tis/T1: Superficial/nonmuscle invasive bladder cancer (NMIBC)
    - T2a/T2b: Muscle invasive bladder cancer (MIBC)
    - T3a/T3b/4a: Locally advanced
  - Regional lymph node (N) staging: Regional lymph nodes (the true pelvis); all others are considered distant metastasis
  - Distant metastasis (M) staging
  - Stage grouping:
    - Stage 0: Tis, N0, M0
    - Stage 1: Ta-T1, N0, M0
    - Stage II: T2, N0, M0
    - Stage III: T3a-T4a, N0, M0
    - Stage IV: T4b, N0, M0 or any T, N1,2,3, M0 or any T, any N, M1

EPIDEMIOLOGY

Incidence

- American Cancer Society 2014 new case estimates: 74,690 (male: 56,390 female: 18,300)
  - Estimated 155,800 deaths in 2014
- 3:1 male–female ratio
- 4th most common cancer in males, 7th most common cancer in females
- Median age of diagnosis is 70 yr

Prevalence

3rd most prevalent cancer in men (high recurrence)

RISK FACTORS

- Tobacco smoking confers a 2–4 times risk over those that have never smoked
  - Risk reduction after quitting takes up to 20 yr
- Occupational exposures:
  - Painters, leather, petroleum, chemical and met al workers, dry cleaners, truck drivers, hairdressers
  - Aromatic amines such as aniline dyes, benzidine, naphthylamine, 4-aminobiphenyl, and

coal soot
- Cyclophosphamide treatment
  – Caused by toxic metabolite, acrolein
- Pelvic radiation
- Risk for squamous cell carcinoma
  – Indwelling catheters, bladder calculi
  – Schistosomiasis (*Schistosoma hematobium*)

Genetics
- No clear hereditary causes identified
- Tumor suppressor p53 is the most commonly altered gene in bladder cancer

PATHOPHYSIOLOGY
- 70% of tumors present as nonmuscle-invasive lesions
  – 70% of these are Ta, 20% T1, 10% CIS
- Risk of recurrence
  – CIS: 50–90%
  – Ta low grade: 50–70%
  – Ta high grade: 60%
  – T1 high grade: 70–80%
  – Risk of recurrence in upper tracts 2–4%
- Risk of progression
  – CIS >50%
  – Ta low grade: 5–10%
  – Ta high grade: 15–40%
  – T1 high grade: 30–50%
    - Most important prognostic factor is grade
    - Concurrent upper-tract UCC in patients with bladder cancer is 2–4%

ASSOCIATED CONDITIONS
Other smoking related illnesses (COPD)

GENERAL PREVENTION
- Avoid occupational exposure and smoking
- Urinalysis for hematuria screening
- High-fat diet has been associated with increased risk of bladder cancer
- Vitamins A and B compounds have not shown conclusive benefit for primary prevention
- Long-term hydration may be beneficial

DIAGNOSIS

HISTORY
- Gross painless hematuria is the most common presenting symptom
- Irritative voiding symptoms (present in 20%)
  – Often associated with CIS
- Smoking history (quantify in pack years and if/when patient quit)
- Occupational exposures (see “Risk Factors”)

PHYSICAL EXAM

- Rarely abnormal in NMIBC
- General
  - Weight loss, abdominal/pelvic masses, lymphadenopathy, flank tenderness
- DRE with bimanual exam in men and women may reveal palpable mass in bladder

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis with microscopy: RBCs
- Urine cytology
  - High specificity (96%), more sensitive for high-grade tumors (50%)
- Other urinary markers
  - FISH (evaluate aneuploidy for chromosomes 3,7,17 and 9p21)
    - Sensitivity 77%, specificity 98%
  - NMP-22 (marker of urothelial cell death)
    - Sensitivity 56%, specificity 85%
- Renal function tests (BUN, Creatinine)
  - May indicate renal impairment secondary to ureteral obstruction
- Liver function tests
  - May be abnormal due to metastasis

Imaging

- CT abdomen/pelvis
  - Can detect lymphadenopathy and other intra-abdominal disease
  - Presence of hydronephrosis is suggestive of muscle-invasive disease
  - CT urography has replaced IVP as standard for evaluating upper tracts
- MRI may be useful for local staging
- Chest x-ray (CXR): Metastasis with muscle invasion
- Bone scan is recommended only in patients with bone pain, elevated calcium, or elevated alkaline phosphatase

Diagnostic Procedures/Surgery

- Cystoscopy is the most accurate initial diagnostic procedure
  - Can be done in office with local anesthesia
- Bladder biopsy
  - Establishes pathologic diagnosis
  - May be definitive treatment if tumor can be completely removed
- Prostatic urethra biopsies are not routinely performed unless there is:
  - Multifocal disease of the bladder
  - CIS of the bladder
  - Visible abnormality in the prostatic urethra
- Retrograde pyelography
  - May be used in setting of renal impairment or contrast allergy
  - Further evaluate equivocal findings on CT

Pathologic Findings

- Carcinoma in situ (CIS) is a urothelial cancer that is flat, high grade, and noninvasive but

has metastatic potential. Patients with bladder CIS have a 20% risk of upper-tract disease
- Histologic types
  - Transitional cell carcinoma (urothelial carcinoma), 90%
  - Squamous cell carcinoma, 3–7%
  - Adenocarcinoma, < 2%
  - Small cell, sarcomas (leiomyosarcoma, rhabdomyosarcoma) uncommon

DIFFERENTIAL DIAGNOSIS
- Hematuria
  - Trauma: Iatrogenic, other
  - Neoplasms: Malignancies: (30% of adults with painless, gross hematuria and ~10% with painless microscopic hematuria have a malignancy), benign tumors, endometriosis
  - Inflammatory causes: UTI (most common cause of hematuria in adults), other infections (Schistosomiasis, TB, syphilis) radiation cystitis
  - Renal/glomerular diseases: Nephritis, Goodpasture syndrome, IGA nephropathy, lupus nephritis, glomerular diseases (membranoproliferative, poststreptococcal, or rapidly progressive glomerulonephritis)
  - Urolithiasis: 85% have hematuria
  - Congenital/Familial causes: Cystic disease, benign familial hematuria, etc.
  - Hematologic causes: Bleeding dyscrasias (eg, hemophilia), Sickle cell anemia/trait (renal papillary necrosis)
  - Vascular causes: Hemangioma, AVM (rare), Nutcracker syndrome, renal artery/vein thrombosis, arterial emboli to kidney
  - Chemical causes: Nephrotoxins (Aminoglycosides, cyclosporine), analgesics, oral contraceptives, Chinese herbs
  - Obstruction: Strictures or posterior urethral valves, hydronephrosis (any cause) benign prostatic hyperplasia: Rule out other causes of hematuria.
  - Other causes: Loin pain hematuria, menses
- Bladder filling defect:
  - Air: Artifactual, postinstrumentation, vesicoenteric fistula
  - Benign tumors: Prostatic enlargement, etc.
  - Blood clot, calculus, fungus ball (bezoar)
  - Congenital: Ureterocele
  - Extrinsic compression
  - Infective, inflammatory: Inflammatory edema
  - Instruments (catheters), foreign body
  - Malignant tumor: Bladder and prostate malignancy, tumors invading urinary bladder
  - Radiologic artifact: Fold in bladder

TREATMENT

GENERAL MEASURES
- Transurethral resection of bladder tumor (TURBT) determines diagnosis (grade/stage/type)
- Primary treatment is surgery
  - Bladder biopsy can be both diagnostic and therapeutic (for nonmuscle-invasive tumors)

  - For T1, repeat TURBT should be performed 2–6 wk after initial resection as upstaging occurs in up to 30% of cases.
- Radical cystectomy with pelvic lymphadenectomy
  - Initial therapy for muscle-invasive tumors
  - May be needed for recurrent high-grade T1 tumors or CIS that has failed to respond to intravesical therapy

MEDICATION

First Line

- Intravesical therapy for higher-risk NMIBC
- BCG (Bacillus Calmette-Guerin) (1)
  - Only after bladder healed (usually 4 wk); 40% reduction in recurrence, 23–27% reduction in progression
  - Maintenance BCG increases recurrence-free time; BCG: Superior to intravesical chemotherapy for CIS
  - Side effects: Cystitis, dysuria, hematuria, malaise, fatigue, low-grade fever
  - Complications: Fever >101.5°F (38.6°C) for >12–24 hr may require broad-spectrum antibiotics and isoniazid
    - Sepsis (0.4%) – fever >102°F (38.8°C) or signs of sepsis. Treat with prednisone, broad-spectrum antibiotics, and anti-tuberculosis drugs
- Mitomycin C
  - Alternative when BCG cannot be used
  - Reduces tumor recurrence up to 40%
  - Given as a single dose within 24 hr of TURBT (40 mg in 20-mL saline or sterile water)
  - Contraindicated with bladder perforation
  - Side effects: Dermatitis, irritative voiding, absorption may cause myelosuppression
- Platinum-based drug regimens are the most effective systemic chemotherapeutic agents (2)
  - Neoadjuvant or adjuvant therapy for invasive disease (Stage II/III)
  - Metastatic disease (Stage IV)
    - MVAC (mitomycin, vinblastine, adriamycin, cisplatin)
    - Overall response rate 40–50%
    - Common toxicities: Mucositis, renal toxicity, myelosuppression, sepsis, cardiac toxicity
  - Gemcitabine and cisplatin
    - Common toxicity: Myelosuppression
    - Overall response rate 40–50%, similar to MVAC with better toxicity profile
- Neoadjuvant platinum-based chemotherapy: 5-yr overall survival benefit of 5%

Second Line

- Valrubicin: Intravesical therapy of BCG-refractory CIS in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality
- Other intravesical agents after BCG failure: Mitomycin C, gemcitabine, interferon α 2b

SURGERY/OTHER PROCEDURES

- "Blue light" (Cysview) cystoscopy FDA approved may improve lesion detection
- Narrow band imaging evolving for diagnosis

ADDITIONAL TREATMENT

Radiation Therapy

- Bladder preservation approaches (trimodality therapy) (3)
  - 1. TURBT: Must be completely resected
  - 2. Chemotherapy: Platinum-based regimens
  - 3. Radiation therapy
  - Optimal patients have solitary T2 tumors that can be completely resected, no hydronephrosis, no associated CIS, normal renal function
  - Usually biopsy mid-treatment: Recommend cystectomy if no response
  - 5-yr survival is similar to radical cystectomy

Additional Therapies

Oncovite (high-dose vitamin A, B6, C, E, and zinc) after TUR and induction BCG had a reduction in recurrence vs. RDA vitamins (secondary prevention)

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 5-yr survival by stage: I, 85–96%; II, 55–65%; III, 38–59%; IV, 15–27%
- Recurrence: CIS, 80%; Ta, 50%; T1, 50–70%
  - Progression: CIS, 20% after a complete response to BCG; Ta, 5%; T1, 30–40%

COMPLICATIONS

- Urinary retention from gross hematuria or tumor infiltrating or blocking bladder outlet
- Ureteral obstruction

FOLLOW-UP

Patient Monitoring

- NMIBC: Cystoscopy and cytology every 3 mo for 2 yr, then every 6 mo for 2 yr, then annually
  - Upper-tract surveillance every 1–2 yr
- Muscle-invasive disease
  - Liver function tests, creatinine, electrolytes, CXR every 6–12 mo
  - Upper-tract imaging, baseline and every 2 yr
  - Cytology every 6–12 mo ± male urethral wash (cutaneous diversion)

Patient Resources

BCAN (Bladder Cancer Advocacy Network) www.bcan.org

REFERENCES

1. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized SWOG Study. *J Urol.* 2000;163:1124–1129.
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003:349:859–866.

3. Shipley WU, Zietman AL, Kaufman DS, et al. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates—The Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. *Semin Radiat Oncol*. 2005; 15:36–41.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Bladder Cancer, Adenocarcinoma
- Bladder Cancer, General Image
- Bladder Cancer, Intravesical Agents (Table)
- Bladder Cancer, Nonmuscle-Invasive Bladder Cancer (Ta, T1).
- Bladder Cancer, Squamous Cell Carcinoma
- Bladder Cancer, Urothelial, Muscle-Invasive (Clinical and Pathologic T2/T3/T4) (MIBC) Neoadjuvant Therapy
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC)
- Bladder Tumor Algorithm
- Hematuria, Gross and Microscopic, Adult
- Reference Tables: TNM Classification: Urinary Bladder Cancer

CODES

ICD9

- 188.0 Malignant neoplasm of trigone of urinary bladder
- 188.8 Malignant neoplasm of other specified sites of bladder
- 188.9 Malignant neoplasm of bladder, part unspecified

ICD10

- C67.0 Malignant neoplasm of trigone of bladder
- C67.8 Malignant neoplasm of overlapping sites of bladder
- C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

70% of bladder cancers present as nonmuscle-invasive lesions.

BLADDER CANCER, NON-MUSCLE-INVASIVE BLADDER CANCER (TA, T1) (NMIBC)

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BASICS

DESCRIPTION

- Bladder cancer is a malignant neoplasm usually arising from originating from the lining of the bladder (urothelium)
  - A papillary tumor confined to the mucosa is classified as stage Ta according to the Tumor, Node, Metastasis (TNM) classification system.
  - Tumors that have invaded the lamina propria are classified as stage T1.
  - Ta and T1 tumors can be removed by transurethral resection (TUR), and are called NMIBC (nonmuscle-invasive bladder cancer)
- Most common histology: Urothelial carcinoma (previously called transitional cell carcinoma/TCC)
- ~70% of bladder cancers are nonmuscle-invasive at presentation
- Challenging management: Due to recurrence and potential to progress to lethal disease
- Due to need for lifelong monitoring, highest cost per patient of any cancer

EPIDEMIOLOGY

Incidence

- In US, all cases estimated 74,690 in 2014
  - 15,580 estimated cancer deaths in 2014
- Highest incidence: Men >60, women >70
- Caucasian > African American > Latino
- 4th most common cancer in men

Prevalence

- 2nd most prevalent cancer in middle-aged and elderly men
- Male:female ~3:1

RISK FACTORS

- Tobacco smoking history (most common risk factor)
  - Overall 2.8× higher incidence in smokers
  - Risk increases with number of pack-years
    - 6× risk for 60 pack year history
  - Latency often >20 yr from time of exposure
  - Quitting decreases risk
    - 15 yr after quitting, relative risk 1.1
- Occupational exposure
  - Organic chemicals, especially aromatic (aryl)-amines
    - Naphthalenes, benzidine, aniline dyes, 4-aminobiphenyl

  - High-risk occupations: Petroleum/rubber/leather/paint/textile workers, hairdressers, truck drivers, aluminum electroplaters
  - Arsenic contamination of drinking water
  - Latency may be 40 yr
- Chemotherapy with cyclophosphamide (Cytoxan)
- Pelvic radiation
  - 4× increased risk after RT for cervical cancer
  - ~1.5× risk after RT for prostate cancer
- Chronic cystitis → SCC
  - Indwelling catheters, chronic bladder calculi, cystitis due to *Schistosoma hematobium*

Genetics

- 2× increased risk for 1st-degree relatives of bladder cancer patients
- Genetics affect susceptibility to carcinogens (eg, slow acetylators NAT2, null GSTM1)
- Lynch syndrome – typically increased upper-tract UC, though some subtypes increase risk of bladder cancer

PATHOPHYSIOLOGY

- Inciting genetic event
  - Low grade (LG): Deletion of part of chr 9 (RB gene) and/or mutation in FGFR-3
  - High grade (HG): Numerous mutations (particularly TP53), aneuploidy of chr 7, 9, 17
- NMIBC comprises ~70% of bladder cancer
  - Recurrence rate: ~60% for LG, >80% for HG
    - Most recurrences within 1st 6 mo after TURBT, but may occur after many years
    - May also recur in upper tracts or prostatic urethra
  - Progression influenced by stage and grade
    - Stage Ta, LG: 5–10%; HG: 15–40% at 5 yr
    - Stage T1, HG 30–50% at 5 yr
  - Eventual death rate 10–25% for HG Ta, 33% for HG T1 (1)
- Other risk factors for progression
  - Architecture: Nodular/sessile/broad based > papillary
  - Multifocality > solitary
  - Size >5 cm
  - Lymphovascular invasion
  - Mutations in *TP53*, *RB*, and *PTEN* predict poor prognosis

ASSOCIATED CONDITIONS

See “Risk Factors”

GENERAL PREVENTION

- Smoking cessation
- Avoidance of occupational exposure
- Hydration long term beneficial

DIAGNOSIS

HISTORY

- Most common in men >50; Males > Females due to smoking prevalence
- 1st occurrence: 85% present with either gross or microscopic hematuria. Painless gross hematuria is hallmark of bladder CA
- Irritative symptoms (eg, dysuria, urgency, frequency) occasionally due to bladder CA, especially CIS
  – Microscopic hematuria typically present if due to cancer
- Smoking history:
  – Record total pack-years, current packs/day, and years since quitting if applicable
- Occupational risk factors

PHYSICAL EXAM

Usually unremarkable for NMIBC

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- U/A, including dipstick and micro evaluation for RBCs
- Urine cytology: High specificity but low sensitivity. Best at detecting HG NMIBC and CIS
- Other urinary tests: Urine cytology, BTA-Stat, NMP22, UroVysion FISH: Low sensitivity and specificity for LG disease. Not generally recommended for routine workup of microscopic hematuria but may be considered for high-risk patients (see "Additional Reading")

Imaging

- Goal: Evaluate renal parenchyma, renal collecting system and ureters
- CT urogram (3-phase CT abd/pelvis with IV contrast): Study of choice for evaluation of gross/microscopic hematuria
- If patient cannot receive IV contrast, consider MRI + RPG (retrograde pyelogram)
  – U/S + RPG if patient cannot receive gadolinium

Diagnostic Procedures/Surgery

- Bladder CA typically detected on cystoscopy
  – Cystoscopy indicated for gross hematuria and most cases of microscopic hematuria (see chapter "Hematuria, gross and microscopic, adult")
    - In office, under local anesthesia, at time of initial presentation. It may be combined with biopsy
    - TURBT under general or spinal anesthesia is definitive
- Retrograde pyelography may be used for equivocal CT urogram or when CT urogram/MRI contraindicated to exclude concomitant upper-tract lesions in patients with hematuria or positive cytology

Pathologic Findings

- Urothelial Dysplasia
  – Precursors to CIS/Urothelial cancer
- Papilloma
  – Papillary lesion with low recurrence risk (0–8%) or progression risk (2%)
- Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)
  – Papillary growth, minimal cytologic atypia
  – Recurrence 35%, progression 4%

- CIS: See chapter "Bladder cancer, urothelial, superficial, carcinoma in situ (CIS)"
- Papillary cancer: Confined to either urothelium (stage Ta) or invasion of lamina propria (stage T1) and may be LG or HG

DIFFERENTIAL DIAGNOSIS

See Section I "Bladder cancer, general" for complete differential diagnosis of hematuria and bladder filing defect

TREATMENT

GENERAL MEASURES

- Resection with selective use of intravesical therapy is the mainstay
- TURBT of all visible tumor: 1st-line treatment; both diagnostic and therapeutic
  - For sessile lesions, HG disease, or CIS, random biopsies of the bladder and prostatic urethra in men should be considered

MEDICATION

First Line

- Intravesical therapy: Adjuvant to surgery to reduce tumor recurrence/progression
  - Intravesical chemotherapy
    - Drugs: Thiotepa, doxorubicin (Adriamycin), mitomycin, valrubicin
    - Single-dose perioperative intravesical chemotherapy within 6 hr of TURBT reduces tumor recurrence for LG disease
    - Marginal (7–14%) reduction in long-term recurrence rate
    - No decrease in tumor progression
  - Intravesical BCG
    - Live suspension of attenuated *Mycobacterium bovis* vaccine strain instilled in bladder via Foley and retained for 2 hr
    - Give 2–4 wk after TURBT; Weekly administration × 6 wk for induction course.
    - Maintenance courses improve efficacy
    - Most effective intravesical agent, with initial response rates up to 84%
    - Most ultimately recur (30% disease-free survival at 10 yr)
    - Decreases risk of progression by ~35%, but benefit mostly seen in maintenance therapy
    - Toxicity: Generally well tolerated though urinary frequency, dysuria, and low-grade fever common
    - Risk of systemic BCG infection (see Section I "BCG sepsis/BCGosis.")
- BCG: Greater efficacy than intravesical chemotherapy though higher morbidity (4)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Repeat TURBT indicated for T1 and HG Ta as 25–50% may harbor worse prognostic findings on 2nd TURBT
- Bladder biopsies (random): Helpful if positive cytology with no obvious lesion
- Laser/electrofulguration: Useful for recurrent, small, LG papillary tumors; may be performed under local anesthesia

- Fluorescence "Blue Light"/Cysview cystoscopy
  - Intravesical agent binds porphyrins in neoplastic tissue and fluoresces under blue light
  - Improves detection of papillary tumors and CIS; Decreases recurrence but not progression
  - Recommended by EAU guidelines
- Narrow band imaging (NBI) is an evolving endoscopic technology
- Radical cystectomy: Indicated in HG NMIBC refractory to BCG, particularly if 2nd induction course fails

ADDITIONAL TREATMENT

Radiation Therapy

No role in superficial disease

Additional Therapies

Adjuvant intravesical chemotherapy/immunotherapy (as above)

Complementary & Alternative Therapies

Mediterranean diet (high intake of fruit, vegetables, legumes) thought to lower risk of urothelial cancer (5)

ONGOING CARE

PROGNOSIS

See "Pathophysiology"

COMPLICATIONS

TURBT: Bleeding, irritative symptoms, bladder perforations (mainly extraperitoneal); usually can be managed conservatively with catheter drainage and anticholinergics

FOLLOW-UP

Patient Monitoring

- Surveillance after TURBT: Cystoscopic and urine cytology every 3–6 mo for 2 yr, then increasing interval as appropriate
  - Schedule resets with each recurrence
- TURBT as necessary, depending on cytology results and cystoscopic appearance
- Upper-tract surveillance studies (CT urogram) every 2–3 yr for HG bladder tumors and CIS

Patient Resources

- Schoenberg, Mark. *The Guide to Living with Bladder Cancer*. Baltimore: The Johns Hopkins University Press, 2000.
- BCAN (Bladder Cancer Advocacy Network) www.bcan.org

REFERENCES

1. Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. *Urol Clin North Am.* 2003;30:765–776.
2. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: A meta-analysis of published results of randomized clinical trials. *J Urol.* 2004;171:2186–2190.
3. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces

the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. *J Urol.* 2002;168:1964–1970.
4. Malmström PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Guérin for non-muscle-invasive bladder cancer. *Eur Urol.* 2009;56:247–256.
5. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean dietary pattern in a randomized trial: Prolonged survival and possible reduced cancer rate. *Arch Intern Med.* 1998;158:1181–1187.

ADDITIONAL READING

- AUA Guideline for the Management of Non-muscle Invasive Bladder Cancer: (stages Ta, T1, and Tis): Update (2007). Available at http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=bc, Accessed on April 2013.
- Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. *Eur Urol.* 2013;64(4):639–653.
- National Comprehensive Cancer Network, Available at http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf, Accessed on November 2013.

See Also (Topic, Algorithm, Media)

- BCG Sepsis/BCGosis
- Bladder Cancer, General
- Bladder Cancer, Intravesical Agents (Section II Table)
- Bladder Cancer, Non-Muscle-Invasive Bladder Cancer (Ta, T1) Image
- Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC)
- Bladder Cancer, Urothelial, Invasive (Clinical and Pathologic T2/T3/T4)
- Bladder Cancer, Urothelial, Metastatic (Clinical and Pathologic N+, M+)
- Bladder Tumor Algorithm
- Bladder Tumors, Benign and Malignant, General Considerations

CODES

ICD9

188.9 Malignant neoplasm of bladder, part unspecified

ICD10

C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

- Greatest risk factor for progression to MIBC is high-grade disease.
- Administration of mitomycin C at the time of TURBT for low-grade NMIBC decreases risk of recurrence but not progression.
- Though the majority of men with high-grade NMIBC respond to BCG, most will ultimately recur.

BLADDER CANCER, SQUAMOUS CELL CARCINOMA

Daniel J. Canter, MD

BASICS

DESCRIPTION

- Squamous cell carcinoma (SCC) of the bladder is a histologic variant of bladder cancer
  - Most frequent histologic form of bladder cancer in countries with endemic schistosomiasis
  - SCC comprises 2–5% of all bladder cancers—most common histologic variant in Western countries

EPIDEMIOLOGY

Incidence

- 2–5% of bladder cancers in Western countries
- Originally reported that patients with spinal cord injuries (SCIs) had an incidence of SCC of the bladder of 2.3%—more recent data only suggests 0.39% incidence
- Approximately 75–80% of all bladder cancers are SCCs in regions with endemic schistosomiasis

Prevalence

Difficult to assess since so many of these patients will ultimately die of bladder cancer

RISK FACTORS

- Schistosomiasis infection
- Transitional cell carcinoma (TCC) can differentiate into any histology
- Smoking
- Chronic bladder infection/irritation
  - Patients with SCIs
  - Chronic indwelling Foley catheter/CIC
  - Chronic infection
  - Bladder stones
  - Leukoplakia
  - Squamous metaplasia
- HPV infection
- Industrial exposures for workers involved in the production of rubber, leather, textiles, and paint (traditionally more associated with the development of pure urothelial carcinoma)

Genetics

- Association with variations in inflammatory genes
- Epidermal growth factor receptor and p53 overexpression implicated as well as p16 abnormalities
- Keratin 10 and caveolin-1 identified as potential markers of differentiation from TCC to SCC

PATHOPHYSIOLOGY (1)

- Schistosomiasis infection
- Transitional cell dedifferentiation

  – Transitional cells possess unique ability to dedifferentiate into any cell type
- Chronic irritation of bladder mucosa due to a variety of etiologies, especially SCIs
- Most common bladder sites are the lateral wall and trigone

ASSOCIATED CONDITIONS
- Neurogenic bladder/SCIs
- Need for chronic indwelling Foley/CIC
- Smoking history
- Living and travel to areas endemic with schistosomiasis

GENERAL PREVENTION
- No good screening test for bladder cancer in general
- Smoking cessation
- Patients with indwelling catheters (Foley, suprapubic tube, etc.) should be screened with yearly cystoscopy +/– biopsy
  – When to start is open to debate
- Treatment of patients infected with schistosomiasis (praziquantel)

DIAGNOSIS

HISTORY
- History of living/travel to countries with endemic schistosomiasis
- In general, in Western countries, patients who have SCC of the bladder present in the same manner as urothelial carcinoma of the bladder
  – Hematuria
  – Constitutional symptoms
  – Flank/back pain due to ureteral obstruction
  – History of chronic irritation to bladder mucosa

PHYSICAL EXAM
- Palpable mass on rectal/vaginal exam
- Gross hematuria

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis/urine culture
- Urinary cytology usually not reliable
- CBC
- Comprehensive metabolic panel, including (liver function testing) LFTs, alkaline phosphatase, and albumin

Imaging
- Cross-sectional imaging of the chest, abdomen, and pelvis based on patient's renal function (CT scan vs. MRI)
- Bone scan if elevated calcium, alkaline phosphatase, or unexplained pain

Diagnostic Procedures/Surgery
- Exam under anesthesia (EUA) and transurethral resection of bladder tumor (TURBT) of primary tumor for histologic diagnosis and clinical staging

- Radical cystectomy with lymph node dissection and urinary diversion is considered 1st-line treatment

Pathologic Findings
- Mixed urothelial and squamous carcinomas are more common than pure SCCs
  - The term SCC of the bladder is used only if tumor is solely composed of squamous cell component, with no urothelial carcinoma component
- Grading unreliable. Mostly considered a high-grade neoplasm
- Histologic findings
  - Squamous metaplasia
  - Keratinized islands
  - Squamous pearls
  - Intercellular bridges
  - Mitotic figures common

DIFFERENTIAL DIAGNOSIS
- Urothelial carcinoma of the bladder
- Squamous metaplasia
- Other histologic variant of bladder (adenocarcinoma, sarcomatoid, etc.)
- Invasive cervical cancer: Often squamous cell

TREATMENT

GENERAL MEASURES
- Treatment is related to stage
- In general, SCC of the bladder presents with locally advanced disease, and radical cystectomy with urinary diversion is an integral part of the treatment paradigm
- Although uncommon, noninvasive lesions can be treated with local resection and diligent surveillance

MEDICATION

First Line
- Systemic chemotherapies have been used with limited experience in treating SCC of the bladder
- Small series have reported positive responses to cisplatin-based therapies, similar to pure urothelial carcinoma
- At present, role for neoadjuvant/adjuvant chemotherapy is poorly defined

Second Line

N/A

SURGERY/OTHER PROCEDURES (2)
- After diagnosis is confirmed, radical cystectomy is 1st-line treatment
- Bladder-preserving therapies can be considered if tumor is nonmuscle invasive and completely resected, and patient is willing to commit to intensive surveillance protocol
- Limited experience with chemoradiotherapy as primary treatment modality

ADDITIONAL TREATMENT

Radiation Therapy
Can be used in adjuvant setting for patients with positive surgical margins at time of surgery

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Related to pathologic stage (3)
  - Evidence suggests that patients with SCC of the bladder tend to present with higher-stage (pT3/T4) disease at the time of radical cystectomy
- Overall survival has ranged from 4.8 to 50%
- 5-yr cancer-specific survival in contemporary series has ranged from 57 to 64%

COMPLICATIONS
- Related to radical cystectomy and urinary diversion
  - Perioperative mortality approaches 2%
  - 40–50% of patients will experience a postoperative complication
  - Gastrointestinal complication is most common, eg, ileus, small bowel obstruction

FOLLOW-UP
Patient Monitoring
- Related to tumor stage at the time of radical cystectomy
  - In general, patients are followed with history, physical exam, laboratory studies (CBC and comprehensive metabolic profile, including liver function tests) and cross-sectional imaging of chest, abdomen, and pelvis every 3–6 mo after surgery for the first 2 yr then semiannually for 2 yr then annually
  - Renal function needs to be followed annually as well

Patient Resources
Bladder Cancer Advocacy Network (www.bcan.org)

REFERENCES

1. Kim SP, Frank I, Cheville JC, et al. The impact of squamous and glandular differentiation on survival after radical cystectomy for urothelial carcinoma. *J Urol*. 2012;188:405–409.
2. Rausch S, Lotan Y, Youssef RF. Squamous cell carcinogenesis and squamous cell carcinoma of the urinary bladder: A contemporary review with focus on nonbilharzial squamous cell carcinoma. *Urol Oncol*. 2014;32(1):32.e11–6.
3. Xylinas E, Rink M, Robinson BD, et al. Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. *Eur J Cancer*. 2013;49(8):1889–1897.

ADDITIONAL READING
N/A

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General
- Bladder Cancer, Squamous Cell Carcinoma Image ☼
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)

CODES

ICD9

188.9 Malignant neoplasm of bladder, part unspecified

ICD10

C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

- With the control of schistosomiasis in endemic regions, the rate of SCC is dropping relative to the diagnosis of urothelial carcinoma.
- Radical cystectomy is the gold standard for muscle-invasive SCC of the bladder.

BLADDER CANCER, UROTHELIAL, METASTATIC (CLINICAL AND PATHOLOGIC N+, M+)

Jean Hoffman-Censits, MD
Wm. Kevin Kelly, DO

BASICS

DESCRIPTION

- Inoperable and metastatic bladder cancers are less common presentations than noninvasive-bladder cancer.
- Though radical cystectomy for muscle-invasive bladder cancer is potentially curative, up to 50% of patients will develop recurrent disease within 2 yr.
- Most deaths from bladder cancer are from metastatic disease.
- Lymph nodes, bones, lung, liver, and peritoneum are the most common sites of metastasis from bladder cancer. The brain can also be a site, especially after systemic chemotherapy. Other unusual sites: Heart, kidney, spleen, pancreas, and reproductive system.
- The 5-yr survival for distant metastasis is 5.4%. This is in comparison to the 5-yr survival for localized bladder cancer of 70.2%.

EPIDEMIOLOGY

Incidence

- 74,690 new cases of bladder cancer will be diagnosed in 2014 with 15,580 deaths
- Bladder cancer is the 4th most common cancer diagnosed in men. Bladder cancer is much more common in men than women, whites, and those over 55 yr of age

Prevalence

An estimated 563,640 people are living with all stages of bladder cancer in US.

RISK FACTORS

- Cigarette smoking
- Chemical and occupational exposure association (aromatic amine exposure, workers in rubber, textile, leather, painting, printing, machinist, hairdressing, dry-cleaning, and trucking industries)
- Pelvic radiation and chemotherapy (Cytoxan)

Genetics

- A family history of bladder cancer increases risk, either from genetic or environmental factors
- Patients with hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) are at increased risk of developing urothelial cancers
- Genetic alterations in FGFR3/RAS, p53, EGFR, PIK3CA, Her-2, and others

PATHOPHYSIOLOGY

- Alterations in genes which contribute to toxin breakdown within the bladder (such as *GST* and *NAT*), may make bladder cancer more likely

- Tumor multifocality and high recurrence rate within the bladder, ureters, and renal pelvis with a bladder cancer history support a field effect, in part from toxin exposure

ASSOCIATED CONDITIONS
- The majority of bladder cancer diagnosed in US has no other associations.
- In Egypt and other endemic regions, chronic bladder inflammation from schistosomiasis infection can lead to squamous cell carcinoma, as can chronic bladder irritation or inflammation, such as from chronic indwelling catheter use.

GENERAL PREVENTION
- Smoking cessation
- Limit or modify chemical exposure
- Hydration may limit toxin exposure

DIAGNOSIS
HISTORY
- Many tumor recurrences are noted during routine radiographic surveillance, which is standard following radical cystectomy.
- Pain from bone metastasis, lymphatic progression in the retroperitoneum, bowel obstruction with carcinomatosis, and symptoms of visceral progression such as in the lungs and liver can be symptoms of metastatic bladder cancer.

PHYSICAL EXAM
- Most with early advanced or metastatic disease have no significant external exam findings.
  - Palpable lymphadenopathy, hepatomegaly from liver involvement, as well as cachexia of malignancy can be noted.
- Leg edema with venous thromboembolism is present (incidence 1–8%); higher incidence with platinum combination therapy.
- Poor nutrition and increased abdominal girth in setting of ascites and soft tissue intra-abdominal recurrence can contribute to edema.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Lab abnormalities can include anemia of chronic disease, iron deficiency anemia in patients with longstanding hematuria, renal insufficiency in patients with ureteral obstruction, transaminitis (elevation of liver transaminases), and elevation in bilirubin in patients with liver involvement.
- Hypercalcemia is rare and associated with poor prognosis (typically associated with squamous differentiation)
- No serum tumor marker for bladder cancer.

Imaging
- Staging guidelines recommend abdomen and pelvis imaging with CT or MRI
- Imaging of the upper tract collecting system
- Chest imaging
- Bone scan if clinical suspicion of bone metastasis by pain or alkaline phosphatase elevation
- PET may be useful but not standard of care

- Documentation of normal cardiac ejection fraction required for Adriamycin

Diagnostic Procedures/Surgery

- Needle biopsy of suspected metastatic lesions
- Confirmatory needle biopsy at the time of radiographic recurrence, particularly for a patient with residual invasive or node-positive disease at cystectomy following preoperative chemotherapy, is at physician discretion

Pathologic Findings

- Urothelial (formerly transitional cell) carcinoma is the most common subtype, and for which the most data exists.
  - Many patients may have urothelial cancer with squamous or other foci of dedifferentiation.
- Less common histologic subtypes are squamous cell carcinoma, adenocarcinoma, and small cell carcinoma.

DIFFERENTIAL DIAGNOSIS

- Pelvic and retroperitoneal adenopathy
  - Malignancy: Lymphoma (non-Hodgkin, Hodgkin, others); metastatic (adrenal, renal, urothelial, prostate, urethral, penile, germ cell, cervical, ovarian, uterine), GI (carcinoid, lymphomas), colorectal, melanoma
  - Infectious/inflammatory:
    - Granulomatous: TB, sarcoidosis, histoplasmosis, lymphogranuloma venereum, Castleman disease, etc.
    - Nongranulomatous: Viral, bacterial (if abscess in local areas), sinus histiocytosis, retroperitoneal fibrosis
  - Other: Cystic retroperitoneal masses (lymphocele, urinoma, hemorrhage) aneurysms
- Bone lesions
  - Congenital (bone islands, others)
  - Endocrine/metabolic (hyperparathyroidism, Paget disease)
  - Neoplasm primary (osteosarcoma) or secondary (prostate, breast, kidney, lung, thyroid)
  - Trauma fracture (stress or healing)
  - Others: Autoimmune diseases, drugs (Vitamin D, fluoride), infection (osteomyelitis), inflammatory/Idiopathic, vascular (hemangiomas, infarct)
- Pulmonary nodules
  - Benign: Abscesses, septic emboli, fungal (histoplasmosis, etc.), parasites, mycobacterial, inflammatory conditions (Wegner granulomatosis), pulmonary AVM, pneumoconiosis, silicosis
  - Malignant: Primary lung cancer, bladder cancer, choriocarcinoma, renal and thyroid cancer, melanoma, Kaposi's sarcoma

TREATMENT

GENERAL MEASURES

- Treatment of urothelial (transitional cell) carcinoma with cisplatin-based chemotherapy has increased survival but cures are limited. With good performance status and renal function

cisplatin-based combination chemotherapy is the initial approach (Grade 1A) (1)
- "Fitness" for cisplatin-based therapy is not well defined: Generally assessment of renal function(>60 mL/min), hearing (>25 dB at 2 contiguous frequencies), performance status (WHO/ECOG performance status 2 or less), baseline peripheral neuropathy and cardiac function (New York Heart Association [NYHA] Class II or better)
- In the setting of impaired renal function correct reversible causes (obstruction, etc.)

MEDICATION

First Line

- Cisplatin-based chemotherapy combinations are the most active and superior to carboplatin regimens. Survival outcome is similar in patients treated with standard multiday MVAC (methotrexate, vinblastine, adriamycin, cisplatin) compared to cisplatin with gemcitabine (GC), with less toxicity in the GC group (1,2)
- High-dose intensity chemotherapy with MVAC plus GMCSF (HD-M-VAC) compared to classic M-VAC led to a better overall response rate (64 vs. 50%) and improved survival (21.8% in the HD-M-VAC vs. 13.5%) at 7 yr. The toxicity profile of HD-M-VAC was superior with better dose intensity, and thus established HD-M-VAC as an alternative to standard M-VAC (3)
  - MV chemotherapy is usually given every 14 days with the AC given along each 28 days
  - HD-M-VAC is also referred to as "dose dense" MVAC (DDMVAC) regimen gives the same drugs at the same doses closer together, all drugs every 14 days with hematopoietic growth factor support and is recommended by the NCCN guidelines
- Adding paclitaxel to cisplatin and gemcitabine, compared to GC led to a modest but not significant improvement in survival and is not endorsed for most patients (4)
- Some typical regimens reported in the literature include
  - MVAC: Methotrexate (30 mg/m^2 on days 1, 15, 22), vinblastine (3 mg/m^2 on days 2, 15, 22), doxorubicin (30 mg/m^2 on day 2), and cisplatin (70 mg/m^2), repeated every 28 days for 6 cycles
  - GC: Gemcitabine (1,000 mg/m^2 days 1, 8, 15) plus cisplatin (70 mg/m^2 day 2), repeated every 28 days for a maximum of 6 cycles

Second Line

- There is no standard therapy for patients who have disease recurrence or progression following 1st-line cisplatin/gemcitabine or MVAC chemotherapy, and clinical trial participation is encouraged.
- Small nonrandomized studies support the use of taxanes, gemcitabine, 5-fluorouracil, methotrexate, pemetrexed, and others in the 2nd line with modest benefit of single-agent therapy.
- The substitution of carboplatin for gemcitabine in the palliative setting in the GC regimen is reasonable for those felt unfit for cisplatin.

SURGERY/OTHER PROCEDURES

- Retrospective series support consideration of salvage surgery for patients who initially present with unresectable or metastatic disease with robust chemotherapy response (5). Survival rates were consistently better in those with pathologic complete response to induction chemotherapy and in those with node only metastasis. (See Section I "Bladder

cancer, urothelial, muscle invasive (clinical and pathologic T2/T3/T4)(MIBC) neoadjuvant therapy.")

ADDITIONAL TREATMENT

Radiation Therapy

Palliative radiotherapy is an option for patients with painful bony metastasis

Additional Therapies

- Studies suggest benefit of zolendronic acid or denosumab in patients with metastatic bladder cancer to bone (6)
- Granulocyte colony-stimulating factor can help limit myelosuppression with cisplatin and others

Complementary & Alternative Therapies

Supportive care includes adequate nutrition and hydration, particularly for patients undergoing multimodality therapy

ONGOING CARE

PROGNOSIS

For patients with metastatic disease, ECOG status ≥ 1, hemoglobin ≤ 10, and visceral involvement are prognostic for overall survival (survival 14.2 mo for those with none of these features vs. 1.7 mo with all 3 features)

COMPLICATIONS

- Cisplatin: Nephrotoxicity, ototoxicity, peripheral neuropathy, fatigue
- Adriamycin (in MVAC regimen): Cardiac toxicity
- MVAC toxicity is a major concern: Myelosuppression, neutropenic fever, sepsis, mucositis, nausea, and vomiting are common (up to 54% may require readmission for toxicity)
- Neutropenia (including life-threating febrile neutropenia) associated with multimodality chemotherapy for bladder cancer. Granulocyte growth factor is standard in the high-dose intensity MVAC regimen, and is used to support patients on gemcitabine and platinum combinations
- Gemcitabine: Rash and cytopenias
- Taxanes (ie, paclitaxel): Fluid retention, neuropathy, myelosuppression
- Ureteral obstruction (tumor or lymphadenopathy) is common and can be alleviated with ureteral stenting or percutaneous nephrostomy drainage

FOLLOW-UP

Patient Monitoring

In patients with metastatic disease on chemotherapy, imaging should be performed every 2–3 mo to assess response. In patients with durable responses of chemotherapy, imaging should be done every 3 mo for the 1st 2 yr of response.

Patient Resources

- Bladder Cancer Advocacy Network
  – http://www.bcan.org/

REFERENCES

1. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2000;18(17):3068–3077.
2. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer*. 2006;42(1):50–54.
3. Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatin- based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol*. 2012;23:406–410.
4. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol*. 2012;30:1107–1113.
5. Dodd P, McCaffrey JA, Herr H, et al. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. *J Clin Oncol* 1999;17:2546–2552.
6. Zaghloul M, Boutrus R, El-Hossieny H, et al. A prospective, randomized, placebo controlled trial of zolendronic acid in bony metastatic bladder cancer. *Int J Clin Oncol*. 2010;15;382–389.

ADDITIONAL READING

NCCN guidelines for Bladder Cancer, version 1.2013, http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf, Accessed January 28, 2014.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General
- Bladder Cancer, Nonurothelial
- Bladder Cancer, Squamous Cell Carcinoma
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Reference Tables: TNM Classsification: Urinary Bladder Cancer

CODES

ICD9

- 188.9 Malignant neoplasm of bladder, part unspecified
- 196.9 Secondary and unspecified malignant neoplasm of lymph nodes, site unspecified
- 198.89 Secondary malignant neoplasm of other specified sites

ICD10

- C67.9 Malignant neoplasm of bladder, unspecified
- C77.9 Secondary and unsp malignant neoplasm of lymph node, unsp
- C79.89 Secondary malignant neoplasm of other specified sites

CLINICAL/SURGICAL PEARLS

- Single-agent chemotherapy provides low response rates of usually short duration.
- For 1st-line chemotherapy, performance status and the presence or absence of visceral metastases are independent prognostic factors for overall survival.
- Brisk diuresis helps limit cisplatin renal toxicity.

BLADDER CANCER, UROTHELIAL, MUSCLE INVASIVE (CLINICAL AND PATHOLOGIC T2/T3/T4) (MIBC)

Zachary L. Smith, MD
S. Bruce Malkowicz, MD, FACS

BASICS

DESCRIPTION

- Muscle-invasive bladder cancer (MIBC) refers to invasion into or through the muscularis propria of the bladder wall (≥T2)
- Depth of invasion important for staging and treatment decisions
- Urothelial carcinoma accounts for >90% of bladder cancers (BCa)
- Less common etiologies include:
  - Squamous cell carcinoma (SCC) (5%)
  - Adenocarcinoma (2%)
  - Urachal carcinoma (<1%)

EPIDEMIOLOGY

Incidence

- 74,690 new cases of BCa in 2014 in US (1)
- Male > Female (4:1)
- 73 yr old: Average age at diagnosis
  - ~90% of patients are >55 yr at diagnosis

Prevalence

>500,000 in US (all stages)

RISK FACTORS

- Cigarette smoking (>50% of cases)
- Occupational exposure (dye, textile, rubber, and leather factory workers)
- Chronic indwelling catheters are risk factor for SCC.
  - Also, schistosomiasis in some parts of Middle East and Africa

Genetics

- Hereditary patterns:
  - Autosomal dominant
  - Multifactorial polygenic
- Cytogenetic abnormalities:
  - Loss of heterozygosity in chromosome 9 (>50% all grades and stages BCa)
  - Loss of chromosomes 17q, 5q, 3p (MIBC)
  - Inactivating mutation in p53, p21, or Rb (MIBC)
  - TP53 and/or P16 abnormalities (high-grade BCa)

PATHOPHYSIOLOGY

- Growth patterns: Papillary (70%), nodular (10%), and sessile or mixed (20%)

- Invasive tumors (T2–T4) are present in 30% at initial presentation
- 50–70% of noninvasive BCa will recur, despite conservative measures
  - Recurrent superficial BCa will progress to MIBC in 10–15%
- High-grade T1 lesions, especially if associated with lymphovascular invasion and/or carcinoma in situ (CIS), have high progression rate, requiring aggressive management
- Metastases occurs via hematogenous and/or lymphatic spread:
  - Location (most to least common): Lymph nodes (obturator, external iliac, common iliac), liver, lung, bone, adrenal
  - Most patients with metastatic disease die within 2 yr

ASSOCIATED CONDITIONS
Those secondary to smoking (lung disease, other malignancies)

GENERAL PREVENTION
- Avoidance of exposure to cigarette smoke and industrial risk factors.
- Appropriate and timely workup of both microscopic and/or gross hematuria (early diagnosis, not prevention)

DIAGNOSIS
HISTORY
- History of smoking or other risk factors
- Prior bladder tumors or hematuria
- Family history of BCa
- Signs and symptoms:
  - Painless hematuria (80%)
  - Irritative voiding symptoms (frequency, urgency, dysuria) (35%)
  - Stigmata of locally invasive or metastatic disease (pelvic pain/fullness, fixed bladder or palpable mass, inguinal lymphadenopathy, flank pain, weight loss, bone pain)

PHYSICAL EXAM
- General: Nutritional status, abdominal/pelvic masses, lymphadenopathy
- Digital rectal exam (male), bimanual pelvic exam (female), which can be performed under anesthesia

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Blood: CBC, electrolytes, LFT (elevated alkaline phosphatase suggests liver or bone involvement)
- Urine:
  - Urinalysis with microscopy
  - Cytology: Specificity ~95%; sensitivity good for high-grade, poor for low-grade
  - Other markers, less widely used: UroVysion (fluorescence in situ hybridization), BTA stat, BTA TRAK, NMP22, ImmunoCyt/uCyt+

Imaging
- Abdominal imaging:
  - CT urogram (triple phase: Noncontrast, nephrographic, excretory) is the current standard

of care
  - MR urogram acceptable, where available
  - If renal insufficiency, retrograde pyelograms combined with noncontrast CT or US
- Chest imaging: Chest x-ray (CXR) or CT
- Bone scan

Diagnostic Procedures/Surgery
- Cystoscopy to evaluate bladder for lesions
- Bladder biopsy or transurethral resection of bladder tumor (TURBT) establishes diagnosis

Pathologic Findings
- BCa will be analyzed by pathologist for grade and depth of invasion
- Grading (WHO/ISUP, 2004):
  - Papillary urothelial neoplasm of low malignant potential (well-differentiated)
  - Low-grade (moderately differentiated)
  - High-grade (poorly differentiated)
- Depth of invasion:
  - Into detrusor muscle (T2)
  - Into perivesical fat (T3)
  - Into adjacent structures (prostate, uterus, vagina, pelvic/abdominal wall) (T4)

DIFFERENTIAL DIAGNOSIS
- Gynecologic and other pelvic tumors directly invading bladder
- Adenocarcinomas more likely to be metastatic in origin
- Mass seen at bladder base on imaging is sometimes actually prostate median lobe

TREATMENT

GENERAL MEASURES
- Preoperative evaluation, as most patients also have significant cardiopulmonary disease
- Discuss treatment options and urinary diversion options
  - If ileal conduit, meet with stoma therapy nurse preop and postop for care/teaching
  - For continent diversion, preop teaching imperative
- If bladder preservation chosen, coordinate with radiation oncology and medical oncology

MEDICATION
First Line
- Intravesical treatments not used for MIBC
- Chemotherapy used as:
  - Neoadjuvant/adjuvant therapy with radical cystectomy (RC) urothelial carcinoma primarily
  - Primary treatment of metastatic disease
  - In combination with radiation therapy (RT) or TURBT for bladder preservation protocols
- Chemotherapy regimens differ based on patient factors:
  - MVAC is the historical gold standard and still commonly used
  - Gemcitabine/cisplatin has equivalent efficacy with much less toxicity and has become more commonly used

Second Line

- Carboplatin substituted for cisplatin in renal insufficiency
- Mitomycin/5-fluorouracil is a newer regimen which has emerging data to support its use
- Taxanes also promising as both single and combination agent

SURGERY/OTHER PROCEDURES

- RC with pelvic lymphadenectomy and urinary diversion considered gold standard therapy for MIBC (2)
  - Complete extirpation and pelvic lymphadenectomy provide best chances for local control and long-term survival
  - Ureteral frozen sections to ensure negative margins before urinary tract reconstruction is standard practice
  - Patients with ≥T3 disease on clinical staging may be offered neoadjuvant chemotherapy
  - RC gives no survival benefit in metastatic disease, but may be palliative in patients with intractable hematuria or pelvic pain
  - Lymphadenectomy may be prognostic and therapeutic:
    - Positive nodes in ~25%
    - Patients with limited nodal burden have higher survival rates
    - Extended lymphadenectomy (to include presacral, paraaortic, and paracaval nodes) may improve survival
    - May identify patients most suited for adjuvant therapies
- Urinary diversion (3):
  - Options include continent catheterizable stoma, continent orthotopic neobladder, or ileal conduit; each with advantages and disadvantages
    - Ileal conduit used most commonly, least complications
    - Neobladders typically reserved for younger, motivated patients who are able to perform self-catheterization if needed
- Partial cystectomy:
  - Strict patient selection criteria: Stage T2 only, solitary lesion allowing for 2-cm margins, lack of CIS, not involving trigone or ureteral orifices
  - Recurrence common within 2 yr
  - Still allows for lymphadenectomy
- Radical TURBT:
  - As a sole therapy, outcomes poor for MIBC
  - Usually palliative in patients who will not tolerate RC or systemic therapy (such as elderly with significant comorbidities)
- Urethrectomy:
  - Simultaneous (during RC) or delayed urethrectomy if CIS or tumor involves prostatic urethra, ducts, or stroma
  - Orthotopic reconstruction should not be made until negative frozen-section distal urethral margin is examined

ADDITIONAL TREATMENT

Radiation Therapy

- RT as a monotherapy is considered inferior to RC
- RT in combination with chemotherapy has a role in selected patients undergoing organ

preservation (see below)

Additional Therapies

- Combination RT and chemotherapy after TURBT is the most efficacious bladder preservation technique
  - Developed for patients who are either not candidates for or refuse RC. Ideal candidates for bladder preservation:
    - Complete visual resection on TURBT
    - Solitary tumor
    - No hydronephrosis
  - 5-yr overall survival 30–50%; better in T2 disease than T3–T4

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prognostic factors:
  - Tumor cell type (SCC and adenocarcinoma less favorable)
  - Tumor grade and stage
  - Disease-free survival correlates with stage
  - Node burden (>8 positive) and node density (>20%) has worse prognosis
- Survival rates after RC:
  - Disease-free survival (5-yr) without positive nodes: 72% (62–84%) for pT2; 40% (19–57%) for pT3; 24% (0–36%) for pT4
  - Disease-free survival with positive nodes: 30% (15–48%)

COMPLICATIONS

- General:
  - Commonly due to local invasion and advancement of disease
    - Urinary obstruction, hydronephrosis
    - Hematuria, clot retention
  - Malnutrition, infection, etc.
- Associated with RC:
  - 90-day hospital readmission: 32%
  - 90-day mortality: ~6%
  - Bowel obstruction (4–10%), ureteral anastomotic stricture (5–10%), PE (2%)

FOLLOW-UP

Patient Monitoring

- Follow-up remains controversial and dependent on disease severity. Example:
  - T1/T2 disease: Semiannual physical exam, serum chemistries, and CXR with CT scan every 2 yr (T1) or yearly (T2)
  - T3/T4 disease: Exam, labs, and CXR every 3 mo with semiannual CT scan
  - If disease free at 5 yr, surveillance can be lessened per patient/practitioner comfort level
  - Patients with intact urethra should be monitored for urethral recurrence

- Consider urethral washing or cystoscopy

Patient Resources

Bladder Cancer Advocacy Network (BCAN): www.bcan.org

REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(1):9–29. doi: 10.3322/caac.21208.
2. Lerner SP, Sternberg CN. Management of metastatic and invasive bladder cancer. In: Wein AJ, et al., eds., *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier, 2012.
3. Dahl DM, McDougal WS. Use of intestinal segments in urinary diversion. In: Wein AJ, et al., eds., *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier, 2012.

ADDITIONAL READING

- American Urological Association Clinical Guidelines, Bladder Cancer, 2007. Available at: www.auanet.org (accessed May 1, 2014).
- Herr HW, Dotan Z, Donat SM, et al. Defining optimal therapy for muscle invasive bladder cancer. *J Urol.* 2007;177(2):437–443.
- Huang GJ, Stein JP. Open radical cystectomy with lymphadenectomy remains the treatment of choice for invasive bladder cancer. *Curr Opin Urol.* 2007;17(5):369–375.
- Smith ZL, Christodouleas JP, Keefe SM, et al. Bladder preservation in the treatment of muscle-invasive bladder cancer (MIBC): A review of the literature and a practical approach to therapy. *BJU Int.* 2013;112(1):13–25.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General
- Bladder Cancer, Nonmuscle-Invasive Bladder Cancer (Ta, T1)
- Bladder Cancer, Urothelial, Metastatic (Clinical and Pathologic N+, M+)
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and PathologicS T2/T3/T4) (MIBC) Image
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC) Neoadjuvant Therapy
- Bladder Mass
- Bladder Tumor Algorithm
- Bladder Tumors, Benign and Malignant, General Considerations
- Bladder Tumors, Benign and Malignant, General Considerations Algorithm
- Reference Tables: TNM Classification: Urinary Bladder Cancer

CODES

ICD9

188.9 Malignant neoplasm of bladder, part unspecified

ICD10

C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

- MIBC represents an aggressive disease with lethal potential.
- Surgical resection in the form of RC is the gold standard therapy.
- Role for multimodal treatment of MIBC with chemoradiotherapy and aggressive TUR is not as well established as RC, however, has shown promising results.

BLADDER CANCER, UROTHELIAL, MUSCLE INVASIVE (CLINICAL AND PATHOLOGIC T2/T3/T4) (MIBC) NEOADJUVANT THERAPY

Jean Hoffman-Censits, MD
William Kevin Kelly, DO

BASICS

DESCRIPTION

- Detrusor muscle-invasive bladder cancer (T2, 3, 4 MIBC) is much less common than noninvasive bladder cancer.
- May present with de novo invasive cancer, a minority progress from superficial bladder cancer
- Radical cystectomy for muscle-invasive bladder cancer is potentially curative; up to 50% of patients will develop recurrence within 2 yr.
  - This high recurrence has led to the increasing use of neoadjuvant chemo before cystectomy.
  - Neoadjuvant cisplatin-based chemo has improved survival vs. radical cystectomy alone.

EPIDEMIOLOGY

Incidence (1)

- 74,690 new cases of bladder cancer will be diagnosed in 2014 with 15,580 deaths
  - Most deaths due to metastatic disease
- Bladder cancer is the 4th most common cancer diagnosed in men
- Bladder cancer is much more common in men than women, whites, and those over 55 yr old

Prevalence

>500,000 in US (all stages)

RISK FACTORS

- Cigarette smoking
- Chemical and occupational exposure association (aromatic amine exposure, workers in rubber, textile, leather, painting, printing, machinist, hairdressing, dry-cleaning, and trucking industries)

Genetics

- A family history of bladder cancer increases risk, either from genetic or environmental factors
- Patients with hereditary nonpolyposis colorectal cancer (HNPCC) are at increased risk of developing urothelial cancers
- Hereditary patterns:
  - Autosomal dominant
  - Multifactorial polygenic
- Cytogenetic abnormalities:

– Loss of heterozygosity in chromosome 9 (>50% all grades and stages BCa)
– Loss of chromosomes 17q, 5q, 3p (MIBC)
– Inactivating mutation in p53, p21, or Rb (MIBC)
– TP53 and/or P16 abnormalities (high-grade BCa)

PATHOPHYSIOLOGY
- Alterations in genes which contribute to toxin breakdown within the bladder (such as *GST* and *NAT*), may make some more likely to develop bladder cancer
- Tumor multifocality and the high rate of recurrence of urothelial cancers within the bladder, ureters, and renal pelvis in patients with a bladder cancer history can be due to the field effect in part from toxin exposure
- T2: Muscularis propria invasion
- T3:Perivesical tissue invasion
- T4: Invasion of pelvic structures (eg, prostate stroma, seminal vesicles, uterus, vagina, pelvic side wall, or abdominal wall)

ASSOCIATED CONDITIONS
- The majority of bladder cancer diagnosed in US has no other associations.
- In Egypt and regions in SE Asia, chronic bladder irritation from Schistosomiasis infection can lead to squamous cell carcinoma, as can chronic bladder irritation or inflammation, such as from chronic indwelling catheter use.

GENERAL PREVENTION
- Smoking cessation
- Limit or modify chemical exposure

DIAGNOSIS
HISTORY
- Gross or microscopic hematuria is the most common presenting sign
- Dysuria, frequency, and urgency are common
- Symptoms of locally advanced disease such as pelvic pain and constipation
- Flank pain or renal insufficiency due to ureteral obstruction by tumor

PHYSICAL EXAM
- Most with muscle-invasive bladder cancer have no significant external exam findings
- Palpable lymphadenopathy, hepatomegaly from liver involvement, or other signs from obstructive processes in later-stage disease.
- Leg edema with DVT
  – Incidence 1–8%; higher in patients treated with platinum combination therapy

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Lab abnormalities can include anemia of chronic disease, iron deficiency anemia in patients with longstanding hematuria, gross or microscopic hematuria, and renal insufficiency in patients with ureteral obstruction.

Imaging
- Staging guidelines recommend abdomen and pelvis imaging with CT or MRI

- Imaging of the upper tract collecting system
- Chest imaging
- Bone scan if clinical suspicion of metastasis or alkaline phosphatase elevation
- PET may be useful in determining metastatic or node-positive disease but not yet standard
- Understaging, despite adequate radiographic and pathologic data from transurethral resection of bladder tumor (TURBT), is common

Diagnostic Procedures/Surgery
- Cystoscopy with TURBT for staging and debulking of invasive disease
  – Detrusor muscle must be present in specimen for accurate pathologic staging
- Examination under anesthesia (EUA) is part of bladder cancer staging; fixation suggests locally advanced disease

Pathologic Findings
- Urothelial (formerly transitional cell) carcinoma is most common. Many patients have urothelial cancer with squamous or other differentiation.
- Less common histologic subtypes: Squamous cell carcinoma (associated with chronic inflammation), adenocarcinoma, and small cell carcinoma with or without sarcomatous changes.

DIFFERENTIAL DIAGNOSIS
- See Section I “Bladder cancer, urothelial, muscle invasive (clinical and pathologic T2/T3/T4)(MIBC)”

TREATMENT

GENERAL MEASURES
- Neoadjuvant cisplatin-based chemo should be considered for patients with muscle invasion (cT2–T4) undergoing radical cystectomy
- Overall survival benefit of 5% with lower recurrence based on meta-analysis (2)
- MVAC (methotrexate, vinblastine, adriamycin, cisplatin) preferred in healthy patients <70 yr. CMV or gemcitabine (GC) are alternatives if older or with comorbidities

MEDICATION

First Line
- Cisplatin-based chemo combinations are superior to carboplatin-based regimens. Carboplatin should not be substituted for cisplatin in patients being treated with curative intent.
- Neoadjuvant chemo has shown benefit in overall survival and in pathologic downstaging
  – Neoadjuvant MVAC trial (methotrexate, vinblastine, adriamycin, cisplatin) vs. cystectomy alone (77 vs. 46 mo 5-yr survival) (3)
- In the advanced and metastatic setting, survival outcome is similar in patients treated with MVAC compared to cisplatin with GC, with less toxicity with GC
- Several studies of neoadjuvant HD-MVAC have yielded similar rates of complete pathologic response at cystectomy compared to MVAC with manageable toxicity. HD-MVAC also referred to as “dose dense" MVAC (DDMVAC) gives the same drugs at the same doses closer together (all drugs every 14 days with hematopoietic factor support) (4)

- HD-MVAC is the neoadjuvant regimen choice at some centers, but GC is also commonly used
- CMV neoadjuvant chemo (cisplatin, methotrexate, vinblastine): Survival benefit at 10 yr (36% survival vs. 30% without chemo) (5)
- Common neoadjuvant regimens (6)
  - MVAC: Methotrexate (30 mg/m^2 days 1, 15, 22), vinblastine (3 mg/m^2 days 2, 15, 22), doxorubicin (30 mg/m^2 day 2), cisplatin (70 mg/m^2 on day 2) every 28 days × 3 cycles
  - CMV: Methotrexate (30 mg/m^2) and vinblastine (4 mg/m^2) days 1 and 8 plus cisplatin (100 mg/m^2 on day 2), with folinic acid (15 mg every 6 hr × 4 doses) days 2, 9, repeated every 28 days × 3 cycles
  - GC: GC (1,000 mg/m^2 days 1, 8, 15) plus cisplatin (70 mg/m^2 day 2) every 28 days × 6 cycles maximum
- "Fitness" for cisplatin is not well defined, but includes: Renal function, hearing, performance status, baseline neuropathy, and cardiac function

Second Line

- For patients treated with perioperative cisplatin-based chemo with disease recurrence, particularly for those with recurrence >12 mo following chemo, cisplatin rechallenge can be considered.
  - With disease progression while on or closely following cisplatin-based chemo, there is no standard second line therapy.
  - Many small studies have shown modest benefit of single agent or combination regimens.

SURGERY/OTHER PROCEDURES

- Radical cystectomy is the treatment of choice for patients with invasive (T2–T4) disease, patients with multifocal tumors, large tumors, hydronephrosis, node-positive disease (N1).
  - Consider consolidative cystectomy in patients with extensive nodes or locally advanced disease with durable responses to chemo.
- Bilateral pelvic lymphadenectomy: Include common iliac, internal iliac, external iliac, hypogastric, presacral, and obturator nodes.
  - Increased number of lymph nodes removed and lymph node density (# positive LN / # total LN removed) in patients with positive lymph nodes can improve recurrence rates (7).
  - A randomized trial of standard vs. extended pelvic lymph node dissection is ongoing.

ADDITIONAL TREATMENT

Radiation Therapy

- Multimodality treatment with chemo-radiotherapy can be considered for patients who are medically inoperable or selected patients who wish for bladder preservation (8).
  - Tumors <5 cm, no carcinoma in situ, no hydronephrosis, complete TURBT resection, T2–T3, functional bladder at baseline.
- Neoadjuvant chemo followed by cystectomy and chemo-radiotherapy have not been compared head to head in a prospective trial

Additional Therapies

- Multidisciplinary evaluation should be considered to asses best plan of care
- For patients who have received standard cisplatin-based neoadjuvant chemo, there is currently no recommendation for adjuvant chemo following cystectomy

- For patients with invasive or node-positive disease following cystectomy who did not receive neoadjuvant chemo, adjuvant platinum-based therapy should be considered
- Positive surgical margins can increase risk of local failure; consider adjuvant radiotherapy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Patients with pathologic complete response (pT0) at radical cystectomy have superior relapse free and overall survival outcomes compared to those with residual invasive disease – 10.6% complete pathologic downstaging
- Treatment with neoadjuvant cisplatin-based chemo increases the rate of pT0 over patients treated with TURBT alone (38 vs. 15%) in the Phase III study of preoperative MVAC compared to cystectomy alone

COMPLICATIONS

- Cisplatin: Nephrotoxicity, ototoxicity, peripheral neuropathy, and fatigue
- Adriamycin (in MVAC): Cardiac toxicity
- Neutropenia, including life threating febrile neutropenia is associated with multimodality chemo for bladder cancer. Granulocyte growth factor is standard in the high-dose intensity MVAC regimen, and can be used to support patients on GC/platinum combinations
- GC: Rash and cytopenias
- Ureteral obstruction (tumor or nodes): Alleviate with ureteral stenting or percutaneous nephrostomy to improve renal function
- 30-day perioperative mortality following cystectomy approximately 1%; average 30-day readmission rate 21–32%
- Perioperative morbidity following cystectomy: Ileus, blood loss, infection, thromboembolism, wound dehiscence, ostomy complications.

FOLLOW-UP

Patient Monitoring

- Following radical cystectomy, imaging of the chest, abdomen and pelvis including upper tract evaluation and CBC and electrolyte assessment should occur every 3–6 mo. Based on recurrence risk for the first 2 yr, then as clinically indicated.
- Urine cytology and electrolytes should be monitored every 3–6 mo. Based on recurrence risk for the first 2 yr., then as clinically indicated.
- Continent diversion: Monitor B12 deficiency

Patient Resources

Bladder Cancer Advocacy Network http://www.bcan.org/

REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin*. 2014 64(1):9–29. doi: 10.3322/ caac.21208.
2. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in

invasive bladder cancer: A systematic review and meta-analysis. *Lancet*. 2003;361(9373):1927
3. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349:859–866.
4. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer*. 2006;42(1):50–54.
5. Griffiths G, Hall R, Sylvester R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. *J Clin Oncol*. 2011;29(16):2171–2177.
6. Raghavan D. Neoadjuvant treatment and bladder preservation options for muscle-invasive urothelial (transitional cell) bladder cancer www.UpToDate. com, Accessed January 26, 2014.
7. Bi L, Huang H, Fan X, et al. Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: A systematic review and meta-analysis of comparative studies.*BJU Int*. 2014;113(5b):E39–E48.
8. Gakis G, Efstathiou J, Lerner SP, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Radical cystectomy and bladder preservation for muscle invasive urothelial carcinoma of the bladder. *Eur Urol*. 2012;63:45–57.

ADDITIONAL READING

NCCN Guidelines for Bladder Cancer, version 1. 2013, http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf, Accessed January 28, 2014.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC) Neoadjuvant Therapy Image
- Bladder Cancer, Urothelial, Metastatic (Clinical and Pathologic N+, M+)
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Bladder Tumor Algorithm
- Reference Tables: TNM Classification: Urinary Bladder cancer

CODES

ICD9

188.9 Malignant neoplasm of bladder, part unspecified

ICD10

C67.9 Malignant neoplasm of bladder, unspecified

CLINICAL/SURGICAL PEARLS

- Outcomes after radical cystectomy indicate increased survival in patients who had more, rather than fewer, lymph nodes resected.
- Patients with pathologic complete response following neoadjuvant chemotherapy appear to have the best long-term survival.

BLADDER CANCER, UROTHELIAL, SUPERFICIAL CARCINOMA IN SITU (CIS) (NMIBC)

Megan M. Merrill, DO
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BASICS

DESCRIPTION

- Carcinoma in situ (CIS) of the bladder is a flat, multifocal, "velvety" lesion of the urothelium
  - CIS is a flat, high-grade tumor that are confined to the mucosa
  - Can be occult and diagnosed by random biopsies of normal appearing mucosa
  - Although can occur alone, most often seen with concomitant high-grade papillary lesions
- Classified as nonmuscle-invasive bladder cancer (NMIBC) similar to stage Ta and T1, however CIS is considered high grade and aggressive with a propensity to invade the bladder wall and metastasize

EPIDEMIOLOGY

Incidence

True incidence not known given the flat superficial nature of this lesion, which can be destroyed by cautery effect during transurethral resection of bladder tumor (TURBT)

Prevalence

- Occurs as isolated CIS in 3–5% cases
- Estimated 5–10% of patients with noninvasive urothelial carcinoma have CIS (1)
- 45–65% patients with invasive urothelial carcinoma have CIS (2)

RISK FACTORS

- No risk factors specific for CIS beyond that of urothelial carcinoma
- Tobacco smoking-cigarettes
- Occupational exposure
  - Organic chemicals: Aromatic amines, benzenes, aniline dyes
  - High-risk occupations: Petroleum, chemical, rubber, textile workers, hairdressers
- Medications
  - Phenacetin-containing analgesics
  - Cyclophosphamide
- Pelvic radiation

Genetics

- p53 mutation most important deletion/mutation found with CIS (2)
- Chromosome 9q deletions common
- Loss of CDKN2/p16 (tumor suppressor gene)

PATHOPHYSIOLOGY

- CIS usually multifocal and can occur in the upper tracts, prostatic ducts, and urethra as well as the bladder

- Natural history—highly aggressive
  - Progression to MIBC in 54–83% of untreated cases (3,4)
  - Increase risk of recurrence if found with NMIBC papillary lesions
- Bacillus Calmette-Guerin (BCG) reduces risk of progression by 35% compared with other intravesical therapies (1,3)
- BCG confers disease-free rate approximately 51% at 3.75 yr (1)
- If concomitant muscle-invasive lesion, prognosis and treatment depends on invasive lesion

ASSOCIATED CONDITIONS
- NMIBC (Ta,T1)
- Invasive bladder cancer (T2,T3,T4)

GENERAL PREVENTION
- Smoking cessation
- Increased fluid intake
- Avoid occupational exposures

DIAGNOSIS
HISTORY
- Age and sex
- Presence of gross hematuria
- Irritative voiding symptoms—dysuria commonly occurs with CIS
- History of bladder cancer
- Family history of bladder cancer
- Smoking history
- Occupational risk factors

PHYSICAL EXAM
- Usually unremarkable
- Bimanual exam should be performed at time of cystoscopy/TURBT—If CIS is found in presence of advanced stage/invasive bladder cancer may appreciate palpable mass

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis, including microscopic evaluation
- Urine cytology—highly specific and sensitive (>90%) for detecting CIS and high-grade urothelial carcinoma (5)
- UroVysion, HA-HAase, and BLCA-4 have a high sensitivity to detect CIS however should not replace classic urine cytology (1) (Grade B)

Imaging
- No imaging specific for diagnosing CIS
- Renal/bladder ultrasound (US): Detects hydronephrosis that may be caused by ureteral obstruction from bladder tumor; bladder US can visualize larger bladder tumors
- Computed tomography (CT) urogram: Triple phase CT abdomen/pelvis is the gold standard for evaluation of painless gross hematuria; can detect more advanced bladder tumors, hydronephrosis, and upper tract filling defects that may represent upper tract urothelial

carcinoma

Diagnostic Procedures/Surgery

- Cystoscopy with bladder biopsy
  - Appearance can be flat, grossly erythematous, granular or cobblestone mucosa or visually normal
  - May be performed in office at initial visit
  - TURBT under general or spinal anesthesia may be required if papillary bladder tumor present
  - Retrograde pyelography also should be performed to assess the upper tracts if not already evaluated with a CT urogram
  - Positive cytology with no visible tumor and negative random bladder biopsies suggests disease outside of bladder
    - Biopsy of prostatic urethra indicated
    - Selective cytology from upper tracts; evaluate for urothelial carcinoma/CIS of renal pelvis or ureters. CIS of upper tracts suspected in absence of solid tumor and with positive cytology, rarely able to obtain adequate biopsy to confirm CIS histologically
- Fluorescent "Blue light" cystoscopy
  - More sensitive than conventional white light cystoscopy for detecting CIS
    - In a prospective study additional detection rate of 20% for all tumors and 23% for CIS (6)
  - False-positives can result in the presence of inflammation, recent TUR, or BCG instillation

Pathologic Findings

- Arises from surface uroepithelium
- Severe cytologic atypia and nuclear aplasia (2)
  - Large, irregular hyperchromatic nuclei
  - Mitotic activity common
- Thought to be a precursor of invasive disease
- Some pathologists use the term "severe dysplasia" to describe CIS

DIFFERENTIAL DIAGNOSIS

- Nonurothelial cancers (squamous cell carcinoma, adenocarcinoma)
- Inflammatory lesion from prior radiation, interstitial cystitis, infection

TREATMENT

GENERAL MEASURES

- Resection of all visible tumor followed by intravesical therapy
- For BCG-refractory CIS: Radical cystectomy

MEDICATION

First Line

- BCG—live suspension of the attenuated *Mycobacterium bovis* vaccine strain
  - Standard of care for CIS
  - Therapy initiated no earlier than 2–4 wk after TURBT/biopsy to give uroepithelium time to heal and prevent systemic complications of BCG

- Administered as induction therapy—6 consecutive weekly bladder instillations; then maintenance treatment recommended for at least 1 yr (1) (Grade A)
- BCG has the highest complete response rate and durable disease-free rate among all intravesical treatments (1) (Grade A)
- Initial response rates approximately 70–90%, however up to 1/2 of patients will recur
- Response to BCG instillation should be assessed at 3 mo
  - If no response can give another 6-wk course of BCG vs. proceed to radical cystectomy
  - Approximately 50% will respond to second course of BCG (1) (Grade B)

Second Line

- Intravesical chemotherapy
  - Mitomycin C—an alternative for patients who cannot tolerate BCG
  - Valrubicin—an option for poor surgical candidates with BCG-refractory disease
  - Gemcitabine

SURGERY/OTHER PROCEDURES

- TURBT—Resection of all visible papillary bladder tumors is essential prior to BCG therapy
- For CIS refractory to intravesical therapy—radical cystectomy
  - Disease-specific survival rates excellent if cystectomy performed early (instead of BCG instillation), however 40–50% could be overtreated (4) (Grade A)

ADDITIONAL TREATMENT

Radiation Therapy

No role in treatment of CIS

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Depends on stage of concomitant invasive papillary urothelial lesion
- CIS alone or with NMIBC—high rate of progression to muscle-invasive disease if untreated
  - See “Pathophysiology”
  - BCG reduces risk of recurrence and progression to muscle-invasive disease
- CIS of prostatic urethra unfavorable (1)
  - Prostatic tissue stromal invasion worst prognosis—cystoprostatectomy advised
- Disease-specific survival rates excellent if cystectomy performed early (instead of BCG instillation), however 40–50% could be overtreated (4) (Grade A)

COMPLICATIONS

- BCG toxicity
  - Low, but serious risk of systemic BCG infection (BCGosis)—avoid treatment in presence of recent TURBT, hematuria, foley trauma, or urinary tract infection
  - Has side effect of dysuria and can be intolerable in some patients

- Usually experienced within the first 6 mo of treatment

FOLLOW-UP

Patient Monitoring

At 3 mo patients should have cystoscopy and urine cytology. If negative, this should be repeated every 3 mo × 2 yr, every 6 mo thereafter until year 5 and then yearly (3)

Patient Resources

American Cancer Society—Bladder Cancer
http://www.cancer.org/acs/groups/cid/documents/webcontent/003085-pdf.pdf

REFERENCES

1. van der Meijden AP, Sylvester R, Oosterlinck W, et al. EUA guidelines on the diagnosis and treatment of urothelial carcinoma in situ. *Eur Urol*. 2005;48:363–371.
2. Nese N, Gupta R, Bui MH, et al. Carcinoma in situ of the urinary bladder: Review of clinicopathologic characteristics with an emphasis on aspects related to molecular diagnostic techniques and prognosis. *J Natl Compr Canc Netw*. 2009;7:48–57.
3. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non-muscle invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol*. 2011;59:997–1008.
4. Sylvester R, van der Meijden AP, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. *Urology*. 2005;66(Suppl 1):90–107.
5. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: Results of a comprehensive literature review and meta-analysis. *Urology*. 2003;61:109–118.
6. Kausch I, Sommerauer M, Montorsi F, et al. Photodynamic diagnosis in non-muscle-invasive bladder cancer: A systematic review and cumulative analysis of prospective studies. *Eur Urol*. 2010;57:595–606.

ADDITIONAL READING

- EAU Guidelines on Non-muscle-invasive (TaT1 and CIS) Bladder Cancer http://www.uroweb.org/gls/pdf/07_Bladder%20Cancer_LR%20II.pdf, Accessed January 28, 2014.
- Guideline for the Management of Nonmuscle Invasive Bladder Cancer: (Stages Ta, T1, and Tis): Update (2007) (Reviewed and validity confirmed 2010). AUA Clinical Practice Guidelines. http//www.auanet.org/content/clinical-practice guidelines/clinicalguidelines.cfm?sub=bc, Accessed November 2013.

See Also (Topic, Algorithm, Media)

- BCG Sepsis/BCGosis
- Bladder Cancer, General
- Bladder Cancer, Intravesical Agents (table)
- Bladder Cancer, Nonmuscle-invasive Bladder Cancer (Ta, T1)
- Bladder Cancer, Urothelial, Metastatic (Clinical and Pathologic N+, M+)
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC) Image
- Bladder Tumor Algorithm

- Bladder Tumors, Benign, and Malignant, General
- Bladder Tumors, Benign and Malignant, General Considerations
- Reference Tables: TNM Classification: Urinary Bladder Cancer

CODES

ICD9

233.7 Carcinoma in situ of bladder

ICD10

D09.0 Carcinoma in situ of bladder

CLINICAL/SURGICAL PEARLS

- Urine cytology is the best marker (>90% sensitivity/specificity) for diagnosis of CIS.
- Positive cytology in absence of visible bladder lesions—differential includes CIS bladder, prostatic urethra, or upper tract urothelial carcinoma.
- BCG is the treatment of choice for CIS of the bladder; highest response rate and most durable disease-free rates of all intravesical therapies.
- To prevent systemic complications of BCG do not administer after TURBT until urothelium healed (approximately 2 wk).
- For BCG refractory CIS: A second induction course BCG can be administered vs. proceeding immediately to radical cystectomy.

BLADDER INJURY, INTRAOPERATIVE

Costas D. Lallas, MD, FACS
Leonard G. Gomella, MD, FACS

BASICS

DESCRIPTION

- Bladder injury during surgery can be either intraperitoneal or extraperitoneal.
- The bladder is the urologic organ most subjected to iatrogenic injury.
- Described during open, endoscopic, laparoscopic, or robotic procedures.
- May be blunt/sharp dissection, trocar, or electrocautery injury.
- Needle or trocar passage during transvaginal tape or pubovaginal sling procedures are particularly high-risk procedures.
- Cystoscopy with overdistension and transurethral bladder tumor resections are also high risk for bladder perforation injury.

EPIDEMIOLOGY

Incidence (1,2)

- Intraoperative bladder injuries account for:
  - Laparoscopic injuries (0.2–8.3%)
  - Laparoscopic injuries intraoperative diagnosis: 53.2%
- Location:
  - Intraperitoneal (38–40%)
  - Extraperitoneal (54–56%) of injuries

Prevalence

N/A

RISK FACTORS

- General factors
  - Inexperienced surgeon
  - Over aggressive TURBT or bladder biopsy
  - Complex surgical anatomy (prior surgery or radiation therapy)
  - Poor laparoscopic visualization
  - Full/overdistended bladder
  - Thin bladder wall (transurethral injury) more common in older females due to thin bladder wall
- Risk factors associated with specific conditions and procedures based on EAU review
  - Cesarean delivery
    - Previous caesarean delivery
    - Previous pelvic surgery
    - Presence of labor
    - Station of presenting fet al part $> +1$
    - Fet al weight > 4 kg
  - Hysterectomy

- Malignancy
- Endometriosis
- Prior pelvic surgery
- Concomitant anti-incontinence or pelvic organ prolapse surgery

– General surgery
- Malignancy
- Diverticulitis
- Inflammatory bowel disease

– Midurethral sling operations
- Retropubic route
- Previous caesarean delivery
- Previous colposuspension
- BMI < 30 kg/m^2
- Rectocele
- Procedures under local anesthesia
- Inexperienced surgeon

– TURBT
- Tumor size
- Elderly patients
- Pretreated bladder (previous TURB, intravesical instillation, radiotherapy)
- Tumor location at the dome or in diverticulum

Genetics

N/A

PATHOPHYSIOLOGY

- Bladder injury with urinary leakage is consistent with complete tear through mucosa, submucosa, and muscularis
- Leakage of urine can be into the extra- or intraperitoneal space
- Perforation of the bladder dome during Veress needle or trocar insertion
- Large bladder perforations during TURBT requiring intervention are rare (0.16–0.57%)
  – Extraperitoneal TURBT perforations are more frequent than intraperitoneal ones

ASSOCIATED CONDITIONS

- Bladder cancer
- Prostate benign and malignant tumors
- Pelvic anatomic anomalies
- Prior pelvic surgery or radiation
- Pelvic trauma
- Tissue fibrosis or inflammation (eg, radiation, chronic catheter)

GENERAL PREVENTION

- Decompress bladder with a catheter placed before initial incision or trocar placement for laparoscopic cases
- Initial use of Veress needle for insufflation
  – Small bladder perforation not as significant as with trocar injury
  – Open “Hasson” trocar technique

- Familiarity with bladder anatomy can minimize risk:
  - Pediatric bladder is primarily intraperitoneal.
  - Adult bladder is retropubic and extraperitoneal.
  - Peritoneum is cephalad to bladder.
  - Bladder is attached laterally and at bladder neck
  - Bladder wall consists of 3 layers: Mucosa, submucosa, muscularis
  - Ureters attached posterolateral in trigone
- Perform bladder biopsy or TURBT with bladder at mid filling
  - Avoid over or underdistention that can increase risk of perforation of bladder

DIAGNOSIS

HISTORY

- Determine any prior surgical or other interventions that can increase the risk of intraoperative bladder injury
  - Past surgical history such as bladder neck suspension, cesarean section, radical prostatectomy, partial cystectomy, ureteral reimplantation, any lower abdominal surgery that may result in the bladder adhering to the posterior fascia
  - Prior pelvic radiation
  - History of neurogenic bladder

PHYSICAL EXAM

- Intraoperative:
  - Findings may be subtle. Need high degree of suspicion
  - Blood or gas in Foley, especially during transperitoneal laparoscopic procedure
    - Anesthesia may be first to recognize if monitoring catheter collection bag
  - Urine in wound
  - For transurethral surgery: Intraoperative abdominal distension/rigidity may be noted or if hypotonic irrigation is being used, patient may develop signs/symptoms of TUR syndrome
- Postoperative:
  - Distended abdomen
  - Peritonitis and abdominal rebound pain
  - Decreased urine production; oliguria or anuria
  - Abdominopelvic ascites
  - Urinoma
  - Urine leakage from wound
  - Bloody urine
  - Fever

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- With urinary ascites elevation in serum BUN and creatinine as well as hyperkalemia and hyponatremia can be seen
  - Elevated creatinine over serum level observed with urine leak due to systemic absorption
- Drain fluid sent for creatinine
  - Urine vs. serum

Imaging

- Postoperative diagnosis (3):
  - Extraperitoneal injury: Contrast contained in the extraperitoneal space
  - Intraperitoneal injury: Contrast extravasates between loops of small bowel and the anterior pararenal fascia
- Cystogram can be done using standard technique or CT imaging with postcontrast evacuation (3)
  - 300 cc gravity filling
  - 3-view cystogram or CT cystogram
  - All cystograms must include a postcontrast evacuation study to evaluate for residual contrast outside of the bladder
- US can identify urinoma
- CT for pelvic "urinary" ascites or urinoma
- Intraoperative diagnosis during transurethral surgery: Intraoperative cystogram can be obtained

Diagnostic Procedures/Surgery (1,4)

- Intraoperative diagnosis:
  - Normal saline with indigo carmine into Foley and observe for extravasation (blue staining)
  - Avoid use of methylene blue due to extensive tissue staining risk
- Intraoperative cystoscopy can be useful in selected situations and may be the most reliable method of immediately assessing bladder wall integrity
- Cystoscopy
  - Recommended after suburethral sling operations via the retropubic route
  - May be considered after sling insertion via the obturator route (controversial as bladder injuries are rare with this technique).
- Cystoscopy after transvaginal mesh procedures is preferable.
- Some authors have recommended routine cystoscopy due to the higher risk of bladder injuries during hysterectomy or after any major gynecologic procedure.

Pathologic Findings

Rupture through mucosa, submucosa, and muscularis of detrusor usually causes urine leak

DIFFERENTIAL DIAGNOSIS

- Prostatourethral injury
- Small or large bowel injury
- Ureteral injury
- Vascular injury

TREATMENT

GENERAL MEASURES

- Prompt recognition improves opportunity for improved outcome.
- Bladder injury can be found intraoperatively or postoperatively, and will be intraperitoneal or extraperitoneal.

- For most bladder injures Foley catheter for 10–14 days with follow-up cystogram is recommended

MEDICATION

First Line

- Consider antibiotics: Gentamicin or fluoroquinolone for 24 hr
- Anticholinergic for postoperative bladder spasm: Oral or suppository

Second Line

N/A

SURGERY/OTHER PROCEDURES (5)

- Laparoscopic or robotic injury:
  - 1-layer laparoscopic or robotic repair
- Intraoperative intraperitoneal injury:
  - Open bladder/2-layer repair
- Intraoperative extraperitoneal injury:
  - Foley or 2-layer repair
- Postoperative intraperitoneal injury:
  - Exploratory laparotomy with repair
- Postoperative extraperitoneal injury:
  - Initial catheter drainage with antibiotics
- Transurethral procedure:
  - Extraperitoneal perforation
    - Exploratory laparotomy with repair for large perforation. Carefully inspect bowel for potential injury
    - Small leak can be initially managed with catheter drainage and close monitoring
  - Extraperitoneal perforation
  - Usually managed with catheter drainage
  - Large perforations complicated by symptomatic collections require drainage, with or without formal closure of the perforation
- Bladder perforation during midurethral sling or transvaginal mesh placement
  - Sling reinsertion and urethral catheterization (1–2 days) should be performed (4,6).

ADDITIONAL TREATMENT

In the setting of any bladder perforation during TURBT intravesical postoperative chemotherapy should not be administered

ONGOING CARE

PROGNOSIS

- Extraperitoneal: Usually heals with Foley catheter drainage and without further intervention
- Intraperitoneal: Good prognosis if identified intraoperatively and repaired. Prognosis worse if delayed diagnosis

COMPLICATIONS

- Peritonitis or abscess
- Ileus

- Fistula
- Reoperation

FOLLOW-UP

Patient Monitoring

- Foley catheter or suprapubic tube to monitor urine output
- Usually no need for outpatient antibiotics

REFERENCES

1. Vakili B, Chesson RR, Kyle BL, et al. The incidence of urinary tract injury during hysterectomy: A prospective analysis based on universal cystoscopy. *Am J Obstet Gynecol.* 2005;192:1599–1604.
2. Ostrzenski, Ostrzenska KM. Bladder injury during laparoscopic surgery. *Obstet Gynecol Surv.* 1998;53(3):175–180.
3. Cass AS. Diagnostic studies in bladder rupture. *Urolog Clinc North Am.* 1989;16:267–273.
4. Gomez, Ceballos L, Coburn M, et al. Consensus statement on bladder injuries. *BJU Int.* 2004;94(1):27–32.
5. Corriere JN, Sandler CM. Diagnosis and management of bladder injuries. *Urol Clin North Am.* 2006;33:67–71.
6. Stav K, Dwyer PL, Rosamilia A, et al. Risk factors for trocar injury to the bladder during mid urethral sling procedures. *J Urol.* 2009;182:174–179.

ADDITIONAL READING

EAU Guidelines on Iatrogenic Trauma - European Association of Urology www.uroweb.org, Accessed February 2, 2014.

See Also (Topic, Algorithm, Media)

- Bladder Trauma
- TUR Syndrome
- Ureter, Intraoperative Injury
- Ureter, Trauma

CODES

ICD9

- 867.0 Injury to bladder and urethra, without mention of open wound into cavity
- 867.1 Injury to bladder and urethra, with open wound into cavity
- 998.2 Accidental puncture or laceration during a procedure, not elsewhere classified

ICD10

- N99.71 Acc pnctr & lac of a GU sys org during a GU sys procedure
- N99.72 Accidental pnctr & lac of a GU sys org during oth procedure
- S37.23×A Laceration of bladder, initial encounter

CLINICAL/SURGICAL PEARLS

- Intraoperatively, visual inspection is a reliable method of assessing bladder injury.

- Extraperitoneal: Usually heals with Foley catheter drainage and without further intervention.
- Intraperitoneal: Good prognosis if identified intraoperatively and repaired. Prognosis worse if delayed diagnosis.
- All cystograms must include a postcontrast evacuation study to evaluate for residual contrast outside of the bladder.

BLADDER OUTLET OBSTRUCTION (BOO)

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Michael J. Naslund, MD

BASICS

DESCRIPTION

- Bladder outlet obstruction (BOO) refers to a pathologic obstruction to urinary flow
- Definitions include the following:
  - A reduction in urinary flow to <12 cc/s during a sustained detrusor contraction of over 40–50 cm H_2O
  - BOO index >40 on the International Continence Society nomogram based on urodynamic testing

EPIDEMIOLOGY

Incidence

2.2–6.8 events of acute urinary retention per 1,000 person years (1)[A]

Prevalence

None

RISK FACTORS

- Increasing age
  - Microscopic BPH starts as early as the 30s but clinical BPH usually presents after the age of 50
- Infection
- Urethral trauma
- Pelvic radiation
- Prior urologic procedures

Genetics

N/A

PATHOPHYSIOLOGY

- BOO can be due to both static and dynamic factors:
- Dynamic factors
  - Stimulation or lack of relaxation of the smooth muscle along the proximal urethra or bladder neck
  - Results in increased resistance along the prostatic urethra
- Static factors
  - Constricted outlet by enlarged prostatic tissue, bladder neck contracture, or urethral stricture
- Outlet obstruction leads to detrusor hypertrophy and the symptoms of BOO

ASSOCIATED CONDITIONS

- BPH

- Urethral stricture disease
- Detrusor sphincter dyssynergia

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Detailed description of obstructive voiding symptoms consistent with BOO
  - Slow urinary stream
  - Urinary hesitancy
  - Intermittent urinary stream
  - Straining to void
  - Sense of incomplete bladder emptying
  - Urinary retention
- History of irritative symptoms
- Medical history of gynecologic, neurologic, and GI illness
- Past surgical history for pelvic and spinal procedures
- Medication review for anticholinergics, α-agonists, psychotropic agents
- Voiding diary
- International Prostate Symptom Score

PHYSICAL EXAM
- Abdominal exam:
  - Palpate for bladder distention (>150 cc retained urine needed to be palpable in an adult)
  - Inguinal hernia can be associated with severe BPH and retention
- Digital rectal exam:
  - Examine for an enlarged prostate
  - Note any findings suspicious for cancer: Nodules, firmness, and asymmetry
  - Assess anal sphincter tone
- Pelvic exam (women) for pelvic organ prolapse and urethral diverticula
- Neurologic exam for gross defects

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- PSA:
  - If elevated, consider prostate cancer, prostatic inflammation, benign prostatic hyperplasia
- Urinalysis:
  - If hematuria or urinary infection is present, further evaluation is necessary (see Chapter on “Hematuria, Gross and Microscopic, Adult”)
- Creatinine
  - Not necessary unless patient is in urinary retention

Imaging
- Renal and bladder US
  - Evaluate for hydronephrosis if there is renal insufficiency

  – Allows noninvasive determination of PVR
- Upper tract imaging with CT urogram to evaluate causes of hematuria
- Uroflowmetry:
  – Measures peak flow, demonstrate voiding pattern, and voided volume
  – Peak flow <10–12 cc/s (for voided volume >150 cc) is suggestive of obstruction, although an acontractile bladder cannot be ruled out
- Cystoscopy: Endoscopic evaluation of urethra and bladder
  – Used to evaluate prostatic length, median lobe component of prostatic obstruction, and bladder mucosa
  – Can reveal other etiology for the BOO, such as strictures, stones, diverticula, urethral masses, and bladder tumors
- Urodynamics: Pressure-flow study to determine if a low flow rate is due to obstruction or reduced bladder contractility:
  – Videourodynamics: Fluoroscopy combined with urodynamics. Recommended in patient suspected to have primary bladder neck obstruction
  – ICS nomogram is the most widely used measurement of BOO; plots maximal flow against detrusor pressure at the time of flow
  – EMG: Evaluates for neurogenic etiology of BOO

Diagnostic Procedures/Surgery

See "Imaging" and "Surgery/other procedures"

Pathologic Findings

Depends on etiology of BOO

DIFFERENTIAL DIAGNOSIS

- Inadequate bladder contractility
- BOO after incontinence surgery
  – The most common etiology of BOO/urinary retention in women
- Prostatic obstruction (BPH)
  – Most common etiology of BOO in men
- Primary bladder neck obstruction
- Infection:
  – Prostatitis, intraurethral condyloma (men and woman), periurethral abscess
- Neurologic:
  – Detrusor sphincter dyssynergia, diabetes mellitus with atonic bladder
- Medications that affect bladder contractility
  – Anesthetics, narcotic, psychotropics
- Urethral caruncle, urethral diverticulum (primarily women)
- Urethral cancer
- Penile cancer (usually advanced)

TREATMENT

GENERAL MEASURES

- Management of BOO depends on etiology and severity.

- A urethral catheter is used for temporary management of severe obstruction or retention.
- A suprapubic tube is used if a urethral catheter cannot be placed (severe stricture or BPH) or urethral catheter is contraindicated (acute prostatitis).
- Long-term treatment of BOO is medical and surgical.

MEDICATION

First Line

- α-Blockers: Rapidly relax the smooth muscle of the bladder neck and prostate without impairing bladder contractility:
  - Alfuzosin (10 mg/d)
  - Doxazosin (start 1 mg/d to max 8 mg; XL form 2–8 mg daily)
  - Silodosin (8 mg/d)
  - Tamsulosin (start 0.4 mg to max 0.8 mg)
  - Terazosin (start 1 mg/d to max 20 mg)
- 5-α-reductase inhibitors in males: Effective in larger glands (>40 cc) to reduce prostate size, improve symptoms, and reduce progression risk:
  - Finasteride (5 mg/d)
  - Dutasteride (0.5 mg/d)

Second Line

- Phosphodiesterase-5 inhibitors (PDE5i) in males
  - Tadalafil only PDE5i currently approved by the FDA for treatment of LUTS in the setting of BPH with or without coexisting erectile dysfunction (2)[A]

SURGERY/OTHER PROCEDURES

- Urethral strictures
  - Urethral dilation
  - Endoscopic incision
  - Open excision (with primary anastomosis, grafts, or flaps)
- Urethrolysis
  - Primary surgical approach to urethral obstruction following anti-incontinence surgery in women
- Sphincterotomy
  - Utilized for patients with detrusor sphincter dyssynergia
- BPH
  - Transurethral needle ablation
  - Transurethral microwave therapy
  - Transurethral incision of prostate
  - Transurethral resection of prostate (TURP)
  - Laser-assisted techniques such as holmium laser enucleation of the prostate (HoLEP), others
  - Photovaporization of prostate
  - Simple open prostatectomy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
- Long-term catheter drainage for patients with severe comorbidities
- Clean intermittent catheterization
- Prostatic stents
- Urinary diversion

Complementary & Alternative Therapies
- Saw Palmetto (Serenoa Repens)
  - No difference in reduction of lower urinary tract symptoms compared to placebo (3)[A]

ONGOING CARE

PROGNOSIS
Excellent with definitive management

COMPLICATIONS
- Urinary retention
- Gross hematuria
- Renal insufficiency/failure
- Bladder stones
- UTIs
- Bladder diverticula and flaccid bladder
- Postobstructive diuresis:
  - Occurs with severe BOO and bilateral ureteral obstruction due to urinary retention
  - Self-limited and corrected by the fluid hydration
  - If the patient cannot keep up with the urine output, then IV replacement with 1/2 normal saline at a rate of 1/2 of the urine output
  - Serum electrolytes must be monitored closely

FOLLOW-UP
Patient Monitoring
- Periodic follow-up visits to assess symptom progression (IPSS)
- Yearly urinalysis and PSA measurement
- Serial measurement of uroflow and PVR urine
- Counsel on the possibility of progression of symptoms and complications
- Management of BPH does not eliminate the risk of developing prostate cancer

Patient Resources
- Urology Care Foundation
  - www.urologyhealth.org

REFERENCES
1. Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and post-void residual urine in men: Separating truth from tradition. *J Urol.* 2008;180:47–54.
2. Dmochowski R, Roehrborn C, Klise S, Xu L, et al. Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: A randomized, placebo controlled 12-week clinical trial. *J Urol.*

2013;189;S135–S140.
3. Barry MJ, Meleth S, Lee JY, et al; Complementary and Alternative Medicine for Urological Symptoms (CAMUS) Study Group. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA*. 2011;306(12):1344–1351.

ADDITIONAL READING

- Dmochowski RR. Bladder outlet obstruction: Etiology and evaluation. *Rev Urol*. 2005;7:S3–S13.
- Groutz A, Blaivas JG, Chaikin DC. Bladder outlet obstruction in women: Definition and characteristics. *Neurourol Urodyn*. 2000;12:213.
- Lepor H. Pathophysiology of benign prostatic hyperplasia in the aging male population. *Rev Urol*. 2005;7:S3–S12.
- McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2387–2398.

See Also (Topic, Algorithm, Media)

- Bladder Neck Contracture
- Bladder Neck Hypertrophy
- Bladder Outlet Obstruction (BOO) Image
- Lower Urinary Tract Symptoms (LUTS)
- Lower Urinary Tract Symptoms (LUTs), Male Algorithm
- Multiple Sclerosis, Urologic Considerations
- Prostate, Benign Enlargement (Benign Prostate Enlargement (BPE)
- Prostate, Benign Hyperplasia (BPH)
- Prostate, Benign Obstruction (Benign Prostatic Obstruction, [BPO])

CODES

ICD9

- 596.0 Bladder neck obstruction
- 600.01 Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)
- 788.29 Other specified retention of urine

ICD10

- N32.0 Bladder-neck obstruction
- N40.1 Enlarged prostate with lower urinary tract symptoms
- R33.8 Other retention of urine

CLINICAL/SURGICAL PEARLS

- If a male patient has lower urinary tract symptoms check to ensure a low post-void residual which generally confirms that treatment is not necessary.
- Strong consideration should be given for evaluation for multiple sclerosis in young female patients with new onset urinary retention.

BLADDER TRAUMA

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BASICS

DESCRIPTION

- Bladder trauma generally comprises blunt and penetrating types of injury.
- When not distended, bladder is protected from injury by bony pelvis.
- Pelvic fracture and bladder distention increase risk of traumatic injury.
- Important to distinguish between extraperitoneal (EBR), intraperitoneal (IBR), and combined EBR/IBR.
- Iatrogenic bladder injury is discussed in the section "Bladder Injury, Intraoperative."

EPIDEMIOLOGY

Incidence

1.6% of blunt abdominal trauma

Prevalence

- Unknown

RISK FACTORS

- Motor vehicle crashes (MVCs)
- Falls
- Industrial trauma (pelvic crush injury)
- Penetrating injuries to lower abdomen
- Bladder outlet obstruction
- Alcohol intoxication (bladder distention and decreased sensorium)
- Pelvic fracture
  - ~80% of bladder injures associated with pelvic fracture
  - ~6% of patients with pelvic fracture sustain a bladder injury
- Urethral injury (present in 15% of cases)

Genetics

N/A

PATHOPHYSIOLOGY

- The bladder is generally well protected from blunt trauma unless significantly distended
- In an adult, the bladder lies in the true pelvis, but can rise to umbilicus when full
- In a child, bladder lies in abdomen and more prone to injury
- EBR or combined EBR/IBR
  - Pelvic fracture leads to shearing injury from bone fragment or compression with rupture
  - Direct injury from penetrating trauma
- IBR
  - Blow to lower abdomen in the presence of a full bladder

ASSOCIATED CONDITIONS
- Bladder neck injury
- Pelvic fracture
- Solid abdominal organ injury
- Urethral injury

GENERAL PREVENTION
- Avoid high-risk activity
- Seatbelt proper positioning and use

DIAGNOSIS
HISTORY
- Type of blunt trauma to pelvis
  - Associated injuries
- For gunshot, number, and trajectory
- Stab wounds type of knife if known
- Gross hematuria
- Alcohol use
- Past urologic history
- Complaints
  - Location of lower abdominal pain
  - Urinary retention
  - Dysuria or voiding complaints

PHYSICAL EXAM
- Abdominal distention
- Lower abdominal/suprapubic tenderness
- Peritonitis
- Seatbelt sign
- Site/extent of abdominal/pelvic bruising
- Site/extent/trajectory of penetrating objects
- Blood at meatus
- Rectal and vaginal exam (assess integrity)
- Open pelvic fractures

ALERT
Gross hematuria is the hallmark sign of injury to the bladder.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis (UA): Blood usually present
- Serum creatinine can be elevated with IBR due to intraperitoneal resorption of urine
- Hyperkalemia, hypernatremia, uremia, acidosis can also be seen with urinary extravasation into the peritoneum
- CBC (assess for leukocytosis and anemia)

Imaging

- Indications for performing cystography:
  - Blunt trauma
    - Pelvic ring fracture with gross or microscopic (3+ or >30 RBC/HPF) hematuria
    - Gross hematuria in presence of otherwise unexplained free intraperitoneal fluid
    - High clinical suspicion (pelvic fluid collection, inability to void, elevated serum creatinine, abdominal distention, suprapubic tenderness, intoxicated or unresponsive, poorly functioning Foley catheter, displaced obturator ring fracture, or large pubic symphysis diastasis
  - Penetrating injury
    - Trajectory suggests bladder injury
    - Involvement of buttock, pelvis, or lower abdomen with any degree of hematuria
    - High clinical suspicion
- If ureteral injury is suspected, this should be assessed preoperatively (CT with delayed images) or intraoperatively (retrograde pyelogram/direct inspection)
- When combined upper and lower tract urologic injuries are suspected, upper tract contrast study should be performed prior to cystogram (retained bladder contrast in abdomen or retroperitoneum can obscure upper tract pathology)

Diagnostic Procedures/Surgery

- Cystogram is easy to do and highly sensitive
  - CT cystogram
    - At least as sensitive as conventional cystography for diagnosing bladder rupture (1)
    - Dilute contrast to limit artifact (1:6)
    - Postdrainage films not necessary
    - Excellent visualization of bladder neck
    - Readily identify foreign bodies
  - Conventional cystogram
    - Dilute contrast 1:2
    - Scout, AP, oblique, and postdrainage films
  - For both CT and conventional cystography, fill bladder to capacity (at least 350 mL in an adult, or determine by formula: (Age in years + 2) × 30.

ALERT
CT with delayed images is inadequate for the diagnosis of bladder injuries: when bladder injury is suspected, a cystogram is mandatory (2).

Pathologic Findings

Injured tissue typically remains healthy, though there is potential for local ischemia (particularly if angio-embolization was performed for pelvic bleeding)

DIFFERENTIAL DIAGNOSIS

- Bladder contusion
- Urethral injury
- Renal or ureteral injury

TREATMENT

GENERAL MEASURES

Stabilize patient if major trauma present

MEDICATION

First Line

For nonoperative management of EBR, antibiotics with gram-positive and gram-negative coverage are recommended while catheter is indwelling

Second Line

N/A

SURGERY/OTHER PROCEDURES

- When associated with significant pelvic bleeding, open pelvic fractures, and abdominal solid organ injury, supportive care is indicated while more urgent injuries are temporized
- IBR
  - Laceration is typically large (6–8 cm), at dome
  - Nonoperative management generally contraindicated secondary to size of defect and morbidity of chemical peritonitis
  - Should be closed in 2 layers with absorbable suture via midline incision
  - Laparoscopic repair has been reported in stable patients with no other injuries (3)
  - Drain is not necessary
  - Foley catheter 7–10 days, with cystogram to confirm absence of extravasation
- EBR
  - Nonoperative management
  - Acceptable in the appropriate patient, but higher complication risk (4)
  - 20-French or larger catheter
  - Cystogram after 10–14 days
  - Antibiotics with gram-positive and gram-negative coverage while catheter is indwelling
  - Contraindications to nonoperative management:
    - Inadequate catheter drainage
    - Vaginal or rectal injury
    - Bladder neck injury
    - Concomitant urethral injury
    - Internal fixation of pelvic fracture
    - Stable and undergoing laparotomy
- Operative repair
  - Midline abdominal incision or Pfannenstiel
  - Avoid unnecessary pelvic dissection, as there can be significant bleeding from original trauma
  - Minimal debridement to ensure healthy wound edges
  - Removal of foreign bodies and bony fragments
  - Assess ureteral orifices if not imaged
  - 2-layer watertight closure with absorbable suture
  - Drain is not necessary, but may be helpful
  - Foley catheter 10–14 days, with cystogram to confirm absence of extravasation
  - Suprapubic tube not necessary

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Injuries to urethra, bladder neck, or ureters may necessitate endoscopic realignment, repair of bladder neck, or ureteral reimplant

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prompt diagnosis and appropriate management allow excellent results and minimal morbidity.
- Complications usually are associated with delay in diagnosis and management.

COMPLICATIONS

Unrecognized injury can result in fistula, sepsis, ileus, incontinence, and stricture.

FOLLOW-UP

Patient Monitoring

- Monitor for signs/symptoms of:
  - Pelvic bleeding
  - Unrecognized abdominal injury
  - UTI
  - Urinary leak

Patient Resources

www.urologyhealth.org/urology/index.cfm?article=99

REFERENCES

1. Quagliano PVDS, Malhotra AK. Diagnosis of blunt bladder injury: A prospective comparative study of computed tomography cystography and conventional retrograde cystography. *J Trauma*. 2006;61(2):410–421.
2. Doyle S, Master VA, McAninch JW. Appropriate use of CT in the diagnosis of bladder rupture. *J Am Coll Surg*. 2005;200(6):973.
3. Kim FJ, Chammas MF Jr, Gewehr EV, et al. Laparoscopic management of intraperitoneal bladder rupture secondary to blunt abdominal trauma using intracorporeal single layer suturing technique. *J Trauma*. 2008;65(1):234–246.
4. Kotkin L, Koch M. Morbidity associated with nonoperative management of extraperitoneal bladder injuries. *J Trauma*. 1995;38(6):895–898.

ADDITIONAL READING

- Figler B, Hoffler CE, Reisman W, et al. Multi-disciplinary update on pelvic fracture associated bladder and urethral injuries. *Injury*. 2012;43(8):1242–1249.
- Gomez RG, Ceballos L, Coburn M, et al. Consensus statement on bladder injuries. *BJU Int.*

2004;94(1):27–32.

See Also (Topic, Algorithm, Media)

- Bladder Injury, Intraoperative
- Bladder Trauma Algorithm
- Bladder Trauma Image
- Ureter, Trauma
- Urethra, Trauma (Anterior and Posterior)

CODES

ICD9

- 867.0 Injury to bladder and urethra, without mention of open wound into cavity
- 867.1 Injury to bladder and urethra, with open wound into cavity

ICD10

- S37.20XA Unspecified injury of bladder, initial encounter
- S37.22XA Contusion of bladder, initial encounter
- S37.23XA Laceration of bladder, initial encounter

CLINICAL/SURGICAL PEARLS

- Gross hematuria is hallmark of bladder injury.
- In addition to diagnosing bladder rupture, CT cystogram is useful in identifying foreign bodies and bladder neck injuries.
- CT with delayed images is inadequate for the diagnosis of bladder injuries: When bladder injury is suspected, a cystogram is mandatory.

BLADDER TUMORS, BENIGN AND MALIGNANT, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Most bladder masses represent a malignant tumor
- Bladder tumors can be benign, low-grade, or aggressive high-grade malignancies
- There are a number of nonneoplastic and inflammatory disorders that can manifest as a focal bladder mass and mimic malignancy

EPIDEMIOLOGY

Incidence

- Bladder cancer: 9th most common cancer
  - 73,510 cases diagnosed in US in 2012 (55,600 males and 17,910 females) (1)
  - 14,880 total deaths in US in 2012 (10,510 males and 4,370 females)
  - Male:female > 3:1
  - Incidence increases with age and peaks in 8th decade of life
  - Median age at diagnosis is 73
  - 3× more common in White than Black men
  - 1.5× more common in White than Black women

Prevalence

Estimated 437,180 male and 148,210 female bladder cancer survivors in US as of 2012 (2)

RISK FACTORS

- Malignant bladder tumors
  - Smoking—main risk factor for bladder cancer
    - 2–6× increased risk urothelial cancer
    - Risk is linearly dose and duration related, with 15–20 yr latency
    - 2nd-hand smoke does not increase risk of bladder cancer formation
  - Chemical exposure:
    - Especially aniline dyes and aromatic amines
    - High-risk industries include textiles, aluminum, dye, leather, launderers, and rubber workers
  - Pelvic irradiation
    - Latency is 15–30 yr
    - Increased risk in prostate and cervical cancer treated with radiation
  - Chemotherapy
    - Cyclophosphamide has a 4–9× increased risk for bladder cancer
  - Inflammation is a risk factor for squamous cell carcinoma (SCC)
    - Indwelling catheters

- Chronic urinary tract infection (UTI)
- Chronic bladder stones
- *Schistosoma hematobium* infection

Genetics

- Heredity plays a minor role
  - History in a 1st-degree increases risk 2×
    - No clear inheritance patterns
- p53 gene on chromosome 17
  - Overexpression leads to higher rates of progression and lower rates of response to chemotherapy
- Loss of Retinoblastoma (Rb) gene on chromosome 9
  - Development of superficial tumors
- Slow metabolizers and slow acetylators more susceptible to environmental carcinogens

PATHOPHYSIOLOGY

- Patterns of spread of bladder cancer
  - Lymphatic
  - Hematogenous—to liver, lung, bone, etc.
  - Implantation
  - Direct extension

ASSOCIATED CONDITIONS

None

GENERAL PREVENTION

- Smoking cessation
  - Decreases risk after approximately 15 yr
- Avoid occupational exposures
- Mediterranean diet: Lowest bladder cancer risk
- Antioxidants including vitamins A, C and E, and micronutrients selenium and zinc may be protective
- Increased fluid intake may be protective

DIAGNOSIS

HISTORY

- Painless, gross hematuria
- Irritative voiding symptoms—frequency, urgency, dysuria
- Mucosuria: Adenocarcinoma, colovesical fistula
- Weight loss, cachexia, bone pain, flank pain
- Inquire about risk factors reviewed earlier
- Egyptian or Middle Eastern heritage are risk factors for SCC

PHYSICAL EXAM

- Rarely abnormal
  - Bimanual exam done under anesthesia before and after transurethral resection of bladder tumor (TURBT)

– Digital rectal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis (for red blood cells) and culture
- Urine cytology
  – More sensitive in high-grade disease and carcinoma in situ (>90%)
- Flow cytometry
  – Measures DNA content of cells to quantitate aneuploid cell populations
- Other urine markers are commercially available (eg, BTA Stat, NMP 22, BladderChek), and have better sensitivities but worse specificities than cytology

Imaging

- Upper tract evaluation can be done with intravenous urogram, retrograde pyelography, computerized tomography (CT), or magnetic resonance imaging
- Metastatic evaluation includes chest imaging and bone scan

Diagnostic Procedures/Surgery

- Cystoscopy with bladder tumor resection or biopsy
  – Fluorescence cystoscopy may increase detection of carcinoma in situ or additional lesions

Pathologic Findings

- **Benign lesions**
  – Nephrogenic adenoma: Metaplastic response to chronic inflammation
  – Von Brunn nests: Benign urothelial cells within the lamina propria
  – Squamous metaplasia: Common in women (40%)
  – Cystitis cystica: Central cystic degeneration of Von Brunn nests
  – Eosinophilic cystitis
  – Malacoplakia: Chronic reaction, Michaelis–Gutmann bodies (bulls-eyed histiocytes) are needed for diagnosis
  – Papilloma: Benign growth, can recur but does not progress or invade
  – Inverted papilloma: Benign lesion with inverted growth pattern
  – Leiomyoma: Benign smooth muscle tumor covered by urothelium
  – Inflammatory pseudotumor (pseudosarcomatous fibromyxoid tumor)
  – Endometriosis
  – TB
  – Schistosomiasis
  – Crohn disease: Fistulas from inflamed small and large bowel
  – Diverticulitis: Colovesical fistulas
- Extrinsic compression resembling masses: Prostate, uterine, and ovarian organs; ureteroceles, extramedullary hematopoiesis; urachal cysts; paraganglionic tissue; hamartomas; amyloidosis; and vascular malformations
- Premalignant lesions
  – Leukoplakia: Squamous metaplasia with 20% risk for SCC
  – Cystitis glandularis: Glandular metaplasia with risk for adenocarcinoma
- Urothelial carcinomas (90% of tumors)
  – Papillary urothelial neoplasia of low malignant potential (PUNLMP)

  - Carcinoma in situ: High-grade tumor confined to urothelium, looks erythematous and velvety
    - Precursor lesion for invasive disease
    - 40–83% progress to muscle invasive disease
  - Urothelial carcinoma
    - 80% are nonmuscle invasive
    - Correlation between grade and stage
- SCC (5%): Seen with chronic inflammation
- Adenocarcinoma (2%): Seen in bladder exstrophy and urachal tumors
  - Important to rule out gastrointestinal primary
- Small cell carcinoma: Aggressive neuroendocrine tumor (rare)

DIFFERENTIAL DIAGNOSIS
- Bladder wall mass: See "Pathologic findings"
- Irritative voiding symptoms: UTI, urinary calculi, interstitial cystitis, bladder cancer, chronic prostatitis

TREATMENT
GENERAL MEASURES
- Bladder cancer: Increase fluid intake; avoid or quit smoking: Best preventive measure; avoid exposure to aromatic amines or aniline dyes other occupational exposure
- Form management of benign bladder lesions see individual topic in index

MEDICATION
First Line
- Bacillus Calmette Guérin (BCG) [A]
  - Attenuated strain of *Mycobacterium bovis*
  - Typical induction course consists of 6 weekly bladder instillations
  - Maintenance schedule improves response
  - Absolute contraindications include immunosuppression, prior history of BCG sepsis, gross hematuria, and immediately following TURBT

Second Line
- Mitomycin C [A]
  - Alkylating antibiotic that inhibits DNA synthesis, decreases recurrence
  - Given as 40 mg in 40 mL of NS or water, given weekly × 8 weeks then monthly × 1 yr
  - Also given perioperatively after TURBT
- Interferon α-2B
  - Given as monotherapy or in combination with low-dose BCG
  - Dose not standardized
- Thiotepa: Alkylating agent
  - Dose ranges from 30 mg in 30 mL of water/saline to 60 mg in 60 mL of water/saline
  - Given weekly × 8 weeks then monthly × 1 yr
  - Myelosuppression when absorbed systemically
- Doxorubicin: Anthracycline antibiotic, prevents recurrence, not progression

- Valrubicin for BCG refractory CIS
  - 800 mg in 75 mL of saline, administered weekly for 6 wk
- Gemcitabine: Activity in nonmuscle-invasive bladder cancer
  - 2 gm in 50–100 mL NS, weekly for 6 wk

SURGERY/OTHER PROCEDURES
- TURBT
  - Diagnostic: Consider repeat resection for T1 disease
  - Therapeutic: For nonmuscle-invasive disease
- Partial cystectomy
  - For selected patients with unifocal disease, urachal tumors, and tumors in diverticula
- Radical cystectomy
  - For muscle-invasive disease
  - Consider for recurrent high-grade superficial disease

ADDITIONAL TREATMENT

Radiation Therapy
- Can be used in bladder sparing protocols
  - External beam radiotherapy combined with chemotherapy to improve outcomes
    - 5-yr overall survival ~50%

Additional Therapies
- Cisplatin-based therapy is 1st line for small cell carcinoma
- Neoadjuvant chemotherapy for locally advanced disease prior to cystectomy
- Chemotherapy for metastatic disease with either methotrexate, vinblastine, doxorubicin and cisplatin, or gemcitabine and cisplatin

Complementary & Alternative Therapies
- Phototherapy: No long-term date
- Laser therapy
- Vitamins (6)
  - Regular vitamin E use for ≥10 yr may be associated with a decreased risk of bladder cancer mortality
  - Megadose multivitamins A, B6, C, and E plus zinc may decrease bladder tumor recurrence in patients receiving BCG immunotherapy
  - Increased carotene intake, including beta-carotene, alpha-carotene and lycopene, is associated with decreased bladder cancer risk

ONGOING CARE

PROGNOSIS
- Progression and recurrence depend upon grade, stage, size, the presence of CIS, multifocality, and frequency of prior recurrences.

COMPLICATIONS
- Bladder perforation from TURBT
- Disease progression and metastases
- Hematuria

- Ureteral obstruction
- UTI or sepsis

FOLLOW-UP

Patient Monitoring

- History and physical, urinalysis, cystoscopy, and urine cytology every 3 mo for 2 yr, then every 6 mo for 2–3 yr, then once a year.
- Periodic upper tract imaging for high-risk patients

Patient Resources

- BCAN http://www.bcan.org/facing-bladder-cancer/support-groups/
- http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-additional

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62(1):10–29.
2. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin.* 2012;62(4):220–241.
3. Wood DP. Urothelial tumors of the bladder. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders, 2012:2309–2334.
4. Hall MC, Chang SS, Dalbagni G, et al. AUA guideline for the management of non–muscle invasive bladder cancer (Ta, T1, CIS): 2007 Update. *J Urol.* 2007;178(6):2314–2330.
5. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med.* 2012;366(16):1477–1488.
6. http://www.livestrong.com/article/277852-vitamin-treatments-for-bladder-cancer/#ixzz2T8kR8Mow (accessed March 6, 2014).

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Bladder Cancer, General Considerations
- Bladder Cancer, SCC
- Bladder Cancer, Urothelial Superficial (Ta, T1) (NMIBC)
- Bladder Cancer, Urothelial, Metastatic (Clinical and Pathologic N+, M+)
- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC)
- Bladder Mass, Differential Diagnosis
- Bladder Tumor Algorithm
- Bladder Tumors, Benign and Malignant, General Considerations Image
- Bladder Wall Calcification, Differential Diagnosis
- Bladder Wall Thickening, Differential Diagnosis
- Cystitis Cystica
- Cystitis Glandularis and Cystitis Glandularis of the Intestinal Type
- Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

CODES

ICD9

- 188.9 Malignant neoplasm of bladder, part unspecified
- 223.3 Benign neoplasm of bladder
- 236.7 Neoplasm of uncertain behavior of bladder

ICD10

- C67.9 Malignant neoplasm of bladder, unspecified
- D30.3 Benign neoplasm of bladder
- D41.4 Neoplasm of uncertain behavior of bladder

CLINICAL/SURGICAL PEARLS

- Painless gross hematuria must be investigated to rule out bladder cancer.
- Smoking is the most common risk factor for bladder cancer.
- TURBT with biopsy is mandatory for diagnosis and staging of all bladder tumors.

BOWEN DISEASE AND ERYTHROPLASIA OF QUEYRAT

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BASICS

DESCRIPTION

- Bowen Disease is squamous cell carcinoma in situ (CIS) of the follicle-bearing epithelium of the shaft and scrotum.
- Erythroplasia of Queyrat (EQ) is squamous cell carcinoma in situ (CIS) arising within the penile mucocutaneous (mucosal) epithelium of the glans penis or inner side of the foreskin. 80–90% of cases are seen in uncircumcised men.
  - Sometimes EQ is referred to as "Bowen disease (BD) of the glans penis."
  - EQ more likely to develop into invasive squamous cell carcinoma of the penis than Bowen disease.

EPIDEMIOLOGY

Incidence

- Penile cancer occurs in $<1\%$ of all malignancies in men, and EQ and BE are a fraction of these
- Most often occurs in Caucasian males
- Mostly in uncircumcised men
- Majority in men ages 50–70, but described in adult males of all ages

Prevalence

N/A

RISK FACTORS

- Uncircumcised men
  - Phimosis present in 75% of cases
  - Smegma thought to be carcinogenic
- Coinfection of HPV type 8 and carcinogenic genital HPV types (16, 18, 39, 51) have been reported (1)

  Relative risk factors:
  - Therapeutic immunosuppression for organ transplants
  - Immunosuppression from HIV/AIDS
  - Arsenic exposure from well-water and other sources
  - Ionizing radiation
  - Thermal injury
  - Chronic dermatoses
  - Lichen sclerosis of the glans penis
  - Smoking
  - Multiple sexual partners
  - Poor genital hygiene
  - Penile trauma

Genetics
N/A

PATHOPHYSIOLOGY
- Carcinogenic insults from:
  - Chronic injury and inflammation from poor hygiene, urine, smegma
  - Radiation
  - Exposure to chemical carcinogens, such as arsenic or smoking
  - HPV infection
- Decreased immune surveillance due to HIV/AIDS or medical immunosuppression

ASSOCIATED CONDITIONS
- Progression to invasive SCC in 5–30% of cases; more likely with EQ
- Lichen sclerosis, balanitis xerotica obliterans (BXO)

GENERAL PREVENTION
- Circumcision
- Daily genital hygiene by retraction of foreskin and cleansing
- Elimination of risk for HPV infection
- Early detection of lesions
- Treatment of phimosis

DIAGNOSIS
HISTORY
- Age: Median age >50
- Sexual promiscuity (increases risk for HPV infection)
- History of phimosis or difficulty retracting foreskin
- History of exposure to ionizing radiation or arsenic
- History of nonhealing wounds, pruritus, bleeding, discharge

PHYSICAL EXAM
- Solitary or multiple nontender erythematous plaques
  - EQ: Velvety, smooth, shiny on glans
  - BD: Scaly, verrucoid plaque on shaft
- Individual lesion may be 10–15 mm in diameter
- Bleeding from lesion
- Presence of ulceration increases likelihood of invasive SCC
- Examination of inguinal nodes
- Important factors to assess:
  - Diameter of lesion
  - Location
  - Number of lesions
  - Morphology (papillary, nodular, ulcerous, or flat)
  - Relationship to other structures (submucosal, corpora spongiosa and/or cavernosa, urethra)

DIAGNOSTIC TESTS & INTERPRETATION

Lab
Lab testing for carcinogenic HPV types

Imaging
Imaging only indicated in instances of clinical suspicion of invasion, and would include MRI or ultrasound

Diagnostic Procedures/Surgery
- Definitive diagnosis may only be made by biopsy
  - Early invasion should be excluded via the use of multiple biopsies

Pathologic Findings
- Pathology will show full-thickness epidermis with:
  - Discordant architecture
  - Abnormal mitoses
  - Dyskeratosis
  - Involvement of associated pilosebaceous apparatus with intact epidermal junction
  - Chronic inflammatory infiltrate into dermis
  - Epithelial rete extension into submucosa that is elongated and bulbous; submucosa shows capillary proliferation and ectasia with plasma-cell rich infiltrate (these distinguish from localized balanitis)

DIFFERENTIAL DIAGNOSIS (2)
- Invasive SCC
  - Ruled out by biopsy
- Bowenoid papulosis
  - Benign course, but histologically similar except abnormal keratinocytes are spread discontinuously throughout epidermis
  - Tendency for multiple lesions that may coalesce
  - Typically in younger patients (ages 25–30)
  - Usually spontaneously regresses
- Invasive SCC
  - Ruled out by biopsy
- Nummular eczema
  - Pruritic, coin-shaped plaques of small grouped papules on erythematous base
- Psoriasis
  - Well-demarcated red or whitish, scaly lesion
  - Usually associated with lesions at other sites
- Superficial basal cell carcinoma
  - Pearly, skin-toned papule or plaque, often with overlying telangiectasias
  - Treated with local excision; low malignant potential
- Balanitis circinata
  - Dry and scaling lesions of the glans in circumcised or uncircumcised males
  - Associated with Reiter's syndrome
  - Can be moist and erythematous in uncircumcised males
- Candidal balanitis
  - Usually found in uncircumcised diabetics

  – Reddened and edematous lesions
  – Usually treated with antifungal therapy
- Zoon balanitis
  – Usually in elderly, uncircumcised males
  – Cayenne pepper-appearing red, raised lesion
  – Usually distinguished from CIS on biopsy by band-like infiltrate of plasma cells

TREATMENT

GENERAL MEASURES (3)

Treatment based on multiple biopsy samples of adequate depth to rule out invasion

MEDICATION

First Line

- Topical therapy
  – 5-fluorouracil cream BID for 4–5 wk or
  – 5% imiquimod cream daily for 16 wk
  – Proven effective for large lesions not amenable to surgery or for recurrent lesions
  – Utilized with rubber condom to increase contact time

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Circumcision can decrease likelihood of recurrence
- With lesions on the foreskin, circumcision, or excision with 5-mm margin is adequate for local control
  – Lesions on the glans are difficult to excise with this strategy when trying to preserve penile anatomy
  – Ensure adequate depth of resection to rule out invasion
- Mohs micrographic surgery has been utilized to accomplish adequate excision without disfigurement
- Nd:YAG, KTP, or carbon dioxide laser ablation has been shown to be effective
  – Nd:YAG preferred due to depth of penetration

ADDITIONAL TREATMENT

Radiation Therapy

Radiation therapy can be used for patients resistant to topical treatment or who are not surgical candidates.

Additional Therapies

Additional therapies include cryotherapy, curettage, and photodynamic therapy, although their effectiveness is limited.

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 5–33% of cases have been reported to transform to SCC
  - 5–10% risk in BD, 10–33% in EQ
  - Carries significant risk of death
- Cure can be achieved up to 80% of the time
- All therapies have recurrence rates of 20–30%

COMPLICATIONS

Progression to invasive squamous cell carcinoma

FOLLOW-UP

Patient Monitoring

- BD and EQ surveillance parallels localized, invasive SCC of the penis with clinical exam:
  - Year 1–2, every 3 mo
  - Year 3–5, every 6 mo
  - Year 5–10, every 12 mo
- Consider re-biopsy of recurrent lesions to rule out transformation to invasive SCC

Patient Resources

Medline Plus: Cancer Penis http://www.nlm.nih.gov/medlineplus/ency/article/001276.htm

REFERENCES

1. Wieland U, Jurk S, Weissenborn S, et al. Erythoplasia of queyrat: Coninfection with cutaneous carcinogenic HPV type 8 and genital papillomaviruses in a carcinoma in situ. *J Invest Dermatol*. 2000;115(3):396–401.
2. Buechner SA. Common skin disorders of the penis. *BJU Int*. 2002;90(5):498–506.
3. Arlette JP. Treatment of Bowen disease and erythroplasia of queyrat. *Br J Dermatol*. 2003;149(Suppl 66):43–49.

ADDITIONAL READING

- NCCN Guidelines Version 1.2013, Penile Cancer; from NCCN.org (Accessed April 10, 2014).
- Pettaway CA, Lance RS, Davis JW, Tumors of the penis. In: Wein, et al. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012.

See Also (Topic, Algorithm, Media)

- Bowen Disease and Erythroplasia of Queyrat Image
- Penis, Cutaneous Lesion
- Penis, Squamous Cell Carcinoma

CODES

ICD9

233.5 Carcinoma in situ of penis

ICD10

D07.4 Carcinoma in situ of penis

CLINICAL/SURGICAL PEARLS

- EQ is SCC in situ arising on the glans or inner side of the foreskin.
- BD is SCC in situ of the penile shaft or scrotum.
- 80–90% of cases seen in uncircumcised men.
- Progression to invasive SCC in 5–30%.

BURNS, EXTERNAL GENITALIA AND PERINEUM

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BASICS

DESCRIPTION

- Burns to the external genitalia and perineum can damage skin, subcutaneous tissue, and surrounding organs and can be due to thermal, electrical, or chemical contact
- Thermal (most common): Includes scalding and immersion injuries, direct contact with flames or hot objects
- Electrical: Passage of an electrical current from 1 point to another through the body
- Chemical: Corrosive and alkali substances found in household and industrial chemicals

EPIDEMIOLOGY

Incidence

- Genital/perineal burns are rarely isolated
- Genitals/perineum involved in 5–13% of burns treated at major burn centers
- Abuse or neglect in 10–15% of childhood burn injuries (higher if < 2 yr of age)

RISK FACTORS

- Age: Very young (scald burns common in abused children) and very old
- Employment: Exposure to flames or caustic substances
- Gender: Women are less likely to experience genital or perineal burns (less exposed)

Genetics

N/A

PATHOPHYSIOLOGY

- Classification (1)
  - 1st-degree (superficial): Epidermis
  - 2nd-degree (partial thickness): Dermis
    - Superficial (involving the superficial, papillary dermis)
    - Deep (involving reticular dermis)
  - 3rd-degree: Underlying subcutaneous tissue
    - Typically not painful due to nerve damage
  - 4th-degree: Bone and muscle
    - Can lead to compartment syndrome
    - Often fatal

ASSOCIATED CONDITIONS

- Child and spousal abuse
- Sexual abuse
- Myoglobinuria (electrical burns)

GENERAL PREVENTION

- Follow occupational-specific safety precautions.
- Handle caustic chemicals with care.

DIAGNOSIS

HISTORY

- Type of burn (thermal, chemical, or electrical)
- Causative agent or heat source (eg, flame vs. water, noxious substance)
- Location and areas involved (Rule of 9s): External genitalia and perineum usually accounts for 1% of body surface area when using “Rule of 9s".
- Possibility of other injuries (eg, fractures from motor vehicle accidents, shrapnel)
- Pediatric considerations
  - Evaluate for scald and immersion injuries

PHYSICAL EXAM

- Complete assessment including ABCD’s of Advanced Trauma Life Support (ATLS). Often associated with concomitant injuries or further burns
  - with electrical burns determine any other entry/exit site of current
- Rule of 9s: Based on total body surface involved. Genitalia/perineum accounts for 1% of body area
- Vital signs (patients with electrical burns will require cardiac monitoring for at least 24 hr)
- Neurologic exam: Evaluate for compartment syndrome, peripheral pulses
- GU: Examine for involvement of phallus, meatus, glans, and scrotum
- Classification:
  - 1st-degree: Characterized by erythema, white plaques, and mild pain
  - 2nd-degree: Characterized by erythema, pain, superficial blisters
  - 3rd/4th-degree: Characterized by eschars, blistering, and absence of pain due to loss of nerve fibers

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Electrolytes: Treatment of burns generally requires large amount of fluid resuscitation
- With electrical burns, monitor creatine kinase and urine myoglobin

Imaging

As indicated by history or physical findings

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

- 3 zones of burns:
  - *Zone of coagulation*: Occurs at point of maximum damage. In this zone, there is irreversible tissue loss due to coagulation of the constituent proteins.
  - *Zone of stasis*: Surrounding zone of stasis is characterized by decreased tissue perfusion. The tissue in this zone is potentially salvageable. The main aim of burn resuscitation is to increase tissue perfusion here and prevent any damage from becoming irreversible. Additional insults – such as prolonged hypotension, infection, or edema – can convert this

zone into an area of complete tissue loss.
- Z*one of hyperemia*: In this outermost zone, tissue perfusion is increased. The tissue here will invariably recover unless there is severe sepsis or prolonged hypoperfusion.

DIFFERENTIAL DIAGNOSIS
- Diagnosis is usually apparent based on history and examination

ALERT
Treat any-life-threatening conditions (ABCD's). IVF: Resuscitation is critical if patient has severe burns.

TREATMENT

GENERAL MEASURES
- Treat any life-threatening conditions (ABCD)
  – Do not attempt to cool wound as this may cause more extensive injury
- Shock may occur; IVF critical
  – >20% total body surface area (TBSA), use modified Brooke formula:
    - 2 mL/kg/TBSA
- Most chemical burns should be copiously irrigated. If agent is known use guidelines:
  – Hydrofluoric acid: Irrigate with calcium gluconate
  – Hydrochloric acid or sulfuric acid: Use bicarbonate irrigation
  – Phenol: No irrigation

MEDICATION
First Line
- Silver sulfadiazine 1%: Apply to affected area
  – Does not penetrate eschar
- Mafenide acetate (Sulfamylon) 11.1%
  – Penetrates eschar
- Pain control
  – Narcotics
  – Anti-inflammatories
- Fluid resuscitation
- Electrolytes as needed
- Tetanus prophylaxis
- Antibiotic prophylaxis not necessary
  – Treat specific infections as they arise.

SURGERY/OTHER PROCEDURES (2,3)
- Most burns, particularly in children, should be managed with conservative treatment and require no surgical intervention.
- Foley catheter or suprapubic drainage may be used, but are often not necessary
- Mainstay of surgical treatment, if needed, is careful debridement.
- Affected areas may require skin coverage:
  – Granulation indicates acceptable graft bed
  – Split-thickness skin grafts have reliable graft take and excellent cosmesis

– Skin grafts can be meshed or unmeshed
– If graft bed health is questionable, can use temporary xenograft
- Wound contractures are not uncommon; treat with z-plasty
- Urethral stricture may develop; should be treated in a delayed fashion (4)
– Catheter drainage may be required in the interim

ONGOING CARE

PROGNOSIS

- Based on degree and extent of burn
- Most burns have matured by 6–12 mo; additional reconstruction may be required at that time

COMPLICATIONS

- Erectile dysfunction
- Scarring/disfigurement
- Urethral strictures

FOLLOW-UP

Patient Monitoring

- Follow-up as indicated

Patient Resources

- American Burn Association
  www.ameriburn.org
- Phoenix Society for Burn Survivors
  www.phoenix-society.org

REFERENCES

1. Hettiaratchy, Dziewulski. ABC's of burns. *Br Med J.* 2004;328:1427–1429.
2. Black PC, Friedrich JB, Engrav LH, et al. Meshed unexpanded split-thickness skin grafting for reconstruction of penile skin loss. *J Urol.* 2004;172(3):976–979.
3. Angel C, Shu T, French D, et al. Genital and perineal burns in children: 10 years of experience at a major burn center. *J Pediatr Surg.* 2002;37(1):99–103.
4. Michielsen D, Van Hee R, Neetens C, et al. Burns to genitalia and perineum. *J Urol.* 1998;159(2):418–419.

ADDITIONAL READING

- Michielsen DP, Lafaire C. Management of genital burns: A review. *Int J Urol.* 2010;17(9):755–758.
- Peck MD, Boileau MA, Grube BJ, et al. The management of burns to the perineum and genitals. *J Burn Care Rehabilitation.* 1990;11(1):54–56.
- Vanni AJ. Trauma to the external genitalia. In: Wessells, ed. *Urological Emergencies*. Totowa NJ: Humana Press, 2013.

See Also (Topic, Algorithm, Media)

- Burns, External Genitalia and Perineum Image

- Penis, Trauma
- Scrotum and Testicle, Trauma

CODES

ICD9

- 942.05 Burn of unspecified degree of genitalia
- 942.15 Erythema [first degree] of genitalia
- 942.25 Blisters, epidermal loss [second degree] of genitalia

ICD10

- T21.06XA Burn of unsp degree of male genital region, init encntr
- T21.07XA Burn of unsp degree of female genital region, init encntr
- T21.16XA Burn of first degree of male genital region, init encntr

CLINICAL/SURGICAL PEARLS

- Genital/perineal burns are rarely isolated.
- Favor conservative management initially.
- Excellent functional and cosmetic results are possible with split-thickness skin grafting.

CALYCEAL DIVERTICULA

Yaniv Shilo, MD
Timothy D. Averch, MD, FACS

BASICS

DESCRIPTION

- Calyceal diverticula are nonsecretory, transitional cell epithelium-lined cystic cavities within the renal parenchyma.
- The cavity is usually filled retrograde from urine in the collecting system.
- Mostly unilateral.
- Most prevalent in upper calyces (70%)
- No gender nor laterality predilection
- Bilateral in 3%
- Sometimes called pelvicaliceal diverticula

EPIDEMIOLOGY

Incidence

<1%

Prevalence

Found in up to 0.45% of routine intravenous pyelogram studies.

RISK FACTORS

N/A

Genetics

N/A

PATHOPHYSIOLOGY

- Congenital in origin due to failure of regression of ureteric bud.
- Urine enters diverticulum passively via narrow communication with collecting system.
- Urine trapped in diverticulum predisposes to infection and stone formation.

ASSOCIATED CONDITIONS

- Flank pain
- Calyceal calculi (9–50%)
- Recurrent urinary tract infection (UTI)
- Hematuria

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Mostly incidental finding on imaging
- Flank pain

- Microhematuria or macrohematuria
- Recurrent UTI

PHYSICAL EXAM
- Usually not suggestive
- Possible flank pain

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis
  - Microhematuria and pyuria
- Urine culture
  - Bacterial persistence

Imaging
- Abdominal x-ray (KUB):
  - May demonstrate characteristic radiopaque "milk of calcium," which appears as a half moon or meniscus-shaped calcification
    - Milk of calcium should change its location when changing positioning from erect to lateral decubitus.
  - Case reports of confusion as being diagnosed as rib metastasis
- Ultrasound (US):
  - Provide diagnosis in up to 80% of the cases.
  - Shows cystic lesion with curvilinear, plaque-like calcification along its posterior wall.
  - Exam while changing positioning is needed to differ from complex cyst.
- Intravenous pyelography (IVP):
  - Delayed imaging demonstrates the diverticulum, as it fills retrogradely from its connection to the renal pelvis or calyx.
- CT urography (CTU):
  - Delayed imaging is critical to demonstrate contrast medium within an apparent cystic mass

Diagnostic Procedures/Surgery
- Retrograde pyelogram:
  - Allows greater distension of the collecting system than can be attained with IVP.
  - Delineating anatomy and assist in planning the appropriate treatment approach.

Pathologic Findings
- Lined by nonsecretory transitional epithelium.
- Retrograde reflux of urine from the calyx via the diverticular neck can cause stasis with stones in calyceal diverticula in up to 50% of cases

DIFFERENTIAL DIAGNOSIS
- Calcified tumor
- Complicated renal cyst
- Kidney abscess
- Nephrolithiasis

TREATMENT

GENERAL MEASURES

- In case of uncomplicated, asymptomatic calyceal diverticulum treatment can be conservative with no further imaging follow-up.
- Indications for therapy include pain, recurrent infection, increased calculus growth, hematuria or large size that compresses or progressively damages contiguous renal parenchyma

MEDICATION

First Line

Antibiotic treatment can be used for recurrent UTIs; otherwise no specific role

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Shock wave lithotripsy (SWL):
  - May be suitable for calyceal diverticulum with small calculi and wide infundibulum (1) [B].
  - Can resolve flank pain.
  - Limitations are due to inadequate passage of stone fragments through the infundibulum and lack of anomaly repair.
- Ureteroscopy (URS):
  - Most suitable as initial treatment for calculi <1.5 cm located in the middle or upper pole diverticulum and specifically in the anterior aspect.
  - Involves mechanical dilatation of the diverticular neck and removal of calculi if present.
  - Ablation of diverticular cavity is not a common practice.
- Percutaneous nephrolithotomy (PCNL):
  - Considered to be the definitive surgical treatment specifically for diverticula containing stone burden >1.5 cm in the posterior aspect.
  - Challenging when only thin layer of parenchyma surrounding the diverticula or located anteriorly.
  - Requires direct access to diverticulum and infundibulum widening.
  - Ablation of the calyceal diverticulum cavity is recommended (2)[B].
- Laparoscopic nephrolithotomy (LAP):
  - May be advantageous in cases of anterior diverticula, diverticula covered with thin layer, diverticula containing large calculi or large diverticula (3)[B].
  - Includes unroofing of the diverticulum and calculi removal if present.
  - Ablation of the remaining cavity and neck.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

- SWL:
  - Stone-free rate is relatively low (up to 60%), however, symptom-free rate is higher (4)[B].
- URS:
  - Stone-free and symptom-free rates can be high when infundibulum is identified
  - In significant number of diverticula the infundibulum cannot be found (4)[B].
- PCNL:
  - Excellent stone-free and symptom-free rates (over 80%).
  - Long-term results remain good.
- LAP:
  - Initial results show high stone-free rate and diverticular ablation.

COMPLICATIONS

- Calyceal diverticula:
  - Secondary infection
  - Chronic pain with stones
  - Compression of surrounding tissue
- SWL:
  - Flank pain
  - Infection
  - Subcapsular or perinephric hematoma
- URS:
  - Bleeding
  - Thermal injury to ureteral wall or renal parenchyma
  - Ureteral perforation
  - Sepsis
- PCNL:
  - Bleeding
  - Urinary extravasation
  - Pneumothorax
  - Hemothorax
  - Collecting system perforation

FOLLOW-UP

Patient Monitoring

- Radiographic imaging with either CTU, IVP, or kidney US should be done 6–8 wk postoperatively.
- Patients with calculi contained in diverticulum may need metabolic evaluation as these patients tend to have metabolic abnormalities similar to patients with nephrolithiasis (5) [B].

Patient Resources
N/A

REFERENCES

1. Streem SB, Yost A. Treatment of caliceal diverticular calculi with extracorporeal shock wave lithotripsy: Patient selection and extended followup. *J Urol.* 1992;148:1043–1046.
2. Shalhav AL, Soble JJ, Nakada SY, et al. Long- term outcome of caliceal diverticula following percutaneous endosurgical management. *J Urol.* 1998;160(5):1635–1639.
3. Gonzalez RD, Whiting B, Canales BK. Laparoscopic calyceal diverticulectomy: Video review of techniques and outcomes. *J Endourol.* 2011;25(10):1591–1595.
4. Rapp DE, Gerber GS. Management of caliceal diverticula. *J Endourol.* 2004;18(9):805–810.
5. Auge BK, Maloney ME, Mathias BJ, et al. Metabolic abnormalities associated with calyceal diverticular stones. *BJU Int.* 2006;97(5):1053–1056.

ADDITIONAL READING

- Canales B, Monga M. Surgical management of the calyceal diverticulum. *Curr Opin Urol.* 2003;13(3):255–260.
- Matlaga BR, Miller NL, Terry C, et al. The pathogenesis of calyceal diverticular calculi. *Urol Res.* 2007;35(1):35–40.

See Also (Topic, Algorithm, Media)
- Calcifications, Renal
- Calyceal Diverticula Image ☼
- Nephrocalcinosis
- Urolithiasis, Adult, General considerations
- Urolithiasis, Renal

CODES

ICD9
- 592.0 Calculus of kidney
- 593.89 Other specified disorders of kidney and ureter
- 753.3 Other specified anomalies of kidney

ICD10
- N20.0 Calculus of kidney
- N28.89 Other specified disorders of kidney and ureter
- Q63.8 Other specified congenital malformations of kidney

CLINICAL/SURGICAL PEARLS
- Usually located on upper calyces.
- Associate disorders include—calyceal calculi, recurrent UTI, and flank pain.
- URS is suitable for anterior midpole or upper diverticula with calculi <1.5 cm.
- PCNL is the treatment of choice in general for calyceal diverticula and specifically for posterior diverticula with thick layer of parenchyma surrounding with calculi >1.5 cm.

- Growing evidence for the effectiveness of LAP approach in cases of anterior diverticula, diverticula covered with thin layer, diverticula containing large calculi or large diverticula.

CATHETERIZABLE STOMA PROBLEMS

Zachary L. Smith, MD
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BASICS

DESCRIPTION

- Catheterizable stomas (CSs) are utilized in all age groups and provide a means of emptying the native bladder or neobladder.
- Most common indications for CS vary with age groups:
  - Pediatrics: Incontinence related to neurologic or congenital conditions
  - Adults: Urinary diversion following extirpative surgery for malignancy
- Location of CS can vary, but is most often located in the umbilicus or right lower quadrant.
- Catheterizable channels are commonly constructed from a segment of small bowel or the appendix.
- Mechanism of CS continence depends on the type of urinary reservoir.
- Patients with CS often have routine catheterization schedules.
- CS problems can be related to the stoma, catheterizable channel, or urinary reservoir.

EPIDEMIOLOGY

Incidence

- Complications are reported in 10–50% of patients with CSs:
  - Stomal stenosis has been reported in up to 40% of CS
  - Most stomal-related complications are reported within the 1st yr following surgery (1)[C].
  - Incontinence is reported in 1–20% of cases and is associated with the mechanism of continence.
  - Parastomal hernias have been noted in 0–5% of patients.

Prevalence

N/A

RISK FACTORS

- Improper stomal positioning
- Infrequent use of CS
- Multiple prior abdominal procedures
- Obesity
- Surgical technique
- Wound infections

Genetics

N/A

PATHOPHYSIOLOGY

- Stomal stenosis can be attributed to infrequent catheterization, scar formation, ischemia secondary to compromised vascular supply to catheterizable channel, or a nontension-free mucocutaneous anastomosis.

- Difficulty catheterizing the CS channel can be attributed to angulation of a mobile and/or redundant channel.
- Significant weight loss or gain
- Improper creation of continence mechanism
- Incomplete detubularization or augmentation of the urinary reservoir can lead to incontinence secondary to low compliance and small reservoir capacity.
- Pouchitis (lower urinary tract infection) can cause temporary failure of the continence mechanism because of the hypercontractility of the bowel segment; can be caused by inflammation of the mucosa.

ASSOCIATED CONDITIONS
- Urologic, gynecologic, and colorectal malignancies
- Spinal dysraphisms
- Traumatic spinal cord injuries

GENERAL PREVENTION
- Maintenance of a regular catheterization regimen
- Several complications can be prevented at the time of surgery when creating the catheterizable channel:
  - Maintenance of vascular supply to catheterizable channel
  - Minimized redundancy catheterizable channel with fixation and stabilization of the continence mechanism
  - Adequate construction of continence mechanism
  - Tension-free mucocutaneous anastomosis
  - Use of V-flap of skin to prevent stomal stenosis

DIAGNOSIS

HISTORY
- Date of surgery
- Indication for CS:
  - Incontinence (urinary vs. fecal)
  - Malignancy
- Attempt to obtain operative reports
- Type of bowel utilized
- History of CS complications
- Catheterization details:
  - Typical catheterization regimen
  - Type and size of catheter used
  - Technique utilized (direction, amount of pressure, etc.)
  - Normal catheterization volumes
  - Time of last normal catheterization
  - Character of urine at the time of last successful catheterization (color, odor, presence of debris, etc.)
- Status of the bladder neck in patients with native bladder intact:
  - Urethral catheterization can be attempted in patients whose native urethra is intact and

who have an open bladder neck.
- Review of systems should focus on abdominal symptomatology.

PHYSICAL EXAM
- Vital signs may reveal tachycardia, hypotension, and fever in patients with peritonitis secondary to perforation of the catheterizable channel or urinary reservoir.
- Abdominal exam evaluating signs of peritonitis
- Inspection of the stoma, evaluating for:
  – Stenosis
  – Mucosal ischemia
  – Abdominal wall deformity suggestive of parastomal hernia
- Catheterization of CS to:
  – Evaluate patency of stoma
  – Determine capacity of urinary reservoir
  – Evaluate continence mechanism
  – Obtain urine sample
  – Instill contrast for imaging.

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Serum electrolytes:
  – Elevated serum creatinine may be noted in patients with urinary retention from the inability to catheterize.
  – Several metabolic abnormalities may be present in patients with urinary reservoirs, depending on bowel segment utilized:
    - Stomach: Hypochloremic, hypokalemic alkalosis
    - Jejunum: Hyponatremic, hypochloremic, hyperkalemic acidosis
    - Ileum: Hyperchloremic acidosis
    - Colon: Hyperchloremic acidosis
- CBC:
  – Leukocytosis suggestive of infection
- Blood and urine cultures in patients presenting with abdominal pain and fever

Imaging
- Contrast study of catheterizable channel and urinary reservoir to evaluate for perforation
- Cross-sectional imaging of the kidneys assessing for the presence of hydronephrosis

ALERT
Have a low threshold for obtaining a cross-sectional imaging study (CT/MRI) with contrast when a perforation of the CS or urinary reservoir is suspected, especially in patients with neurologic deficits.

Diagnostic Procedures/Surgery
Urodynamics in patients with incontinence may reveal uninhibited contractions or a poorly compliant high-pressure reservoir.

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS

- Perforation of CS channel or urinary reservoir
- Stomal stenosis
- Incontinence
- False passage
- Parastomal hernia
- Fistula
- Inability to catheterize due to redundancy of catheterizable channel

TREATMENT

ALERT
Perforation of CS conduit or urinary reservoir mandates emergent exploratory laparotomy, drainage of urinary extravasation, and repair of urinary reservoir.

GENERAL MEASURES

- Good hygiene
- Routine catheterization of CS
- Early intervention with difficulty

MEDICATION

First Line

- Incontinence related to uninhibited pouch contractions:
  - Anticholinergics (oxybutynin, tolterodine, etc.) (2)[C]
- Pouchitis may sometimes be due to infection and can be treated with appropriate antibiotics.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Stomal stenosis:
  - Elective surgical revision with V-flap of skin (3)[C]
- Incontinence:
  - Elective surgical revision of continence mechanism
  - Injection of bulking agent into CS
  - Augmentation of urinary reservoir with intestinal patch in cases of high pressures and poor compliance (2)[C]
- Parastomal hernia:
  - Elective hernia repair with or without repositioning stoma site on abdominal wall
  - Surveillance in asymptomatic patients
- Fistula:
  - Elective revision
- Inability to catheterize secondary to false passage or redundancy of CS channel:
  - Elective revision
  - Occasionally, minor false passages can be treated with an indwelling catheter for a short

period to allow healing of channel.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Stomal stenosis:
  - Routine catheterization schedule
  - Dilatation of stenosis
- Inability to catheterize secondary to false passage or redundancy of CS channel:
  - Change type of catheter
  - Change method of catheterization

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Success following stomal revisions for stenosis ranges from 80–95% (1)[C].

COMPLICATIONS

Recurrence of prior complication

FOLLOW-UP

Patient Monitoring

- Maintenance of routine catheterization schedule
- Additional follow-up with enterostomal therapist

Patient Resources

- United Ostomy Associations of America, Inc. www.ostomy.org
- Bladder Cancer Advocacy Network. www.bcan.org

REFERENCES

1. Thomas JC, Dietrich MS, Trusler L, et al. Continent catheterizable channels and the timing of their complications. *J Urol.* 2006;176:1816–1820.
2. Farnham SB, Cookson MS. Surgical complications of urinary diversion. *World J Urol.* 2004;22:157–167.
3. Hellenthal NJ, Eandi JA, DeLair SM, et al. Umbilical stomal stenosis: A simple surgical revision technique. *Urology.* 2007;69:771–772.

ADDITIONAL READING

- Benson MC, McKiernan JM, Olsson CA. Cutaneous continent urinary diversion. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds., *Campbell-Walsh Urology.* 10th ed. Philadelphia, PA: Elsevier; 2012.
- Skinner E, et al. Complications of continent cutaneous urinary diversion. In: Taneja SS, Smith RB, Ehrlich RM, eds. *Complications of Urologic Surgery, Prevention and Management.* 4th ed. Philadelphia, PA: WB Saunders; 2010.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, Urothelial, Muscle Invasive (Clinical and Pathologic T2/T3/T4) (MIBC)
- Bladder Cancer, Squamous Cell Carcinoma
- Catheterizable Stoma Problems Image ☼
- Parastomal Hernia
- Pouchitis
- Urostomy Problems

CODES

ICD9

- 596.82 Mechanical complication of cystostomy
- 596.83 Other complication of cystostomy
- V55.5 Attention to cystostomy

ICD10

- N99.512 Cystostomy malfunction
- N99.518 Other cystostomy complication
- Z43.5 Encounter for attention to cystostomy

CLINICAL/SURGICAL PEARLS

- Cathterizable stomas are used for varying reasons throughout one's life. Benign/neurogenic causes most common in children, malignant causes most common in adults.
- Stomal stenosis is by far the most common complication of cathterizable stomas.
- Surgical revision is often required for most cathterizable stomas complications.
- Good technique and cathterizable stomas maintenance with a routine catheterization schedule can prevent most complications.

CHORDEE

Jennifer A. Hagerty, DO

BASICS

DESCRIPTION

- Chordee is ventral penile curvature that occurs with or without hypospadias:
  - Epispadias can occur with dorsal curvature
  - Lateral curvature also can occur with or without hypospadias

EPIDEMIOLOGY

Incidence

The incidence of chordee is unknown

Prevalence

- 44% of fetuses through the 2nd trimester suggesting chordee is a normal part of development (1)[A]
- Chordee occurs without hypospadias in 4–10% of cases of congenital chordee (2)[C]
- Hypospadias occurs in 1 of 250 live births (3)[A]
  - Chordee is identified in 1/3 of these patients (3)[A]

RISK FACTORS

- Congenital
- Prior penile surgery
- Trauma

Genetics

- Found in syndromes associated with hypospadias
- Chromosomal abnormalities found in 22% of individuals with severe hypospadias associated with undescended testicles
- 14% of hypospadias in siblings
- 8% incidence in offspring

PATHOPHYSIOLOGY

- Chordee could be considered an arrest of normal embryologic development
- Different proposed etiologies for chordee without hypospadias (2,4):
  - Class I: Results when corpus spongiosum, dartos, and Buck fasciae are deficient over the involved portion of the urethra; urethra is just below the skin, and the dense fibrous tissue beneath the urethra is responsible for the chordee.
  - Class II: Spongiosum is normal while the dartos and Buck fasciae are dysgenetic.
  - Class III: Only the dartos fascia is deficient.
  - Class IV: Corporeal disproportion.

ASSOCIATED CONDITIONS

- Hypospadias
- Epispadias

- Penile torsion
- Cryptorchidism
- Disorders of sexual development

GENERAL PREVENTION
None known

DIAGNOSIS
HISTORY
- Visualized curvature of the penis with an erection
- Presence of hypospadias

PHYSICAL EXAM
- Observe the individual's erection if possible
- Possible coexisting findings:
  - Hypospadias or epispadias
  - Incomplete foreskin ventrally
  - Penoscrotal webbing
  - Penile torsion
  - Hypoplasia of the ventral shaft skin
  - Cryptorchidism

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Routine lab testing not typically indicated
- Chromosomal testing and/or biochemical testing in the individual with a suspected syndrome or disorder of sexual differentiation

Imaging
- Renal and bladder ultrasound routinely recommended only in individuals with:
  - Severe hypospadias
  - Hypospadias associated with other organ system anomalies

Diagnostic Procedures/Surgery
- Intraoperative artificial erection test at the time of repair
  - Infusion of injectable saline into the corpora with a tourniquet at the base of the penis

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Disorder of sex development
- Epispadias
- Hypospadias
- Normal penile variant
- Penile torsion

TREATMENT

GENERAL MEASURES
Chordee repair is the standard approach

MEDICATION
First Line
None usually indicated specifically for chordee

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Specific surgery dependant on the associated conditions and the severity of the curvature
- Performed typically after 6 mo of age
- General points:
  - Following penile skin release, induce artificial erection. This should be repeated to confirm correction.
  - Chordee without hypospadias often can be corrected by penile degloving with excision of the fibrous tissue superficial to Buck fascia.
  - More moderate chordee requires simple plication and/or excision of ellipses from the site of maximum curvature.
  - In the most severe cases, often associated with hypospadias the urethra may be foreshortened and need to be transected.
  - Chordee secondary to corporeal disproportion involves incising the tunica albuginea on the ventral surface of the penis, transversely over the point of maximal curvature; than covering the defect with either a free dermal, tunica vaginalis or single ply small intestinal submucosal (SIS) graft.
  - It is critical to identify and preserve the neurovascular bundles during dissection and plication.
  - Skin flaps may be required for penile skin coverage after correction of the chordee.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
- Excellent prognosis postoperatively with a low complication rate
- There may be progression of chordee after puberty (5)[C]

COMPLICATIONS
Recurrence of chordee

FOLLOW-UP

Patient Monitoring
- Postoperative checkup within several weeks after surgery
- Consider follow-up after puberty

Patient Resources
- http://men.webmd.com/guide/chordee-repair-treatment
- http://www.mayoclinic.com/health/hypospadias/DS00884

REFERENCES

1. Kaplan GW, Lamm DL. Embyrogenesis of Chordee. *J Urol*. 1975;114:769–772.
2. Kramer S, Aydin G, Kelalis P. Chordee without hypospadias in children. *J Urol*. 1982;128:559–561.
3. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. *Pediatrics*. 1997;100:831–834.
4. Devine CJ Jr., Horton CE. Chordee without hypospadias. *J Urol*. 1973;110:264–271.
5. Vandersteen DR, Husmann DA. Late onset recurrent penile chordee after successful correction at hypospadias repair. *J Urol*. 1998;160:1131–1133.

ADDITIONAL READING

Bologna RA, Noah TA, Nasrallah PF, et al. Chordee: Varied opinions and treatments as documented in a survey of the American Academy of Pediatrics, Section of Urology. *Urology*. 1999;53:608–612.

See Also (Topic, Algorithm, Media)
- Chordee Image
- Disorders of Sexual Development (DSD)
- Epispadias
- Hypospadias

CODES

ICD9
- 607.89 Other specified disorders of penis
- 752.61 Hypospadias
- 752.63 Congenital chordee

ICD10
- N48.89 Other specified disorders of penis
- Q54.4 Congenital chordee
- Q54.9 Hypospadias, unspecified

CLINICAL/SURGICAL PEARLS
- Chordee most commonly occurs with hypospadias.
- Repair recommended after 6 mo of age.
- Consider ongoing monitoring after puberty.

CHRONIC KIDNEY DISEASE, ADULT (RENAL FAILURE, CHRONIC)

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Gerald L. Andriole, MD, FACS

BASICS

DESCRIPTION

- Defined as presence of kidney damage or impaired GFR (< 60 mL/min/1.73 m^2) for > 3 mo (1)
  - if less than 3 months considered acute kidney injury (AKI)
  - Irrespective of cause kidney damage defined as:
    - Pathologic abnormalities
    - Urinary, blood, or imaging abnormalities
    - Kidney transplantation
- Classification based on Kidney Disease Outcomes Quality Initiative (NKF KDOQI):
  - Stage 1: Kidney damage with normal renal function (GFR > 90 mL/min/1.73 m^2)
  - Stage 2: Mild renal dysfunction (GFR 60–89 mL/min/1.73 m^2)
  - Stage 3: Moderate renal dysfunction (GFR 30–59 mL/min/1.73 m^2)
  - Stage 4: Severe renal dysfunction (GFR 15–30 mL/min/1.73 m^2)
  - Stage 5: Kidney failure (GFR < 15 or dialysis mL/min/1.73 m^2)

EPIDEMIOLOGY

Incidence

- Stage 1 or 2 CKD progress to more advanced stages at 0.5% per year
- Stage 3 or 4 progress to end-stage renal disease at 1.5% per year (3)

Prevalence

- 10% in noninstitutionalized adults
  - Corresponds to > 20 million people (4)
  - 398,000 treated by dialysis in 2000, expected to increase to > 2 million people by 2030 (2)
  - Prevalence in US population
    - Stage 1: 1.8%
    - Stage 2: 3.2%
    - Stage 3: 7.7%
    - Stage 4/5: 0.35% (3)

RISK FACTORS

- Diabetes
- Hypertension
- Cardiovascular disease
- Family history
- Age > 60

- Urinary tract obstruction
- Urinary calculi
- Nephrotoxic drugs
- Obesity
- Neoplasia
- Loss of kidney mass
- Race
  - African American, American Indian, Hispanic, Asian, or Pacific Islander

Genetics

- Complex phenotype impacted by various genetic factors in addition to environmental factors and comorbid disease
  - CYP4A11 gene involved in renal vasoconstriction and natriuresis and is associated with increased risk in African Americans (6)
  - APOL1 associated with focal segmental glomerulosclerosis and hypertension associated ESRD (7)

PATHOPHYSIOLOGY

- Heterogenous condition with various causes
  - Diabetic kidney disease
  - Nondiabetic kidney disease
    - Glomerular disease
    - Vascular diseases
    - Tubulointerstitial disease
    - Cystic disease (polycystic kidney disease)
  - Transplant nephropathy
    - Acute rejection
    - Chronic rejection
    - Calcineurin toxicity
    - Glomerulonephropathy

ASSOCIATED CONDITIONS

See risk factors

GENERAL PREVENTION

- Screening and treatment of associated risk factors
  - Screening selected populations:
    - Age >50
    - History of DM (diabetes melitus), HTN (hypertension), or CV (cardiovascular) disease
    - Family history
    - Exposure to nephrotoxins

DIAGNOSIS

HISTORY

- Silent, asymptomatic until late stages
  - Evaluate for symptoms of associated conditions/risk factors

- Symptoms of uremia in ESRD
  - Anorexia
  - Decreased urine output
  - Increased thirst
  - Mental status changes
  - Muscle cramps
  - Nausea
  - Vomiting

PHYSICAL EXAM

- Physical exam findings uncommon until late stages of disease
  - Findings associated with increased risk
    - BP >130/85
    - Obesity/increased waist circumference
  - Manifestations of advanced kidney disease
    - Volume overload/edema
    - Pruritus
    - Visual disturbances
    - Weight Loss
    - Confusion

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Chemistry
  - Elevated creatinine
  - Elevated blood urea nitrogen
  - Hyperkalemia
  - Acidosis
  - Hyperphosphatemia
- Urinalysis with microscopy
  - Hematuria
  - Casts: RBC (glomerulonephritis), WBC (interstitial nephritis)
  - Fat bodies (nephrotic syndrome)
- Hyperparathyroidism
  - Results from altered calcium and phosphorus metabolism
- Anemia
- Proteinuria/albuminuria
  - Albuminuria indicates increased glomerular permeability to macromolecules
  - Albumin to creatinine ratio >30 mg/g indicates increased risk of CKD progression, ESRD, cardiovascular and all cause mortality.
- GFR
  - Estimated GFR (mL/min/1.73 m^2) = $1.86 \times (SCR)^{-1.154} \times (age)^{-0.203} \times$ (0.742 if female) $\times$ (1.1212 if African American)

Imaging

- Broad range of findings depending on etiology and imaging modality (US, CT scan, MRI,

angiography, isotope scans)
  – Hydronephrosis: Potentially reversible
  – Polycystic kidneys
  – Atrophic kidneys
  – Increased echogenicity (on ultrasound)
  – Renal artery stenosis
  – Cortical scarring

Diagnostic Procedures/Surgery

- Renal biopsy is indicated in selected cases and choices can vary greatly with nephrologists
  – Isolated glomerular hematuria with proteinuria
  – Nephrotic syndrome
  – Acute nephritic syndrome
  – Acute/rapidly progressive kidney disease
- Urologic evaluation if gross or microscopic hematuria
  – Cystoscopy
  – Upper tract imaging
- Angiography (CT or MR angiogram) if suspected atherosclerotic renovascular disease (asymmetric renal size)

Pathologic Findings

- *Renal biopsy findings*
  – Reveals tubulointerstitial, glomerular, or vascular disease
  – May also be seen on nephrectomy/partial nephrectomy specimens

DIFFERENTIAL DIAGNOSIS

- Kidney damage with duration >3 mo is diagnostic regardless of cause
- Differentiate from acute kidney disease based on duration and underlying etiology
  – Acute kidney injury
  – Alport syndrome
  – Autosomal dominant polycystic kidney disease.
  – Chronic glomerulonephritis
  – Diabetic nephropathy
  – Goodpasture syndrome
  – Multiple myeloma
  – Nephrolithiasis
  – Nephrosclerosis
  – Rapidly progressive glomerulonephritis
  – Renal artery stenosis
  – Systemic lupus erythematosus
  – Urinary obstruction
  – Wegener granulomatosis

TREATMENT

GENERAL MEASURES

- Use CKD staging to guide management (ie, risk for progression and complications of CKD). See table in Section II "Chronic Kidney Disease (CKD)."
- Goal is reduction of morbidity and mortality from associated comorbidities
  - Patient more likely to die of cardiovascular disease than progress to dialysis (3)
  - Blood glucose control (HbA1c <7)
  - Treatment of proteinuria and hypertension
  - Treatment of dyslipidemia to prevent cardiovascular events
  - Addressing alterations in bone metabolism (hyperphosphatemia, Vitamin D deficiency)
  - Prevention of contrast-induced nephropathy (patient at risk if GFR <60)
  - Avoidance of Gadolinium when GFR <30 to prevent nephrogenic systemic fibrosis

MEDICATION

First Line

- ACE inhibitors (ACE-I) (captopril, enalapril, ramipril, others) or angiotensin II receptor blockers (ARBs) (losartan, olmesartan, telmisartan others)
  - Indicated with random protein to creatinine ratio >200 mg/G
  - Do not use ACE-I and Angiotensin II receptor blockers (*ARBs*) concurrently: Risk of hypotension and worsening renal function
  - Monitor for hypotension, hypokalemia, or worsening renal function
  - Common ACE-I side effects include cough, angioedema, or allergy
- Statin therapy
  - Goal LDL (low density lipids) <100 and triglyceride <150
  - Side effects include myalgia, liver dysfunction, GI disturbance, and rash

Second Line

- Erythropoiesis-stimulating agents
  - Optimal hemoglobin unknown
  - Increased risk of cardiovascular events and death with hemoglobin >11 g/dL
  - Indicated to prevent transfusion-related risks (patient with Hg <10 and rate of decline suggesting need for blood transfusion)
    - Examples include erythropoietin α and darbepoetin α

SURGERY/OTHER PROCEDURES

- Dialysis access as appropriate (vascular or peritoneal)
- Renal transplantation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Dietary modifications
- Patient education
- Smoking cessation
- Weight loss

Complementary & Alternative Therapies

Avoidance of herbal remedies which may have nephrotoxic effects.

ONGOING CARE

PROGNOSIS

- Variable depending on stage, patient risk factors, and management of comorbidities
  - 10–100 × increased risk of cardiovascular comorbidities in ESRD patients
  - 13–29% 1-yr mortality in patients initiating hemodialysis (5)

COMPLICATIONS

- CKD patients at increased risk of progression, cardiovascular disease, hypertension, anemia, disorders of mineral metabolism, and death
- Degree of proteinuria correlates with risk of progression

FOLLOW-UP

Patient Monitoring

- Stage 1-2
  - Monitor GFR, proteinuria, and blood pressure
    - Clinical abnormalities rare at this stage but patients must be monitored for progression
    - Monitor HbA1c and microalbumin in diabetics
    - Evaluation every 12 mo, at least every 6 mo if proteinuria present
- Stage 3
  - Monitor GFR, proteinuria, blood pressure, HbA1c, serum electrolytes, and hemoglobin
    - Elevations of phosphorous, potassium, and anemia may be seen
    - Evaluation every 3 mo
    - Referral to nephrology when GFR approaches 30 mL/min
- Stage 4
  - Monitor GFR, proteinuria, blood pressure, HbA1c, serum electrolytes, and hemoglobin
    - Significant electrolyte abnormalities common; monthly follow-up with nephrology
- Stage 5
  - Severe electrolyte abnormalities and anemia present: Ongoing follow-up with renal replacement therapy

Patient Resources

- National Kidney Foundation
  - www.kidney.org/patients

REFERENCES

1. National Kidney Foundation : K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–S266.
2. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol*. 2005;16:180–188.
3. Stevens LA, Li S, Wang C, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: Results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2010;55(3 suppl 2):S23–S33.
4. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41:1–12.
5. Chan M, Dall AT, Fletcher KE, et al. Outcomes in patients with chronic kidney disease

referred late to nephrologists: A meta-analysis. *Am J Med.* 2007;120:1063–1070.
6. Keene KL, Mychaleckyj JC, Leak TS, et al. Exploration of the utility of ancestry informative markers for genetic association studies of African Americans with type 2 diabetes and end stage renal disease. *Hum Genet.* 2008;124:147–154.
7. Hsu CC, Kao WH, Coresh J, et al. Apolipoprotein E and progression of chronic kidney disease. *JAMA*. 2005;293:2892–2899.

ADDITIONAL READING

KDIGO. Summary of recommendation statements. *Kidney Int.* 2013;3(suppl):5.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Chronic Kidney Disease, Pediatric (Renal Failure, Chronic)
- See Table in Section II "Chronic Kidney Disease (CKD)."

CODES

ICD9

- 585.5 Chronic kidney disease, Stage V
- 585.6 End stage renal disease
- 585.9 Chronic kidney disease, unspecified

ICD10

- N18.5 Chronic kidney disease, stage 5
- N18.6 End stage renal disease
- N18.9 Chronic kidney disease, unspecified

CLINICAL/SURGICAL PEARLS

- Degree of proteinuria predicts progression.
- Differentiate from acute renal failure based on duration.
- Treat potentially reversible causes (ie, hydronephrosis).

CHRONIC KIDNEY DISEASE, PEDIATRIC (RENAL FAILURE, CHRONIC)

Timothy E. Bunchman, MD
Megan M. Lo, MD

BASICS

DESCRIPTION

- National Kidney Foundation (NKF) defines chronic kidney disease (CKD) as evidence of structural or functional kidney abnormalities (abnormal urinalysis, imaging studies, or histology) that persist for at least 3 mo, with or without a decreased glomerular filtration rate (GFR), as defined by a GFR of <60 mL/min per 1.73 m^2 (1)
  - This definition is not applicable to children younger than 2 yr, because they normally have a low GFR, even when corrected for body surface area
- CKD in pediatrics
  - 70% tubular interstitial disease (TID)
  - 30% chronic glomerular disease (CGD).
- CKD in children is often related to congenital abnormalities. The presentation often can be silent or associated with: Polyuria and polydipsia and failure to grow.
- TID is often congenital and associated with different syndromes: Posterior urethral valves (PUVs), Eagle-Barrett syndrome (EBS), and renal dysplasia (most genetic syndromes are associated with dysplasia).
- CGD is often associated with hypertension, hematuria, proteinuria, and edema.
- The peak age of the diagnoses of end-stage renal disease is about 5 yr of age. The second age of presentation of loss of kidney function is around the age of puberty.

EPIDEMIOLOGY

Incidence

10–15 cases per million per year

Prevalence

50–100 per million per year

RISK FACTORS

- Primary risk factor for dysplasia is associated congenital diseases and/or syndromes.
- Familial renal disease; may present at any age
  - Alport syndrome
  - Benign familial hematuria
  - IgA nephropathy
  - Polycystic kidney disease
- Higher in males, African Americans

Genetics

Diverse based upon cause. For example, mutations in HNF1B are causative for cystic dysplasia of the kidney.

PATHOPHYSIOLOGY

- In interstitial renal disease, the degree of CKD is related to the amount of renal mass. In those patients who were born with small kidneys or have associated obstructive uropathy (PUV, EBS, megaureter syndrome) often will have early progressive loss of renal function.
- Glomerular-based renal disease is more common in the school age and greater population.
  - The clinical presentation of glomerulonephritis is associated with edema, hypertension, as well as blood and protein in the urine; most need a renal biopsy.

ASSOCIATED CONDITIONS

- Hearing loss
- Short stature

GENERAL PREVENTION

- In CKD associated with congenital renal disease there is no true prevention.
- Often the use of prenatal ultrasounds can identify infants at risk but they are not 100% diagnostic.
  - Serial ultrasounds over time may identify lack of interstitial renal disease, primarily looking for renal growth.
  - Further, a low level of amniotic fluid at the time of birth also correlates with poor renal function.
- Prevention from a glomerular-based renal disease is limited as these are usually related to autoimmune diseases. Therefore, the general prevention in all areas of CKD is prevention of complications of CKD.

DIAGNOSIS

- In glomerular-based renal disease the history is associated with grossly bloody urine, hematuria, proteinuria, hypertension, and edema. Tissue pathology is generally needed for diagnosis.
- In the review of systems, the findings of polyuria, polydipsia, and exclusion of diabetes is important. These children also can have associated growth impairment.
- Family history is important in certain renal disease, specifically in the area of the familial renal disease such as IgA nephropathy, Alport, polycystic kidney disease, and rarely benign familial hematuria.
  - In addition, eliciting a history of reflux nephropathy, recurrent urinary tract infections, and congenital renal abnormalities within the family is important.
  - Further a family history of dialysis or transplantation or unexplained hypertension earlier in life may be important.
- In the classic Alport syndrome (a male predominant disease) there is an association with high-frequency hearing loss, often in the 2nd or 3rd decade of life.

PHYSICAL EXAM

- Often these children have a benign exam
  - In TID, the blood pressure and poor growth are important.
  - In CGD, kids often have hypertension.
  - Can have associated edema, ascites, and cardiovascular abnormalities.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Basic metabolic panel, renal function testing
- Regardless of the etiology of CKD, at levels of CKD 3 or greater (roughly 50% kidney function), one can have:
  - Metabolic acidosis (low CO_2)
  - Abnormal parathyroid activity
    - Low calcium, elevated phosphorus, and elevated PTH
  - Anemia that is usually related to a combination of iron deficiency, as well as the lack of natural erythropoiesis.
- C3 C4 complement
  - Decreased in some glomerulonephritis and lupus nephritis
- Urinalysis:
  - In TID, the urine is usually benign with inability to concentrate the urine regardless of the time of day.
  - In CGD, often these patients can have blood and protein and red cell casts.
- Urine protein: Creatinine ratio, rarely 24-hr urine for protein.

Imaging

- In TID the renal imaging is important.
  - Often these patients can have normal to small looking kidneys seen on ultrasound. The echogenic texture will be important. Further, some degree of obstructive uropathy may be seen.
  - Voiding cystourethrogram may be indicated
  - In those patients who have obstructive uropathy, either at a UPJ or UVJ, a diuretic renal scan or MAG3 scan may be important.
- In CGD, renal imaging may show nephromegaly. Otherwise, ultrasound will be nonspecific.

Diagnostic Procedures/Surgery

- In glomerular-based renal diseases renal biopsy is often required.
- Indication for biopsy in patients with CGD is: A normal complementemic glomerulonephritis or a persistent low C3, and a low C4.
- Other indications: Glomerulonephritis associated with an elevated anti-dsDNA (lupus), hemoptysis with associated renal glomerulonephritis (pulmonary, renal disease), and in patients with persistent low C3 without normalization after 12 wk, which excludes postinfectious glomerulonephritis (historically poststreptococcal glomerulonephritis).

Pathologic Findings

- Histologic analysis in interstitial renal disease is not essential.
- In glomerular-based renal diseases, renal biopsy is often required.
- Depending on underlying cause, the pathologic findings are vastly different on H&E, immunofluorescence, and electron microscopy.

DIFFERENTIAL DIAGNOSIS

- As mentioned for TID, polyuria, polydipsia can also be associated with diabetes, which is an easy diagnosis to exclude based on urinalysis and blood work.
- Differential diagnosis of CKD is limited to underlying disease

– Congenital renal anomalies: Obstructive uropathy, renal hypoplasia or dysplasia, reflux nephropathy, polycystic kidney disease
– Glomerular disease: Focal segmental glomerulosclerosis (FSGS).
– Others: Hemolytic uremic syndrome, genetic diseases (cystinosis, oxalosis, Alport syndrome), interstitial nephritis
– Rare in childhood: Diabetic nephropathy and hypertension

TREATMENT

GENERAL MEASURES

- In chronic interstitial renal disease with polyuria/polydipsia, more fluid and sodium are needed to maintain euvolemia.
- In both groups, attention to potassium and phosphorus load is important.
- All NSAIDS should be avoided. Levels of potential nephrotoxins, if measurable such as vancomycin or gentamicin, should be followed at least twice weekly; with an initial level no later than 24–48 hr after starting.
- Damage from CT contrast should be minimized with pre- and postprocedure IV hydration.

MEDICATION

First Line

- Treatment of metabolic acidosis with either liquid form of Bicitra or the pill form of bicarbonate to normalize the CO_2. This will preserve growth as well as bone integrity.
- Treatment of phosphorus restriction, phosphorus binding (nonaluminum binders such as $CaCO_3$, Calcium acetate, or sevelamer products), and institution of vitamin D to preserve and prevent secondary hyperparathyroidism and prevent bone disease.
- Treatment with replacement doses of iron sucrose 1–3 mg/kg per dose and use of erythropoietic agents (epoetin, darbepoetin) are used for anemia.

Second Line

- Those that were mentioned above including antihypertensive agents if indicated.
- Often ACE inhibitors and angiotensin receptor blockers (ARBS) are used for glomerular-based renal disease because of proteinuria but are contraindicated in possible pregnancy (birth defects) and low GFR (renal failure, hyperkalemia)

SURGERY/OTHER PROCEDURES

In TID, patients may require cystoscopy with ablation of PUVs. UPJ or UVJ obstructions may need to be relieved. Reflux may need to be corrected, if high grade and not resolving spontaneously.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Dialysis (peritoneal or hemodialysis) or kidney transplant should be considered when GFR falls into the 20's or growth and metabolic control can no longer be maintained with medical management.

Complementary & Alternative Therapies

- Nutrition is important: At least 2 g/kg/d protein would be needed in order to maintain adequate protein stores and growth.
- Nutrition in CGD is associated with salt and water restriction. Therefore, the nutrition construction may be opposite in terms of the sodium and water load.

ONGOING CARE

PROGNOSIS

- Difficult to predict early in life.
- Lack of renal growth with a creatinine greater than 1 at a year of age, associated hematuria, proteinuria, and hypertension in patients with TID portends the need for future dialysis and transplantation.
- CGD prognosis is directly related to underlying cause.
- Certain diseases such as lupus, Wegener, Goodpasture, membranous nephropathy, and IgA nephropathy can be amenable to therapy.
- Other renal diseases such as focal sclerosis maybe less amenable to therapy.

COMPLICATIONS

- Growth impairment in children is a known complication, independent of the etiology of CKD (2)
- Hypertension is also a risk factor.
- Protein restriction, used in adult CKD to slow disease progression, cannot be used with kids as this would further hinder their growth and development.

FOLLOW-UP

- Newborns and infants should be seen as frequently as every 1–2 wk in order to ensure maintenance of euvolemia.
- Primary care physicians need to be instructed that patients with interstitial disease will get dehydrated more quickly than the average patient; therefore, attention to their care at the time of vomiting and diarrhea is important for these patients will become volume depleted in a hurry.

Patient Monitoring

Glomerular-based renal diseases are associated with salt and water restriction as well as blood pressure control.

Patient Resources

- American Society of Pediatric Nephrology. www.aspneph.com/parentpatient.asp
- National Kidney Disease Educational Program. www.nkdep.nih.gov
- NKF Cares: Patient Information Center. www.kidney.org/patients

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1–S266.
2. Wesseling-Perry K. Bone disease in pediatric chronic kidney disease. *Pediatr Nephrol.* 2013;28:569–576.

ADDITIONAL READING

- Avner ED, Harmon WE, Niaudet P, et al., eds., *Pediatric Nephrology*. 6th ed. Springer; 2009.
- Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. 1st ed. Mosby; 2008.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Pediatric (Renal Failure, Acute)
- Megaureter, Congenital
- Posterior Urethral Valves
- Prune Belly (Eagle-Barrett or Triad) Syndrome

CODES

ICD9

- 582.89 Chronic glomerulonephritis with other specified pathological lesion in kidney
- 585.9 Chronic kidney disease, unspecified
- 753.8 Other specified anomalies of bladder and urethra

ICD10

- N03.9 Chronic nephritic syndrome with unsp morphologic changes
- N18.9 Chronic kidney disease, unspecified
- Q64.79 Other congenital malformations of bladder and urethra

CLINICAL/SURGICAL PEARLS

- Patients with interstitial disease or obstructive uropathy require IV hydration while NPO prior to procedures.
- In contrast to adults, diabetic nephropathy and hypertension are rare causes of CKD in children.
- Small changes in creatinine reflect large changes in GFR for children with CKD.
- Baseline creatinine with attention to any changes after potential renal insult (CT contrast, hypovolemia/hypertension, medications, etc.) is an important measure for monitoring and prevention of progression of CKD.

CHYLOUS ASCITES

Brett S. Carver, MD

BASICS

DESCRIPTION

- Chylous ascites is characterized by the accumulation of chyle in the peritoneal cavity.
- Results from the obstruction or injury of the thoracic duct or cisterna chyli of the lymphatic system.
- Lymphatic leakage from the lymph vessels draining the intestines.
- Characterized as a milky fluid due to the high triglyceride component.
- This section focuses primarily on chylous ascites associated with retroperitoneal lymph node dissection (RPLND) for testicular cancer

EPIDEMIOLOGY

Incidence

Chylous ascites is reported to occur in ~1% of patients undergoing a primary RPLND for testicular cancer and 3% of postchemotherapy RPLNDs.

Prevalence

N/A

RISK FACTORS

- Predisposing factors for chylous ascites associated with RPLND:
  - Surgical resection of the vena cava.
  - Suprahilar dissection.
  - Simultaneous hepatic resection.
  - In addition, patients undergoing reoperative RPLND are at an increased risk.

Genetics

N/A

PATHOPHYSIOLOGY (1)

- Chylous ascites is caused by injury or obstruction of the thoracic duct or cisterna chyli.
- Surgical injury, ligation of the thoracic duct.
- Retroperitoneal tumor associated with obstruction of the thoracic duct.
- Leakage of fat containing lymphatic fluid into the peritoneum.

ASSOCIATED CONDITIONS

- Testicular cancer
- Peritonitis
- Ileus or small-bowel obstruction
- Failure to thrive

GENERAL PREVENTION

- Appropriate ligation of lymphatic vessels during surgery to minimize lymphatic leak.
- Preservation of the thoracic duct.

- Oral diet with low lipid, high medium-chain triglyceride content.

DIAGNOSIS

HISTORY

- Patients often present following RPLND with symptoms of abdominal distention and pain, decreased appetite, nausea, and vomiting.
- Shortness of breath may also be present associated with increased abdominal pressures.
- Secondary infection associated with peritonitis with symptoms of fever, chills, abdominal pain, and lethargy.

PHYSICAL EXAM

The most common finding on physical exam is distension of the abdomen with flank bulging. The abdomen is dull to percussion and may demonstrate a fluid wave upon palpation.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum tumor markers (AFP, HCG, LDH) should be obtained to rule out recurrence.
- Aspiration of the abdominal fluid reveals a milky white fluid, which should be sent for triglyceride testing and culture to rule out a secondary infection.
  - A fluid triglyceride level >110 mg/dL is diagnostic.

Imaging

- CT scan of the abdomen and pelvis is the imaging modality of choice to evaluate for the presence of ascites and rule out retroperitoneal recurrent disease.
- Abdominal ultrasonography may be used to document ascites and guide aspiration.

Diagnostic Procedures/Surgery

Abdominal paracentesis is performed to aspirate the ascites for diagnostic testing.

Pathologic Findings

Chylous ascites is grossly defined as a milky white fluid. Lab testing will reveal elevated triglyceride content.

DIFFERENTIAL DIAGNOSIS

- Chylous ascites can be caused by other conditions beyond RPLND for testicular cancer:
  - Postoperative
    - Abdominal aneurysm repair
    - Peritoneal dialysis catheter placement
  - Infectious/inflammatory
    - Pancreatitis
    - Retroperitoneal radiation
    - Pericarditis
    - Celiac disease
    - Retroperitoneal fibrosis
    - Sarcoid
    - TB
    - Filariasis
    - Mycobacterium avium-intracellulare (AIDS related)

- Neoplasm
  - Lymphoma
  - Kaposi sarcoma
  - Other solid tumors
- Other causes
  - Cirrhosis
  - Carcinoid
  - Nephrotic syndrome
  - Trauma
  - Right-sided heart failure
  - Dilated cardiomyopathy
  - Idiopathic
  - Congenital causes (defects of lacteal formation)

TREATMENT

GENERAL MEASURES

- All patients with abdominal distention following an RPLND should be evaluated for:
  - Ascites (nonchylous)
  - Ileus
  - Small-bowel obstruction
  - Recurrent disease in the abdomen or retroperitoneum.
- The majority of chylous effusions will heal spontaneously. Abdominal paracentesis is diagnostic and often therapeutic in relieving symptoms associated with increased abdominal pressures.

MEDICATION

First Line

- Low lipid, high medium chain triglyceride oral diet.
  - MCT oil supplement
    - 1 tablespoon (15 mL) 3–4 times/d
    - Mix with juices or otherwise incorporated into low-fat diet
    - Do not use in patients with advanced cirrhosis: Risk of narcosis and coma
- Somatostatin analogs have been demonstrated to be effective in reducing lymphorrhagia.
  - Octreotide 100 mcg administered subcutaneously 3 times per day

Second Line

- Total parental nutrition is to be utilized in patients who fail oral diet modifications.
  - Bowel rest may enhance recovery if conservative approaches are not successful

SURGERY/OTHER PROCEDURES

- Abdominal paracentesis, repeated as necessary.
  - Primarily for pain control and dyspnea
- Surgical exploration with direct ligation of lymphatic vessels for persistent chylous ascites (2).
- Peritoneal venous shunts for refractory chylous ascites.

- Direct lymphatic vessel ligation or embolization of large leaking vessels using interventional radiologic techniques.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Orlistat (Xenical) has been used successfully in a nontesticular cancer case of chylous ascites (3)

ONGOING CARE

PROGNOSIS

The prognosis is excellent for the vast majority of cases as most will respond to conservative management.

COMPLICATIONS

- The complications of chylous ascites related to increased abdominal pressure:
  - Renal failure
  - Venous thrombosis
  - Pulmonary embolism
  - Atelectasis
  - Pneumonia
- The gastrointestinal complications of chylous ascites include ileus and small-bowel obstruction.
  - Malnourishment and failure to thrive may also occur due to protein-losing enteropathy with chronic diarrhea (steatorrhea), malabsorption, and malnutrition

FOLLOW-UP

Patient Monitoring

- Follow-up protocols should be followed according to guidelines established by the National Comprehensive Cancer Network for testicular cancer patients.
- After initial treatment of chylous ascites, patients should be seen in follow-up to monitor for recurrent ascites.

Patient Resources

N/A

REFERENCES

1. Carver BS, Sheinfeld J. Germ cell tumors of the testis. *Ann Surg Oncol.* 2005;12(11):871–880.
2. Castillo OA, Litvak JP, Kerkebe M, et al. Case report: laparoscopic management of massive chylous ascites after salvage laparoscopic retroperitoneal lymph-node dissection. *J Endourol.* 2006;20(6):394–396.
3. Chen J, Lin RK, Hassanein T. Use of orlistat (xenical) to treat chylous ascites. *J Clin*

Gastroenterol. 2005;39(9):831–833.

ADDITIONAL READING

- Bosl GJ, Feldman DR, Bajorin DF, et al. Cancer of the testis. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2011:1280–1301.
- Evans JG, Spiess PE, Kamat AM, et al. Chylous ascites after post-chemotherapy retroperitoneal lymph node dissection: Review of the M. D. Anderson experience. *J Urol.* 2006;176(4 Pt 1):1463–1467.
- Link RE, Amin N, Kavoussi LR. Chylous ascites following retroperitoneal lymphadenectomy for testes cancer. *Nat Clin Pract Urol.* 2006;3(4):226–232.

See Also (Topic, Algorithm, Media)

- Chylous Ascites Image
- Lymphatic Ascites
- Testis Cancer, Adult General Considerations

CODES

ICD9

- 125.9 Unspecified filariasis
- 457.8 Other noninfectious disorders of lymphatic channels

ICD10

- B74.9 Filariasis, unspecified
- I89.8 Oth noninfective disorders of lymphatic vessels and nodes

CLINICAL/SURGICAL PEARLS

- Chylous ascites occurs in ~1–3% of patients undergoing a RPLND.
- Risk factors include vena cava resection, suprahilar dissections, and concomitant hepatic surgery.
- Initial management includes paracentesis for symptom of pain or pulmonary compromise and low lipid, high medium-chain triglyceride oral diet.

CHYLURIA

Matthew A. Uhlman, MD, MBA
James A. Brown, MD, FACS

BASICS

DESCRIPTION

- Chyluria is the presence of chyle (a combination of lymphatic fluid and triglycerides) in urine
- Presents as milky white urine that can be constant or present primarily after meals
- Often self-limiting or resolves with conservative treatment including dietary changes
- Extended chyluria can lead to malnutrition, vitamin deficiencies, and immunosuppression (due to depletion of fat soluble vitamins) (1)[C]

EPIDEMIOLOGY

Incidence

- 2–10% of patients infected with filariasis can develop chyluria (2)[C]
- Extremely low rates of clinically significant chyluria (1)[C]
  - Clinically significant in $<1\%$ of postsurgical patients
  - Reports of subclinical chyluria based on CT in 3–41% of postpartial nephrectomy or radiofrequency ablation (RFA) patients (2,3)[C][B]

Prevalence

- 120 million people suffer from filariasis worldwide, primarily in Asia, Africa, Pacific Islands, and South America (2)[C]
- Chyluria is a manifestation of chronic infection, most often by *Wuchereria Bancrofti, Brugia malayi,* or *Brugia timori* (2)[C]
- Rare in developed countries
- Nontropical chyluria most often caused by trauma, renal surgery, infection, mass effect (AAA, tumor, abscess), pregnancy, or congenital abnormality (1)[C]

RISK FACTORS

- **Parasitic chyluria**
  - *W. bancrofti*, *B. malayi,* and *B. timori* are primary causes of filariasis. All are transmitted by mosquito. Less common parasitic infections have been reported to cause chyluria (*echinococcus, bilharzias, onchocerca, ascariasis*) (1,2)[C]
- **Nontropical chyluria**
  - Retroperitoneal surgery (most often radical or partial nephrectomy, RFA, or renal tumors) (1,3,4)[C][B]
  - Trauma
  - Mass effect: Retroperitoneal tumors (primary or metastatic) or lymphadenopathy
  - Infectious: TB, abscess
  - Aortic aneurysm
  - Pregnancy

– Congenital fistula or lymphangioma

PATHOPHYSIOLOGY

- **Parasitic**
  - Adult filariasis causes lymphangitis
  - Obstruction of suprarenal lymphatics (thoracic duct or upper retroperitoneal lymph drainage)
  - Results in rupture of lymphatic vessel into calyceal fornix, forming intrarenal lymphatic urinary fistula
  - Lymphatic HTN, with valvular incompetence:
    - With obstruction between intestinal lacteals and thoracic duct, the resulting cavernous malformation opens into the urinary system, creating a fistula
    - Common fistula sites are renal fornix, pelvicalyceal system, trigone, and prostatic urethra
    - Primary causal agents: *W. bancrofti*, *B. malayi,* and *B. timori*
    - Less commonly caused by external compression or trauma
- **Nontropical**
  - Disruption of peripelvic lymphatics during surgery allows backflow into pyelocaliceal system (1)[C]
  - Congenital fistulous connections between urinary tract and lymphatic system have been described, primarily in children

ASSOCIATED CONDITIONS

W. bancrofti, B. malayi, and *B. timori* are considered the three causative agents of lymphatic filariasis. Mosquitos serve as vectors for all 3 nematodes (2)[C]

GENERAL PREVENTION

- Control of mosquito vector that transmits *W. bancrofti*, *B. malayi,* and *B. timori* (2)[C]
- Insect repellant and mosquito nets in endemic areas
- Diethylcarbamazine (DEC) fortified salt
- Annual DEC + albendazole are used to treat asymptomatic filariasis via action on microfilaria

DIAGNOSIS

HISTORY

- Patient complaints of intermittent or continuous milky or cloudy urine
  - If intermittent, most often occurs following meals
- Country of origin of patient:
  - Asia, Africa, Pacific Islands, South America
- Travel to tropical regions
- History of trauma
- History of renal surgery within prior 2 yr
- History of TB exposure/infection
- Significant weight loss, anemia, lower urinary tract symptoms (frequency, urgency, dysuria), hematuria, nutritional deficiency, proteinuria, or signs of immunosuppression
- Heavy chyluria can cause clot colic or, rarely, urinary retention

PHYSICAL EXAM

- Elephantiasis of lower limbs and genitals
- Lymphadenitis/lymphangitis
- Male groin exam may reveal hydrocele or epididymitis
- Palpable abdominal or flank mass
- Chylous output from surgical wound or surgical drain

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis typically positive for albuminuria
- Postprandial urinary triglycerides
- Fat globules in urine identified by Sudan III stain
- Peripheral blood eosinophilia, may indicate parasitic infection
- Evaluate for TB if clinically indicated (tuberculin test, urine stain, and culture for acid-fast bacillus)
- ICT antigen card test (immunochromatographic card test, a commercial assay) is widely used in the diagnosis of *W. bancrofti*
- WB rapid and panLF rapid (2 commercially available assays) tests detect *W. bancrofti, B. malayi,* and *B. timori*

Imaging

- Abdominal/pelvic CT (3,4)[B]:
  - Exclude retroperitoneal mass
  - Fat fluid level seen in the urinary tract
  - Can demonstrate contrast communication between collecting system and perinephric collection but does not show communications between perinephric collection and lymphatics
- Lymphangiography (traditional or magnetic resonance)
  - Demonstrates abnormal lymphatics and entrance of contrast material into renal collecting system
- Lymphoscintigraphy
  - Can be useful in delineating site of fistula, though not as precise as lymphangiography
- Retrograde pyelography
  - Rarely warranted, but may show diffuse pyelolymphatic backflow

Diagnostic Procedures/Surgery

- Blood smear: Examine for microfilariae (early stage in life cycle of nematodes) using Giemsa stain
- Cystourethroscopy: Can help localize site of milky efflux of urine. Rarely, efflux seen from bladder or posterior urethra.
- Retrograde pyelography: Rarely warranted, but may show diffuse pyelolymphatic backflow

Pathologic Findings

Lipid contents of chyluria are mainly chylomicrons, 90% of which are in the form of triglycerides

DIFFERENTIAL DIAGNOSIS

- Filariasis from *W. bancrofti, B. malayi,* or *B. timori*
- Pyelolymphatic fistula
- Phosphaturia, most common cause of cloudy urine
- Pyuria
- Hyperuricosuria
- Nephropathy—urinary sediment can cause cloudy appearing urine
- Enterovesical fistula

TREATMENT

GENERAL MEASURES

- **Nontropical**
  - Up to 50% of cases resolve spontaneously under dietary restriction (1)[C]
  - Bed rest and/or use of abdominal binder to increase abdominal pressure may allow spontaneous closure.
  - Medium-chain triglyceride (MCT) diet (avoidance of long-chain triglycerides)
    - MCTs are transported via portal system, not by chylomicrons through lymphatics
  - Ureteral stent placement to reduce renal pelvis pressure

MEDICATION

Nontropical

Dietary modifications to reduce chylomicrons in diet—recommendations are often for fat-free or very low-fat diet, though this should not be observed for more than several weeks given the body's need for some fats

Parasitic Chyluria

- DEC and albendazole, or ivermectin and albendazole
- DEC fortified salt can be used to treat and prevent lymphatic filariasis

SURGERY/OTHER PROCEDURES

- Procedures of choice involve disconnection of renal pedicle lymphatics (1,5,6)[C][A]
- Nephrolysis:
  - Stripping and ligation of all lymphatic vessels to the kidney and upper ureter; open and laparoscopic techniques described
  - Laparoscopic transabdominal and retroperitoneoscopic approaches described
  - Success rates 80–98%; recurrence rates 3–25%
- Endoscopic coagulation of fistula
- Lymphangiovenous anastomosis with ligation of renal lymphatics
- Renal autotransplantation
- Nephrectomy was described prior to minimally invasive techniques

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Sclerotherapy with various agents instilled into collecting system (1,3)[C][B]

- Povidone iodine (5%) and dextrose (50%) in renal pelvic instillation sclerotherapy; 87% success reported
- Silver nitrate (1–3%) instillation into the affected collecting system causes sclerosis of lymphatic fistulas; 48% success reported
- Case reports of successful sclerotherapy with:
  - N-butyl-2-cyanoacrylate (component of medical cyanoacrylate glues)
  - Radiographic contrast media

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Rarely fatal, with high success rates reported for surgical intervention
- Recurrence rates after surgery reported as high as 25%

COMPLICATIONS

- Hypoalbuminemia and anasarca from massive protein loss (1)[C]
- Immunosuppression from fat soluble vitamin loss in chronic cases (1)[C]
- Underlying filariasis may cause epididymitis, hydrocele, and elephantiasis of the penis/scrotum and lower extremities

FOLLOW-UP

Patient Monitoring

- Treatment failures are readily apparent as urine returns to milky color (1,5)[C][A]
- Re-evaluate if chyluria recurs following treatment; consider the contralateral kidney as the source

Patient Resources

N/A

REFERENCES

1. Kim RJ, Joudi FN. Chyluria after partial nephrectomy: Case report and review of the literature. *ScientificWorldJournal.* 2009;9:1–4.
2. Tandon V, Singh H, Dwivedi US, et al. Filarial chyluria: Long-term experience of a university hospital in India. *Int J Urol.* 2004;11:193–199.
3. Panchal VJ, Chen R, Ghahremani GG. Non-tropical chyluria: CT diagnosis. *Abdom Imaging.* 2012;37(3):494–500.
4. Kaur H, Matin SF, Javadi S, et al. Chyluria after radiofrequency ablation of renal tumors. *J Vasc Interv Radiol.* 2011;22:924–927.
5. Zhang CJ, Chen RF, Zhu HT, et al. Retroperitoneoscopic renal pedicle lymphatic disconnection for chyluria in presence of complex renal vasculature. *Urology.* 2012;80:1273–1276.
6. Gomella LG, Shenot P, Abdel-Meguid TA. Extraperitoneal laparoscopic nephrolysis for the treatment of chyluria. *Br J Urol.* 1998;81(2):320–321.

ADDITIONAL READING

Kaul A, Bhadhuria D, Bhat S, et al. Chyluria: A mimicker of nephrotic syndrome. *Ann Saudi Med.* 2012;32(6):593–595.

See Also (Topic, Algorithm, Media)

- Chyluria Image ☼
- Filariasis, Urologic Considerations
- Urine, Abnormal Colored

CODES

ICD9

- 125.0 Bancroftian filariasis
- 125.9 Unspecified filariasis
- 791.1 Chyluria

ICD10

- B74.0 Filariasis due to Wuchereria bancrofti
- B74.9 Filariasis, unspecified
- R82.0 Chyluria

CLINICAL/SURGICAL PEARLS

- Milky or cloudy urine (often after meals) is the most common presentation, though phosphaturia is the most common cause of cloudy urine.
- *W. bancrofti*, *B. malayi,* and *B. timori* are the primary causes of filariasis, the most common cause of chyluria (parasitic chyluria).
- Following renal surgery, incidence of chyluria (up to 41% on CT) is likely much higher than is clinically significant (<<1%).
- Up to 50% of cases of chyluria resolve spontaneously with a medium chain fatty acid or very low-fat diet.
- There is no “best” imaging technique, though lymphangiography can demonstrate entrance of contrast from lymphatics into the collecting system.

CIRCUMCISION, ADULT CONSIDERATIONS

Irvin H. Hirsch, MD

BASICS

DESCRIPTION

- Circumcision involves the removal of the prepuce. This section addresses adult circumcision issues.
- Adult circumcision is indicated for elective treatment of balanitis (glans inflammation), posthitis (prepuce inflammation), removal of preputial lesions, and at patient request for cultural and religious preference.
- Emergent circumcision may be necessary for treatment of paraphimosis after failed attempt at manual reduction.
- Circumcision may be necessary as part of surgical procedures requiring degloving exposure of the penis (penile fracture repair or Peyronie disease).
- Circumcision is the most common operation performed worldwide.
- There is some controversy concerning the need for circumcision and potential effects on sexual satisfaction. This is weighed against the potential health benefits.

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Male circumcision, largely in newborns, is performed in 77% of US males and in 30% of males worldwide.
- Circumcision rate in newborns has declined from 83% in the 1960s to 77% in 2010.
  - These incidence rates do not include out-of-hospital circumcisions
- Increasingly adult circumcision has been advocated as an important adjunct to STD and HIV prevention in developing countries (1).

RISK FACTORS

- Diabetes mellitus
- Genital lesions

Genetics

N/A

PATHOPHYSIOLOGY

- The prepuce serves as a specialized, junctional mucocutaneous tissue marking the boundary between mucosa and skin; it is similar to the eyelids, anus, and lips.
- Condition that can cause problems:
  - Lack of genital hygiene
  - Chronic balanoposthitis may lead to phimosis

ASSOCIATED CONDITIONS

- Diabetes mellitus
- Balanitis
- Lichen sclerosus/urethral stricture
- Penile condylomata
- Squamous cell carcinoma
- Erectile dysfunction
- Peyronie disease

ALERT
The American Urologic Association (AUA) policy statement now considers circumcision to be of a health benefit, citing a 50–60% risk reduction in HIV transmission in some African nations.

GENERAL PREVENTION
- Local hygiene measures may prevent balanitis and its sequelae.
- Although male circumcision should not be substituted for other HIV risk-reduction strategies, it has been shown to reduce the risk for HIV and some STDs in heterosexual men.
  - Despite these data, male circumcision has not been demonstrated to reduce the risk for HIV or other STDs among men who have sex with men (MSM).
- Good visualization of the glans penis is crucial in all cases of circumcision to limit complications.

DIAGNOSIS
HISTORY
- Penile pain with or without erection
- Dyspareunia
- Postcoital pain

PHYSICAL EXAM
- Inability to retract prepuce (phimosis)
- Inability to reduce prepuce (paraphimosis)
- Preputial erythema or excoriation
- Glans erythema
- Malodorous secretion (smegma)
- Associated penile lesion

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- UA
- Urine culture if indicated
- STD testing if indicated

Imaging
N/A

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
- Acute and chronic inflammation
- Plasma cell infiltrate (Zoon balanitis)
- Lichen sclerosus (BXO blanaitis xerotica obliterans)

DIFFERENTIAL DIAGNOSIS
N/A

TREATMENT

GENERAL MEASURES
Circumcision for balanitis in adults should be performed after exhausting nonsurgical medical approaches.

MEDICATION
First Line
- Topical antibiotics
- Topical steroids
- Topical antifungals

Second Line
N/A

SURGERY/OTHER PROCEDURES
- General anesthesia may be utilized
- Local anesthesia is recommended when tolerated
- Lidocaine/bupivacaine combination is injected at the level of the infrapubic bone and around the base of the penis. Avoid epinephrine.
- Technique is selected based on surgeon's preference: Sleeve technique or dorsal slit circumcision.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
- For high risk or anticoagulated patients an isolated dorsal slit may be oversewn without circumcision.
- Nonsurgical preputial compression devices are currently under investigation for HPV, HSV, and HIV risk-reduction programs in developing countries (Prepex or Shang Ring). The prepuce sloughs after 7 days.

ONGOING CARE

PROGNOSIS
Patient satisfaction is high

COMPLICATIONS (2)

- The majority of complications relating to circumcision are minor and should be easily treated
- While very infrequent, challenging complications requiring complex reconstructive surgery and should be referred to a center specializing in these reconstructions.
- Early
  - Hematoma and bleeding
  - Infection
  - Urinary retention due to tight bandaging
  - Glans necrosis
  - Removal of inadequate or excessive skin
  - Partial penile amputation
- Late
  - Urethral injury/urethrocutaneous fistula
  - Meatal stenosis
  - Hypesthesia or hyperesthesia of penis
  - Penile scarring and deformity
    - Skin bridges between the glans and penile shaft
  - Concealed/buried penis
  - Inclusion cysts
  - Erectile dysfunction

FOLLOW-UP

Patient Monitoring

- Routine postoperative care.
- Follow for alterations in penile sensation and erectile function.

Patient Resources

www.aafp.org/afp/1999/0315/p1514/html

REFERENCES

1. World Health Organization, Department of Reproductive Health and Research and Joint United Nations Programme on HIV/AIDS (UNAIDS). Male circumcision: Global trends and determinants of prevalence, safety and acceptability WHO Press, 2007.
2. Fink KS, Carson CC, DeVellis RF. Adult circumcision outcomes study: Effect on erectile function, penile sensitivity, sexual activity and satisfaction. *J Urol.* 2002;167(5):2113–2116.

ADDITIONAL READING

- Cold CJ, Taylor JR. The prepuce. *BJU Int.* 1999;83(suppl 1):34–44.
- Millett GA, Flores SA, Marks G, et al. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: A meta-analysis. *JAMA.* 2008;300:1674–1684.
- Summerton DJ, Kitrey ND, Lumen N, et al. EAU guidelines on iatrogenic trauma. *Eur Urol.* 2012;62:628–639.
- UNAIDS, WHO. New data on male circumcision and HIV prevention: Policy and programme implications: WHO/UNAIDS technical consultation male circumcision and HIV prevention:

Research implications for policy and programming. Geneva: Joint United Nations Programme on HIV/AIDS and World Health Organization; 2007.

See Also (Topic, Algorithm, Media)

- Circumcision, Pediatric Considerations
- Penis, Cysts
- Phimosis and Paraphimosis

CODES

ICD9

- 605 Redundant prepuce and phimosis
- 607.1 Balanoposthitis
- V50.2 Routine or ritual circumcision

ICD10

- N47.2 Paraphimosis
- N48.1 Balanitis
- Z41.2 Encounter for routine and ritual male circumcision

CLINICAL/SURGICAL PEARLS

- These measures reduce risk of neural injury: minimize use of electrocautery and limit excision superficial to Buck fascia.
- Assure hemostasis of frenular artery.

CIRCUMCISION, PEDIATRIC CONSIDERATIONS

Mary Ellen T. Dolat, MD
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BASICS

DESCRIPTION

- Circumcision is the surgical removal of the foreskin (prepuce) from the penis.
- One of the oldest surgical procedures
- One of the most commonly performed surgical procedures in practice today
- There is some controversy concerning the need for circumcision and potential effects on sexual satisfaction in adulthood. This is weighed against the potential health benefits.

EPIDEMIOLOGY

- Few data are available to help estimate accurately the number of newborns circumcised worldwide.
  - Country of origin, ethnicity, religious affiliation, and birth in a rural vs. an urban hospital clearly influences a child's likelihood of being circumcised.
  - In addition, lack of (or the type of) health insurance may influence a child's likelihood of being circumcised.
- Most common reasons reported by US parents for choosing circumcision
  - Health/medical benefits including hygiene (40–60%)
  - Social concerns (23–37%)
  - Religious requirements (11–19%)

Incidence

- Circumcision rate in newborns has declined from 83% in the 1960s to 77% in 2010.
  - These incidence rates do not include out-of-hospital circumcisions

Prevalence

- 79% of men surveyed reported being circumcised (range: 42% for Mexican American; 88% for non-Hispanic Caucasian) (1)
  - Prevalence rates are limited by the accuracy of the self-report

RISK FACTORS

- Urinary tract infection
  - An increased risk for UTI in uncircumcised males younger than 1 yr; risk being the greatest toward the 1st 6 mo
  - Given that the risk of UTI in infant males is ~1%, the number needed to circumcise to prevent UTI is ~100
  - The benefits of male circumcision are, therefore, likely to be greater in boys at higher risk for UTI, such as infants with underlying anatomic defects
- Need for future circumcision
  - Future medical complications for boys (and men) who are uncircumcised as newborns include balanitis, severe phimosis, and paraphimosis.

  - For parents, there exists ~2–5% risk that their sons will need a circumcision for a medical indication if they choose not to circumcise their sons as newborns (2)
- Penile cancer (see "Circumcision, Adult Considerations")
  - The relationship among hygiene, phimosis, and penile cancer is uncertain
  - In a Danish study of penile cancer, there was a statistical decline in the rates of penile cancer over a 50-yr period despite a national circumcision rate of 1.6%. These data correlated with better penile hygiene resulting from improvements in sanitary conditions.
  - Based on the low incidence of penile cancer in Israel (high prevalence of circumcision) and in Scandinavian countries (low prevalence of circumcision), 2 ways of preventing penile cancer:
    - Remove the foreskin
    - Practice good penile hygiene
- Sexually transmitted disease (refer to the Chapter, "Circumcision, Adult Considerations")

Genetics

N/A

PATHOPHYSIOLOGY

- Prepuce serves as a specialized, junctional mucocutaneous tissue marking the boundary between mucosa and skin; it is similar to the eyelids, anus, and lips.
- Most neonates have a physiologic phimosis
- During childhood, the growth of the penile body, accumulation of epithelial debris, and intermittent penile erections eventually separate the prepuce from the glans, permitting retraction
- During the 1st 6 mo of life, there are more uropathogenic organisms around the urethral meatus of an uncircumcised male infant than around those of circumcised male infants; this colonization decreases in both groups after the 1st 6 mo (3)
- Boys with vesicoureteral reflux who are uncircumcised have a higher risk of UTI

ASSOCIATED CONDITIONS

- Phimosis
- Paraphimosis

GENERAL PREVENTION

Gentle periodic retraction during the newborn period will help prevent phimosis for the inability to retract foreskin later in life

DIAGNOSIS

HISTORY

- Prior history of posthitis or balanitis
- Prior history of meatitis
- Report of "ballooning" of the distal foreskin during voiding
- Prior history of circumcision
  - Incomplete removal of foreskin
  - Iatrogenic phimosis
- Some parents report "infected whitish pus," which in most instances is due to normal

secretion of smegma

PHYSICAL EXAM

- In newborns, perform a complete male genital exam
  - In rare instances, a well-formed phallic structure in a baby with nonpalpable testes may be due to congenital adrenal hyperplasia
- Look for penile developmental variations that may be a contraindication of a newborn circumcision (see "Differential Diagnosis")
- Some instances with newborns with incomplete foreskin development (ie, does not have natural phimosis), may still be amenable to a newborn clamp circumcision
  - Recommend obtaining a pediatric urology consultation to determine whether the baby would be a candidate for newborn circumcision

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Not necessary unless there is suspicion for intersex anomaly

Imaging

Not necessary unless there is suspicion for intersex anomaly

Diagnostic Procedures/Surgery

Not necessary unless there is suspicion for intersex anomaly

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- The penis should be carefully examined before the procedure to identify the following conditions that may preclude a circumcision
  - Webbed penis
  - Microphallus
  - Chordee
  - Epispadias
  - Hypospadias
  - Megameatus intact prepuce (MIP) variant of hypospadias
    - The foreskin is normally developed; the abnormal urethra is noted after the foreskin has been pulled back (or after the neonatal circumcision has already been performed)

TREATMENT

ALERT

In cases of Disorders of Sexual Development (DSD) with sex assignment concerns or significant anomaly such as hypospadius the infant should not undergo neonatal circumcision.

GENERAL MEASURES

- The AAP states that: The health benefits of newborn male circumcision outweigh the risks but the scientific evidence is not strong enough for the AAP to recommend routine

circumcision of all newborns. The AAP advises parents to learn the facts about circumcision and weigh the risks and benefits.
- Most routine circumcision is performed between 2 and 10 days of life.
- Contraindications to newborn circumcision include:
  - Congenital penile anomalies (see "Differential Diagnosis")
  - Significantly premature infants
  - Blood dyscrasias
  - Babies with a family history of bleeding disorders
  - Disorders of Sexual Development (DSD)
- Relative contraindications to newborn circumcision:
  - Incomplete foreskin development
  - Prominent suprapubic fat pad (retrusive penis)

MEDICATION

First Line

- Analgesia is safe and effective in reducing the procedural pain associated with newborn circumcision
  - Dorsal penile nerve block
    - 1% lidocaine without epinephrine
  - Subcutaneous ring block
    - 1% lidocaine without epinephrine
  - Topical cream may cause a higher incidence of skin irritation in low–birth-weight infants
    - Lidocaine–prilocaine (2.5% lidocaine and 2.5% prilocaine) applied for 30–40 min

ALERT
Epinephrine should not be used for pediatric circumcsion.

Second Line

- Nonpharmacologic techniques (eg, sucrose pacifier) alone are insufficient to prevent pain and are not recommended as the sole method of analgesia
  - Sucrose on a pacifier has been demonstrated to be more effective than water alone for decreasing crying during circumcision (2)

SURGERY/OTHER PROCEDURES

- Common methods for the newborn circumcision
  - Gomco clamp
  - Plastibell
  - Mogen clamp
- After the newborn and infant periods, circumcision is performed under general anesthesia

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Traditional religious providers perform the procedures in community settings

ONGOING CARE

PROGNOSIS

Some groups believe that circumcision may reduce or increase the sensitivity of the tip of the penis, potentially impacting sexual pleasure later in life. The data are conflicting and mostly these subjective findings are not conclusive.

COMPLICATIONS

- Large US hospital-based studies estimate the risk of a significant acute circumcision complication to be between 0.19–0.22%.
- From neonatal circumcisions using clamp techniques
  - Gomco clamp
    - Mainly related to technical factors
    - Insufficient or inadequate skin removal requiring additional revision procedure
    - Since the met al bell completely covers the glans, glans injury is extremely rare
  - Plastibell
    - Incomplete circumcision
    - Retained Plastibell ring
  - Mogen clamp
    - Potential for injury to glans, including partial amputation
- Immediate complications
  - Significant bleeding (0.08–0.18%)
    - Postcircumcision bleeding may be the 1st manifestation on an underlying bleeding disorder
  - Significant infection (0.06%)
  - Significant penile injury (0.04%)
- Late complications
  - Phimosis (iatrogenic)
  - Adhesions
  - Skin bridges
  - Excess foreskin
  - Insufficient penile skin
  - Penile inclusion cysts
  - Meatal stenosis
  - Penile torsion
  - Urethrocutaneous fistula

FOLLOW-UP

Patient Monitoring

- A small amount of petroleum jelly may help with discomfort due to diaper friction the 1st few days postop.
- Bandaging is optional after the 1st 1–2 days.
- Healing usually take place within 10 days.
- Clean site with warm water and avoid baby diaper wipes.

Patient Resources
American Academy of Pediatrics. Patient Education ONLINE. www.patiented.aap.org

REFERENCES

1. Nelson CP, Dunn R, Wan J, et al. The increasing incidence of newborn circumcision: Data from the nationwide inpatient sample. *J Urol*. 2005;173:978–981.
2. Lerman SE, Liao JC. Neonatal circumcision. *Pediatr Clin North Am*. 2001;48:1539–1557.
3. American Academy of Pediatrics Task Force on Circumcision. Circumcision policy statement. *Pediatrics*. 2012;130(3):585–586.

ADDITIONAL READING

- Cold CJ, Taylor JR. The prepuce. *BJU Int*. 1999;83 suppl 1:34–44.
- Perera CL, Bridgewater FH, Thavaneswaran P, et al. Safety and efficacy of nontherapeutic male circumcision: A systematic review. *Ann Fam Med*. 2010;8:64–72.
- Weiss HA, Larke N, Halperin D, et al. Complications of circumcision in male neonates, infants and children: A systematic review. *BMC Urol*. 2010;10:2.

See Also (Topic, Algorithm, Media)
- Circumcision, Adult Considerations
- Circumcision, Pediatric Considerations Images
- Disorders of Sexual Development (DSD)
- Hypospadias

CODES

ICD9
V50.2 Routine or ritual circumcision

ICD10
Z41.2 Encounter for routine and ritual male circumcision

CLINICAL/SURGICAL PEARLS
- Make sure to carefully inspect the penis for any congenital defects such as hypospadias or chordee before proceeding with neonatal circumcision. It is best to delay circumcision until the primary defect can be repaired as the foreskin may be used in reconstructive procedure.
- The choice of neonatal circumcision is a matter of the physician's personal preference. For circumcisions using a Gomco clamp, or Plastibell, select the correct size of the bell; this would ensure adequate foreskin removal.
- Always consider the cultural and religious beliefs of the family when counseling about newborn circumcision.

CONDYLOMA ACUMINATA (VENERAL WARTS)

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BASICS

DESCRIPTION

- Anogenital epidermal lesions caused by the transmission of human papilloma virus (HPV)
- The most common viral sexually transmitted infection in the US, they are also called genital warts, or venereal warts
- Most common sites: Penis, vulva, vagina, cervix, perineum, and perianal area.
- Less commonly, urethra, bladder, oropharynx, larynx, and trachea

EPIDEMIOLOGY

Incidence (1)

- Most common STD
- ~1% of sexually active adults in the US

Prevalence

- Highest prevalence: 18–28 yr olds and exceeds 50%
- HPV DNA can be detected in 10–15% of the US population
- HPV 6 and 11 account >90% of visible genital warts.

RISK FACTORS

- Increased risk with number of sex partners, frequency of sexual activity, early coitus, and presence of condyloma on partners
- Age <25
- Immunocompromised status
- Cigarette smoking and oral contraceptives may be associated with an increased risk.
- Onset of sexual activity at an early age

PATHOPHYSIOLOGY

- HPV is a double-stranded, circular DNA genome consisting of ~8,000 base pairs. Subtypes 6 and 11 are associated with the majority of genital warts. Types 16, 18 most often associated with potential for malignancy.
- >80 different subtypes can potentially associate with condylomata.
- HPV subtypes associated with malignancy include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 82 (2)
- Transmission is by direct sexual contact.
- Less common mode is autoinoculation from nongenital lesions.
- Basal layer of epidermis is invaded by the virus.
- Latent phase can last months to years.

ASSOCIATED CONDITIONS

- Penile cancer
- Anal cancer

- Cervical cancer
- Buschke-Lowenstein tumor

GENERAL PREVENTION
- Sexual abstinence
- Condoms
- Pre-exposure vaccination (Gardasil, Cervarix, Hepatitis B)

DIAGNOSIS
HISTORY
- Age and sex of patient
- History of recent sexual exposure
- Number of partners and frequency of sexual intercourse
- Visible warts usually seen within 2–3 mo after exposure
- Practice of anal intercourse
- Immunocompromised state

PHYSICAL EXAM
- Lesions are pinkish to red-grayish white cauliflower-like lesions found on moist surfaces, often coalescing.
- Lesions appear pearly white and granular
- Larger lesions may be verrucous or flat in configuration
- With magnifications, a central venule can be seen within each projection.
- Male: Examine penis, meatus, scrotum, perineum, suprapubic, and perianal region
- Female: Vagina, introitus, perineum, cervix, and perianal region
- Examine for evidence of coexisting STD (ulcers, discharge, adenopathy).

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- HPV cannot be readily grown in culture.
- Cytologic testing with Pap smear: Exfoliated genital cells are stained and examined for koilocytosis and neoplasia
- Serologic assays not useful in screening for HPV injection, but may provide prognostic information for patients with abnormal Pap smears
- Histologic analysis from biopsy specimens
- Rapid commercial screening tests available and are fairly accurate: ViraPap, ThinPrep Pap, Hybrid capture II
- If necessary, molecular characterization for diagnosis and serotyping (eg, Southern and/or slot blot hybridization, PCR)
- Consider screening for other associated STDs: HIV, GC, chlamydia, syphilis

Diagnostic Procedures/Surgery
- Magnification with colposcope or 10× handheld magnifying lens of the suspected region after application of 3–5% acetic acid-soaked gauze pad for 5 min allows visualization of nonvisible lesions, but has low specificity. (3,4)
  – However, the Centers for Disease Control (CDC) no longer recommends acetic acid soaks

to improve diagnosis. The soaks are associated with many false positives.
- Subclinical lesions may appear shiny white.
- Urethroscopy for any patients with suspected urethral warts, with care to occlude proximal urethra to prevent flushing of virus toward bladder
- Proctoscopy for patients at risk for anal condyloma

Pathologic Findings
- Branching, villous, papillary connective tissue stroma covered by epithelium.
- Superficial hyperkeratosis and thickening of the epidermis (acanthosis).
- Clear vacuolization of the prickle cells (koilocytosis), characteristic of HPV infection, is seen.
- There is no evidence of invasion of the underlying stroma

DIFFERENTIAL DIAGNOSIS
- Bowen disease and erythroplasia of Queyrat
- Bowenoid papulosis
- Buschke-Löwenstein tumor
- Condyloma latum (syphilis)
- Extramammary Paget disease
- Fibroepitheliomas
- Herpes simplex virus
- Malignant melanoma
- Molluscum contagiosum
- Nevi
- Pearly penile papules
- Seborrheic keratosis
- Squamous cell carcinoma/basal cell carcinoma

TREATMENT

GENERAL MEASURES (5)
- Diagnosis usually based on observation of characteristic lesions.
- Main goal of treatment is to remove visual presence of warts.
- Current therapies have an equally low effectiveness in preventing wart recurrence and may not reduce disease transmission.
- Vaccine: HPV quadrivalent recombinant (types 6, 11, 16, and 18): Gardasil (Merck) is currently available for administration to females of ages 9–26 for prevention of condyloma acuminata and associated diseases. HPV bivalent Cervarix (types 16 and 18) (GSK)
- Gardasil can also be used in males aged 9–26 to prevent genital warts. Administration to males prior to start of sexual activity is optimal.
- Topical therapy may take up to 3 mo to observe a response.

MEDICATION
First Line
- Podophyllin (Podoben 25%, Podocon, Podofin):
  – Applied to lesion (concentration 10–25%) by health care worker once weekly for up to 6 wk

- Podofilox (Condylox):
  – Self-application of a 0.5% solution to warts twice daily for 3 days, followed by 4 days without treatment; can be repeated 4–6 times.
- 5-FU (Efudex, Fluoroplex):
  – Topical treatment with 5% cream 1–3 times per week for several weeks, as needed. Maybe also used as an intraurethral instillation but not without irritative complications.
- Trichloroacetic acid (Tri-Chlor):
  – An 80–90% solution of trichloroacetic acid; apply directly to lesions; repeat weekly
- Imiquimod (Aldara):
  – Potent inducer of interferon-α, which enhances cell-mediated cytolytic activity. Available as a 5% cream applied to external lesions 3 times per week up to a maximum of 16 wk

Second Line

Interferon-α IM or intralesional 3 million units 3 times a week for 3 wk

SURGERY/OTHER PROCEDURES

- Electrosurgery (electrodesiccation/loop electrosurgical excisional procedure): To destroy lesions; local anesthesia is usually sufficient
- CO_2 laser therapy: Useful for lesions that have not responded to other therapies and for extensive disease. Magnification necessary to maximize efficacy; may produce less scarring
- Holmium laser can be used to remove intraurethral warts via cystoscopy.
- Surgical excision: Often reserved for extensive disease; also effective for isolated warts
- Cryotherapy: Application of liquid nitrogen on patients without extensive disease. This procedure can be repeated at 1- or 2-wk intervals.

ONGOING CARE

PROGNOSIS

- Subclinical infections are probably not curative.
- Women should still undergo routine Pap smears.
- Cervical cancer is associated with HPV infection. HPV infection is not solely responsible for the malignant transformation of genital cells, but it may be a cofactor in development of malignancy. HPV 6 and 11 are low-risk subtypes, and are seldom associated with malignancy.
- Homosexuals are at 25–50 times greater risk for anal cancer.
- Long-term, increased risk of malignancy secondary to HPV infection (HPV types 16, 18, 31, 33, and 51 are at highest risk of anogenital malignancy).

COMPLICATIONS

Malignant transformation: Penile carcinoma, cervical carcinoma, anal cancer, and Buschke-Löwenstein tumor

FOLLOW-UP

Patient Monitoring

- Educate the patient about self-exam.
- Patients should be examined shortly after therapy, to evaluate initial response rates.
- Encourage use of condoms if sexually active.

- Surveillance urethroscopy is recommended 3–6 mo after treatment of intraurethral lesions.

Patient Resources

- Centers for Disease Control and Prevention
  – http://www.cdc.gov/std/hpv/default.htm

REFERENCES

1. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1–110.
2. Cogliano V, Baan R, Straif K, et al. Carcinogenicity of human papillomaviruses. *Lancet Oncol.* 2005;6:204.
3. Naucler P, Ryd W, Törnberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med.* 2007;357:1589–1597.
4. Widdice LE, Moscicki AB. Updated guidelines for papanicolaou tests, colposcopy, and human papillomavirus testing in adolescents. *J Adolesc Health.* 2008;43(4 suppl):S41–S51.
5. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-2):1–24.

ADDITIONAL READING

- Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med.* 1997;102(5A):28–37.
- Chuang TY. Condylomata acuminata (genital warts). An epidemiologic view. *J Am Acad Dermatol.* 1987;16(2 Pt 1):376–384.
- Leung AK, Kellner JD, Davies HD. Genital infection with human papillomavirus in adolescents. *Adv Ther.* 2005;22(3):187–197.
- Maymon R, Shulman A, Maymon B, et al. Penile condylomata: A gynecological epidemic disease: A review of the current approach and management aspects. *Obstet Gynecol Surv.* 1994;49(11):790–800.

See Also (Topic, Algorithm, Media)

- Bowen Disease and Erythroplasia of Queyrat
- Bowenoid Papulosis
- Buschke-Löwenstein Tumor
- Condyloma Latum (Syphilis)
- Fibroepitheliomas
- Herpes Simplex Virus
- Malignant Melanoma
- Molluscum Contagiosum
- Pearly Penile Papules
- Penis, Cancer General
- Penis, Lesion
- Seborrheic Keratosis
- Urethra, Condyloma (Warts)

CODES

ICD9

- 078.11 Condyloma acuminatum
- 079.4 Human papillomavirus in conditions classified elsewhere and of unspecified site

ICD10

- A63.0 Anogenital (venereal) warts
- B97.7 Papillomavirus as the cause of diseases classified elsewhere

CLINICAL/SURGICAL PEARLS

- HPV types 6, 11, 16, and 18 most common subtypes.
- Women who have received the HPV vaccine should still undergo routine screening with Pap smears.
- Eliminating warts may not decrease infectivity or transmission.
- Men along with women may benefit from vaccination.
- Vaccines are not recommended for use in women >26 yr of age.
- In absence of lesions, treatment is not recommended for individuals with subclinical infections.

CONTRAST ALLERGY AND REACTIONS

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BASICS

DESCRIPTION

- Allergy reactions to IV contrast used for radiologic imaging are common, can range from mild to moderate, and occasionally life threatening.
- Often an immune system–based response to IV administration of contrast used for common urologic studies such as excretory urography and CT.
- Contrast allergy and reactions can be divided into 3 groups:
  - Idiosyncratic anaphylactoid reactions
  - Nonidiosyncratic reactions
  - Delayed reactions
- Reactions to MRI contrast media are discussed in Section II "Nephrogenic Systemic Fibrosis/Fibrosing Dermatopathy (NSF/NFD)."
- "Contrast Induced Nephropathy" is discussed in Section II.

EPIDEMIOLOGY

Incidence

- Overall rate of ADR (adverse drug reaction) for ionic high-osmolar contrast media (HOCM) is 11–12% and 0.2–3% for nonionic low-osmolar contrast media (LOCM) (1)[B]
- It is estimated that up to 12% of patients may experience a contrast-related reaction.

Prevalence

N/A

RISK FACTORS

- History of asthma/bronchospasm (10 times), previous reaction (5 times), allergy or atopy (2–3 times) (2)[B]
- Other significant risks include: Cardiac disease, dehydration, sickle cell disease, polycythemia, multiple myeloma, pheochromocytoma, renal disease, anxiety, and the use of ionic vs. nonionic contrast material
- Possible risk factors: β-blockers, IL-2, aspirin, NSAIDs
- Concomitant shellfish allergy or iodine allergy, while a common misnomer, does not confer a higher risk of cross-reaction to radiocontrast media (RCM)

Genetics

N/A

PATHOPHYSIOLOGY

- Idiosyncratic anaphylactoid:
  - Not dose dependent
  - Most serious and potentially fatal type of reaction

  - Occurs without warning, previous exposure not a prerequisite, not preventable
  - Not considered anaphylactic due to lack of IgE antibody formation
  - Usually begins with or immediately after injection of RCM (<30 min)
- Nonidiosyncratic:
  - Dose dependent
  - Related to osmolality, chemical composition, volume, and concentration of contrast medium used
  - Idiosyncratic and nonidiosyncratic reactions may be classified as minor, moderate, or severe
  - Minor: Urticaria, nausea and vomiting, sense of warmth, pruritus, diaphoresis
  - Moderate: Faintness, severe vomiting, facial edema, laryngeal edema, mild bronchospasm
  - Severe: Hypotensive shock, pulmonary edema, respiratory arrest, seizures, cardiovascular collapse
- Delayed:
  - Occurs 1 hr to 7 days from injection of RCM
  - Usually mild to moderate, transient, and self-limiting
  - Commonly includes rash, urticaria, pruritus, and erythema

ASSOCIATED CONDITIONS

- Asthma
- Cardiac disease
- Dehydration
- History of allergy or atopy
- Previous adverse drug reaction
- Renal disease
- Sickle cell disease
- Renal insufficiency

GENERAL PREVENTION

- Use of alternative imaging in patients with history of previous ADR
- These measures may decrease likelihood of ADR but will not eliminate all risk (3)[B].
  - Use of nonionic LOCM
  - Antihistamines (diphenhydramine 50 mg 1 hr prior to study). An H_2-blocker can be used in conjunction with H_1, but never without H_1-blockers
  - Preprocedure hydration
- Patients with pre-existing renal impairment should stop metformin 24 hr prior to procedure and be well hydrated to avoid RCM-related biguanide lactic acidosis and contrast-induced nephropathy.
  - In patients with normal renal function on metformin the following comorbidities should prompt discontinuation of metformin before the contrast:
    - Liver dysfunction, alcohol abuse, cardiac failure, myocardial or peripheral muscle ischemia, sepsis
- To limit risk for contrast-induced nephropathy, special arrangements should be made with the radiology department for any patient with a GFR <60 mL/min/1.73 m^2.
- Prevention in patient with known allergy:

– Review radiology department procedures at site where testing scheduled.
– Give methylprednisolone (Medrol) 32 mg PO 12 and 2 hr prior to scheduled test and 50 mg diphenhydramine
– Patients with allergies to other substances (food, medicines), with history of asthma, who are allergic to iodinated contrast, who are receiving gadolinium (or those with allergy to gadolinium who are to receive IV contrast) DO NOT need steroid prep.

DIAGNOSIS

HISTORY (4)

- Previous ADR
- Cardiac or renal disease
- Metformin with chronic renal diisease
- Allergies

PHYSICAL EXAM

- Monitor vital signs (BP, heart rate, respirations)
  – Hypotension and rarely shock
- Observe for:
  – Urticaria, bronchospasm, wheezing, stridor shortness of breath, flushing, pruritus, angioedema

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- In acute setting, no labs are usually needed
- Blood gas may be useful
- The following may be obtained immediately after the reaction to help with the diagnosis: Elevated tryptase or histamine (released from activated mast cells).

Imaging

N/A

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

Complex of symptoms immediately after contrast administration supports diagnosis

TREATMENT

GENERAL MEASURES

- Any facility that administers IV contrast should be equipped to treat common reactions noted below as well as initial steps in cardiac/respiratory arrest.
- The American College of Radiology classifies acute contrast reactions and treatment in adults as noted below. Treatment is similar in children with appropriate dose modifications.
  – Hives

- Mild (scattered/transient): Observe or PO diphenhydramine or PO fexofenadine
- Moderate (numerous/bothersome): PO/IM/IV diphenhydramine or PO fexofenadine
- Severe (widespread/progressive): Consider IM/IV diphenhydramine; consider IM/IV epinephrine

– Diffuse erythema: IV access, monitor vitals, pulse oximeter, O_2 mask
- If hypotensive NS or LR IV bolus 1 L
- If no fluid response consider IM/IV epinephrine

– Bronchospasm: IV access, monitor vitals, pulse oximeter, O_2 mask
- Mild: β-agonist inhaler (eg, albuterol); consider rapid response team or ER admit
- Moderate: Consider IM/IV epinephrine; consider rapid response team or ER admit
- Severe: IM/IV epinephrine and rapid response team/911

– Laryngeal edema: IV access, monitor vitals, pulse oximeter, O_2 mask, IM/IV epinephrine; consider rapid response team/911 based on response

– Hypotension (systolic BP <90 mm Hg): IV access, monitor vitals, pulse oximeter, O_2 mask, elevate legs 60°; consider NS or LR IV bolus 1 L
- With bradycardia (pulse <60 BPM [vasovagal] as above; give atropine; consider rapid response team/911
- With tachycardia (pulse >100 BPM [anaphylactoid reaction]) IM/IV epinephrine; consider rapid response team based on response

– Hypertensive crisis (DBP >120 mm Hg; SBP >200 mm Hg; IV access, monitor vitals, pulse oximeter, O_2 mask; IV labet alol or nitroglycerine SL and furosemide; rapid response team/911

– Unresponsive and pulseless: Check for responsiveness; rapid response team/911; initiate CPR; apply AED device; epinephrine IV (10 mL 1:10,000)

– Pulmonary edema: IV access, monitor vitals, pulse oximeter, O_2 mask; elevate head of bed; IV furosemide, IV morphine; rapid response team/911

– Seizures: Protect patient; turn on side to avoid aspiration; suction airway as needed; IV access, monitor vitals, pulse oximeter, O_2 mask; if unremitting rapid response team/911 lorazepam IV

– Hypoglycemia: IV access, O_2 mask; oral 2 sugar packets or 4 oz fruit juice or D50W I amp IV with D5W or D5NS 100 mL/h adjunctively; if no IV glucagon 1 mg IM

– Anxiety/panic attack: Diagnosis of exclusion; monitor for evolving reactions if present; IV access, monitor vitals, pulse oximeter; reassure patient

– Reaction rebound prevention: IV steroids help short-term recurrence but not acute treatment benefit; consider IV hydrocortisone/methylprednisolone with severe allergic reaction prior to transport to ED

MEDICATION

First Line

- Based on guidelines noted above (5):
  – Albuterol: 2 puffs (90 mcg/puff)
  – Atropine 0.6–1 mg slow IV with NS flush up to 3 mg
  – Benadryl

- 25–50 mg PO
- 25–50 mg IV slowly over 2 min

– Epinephrine
- 0.3 mg (0.3 mL 1:1,000 solution) IM
- EpiPen or (equivalent) IM 0.3 mL 1:1,000 solution
- 1 mL 1:10,000 solution slow IV injection over 5 min repeated every 5–10 min as needed for severe reaction

– Furosemide 20–40 mg IV over 2 min
– Fexofenadine: 180 mg PO
– Glucagon: 1 mg IM
– Hydrocortisone 200 mg IV over 2 min
– Labet alol: 20 IV over 2 min; double dose every 10 min PRN
– Lorazepam 2–4 mg IV slow push; 4 mg max
– Methylprednisolone: 40 mg IV over 2 min
– Morphine: 1–3 mg IV, repeat every 5–10 min PRN
– Nitroglycerine: 0.4 mg tablet SL repeat every 5–10 min PRN

Second Line
N/A

SURGERY/OTHER PROCEDURES
N/A

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
For life-threatening reactions: ABCs of resuscitation, IV fluids, vasopressors for BP support if IV fluids not adequate

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Depends on severity of ADR
- Risk of death of 1 in 170,000 for both ionic HOCM and nonionic LOCM

COMPLICATIONS
- Renal failure occurs in up to 5%
- Generally supportive measures only with renal function returning to normal in a few weeks
- Contrast-induced nephropathy (CIN)

FOLLOW-UP
Patient Monitoring
- Appropriate supportive measures until recovery depending on severity of ADR
- For patients with renal insufficiency on metformin follow-up renal function monitoring

recommended.

Patient Resources
N/A

REFERENCES

1. Cochran ST, Bomyea K. Trends in adverse events from iodinated contrast media. *Acad Radiol.* 2002;9(suppl 1):S65–S68.
2. Hagan JB. Anaphylactoid and adverse reactions to radiocontrast agents. *Immunol Allergy Clin North Am.* 2004;24:507–519.
3. Liccardi G, Lobefalo G, Di Florio E, et al. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. *J Investig Allergol Clin Immunol.* 2008;18(1):1–11.
4. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: A medical myth exposed. *J Emerg Med.* 2010;39(5):701–707.
5. ACR Manual on Contrast Media Version 9 2013 (www.acr.org). Accessed October 2013.

ADDITIONAL READING

- Brockow K, Christiansen C, Kanny G, et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy.* 2005;60:150–158.
- Schopp JG, Iyer RS, Wang CL, et al. Allergic reactions to iodinated contrast media: Premedication considerations for patients at risk. *Emerg Radiol.* 2013;20(4):299–306.

See Also (Topic, Algorithm, Media)
- Contrast-Induced Nephropathy (CIN)
- Nephrogenic Systemic Fibrosis/Fibrosing Dermatopathy (NSF/NFD)
- Reference Tables: Contrast Agents, Genitourinary

CODES

ICD9
- 708.0 Allergic urticaria
- 995.0 Other anaphylactic reaction
- 995.27 Other drug allergy

ICD10
- L50.0 Allergic urticaria
- T50.8X5A Adverse effect of diagnostic agents, initial encounter
- T88.6XXA Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter

CLINICAL/SURGICAL PEARLS

A shellfish or iodine allergy does not correlate with contrast media allergy.

CUSHING DISEASE AND SYNDROME

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BASICS

DESCRIPTION

- Cushing disease is hypercortisolism due to an ACTH-secreting pituitary adenoma
- Cushing syndrome is the cluster of symptoms attributable to hypercortisolism
- Pituitary adenomas account for 70% of patients with endogenously elevated cortisol (15% primary adrenal tumor, 15% ectopic ACTH production)
- Iatrogenic supplementation of glucocorticoids is the most common cause of hypercortisolism

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Cushing disease: 1.2–2.4 per million
- Cushing syndrome 4–5× more common in women than men
- In diabetics, prevalence 2–5%

RISK FACTORS

- Iatrogenic exposure to glucocorticoids
  - Includes steroid creams or nasal sprays

Genetics

- Associated with MEN-1, Carney complex
- GNAS1 gene mutation (McCune-Albright syndrome)

PATHOPHYSIOLOGY

- Elevated serum levels of cortisol, either from exogenous intake or endogenous production
- Hypothalamus-pituitary-adrenal physiology
  - ACTH (anterior pituitary), stimulates cortisol production in zona fasciculate of adrenal cortex
  - ACTH release governed by CRH (hypothalamus)
  - Cortisol—feedback regulation of CRH/ACTH production
- Cushing syndrome causes:
  - Exogenous intake (most common)
  - Cushing disease (70% of endogenous Cushing)
  - Adrenal adenoma/carcinoma (10% of endogenous Cushing)
  - Ectopic ACTH producer (10%): Neuroendocrine tumor (small-cell lung cancer, thymoma, ovarian tumors)
  - Other: ACTH-independent macronodular adrenal hyperplasia, ectopic CRH production

ASSOCIATED CONDITIONS

- Pituitary tumor
- Steroid administration
- Adrenal adenoma/carcinoma

GENERAL PREVENTION

Diligent management of glucocorticoid administration

DIAGNOSIS

HISTORY

- Progressive weight gain
- Fatigue
- Proximal limb weakness
- Skin abnormalities: Easy bruisability, and striae
- Abnormal menses/decreased libido
- Impotence
- New-onset hypertension/diabetes
- Frequent infections
- Osteopenia/osteoporosis
- Visual disturbances due to pituitary impinging optic nerves

PHYSICAL EXAM

- Obesity/weight gain (80%)
- Thin skin with striae (70%)
- Moon facies (75%)
- Buffalo hump (50%)
- Hypertension (75%)
- Truncal obesity (50%)
- Amenorrhea (60%)
- Loss of visual fields

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC, serum glucose, electrolytes, lipids
  - Hyperglycemia, hypokalemia, neutrophilia, lymphopenia, hyperlipidemia consistent with Cushing
- Initial screen: Late-night salivary cortisol and 24-hr urinary free cortisol. (Note: Establishes hypercortisolemia, not etiology)
  - Elevated late-night salivary cortisol: In Cushing syndrome, diurnal variation of cortisol levels is lost → high levels of cortisol suggest Cushing syndrome
  - 24-hr urinary free cortisol × 3 samples: Sensitivity 90–97%, specificity 85–96%
- Second-line tests: Late-night serum cortisol, low-dose DST
- Determining etiology of hypercortisolemia
  - Plasma ACTH concentration
    - Elevated in Cushing disease/ectopic tumor
    - Decreased in adrenal adenoma/carcinoma, nodular adrenal hyperplasia, steroid use
  - High dose DST

- May distinguish pituitary from ectopic ACTH-secreting tumor (failure to suppress cortisol suggests ectopic tumor)

– Inferior petrosal vein sampling: Higher sensitivity and specificity than high-dose DST

Imaging

- Brain MRI if pituitary lesion suspected
- CT abdomen/pelvis adrenal protocol for ACTH-independent hypercortisolism to evaluate for adrenal adenoma/carcinoma

Diagnostic Procedures/Surgery

Inferior petrosal vein sampling to diagnose and localize pituitary adenoma

Pathologic Findings

- Pituitary adenoma
- Adrenal adenoma/carcinoma
- Micronodular/macronodular adrenal hyperplasia

DIFFERENTIAL DIAGNOSIS

- Alcoholism (pseudo-Cushing)
- Anorexia nervosa
- Bulimia
- Depression
- Hypertension
- Obesity
- Polycystic ovarian syndrome

TREATMENT

GENERAL MEASURES

- Multidisciplinary approach: Endocrinologist, neurosurgeon, adrenal surgeon
- Surgical therapy is the mainstay of treatment

MEDICATION

First Line

- Medical therapy only indicated when surgery not possible

– Ketoconazole: Considered medical treatment of choice; not FDA approved for this indication.
  - Inhibits cytochrome p450
  - 200–400 mg 2 or 3 times a day
  - Side effects: Reversible hepatotoxicity, headache, sedation, nausea, and vomiting.
  - Reduced androgen production may lead to gynecomastia, decreased libido, and impotence in males

– Mitotane: Suppresses cortisol production by inhibiting 11β-hydroxylase
  - Primarily used for adrenocortical carcinoma
  - 0.5 g start, gradually increase to 2–3 g/d

– Metyrapone: Inhibits 11β-hydroxylase
  - 500–750 mg 3 or 4 times a day

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Cushing disease:
  - Trans-sphenoidal resection of pituitary adenoma: Gold standard
    - Cure in 60–80% of patients
  - Bilateral adrenalectomy if disease refractory to pituitary surgery or if life-threatening hypercortisolism
- Ectopic ACTH-secreting tumor: Surgical resection
  - Bilateral adrenalectomy reserved for unresectable disease
- Ipsilateral adrenalectomy for primary cortisol-secreting adrenal masses

ADDITIONAL TREATMENT
Radiation Therapy
Pituitary irradiation effective in 15% of refractory cases—not considered primary therapy

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Prognosis good for adrenal adenoma or Cushing disease, worse for adrenocortical carcinoma
- Prognosis for ectopic ACTH-producing tumors typically poor

COMPLICATIONS
- Bilateral adrenalectomy
  - Adrenal insufficiency
  - Osteoporosis
  - Increased infection risk
  - Nelson syndrome (pituitary adenoma)

FOLLOW-UP
Patient Monitoring
- Postoperative monitoring for adrenal insufficiency
- Pre- and postoperative management is complex and should be coordinated by endocrinologist
- Post operative hydorcortisone replacement with prolonged wean to allow pituitary adrenal axis to recalibrate
- After primary treatment (pituitary surgery), any new-onset symptoms → reevaluation

Patient Resources
NIH Medline Plus. http://www.nlm.nih.gov/medlineplus/ency/article/000410.htm. Accessed December 2013.

REFERENCES
1. Nieman LK, Ilias I. Evaluation and treatment of Cushing's syndrome. *Am J Med.* 2005;118:1340–1346.
2. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008;93:1526–1540.
3. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med.* 2003;138(12):980–991.

ADDITIONAL READING

- Aggarwal S, Yadav K, Sharma AP, et al. Laparoscopic bilateral transperitoneal adrenalectomy for Cushing syndrome: Surgical challenges and lessons learnt. *Surg Laparosc Endosc Percutan Tech.* 2013;23(3):324–328.
- Lake MG, Krook LS, Cruz SV. Pituitary adenomas: An overview. *Am Fam Physician.* 2013;88(5):319–327.

See Also (Topic, Algorithm, Media)
- Adrenal Adenoma
- Adrenal Cortical carcinoma
- Adrenal Mass
- Cushing Syndrome Algorithm
- Nelson Syndrome

CODES

ICD9
255.0 Cushing's syndrome

ICD10
- E24.0 Pituitary-dependent Cushing's disease
- E24.8 Other Cushing's syndrome
- E24.9 Cushing's syndrome, unspecified

CLINICAL/SURGICAL PEARLS

- Initial diagnostic studies for suspected Cushing syndrome include late-night salivary cortisol and 24-hr urinary free cortisol.
- Most common cause of endogenous Cushing syndrome is a pituitary adenoma.
- Muscle weakness +/− skin hyperpigmentation after bilateral adrenalectomy may be due to pituitary adenoma (Nelson syndrome).

CYSTITIS, GENERAL CONSIDERATIONS

Kelly A. Healy, MD
Demetrius H. Bagley, MD, FACS

BASICS

DESCRIPTION

- Inflammatory process of the bladder
- Occurs more frequently in women.
- In men, isolated cystitis is rare and often associated with prostatitis that results in secondary bacterial infection of the bladder.
- Clinical syndrome of dysuria, frequency, urgency, and suprapubic pain
- Can be caused by infection (bacterial, viral, fungal, less commonly parasitic), radiation, interstitial cystitis (IC) or due to other irritants (drugs), or a complication of another illness
- Geriatric considerations:
  - Bacterial cystitis increases with advancing age.
- Pediatric considerations:
  - Cystitis in children is rare. Bacterial cystitis in an infant necessitates a urologic workup.
  - Eosinophilic cystitis most common in this age group.
- Pregnancy considerations:
  - Bacterial cystitis in pregnancy requires appropriate antibiotic coverage to prevent complications to the mother or fetus.
  - Screening and treatment of asymptomatic bacteriuria in pregnant women is encouraged to prevent the development of cystitis or more severe UTI and fet al harm.

EPIDEMIOLOGY

Incidence

- 33% of women experience an episode of bacterial cystitis by age 24. 50% of women will have an episode in their lifetime (1).
- Annual incidence of 0.5–0.7 infections per patient-year in this group
- Bacterial cystitis in healthy men is rare:
  - Annual incidence $<0.01\%$ in men aged 21–50 yr.
- Hemorrhagic cystitis occurs in 10–15% of patients after bone marrow transplantation while on immunosuppression. The BK virus is present in 80% of population but is reactivated only with immunosuppression (2).
  - Adenovirus in the urine preceding transplantation is greatest associated factor
- Reported rates of IC from 52/100,000 to 67/100,000

Prevalence

N/A

RISK FACTORS

- Bacterial cystitis:
  - Young women: Sexual activity, use of spermicidal condoms or diaphragm, and genetic factors such as blood type or maternal history of recurrent cystitis

– Healthy, noninstitutionalized older women: Postmenopausal changes in the perineal epithelium and vaginal microflora, incontinence, diabetes, and history of cystitis

Genetics
N/A

PATHOPHYSIOLOGY (3)
- Bacterial cystitis in females is usually an ascending infection.
- In males, it occurs in association with urethral or prostatic obstruction, prostatitis, foreign bodies, or tumors.
- Increases in tumor necrosis factor in bladder mucosa
- Increased mast cell degranulation and histamine release
- Changes in purinergic signaling

ASSOCIATED CONDITIONS
See "Differential Diagnosis."

GENERAL PREVENTION
- Infectious: Minimize bacterial exposure, avoid indwelling Foley catheter if possible; intermittent catheterization if prolonged catheter needed
- Hemorrhagic: Avoid radiation or cyclophosphamide/iphosphamide exposure

DIAGNOSIS

HISTORY
- Characterization of symptoms: Frequency, urgency, dysuria, suprapubic pain, perineal or scrotal pain, dyspareunia
- Exposure to radiation:
  – Obliterative endarteritis causing ischemia
  – May occur several years after exposure.
- Exposure to cyclophosphamide/iphosphamide:
  – Common cause of hemorrhagic cystitis thought to be due to acrolein metabolite dwelling in bladder
- History of UTI; previous treatments
- If patient immunosuppressed:
  – Suspect viral or fungal infection
- Use of personal hygiene products that can cause local irritation (douches, vaginal preparations)
- Indwelling catheters
- History of hematuria
- History of fevers, chills
- Symptoms of vaginitis or discharge present

PHYSICAL EXAM
- Vital signs: Fever, tachycardia (from anemia or sepsis), pallor (anemia due to hemorrhagic cystitis)
- Abdomen: Suprapubic tenderness, costovertebral angle tenderness
- GYN: Bladder or vaginal tenderness, vaginal discharge

- GU, male: Tender and/or boggy prostate, testicular tenderness, penile discharge

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis with microscopy
- Urine culture:
  - Anaerobic, aerobic
    - Midstream standard
    - Catheterize sample if concerns about contamination
  - Fungal and viral cultures only if high suspicion
  - A recent study compared catheterized urine with midstream urine cultures in acute cystitis (4)
    - Cultures of voided midstream urine with acute uncomplicated cystitis accurately showed evidence of bladder *Escherichia coli* but not of enterococci or group B streptococci
    - These bacteria which are often isolated with *E. coli* but appear to rarely cause cystitis by themselves (urethral contaminants)
- CBC: Anemia in hemorrhagic cystitis, leukocytosis in infectious cystitis
- Creatinine
- Urine cytology: If patient with symptoms of cystitis, risk factors for urothelial or other bladder cancer, and negative workup for UTI or overactive bladder
- Urine culture for Mycobacterium in presence of sterile pyuria and suspicion for TB
- Vaginal discharge evaluation if present

Imaging

- CT urogram or US:
  - To rule out associated upper-tract pathology
  - May show thickened bladder wall or filling defect such as blood clots or tumor
- Cystogram:
  - To rule out vesicoureteral reflux if considering intravesical formalin treatment for hemorrhagic cystitis

Diagnostic Procedures/Surgery

- Cystoscopy for hematuria workup or if the diagnosis is not apparent
- Cystoscopy with hydrodistention for the diagnosis of IC
- Bladder biopsy: To rule out carcinoma in situ or for tissue culture

Pathologic Findings

- Evidence of acute or chronic inflammation
- Michaelis–Gutmann bodies in malakoplakia

DIFFERENTIAL DIAGNOSIS

- Anxiety
- Balanitis
- Bladder cancer or other malignancy
- Chronic pelvic pain syndromes
- Cystitis cystica, cystitis glandularis
- Diabetes insipidus, excess fluid intake

- Diabetes mellitus
- Diuretics, excessive caffeine, alcohol
- Eosinophilic cystitis
- Epididymitis
- Extrinsic bladder compression (eg, pelvic tumor, radiation-induced fibrosis)
- Genital herpes
- Hemorrhagic cystitis
- Infectious cystitis: Bacterial, viral, parasitic, fungal
- IC (painful bladder syndrome)
- Neurogenic bladder, chronic urinary retention
- Overactive bladder
- Prostatitis
- Prostatodynia
- Pyelonephritis
- Urethral syndrome
- Urethritis (eg, gonorrhea, chlamydia)
- Urinary calculi
- Vulvovaginitis and/or pelvic inflammatory disease

TREATMENT

GENERAL MEASURES

- Encourage adequate hydration.
- Proper toilet hygiene for females to limit urethral exposure to pathogens
  - Cleansing perineum "from front to back" (controversial)
- Encourage voiding immediately before and after sexual activity in females.

MEDICATION

First Line

- Antimicrobials for bacterial cystitis
  - TMP–SMZ for 3 days is a standard therapy for simple uncomplicated bacterial cystitis in females.
  - Other combinations may include cephalexin, 250–500 mg q6h for 1–3 days; ciprofloxacin, 250–500 mg q12h for 1–3 days; nitrofurantoin (macrocrystals), 100 mg q12h for 7 days; ofloxacin, 200 mg q12h for 1–3 days
- Phenazopyridine (Pyridium) for relief of dysuria:
  - Pregnancy category B
  - Contraindicated in glomerulonephritis, renal insufficiency or failure, severe hepatitis, G6PD deficiency
  - Side effects: Orange urine, renal failure, rash, nausea, headache, vertigo, hemolytic anemia, methemoglobinemia
  - Dose:
    - Adults: 200 mg PO TID
    - Pediatric: 4 mg/kg PO TID

Second Line

Based on culture if initial antibiotic not successful in bacterial cystitis

SURGERY/OTHER PROCEDURES
- Cystoscopy with biopsy to diagnose cystitis cystica or glandularis
- Cystoscopy with hydrodistention to diagnose IC; look for characteristic glomerulations.
- Cystoscopy with clot evacuation and electro or laser fulguration for hemorrhagic cystitis
- Cystectomy for refractory hemorrhagic cystitis is rarely necessary

ADDITIONAL TREATMENT

Radiation Therapy

May induce radiation cystitis

Additional Therapies
- Intravesical installations of alum, silver nitrate for hemorrhagic cystitis
- Hyperbaric oxygen for hemorrhagic cystitis.

Complementary & Alternative Therapies

Cranberry tablets for prevention of recurrent bacterial cystitis; evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs.

ONGOING CARE

PROGNOSIS

Simple bacterial cystitis prognosis is excellent.

COMPLICATIONS
- Depends on etiology of cystitis
- Untreated simple bacterial cystitis can cause pyelonephritis.
- Hemorrhagic cystitis may recur and/or be refractory to therapy, resulting in multiple transfusions or requiring cystoscopy and fulguration.

FOLLOW-UP

Patient Monitoring
- Urinalysis
- History and physical exam
- Females with >3 episodes of cystitis per year should be considered candidates for prophylaxis:
  - Prior to institution of therapy, exclude anatomic abnormality (eg, stones, reflux, fistula).
  - Single dosing at bedtime or at time of intercourse is recommended.
  - Common oral agents are TMP–SMZ (40 mg/200 mg), nitrofurantoin (100 mg), and cephalexin (250 mg).

Patient Resources

http://www.bladderandbowelfoundation.org/bladder/bladder-problems/bacterial-cystitis.aspN/A

REFERENCES

1. Wang A, Nizran P, Malone MA, et al. Urinary tract infections. *Prim Care.* 2013;40(3):687–

706.
2. Rinaldo CH, Tylden GD, Sharma BN. The human polyomavirus BK (BKPyV): Virological background and clinical implications. *APMIS*. 2013;121(8):728–745.
3. Payne H, Adamson A, Bahl A, et al. Chemical- and radiation-induced haemorrhagic cystitis. Current treatments and challenges. *BJU Int*. 2013;112(7):885–897.
4. Hooton TM, Roberts PL, Cox ME, et al. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med*. 2013;369(20):1883–1891.

ADDITIONAL READING

• Del Pizzo JJ, Chew BH, Jacobs SC, et al. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: Long-term followup. *J Urol*. 1998;160(3 Pt 1):731–733.
• Epidemiology of interstitial cystitis. Executive Committee Summary and Task Force Meeting Report. October 29, 2003. NIDDK. (http://archives.niddk.nih.gov/ic2003/TaskForce_Meeting_Report.pdf)
• Hu KK, Boyko EJ, Scholes D, et al. Risk factors for urinary tract infections in postmenopausal women. *Arch Intern Med*. 2004;164:989–993.
• Sencer SF, Haake RJ, Weisdorf DJ. Hemorrhagic cystitis after bone marrow transplantation. Risk factors and complications. *Transplantation*. 1993;56(4):875–879.
• Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis*. 1999;29:745–758.

See Also (Topic, Algorithm, Media)

• Bacteruria and Pyuria
• Cystitis, Hemorrhagic (Infectious, Noninfectious, Radiation)
• Cystitis, Radiation
• Interstitial Cystitis
• Prostatitis, General
• Pyuria Algorithm
• Urinary Tract Infection (UTI), Adult Female
• Urinary Tract Infection (UTI), Adult Male
• Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

• 595.82 Irradiation cystitis
• 595.89 Other specified types of cystitis
• 595.9 Cystitis, unspecified

ICD10

• N30.40 Irradiation cystitis without hematuria
• N30.80 Other cystitis without hematuria
• N30.90 Cystitis, unspecified without hematuria

CLINICAL/SURGICAL PEARLS

- Acute cystitis in females is most commonly bacterial and typically responds to a short course of antibiotic.
- Cystitis in the male is much less common and usually indicates a need for further evaluation.

CYSTITIS, HEMORRHAGIC (INFECTIOUS, NONINFECTIOUS, RADIATION)

Ahmad Shabsigh, MD, FACS

BASICS

DESCRIPTION

- Inflammation leading to damage of the bladder's urethelium and blood vessels, causing hematuria and irritative voiding symptoms.
- Hemorrhagic cystitis (HC) is commonly caused by severe infection, cyclophosphamide, and radiation therapy induced.

EPIDEMIOLOGY

Incidence

- Cyclophosphamide-induced HC: 5–7%
- Radiation-induced HC: 10–15% in patients with history of pelvic radiation.
- 7–70% of hematopoietic stem cell transplants.

RISK FACTORS

- No age, sex, or race predilection.
- Infections.
- Exposure to certain industrial chemicals, such as aniline or toluidine derivatives.
- Previous treatment with oxazaphosphorine alkylating agents (for lymphoproliferative disorders, solid tumors, collagen diseases) such as cyclophosphamide, isophosphamide.
- History of prior pelvic radiation (prostate and cervical cancers).
- Reactivation of BK virus (BKV) infection in bone marrow transplant patients.

Genetics

N/A

PATHOPHYSIOLOGY

- Cyclophosphamide: Acrolein enters the urethelium. Activates platelet-activating factor, nitric oxide, tumor necrosis factor-α, and IL-1, eventually forming peroxynitrite that causes damage.
- Radiation-induced cystitis results from a progressive obliterative endarteritis leading to mucosal ischemia, ulceration, and neovascularity.
- Penicillin toxicity is immune-mediated, whereas danazol toxicity is likely from damaging vascular changes.

ASSOCIATED CONDITIONS

See "Differential Diagnosis."

GENERAL PREVENTION

- Patients treated with cyclophosphamide once had a very high incidence of HC (~70%), with high mortality rates (as high as 75%) if it became severe
- IV hydration, frequent bladder emptying, and sometimes indwelling catheters with bladder

irrigations are used to reduce the time toxins are in contact with the bladder wall (1)[A]

- Mercaptoethane sulfonate Na (MESNA) and N-acetylcysteine (Mucomyst) bind to acrolein, creating nontoxic compounds.
- WF-10 (2)[A], sodium pentosan polysulfate (Elmiron), and amifostine (Ethyol) have been investigated in prevention of radiation-induced cystitis.
- Infectious: Minimize bacterial exposure, avoid indwelling Foley catheter if possible; intermittent catheterization if prolonged catheter needed

DIAGNOSIS

HISTORY

- Gross hematuria (with or without pain)
- Frequency, urgency, dysuria
- Urinary retention from clots
- Occasional mucosal sloughing
- Suprapubic pain
- Fevers with chills
- Previous history of cyclophosphamide therapy, pelvic radiation, bone marrow transplant

PHYSICAL EXAM

- Suprapubic pain/mass: Distended bladder, infected and/or clot-filled bladder
- Signs and symptoms of hypovolemia, hemorrhagic shock, or anemia if severe
- Ocular infections: Common with adenovirus infection
- Large hypertrophied tongue: Amyloidosis

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine for analysis, cytology, and cultures (including fungal and viral cultures, if indicated)
- Coagulation factors (especially platelets, which can be depleted)
- Serial hematocrits
- Serum creatinine
- Blood tests for collagen disease markers, if indicated

Imaging

- CT urogram:
  - Often done as part of hematuria workup
  - Rules out other urologic abnormalities
  - Usually not able to diagnose HC, but may show clots in the lumen, a thickened irregular bladder wall, and/or small capacity.

Diagnostic Procedures/Surgery

- Cystoscopy ± biopsy, ± clot evacuation
- Consider electro- or laser fulguration if focal bleeding visualized.

Pathologic Findings

- Urothelial damage: Edema, necrosis, ulceration, hemorrhage, leukocyte infiltration, and neovascularization
- May reveal amyloid deposits; eosinophilic inflammatory response of schistosomiasis; IgG,

IgM, and C3 depositions; penicillin toxicity; whitish pseudomembranes or plaques of fungal infections; inclusion bodies of viral infections

DIFFERENTIAL DIAGNOSIS

- Oxazaphosphorine agents (cyclophosphamide and isophosphamide):
  - Most common cause of severe HC
  - Acrolein, a liver metabolite of the agents, is the toxin believed to be directly implicated.
  - Higher dosages, IV route of administration (vs. oral), and increased contact time between the bladder wall and the acrolein (because of dehydration and/or infrequent emptying) all worsen HC.
- Pelvic radiation:
  - Usually initiated by bladder distension, minor trauma, infection, instrumentation
  - Acute episodes wane within 12–18 mo
  - Can occur as late as 15–20 yr after exposure
- Viral infection:
  - Adenovirus 11 and 35, influenza A, CMV, Polyomavirus hominis 1, the BKV, and JC viruses
  - Typically seen in immunocompromised patients after BMT
  - May present dramatically, but usually resolves spontaneously in <2 wk
- Other infections rarely cause severe HC:
  - Bacterial: *Escherichia coli*, *Staphylococcus saprophyticus*, Proteus, Klebsiella, *Mycobacterium tuberculosis*
  - Fungal: Candida, Aspergillus, Cryptococcus, Torulopsis
  - Parasitic: *Schistosoma haematobium*, *Echinococcus granulosus*
- Systemic hematologic disease: Rare; often refractory to fulguration and irrigation
- Systemic amyloidosis associated with rheumatoid arthritis or Crohn disease
- Chemical toxins:
  - Anilines, toluidines, and chlordimeform are common industrial exposures (dyes, pesticides).
  - Overdoses of methenamine mandelate; accidental urethral instillation of gentian violet douche or nonoxynol-9 contraceptive
  - Thiotepa and acetic acid intravesically
- Medications:
  - Penicillin, piperacillin, methicillin, carbenicillin, danazol, bleomycin, allopurinol, busulfan
- Prolonged high-altitude travel (Boon disease)
- Carcinomas of the urinary tract
- Acute UTIs
- Benign prostatic hypertrophy
- Trauma to the urinary system
- Arteriovenous malformation, vascular fistulae

TREATMENT

GENERAL MEASURES

- Catheterization/bladder irrigation with normal saline to clear bleeding and evacuate clots

- Remove the offending toxin.
- Treat the infectious agent.
- Hydration and diuresis
- Blood products transfusion, when necessary

MEDICATION

First Line

- Alum irrigation often considered 1st line:
  - Astringent, forms precipitates over bleeding surface
  - 1–4% solution at 300–1,000 mL/h
  - No need for anesthesia
  - Adverse effects: Spasms, precipitation and clogged catheters, rare encephalopathy from aluminum toxicity
- ε-Aminocaproic acid (Amicar):
  - Inhibits clot lysis by urinary urokinase
  - Can be given orally or parenterally
  - Contraindicated in upper-tract bleeding, as dense clots can lead to ureteral obstruction
- Silver nitrate instillation:
  - 0.5–1% solution in bladder for 10–20 min, followed by saline flush
  - Causes a chemical cauterization
  - Painful, requires anesthesia
  - Adverse effect: Build-up can clog catheters
  - Duration of response is often short
- Prostaglandin instillation:
  - Carboprost tromethamine (synthetic PGF2) 0.1–0.8 mg/dL solution. Dwell for 1–4 hr, 4 times a day for 5–7 days
  - Stabilizes membranes, decreasing edema; causes vasoconstriction and platelet aggregation
  - Low morbidity: No anesthesia required, no precipitate forms, so no clogging of catheters
  - Adverse effects: Cost, requires intensive nursing care, moderate bladder spasms
- Phenol instillation:
  - 30 mL 100% phenol in 30 mL of glycine for 1 min, then ethanol and saline washes
  - Destroys urothelium, not muscularis; less bladder fibrosis than with formalin
  - Painful, requires anesthesia
  - Duration of response is often short
- Low-dose cidofovir (3)
  - 5 mg/kg in 60 mL of 0.9% NaCl intravesical over 15 min.

Second Line

- Hyaluronic acid:
  - Constitutes a protective barrier.
  - Intravesical treatment of 40 mg every week for 4–6 wk. If responds add monthly treatments
- Formalin instillation:
  - 1–4% solution of $\leq$50 mL for 5–30 min, with patient in reverse Trendelenburg to minimize vesicoureteral reflux.
  - Check cystogram before instillation to rule out reflux or extravasation; may need to

occlude ureter with balloon to prevent potentially fatal renal absorption.
  – Hydrolyzes proteins, coagulating mucosa and submucosa; 80% effective
  – Very painful, requires anesthesia.
  – Adverse effects: Reflux could cause ureteral fibrosis and obstruction or papillary necrosis; extravasation causes peritonitis and/or fistulas.
- Pentosan polysulfate 100 mg TID

SURGERY/OTHER PROCEDURES
- Repeated cystoscopic laser ablation or cauterization
- Consider the following after all conservative modalities have failed, and patient is unstable.
  – Bilateral percutaneous nephrostomy tubes with occlusive balloons decrease the exposure of new clots to urokinase, allowing bladder to self-tamponade. Would consider this option prior to formalin instillation.
  – Supravesical urinary diversion, cutaneous ureterostomy, ureterosigmoidostomy, cystectomy in severe retractable cases.

ADDITIONAL TREATMENT

Radiation Therapy

Contraindicated; a recognized cause of HC

Additional Therapies
- Hyperbaric oxygen (4):
  – Promotes granulation tissue and neovascularization, causes vasoconstriction.
  – Better for radiation-induced cystitis.
  – Requires a hyperbaric chamber, which may not always be readily available.
  – May require 30–60 daily treatments.
  – High rate of recurrence.
- Selective hypogastric artery embolization:
  – Under local anesthesia on risky patients.
  – Complications: Gluteal claudication, bladder necrosis, lower limb paralysis, or impotence.
  – Low success, as most bleeding is venous.

Complementary & Alternative Therapies

Supportive care. Blood products, platelets, reverse anticoagulation.

ONGOING CARE

PROGNOSIS
- Related to the successful treatment of etiology of HC.
- Long term increases risk of secondary urothelial malignancy.

COMPLICATIONS
- Anemia, renal failure.
- Bladder fibrosis with small, noncompliant bladder; may need surgical reconstruction.
- Bladder perforation.
- Increased risk for transitional cell carcinoma from radiation, cyclophosphamide, and similar agents; may be years later
- Secondary UTIs from prolonged catheterization.

• Vesicoureteral reflux resulting from bladder fibrosis.

FOLLOW-UP

Patient Monitoring

• Repeated hematocrit, platelets, renal function, urine culture, and sensitivities.
• Maintain sterile urine.
• Continue hydration for many days after bleeding ceases as rebleeding is common.
• Evaluate long-term sequelae after acute episode.
• May need repeat cystoscopy

Patient Resources

http://emedicine.medscape.com

REFERENCES

1. Vose JM, Reed EC, Pippert GC, et al. Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: A randomized trial. *J Clin Oncol.* 1993;11:1306–1310.
2. Veerasarn V, Khorprasert C, Lorvidhaya V, et al. Reduced recurrence of late hemorrhagic radiation cystitis by WF10 therapy in cervical cancer patients: A multicenter, randomized, two-arm, open-label trial. *Radiother Oncol.* 2004;73:179–185.
3. Ganguly N, Clough LA, Dubois LK, et al. Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation: A retrospective analysis of an algorithmic approach. *Transpl Infect Dis.* 2010;12(5):406–411.
4. Del Pizzo JJ, Chew BH, Jacobs SC, et al. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen: Long-term followup. *J Urol.* 1998;160:731–733.

ADDITIONAL READING

Decker DB, Karam JA, Wilcox DT. Pediatric hemorrhagic cystitis. *J Pediatr Urol.* 2009;5(4):254–264.

See Also (Topic, Algorithm, Media)

• Chemotherapy Toxicity, Urologic Consideration
• Cystitis, General Considerations
• Cystitis, Hemorrhagic (Infectious, Non-Infectious, Radiation) Image ☼
• Cystitis, Radiation
• Cystitis, Viral
• Cytoxan (Cyclophosphamide) Toxicity
• Polyoma Virus (BK, JC), Urologic Consideration

CODES

ICD9

• 595.4 Cystitis in diseases classified elsewhere
• 595.82 Irradiation cystitis
• 595.89 Other specified types of cystitis

ICD10

- N30.40 Irradiation cystitis without hematuria
- N30.90 Cystitis, unspecified without hematuria
- N30.91 Cystitis, unspecified with hematuria

CLINICAL/SURGICAL PEARLS

Optimum treatment for chemotherapy-induced HC is prevention (aggressive hydration and/or prophylactic mesna therapy).

CYSTOCELE

Alana M. Murphy, MD

BASICS

DESCRIPTION

- Cystocele is prolapse of the bladder into the vagina
- Also referred to as anterior compartment prolapse

EPIDEMIOLOGY

Incidence

11% lifetime risk of surgery for pelvic organ prolapse (POP) or urinary incontinence (UI) (1)

Prevalence

- Difficult to determine due to several factors:
  - Data mostly reported in the context of surgical treatment
  - Cystocele may be asymptomatic
  - Diagnosis requires a vaginal exam
- POP quantification (POP-Q) distribution in an observational study of women 18–82 yr old seeking routine gynecologic care (2):
  - POP-Q stage 0: 6.4%
  - POP-Q stage 1: 43.3%
  - POP-Q stage 2: 47.7%
  - POP-Q stage 3: 2.6%

RISK FACTORS

- Increasing age
- Parity
- Vaginal delivery (nerve, muscle, and connective tissue damage)
  - Instrumented vaginal delivery may be associated with a higher risk of POP compared to spontaneous vaginal delivery
- Race (3)
  - Hispanic women have highest prevalence of POP
- Increased intra-abdominal pressure (obesity, chronic cough, constipation)
- Pelvic surgery (hysterectomy, radical cystectomy)
- Congenital connective tissue disorders (Ehlers–Danlos syndrome)

Genetics

- Connective tissue disorders, bladder exstrophy
- POP prevalence rates differ according to race suggesting a genetic component (3)

PATHOPHYSIOLOGY

- Weakening of supporting and suspending structures: Cardinal ligaments, uterosacral ligaments, endopelvic fascia, pubocervical fascia, levator ani muscles
- Defect location:
  - Central: Attenuation of the pubocervical fascia in the midline

- Lateral: Disruption of lateral attachments of the endopelvic fascia to the arcus tendineus fascia pelvis (ATFP)
- Combined defects

ASSOCIATED CONDITIONS

- Multicompartment POP
  - Always suspect concomitant apical prolapse in the setting of stage ≥3 cystocele
- Storage symptoms/signs: Stress UI, urinary urgency, urgency urinary incontinence (UI)
- Voiding symptoms/signs: Weak urinary stream, urinary hesitancy, elevated postvoid residual (PVR) urine, bladder outlet obstruction, urinary retention

GENERAL PREVENTION

- Reduction of modifiable risk factors
- Additional studies examining the role of prophylactic vaginal support at the time of pelvic surgery (eg, hysterectomy) are needed

DIAGNOSIS

HISTORY

- Symptoms/signs: Pelvic pressure, vaginal pressure, sensation of a vaginal bulge, stress/urgency/ overflow UI, obstructive voiding symptoms, recurrent urinary tract infections (UTIs)
- Previous pelvic/vaginal surgical procedures
- Hormonal status
- Obstetric history
- Comorbidities

PHYSICAL EXAM

- Assessment of POP should be performed during a Valsalva maneuver
- Leading edge of POP should be used for staging purposes
- Examining a patient in a standing position may help determine the maximum extent of POP
- Assessment of the anterior compartment should be performed with support of the apical and posterior compartment to ensure the elimination of potentially distracting apical and posterior POP
- Baden-Walker grading system:
  - Grade 0: No POP
  - Grade 1: Leading edge descends halfway to the hymen
  - Grade 2: Leading edge descends to the hymen
  - Grade 3: Leading edge descends halfway past the hymen
  - Grade 4: Procidentia or vault eversion
- POP-Q staging system:
  - POP described using 9 reference measurements, including 2 measurements specific to the anterior vaginal wall
    - Aa: Distal anterior vaginal wall
    - Ba: Proximal anterior vaginal wall
  - Stage 0: No POP
  - Stage 1: Leading edge is >1 cm above the hymen

– Stage 2: Leading edge is between 1 cm above and 1 cm below the hymen (-1, 0, +1)
– Stage 3: Leading edge is >1 cm below the hymen but less than total vaginal length – 2 cm (TVL – 2 cm)
– Stage 4: Leading edge is below hymen by more than TVL – 2 cm

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- No lab testing is required for the diagnosis of a cystocele
- Urinalysis and urine culture as indicated

Imaging

- No imaging is required for the diagnosis or management of a cystocele
- A cystocele may inadvertently be detected on imaging studies, such as a cystogram
- Dynamic magnetic resonance imaging (MRI) with contrast:
  – Examines pelvic structures in relation to one another during a Valsalva maneuver
  – Aids in differentiation between a cystocele and an enterocele
  – Aids in assessment of multicompartment POP

Diagnostic Procedures/Surgery

- Pelvic exam
  – Employ standardized staging system (POP-Q or Baden-Walker)
- PVR assessment
- Urodynamics
  – Only indicated to characterize associated storage and voiding symptoms/signs

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Cystocele
- Enterocele
- Anterior vaginal wall masses: Urethral diverticulum, Skene gland cyst, epidermal inclusion cyst, leiomyoma, ectopic ureterocele, Bartholin duct cyst, Gartner duct cyst

TREATMENT

GENERAL MEASURES

- Observation
- Pelvic floor exercises (Kegel exercises) (4)[B]
- Vaginal pessary
- Surgical repair

MEDICATION

First Line

There are no data to support systemic or topical estrogen or other medications as a therapy for the treatment of cystocele.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Preoperative preparation:
  - Optional hormone replacement with topical estrogen
- Perioperative factors:
  - Single dose of preoperative antibiotics
  - DVT prophylaxis with sequential compression devices
  - Optional vaginal packing
  - Optional temporary urethral catheterization
    - Consider in the setting of a multicompartment repair with or without an anti-incontinence procedure
- Transvaginal vs. transabdominal repair:
  - Transvaginal repair:
    - Central defect repair: Plication of pubocervical fascia in the midline with horizontal mattress sutures
    - Lateral defect repair: Reattachment of the endopelvic fascia to the ATFP
    - Transvaginal mesh grafts provide a superior anatomic outcome but are associated with higher complication rates (5)[A]
  - Transabdominal repair:
    - Only repair lateral defects
- Closure of the vagina (colpocleisis):
  - Excellent option for geriatric women who no longer desire the ability to maintain sexual activity
- Perform a simultaneous repair of all POP defects and an anti-incontinence procedure for demonstrable stress UI
- Consider a prophylactic concomitant anti-incontinence procedure in patients with stage ≥ 3 cystocele and/or history of stress UI

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Observation:
  - Appropriate if a patient is not symptomatic
- Pelvic floor exercises (Kegel exercises) (4)[B]
- Vaginal pessary:
  - Good option for poor surgical candidates
  - May be used as a temporary solution
  - Risk of vaginal discharge, vaginal ulceration, vesicovaginal and rectovaginal fistula formation

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Recurrence rates as high as 30–70%
- Close to 30% of women will require reoperation for symptomatic POP (1)

COMPLICATIONS

- Bladder injury
- Ureteral injury/obstruction
- Bleeding
- Dyspareunia
- *de novo* stress UI
- Recurrent cystocele

FOLLOW-UP

Patient Monitoring

Evaluation for recurrent POP should largely be based on symptoms or clinical signs (elevated PVR, urinary retention, recurrent UTIs)

Patient Resources

- American Urogynecologic Society. http://www.voicesforpfd.org/p/cm/ld/fid=6
- International Urogynecological Association. www.iuga.org/resource/resmgr/Brochures/eng_pop.pdf

REFERENCES

1. Olsen AL, Smith VJ, Bergstrom JO, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol*. 1997;89:501–506.
2. Swift SE. The distribution of pelvic organ support in a population of female subjects seen for routine gynecologic healthcare. *Am J Obstet Gynecol*. 2000;183:277–285.
3. Nygaard I, Barber MD, Burgio KL, et al. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA*. 2008;300:1311–1316.
4. Braekken IH, Majida M, Engh ME, et al. Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. *Am J Obstet Gynecol*. 2010;203:e1–e7.
5. Altman D, Väyrynen T, Engh ME, et al. Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. *N Engl J Med*. 2011;364:1826–1836.

ADDITIONAL READING

- Chow D, Rodriguez LV. Epidemiology and prevalence of pelvic organ prolapse. *Curr Opin Urol*. 2013;23:293–298.
- Walters MD. Surgical correction of anterior vaginal wall prolapse. In: Walters MD, Karram MM, eds. *Urogynecology and Reconstructive Pelvic Surgery*, 3rd ed. Philadelphia, PA: Mosby Elsevier; 2007.

See Also (Topic, Algorithm, Media)

- Baden-Walker Staging
- Cystocele, Grading
- Cystocoele Enterocele Algorithm
- Cystocele Image

- Pelvic Organ Prolapse (Cystocele and Enterocoele)
- Pelvic Organ Prolapse Quantification System (POP-Q)
- Rectocele, Urologic Considerations
- Vaginal Mesh Erosion
- Vaginal Pessaries, Urologic Considerations
- Vaginal Prolapse

CODES

ICD9

- 618.01 Cystocele, midline
- 618.02 Cystocele, lateral

ICD10

- N81.10 Cystocele, unspecified
- N81.11 Cystocele, midline
- N81.12 Cystocele, lateral

CLINICAL/SURGICAL PEARLS

- Management of a cystocele should largely be based on patient preference and symptoms.
- Always suspect concomitant apical prolapse in the setting of stage ≥ 3 cystocele or a recurrent cystocele.
- Mesh grafts for cystocele repair provide a superior anatomic outcome but they are associated with higher complication rates.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLUS, UROLOGIC CONSIDERATIONS

Joshua D. Roth, MD
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BASICS

DESCRIPTION

- Deep vein thrombosis (DVT): Aggregation of platelets and fibrin within a deep vein of the leg or pelvis that may lead to venous obstruction.
- Pulmonary embolism (PE): Blockage of the pulmonary artery or one of its branches by a thrombus that has traveled from elsewhere in the body through the bloodstream. Can be an acute life-threatening illness.
- Venous thromboembolism (VTE or DVT/PE) is the disease process by which a DVT can embolize and become a life-threatening PE.

EPIDEMIOLOGY

Incidence

- DVT
  - 160/100,000/yr (1)
  - Increases with age: 1/100 if age ≥80
- PE (1)
  - 70/100,000/yr, with a 1-wk survival rate of 71%; 25% present with sudden death
  - PE is believed to be the most common cause of postoperative death in the urologic population
- VTE risk in urologic populations (2)
  - Radical cystectomy: 3.7%
  - Percutaneous nephrostomy in patients with/without malignancy: 3.6%/0.8%
  - Nephrectomy with/without malignancy: 2.0%/0.4%
  - Radical prostatectomy: 1.5%
  - Transurethral resection of bladder tumors/prostate: <0.5%
  - Incontinence repair: 0.3%

Prevalence

Prevalence of genetic mutations causing inherited thrombophilia: <1–5%, which cause a 3–10× increase risk of VTE in heterozygous state (3)

RISK FACTORS

- Patient-specific risk factors (1)
  - Surgery
  - Trauma (major or lower extremity)
  - Immobility, paresis
  - Malignancy
  - Cancer therapy (hormonal, chemotherapy, or radiotherapy)

- Previous VTE
- Increasing age (≥60)
- Pregnancy and the postpartum period
- Estrogen-containing oral contraception
- Selective estrogen receptor modulators
- Acute medical illness
- Heart or respiratory failure
- Inflammatory bowel disease
- Nephrotic syndrome
- Myeloproliferative disorders
- Paroxysmal nocturnal hemoglobinuria
- Obesity
- Smoking
- Varicose veins
- Central venous catheterization
- Inherited or acquired thrombophilia

Genetics

- Inherited risk factors for DVT/PE (3)
  - Family history
  - Factor V Leiden mutation
  - Prothrombin G20210A
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
  - Sickle cell trait

PATHOPHYSIOLOGY

- Most PEs arise from DVTs
- DVTs arise from initiating factors of Virchow's triad:
  - Hypercoagulability: Regional activation of coagulation cascade leading to obstruction, edema, pain
  - Stasis: Stagnant hypoxemia causes endothelial injury
  - Injury: Platelet accumulation and fibrin deposition
- Need to differentiate from superficial thrombophlebitis/thrombosis that does not usually lead to DVT/PE

ASSOCIATED CONDITIONS

Paradoxical embolism: Systemic embolisms of venous origin that occur in patients with atrial or ventricular septal defects, which allow the embolus to pass into the arterial circulation

GENERAL PREVENTION

- DVT prophylaxis (ppx)
  - Mechanical (nonpharmacologic) therapies
    - Early postoperative ambulation
    - Graduated compression stockings (GCSs)
    - Intermittent pneumatic compression (IPC)

- Pharmacologic therapies
  - Subcutaneous low-dose unfractionated heparin (LDUH)
  - Subcutaneous low–molecular-weight heparin (LMWH)
- Recommendations (4)
  - Very low–risk surgery (VTE risk <0.5%)
    - No specific pharmacologic (B) or mechanical (C) ppx
  - Low-risk surgery (VTE risk ~1.5%)
    - Mechanical ppx, preferably with IPC (C)
  - Moderate-risk surgery (VTE risk ~3.0%) who are not at high risk for bleeding complications
    - LMHW/LDUH (B), or mechanical ppx, preferably with IPC (C)
  - Moderate-risk surgery (VTE risk ~3.0%) who are at high risk for bleeding complications
    - Mechanical ppx, preferably with IPC (C)
  - High-risk surgery who are not at high risk for bleeding complications
    - LMHW/LDUH (B) and mechanical ppx, with IPC or GCS (C)
  - High-risk patient undergoing cancer surgery who are not at high risk for bleeding complications
    - 4 wk of LMWH (B)
  - High-risk patient who are at high risk for bleeding complications
    - Mechanical ppx, preferably with IPC until the risk of bleeding diminishes
  - High-risk patients with contraindications to LMWH/LDUH who are not at high risk for bleeding complications
    - Low-dose aspirin (C), fondaparinux (C), or mechanical ppx, preferably with IPC (C)
  - Inferior vena cava (IVC) filters should not be used for primary VTE prevention
  - No need for periodic ultrasound surveillance

DIAGNOSIS

HISTORY

- Recent high-risk surgery, or other risk factors for VTE
  - DVT
    - History of prolonged immobilization, postoperative stasis, especially in patient with risk factors
    - Complaint of calf pain, swelling, or discoloration
  - PE
    - High clinical suspicion with above history
    - Acute onset of dyspnea, tachycardia, arrhythmia, hypotension

PHYSICAL EXAM

- DVT: Determined by level of obstruction
  - Inspection: Unilateral edema, discoloration below level of occlusion, dilated superficial veins
  - Palpation: Tender cord or knot, Homans' sign (limitation of passive dorsiflexion of foot, 55% unreliable)
- PE
  - Inspection: Cyanotic, dyspneic, prominent jugular veins, hemoptysis, tachypnea

– Palpation: Tachycardia, arrhythmia
– Auscultation: Pleural rub, rales, S3–S4 heart sounds

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- DVT
  – D-dimers: Sensitivity approaches 95% for ELISA method
- PE
  – ABG: Increased $P(A\text{-}a)O_2$ gradient
  – $PaO_2 < 80$ mm Hg

Imaging

- DVT
  – Central venography (gold standard): Invasive, expensive, not always available, contrast risks
  – Doppler ultrasound (US)/sonography: 90% accurate above knee, versatile, noninvasive, painless
  – Venous duplex ultrasound
    ○ Grayscale US to visualize the structure of the veins and color Doppler US to visualize the flow of blood through the vein; more accurate than Doppler and plethysmography
- PE
  – Chest x-ray (CXR)
    ○ Generally unremarkable, but can sometimes see a small, unilateral effusion
    ○ Westermark sign: Asymmetric vascular markings with segmental or lobar ischemia
  – Ventilation/perfusion scan (V/Q scan)
    ○ A perfusion defect in ≥ 1 pulmonary segment or all unmatched with ventilation defects support a high probability of PE
    ○ Negative result is very predictive
  – Computed tomography (CT)
    ○ Most common test used to diagnose PE

Diagnostic Procedures/Surgery

- Pulmonary Angiography
  – Injection of contrast into the pulmonary circulation, fluoroscopy of the lungs
  – Gold standard for diagnosing PE; rarely done

Pathologic Findings

Thrombi are a woven congealed mass of fibrin and platelets

DIFFERENTIAL DIAGNOSIS

- DVT: Cellulitis, thrombophlebitis, muscle sprain/strain, claudication, lymphedema
- PE: Pneumonitis/pneumonia, pneumothorax, CHF, esophageal perforation, myocardial infarction

TREATMENT

ALERT

DVT and PE are potentially life-threatening and acute decline in status can occur. This condition must be treated/diagnosed quickly and level of suspicion must always be high in postoperative patients.

GENERAL MEASURES

- DVT: Extremity elevation, early ambulation, pain relief
- PE: Oxygen therapy, fluid resuscitation, maintain cardiac output with pressors if needed
- Overall management of anticoagulation and antiplatelet therapy can be found in Section VII: Reference Tables: Anticoagulation and Antiplatelet Therapy in Urologic Practice

MEDICATION

First Line

- DVT proximal to knee anticoagulation with (4):
  - LMWH
  - Fondaparinux
  - Above favored over IV unfractionated heparin (UH) drip (B)
  - Early initiation of oral warfarin, with continued parenteral anticoagulation until INR is reached for >24 hr.
- DVT Distal to knee
  - Without severe symptoms/risk factors: Serial noninvasive imaging for 2 wk over anticoagulation (C). If thrombus extends, recommend therapeutic anticoagulation (B/C).
  - With severe symptoms/risk factors: Anticoagulation (as above) over imaging (C).
- PE (4)
  - Systemic anticoagulation as for DVT (B/C)
  - PEs with hypotension: Systemic thrombolysis with streptokinase is recommended (C).

Second Line

- DVT/PE
  - In patients with heparin-induced thrombocytopenia (HIT), LMW heparin (argatroban, lepirudin, and danaparoid) can be used

SURGERY/OTHER PROCEDURES

- DVT
  - Venous thrombectomy: Rarely needed
  - IVC filter:
    - Used as prophylaxis in high-risk or multitrauma patients
    - Recommended for acute DVT with contradic-tion to anticoagulation (4)[B]
- PE
  - Pulmonary embolectomy: Considered rarely for patient who remains in shock despite medical therapy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Will need 3 mo of anticoagulation therapy for postsurgical DVT/PE (4)[B]

- Protamine can reverse unfractionated heparin if needed. Protamine is not as effective with LMWH but should be used if excessive bleeding is encountered

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 10–30% of all patients with VTE suffer mortality within 30 days (3)
- Following anticoagulation therapy, 1/3 of all VTE patients will experience a recurrence within 10 yr (3)
  – Highest risk of recurrence is in the 1st year (3)
- 1/3–1/2 of those with LE DVTs develop postthrombotic syndrome (3)

COMPLICATIONS

- DVT: Pulmonary embolus; postthrombotic syndrome: Destruction of valves leads to chronic pain, swelling, skin necrosis, ulceration
- PE: Death, pulmonary infarction, pain, arrhythmia, shortness of breath
- VTE: Requires anticoagulation with its associated risk factors (increased bleeding risk), increased healthcare costs, prolonged hospitalization, rehospitalizations
- Heparin-induced thrombocytopenia with unfractionated heparin

FOLLOW-UP

Patient Monitoring

- Patients on heparin: Follow aPTT
- If necessary LMWH therapy can be followed by antifactor Xa assays
- Patients on warfarin need close monitoring of their INR for a goal between 2.0 and 3.0 (3) [B]

Patient Resources

- The Coalition to Prevent Deep-Vein Thrombosis http://www.preventdvt.org
- The National Blood Clot Alliance http://www.stoptheclot.org

REFERENCES

1. Rice KR, Brassell SA, McLeod DG. Venous Thromboembolism in Urologic Surgery: Prophylaxis, Diagnosis, and Treatment. *Rev Urol.* 2010;12(2/3):e111–e124.
2. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost.* 2003;90:446.
3. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: A public health concern. *Am J Prev Med.* 2010;38(4S):S495–S501.
4. Guyatt GH, Akl EA, Crowther M, et al. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(suppl 2):7S–47S.

ADDITIONAL READING

Best Practice Statement for the Prevention of Deep Vein Thrombosis in Patients Undergoing

Urologic Surgery, AUA 2008. Accessed March 2013 at http://www.auanet.org/content/media/dvt.pdf

See Also (Topic, Algorithm, Media)

- Reference Tables: Anticoagulation and Antiplatelet Therapy in Urologic Practice
- Deep Venous Thrombosis and Pulmonary Embolus, Urologic Considerations Image
- Deep Venous Thrombosis, Prophylaxis, AUA Guidelines

CODES

ICD9

- 415.11 Iatrogenic pulmonary embolism and infarction
- 453.40 Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
- 997.2 Peripheral vascular complications, not elsewhere classified

ICD10

- I26.99 Other pulmonary embolism without acute cor pulmonale
- I82.409 Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity
- T81.72XA Complication of vein following a procedure, NEC, init

CLINICAL/SURGICAL PEARLS

- Prophylaxis can help prevent DVT/PE.
- PE usually develops from a venous thrombus involving the proximal lower extremity.
- DVT/PE are potentially life threatening—have a high index of suspicion.
- Early diagnosis and treatment are key.

DETRUSOR OVERACTIVITY

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BASICS

DESCRIPTION

- Detrusor overactivity (DO) is occurrence of involuntary detrusor contractions during filling cystometry
  - Spontaneous or provoked
  - Contractions produce a wave form on cystometrogram of variable duration and amplitude
  - Phasic or terminal
  - Can be associated with symptoms
  - Neurogenic DO: DO with evidence of a relevant neurologic disorder
  - Idiopathic DO: DO without a neurologic cause

EPIDEMIOLOGY (1,2)

- DO is a common cause of symptoms of overactive bladder (OAB) syndrome, however since it is defined by urodynamics, it may not be documented if urodynamics are not preformed
- Symptoms associated with DO (urgency, frequency, and urgency incontinence) are more commonly treated rather than DO per se
- OAB is a symptom complex and is diagnosed without urodynamics and therefore may be diagnosed in the presence or absence of DO
- Approximately one-third of patients with OAB have incontinence
  - OAB is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology
  - Urinary incontinence accounts for 2% of healthcare cost in the United States

Prevalence

- OAB present in 17% of women and 16% of men
  - Increases with age
- DO present in 33% of women with OAB
- DO is present in 36% of patients with no OAB symptoms

RISK FACTORS

- Neurogenic and idiopathic DO
  - Most neurologic disorders are risk factors for DO (ie, stroke, neurodegenerative disorders, multiple sclerosis)
  - Pelvic surgeries, metabolic syndrome, diabetes, pelvic floor disorders, bladder outlet obstruction

PATHOPHYSIOLOGY

- Increased connectivity and excitability between detrusor muscle and nerves
- Inflammation

- Increased afferent activity
- Neurologic lesions of the CNS above the sacral micturition center

ASSOCIATED CONDITIONS

OAB, pelvic floor disorders, urinary incontinence, bladder outlet obstruction, neurologic lesions above the sacral micturition center, detrusor external sphincter dyssynergia

GENERAL PREVENTION

- Avoiding large fluid intake or the consumption of "bladder irritants" such as caffeine.
- Timed voiding and avoiding bladder overdistension

DIAGNOSIS

ALERT

DO, by definition can only be diagnosed by urodynamics. Therefore it is more practical to talk in terms of diagnosing OAB.

HISTORY (3)

- Past medical and surgical history
- Medications (diuretics, psychoactive drugs)
- Lower urinary tract symptoms survey
- Women with DO and OAB:
  - Are twice as likely to have urge urinary incontinence.
  - Have a higher symptom score on questionnaires
  - Higher episodes of daytime voiding and nocturia
  - Have lower functional bladder capacities

PHYSICAL EXAM

- Rule out the presence of exacerbating conditions
  - Pelvic and vaginal exam
  - Neurologic exam: Peripheral sensation and motor assessment
  - Postvoid residual

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: Determine presence of infection, hematuria, glycosuria
- Urine culture: Rule out infection
- Urine cytology: Rule out malignancy

Diagnostic Procedures/Surgery

- Urodynamic testing
  - Filling cystometry: Measurement of the pressure/volume relationship of the bladder during filling

Imaging

- Can involve videourodynamics with cystogram and voiding cystourethrogram
  - Renal ultrasound can also rule out the presence of hydronephrosis caused by high bladder pressures

Pathologic Findings
DO is characterized by the presence of contractions that produce a wave form on cystometrogram of variable duration and amplitude

DIFFERENTIAL DIAGNOSIS
- Bladder calculi
- Bladder cancer/carcinoma in situ
- Bladder outlet obstruction/Prostatic hypertrophy
- Congestive heart failure
- Detrusor external sphincter dyssynergia
- Diabetes
- Interstitial cystitis/Painful bladder syndrome
- Pelvic pain syndrome
- Medications
- Neurogenic bladder
- Pelvic organ prolapse
- Polyuria/polydipsia
- Sexually transmitted infection
- Stress incontinence
- Testing artifact during UDS evaluation (false positive)
- Urethral diverticulum
- UTI

TREATMENT

GENERAL MEASURES
- Treatment aimed at inhibiting involuntary detrusor contractions and decreasing intravesical pressures
- There are a number of options used to treat symptoms associated with DO. Only antimuscarinics, botulinum toxin, and augmentation cystoplasy have been proven to actually reduce or eliminate DO
- Behavioral modifications: Timed voiding, decrease fluid intake, avoid caffeine
  – Pelvic floor exercises (Kegel): With or without biofeedback

MEDICATION
- Antimuscarinics: Inhibit the effect of acetylcholine at postjunctional muscarinic receptors on detrusor muscle cells
  – Tolterodine (2–4 mg/d)
  – Trospium XR (60 mg/d)
  – Darifenacin (7.5–15 mg/d)
  – Solifenacin (5–10 mg/d)
  – Oxybutynin (IR 7.5–20 mg/d, XL 5–30 mg/d, patch twice weekly),
  – Fesoterodine (4–8 mg/d)
- β3-adrenergic receptor agonist: Promotes detrusor muscle relaxation

SURGERY/OTHER PROCEDURES

- Intravesical botulinum toxin (OnabotulinumtoxinA) injection:
  - Approved for treatment of neurogenic detrusor overactivity and OAB
- Sacral neuromodulation: Stimulation of S3 nerve root (InterStim)
- Posterior tibial nerve stimulation (PTNS): Urgent PC™
- Augmentation cystoplatsy/Urinary diversion: Increase functional bladder capacity and reduce intravesical pressure
- Pelvic floor reconstruction: If concomitant pelvic floor disorder

Additional Therapies
- Infection prophylaxis
- Clean intermittent catheterization
  - Decrease bladder pressure if urinary retention present

ONGOING CARE

PROGNOSIS
- Stepwise approach to treatment with least invasive pharmacologic options as first line
  - Patient may develop refractory OAB that may require second- or third-line treatment

COMPLICATIONS
- Urinary incontinence: Social and hygienic issues
- UTIs
- Renal deterioration
  - High economic burden

FOLLOW-UP
Patient Monitoring
- Periodic patient follow-up
  - Symptom assessment
  - Treatment compliance
  - Minimize medication side effects
  - Repeat urodynamic evaluation

Patient Resources
- National Association For Continence: www.nafc.org/bladder-health
- National Kidney and Urologic Diseases Information Clearing House: http://kidney.niddk.nih.gov/kudiseases/pubs/urodynamic/

REFERENCES

1. Garnett S, Abrams P. The natural history of the overactive bladder and detrusor overactivity. A review of the evidence regarding the long-term outcome of the overactive bladder. *J Urol.* 2003;169:843–849.
2. Haylen B, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn.* 2010;29:4–20.
3. Abrams P, Chapple CR, Jünemann KP, et al. Urinary urgency: A review of its assessment as the key symptom of the overactive bladder syndrome. *World J Urol.* 2012;30:385–392.

ADDITIONAL READING

- Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: Report from the standardization sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167–178.
- Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188(suppl 6):2455–2463.
- Kanai A, Zabbarova I, Oefelein M, et al. Mechanisms of action of botulinum neurotoxins, β3-adrenergic receptor agonists, and PDE5 inhibitors in modulating detrusor function in overactive bladders: ICI-RS 2011. *Neurourol Urodyn*. 2012;31(3):300–308.
- Winters JC, Dmochowski RR, Goldman HB, et al. Urodynamic studies in adults: AUA/SUFU guideline. *J Urol*. 2012;188(6 suppl):2464–2472.

See Also (Topic, Algorithm, Media)

- Detrusor Overactivity Image
- Incontinence, Urinary, Adult Female
- Incontinence, Urinary, Adult Male
- Overactive Bladder (OAB)
- Urgency, Urinary (Frequency and Urgency)
- Sacral Neuromodulation

CODES

ICD9

- 596.51 Hypertonicity of bladder
- 788.41 Urinary frequency
- 788.63 Urgency of urination

ICD10

- N32.81 Overactive bladder
- R35.0 Frequency of micturition
- R39.15 Urgency of urination

CLINICAL/SURGICAL PEARLS

- OAB is not synonymous with detrusor overactivity; the key symptom of OAB is urinary urgency.
- DO demonstrated on cystometry needs to be correlated with patient's symptoms.
- Treatment indicated if potential complications or patient driven.
- Only antimuscarinics, botulinum toxin, and augmentation cystoplasy have been proven to actually reduce or eliminate DO.

DETRUSOR SPHINCTER DYSSYNERGIA (DSD)

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BASICS

DESCRIPTION

- Detrusor sphincter dyssynergia (DSD) is found in cases of neurogenic lower urinary tract dysfunction
- DSD is contraction of the sphincter mechanism occurring simultaneously with uninhibited involuntary contraction of the bladder detrusor muscle (neurogenic detrusor overactivity [NDO])

EPIDEMIOLOGY

Incidence

- Unknown
  - Depends on incidence of underlying neurologic condition

Prevalence

- Prevalent in those with spinal cord lesions
  - More prevalent at higher levels (cervical) than lower (sacral) injury or disease
- May affect those with multiple sclerosis (MS), spinal cord tumor, traumatic spinal cord injury (SCI), arteriovenous malformation
- Uninhibited involuntary detrusor contraction (ie, NDO) must be present for DSD to occur

RISK FACTORS

- Neurologic processes affecting central nervous system (CNS)
  - Below level of the pons
- Associated with autonomic hyperreflexia

Genetics

None

PATHOPHYSIOLOGY

- DSD causes functional outflow obstruction
  - Dramatic elevation of intravesical pressure
    - Damages urinary tract directly with pressure and poor upper tract drainage
    - Secondarily with infection and urolithiasis
- DSD always associated with NDO
  - NDO may occur with synergic sphincter function (without DSD)
- Pontine mesencephalic reticular formation
  - Coordinates sphincter relaxation with detrusor contraction
    - Spinal cord lesions impair transmission of coordinating influences from the pons during reflex detrusor contraction
    - Uninhibited detrusor contraction stimulates a reflex sphincter contraction, resulting in bladder outflow obstruction

- 10–20% patients have internal (bladder neck) sphincter dyssynergia coexistent with external sphincter dyssynergia

ASSOCIATED CONDITIONS
- SCI
- MS
- Transverse myelitis

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Neurologic disease
  - Date of onset, duration of process
- Urinary voiding symptoms
  - Frequency, urgency, urge incontinence
- Method of urinary management
  - Condom catheter urinary collection
  - Intermittent self-catheterization
  - Indwelling urethral or suprapubic catheter
- Urinary tract infection (UTI)
  - Severity of infection
    - Response to antibiotics
    - Need for parenteral antibiotics
  - Frequency of occurrence of infection
  - Urolithiasis
    - Episodes of lithiasis
    - Surgical intervention

PHYSICAL EXAM
- Fever
- Parenchymal UTI
  - Men
    - Prostate, testes/epididymis, renal
  - Female
    - Renal
- Hypertension
  - During manipulation of GI/GU systems, autonomic hyperreflexia may result
- Generalized edema
  - Severe renal insufficiency
- Palpable flank mass
  - Secondary hydronephrosis
- Flank tenderness
  - Ureteral obstruction
  - Pyelonephritis

- Abdominal mass
  - Distended bladder, urinary retention
- Incontinence of urine
  - Spontaneously
  - With stress maneuvers
  - During abdominal/pelvic palpation
- Testicular mass
  - Epididymo-orchitis/epididymitis
  - Secondary abscess formation
  - Hydrocele from recurrent infection
- Prostate mass/nodule
  - Focal prostatitis
  - Prostate abscess

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Blood studies
  - Serum chemistry
    - Renal function, electrolyte levels
  - Complete blood count
    - Secondary anemia due to decreased renal function or chronic infection
- Urine studies
  - Urinalysis
    - Proteinuria: Renal dysfunction
    - Pyuria, nitrite, leukocyte esterase: Acute or chronic infection
    - Hematuria: Infection or lithiasis

Imaging

- Renal ultrasound (US)
  - Effective in screening for upper urinary tracts
    - Calculus
    - Hydronephrosis
    - Masses
- Excretory urography (ExU)
  - Contraindicated in those with decreased renal function (serum creatinine >2.0)
  - Delayed excretion of contract with high urinary storage pressures
  - Hydroureteronephrosis
    - Marked elevation of intravesical pressure
    - May be due to urinary calculi
- Voiding cystourethrogram
  - Bladder
    - Wall thickening
    - Trabeculation
    - Diverticulum formation
    - Incomplete emptying
  - Ureter

    - Vesicoureteral reflux
    - Hydroureter
    - Hydroureteronephrosis
  - Urethra
    - Prostatic urethral dilated
    - Membranous urethra persistently narrow, stenotic, nonrelaxing
    - Distal urethra normal; rule out stricture
- Nuclear medicine renal scan
  - Objective quantification of GFR
  - Sequential studies can detect deterioration of renal function prior to elevation of serum creatinine

Diagnostic Procedures/Surgery
- Urodynamic evaluation
  - Essential to diagnose detrusor overactivity with detrusor sphincter dyssynergy
- Cystoscopy
  - Normal penile urethral
  - Spastic, nonrelaxing, stenotic membranous urethral
  - Dilated prostatic urethra
  - Bladder trabeculation/diverticula
  - Rule out calculus or bladder tumor

Pathologic Findings
None

DIFFERENTIAL DIAGNOSIS
- Detrusor overactivity and bladder outflow obstruction
  - Benign prostatic hyperplasia
  - Adenocarcinoma of the prostate
  - Urethral stricture disease
  - Urethral tumor
- Urinary retention/incomplete emptying and neurologic disease
  - Impaired detrusor contractility
  - Detrusor areflexia

TREATMENT

GENERAL MEASURES
- Intermittent catheterization
- Decrease intravesical pressure
  - Decrease bladder contractility
    - Low-pressure urinary storage
  - Defeat sphincter function to establish low-pressure urinary drainage per urethra
    - Only option for males
    - No effective external urinary collection device for females

MEDICATION

First Line

- Anticholinergic therapy
  - Effective in improving urinary storage under low pressure
    - Hyoscyamine 0.375 mg PO BID-TID
    - Oxybutynin 5 mg PO TID-QID
    - Oxybutynin extended release 5–40 mg/d PO
    - Tolterodine 2–4 mg PO BID
- α-Adrenergic blockade
  - Decrease internal sphincter function
  - Largely ineffective for external sphincter dyssynergia
    - Alfuzosin 10 mg/d PO
    - Phenoxybenzamine 10 mg PO BID (nonselective)
    - Terazosin 2–5 mg PO daily-BID
    - Doxazosin 2–8 mg/d PO
    - Tamsulosin 0.4 mg PO daily

Second Line

- Botulinum toxin injection into the external sphincter for DSD
  - Short lived
  - Requires repeated injections (1)[B]

SURGERY/OTHER PROCEDURES

- Endoscopic sphincter ablation
  - Only in males as it requires condom catheter urinary collection
    - Electrosurgical or laser sphincterotomy: Incise external sphincter from bulbous urethra to midprostatic urethra
    - Further incision through the prostate and bladder neck may be required if internal dyssynergia is present
- Sphincter stent prosthesis placement
  - Wire mesh stent placed endoscopically
  - Bridges midprostatic to bulbous urethra (2)[A]
    - Maintains caliber of membranous urethra at 42 French
    - Suprapubic tube cystostomy may be required in perioperative period
- Augmentation cystoplasty
  - Bladder is incised in clamshell fashion to disrupt detrusor contraction
  - Gastrointestinal segment used to enlarge bladder, increasing urinary storage with decreased pressure
    - May use large intestine, ileum, or gastric segment
    - Requires intermittent catheterization for urinary drainage
    - Limited dexterity may mandate creation of continent catheterizable stoma for the urinary reservoir, especially in females
- Ileal conduit cutaneous vesicostomy
  - Conduit of ileum connecting dome of bladder to anterior abdominal wall
    - Continuous low-pressure drainage through incontinent ileal conduit urostomy requires stomal appliance for urinary collection

- Useful for those who cannot perform self-catheterization (ie, quadriplegia)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Sacral deafferentation with sacral nerve root stimulation
  - Deafferentation with dorsal rhizotomy abolishes spontaneous detrusor contraction, improving urinary storage
  - Nerve root stimulation allows control over detrusor contraction
  - Obstruction by sphincter may require adjunctive sphincteric ablation

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent prognosis if effectively treated
- Untreated, ~50% of men will develop significant complication

COMPLICATIONS

- Vesicoureteral reflux
- Renal insufficiency
- Urolithiasis
- Urosepsis

FOLLOW-UP

Patient Monitoring

- Annual evaluation
  - Urodynamic testing
    - Assure low intravesical pressure
  - Upper tract imaging (Ultrasound most comonly used; decreasing reliance on excretory urogram)
    - Rule out upper tract changes (calculi, hydroneprhosis)
- Serum chemistry
  - Confirm normal renal function and electrolyte balance

Patient Resources

N/A

REFERENCES

1. Schurch B, Hauri D, Rodic B, et al. Botulinum-A toxin as treatment of detrusor sphincter dyssynergia: A prospective study in 24 spinal cord injury patients. *J Urol.* 1996;155:1023–1029.
2. Chancellor M, Gajewski J, Ackman CF, et al. Long-term follow-up of the North American Multicenter UroLume Trial for the treatment of external detrusor-sphincter dyssynergia. *J Urol.* 1999;161:1545–1550.

ADDITIONAL READING

- Blaivas JG. The neurophysiology of micturition: A clinical study of 550 patients. *J Urol.* 1982;127:958–964.
- Consortium for Spinal Cord Medicine. Bladder management for adults with spinal cord injury: A clinical practice guideline for health care providers. Available at http://www.nxtbook.com/nxtbooks/pva/bladdermanagement/index.php, Accessed April 2013.
- Fowler C. Neurological disorders of micturition and their treatment. *Brain.* 1999;146:1213–1231.
- Kaplan SA, Chancellor MB, Blaivas JG. Bladder and sphincter behavior in patients with spinal cord lesions. *J Urol.* 1991;146:113–117.

See Also (Topic, Algorithm, Media)

- Detrusor-Sphincter Dyssynergia (DSD) Image ☼
- Guillain–Barré Syndrome (Transverse Myelitis), Urologic Considerations
- Multiple Sclerosis, Urologic Considerations
- Spinal Cord Injury, Urologic Considerations
- Urodynamics, Indications and Normal Values

CODES

ICD9

- 596.0 Bladder neck obstruction
- 596.54 Neurogenic bladder NOS
- 596.55 Detrusor sphincter dyssynergia

ICD10

- N31.8 Other neuromuscular dysfunction of bladder
- N31.9 Neuromuscular dysfunction of bladder, unspecified
- N36.44 Muscular disorders of urethra

CLINICAL/SURGICAL PEARLS

- DSD is always associated with NDO.
- Anticholinergic therapy and α-Adrenergic blockade are 1st-line medical therapy.
- If left untreated, ~50% of men will develop significant complication.

DIABETES MELLITUS, UROLOGIC CONSIDERATIONS

Thomas M. Facelle, MD
Mark L. Jordan, MD, FACS

BASICS

DESCRIPTION

- Hyperglycemia with secondary metabolic abnormalities
- Two subtypes including insulin deficiency (DM1) and insulin resistance (DM2)

EPIDEMIOLOGY

Incidence

- 30% with DM1 and 10–40% with DM2 will develop kidney failure.
- 59% with DM will have urologic complications/symptoms

Prevalence

8.3% of US population in 2010 was diabetic (1)

RISK FACTORS

- Likely genetic and environmental interplay for DM1
- Genetic predisposition for DM2
  - Environmental: Visceral obesity for DM2

Genetics

- DM1: Approx one-third genetic contribution
  - HLA-DR3, HLA-DR4
- Strong hereditary component for DM2
  - 70% twin concordance after age 40
  - Several loci identified affecting pancreatic B-cell function and propensity to visceral obesity

PATHOPHYSIOLOGY

- Urinary tract infections (UTIs)
  - Neutrophil dysfunction due to hyperglycemia
  - Patients with DM are at increased risk and are classified as “complicated” UTI due to risk of progression to more severe manifestations such as abscess, emphysematous pyelonephritis, and papillary necrosis
  - UTI increased incidence in women with DM but not men
  - 80% have upper tract infections
  - Often atypical organisms, eg, yeast
  - Risk of xanthogranulomatous pyelonephritis (XGP) with stones
- Erectile dysfunction (ED)
  - 3× more common in men with DM
  - 15% at age 30, 55% at age 60 (2)
  - 12% of men diagnosed with DM due to declining sexual function
  - Caused by peripheral neuropathy, arterial insufficiency, changes in cavernous smooth

muscle, and endothelial dysfunction
  – Increased rates of hypogonadism
• Voiding dysfunction
  – Sensory and motor neuropathy
  – Impaired sensation and detrusor function
  – Chronic bladder distension or overactivity
  – Incontinence prevalent in women (3)
• End-stage renal disease (ESRD)
  – DM most common cause (44%)
  – Preceded by onset of proteinuria
• Polyuria
  – In setting of glycosuria—osmotic diuresis
• Infertility
  – ED and androgen deficiency
• Bladder cancer
  – Increased incidence and mortality seen in men and women with DM (4)
  – DM medication pioglitazone associated with increased bladder cancer risk

ASSOCIATED CONDITIONS
• Obesity
• Metabolic syndrome
• New onset diabetes after transplant (NODAT)
  – Seen in up to 30% of nondiabetic renal transplant patients
• Papillary necrosis
• Retrograde ejaculation

GENERAL PREVENTION
• Glycemic control
• Weight reduction

DIAGNOSIS
HISTORY
• General
  – Polyuria, polydipsia
  – Weight loss, malaise
  – Family history
  – ED, especially in younger man
• UTI
  – Recurrent UTI (may be asymptomatic)
  – Fever, nausea, vomiting, flank pain
  – Dysuria, hematuria
• Voiding dysfunction
  – Urgency, frequency, weak stream, retention
• Bladder cancer
  – Hematuria, pioglitazone use

PHYSICAL EXAM

- Flank
  - CVA tenderness
- Abdomen
  - Distended bladder, bladder mass
- External genitalia
  - Phimosis, balanitis, yeast dermatitis
  - Testicular atrophy, varicocele
  - Peyronie plaques
- Rectal
  - Tone, bulbocavernosus reflex
- Prostate
  - Symmetry, nodules, tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- General
  - Fasting glucose >126 mg/dL
  - Oral GTT, 2-hr value >200 mg/dL
  - Microalbuminuria (30–300 mg/dL) predicts renal disease
- UTI
  - Urinalysis, urine culture, and sensitivities
  - BUN, creatinine
- ED
  - Consider testosterone level, esp if low libido
    - if low, follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- Voiding dysfunction
  - UA, C&S
  - Urine specific gravity if polyuric: Dilute if <1.007
  - Metabolic panel including serum creatinine
- Infertility
  - Testosterone, FSH, LH, prolactin
  - Semen analysis

Imaging

- UTI
  - Consider CT scan if symptoms severe to rule out urolithiasis and/or emphysematous pyelonephritis especially if flank pain
  - R/O papillary necrosis
- ED
  - Cavernosal Doppler ultrasound (select cases)
- Voiding dysfunction
  - Renal and bladder ultrasound

Diagnostic Procedures/Surgery

- Voiding dysfunction

- Post-void residual (PVR)
  - Via straight cath or bladder scan
  - Generally acceptable if <150 mL
- Voiding diary: Voiding volumes and frequency
- Uroflow
  - Normal 20–25 mL/s in men, 25–30 mL/s in women
  - Diminished if <10 mL/s
- Cystometrogram (CMG): Capacity, voiding pressure, detrusor instability

Pathologic Findings

- Diabetic nephropathy
  - Microangiopathy and glomerulopathy (5)
    - Thickened glomerlular capillary basement membrane; diffuse mesangial sclerosis; nodular glomerulosclerosis
  - Ischemia leads to tubular atrophy and interstitial fibrosis
  - Renal artery atherosclerosis

DIFFERENTIAL DIAGNOSIS

- UTI: Cystitis, pyelonephritis, emphysematous pyelonephritis, emphysematous cystitis, XGP, urolithiasis, papillary necrosis, perinephric abscess, sexually transmitted urethritis
- Voiding dysfunction: Bladder outlet obstruction, urethral stricture, neurogenic bladder, UTI, interstitial cystitis
- Polyuria: Excess fluid intake, diabetes insipidus, renal failure
- Infertility: Ejaculatory obstruction, retrograde ejaculation, varicocele, testicular causes

TREATMENT

GENERAL MEASURES

- Educate patients regarding urologic manifestations of diabetes
- Glycemic control
  - Dietary improvement, weight loss, exercise

MEDICATION

First Line

- UTI
  - DM is an underlying condition that makes any UTI a complicated UTI
  - Antibiotics (oral vs. intravenous)
  - Fluid resuscitation
- ED
  - Oral phosphodiesterase inhibitors (sildenafil, vardenafil, tadalafil, avandafil)
- Voiding dysfunction
  - α-Blockers if outlet obstruction (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin)
    - Add 5α-reductase inhibitor (finasteride, dutasteride) if significant benign prostatic enlargement (eg, >40 g)
  - Anticholinergics for detrusor overactivity
- Ejaculatory failure

  – α-Agonist (pseudoephedrine)
- Diabetic nephropathy
  – ACE inhibitor if proteinuria for renal protection

Second Line
- ED
  – Intraurethral suppository (MUSE)
  – Intracavernosal injection (alprostadil, Bimix, Trimix)
  – Testosterone replacement if androgen deficient
- Voiding dysfunction
  – α3-Agonist (mirabegron) for overactivity

SURGERY/OTHER PROCEDURES
- UTI
  – Retention: Catheter placement, suprapubic tube
  – Urolithiasis: Ureteral stent, nephrostomy tube, ureteroscopy, extracorporeal shock wave lithotripsy
  – XGP: Nephrectomy
- ED
  – Penile prosthesis
- Voiding dysfunction
  – Sacral nerve stimulation (InterStim)—efficacy for overactivity and retention
  – Bladder outlet obstruction: Transurethral resection of prostate, photoselective vaporization of prostate, etc.
  – Urinary diversion (uncommon)
- Infertility
  – Assisted reproduction
- Bladder cancer
  – Transurethral resection, cystectomy

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Voiding dysfunction
  – Bladder training, biofeedback, timed voiding
  – Clean intermittent catheterization (CIC) for retention
- Erectile dysfunction
  – Vacuum erection device

Complementary & Alternative Therapies
- UTI
  – Cranberry extract
- Voiding dysfunction
  – Acupuncture to sacral dermatome

ONGOING CARE

PROGNOSIS

- Good with tight glycemic control
- Onset of proteinuria typically heralds future renal failure
- Diabetic cystopathy typically permanent

COMPLICATIONS

- UTI
  - Upper tract infection
  - Staghorn calculi; XGP
  - Renal failure
- Voiding dysfunction
  - UTI
  - Upper tract damage/renal failure
  - Incontinence
  - Bladder stones
  - Atonic bladder
- Diabetic nephropathy
  - ESRD
  - Dialysis dependence

FOLLOW-UP

Patient Monitoring

- General
  - Periodic serum glucose
  - Hemoglobin A1C
  - Creatinine
  - Urine protein and microalbumin
- ED
  - Testosterone replacement: Check serum testosterone, prostate-specific antigen (PSA), serial hematocrit for elevation
- Voiding dysfunction
  - Symptomatology
  - BUN/creatinine
  - PVR
  - Repeat urodynamics as needed

Patient Resources

- Centers For Disease Control and Prevention, Diabetes Public Health Resource: http://www.cdc.gov/diabetes
- American Diabetes Association: http://www.diabetes.org
- National Diabetes Education Foundation: http://ndep.nih.gov/

REFERENCES

1. Masharani U. Diabetes mellitus and hypoglycemia. In: Papadakis MA, McPhee SJ, eds. *Current Medical Diagnosis and Treatment.* New York, NY: McGraw Hill, 2013.

2. Lue T. Physiology of penile erection and pathophysiology of erectile dysfunction. In: Wein, A, ed. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders, 2011.
3. Goldstraw MA, Kirby MG, Bhardwa J, et al. Diabetes and the urologist: A growing problem. *Br J Urol*. 2006;99:513–517.
4. Zhu Z, Zhang X, Shen Z, et al. Diabetes mellitus and risk of bladder cancer: A meta-analysis of cohort studies. *PLOS One*. 2013;8(2):e56662.
5. Alpers CE. The Kidney. In: Kumar V, Abbas AK, Fausto N, Aster J, eds. *Robbins & Cotran Pathologic Basis of Disease*, 8th ed. Philadelphia, PA: Saunders, 2009.

ADDITIONAL READING

• Brown JS, Wessells H, Chancellor MB, et al. Urologic complications of diabetes. *Diabetes Care*. 2005;28:177–185.
• Costabile R. Optimizing treatment for diabetes mellitus induced erectile dysfunction. *J Urol*. 2003;170:S35–S38.
• Michel MC, Mehlburger L, Schumacher H, et al. Effect of diabetes on lower urinary tract symptoms in patients with benign prostatic hyperplasia. *J Urol*. 2000;163(6):1725–1729.

See Also (Topic, Algorithm, Media)

• Diabetes Mellitus, Urologic Considerations Image ☼
• Erectile Dysfunction (ED)/Impotence
• Infertility, Urologic Considerations
• Neurogenic Bladder, General
• Pyelonephritis, Emphysematous
• Pyelonephritis, Xanthogranulomatous
• Urinary tract infection (UTI), Complicated, Adult
• Urinary tract infection (UTI), Complicated, Pediatric

CODES

ICD9

• 250.40 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
• 250.41 Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
• 585.6 End stage renal disease

ICD10

• E10.29 Type 1 diabetes mellitus w oth diabetic kidney complication
• E11.29 Type 2 diabetes mellitus w oth diabetic kidney complication
• N18.6 End stage renal disease

CLINICAL/SURGICAL PEARLS

• DM predisposes to urinary infections of greater severity with likely upper tract involvement.
• Most common voiding symptom is overactivity.
• ED may be the presenting sign of DM.
• Tight glycemic control is necessary to reduce progression of symptoms.

DISORDERS OF SEXUAL DEVELOPMENT (DSD)

Luigi Avolio, MD

BASICS

DESCRIPTION

- Congenital condition in which development of chromosomal, gonadal, or anatomic sex is atypical (1)
- Chromosomal sex is inconsistent with phenotypical sex
- DSD is the result of a discordance among the 3 sex determination processes (chromosomal, gonadic, and phenotypic)
- Ambiguous genitalia and intersex disorders are no longer considered correct terms
  - Classification
    - Sex chromosome DSD
    - XX DSD
    - XY DSD

EPIDEMIOLOGY

Incidence

- 1 in 5,000 live births
  - Congenital adrenal hyperplasia (CAH) represents 60–70% of neonatal DSD (1 case per 15,000 live births)

Prevalence

N/A

RISK FACTORS

- Family history of DSD
- In utero exposure to androgens
  - Ovarian tumors
  - Maternal ingestion

Genetics

- XX DSD
  - 21α-hydroxylase deficiency (21OHD), Mendelian Inheritance in Man, MIM #201910 (online reference http://www.ncbi.nlm.nih.gov/omim/)
  - CYP21 gene-chr.6p21.33. Autosomal recessive
  - 3β-hydroxysteroid dehydrogenase deficiency, MIM #201810, HSD3B2 gene-chr.1p12. Autosomal recessive
  - P450 oxidoreductase deficiency, MIM#613571, POR gene-chr.7q11.23. Autosomal recessive
  - 11β-hydroxylase deficiency, MIM#103900, CYP11B1 gene-chr.8q24.3. Autosomal dominant
  - Aromatase deficiency, MIM#613546, CYP19 gene-chr.15q21.2. Autosomal recessive
  - Familial glucocorticoid resistance, MIM + 138040, NR3C1 gene-chr.5q31.3

- XY DSD
  - Deficiency of 7-dehydrocholesterol reductase, MIM#270400, DHCR7 gene-chr.11q13.4. Autosomal recessive
  - Leydig cell hypoplasia, MIM#238320, LHCGR gene-chr.2p16.3. Autosomal recessive
  - Steroid 5α-reductase Type 2 deficiency, MIM#264600, SRD5A2 gene-chr.2p23.1. Autosomal recessive
  - Steroidogenic acute regulatory protein, MIM#201710, StAR gene-chr.8p11.23. Autosomal recessive
  - P450 side-chain cleavage deficiency, MIM#613743, CYP11A1 gene-chr.15q24.1. Autosomal recessive
  - 3β-hydroxysteroid dehydrogenase deficiency, MIM #201810, HSD3B2 gene-chr.1p12. Autosomal recessive
  - P450 oxidoreductase deficiency, MIM#613571, POR gene-chr.7q11.23. Autosomal recessive
  - 17α-hydroxylase/17,20-lyase deficiency, MIM#202110, CYP17A1 gene-chr.10q24.32. Autosomal recessive
  - 17β-hydroxysteroid dehydrogenase Type 3 deficiency, MIM#264300, HSD17B3 gene-chr.9q22.32. Autosomal recessive
  - Disorder of the Androgen Receptor (AR), MIM#300068, AR gene-chr.Xq12. X-linked recessive
  - Anti-müllerian hormone (AMH) gene or its receptor, MIM#300068, AMH gene-chr.19p13.3 (type I), AMHR2 gene-chr.12q13.13 (type II). Autosomal recessive (2).

ALERT
The possible risk of an immediate life-threatening adrenal crisis must be considered in case of neonatal salt-wasting CAH and the general status of the child, including hydration, blood pressure, and jaundice, should be documented.

PATHOPHYSIOLOGY

- XX DSD
  - Disorders of ovarian development
    - (ovotesticular DSD): Ovary may contain some testicular tissue (unilateral 50%—ovotestis on one side and normal gonad in the other side; lateral 20%—a testis on one side and an ovary on the other; bilateral ovotestis 30%) that secretes adequate amounts of testosterone and AMH
  - Disorders of androgen excess
    - 21-hydroxylase deficiency is the most common cause of 46XX DSD. Impaired cortisol biosynthesis relieves feedback inhibition and thus increases ACTH secretion, which leads to hyperplasia of the adrenals and to disordered steroidogenesis: As a consequence cortisol precursors are shunted to androgen synthesis.
- XY DSD
  - Disorders of testis development
  - Disorders of androgen synthesis
    - Deficiency of 7-dehydrocholesterol reductase (DHCR7) results in a failure of cholesterol synthesis

- Disorders of androgen action
- Persistent müllerian duct syndrome (PMDS)

ASSOCIATED CONDITIONS
- Turner syndrome, Klinefelter syndrome, Reifenstein syndrome
- Inguinal hernia
- Amenorrhea
- Infertility

GENERAL PREVENTION
- Prenatal treatment of fetuses at risk for CAH with dexamethasone
- Chorionic villus sample
- Amniocentesis

DIAGNOSIS
HISTORY
- Family anamnesis
  - DSDs, genital abnormalities, amenorrhea, sterility, hirsutism
  - Early infant deaths (missed adrenogenital syndrome)
- Maternal exposure to androgens
- History of maternal virilization (androgen-producing tumor)

PHYSICAL EXAM
- External genitalia
  - Phallic structure (length, breadth, and amount of erectile tissue)
    - Normal penile length is ≥ 2.5 cm, and normal penile diameter is ≥ 0.9 cm
    - Normal clitoral width is from 2 to 6 mm; length > 9 mm unusual
  - Position of urethral meatus
  - Number of orifices in the perineum and their characteristics
  - Labioscrotal folds (separated or fused)
  - Asymmetry (ovotesticular DSD can produce virilization on only one side)
- Gonads
  - Palpable gonads (testis, very rarely ovotestis)
- Abdomen
  - Mass referable to enlarged uterus

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Karyotype
- Serum levels of sodium, potassium, and 17-hydroxyprogesterone
- Androgens (testosterone, dihydrotesterone, androstenedione)
- Cortisol, gonadotrophins, and AMH levels
- Stimulation test with human chorionic gonadotropin (suspected defect of androgen production)

Imaging
- Abdominal/Pelvic ultrasound (utero presence)

- Cystogram/genitogram (visualization of vagina, sinus)
- MRI

Diagnostic Procedures/Surgery
- Laparoscopy to define internal anatomy
- Cysto/vaginoscopy to confirm anatomy and level of confluence of urogenital sinus
- Gonadal biopsy to analyze presence of ovarian and/or testicular tissue
- Skin biopsy to obtain cellular lines

Pathologic Findings
Identification of ovarian tissue, testicular tissue, ovotestes, or streak gonads according to related specific disorders

DIFFERENTIAL DIAGNOSIS
- Hypopituitarism
- Hypospadias
- Hydrocele and hernia
- Menstruation disorders
- Microphallus
- Gonadoblastoma

TREATMENT

GENERAL MEASURES
- Gender assignment avoiding hasty decision
- Expert evaluation by an experienced multidisciplinary team

MEDICATION
First Line
- Newborn with salt-wasting CAH
  - Fluid and electrolytes replacement
  - Glucocorticoid and mineralocorticoid replacement
    - Hydrocortisone 10 mg/m^2/d
    - Fludrocortisone 0.1–0.2 mg/d
    - Oral sodium chloride, 1–2 g/d added to formula or breast milk

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Masculinizing genitoplasty (between the ages of 6 and 18 mo)
  - Hormonal treatment with testosterone preparation to stimulate phallus
  - Surgical excision of müllerian structures
  - Phalloplasty (hypospadias repair, chordee correction, scrotal transposition)
  - Orchidopexy
- Feminizing genitoplasty (during the 1st 6 mo of life) (3)
  - Clitoroplasty preserving innervation to reduce the size of the gland and shaft
  - Vaginoplasty and labioplasty to separate vagina and urethra from the common urogenital

sinus
- Gonads
  - 46XX DSD: Normal ovaries, no treatment necessary
  - 46XY DSD:
    - Female gender assigned: Orchiectomy (timing is subject of debate)
    - Male gender assigned: Orchidopexy
  - Ovotesticular DSD:
    - Gonadal biopsy
    - Excision of dysgenetic gonads (streak)
- Müllerian remnants
  - Small asymptomatics are managed conservatively
  - Symptomatic remnants are treated surgically (endoscopic incision or unroofing, laparoscopic/robotic excision)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Some patient groups strongly advocate to delay any surgical procedures until patients are competent to provide informed consensus

ONGOING CARE

PROGNOSIS

Many patients can remain fertile (CAH, some ovotesticular DSD, XY DSD 5α-RD)

COMPLICATIONS

- Acute adrenal insufficiency in CAH not adequately treated
- Damages to clitoral innervation (clitoroplasty)
- Stenosis of the vaginal introitus (vaginoplasty)
- Meatal stenosis, fistula (hypospadias repair)
- Rectal injury (urogenital sinus mobilization)

FOLLOW-UP

Patient Monitoring

- Sexual function (adequate vaginal introitus, adequate penis reconstruction)
- Risk of gonadoblastoma in gonadal dysgenesis is 12% (occurrence of neoplasia is primarily associated with the Y chromosome containing karyotypes)
- Lifelong psychosocial support mandatory for all patients with DSD

Patient Resources

- http://www.hopkinschildrens.org (all DSDs)
- http://www.accordalliance.org (all DSDs)
- http://www.isna.org (all DSDs)

- http://www.caresfoundation.org (CAH)
- http://www.ahn.org.uk (CAH)
- http://heainfo.org (hypospadias and epispadias)
- http://www.aisdsd.org (androgen insensitivity DSD)

REFERENCES

1. Hughes IA, Houk C, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Arch Dis Child*. 2006;91:554–563.
2. Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. *Best Pract Res Clin Endocrinol Metab*. 2010;24:197–218.
3. Romao RL, Salle JL, Wherrett DK. Update on the management of disorders of sex development. *Pediatr Clin North Am*. 2012;59:853–869.

ADDITIONAL READING

- Auchus RJ, Chang AY. 46,XX DSD: the masculinised female. *Best Pract Res Clin Endocrinol Metab*. 2010;24:219–242.
- Barbaro M, Wedell A, Nordenström A. Disorders of sex development. *Semin Fet al Neonatal Med*. 2011;16:119–127.
- Barthold JS. Disorders of sex differentiation: a pediatric urologist's perspective of new terminology and recommendations. *J Urol*. 2011;185:393–400.
- http://www.ncbi.nlm.nih.gov/omim/ (Online Mendelian Inheritance in Man®)

See Also (Topic, Algorithm, Media)

- Androgen Insensitivity Syndrome (AIS; OR Androgen Resistance Syndrome), Complete (CAIS) and Partial (PAIS)
- Congenital Adrenal Hyperplasia
- Disorders of Sexual Development (DSD) Image
- Disorders of Sexual Development (DSD) Algorithm
- Müllerian Duct Remnants and Persistent Müllerian Duct Syndrome (PMDS)
- Pseudohermaphroditism, Male and Female

CODES

ICD9

- 255.2 Adrenogenital disorders
- 259.50 Androgen insensitivity, unspecified
- 752.7 Indeterminate sex and pseudohermaphroditism

ICD10

- E25.0 Congenital adrenogenital disorders assoc w enzyme deficiency
- E34.50 Androgen insensitivity syndrome, unspecified
- Q56.4 Indeterminate sex, unspecified

CLINICAL/SURGICAL PEARLS

- DSD should be managed by a specialized multidisciplinary team.

- Gender assignment should be made after thorough investigation by the team.
- DSD is a heterogeneous group of conditions with different underlying molecular causes. Many disease genes remain to be identified.
- Infants with a DSD and who present with truly ambiguous genitalia are a rare occurrence.

DYSFUNCTIONAL ELIMINATION SYNDROME

Jennifer A. Hagerty, DO

BASICS

DESCRIPTION

- Dysfunctional voiding; various symptoms from mild daytime frequency and postvoid dribbling to daytime and nighttime wetting, urgency, urge incontinence, pelvic holding maneuvers, and urinary tract infections (UTIs)
- Sometimes referred to as bowel bladder dysfunction (BBD).
- Dysfunctional voiding often associated with bowel dysfunction; constipation, encopresis, or fecal impaction (1)[C]
  - Constipation and rectal dilation interferes with normal bladder function
  - No identifiable neurologic cause

EPIDEMIOLOGY

Incidence

Constipation is present in up to 50% of children with dysfunctional voiding (2)[C]

Prevalence

20–30% school-aged children have dysfunctional voiding (3)[C]

RISK FACTORS

- UTIs
- Sexual abuse
- Attention deficit/hyperactivity disorder
- Stressors during or after toilet training

Genetics

- Ochoa syndrome, a genetic disorder with an autosomal recessive inheritance pattern
  - Associated with dysfunctional voiding

PATHOPHYSIOLOGY

- Voiding dysfunction (variable etiologies):
  - Small bladder capacity
  - Large bladder capacity secondary to urine holding
  - Discoordinated voiding with difficulty relaxing the sphincter during voiding
- Often associated with constipation
  - Rectum close to posterior wall of bladder
  - Large amount stool:
    - Obstruction by compression of the bladder and bladder neck
    - Or bladder instability leading to urgency and frequency

ASSOCIATED CONDITIONS

- Vesicoureteral reflux (VUR)
- UTIs

- Encopresis
- Incontinence
- VUR
- Urge syndrome

GENERAL PREVENTION
None have been identified

DIAGNOSIS
HISTORY
- Present typically after toilet training
- Diurnal and/or nocturnal enuresis
- Frequency and urgency
- Hesitancy
- UTIs
- Difficulty stooling, hard or infrequent stools
- Encopresis

PHYSICAL EXAM
- Typically normal physical exam
  - Evaluate for neurologic dysfunction
  - Examine the external genitalia for anatomic causes of symptoms
  - Evaluate for a distended bladder and palpable stool
  - Consider rectal exam for fecal retention

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Urinalysis and urine culture; rule out bacteriuria and glucosuria

Imaging
- Renal/bladder ultrasound; evaluate for hydronephrosis, thickened and/or distended bladder, post-void residual, stool in the rectum
- MRI lumbar spine if concern for a neurogenic cause to evaluate for a tethered cord
- Voiding cystourethrogram to evaluate for VUR in patients with febrile UTIs.
  - Also information on bladder capacity and emptying, and appearance of the bladder and urethra
  - Spinning top urethra; widening of the urethra in females during voiding

Diagnostic Procedures/Surgery
- Voiding and stooling diary to assess frequency and volume of voids and stooling frequency and consistency
- Uroflowmetry; evaluate pattern
  - Flow rates different than adults and less reliable; curve more diagnostic
    - Bell shaped—normal
    - Tower shaped—overactive bladder
    - Low flat curve—outlet obstruction
    - Staccato pattern—sphincter overactivity

    - Interrupted flow—underactive bladder
- Urodynamics; patients refractory to conventional therapy
  – Evaluate the filling and emptying phases of the bladder
  – Can be done in conjunction with fluoroscopy

DIFFERENTIAL DIAGNOSIS
- Nonneurogenic neurogenic bladder
- Neurogenic bladder
- Ochoa syndrome
- Overactive bladder
- Giggle Incontinence

TREATMENT

GENERAL MEASURES
- Behavioral modification: Education on voiding patterns
  – Timed voiding
  – Correct positions to void
  – Relaxation techniques
  – Proper hydration
- Bowel Management
  – Education on correlation between the bladder and bowel activity
  – Daily toilet time
  – Dietary modifications; high fiber

MEDICATION

First Line
- *Treatment of constipation prior to medications for bladder symptoms; disimpaction followed by maintenance therapy*
  – *Initial cleanout with laxatives and enemas*
  – *Maintain soft daily stools with a combination of fiber, fluids, laxatives, and softeners*
- Antimuscarinics; overactive bladders
  – Reduce the intensity and frequency of bladder contractions
- α-Adrenergic blockers; bladder neck obstruction
  – Relaxation of the bladder neck to improve bladder emptying
- Prophylactic antibiotics; prevention of recurrent UTIs until dysfunctional elimination improved

Second Line
- Tricyclic antidepressants for urge incontinence
  – Mechanism not known; not FDA approved in children

SURGERY/OTHER PROCEDURES
- Biofeedback
- Transcutaneous electrical nerve stimulation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Clean intermittent catheterization with impaired bladder contractility

Complementary & Alternative Therapies

- Acupuncture
  – Low utility in children given use of needles
- Probiotics; prevention of UTIs and treatment of constipation
- Cranberry supplements; potential for UTI prevention

ONGOING CARE

PROGNOSIS

Most children have resolution of symptoms in a short period of time with behavioral modifications; however, some children may have persistence requiring more intensive management.

COMPLICATIONS

- UTIs
- Urinary incontinence
- Urinary retention
- Hydronephrosis

FOLLOW-UP

Patient Monitoring

- Voiding/stooling diary
- Uroflowmetry
- Post-void residual monitoring

Patient Resources

- http://kidshealth.org/parent/general/sick/constipation.html
- http://kidshealth.org/parent/medical/kidney/recurrent_uti_infections.html
- http://www.medicine.virginia.edu/clinical/departments/urology/patients/peds-urology/parents/DysfunctionalEliminationSyndrome-page

REFERENCES

1. Koff SA, Wagner TT, Jayanthi VR. The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. *J Urol.* 1998;160:1019.
2. Chase JW, Homsy Y, Siggaard C, et al Functional constipation in children. *J Urol.* 2004;171:2641.
3. Lee SD, Sohn DW, Lee JZ, et al. An epidemiological study of enuresis in Korean children. *BJU Int.* 2000;85:869–873.

ADDITIONAL READING

- Ballek NK, McKenna, PH. Lower urinary tract dysfunction in childhood. *Urol Clin North Am.* 2010;37:215–228.

• Nijman RJ. Diagnosis and management of urinary incontinence and functional fecal incontinence (encopresis) in children. *Gastroenterol Clin North Am.* 2008;37:731–748.

See Also (Topic, Algorithm, Media)
• Encopresis, Urologic Considerations
• Enuresis, Pediatric
• Incontinence, Urinary, Pediatric
• Urinary Retention, Pediatric
• Urinary Tract Infection, Pediatric
• Vesicoureteral Reflux, Pediatric
• Dysfunctional Elimination Syndrome Image

CODES

ICD9
• 599.0 Urinary tract infection, site not specified
• 788.3 Urinary incontinence
• 788.41 Urinary frequency

ICD10
• N39.0 Urinary tract infection, site not specified
• R32 Unspecified urinary incontinence
• R35.0 Frequency of micturition

CLINICAL/SURGICAL PEARLS

• Constipation is often associated with bladder dysfunction in children.
• Treatment of constipation alone may lead to complete resolution of urinary complaints.
• Vesicoureteral reflux may resolve after treatment of voiding dysfunction.
• Education of the correlation between stooling patterns and voiding complaints is a very important part of treatment; if understanding is poor there is often low compliance.

DYSORGASMIA (PAINFUL ORGASM), MALE

John Patrick Mulhall, MBBCh, FACS, FECSM

BASICS

DESCRIPTION

- Dysorgasmia specifically refers to pain that occurs immediately preceding, at or immediately following orgasm.
- The pain is usually located in the penis or testicles but may be present in the lower abdomen, groin, perineum, or elsewhere.
- The severity of pain ranges from mild and of nuisance value to crippling and may last seconds to hours after orgasm.
- The condition is best identified and studied in the postradical prostatectomy setting.
- Ejaculatory pain may be seen in other conditions such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), or NIH category III prostatitis, and is discussed in Section II ("Ejaculation, painful").

EPIDEMIOLOGY

Incidence

- The most frequent correlate of dysorgasmia is radical prostatectomy and this condition occurs in about 10–15% of patients.
- In this population, the pain is usually self-limiting with most sufferers experiencing complete resolution by 2 yr postoperatively

Prevalence

N/A

RISK FACTORS

- Radical prostatectomy
- Prostate radiation
- Chronic pelvic pain syndrome (CPPS)

Genetics

None known

PATHOPHYSIOLOGY

- While unproven one of the postulated mechanisms is that the pain is related to pelvic floor or bladder neck spasm.
  – This is the rationale for the use of α-blockers.
- Dysorgasmia decreases in frequency and degree over time after RP.

ASSOCIATED CONDITIONS

- Chronic pelvic pain syndrome (NIH category III prostatitis)
- Erectile dysfunction (1)
- Prostate cancer

GENERAL PREVENTION

None known

DIAGNOSIS

HISTORY

- Medical history
- Focusing on assessment of orgasmic pain location, severity and duration.
- Prior history of radical prostatectomy, radiation therapy, or CPPS.

PHYSICAL EXAM

- General physical exam
- Genital exam (although often there are no specific findings)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

None are useful

Imaging

None are useful

Diagnostic Procedures/Surgery

None

Pathologic Findings

None

DIFFERENTIAL DIAGNOSIS

- Penile pain:
  - Penile compressive neuropathy
  - Penile trauma
  - Peyronie disease
  - Sexually transmitted infection (STI)
  - Ureteral stone
- Testicular pain:
  - Epididymitis
  - Orchitis
  - Testicular tumor
  - Trauma

TREATMENT

GENERAL MEASURES

Reassurance that the condition is most often self-limiting

MEDICATION

First Line

- α-Blockers (daily initially; if successful attempt on-demand) (2).
- Up to 70% of men using α-blockers will have significant improvement in pain.
- Side effects include syncope, orthostasis, retrograde ejaculation, asthenia, and nasal

congestion
  – Alfuzosin 10 mg/d
  – Doxazosin start 1 mg/d to max 8 mg
  – Silodosin 8 mg/d
  – Tamsulosin start 0.4 mg to max 0.8 mg
  – Terazosin start 1 mg/d to max 20 mg

Second Line
- Centrally acting pain relievers
- Optimum dose and duration not established
- Gabapentin
  – 900 to 1,800 mg/d and given in divided doses (3 times a day) using 300 or 400 mg capsules
- Pregabalin
  – Begin dosing at 150 mg/d, increase to 300 mg/d within 1 wk. Maximum dose of 600 mg/d

SURGERY/OTHER PROCEDURES
Case reports exist of excision of retained seminal vesicle following radical prostatectomy with relief of symptoms (3)

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Recovery is expected following radical prostatectomy.
- At 24 mo, a statistically significant decrease in symptoms was seen in one study (4).
  – 72%, 26%, and 7% of patients still complained of pain at 12, 18, and 24 mo, respectively.

COMPLICATIONS
N/A

FOLLOW-UP
Patient Monitoring
Routine radical prostatectomy follow-up appears most appropriate.

Patient Resources
N/A

REFERENCES
1. Mehta A, Stember DS, O'Brien K, et al. Defining the aetiology of erectile dysfunction in

men with chronic pelvic pain syndrome. *Andrology*. 2013;1(3):483–486.
2. Barnas J, Parker M, Guhring P, et al. The utility of tamsulosin in the management of orgasm-associated pain: A pilot analysis. *Eur Urol.* 2005;47:361–365.
3. Yamamoto A, et al. Case Reports: Robot-Assisted Seminal Vesiculectomy for Dysorgasmia Following Seminal Vesicle-Sparing Radical Prostatectomy bjui. org: 29/01/2013. DOI: 10.1002/BJUIw-2012-072-web
4. Matsushita K, Tal R, Mulhall JP. The evolution of orgasmic pain (dysorgasmia) following radical prostatectomy. *J Sex Med.* 2012;9(5):1454–1458.

ADDITIONAL READING

- Anothaisintawee T, Attia J, Nickel JC, et al. Management of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis. *JAMA*. 2011;305:78–86.
- Salonia A, Burnett AL, Graefen M, et al. Prevention and management of postprostatectomy sexual dysfunctions part 2: Recovery and preservation of erectile function, sexual desire, and orgasmic function. *Eur Urol.* 2012;62:273–286.

See Also (Topic, Algorithm, Media)

- Ejaculatory Disturbances (Delayed, Decreased, or Absent)
- Ejaculation, Painful
- Post-orgasm Illness Syndrome (POIS)
- Prostatitis, Chronic Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B)

CODES

ICD9

- 607.89 Other specified disorders of penis
- 608.89 Other specified disorders of male genital organs
- 789.09 Abdominal pain, other specified site

ICD10

- N48.89 Other specified disorders of penis
- N50.8 Other specified disorders of male genital organs
- N53.12 Painful ejaculation

CLINICAL/SURGICAL PEARLS

- Dysorgasmia is common after radical prostatectomy.
- It is usually self-limiting.
- It is often responsive to α-blocker therapy.

DYSPAREUNIA, FEMALE

Bradley C. Gill, MD, MS
Sandip P. Vasavada, MD, FACS

BASICS

DESCRIPTION

- Dyspareunia is defined as pain associated with sexual intercourse.
  - Most often used in associated with female sexual dysfunction and is the focus of this section.
- Present since 1st (primary) intercourse or acquired (secondary) thereafter.
- Etiologies can be physiologic and/or psychological.

EPIDEMIOLOGY

Incidence

Lacking disclosure to clinicians and treatment pursuit suggests underestimation

Prevalence

Up to a 60% prevalence in women, but varies widely by sample and definition

RISK FACTORS

- Menopause (physiologic or iatrogenic)
- Physical trauma (physiologic or iatrogenic)
- Psychological trauma (supporting evidence is mixed)
- Tissue irritation (infection, inflammation, malignancy, etc.)
- Urogenital anatomy (congenital)

Genetics

Early menopause should be considered

PATHOPHYSIOLOGY

- Pain results from irritation or trauma to the female reproductive tissues.
- Can be entrance, vaginal, or deep-thrust dyspareunia per the etiology.

ASSOCIATED CONDITIONS

- Vaginal atrophy
- Urogenital malformations
- Posttraumatic stress disorder (prior physical or psychological trauma)
- Pelvic inflammatory disease
- Endometriosis

GENERAL PREVENTION

- Maintenance of vaginal mucosal integrity
- Good hygiene and health maintenance

DIAGNOSIS

HISTORY

- Description of pain
  - Specific localization: Superficial, deep, anterior, posterior
  - Timing and duration: When starting, throughout, after finishing
  - Consistency with intercourse: Occasional; sometimes, always
  - Character: Burning, sharp, aching, throbbing
  - Associations: Discharge, bleeding, urinary symptoms, bowel symptoms
- Factors altering the pain
  - Positioning, specific maneuvers, location
  - Use of lubricants, condoms, sex toys, hygiene products
  - Specific partners or partner-related factors
  - Timing of menstrual cycle
  - Bowel or bladder habits
- Urogenital conditions
  - Sexually transmitted or urinary tract infections
  - Complicated pregnancies
  - Endometriosis
  - Uterine fibroids
  - Inflammatory bowel disease
- Urogenital interventions
  - Surgery or radiation
  - Injections or topical therapy
- Urogenital trauma
  - Vaginal childbirth injuries
  - Difficult or forced intercourse
- Systemic conditions
  - Menopause (physiologic or iatrogenic)
  - Pain disorders or fibromyalgia
  - Cancer
  - Other chronic diseases
- Current or prior abuse
  - Sexual abuse
  - Verbal or physical abuse

PHYSICAL EXAM

- Visual inspection of external genitalia
  - Distribution of pubic hair
  - Diffuse vulvo-vestibulitis
  - Ulcerations, pustules, discharge, or bleeding
  - Inflamed Bartholin or Skene glands
  - Prolapsed urethra, vagina, or cervix
  - Skin or mucosal lesions suspicious for cancer
- Speculum exam
  - Diffuse vaginitis or cervicitis
  - Mucosal rugae, moisture, thinning, or excoriation
  - Ulcerations, pustules, discharge, or bleeding

  - Cystocele, rectocele, or enterocele
  - Vaginal wall masses
  - Mucosal lesions suspicious for cancer
- Diagnostic sampling with cervical surface scrapings, brushings, and culture swabs
  - Ulcerations, pustules, or discharge
  - Masses, skin changes, mucosal changes, bleeding
- Palpation of external genitalia, vaginal sidewalls, pelvic floor muscles, cervix, and ovaries
  - Bartholin or Skene gland tenderness
  - Urethral or vaginal sidewall mass
  - Surgically placed foreign bodies
  - Pelvic floor muscle tension, spasm, or tenderness
  - Cervical motion, ovarian, or adnexal tenderness
  - Vaginal cul-de-sac mass or tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture to screen for infection or cystitis
- Endocervical swabs for gonorrhea, chlamydia, or bacterial vaginosis
- Cervical scrapings or brushings for malignancy and human papilloma virus
- Vaginal pH, wet mount, or whiff test for bacterial or fungal infection

Imaging

- Transvaginal ultrasound for reproductive organ or pelvic masses
- Transabdominal ultrasound for abdominal masses
- Pelvic magnetic resonance imaging for urethral diverticula or pelvic masses

Diagnostic Procedures/Surgery

- Cystourethroscopy for cystitis, urethritis, urethral diverticula
- Double balloon urethrography for urethral diverticula
- Colposcopy for human papilloma virus or uterocervical malignancies
- Colonoscopy for inflammatory bowel disease or colorectal malignancy
- Diagnostic laparoscopy for endometriosis or pelvic masses

DIFFERENTIAL DIAGNOSIS

- Congenital
  - Vaginal agenesis, vaginal malformation, imperforate hymen, rigid hymen, retroverted uterus
- Gynecologic
  - Structural: Hymenal remnant, introital or vaginal stenosis, prolapse, childbirth, adhesions
  - Cellular: Vaginal atrophy, lichen sclerosis, vulvar hyperplasia, cancer
  - Infectious: Sexually transmitted, viral, bacterial vaginosis, fungal, pelvic inflammatory disease
  - Allergic: Contraceptive device, condom, latex, semen, hygiene product, sex toy
  - Reproductive: Endometriosis, fibroids, ectopic pregnancy, adnexal cyst, ovarian cyst
  - Iatrogenic: Implanted mesh erosion, exposed suture, postoperative fistula
- Urologic
  - Urethral prolapse, urethral caruncle, urethral diverticulum, urethral cancer, urethritis,

cystitis
- Colorectal
  – Inflammatory bowel disease, abscess, hemorrhoids, constipation, rectal cancer
- Musculoskelet al
  – Vaginismus, pelvic floor muscle spasm, trauma, chronic pain disorder, fibromyalgia
- Psychological
  – Posttraumatic stress disorder, sexual aversion disorder, genital sexual arousal disorder

TREATMENT

GENERAL MEASURES
- Behavioral (1,2)
  – Identify and eliminate any allergy-related hygienic or sexual practices
  – Encourage using water-based lubrication or hypoallergenic products
  – Utilize infection prophylaxis like postcoital voiding when appropriate for UTI issues
  – Psychological counseling, couples therapy, or relaxation exercises as indicated
- Careful consideration of replacing condoms or other barrier devices with another contraceptive

MEDICATION
First Line
- Ospemifene is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
  – 1 tablet (60 mg) taken orally once daily with food
  – Do not use estrogens or estrogen agonist/antagonist or fluconazole concomitantly
- Appropriate dose and duration of antibiotics or antifungals for infection
- Topical estrogen for atrophy considering benefits over systemic forms
- Topical corticosteroids for vulvar hyperplasia or testosterone for lichen sclerosis

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Laparoscopic endometriosis excision or ablation
- Laparoscopic lysis of adhesions if indicated
- Laparoscopic sacral colpopexy for problematic retroverted uterus
- Urethral diverticulectomy if indicated
- Excision of implanted mesh, eroded sutures, or other foreign body
- Trigger point injections for muscle spasm

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Daily passive dilation with progressive vaginal dilators for stenosis
- Use of pessary for problematic retroverted uterus
- Pelvic floor physiotherapy or biofeedback for muscle spasms

- Ultrasound or electrical stimulation for persistent muscle spasm
- Tibolone (synthetic steroid) is commonly used in Europe in postmenopausal women with desire and arousal disorders

Complementary & Alternative Therapies

- Education, sex therapy, psychotherapy, and cognitive behavioral therapy are also important in the multidisciplinary management of sexual dysfunction including those with a history of sexual abuse.
- Currently there are limited studies on the effectiveness of herbal remedies to aid female sexual dysfunction in general.

ONGOING CARE

PROGNOSIS

- Results vary with etiology and treatment of many is long term
- Multimodal approach to any etiology should be most beneficial

FOLLOW-UP

Patient Monitoring

- Frequent follow-up with initiation of new behavioral or medical therapies is best
- Upon resolution and improved patient satisfaction follow-up may be spaced out

REFERENCES

1. Dhingra C, Kellogg-Spadt S, McKinney TB. Urogynecological causes of pain and the effect of pain on sexual function in women. *Female Pelvic Med Reconst Surg*. 2012;18(5):259–267.
2. Fugl-Meyer KS, Bohm-Starke N, Damsted Petersen C. Standard operating procedures for female genital sexual pain. *J Sex Med*. 2013;10(1):83–93.

ADDITIONAL READING

- Frenkl TL, Potts JM. Sexually transmitted infections. In: Wein A, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds, *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier/Saunders; 2012. Chapter 13. pp. 402–416.
- Moore CK. Female sexual function and dysfunction. In: Wein A, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds, *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier/Saunders; 2012. Chapter 30. pp. 823–833.
- Rovner ES. Bladder and female urethral diverticula. In: Wein A, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds, *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier/Saunders; 2012. Chapter 78. pp. 2262–2289.

See Also (Topic, Algorithm, Media)

- Dysorgasmia
- Dyspareunia Algorithm
- Dyspareunia, Male
- Sexual Dysfunction, Female
- Urinary Tract Infections
- Urogenital Prolapse
- Urethra, Diverticulum, Female (Urethral Diverticulum)

• Vaginal Atrophy, Urologic Considerations

CODES

ICD9

• 302.76 Dyspareunia, psychogenic
• 625.0 Dyspareunia
• 627.3 Postmenopausal atrophic vaginitis

ICD10

• F52.6 Dyspareunia not due to a substance or known physiol cond
• N94.1 Dyspareunia
• N95.2 Postmenopausal atrophic vaginitis

CLINICAL/SURGICAL PEARLS

• Do not discount behavioral interventions.
• Topical estrogen can work wonders.
• Changing the hygiene routine can help.

DYSURIA

Mohamed S. Ismail, MBChB, MRCS, PhD
Francis Xavier Keeley, Jr., MD, FRCS

BASICS

DESCRIPTION

- Dysuria is the symptom of discomfort, burning, or pain during micturition.
- It is often associated with other lower urinary tract symptoms.

EPIDEMIOLOGY

Incidence

- Dysuria accounts for up to 15% of visits to family doctors
- In men the incidence increases with age and 5% of men seeks medical help for dysuria

Prevalence

In the United States the reported prevalence of dysuria is 25%

RISK FACTORS

See associated conditions

Genetics

N/A

PATHOPHYSIOLOGY

- Dysuria results from the irritation of the urethra or bladder by inflammation or irritants
- The transient receptor potential subfamily vanilloid type 1 receptor (TRPV1) exists in the urethra
- Inflammatory mediators such as leukotrienes activate TRPV1 and result in pain and burning during voiding

ASSOCIATED CONDITIONS

- Bladder or urethral cancer
- BPH
- Connective tissue diseases
  - Behçet disease
  - Reiter (reactive arthritis) syndrome
- Pregnancy
- STD
- Urethral stricture disease
- Urinary tract infection
- Urolithiasis

GENERAL PREVENTION

- Hydration to flush out the urinary tract
- Women should wipe from front to back after bowel movements
- Women should empty the bladder immediately after intercourse

- Keep the genital area clean and dry
- Avoid irritating soap and vaginal products
- Treat infection with antibiotics

DIAGNOSIS

ALERT
Unexplained dysuria may indicate carcinoma in situ of the bladder.

HISTORY

- The cause of dysuria can be challenging to diagnose
- Dysuria is frequently associated with other lower urinary tract symptoms such as urinary frequency, hesitancy, urgency, and nocturia (1)
- Age and sex (2)
  - Dysuria is more common in women
  - The most common cause in young women is urethritis, in middle age women gynecologic causes, and in elderly women urinary tract infection
  - The most common cause in young men is urolithiasis and in elderly are benign prostatic hyperplasia (BPH) and urinary tract infection
  - Dysuria in children may suggest sexual abuse
- Onset
  - Sudden onset symptoms suggest acute bacterial infection
  - Gradual onset symptoms may suggest Chlamydia trachomatis infection
- Timing of pain
  - At the onset of voiding indicates inflammation such as urethritis
  - At the middle of voiding indicates obstruction such as urethral stricture or BPH
  - At the end of voiding usually indicates bladder pathology such as cystitis
- Location of pain
  - External discomfort associated with vaginal infection or inflammation
  - Internal discomfort indicates bladder or urethral origin
- Associated symptoms
  - Frequency, urgency, and suprapubic pain suggest diagnosis of interstitial cystitis
  - Frequency, nocturia, and reduced flow suggest bladder outlet obstruction or urethral stricture
  - Fever, rigor, and flank pain suggest pyelonephritis or urolithiasis
  - Urethral discharge in young age indicates sexually transmitted diseases
  - Vaginal irritation, discharge, and dyspareunia indicate genital tract infection such as:
  - Vulvo-vaginitis, atrophic vaginitis, or sexually transmitted diseases
  - Dyspareunia + dribbling + dysuria (“3 Ds”) suggests a urethral diverticulum in females
  - The presence of joint or back pain may indicate connective tissue diseases
  - Significant urgency occurs as a result of irritation of the bladder trigone and posterior urethras due to inflammation, bladder stone, or tumor.
  - Oral and genital ulcers, uveitis, vasculitis with dysuria suggest Behçet disease
- History of recent surgery such as urethral instrumentation or continence surgery and history of recent catheterization should be obtained to rule out infection, inflammation, and

urethral erosion.
- Sexual history
  – Sexual behavior
  – The use of contraceptives, diaphragms, condoms, etc.
  – Previous history of sexually transmitted diseases and history of urethral scarring
- Drug history: Drugs associated with dysuria are ticarcillin, penicillin G, cyclophosphamide, saw palmetto, dopamine

PHYSICAL EXAM
- General exam and observation should be recorded
- Abdominal exam
  – Inspection: Look for skin rash and abdominal distension which indicate full bladder
  – Palpation: Feel for loin tenderness, palpable bladder, suprapubic tenderness, abdominal masses, and midline pulsation
  – Percussion: To detect full bladder or any other abdominal mass
  – Auscultation: To rule out other causes of abdominal distension
- Male genital exam
  – Look for any penile lesions, urethral discharge, meatal stenosis, balanitis, perineal bruising, and abnormalities in the foreskin
  – Examine the scrotum for swelling, tenderness, and testicular masses
  – Digital rectal exam to rule out prostatitis, benign prostatic enlargement, and prostate cancer
- Female genital exam (3)
  – Look for vaginal and urethral discharge
  – Vulval lesions such as ulcers, vesicles, and rash
  – Identify urethral lumps that indicate urethral caruncle, diverticulum, or stones. Look for signs of atrophic vaginitis
  – Pelvic exam: Adnexal and cervical tenderness which indicates pelvic inflammatory disease, urethral tenderness, and urethral masses
  – Bimanual exam to look for pelvic masses

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urine dipstick is a useful and easy test to screen for urinary tract infection
  – A positive test for nitrites is suggestive of urinary tract infection. A negative test does not rule out infection
  – A positive leukocyte esterase suggests the presence of white blood cells in the urine which is associated with inflammation. It has 75% sensitivity to detect infection
- Urine microscopy
  – Pyuria is defined by the presence of 3–5 white blood cells per high-power field
  – Hematuria is defined by the presence of 3–5 red blood cells per high-power field
  – Sterile pyuria is present in urolithiasis, transitional cell carcinoma, and atypical microorganisms such as tuberculosis
- Gram staining demonstrate the urinary pathogens
- Urine culture and sensitivity identify the causative microorganism of urinary tract infection and its antimicrobial sensitivities. Bacterial count of more than 1,000 colony forming units

is diagnostic
- Vaginal and urethral smears: Important for the diagnosis of sexually transmitted diseases
- Vaginal PH measurement, potassium hydroxide microscopy, and yeast culture are indicated in patients with unexplained or recurrent dysuria
- Chlamydia: Nucleic amplification testing (NAAT) of vaginal swabs for women or 1st-catch urine for men

Imaging
- Renal ultrasound scan in suspected cases of upper tract pathology, urolithiasis, and bladder abnormalities
- Plain abdominal x-ray in suspected cases of urolithiasis and emphysematous pyelonephritis and cystitis
- Other imaging modalities can be arranged according to the suspected diagnosis such as voiding cystourethrography, retrograde urethrogram, computerized tomogram with intravenous contrast, magnetic resonance imaging

Diagnostic Procedures/Surgery
Cystoscopy: Allows careful assessment of the urethra and bladder.

Pathologic Findings
Based on specific diagnosis

DIFFERENTIAL DIAGNOSIS
- Disease of the urinary tract
  - Urinary tract infection
  - Urolithiasis, bladder calculus, crystalluria
  - Interstitial cystitis
  - Prostatitis (acute, chronic bacterial and chronic pelvic pain syndrome)
  - Malignancy (carcinoma in situ, prostate cancer, urethral cancer)
- Diseases of the genital tract
  - Sexually transmitted disease: Gonorrhea, Chlamydia, and herpes simplex infection
  - Vulvo-vaginitis, cervicitis, pelvic inflammatory disease
  - Epididymitis
  - Urethral diverticulum
- Systemic diseases
  - Connective tissue diseases: Reiter (reactive arthritis) syndrome and Behçet disease
- Local irritants
  - Chemicals irritants: Cyclophosphamide, laundry detergents, bubble baths, intravaginal lubricants
  - Mechanical irritation: Radiation cystitis
- Infants and adolescents
  - Labial adhesions
  - Exploratory sexual activity, masturbation
- Diverticulosis

TREATMENT

GENERAL MEASURES
- Encourage good hydration
- Personal hygiene
- Protective measures against STD
- Treat the primary cause

MEDICATION
First Line
- Mainly directed to relief symptoms and treat the underlying cause
- Symptomatic relief can be achieved by using phenazopyridine hydrochloride 200 mg PO TID
- Urinary tract infections are treated with oral antibiotics according to the causative microorganism. In men presumptive organisms are gram negative. Chronic bacterial prostatitis may require a prolonged course
- Urethritis in males is typically due to Chlamydia or gonorrhea

Second Line
- Associated symptoms of urgency can be treated with antimuscarinic drugs such as solifenacin 5 mg PO OD
- Associated symptoms of bladder outlet obstruction can be treated with α-blockers such as tamsulosin 0.4 mg PO OD

SURGERY/OTHER PROCEDURES
Surgical management is reserved for specific causes such as stones, bladder tumors, urethral diverticulum, and bladder outlet obstruction

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
Interstitial cystitis is treated by replacing the glycosaminoglycan layer in the bladder using sodium hyaluronate

Complementary & Alternative Therapies
Acupuncture, nutritional therapy, pelvic floor exercises, and biofeedback can be useful complementary treatments for dysuria

ONGOING CARE
PROGNOSIS
- Prognosis depend on the causative factor
- Urinary tract infection has a good prognosis

COMPLICATIONS
Based on the primary diagnosis

FOLLOW-UP
Patient Monitoring
Based on the primary diagnosis

Patient Resources
http://www.aafp.org

REFERENCES

1. Bremnor J, Sadovsky R. Evaluation of dysuria in adults. *Am Fam Physician*. 2002;65:1589–1597.
2. Roberts RG, Hartlaub PP. Evaluation of dysuria in men. *Am Fam Physician*. 1999;60:865–872.
3. Kurowski K. The women with dysuria. *Am Fam Physician*. 1998;57:2155–2164.

ADDITIONAL READING

• Ismail M, Mackenzie K, Hashim H. Contemporary treatment options for chronic prostatitis/chronic pelvic pain syndrome. *Drugs Today (Barc)*. 2013;49(7):457–462.
• Saini S, Secord E. Dysuria in a young man. *Contemp Pediatrics*. 2014;14. (http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/dysuria-young-man?page=full accessed August 8, 2014)

See Also (Topic, Algorithm, Media)

• Bacteruria and Pyuria
• Cystitis, General Considerations
• Dysuria Algorithm
• Prostatitis, Chronic Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B)
• Prostatitis, General
• Sexually Transmitted Infections (STI) (Sexually Transmitted Diseases [STDs]), General
• Urethra, Stricture, Male
• Urethritis, Gonococcal and Nongonococcal
• Urgency, Urinary (Frequency and Urgency)

CODES

ICD9

• 592.9 Urinary calculus, unspecified
• 597.80 Urethritis, unspecified
• 788.1 Dysuria

ICD10

• N20.9 Urinary calculus, unspecified
• N34.2 Other urethritis
• R30.0 Dysuria

CLINICAL/SURGICAL PEARLS

• Unexplained persistent dysuria should NEVER be ignored; must rule out occult malignancy, such as carcinoma in situ of the bladder.
• Persistent hematuria after adequate treatment of dysuria related to UTI must have formal

hematuria workup.

EDEMA, EXTERNAL GENITALIA (LYMPHADEMA, PENO-SCROTAL EDEMA)

Megan M. Merrill, DO

BASICS

DESCRIPTION

Pitting or nonpitting edema of 1 or both sides of the penile shaft and scrotal skin due to the accumulation of transudative fluid in the dartos (scrotal) or subcutaneous layer of the penile skin

EPIDEMIOLOGY

Incidence

The incidence is not well documented

Prevalence

Prevalent condition in nursing home and hospitalized patients

RISK FACTORS

- Chronic liver disease
- Congestive heart failure
- Epididymo-orchitis
- Genital trauma or penile fracture
- Hypervolemia
- Indwelling Foley catheter
- Lymphoma
- Medications known to cause lymphedema
- Paraphimosis
- Pelvic or inguinal surgery
- Peritoneal dialysis
- Radiation to the pelvic or inguinal region
- Retroperitoneal surgery
- Squamous carcinoma of the penis

Genetics

- Fragile X Syndrome—mutation in FMR-1 on X chromosome
  - Physical manifestation of macro-orchidism/scrotal edema that becomes more apparent in puberty (1)

PATHOPHYSIOLOGY

- Accumulation of transudate within the subcutaneous tissue of the penile shaft and scrotal skin
  - May be localized to the genital region or part of more extensive lower extremity edema or massive body edema (anasarca)
    - In generalized edema capillary hemodynamics are altered and fluid moves from vascular

space to interstitium according to Starling's law (2)
Net filtration = LpS × (Δ Hp - Δ Op)
Lp = permeability of capillary wall
S = surface area for fluid movement
Hp = hydraulic pressure
Op = oncotic pressure
- Hypoalbuminemia contributes to change in oncotic pressure and worsens edema (2)

– Transient lymphedema can be seen after pelvic surgery, such as radical prostatectomy or radical cystectomy
– Often is localized to the peno-scrotal region

- Rarely, sexually transmitted diseases (STDs) such as lymphogranuloma venereum (LGV) or donovanosis (granuloma inguinale) may cause lymphangitis and lymphatic genital obstruction resulting in chronic fibrosis (elephantiasis) (3)

ASSOCIATED CONDITIONS

- Advanced prostate cancer
- Anasarca
- Ascites/hepatic failure
- Congestive heart failure
- Fournier gangrene
- Lymphatic obstruction (lymphangitis filariasis)
- Lymphoma
- Pelvic or inguinal surgery (eg, pelvic or ilioinguinal lymphadenectomy)
- Paraphimosis
- Renal insufficiency/peritoneal dialysis
- Retroperitoneal lymphadenectomy
- Testicular torsion

GENERAL PREVENTION

- Maintenance of euvolemia
- Foley catheter care

DIAGNOSIS

ALERT

- Edema of the penis and scrotum in an uncircumcised male may indicate paraphimosis, which requires immediate foreskin reduction to avoid glans penis vascular compromise (3).
- Edema of the scrotum with areas of necrosis or devitalized skin may indicate Fournier gangrene and requires emergent urologic consultation and surgical debridement.

HISTORY

- Acute vs. chronic condition
- Acute scrotal pain in a child or young adult may indicate torsion.
- Circumcision: Severe paraphimosis can compromise the glans penis
- Trauma
- Recent inguinal, pelvic or retroperitoneal surgery

- History of lower extremity lymphedema
- History of STDs
- Peritoneal dialysis: Dialysate can leak through inguinal hernias into the scrotum
- Medication history:
  – Pantoprazole, sirolimus, and mycophenolate can cause lymphedema.
  – Angiotensin-converting enzyme (ACE) inhibitors: Angioedema of the genitals reported
- Indwelling Foley catheter
  – BPH or indwelling Foley catheter patients can develop epididymo-orchitis.

PHYSICAL EXAM
- Examine for anasarca
- Evaluate for lower extremity edema
- Pitting or nonpitting edema of the penile shaft and/or scrotal skin
- Note the presence/correct placement of an indwelling Foley catheter
- Reduce foreskin in uncircumcised males
- Inspect for skin integrity
- Bruising or induration with crepitance seen in Fournier gangrene
- Foul odor associated with Fournier gangrene
- Examine testis and epididymis for signs of epididymo-orchitis
- Examine scrotum/ spermatic cord in supine and standing position for presence of varicocele
- Transilluminate the scrotum for hydrocele
- Examine external inguinal ring for herniation
- Cremasteric reflex test for testicular viability
- Evaluate for the presence of inflatable penile prosthesis (IPP), artificial urinary sphincter (AUS), or other foreign body

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- No specific lab tests
- Urinalysis may suggest infection/epididymo-orchitis
- Elevated brain natriuretic peptide (BNP) associated with hypervolemia
- Fractional sodium excretion may suggest fluid overload
- Albumin/pre-albumin levels assess nutritional status

Imaging
- Scrotal ultrasound (US) confirms thickened subcutaneous tissue and may suggest etiology.
- CT may suggest retroperitoneal etiology.

Diagnostic Procedures/Surgery

Physical exam significant for pitting edema of the genital skin

Pathologic Findings

Edematous subcutaneous tissue of the scrotum and penile shaft with possible areas of devitalized skin or necrosis

DIFFERENTIAL DIAGNOSIS
- Acute idiopathic scrotal edema
- Angioedema of the genital skin

- Cellulitis
- Chemical or allergic dermatitis
- Elephantiasis
- Epididymo-orchitis
- Fournier gangrene
- Hydrocele
- Idiopathic scrotal edema (usually children)
- Inguinal hernia
- Paraphimosis
- Retroperitoneal mass
- Squamous carcinoma of the penis
- Testicular torsion
- Varicocele

TREATMENT

GENERAL MEASURES
- Scrotal elevation
- Genital or scrotal compression NOT recommended
- Meticulous care of skin breakdown
- Correction of hypervolemia
- Dialysis if due to severe hypervolemia
- Evaluate for urinary retention—Foley catheter if indicated
- Immediate postoperative edema usually resolves spontaneously

MEDICATION
First Line
- Limited utility
- Diuretics may be of some utility
- Chemotherapy for lymphoma

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Indicated to address the etiologic process: Testicular torsion, inguinal hernia, penile fracture, or Fournier gangrene
- Manual reduction of foreskin or dorsal slit if necessary to address paraphimosis
- Rarely, radical excision with gracilis flap may be required for severe refractory cases

ADDITIONAL TREATMENT
Radiation Therapy
While this can be a cause of genital lymphedema, it may have a role in primary palliative treatment of prostate, penile, and retroperitoneal malignancies causing scrotal edema.

Additional Therapies
Supportive undergarments/briefs for patient comfort

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Depends on etiology

COMPLICATIONS
- Skin breakdown/ulceration
- Urinary retention/difficulty voiding
- Genital and scrotal compression is NOT recommended

FOLLOW-UP
Patient Monitoring
- Physical exam for resolution
- Monitor underlying condition, appropriate labs, nutritional status

Patient Resources
Sterns RH. Patient information: Edema (swelling) (Beyond the Basics). In: *UpToDate*, Basow DS, ed. UpToDate. Wolters Kluwer, Philadelphia (www.uptodate.com, accessed August 8, 2014).

REFERENCES

1. Lachiewicz AM, Dawson DV. Do young boys with fragile X syndrome have macroorchidism? *Pediatrics.* 1994;93:992–995.
2. Sterns RH. Pathophysiology and etiology of edema in adults. In: *UpToDate*, Basow DS, ed. UpToDate. Wolters Kluwer, Philadelphia (www.uptodate.com, accessed August 8, 2014).
3. Weinberger LN, Zirwas MJ, English JC 3rd. A diagnostic algorithm for male genital oedema. *J Eur Acad Dermatol Venereol.* 2007;21(2):156–162.

ADDITIONAL READING

Rabinowitz R, Hulbert WC Jr. Acute scrotal swelling. *Urol Clin N Am.* 1995:22(1):101–105.

See Also (Topic, Algorithm, Media)
- Edema, Lower Extremity, Urologic Considerations
- Fournier Gangrene
- Testicular Torsion
- Paraphimosis
- Edema, External Genitalia (Lymphedema, Peno-Scrotal Edema) Image

CODES

ICD9
- 605 Redundant prepuce and phimosis
- 607.83 Edema of penis
- 608.86 Edema of male genital organs

ICD10

- N47.1 Phimosis
- N48.89 Other specified disorders of penis
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

- Determine the patient's fluid status to rule out hypervolemia as the cause of genital edema.
- Acute scrotal pain, swelling, lack of cremasteric reflex, and a high-riding ipsilateral testis could indicate testicular torsion.
- Evaluate for paraphimosis in uncircumcised males.
- Crepitance, induration, necrosis, and foul odor suggest Fournier gangrene and require emergent surgical debridement.
- Complications of edema may include urinary retention and skin breakdown—these should be evaluated for and treated accordingly.

EJACULATION, PREMATURE (PREMATURE EJACULATION)

Elizabeth K. Peacock, MD
James S. Rosoff, MD

BASICS

DESCRIPTION

- Definition of premature ejaculation (PE) remains controversial:
  - ISSM (2008): Ejaculation within about a minute and inability to delay ejaculation with all or nearly all vaginal penetrations causing negative personal consequences (1)
  - WHO (2004): Inability to delay ejaculation with ejaculation before/soon after starting intercourse (15 s)
  - AUA (2004): Ejaculation sooner than desired, before or shortly after penetration that causes distress to 1/both partners
  - EAU (2001): Inability to control ejaculation for sufficient time before vaginal penetration
  - APA (2001): Persistent or recurrent ejaculation with minimal sexual stimulation
- May also be classified as *primary* (lifelong PE) or *secondary* (acquired PE)
- ICD-10 uses 15 s of intravaginal ejaculatory latency time (IELT) as a cutoff

EPIDEMIOLOGY

Incidence

Unknown

Prevalence

- PE is the most common sexual dysfunction in men < 40
- Approximately 20–30% in this group

RISK FACTORS

- Increased levels of arousal due to new partner or situation
- Low frequency of sexual activity

Genetics

Polymorphism in the serotonin transporter promoter region (5-HTTLPR) may play a genetic role in the etiology and/or treatment of PE, though this is controversial.

PATHOPHYSIOLOGY

- Serotonin receptor stimulation (5-hydroxytryptamine):
  - Serotonin 5-HT_{2c} receptors inhibit ejaculation, 5-HT_{1a} receptors facilitate ejaculation
  - Hyposensitivity of 5-HT_{2c} or hypersensitivity of 5-HT_{1a} may cause PE
  - Increase in serotonin transporter (5-HTT) may play a genetic role in PE
- Consider psychological factors, hormone alterations, penile sensitivity, circumcision status, chronic prostatitis as potential causes though with limited evidence supporting these

ASSOCIATED CONDITIONS

- Erectile dysfunction
- General anxiety

- Situational anxiety
- Depression
- Substance abuse
- Relationship distress
- Prostatitis

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Time to ejaculation is essential
  - Duration/frequency of PE
  - Rate of occurrence of PE
  - Degree of sexual stimulation causing PE
  - Nature/frequency of sexual activity including foreplay, masturbation, and intercourse
- Discuss length of time experiencing PE, perceived lack of control, and resultant sexual dissatisfaction
- Any indication of ED
- Issues with the partner, such as dyspareunia or other medical problems
- Rule out symptoms consistent with cystitis or prostatitis
- Medication history: Consider PE due to withdrawal from narcotics or trifluoperazine (Stelazine)
- Sexual History
  - Global to all sexual encounters, or with specific situations and/or partners
  - Religious upbringing
  - Early sexual experiences
  - Sexual relationships, past and present
  - Conflicts or concerns within current relationship
  - Traumatic sexual experiences

PHYSICAL EXAM
- Complete physical exam with focus to rule out biologic causes including recent pelvic surgery or infectious source
- Rectal exam to assess for prostatitis
- Rare to have findings on exam that would define etiology or change management

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Usually unnecessary

Imaging
N/A

Diagnostic Procedures/Surgery
N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS
- Erectile dysfunction
- Generalized anxiety disorder
- Other anxiety states
- Substance abuse

TREATMENT

GENERAL MEASURES
- Behavioral treatment:
  - Stop–squeeze method (Masters and Johnson) involves removal of penis at point of ejaculation with squeezing of glans or frenulum
  - Start–stop method (Seman) involves a pause in intercourse at point of ejaculation
  - High initial success rates are reported, but poor long-term rates are present due to the time-consuming nature of treatment
- Psychotherapy may be beneficial
- Combination of pharmacotherapy and psychotherapy is suggested as current model for treatment

MEDICATION
First Line
- No medications are approved for treatment of PE in the United States
  - SSRIs:
    - Elevates level of serotonin in synapse that results in prolongation of ejaculatory latency time
    - 1st-line pharmacotherapeutic approach (off-label)
    - Daily treatment with PO paroxetine 20–40 mg (greatest evidence), sertraline 25–200 mg, fluoxetine 5–20 mg
    - Newer agents have not been effective (fluvoxamine/venlafaxine)
    - Dapoxetine approved in Europe only for on-demand dosing for PE
  - Topical agents:
    - EMLA: Lidocaine–prilocaine 2.5% cream
    - TEMPE: Metered-dose aerosol spray with lidocaine 7.5 mg and prilocaine 2.5 mg per spray

Second Line
- Clomipramine:
  - Tricyclic antidepressant
  - Daily treatment with 25–50 mg or on-demand treatment with 50 mg 5 hrs prior to intercourse
- Tramadol (synthetic opioid analgesic) with potential treatment role in PE (little evidence) (2)

SURGERY/OTHER PROCEDURES
CT-guided cryoablation of unilateral dorsal penile nerve (single study, 24 patients) (3)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended authorization of a cutaneous spray containing a mixture of 150 mg lidocaine and 50 mg prilocaine per milliliter applied to the glans

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Varies by treatment modality. May have up to 80% success rate with medication and/or behavioral modification

COMPLICATIONS

- Medications carry side effects, but complications of PE are limited
- Rarely, a problem with fertility may exist due to inability to complete intercourse
- May provoke anxiety or depression if PE is severe
- May interfere with development of sexual relationship

FOLLOW-UP

Patient Monitoring

N/A

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=122

REFERENCES

1. McMahon CG, Althof S, Waldinger MD, et al. An evidence-based definition of lifelong premature ejaculation: Report of the International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *BJU Int*. 2008;102(3):338–350.
2. Montague DK, Jarow J, Broderick GA, et al. AUA guideline on the pharmacologic management of premature ejaculation. *J Urol*. 2004;172(1):290–294.
3. David Prologo J, Snyder LL, Cherullo E, et al. Percutaneous CT-guided cryoablation of the dorsal penile nerve for treatment of symptomatic premature ejaculation. *J Vasc Interv Radiol*. 2013;24(2):214–219.

ADDITIONAL READING

Bejma JP, Hellstrom WJG. Premature ejaculation. *AUA Update Series*. 2007;26:366–372.

See Also (Topic, Algorithm, Media)

- Dysorgasmia (Painful Orgasm), Male
- Ejaculatory Disturbances (Delayed, Decreased, or Absent)
- Ejaculation Premature Algorithm

CODES

ICD9

302.75 Premature ejaculation

ICD10

F52.4 Premature ejaculation

CLINICAL/SURGICAL PEARLS

- Exact definition of PE remains controversial.
- Combination of pharmacotherapy (off-label use) and psychotherapy is likely the most beneficial treatment.

EJACULATORY DISTURBANCES (DELAYED, DECREASED, ABSENT)

Pravin K. Rao, MD

BASICS

DESCRIPTION

- Anorgasmia or delayed orgasm/ejaculation
  - Difficulty/inability to reach orgasm
- Low volume ejaculate
  - Suspect if <1.5 cc ejaculate volume
- Aspermia
  - Orgasm with zero ejaculate volume
- Retrograde ejaculation
  - Sperm seen in post-ejaculatory urine
- Ejaculatory duct obstruction (EDO)
  - Congenital, acquired, iatrogenic
- Failure of emissions
  - Can also cause low/zero volume

EPIDEMIOLOGY

Incidence

- Increased in aging (age 50–80 yr) men with BPH/LUTS (1)[B]
  - 46% decreased ejaculation
  - 5% anejaculation
- Men on tamsulosin 0.8 mg
  - ~90% report decreased ejaculatory volume (2)[B]
- Selective serotonin reuptake inhibitors (SSRIs)
  - 16–37% delayed or difficult orgasm
- Anorgasmia is rare:
  - 0.14–0.4% in general population

Prevalence

N/A

RISK FACTORS

- Age
- Benign prostatic hyperplasia
- Lower urinary tract symptoms
- Prostatitis/Ejaculatory duct stones
- Depression and related medications
- Hypogonadism
- Hypertension medications
- Prostate/Urethral /Bladder neck surgery

- Retroperitoneal lymph node dissection (RPLND)
- Cystic fibrosis
- Neurologic conditions/Diabetes
  - Multiple sclerosis, spinal cord injury (SCI), spina bifida, diabetes
- Rectal surgery
- Radiation therapy

Genetics

N/A

PATHOPHYSIOLOGY

- Normal ejaculation:
  - Central control in multiple brain regions
    - Can promote or inhibit ejaculation
  - Sympathetic (T12–L3):
    - Hypogastric nerve (thoracolumbar)
    - Seminal emission by contraction of epididymis, vas deferens/ampulla, seminal vesicle (SV), and prostate smooth muscle
    - Bladder neck closure preventing retrograde ejaculation
  - Parasympathetic (S2–S4):
    - Pelvic nerve
    - Gland secretions of prostate SV
  - Somatic (S2–S4):
    - Pudendal nerve
    - Efferents from sacral cord
    - Contraction of bulbocavernosal and ischiocavernosal muscles
    - Relaxation of external urethral sphincter
    - Projectile expulsion of ejaculate
  - Sensory
    - Pudendal nerve
    - Tactile stimulation of penis can activate ejaculatory reflex
- Anorgasmia/Delayed orgasm
  - Hypogonadism
  - Medication side effect
  - Psychological/Psychiatric (depression)
- Retrograde ejaculation
  - Damage to ejaculatory nerves/reflexes
  - Bladder neck surgery or dysfunction
  - Medications affecting bladder neck
- Low volume ejaculate
  - Poor development/absence of accessory sex organs
  - Retrograde ejaculation or functional problem
  - Medications affecting accessory glands
  - Decreased prostate and SV secretions seen in hypogonadism
- Ejaculation requires intact, properly developed, and coordinated accessory sex organs, nerves, and muscles

  - Congenital, acquired, iatrogenic, infectious, inflammatory causes can all prevent normal ejaculation
  - Functional causes may lead to the complaint of decreased force of ejaculate
  - Ejaculate volume commonly decreases by ~0.03 mL each year with advanced age

ASSOCIATED CONDITIONS

- Psychological/Psychiatric conditions
- See Risk Factors

GENERAL PREVENTION

- Avoidance of bladder neck procedures
  - Transurethral prostate, bladder neck surgery
- Avoidance/decreased use of medications
  - SSRI, α − blockers, 5α-reductase inhibitors
- Nerve sparing at time of RPLND
- Strict diabetic control

DIAGNOSIS

HISTORY

- Duration of symptoms
- No defined criteria for diagnosis of delayed ejaculation
  - Mostly normal men ejaculate after 4–10 min of penetration
  - Presence of significant distress to patient or partner important to diagnosis
- Presence or absence of orgasm
- Perceived ejaculate volume
- Sources of stress/psychological disturbance
- Past medical history
- Retroperitoneal and genitourinary operations
- Family history of cystic fibrosis
  - See vas deferens, congenital absence
- Medications:
  - Antidepressants/antipsychotics
  - Bladder outlet medications
  - Antihypertensives (clonidine)
  - Methyldopa

PHYSICAL EXAM

- Absence or diminished development of epididymides and vasa deferentia
  - Congenital bilateral or unilateral absence of the vas deferens (CBAVD/CUAVD)
- Enlarged SV
  - EDO
- Hypospadias or epispadias
  - Hypogonadism

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Semen analysis
  - Volume: Suspect if ejaculate volume < 1.5 cc
  - Concentration: Low volume azoospermia suspicious for EDO
  - Absence of seminal fructose suggests EDO
- Post-ejaculatory urinalysis (PEU): > 10–15 sperm/HPF demonstrates retrograde ejaculation

Imaging

- Transrectal ultrasound (TRUS)
  - Usually done for low volume azoospermia
    - For patients with negative PEU
  - Normal SV A-P diameter < 1.5 cm
- MRI
  - Can help identify structural abnormalities

Diagnostic Procedures/Surgery

- TRUS with SV aspiration: Presence of numerous sperm suggests obstruction
  - Rare: Seminal vesiculography

Pathologic Findings

Scar tissue at ejaculatory duct

DIFFERENTIAL DIAGNOSIS

- Anorgasmia
- Retarded/Delayed orgasm
- Erectile dysfunction
  - May present as inability to reach orgasm, or with weak force of ejaculate
- Retrograde ejaculation
- Aspermia
- EDO (ejaculatory duct obstruction)

TREATMENT

GENERAL MEASURES

- Remove/modify correctible causes
  - Medications
    - Alfuzosin 21% vs. tamsulosin 90% of patients reported reduced ejaculatory volume (2) [B]
  - Psychological/Stress factors
- Psychological assessment/counseling
- Treat erectile dysfunction
- Sexual counseling on techniques for optimal arousal

MEDICATION

First Line

- Anorgasmia/Delayed ejaculation
  - No drug treatments FDA approved
  - Medications that can be tried include:

- Pseudoephedrine
- Yohimbine

- See “Retrograde Ejaculation”

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Most procedures reserved for infertility treatment
- Transurethral resection of ejaculatory ducts (TUREDs) for EDO
- Penile vibratory stimulation (PVS)
  - For anorgasmic/anejaculatory men
  - Integration with cognitive-behavioral therapy
  - High success (>75%) in SCI, though usually for fertility purposes
  - Procedure: Apply to ventral/frenular region for 1–3 min at a time, with 1 min rest periods, for up to 15–20 min
  - See images of PVS devices:
    - Ferticare
    - Viberect (dorsal and ventral stimulation)
- Electroejaculation (EEJ) via rectal probe
- Autonomic dysreflexia
  - Risk for SCI lesions above T6
  - Can occur with PVS or EEJ
  - Consider nifedipine 10–20 mg PO 10–15 min before treatment initiated
  - Monitor at-risk patients for hypertension, tachycardia, sweats
- Retrieval of sperm from bladder
  - See “Retrograde Ejaculation”
- Testicular or epididymal sperm retrieval
  - Requires IVF/ICSI
  - Donor sperm or adoption may circumvent the need for IVF/ICSI

ALERT
Men with spinca cord injury (SCI) above the T6 level are at risk of autonomic dysreflexia (3).

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Pelvic floor physical therapy for associated symptoms of pain or voiding symptoms
- Cognitive-behavioral sex therapy
- Changing idiosyncratic masturbation style if present

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

- Depends on the etiology, duration, and severity
- >40% SCI men doing PVS with home insemina-tion can achieve pregnancy (3)[B]

COMPLICATIONS

- Infertility implications
- Relationship stress and difficulty

FOLLOW-UP

Patient Monitoring

Based on response to therapy and needs of specific patient

Patient Resources

N/A

REFERENCES

1. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: The multinational survey of the aging male (MSAM-7). *Eur Urol*. 2003;44(6):637–649.
2. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol*. 2006;176(4 Pt 1):1529–1533.
3. Sønksen J, Fode M, Löchner-Ernst D, et al. Vibratory ejaculation in 140 spinal cord injured men and home insemination of their partners. *Spinal Cord*. 2012;50(1):63–66.

ADDITIONAL READING

- Fode M, Krogh-Jespersen S, Brackett NL, et al. Male sexual dysfunction and infertility associated with neurological disorders. *Asian J Androl*. 2012;14(1):61–68.
- Nelson CJ, Mulhall JP. Male orgasmic disorders: What do we know? *Comtemp Urol*. 2007; February

See Also (Topic, Algorithm, Media)

- Anorgasmia/Dysorgasmia
- Ejaculation, Painful
- Ejaculation, Premature
- Ejaculatory Disturbances (Delayed, Decreased, or Absent) Images
- Ejaculatory Duct Obstruction
- Retrograde Ejaculation
- Vas Deferens, Congenital Absence

CODES

ICD9

- 302.79 Psychosexual dysfunction with other specified psychosexual dysfunctions
- 608.87 Retrograde ejaculation
- 608.89 Other specified disorders of male genital organs

ICD10

- F52.32 Male orgasmic disorder
- N53.14 Retrograde ejaculation
- N53.19 Other ejaculatory dysfunction

CLINICAL/SURGICAL PEARLS

Inclusion of partner in treatment important if recommending change in sexual practice.

ENURESIS, ADULT

Katie S. Murray, DO
Tomas L. Griebling, MD, MPH, FACS

BASICS

DESCRIPTION

- Enuresis is repeated inability to control urine
  - Primary: Starts in childhood and never resolves and continues into adulthood
  - Secondary: New onset in adulthood
- Nocturnal enuresis (NE) is involuntary urination while asleep after the age at which bladder control usually occurs

EPIDEMIOLOGY

2.3% of adult population affected (1)[A]

RISK FACTORS

- Family history of NE
  - If both parents have NE, children have 80% chance

Genetics

- Possibly hereditary
- Related to site on chromosome 13

PATHOPHYSIOLOGY

- Unknown in most situations
- Recognized hypotheses
  - Obstructive sleep apnea causing diminished vasopressin secretion
  - Disturbance in sensation, cortical arousal, or urinary sphincter function
  - Decreased bladder capacity initiating involuntary voiding reflex
  - Nocturnal polyuria because vasopressin secretion or reduction in renal sensitivity to the antidiuretic (2)[B]
  - Detrusor instability during filling phase
  - Urine production increased in recumbent position in patients with peripheral edema or congestive heart failure
- Normal physiology decreases nighttime, relative to daytime, urinary output. Excess production of urine at night, in the setting of a normal 24-hr urine output, is termed nocturnal polyuria
  - Nocturnal polyuria is nighttime excretion of $>35\%$ of a 24-hr urine volume

ASSOCIATED CONDITIONS

- Benign prostatic hypertrophy
- Daytime urinary incontinence
- Psychological disorders including depression
- Sleep apnea

GENERAL PREVENTION
- Timed voiding
- Complete bladder emptying
- Avoidance of caffeine and alcohol
- Adjust timing of fluid intake

DIAGNOSIS
HISTORY
- Have never achieved nocturnal continence of urine
- Nonspecific urinary symptoms
- Ask about known or potential medical history
- Complete surgical and trauma/incident history
- Obtain record of fluid intake habits
- Review medications and times of administration
- Voiding diaries to evaluate frequency, volume, and patterns
- International prostate symptom score (IPSS) in men

PHYSICAL EXAM
- Full urologic exam (pelvic exam in women and DRE in men)
- Full neurologic exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis and urine culture: Rule out urinary tract infection, hematuria, proteinuria, glycosuria
- Creatinine: Rule out renal insufficiency
- Urine cytology (if other symptoms such as irritative voiding symptoms make carcinoma a concern)

Imaging
- Post-void residual bladder scan
- Renal/ureteral imaging to evaluate for abnormalities such as ectopic ureters
  - CT urogram
  - Renal ultrasound

Diagnostic Procedures/Surgery
- Bladder diaries/frequency–volume charts
- Cystoscopy with retrograde pyelograms to evaluate bladder and ureters
- Urodynamic testing (3)[B]
  - Identify anatomical urethral abnormalities
  - Identify anatomical bladder abnormalities
  - Evaluate bladder function for possible neurogenic bladder findings
  - May find abnormalities in up to 90% of patients (4)[B]
- Consider sleep medicine consultation and/or polysomnography if clinical concern for sleep apnea

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Obstructive sleep apnea
- Anxiety or psychological disorders
- Anatomic abnormalities
- Idiopathic detrusor instability
- Neurologic disorders

TREATMENT

GENERAL MEASURES

- Conservative measures have varying success rates
- Education is key when attempting to improve enuresis without medical therapy
- Timed voiding
- Complete bladder emptying
- If associated with BPH in men management with α-blockers for 5α-reductase inhibitors
- Avoidance of caffeine and alcohol
- Adjust timing of fluid intake
  - Restrict fluid intake in evening to reduce urine output at night
  - Take diuretic medications early in a day

MEDICATION

First Line

- If due to prostatic hypertrophy: See Section I "Bladder Outlet Obstruction (BOO)."
- Antimuscarinics or β3-agonists (3)[B]
  - Inhibit the effect of acetylcholine at postjunc-tional muscarinic receptors on detrusor muscle cells
  - β3-Adrenergic agonist promotes detrusor muscle relaxation
  - Varying results (5–40%), depends on whether detrusor instability is root cause of enuresis
  - Side effects: Dry mouth, constipation, blurred vision, confusion
- Antimuscarinics
  - Tolterodine (2–4 mg/d)
  - Trospium XR (60 mg/d)
  - Darifenacin (7.5–15 mg/d)
  - Solifenacin(5–10 mg/d)
  - Oxybutynin (IR 7.5–20 mg/d, XL 5–30 mg/d, patch twice weekly)
  - Fesoterodine (4–8 mg/d)
- β3-adrenergic agonist
  - Mirabegron (25–50 mg/d)

Second Line

- DDAVP (Desmopressin) (5)[B]
  - Not currently FDA approved for this clinical indication (has European regulatory approval)
  - Analog of vasopressin

- Decreases urine production for about 5 hr
- Decreases number of enuresis events but may not eliminate it completely
  - Oral 0.2 mg at bedtime; increase to 0.6 mg to response
  - Intranasal formulations are no longer indicated for the treatment of primary NE due to risk for severe hyponatremia with seizures and death
  - Side effects: Nasal irritation, dry mouth, sleep disruption, water intoxication, seizures, heart failure, electrolyte disturbances, hyponatremic coma
  - Use with extreme caution if at all in geriatric patients (>65 yr) due to risk of severe hyponatremia and other adverse events

• Imipramine (5)[B]
- Tricyclic antidepressant
- Mild anticholinergic effect and α-action to increase internal sphincter tone
- Side effects: Sleep abnormalities, decrease appetite, personality disturbances

SURGERY/OTHER PROCEDURES
• Consideration after all conservative and pharmacologic measures have failed
• If urodynamic testing shows detrusor overactivity, may consider additional interventions
- Botulinum toxin injections
- Sacral neuromodulation
- Posterior tibial neuromodulation
- Augmentation cystoplasty
- Urinary diversion

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
• Psychological counseling
- Assist with coping mechanisms and finding any potential underlying issues

Complementary & Alternative Therapies
• Enuresis (bedwetting) alarms
• Timed voiding through the day and night
• Decrease fluid hydration prior to bed
• Empty bladder to completion prior to bed

ONGOING CARE
PROGNOSIS
• Many patients may eventually become dry
- This is more likely in children

COMPLICATIONS
• Urea dermatitis
• Skin breakdown and superficial ulcers from direct contact of urine on skin
• Psychological effects
- Job changes/decreased work performance

– Depression
– Low self-esteem
– Decreased social activities

FOLLOW-UP

Patient Monitoring

- Long-term follow-up until resolution or satisfaction by the patient
- Psychological counseling and follow-up if necessary

Patient Resources

- The Simon Foundation for Continence (simonfoundation.org)
- National Association for Continence (www.nafc.org)

REFERENCES

1. Yeung CK, Sihoe JD, Sit FK, et al. Characteristics of primary nocturnal enuresis in adults: An epidemiological study. *BJU Int*. 2004;93:341–345.
2. Natsume O, Kaneko Y, Hirayama A, et al. Fluid control in elderly patients with nocturia. *Int J Urol*. 2009;16:307–313.
3. Yucel S, Kutlu O, Kukul E, et al. Impact of urodynamics in treatment of primary nocturnal enuresis persisting into adulthood. *Urology*. 2004;64:1020–1025.
4. Yeung CK, Sihoe JD, Sit FK, et al. Urodynamic findings in adults with primary nocturnal enuresis. *J Urol*. 2004;171:2595–2598.
5. Vandersteem DR, Husmann DA. Treatment of primary nocturnal enuresis persisting into adulthood. *J Urol*. 1999;161:90–92.

ADDITIONAL READING

http://www.nafc.org/bladder-bowel/bedwetting-2/adult-bedwetting/

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Enuresis Algorithm
- Enuresis, Pediatrics
- Incontinence, Adult Male
- Nocturia
- Urge Incontinence
- Urgency, Urinary (Frequency and Urgency)

CODES

ICD9

- 307.6 Enuresis
- 788.30 Urinary incontinence, unspecified
- 788.36 Nocturnal enuresis

ICD10

- F98.0 Enuresis not due to a substance or known physiol condition
- N39.44 Nocturnal enuresis

- R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

- Evaluating for underlying conditions is important in new onset enuresis.
- Social implications are common.
- Enuresis raised the risk for nighttime falls in elderly.

ENURESIS, PEDIATRIC

Ellen Shapiro, MD, FACS
Daniel A. Wollin, MD

BASICS

DESCRIPTION

- Terminology based on 2006 (International Children's Continence Society) ICCS standards (1)
  - Enuresis is intermittent incontinence of urine while sleeping usually referred to as nocturnal enuresis (NE).
  - This term is used with or without daytime incontinence or other lower urinary tract symptoms (LUTSs)
- Monosymptomatic enuresis (MNE) is nocturnal incontinence without other LUTSs
  - MNE is abnormal in children ≥ 5 yr of age
- Non-NMNE may coexist with increased/decreased voiding frequency, daytime incontinence, urgency, hesitancy, straining, a weak stream, intermittency, holding maneuvers, a feeling of incomplete emptying, post-void dribble and genital/LUT pain
- Primary enuresis if the child has been dry for <6 mo; secondary if the child has been dry for at least 6 mo

EPIDEMIOLOGY

Incidence

- 15% of normal children have NE at age 5
- Of all children with incontinence:
  - 70% with NE only
  - 15% with daytime incontinence only
  - 15% with daytime incontinence and NE
  - 2–3% have NE into early adulthood without treatment

Prevalence

5–7 million with NE in the United States

RISK FACTORS

NE is multifactorial (see "Pathophysiology"")

Genetics

- Primary NE tends to be familial:
  - Both parents with history of NE—77% of children
  - If one parent with history of NE—44% of children
- Several chromosomes have been linked to NE, including 12q, 13q, 22q
  - 5HTR2A gene (13q14, serotonin receptor) mutation shown to be associated with NMNE

PATHOPHYSIOLOGY

- Complex, involving central nervous system, circadian rhythm (sleep and diuresis), and bladder function abnormalities
- 3 major pathogenic mechanisms:

  - Increased arousal threshold
  - Nocturnal polyuria
  - Detrusor overactivity
- Some children lack normal nocturnal increase in vasopressin secretion leading to nocturnal polyuria, but not all children with polyuria are vasopressin deficient
- Overactive bladder leading to "small for age" bladder volume associated with NMNE

ASSOCIATED CONDITIONS

- Neuropsychiatric disorders (children with attention deficit hyperactivity disorder 2.7 × more likely to have NE)
- Upper airway obstruction and nocturnal sleep apnea. Apneic episodes result in increased secretion of atrial natriuretic factor
- Constipation
- Urinary tract infection

GENERAL PREVENTION

MNE may not be preventable but parents should maintain regular voiding and bowel patterns —may help reduce risk of developing NMNE with LUTS.

DIAGNOSIS

HISTORY

- Detailed history helps determine treatment strategies
- Number of nights per week enuresis occurs?
- Symptoms suggestive of underlying bladder dysfunction:
  - Drops of urine in underclothing before or after voiding
  - Frequency of leakage (intermittent or continuous)
  - Daytime incontinence in child over 31/2 yr of age
  - Sudden urge to void
  - Straining, posturing, holding maneuvers
  - Interrupted micturition
  - History of urinary tract infection
  - Urinary tract malformation
    - Spinal cord or vertebral malformation
- Comorbidities that may predict treatment resistance:
  - Constipation and encopresis
  - Behavioral, psychological/psychiatric problems such as ADHD, ADD, autism
  - Motor and/or learning disabilities or delayed development
  - Pattern of fluid intake (incl. caffeine)
    - Does patient drink during the night?

PHYSICAL EXAM

- Abdominal exam for distended bowel/bladder
- Lower back inspection for stigmata of occult spinal dysraphism/tethered cord (sacral dimple, hair tuft, hemangioma, lipoma or other neurocutaneous signatures, absence of a palpable sacrum, or excess fat overlying the sacral region suggestive of a lumbosacral abnormality)

- Genital exam for congenital anomalies such as ectopic ureter or a urogenital sinus (with incontinence due to pooling of urine in the vagina)
  - Labial adhesions in girls
  - Urethral abnormalities or phimosis in boys
- Gait abnormalities, high arched foot

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Macroscopic urinalysis (dipstick) to determine glucosuria, proteinuria or UTI. If glucosuria present, obtain serum glucose at that time
- Microscopic urinalysis and culture if history of UTI or symptoms suggestive of infection

Imaging

- Children with MNE do not need imaging but a post-void residual (PVR) by bladder scan is useful
  - US: May be considered in male patients, especially those who have failed initial therapy to ensure no anatomic problem
  - Some suggest most males with enuresis should have bladder US to rule out posterior urethral valves
- Children with history of UTI or NMNE should undergo:
  - Renal US
  - PVR
  - VCUG when diagnosis suggests posterior urethral valves or in older males; also used to evaluate for bulbar stricture (unusual)
  - Abdominal x-ray to evaluate for vertebral abnormality; also assesses degree of stool retention although history is usually sufficient
  - MRI of the spine for children suspected of having a neurogenic bladder as etiology, for those patients who are compliant and fail all therapeutic alternatives for NMNE, or who have a neurocutaneous signature or other physical findings on the lower spine or physical exam

Diagnostic Procedures/Surgery

- Uroflowmetry: Assesses bladder outlet obstruction or hypocontractility; evaluates voiding pattern (staccato)
- Urodynamics: Helpful in evaluating bladder compliance and function in children with severe dysfunctional voiding or enuresis due to neurogenic bladder or posterior urethral valves
- Cystoscopy: Routine use should be avoided
  - May be helpful in the assessment of select patients with potential anatomic causes

Pathologic Findings

- Neurogenic bladder
- Ectopic ureter
- Posterior urethral valves
- Urethral stricture

DIFFERENTIAL DIAGNOSIS

- Ectopic ureter in girls, extremely rare in boys

- Giggle incontinence (enuresis risoria)
- Neurogenic bladder
- Nonneurogenic neurogenic bladder
- Posterior urethral valves (boys)
- Tethered cord
- Urethral stricture
- Vaginal voiding

TREATMENT

GENERAL MEASURES (2–6)

- Before embarking on any therapy, the interest and ability of the child and family to comply should be determined
- Patience and compliance should be emphasized because many months may be required to achieve improvement or resolution
- Motivational therapy should be encouraged in almost every case; it is useful in conjunction with other treatments
- Behavioral therapy is prerequisite to medications in most patients with monosymptomatic NE
- Enuresis alarm for MNE works with well-motivated families and children
  - Treatment may take 2–3 mo
  - Mechanism of action for behavioral therapy unclear
  - Initial cure rate as high as 70%; suggest 4 mo of consecutive dryness
  - Relapse can be high, but 50% achieve long-term cure

MEDICATION

First Line

- DDAVP (desmopressin) for NE:
  - 0.2–0.6 mg PO 1 hr before bed. No fluid intake 2 hr before and 8 hr after bedtime
  - Success rate ~20–50%
  - Caution in patients with cystic fibrosis (hyponatremic dehydration)
  - Tapering schedule imperative
  - Give parents copy of FDA warning (Dec 2007) regarding fluid intoxication and seizures (see “Additional Reading”)

Second Line

- Imipramine for NE: Tricyclic antidepressant with anticholinergic effects
  - Success rates of 25–40%, but relapse rates can be high
  - 25–50 mg
  - Tapering schedule imperative

ALERT

Imipramine overdose can result in seizure, hypotension, coma, and fatal arrhythmias; may prolong QT interval.

- Oxybutynin (anticholinergic) for NMNE:
  - 2.5–5 mg BID–QID (0.2 mg/kg/dose) when PVR negligible

- Available in long-acting form (5–10 mg/d)
- Success primarily when the medication is used with a well-organized treatment program including voiding 1st thing in the morning, timed voiding during the day, and regular bowel habits.
- Patients should be seen in 4–6 wk for evaluation including urinalysis and PVR. If elevated PVR, lower the dose and institute double voiding.

• Tolterodine (anticholinergic) for polysymptomatic or daytime incontinence:
- 1–2 mg BID. Also available in long-acting form (2–4 mg/d)
- More success when the medication is used with a well-organized treatment program

• Low-dose prophylactic antibiotics for NMNE:
- Helpful for children with recurrent UTI or bacteriuria with LUTS and voiding dysfunction
- Nitrofurantoin recommended 1–2 mg/kg QHS

SURGERY/OTHER PROCEDURES

• Only in cases of congenital anomalies (ectopic ureter, posterior urethral valves, etc.)
• Neurosurgical intervention for spinal anomalies, tethered cord

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

• Children with dysfunctional voiding/elimination syndromes may benefit from elimination retraining program and selective use of anticholinergic medications
- Use toilet at regular intervals during the day (every 21/2–3 hr)
- Waking children prior to the bedtime of the parents does not promote long-term dryness

• Fluid restriction useful and mandatory especially with dDAVP
• Treat constipation if present—patient should have at least daily bowel movements that are easy for the child to pass

Complementary & Alternative Therapies

• Pediatric biofeedback can be effective in cases of dysfunctional voiding. Most helpful in addition to improved voiding and bowel habits
- Child must have sufficient cognitive ability to understand teaching

ONGOING CARE

PROGNOSIS

• After age 5, spontaneous resolution rate of 15%/yr for bedwetters
• After age 15, <1% have NE
• Over 6.5 yr of follow-up:
- 91% no longer incontinent during the day
- 84% no longer wet at night
- With UTI history UTI, 82% no longer have infections

COMPLICATIONS

• Recurrent UTI
• Persistence of incontinence and LUTS—requires further investigation with VUDs and MRI

- Persistence of enuresis into adulthood (2–3%)
- Social consequences/withdrawal

FOLLOW-UP

Patient Monitoring

- Children with history of UTI or organic causes of enuresis should be followed for the specific condition
- Monitor closely while on medication to treat the enuresis (PVR and urinalysis)

Patient Resources

International Children's Continence Society. http://i-c-c-s.org/parents/

REFERENCES

1. Neveus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Report from the Standardization Committee of the International Children's Continence Society. *J Urol*. 2006;176(1):314–324.
2. Vande Walle J, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis. *Eur J Pediatr*. 2012;171(6):971–983.
3. O'Flynn N. Nocturnal enuresis in children and young people: NICE clinical guideline British Journal of General Practice. 2011;61:360–362.
4. Jones EA. Urinary incontinence in children. In: Litwin MS, Saigal CS, eds. *Urologic Diseases in America*. Washington, DC: US Government Publishing Office; 2007.
5. Chase J, Austin P, Hoebeke P, et al. The management of dysfunctional voiding in children: A report from the Standardization Committee of the International Children's Continence Society. *J Urol*. 2010;183(4):1296–1302.
6. Neveus T, Eggert P, Evans J, et al. Evaluation of and treatment for monosymptomatic enuresis: A standardization document from the International Children's Continence Society. *J Urol*. 2010;183(2):441–447.

ADDITIONAL READING

2007 FDA advisory on DDAVP.
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProvi

See Also (Topic, Algorithm, Media)

- Dysfunctional elimination syndrome
- Enuresis, Adult
- Enuresis, Pediatric Algorithm
- Urinary Tract Infection, Pediatric
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

- 307.6 Enuresis
- 788.30 Urinary incontinence, unspecified

• 788.36 Nocturnal enuresis

ICD10

• F98.0 Enuresis not due to a substance or known physiol condition
• N39.44 Nocturnal enuresis
• R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

The primary therapy for all children with NE should be initial behavioral management before relying on medications.

EPIDIDYMIS, MASS (EPIDIDYMAL TUMORS AND CYSTS)

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Judd W. Moul, MD, FACS

BASICS

DESCRIPTION
- Small, discernible growth anywhere along the epididymis
- Frequently asymptomatic, discovered on routine genital exam or incidentally by the patient
- Pain may be presenting symptom

EPIDEMIOLOGY
Incidence
- Not well defined
- Epididymal cysts are usually asymptomatic and may occur in up to 30% of asymptomatic males
- Cysts more common with advancing age
- Adenomatoid tumors—benign and most common (1)

Prevalence
Not well defined

RISK FACTORS
- Aging
- Von Hippel–Lindau disease associated with cystadenoma
- DES exposure in utero: Epididymal cysts
- Prior vasectomy

Genetics
Epididymal cystadenoma associated with Von Hippel–Lindau syndrome (hereditary, autosomal dominant)

PATHOPHYSIOLOGY
- Most solid lesions benign (such as adenomatoid tumors)
- Malignant lesions uncommon
- Metastatic disease is rare but reported

ASSOCIATED CONDITIONS
- Von Hippel–Lindau disease
- Young syndrome

GENERAL PREVENTION
- Routine self-exam for identification of scrotal content masses
- Routine genital exam by physician

DIAGNOSIS

HISTORY

- Age: Cystic lesions increase with age
- Timing of identification
- Interval growth
- Associated pain
- Dysuria, hematuria, frequency, urgency, tenderness—consider epididymitis
- Exposure to tuberculosis (TB)
- History of sarcoidosis, histoplasmosis
- History of vasectomy
- History of urinary tract infection (UTI) or sexually transmitted infection
  - History of anal insertive intercourse increases risk of coliform or STD infection
- Recent GU manipulation
  - Bacillus Calmette–Guérin (BCG) instillation
  - Catheterization
  - Transurethral procedure

PHYSICAL EXAM

- Scrotal exam
  - Identify location of mass—single or multiple
  - Compare with contralateral scrotal contents
  - Evaluate if fixed, mobile, indurated, or encroaching on other structures
  - Identify spermatic cord/vas deferens
  - Scars from vasectomy—sperm granuloma, epidermal inclusion cyst
  - Examine testicle for associated masses
- Inguinal exam
  - Evaluate for lymphadenopathy
  - Hernia

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: to evaluate for UTI. Include urine culture if suspicious for infection.
- Tumor markers if any concern for testicular mass
  - α-Fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), lactate dehydrogenase (LDH)
- Purified protein derivative (PPD) if TB suspected

Imaging

- Scrotal ultrasound
  - Solid vs. cystic
  - Location—testicular or paratesticular
  - Vascular or avascular
  - Cannot reliably differentiate between malignant or benign
- Chest x-ray if TB suspected
- If rhabdomyosarcoma and >10 yr old—CT scan of the abdomen and pelvic with contrast to evaluate for retroperitoneal nodes (2)[A]

Diagnostic Procedures/Surgery

- Rarely needed for epididymal lesions

- Inguinal approach
- Frozen section for pathology; proceed to orchiectomy with high cord ligation if malignant

Pathologic Findings

- Benign
  - Adenomatoid
  - Epididymal cystadenoma/papillary cystadenoma
  - Spermatocele
- Malignant
  - Rhabdosarcoma
  - Leiomyosarcoma
  - Fibrosarcoma
  - Metastatic carcinoma

DIFFERENTIAL DIAGNOSIS

- Adenomatoid tumor of the epididymis:
  - Most common solid tumor of the epididymis
- Ectopic tissues:
  - Adrenal cortical rests
  - Splenogonadal fusion
- Epidermoid cyst
- Epididymal calcinosis
- Epididymal cystadenoma/papillary cystadenoma:
  - 2/3 associated with von Hippel–Lindau syndrome
  - 1/3 of all epididymal tumors
  - 2/3 associated with VHL syndrome
  - On US, most common appearance is 15–20-mm solid mass with small cystic components.
- Epididymitis:
  - Acute; very tender on exam
  - Chronic; may have secondary calcification
  - Common cause of epididymal pain
- Fibroma of epididymis
- Fibrous pseudotumor
- Funiculitis
- Granulomas: Sarcoidosis, TB, histoplasmosis
- Hernia
- Hydrocele
- Hydrocele of the cord
- Leiomyoma
- Malignant epididymal tumor:
  - Primary (very rare): Liposarcoma, rhabdomyosarcoma (high on differential in children), leiomyosarcoma, adenocarcinoma, lymphoma
  - Metastatic: Prostate, kidney, stomach most common
- Papillary cystadenoma
- Polyorchidism
- Sarcoid

- Sperm granuloma:
  - Seen in 40% postvasectomy or 2.5% idiopathic in general population
  - Granulomatous lesion with few giant cells
  - Consequence of extravasation of spermatozoa generally postvasectomy (of vasectomized men and of general population)
- Testicular tumor
- TB of the epididymis
- Varicocele
- Vasitis and vasitis nodosa (usually associated with epididymitis)
- Young syndrome (obstructive azoospermia, sinusitis, bronchiectasis)

TREATMENT

GENERAL MEASURES

- As most epididymal lesions are benign, observation for asymptomatic cystic lesions
- Epididymitis
  - Consider sexually transmitted infection as source in young men and treat accordingly (See "Sexually Transmitted Infections [STIs] (Sexually Transmitted Diseases [STDs]), General)"
  - Older men more likely to be infected by enteric organisms *Escherichia coli*, other coliforms, and Pseudomonas

MEDICATION

First Line

- Epididymitis (3)[A]
  - < 35 year old: Consider gonorrhea and chlamydia
    - Ceftriaxone IM 500 mg × 1 AND
    - Azithromycin 1 g PO × 1
  - > 35 year old: Enteric organisms
    - Levofloxacin 500 mg PO daily × 10 days
- TB: Treat according to current CDC guidelines (http://www.cdc.gov/tb/)

Second Line

- Epididymitis (3)[A]
  - Doxycycline 100 mg PO BID × 10 days in lieu of azithromycin

SURGERY/OTHER PROCEDURES

- Excision of suspicious lesion via inguinal approach
- Frozen section
- If positive for malignancy, radical orchiectomy
- Further surgical therapy guided by pathology but may include retroperitoneal lymph node dissection if rhabdomyosarcoma

ADDITIONAL TREATMENT

Radiation Therapy

Use of radiation for local control of rhabdomyosarcoma in young patient is controversial

Additional Therapies

- Chemotherapy
  - Vincristine, cyclophosphamide, dactinomycin may have a role in rhabdomyosarcoma depending on extent of disease and oncologist recommendations (4)[A]

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Adenomatoid tumors
  - Benign, excellent prognosis
- Rhabdomyosarcoma
  - In children with low stage disease survival may be as high as 90%. Worst stage (IV), survival is ~5.2% (4)[A]

COMPLICATIONS

- Untreated epididymitis can cause severe systemic illness.
  - More advanced infections can present with testicular swelling and pain (epididymo-orchitis).
- If radiation or chemotherapy needed:
  - infertility, higher risk for secondary neoplasms including lymphoma, leukemia, soft tissue sarcomas

FOLLOW-UP

Patient Monitoring

- Oncologic follow-up if malignant disease
- Teach patient testicular self-exam

Patient Resources

National Cancer Institute.
http://www.cancer.gov/cancertopics/pdq/treatment/childrhabdomyosarcoma/Patient

REFERENCES

1. Montgomery JS, Blood DA. The diagnosis and management of scrotal masses. *Med Clin North Am.* 2011;95(1):235–244.
2. Grimsby GM, Ritchey ML. Pediatric urologic oncology. *Pediatr Clin North Am.* 2012;59(4):947–959.
3. Workowski KA1, Berman S; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR.* 2010;59(No. RR-12):1–110.
4. Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: Long-term results from the international society of pediatric oncology MMT95 study. *J Clin Oncol.* 2012;30(20):2457–2465.

ADDITIONAL READING

Rubenstein RA, Dogra VS, Seftel AD, et al. Benign intrascrotal lesions. *J Urol*. 2004;171(5):1765–1772.

See Also (Topic, Algorithm, Media)
- Adenomatoid Tumors, Testicular and Paratesticular
- Epididymal Cystadenoma/Papillary Cystadenoma
- Epididymis, Mass (Epididymal Tumor and Cysts) Images
- Epididymis, Metastasis to
- Epididymitis
- Hydrocele
- Paratesticular tumors
- Scrotum and Testicle, Mass
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General
- Sperm Granuloma
- Spermatocele
- Von Hippel–Lindau Disease

CODES

ICD9
- 222.3 Benign neoplasm of epididymis
- 608.89 Other specified disorders of male genital organs

ICD10
- D29.30 Benign neoplasm of unspecified epididymis
- D29.31 Benign neoplasm of right epididymis
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

- Most epididymal lesions are benign and should be followed serially.
- Treatment for epididymitis is guided by risk of STIs as a source.
- Ultrasound is important to delineate a testicular vs. paratesticular origin of the mass.
- Ultrasound cannot reliably differentiate malignant solid tumors from benign tumors.
- Rhabdomyosarcoma predominantly occurs in children.

EPIDIDYMITIS

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BASICS

DESCRIPTION

- Epididymitis is an inflammatory condition of the epididymis
  - Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts < 6 wk
    - Usually infectious but occasionally inflammatory due to trauma or other cause
  - Chronic epididymitis is characterized by a ≥ 6-wk history of symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis
- Infectious epididymitis is often associated with orchitis
  - Left untreated localized infectious epididymitis can lead to more extensive infection to include the testicle
- Thought to be the most common cause of scrotal pain in men

EPIDEMIOLOGY (1)

Incidence

Estimated at 1 in 100 males in the United States

Prevalence

- 42% of cases are in males 20–39 yr old
- Reported from infancy to the elderly population

RISK FACTORS

- High-risk sexual behavior (multiple sexual partners, sex without condoms)
- Poor hygiene
- Being uncircumcised
- Instrumentation or manipulation of the genitourinary tract
  - Catheterization, transurethral surgery
- Urinary tract obstruction (benign prostate hypertrophy, urethral strictures, bladder cancer, prostate cancer)
- Amiodarone usage
- Tuberculosis (TB)
- Treatment with Bacillus Calmette–Guérin (BCG) for superficial bladder cancer
- Systemic inflammatory diseases (Behçet disease, sarcoidosis)

Genetics

N/A

PATHOPHYSIOLOGY

- Acute infectious epididymitis (< 6-wk duration) is often due to retrograde spread of infection toward the epididymis
  - Infants and children

- Associated with congenital genitourinary abnormalities
- Reactive process after a nongenitourinary viral infection

– Sexually active males
- Associated with sexually transmitted diseases (STDs), often *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

– Elderly males
- Associated with urinary stasis from benign prostate hypertrophy and catheterization

• Other infectious causes:
– Bacterial
- *Escherichia coli*, *Salmonella enterica*, *Ureaplasma urealyticum*, *Corynebacterium pseudotuberculosis*, *Mycoplasma genitalium*, *Brucella ovis*, *Pseudomonas* species, *Toxoplasma* species

– Fungal (more common with HIV)
- *Cryptococcus* species

– Filarial
- *Wucheria bancrofti*

– Viral (more common with HIV)
- Cytomegalovirus

• Noninfectious epididymitis
– Trauma
– Amiodarone usage
- Antiamiodarone antibodies interact with the elevated concentration of amiodarone in the epididymis, leading to inflammation

– Behçet disease
- Etiology of epididymitis is unclear

– Sarcoidosis
- Noncaseating granulomas in the epididymis lead to inflammation

• Chronic epididymitis (>6-wk duration)
– Inadequately treated acute epididymitis
– Postvasectomy syndrome
- Reported in 1 in 100 males

• TB
– Suspected to be due to hematogenous spread; usually a chronic granulomatous reaction

• BCG treatment for superficial bladder cancer can lead to epididymitis

ASSOCIATED CONDITIONS

• Orchitis
• Hydrocele
• Immunosuppression

GENERAL PREVENTION

• Condom usage
• Proper hygiene
• Avoiding unnecessary instrumentation of the genitourinary tract

ALERT

Emergency evaluation for testicular torsion is indicated when the onset of pain is sudden, pain is severe, or the test results available during the initial examination do not support a diagnosis of infection.

DIAGNOSIS

HISTORY

- Testicular pain
  - Gradually worsens in epididymitis
  - Rapid onset and intense in testicular torsion
- Sexual intercourse without condom including anal receptive unprotected sex
- Instrumentation of the genitourinary tract
- Review of systems may help elucidate other causes (ie, amiodarone usage, TB, Behçet disease, sarcoidosis)
- Chronic Epididymitis Symptom Index (CESI) has been described for cases that last >3 mo

PHYSICAL EXAM

- Epididymal tenderness
  - Positive in 90–97% of patients
  - Ipsilateral and contralateral testicle may be involved
  - Spermatic cord may be involved
- Erythema of the scrotum
- Fever
- Genital exam
  - Lesions related to STDs
  - Urethral discharge
  - Ulcerations from Behçet disease
  - Hydrocele
    - A reactive process sometimes related to the epididymal inflammation
- Prostate exam
  - Rule out prostatitis, especially in males with chronic epididymitis
- Prehn sign
  - Used to rule out testicular torsion
  - Alleviation of pain, with elevation of the testicle, is more consistent with epididymitis (negative Prehn sign)
  - Only positive in 8% of children with epididymitis

DIAGNOSTIC TESTS & INTERPRETATION

Lab (3)

- Used to rule in a source of infection
- Urethral exudate
  - Gram stain with at least 5 white blood cells (WBC) per oil immersion field
    - Gram-negative bacilli is suggestive of *E. coli* infection and underlying cystitis
    - Intracellular gram-negative diplococci suggests a diagnosis of *N. gonorrhoeae* infection
    - Findings of only WBC are suggestive of *C. trachomatis* in 2/3 of cases
  - Send for culture and sensitivity

- Urine analysis
  - Assess for leukocyte esterase or at least 10 WBC per high power field
- Urine culture (midstream clean catch)
  - Send for culture and sensitivity
- C-reactive protein
  - Acute phase protein that is elevated in epididymitis
  - Sensitivity of 96.2%; specificity of 94.2%
- When an STD is suspected, the patient should be screened for other STDs, including human immunodeficiency virus (HIV)

Imaging (4,5)

- Color Doppler scrotal ultrasound (US)
  - Hyperemia and swelling in epididymitis
    - Sensitivity of 70%; specificity of 88%
    - Negative US, when positive clinical findings, should not necessarily alter management
  - Decreased blood flow in testicular torsion
    - Sensitivity of 100%
  - May identify an abscess
- Radionuclide imaging with Tc-99m pertechnetate
  - High sensitivity and specificity in differentiating testicular torsion from epididymitis
  - Rarely used in the United States

Diagnostic Procedures/Surgery

- Testicular exploration
  - Not used as 1st-line diagnostic procedure
  - Used when clinical suspicion for testicular torsion is high
- In infants and children with epididymitis, up to 75% have genitourinary abnormalities
  - Renal ultrasound and voiding cystourethrography are recommended when there are clinical signs of epididymitis and a positive urine culture

Pathologic Findings

- Inflammation
- Infection
- Possible fibrosis

DIFFERENTIAL DIAGNOSIS

- Abscess
- Chronic pelvic pain syndrome
- Epididymitis (acute vs. chronic)
- Interstitial cystitis
- Orchitis
- Partial spermatic cord torsion
- Prostatitis
- Referred pain (inguinal hernia renal colic, aneurysm, hip pain, lower back pain)
- Spermatocele
- Testicular cancer
- Testicular torsion

- Varicocele

TREATMENT

GENERAL MEASURES

- Acute epididymitis
  - Treat infections
  - Decrease inflammation (NSAIDs)
  - Pain control (NSAIDs, prescription pain medications)
  - Scrotal support
  - Ice/heat based on response
  - Avoid sexual activity for at least 1 wk following the initiation of therapy and until symptoms resolved
- Chronic epididymitis
  - Course of antibiotics is appropriate initially; if no relief observation and reassurance are recommended for mild symptoms
  - Scrotal support
  - Avoid aggravating activities
  - Local heat therapy/Sitz baths

MEDICATION (1)

First Line

- For infections tailor therapy to age and history
  - Ciprofloxacin and other quinolones are no longer recommended for gonococcal/nongonococcal infections due to resistance
- Empiric therapy to treat *N.* gonorrhea and *C. trachomatis* should be initiated pending lab results
  - Ceftriaxone 250 mg intramuscularly in a single dose along with either
    - Azithromycin 1 g PO × 1 dose OR
    - Doxycycline 100 mg orally BID for 10 days
- Epididymitis due to enteric organisms
  - Levofloxacin 500 mg orally once daily for 10 days or ofloxacin 300 mg orally twice daily for 10 days
- Epididymitis due to TB
  - Systemic antibiotics based on most current CDC guidelines or local guidelines if available local guidelines
- Epididymitis due to intravesical BCG
  - Fluoroquinolone (eg, levofloxacin 500 mg once daily)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Drainage if abscess present
- Epididymectomy (2)
  - Not used as 1st-line treatment

  – Reserved for severe acute or chronic epididymitis/epididymalgia
  – Patient needs to understand that there is only at best a 50% chance of pain relief
  – Outcomes appear improved in the setting of postvasectomy chronic epididymitis
  – Fertility issues need to be addressed
- Testicular denervation
  – Not widely used
  – Reserved for patients who failed conservative management
  – Pain relief noted in 71% of cases

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Scrotal elevation
- Limitation of activity
- Ice packs

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Pain often improves within 48–72 hr after treatment of acute epididymitis
  – Induration may remain for up to 4 wk
- Chronic cases can be difficult to treat

COMPLICATIONS

- Chronic or recurrent epididymitis
- Epididymal and/or testicular abscess
- Infertility
- Testicular atrophy
- Fournier gangrene

FOLLOW-UP

Patient Monitoring

- Patients should follow up within 3–7 days after initiation of treatment, especially if symptoms have not improved
- Infants and children may need to be assessed for genitourinary abnormalities
- Elderly males may need to be assessed for urinary tract obstructions
- Screening and treatment of partners for STDs

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=114

REFERENCES

1. Centers for Disease Control and Prevention. Epididymitis. *MMWR*. 2010;59(No. RR-12):67–69.

2. Hori S, Sengupta A, Shukla CJ, et al. Long-term outcome of epididymectomy for the management of chronic epididymal pain. *J Urol.* 2009;182:1407–1412.
3. Tracy CR, Steers WD, Costabile R. Diagnosis and management of epididymitis. *Urol Clin N Am.* 2008;35:101–108.
4. Wu HC, Sun SS, Kao A, et al. Comparison of radionuclide imaging and ultrasonography in the differentiation of acute testicular torsion and inflammatory testicular disease. *Clin Nucl Med.* 2002;27:490–493.
5. Yin S, Trainor JL. Diagnosis and management of testicular torsion, torsion of the appendix testis, and epididymitis. *Clin Pediatr Emerg Med.* 2009;10:38–44.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Acute Scrotum
- Acute Scrotum Algorithm
- Epididymitis Image
- Behçet Disease
- Orchitis, General Considerations
- Scrotum and Testicle, Mass
- Scrotum and Testicle, Mass Algorithm

CODES

ICD9

- 016.40 Tuberculosis of epididymis, unspecified
- 098.0 Gonococcal infection (acute) of lower genitourinary tract
- 604.90 Orchitis and epididymitis, unspecified

ICD10

- A18.15 Tuberculosis of other male genital organs
- A54.23 Gonococcal infection of other male genital organs
- N45.1 Epididymitis

CLINICAL/SURGICAL PEARLS

- In men <35-yr-old STI/STD with *C. trachomatis* and *N. gonorrhoeae* are the most common organisms responsible for bacterial epididymitis.
- In older men suspect coliform bacteria.
- Testicular torsion needs to be ruled out in cases of acute scrotal pain (clinical exam and Doppler US as appropriate).

EPISPADIAS

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BASICS

DESCRIPTION

- Congenital anomaly characterized by a dorsal opening of the urethra, resulting in dorsal chordee and widely displaced corporeal bodies.
- Often associated with the so-called "exstrophy–epispadias complex" a wide spectrum of abnormalities that can include classic bladder exstrophy, epispadias, and cloacal exstrophy.
  – Each of these anomalies is considered to arise from the same basic embryologic defect.

EPIDEMIOLOGY

Incidence

- 1 in 117,000 newborn males (1)[A]
- 1 in 484,000 newborn females (1)[A]
- Male > Female (3:1–5:1) (1)[A]

Prevalence

N/A

RISK FACTORS

None identified

Genetics

None sporadic

PATHOPHYSIOLOGY

- On the same spectrum of exstrophy
- Failure of medial migration of mesenchyme between the ectodermal and endodermal layers of the cloacal membrane due to premature rupture of the cloacal membrane
- The mesenchyme that forms the genital tubercles at the 5th wk of gestation fails to migrate completely toward the midline, resulting in a defect in the dorsal urethral wall

ASSOCIATED CONDITIONS

- Exstrophy
- Urinary incontinence
- VUR: Incidence of 30–75% (1)
- Inguinal hernias: Incidence of 33% (1)
- 2.8% concomitant renal anomalies, duplicated collecting system most common
- Concomitant colorectal anomalies with 1.8% (exstrophy/epispadias), imperforate anus most common

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Usually recognized at birth
- Less severe forms, especially in females, may go unrecognized until the child experiences persistent urinary incontinence after toilet-training or UTIs
- Urinary incontinence due to open bladder outlet and absence of urinary sphincter. The more proximal the urethral meatus, the greater the degree of incontinence
- There may be a family history of exstrophy–epispadias, although rare

PHYSICAL EXAM

- Males:
  - Displaced meatus, ranging from glans to penile shaft to peno-pubic region to subsymphyseal location
  - Open urethral plate visible on dorsum of phallus
  - Divergent peno-pubic attachments due to public diastasis, resulting in splaying of corpora cavernosa and a short, pendular penis with dorsal chordee, similar to that seen in exstrophy
  - Ventral hood of foreskin
  - Assess position of testes
- Females:
  - 3 degrees of female epispadias, according to Davis (1)
    - I: Urethral orifice appears patulous
    - II: Urethra split dorsally along most of urethra
    - III: Urethra open dorsally along its entire length into the bladder neck, rendering patient incontinent. Most common female type
  - Bifid clitoris
  - Mons pubis depressed and covered in glabrous skin
  - Labia minora poorly developed and terminated anteriorly at clitoris
  - Vagina and internal genitalia usually normal
- Other:
  - Should assess for any degree of bladder prolapse or exstrophy
  - Low-set umbilicus with exstrophy
  - Public diastasis due to outward rotation of innominate bones, usually not as wide as in exstrophy–epispadias complex
  - Evaluate for inguinal hernias

DIAGNOSTIC TESTS & INTERPRETATION

Lab

CBC, renal profile

Imaging

- Plain x-ray to assess orientation of pelvic bones; osteotomies should be done if pubic diastasis is >4 cm.
- Renal/bladder US to assess presence/absence of 2 kidneys and presence/absence of hydronephrosis, due to increased risk of renal agenesis, ectopic renal location, and VUR.
- Voiding cystourethrogram to assess bladder capacity, bladder outlet, presence/absence of

VUR.

Diagnostic Procedures/Surgery
Cystourethroscopy to assess length of urethra, presence/competency of sphincter, bladder capacity/quality, location/quality of ureteral orifices.

Pathologic Findings
- N/A

DIFFERENTIAL DIAGNOSIS
- Varying degree of epispadias
- Classic bladder exstrophy

TREATMENT

GENERAL MEASURES
- Usually managed along with bladder exstrophy, which is commonly present.
- Complete continence may not be achieved for months to years after initial surgery.
- In males, continence may not occur until puberty with maturation of prostate.

MEDICATION
First Line
Anticholinergic therapy may help with bladder development and modeling to promote increased capacity with good compliance once surgery has increased outlet resistance.

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Goals:
  - Protection of upper tracts, including correction of VUR and maintenance of a low-pressure system
  - Achieve urinary continence
  - Reconstruction of external genitalia for optimal functional and cosmetic results
- 1st stage:
  - Bladder closure between 3 to 6 mo of age. Patient is left with an epispadias
  - Can also be done as a single stage with bladder closure and urethral reconstruction known as the “Complete Primary Repair of Exstrophy.” Higher incidence of glanular loss than staged repair
  - Osteotomies are needed if the pubic diastasis is 4 cm or greater on plain x-ray. It was once thought that if the surgery was done in the 1st 48 hr of life that osteotomies are not needed. Current management favors osteotomies to maximize continence
  - Patients need to be immobilized after surgery to allow pelvic bone healing if osteotomies are needed
- 2nd stage:
  - Typically performed 6 mo to a year after 1st stage
- Males:
  - Administer testosterone stimulation preoperatively if penile length not adequate.

  - At 6 to 12 mo of age, perform modified Cantwell–Ransley epispadias repair, involving tubularization of intact urethral plate with reverse meatal advancement and transposition of urethra ventral to corpora cavernosa
  - Also must correct dorsal chordee by division of suspensory ligaments, freeing attachments from undersurface of inferior public ramus, and medially rotating the corpora cavernosa, and occasionally performing cavernostomy
- Females:
  - At 12–18 mo of age, perform genitoplasty and urethroplasty
  - Edges of urethra approximated for tubularization
  - Clitoris and labia minora reapproximated
  - Mons may be reconfigured
- 3rd stage:
  - Most commonly, Young–Dees–Leadbetter bladder neck reconstruction affords best chance at continence
  - Often, ureters must be reimplanted at same time due to proximity to bladder neck or VUR. Cohen technique usually preferred

ADDITIONAL TREATMENT

Further surgery may be necessary to correct complications of initial surgery or to achieve improved cosmesis or complete continence.

Additional Therapies

N/A

Complementary & Alternative Therapies

Psychological: If signs of self-esteem or sexual dysfunction arise, psychological therapy plays a crucial role and should be implemented early on in diagnosis of emotional issues.

ONGOING CARE

PROGNOSIS

- Continence rates after bladder neck reconstruction range from 70% to 87% (2 – 5).
- Satisfactory cosmesis after penile reconstruction ranges from 55% to 84% (6,7).
- Erectile function is almost universally preserved.
- The ability to participate in satisfactory intercourse and to have children is difficult to assess, as this requires long-term follow-up. Most reports seem to indicate the majority of patients can have intercourse and many males have even fathered children.

COMPLICATIONS

- The most common is fistula formation, with an incidence of 4–40% after urethroplasty in males, although many of these will close spontaneously (2,4,7).
- Other less common complications are stricture, meatal stenosis, wound infection, diverticulum, and ureteral obstruction.
- If there is tension on the closure, dehiscence is a major complication that might result.

FOLLOW-UP

Patient Monitoring

- After epispadias repair:

  – Remove urethral catheter 1–2 wk after surgery
  – Regular cystoscopy to assess urethra and bladder capacity
  – Regular upper tract monitoring with renal/bladder US to ensure healthy upper tracts.
- After bladder neck repair:
  – Initiate suprapubic tube capping trials a few weeks after surgery
  – Can remove SP tube once PVRS are minimal
  – Continuation of prophylactic antibiotics until resolution of VUR confirmed and child voiding well
  – Regular upper tract monitoring with US
  – Urodynamics may be necessary with cystometrogram and urethral pressure profilometry in cases of persistent incontinence or infection

Patient Resources

- PubMed Health. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002264/

REFERENCES

1. Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ, Kavoussi LR, Partin AW, et al. eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2012:3497–3553.
2. Kramer SA, Kelalis PP. Assessment of urinary continence in epispadias: Review of 94 patients. *J Urol*. 1982;128:290–293.
3. Arap S, Nahas WC, Giron AM, et al. Incontinent epispadias: Surgical treatment of 38 cases. *J Urol*. 1988;140:577–581.
4. Ben-Chaim J, Peppas DS, Jeffs RD, et al. Complete male epispadias: Genital reconstruction and achieving continence. *J Urol*. 1995;153:1665–1667.
5. Gearhart JP, Peppas DS, Jeffs RD. Complete genitourinary reconstruction in female epispadias. *J Urol*. 1993;149:1110–1113.
6. Mesrobian HJ, Kelalis PP, Kramer SA. Long-term followup of cosmetic appearance and genital function in boys with exstrophy: Review of 53 patients. *J Urol*. 1986;136:256–258.
7. Kajbafzadeh AM, Duffy PG, Ransley PG. The evolution of penile reconstruction in epispadias repair: A report of 180 cases. *J Urol*. 1995;154:858–861.

ADDITIONAL READING

- Hankinson JC, Eldridge MA, Ostrander R, et al. Emotional and behavioral functioning in children with bladder exstrophy-epispadias complex: A developmental perspective. *J Pediatr Urol*. 2013;S1477–5131(13):192–197.
- Lloyd JC, Wiener JS, Gargollo PC, et al. Contemporary epidemiological trends in complex congenital genitourinary anomalies. *J Urol*. 2013;190(suppl 4):1590–1595.
- Stec AA, Baradaran N, Gearhart JP. Congenital renal anomalies in patients with classic bladder exstrophy. *Urology*. 2012;79(1):207–209.
- Stec Stec, Baradaran N, Tran C, et al. Colorectal anomalies in patients with classic bladder exstrophy. *J Pediatr Surg*. 2011;46(9):1790–1793.
- Suson KD, Preece J, Baradaran N, et al. The fate of the complete female epispadias and exstrophy bladder - Is there a difference? *J Urol*. 2013;190(suppl 4):1583–1588.

See Also (Topic, Algorithm, Media)

- Epispadias Image ☼
- Exstrophy, Bladder (Classic Exstrophy)
- Exstrophy, Cloacal
- Exstrophy–Epispadias Complex

CODES

ICD9

- 752.62 Epispadias
- 753.5 Exstrophy of urinary bladder
- 753.8 Other specified anomalies of bladder and urethra

ICD10

- Q64.0 Epispadias
- Q64.10 Exstrophy of urinary bladder, unspecified

CLINICAL/SURGICAL PEARLS

- Female epispadias is not well recognized. It often presents after birth because of complaints of incontinence.
- Antenatal ultrasonography may be suggestive of exstrophy–epispadias complex: Findings of abnormal genitalia, low set umbilical cord, inability to identify bladder on ultrasound.

ERECTILE DYSFUNCTION, FOLLOWING PELVIC SURGERY OR RADIATION

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BASICS

DESCRIPTION

- Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection for sexual activity, is very common after major pelvic surgery or radiation.
- Curative therapy for prostate cancer, particularly radical prostatectomy (RP) and radiation therapy (RT), are well-defined causes of ED.
- ED after pelvic surgery is sudden in onset with gradual improvement within 24 mo postoperatively.
- ED after pelvic RT has an insidious onset, with a "honeymoon" period of 1 yr following treatment and significant worsening between 3–5 yr.

EPIDEMIOLOGY

Incidence

Not reported

Prevalence

- Rates of ED post-RP/RT vary widely due to definitions, patient populations, and time-point following treatment
- 30–90% after RP
- 6–90% after RT, including brachytherapy (BT)
- Prospective, multicenter, cohort study reported 2-yr ED rates: (1)[B]
  - 65% post RP
  - 63% post external beam RT
  - 57% post BT

RISK FACTORS

- Age
- Pretreatment erectile function
- Quality of nerve sparing
- Surgeon experience and volume
- Concomitant androgen deprivation therapy (ADT) with RT
- RT dose and duration
- Cardiovascular disease and risk factors

Genetics

- Single nucleotide polymorphisms (SNPs) have been identified that are associated with ED following RT but require validation.
- Genetics of cavernous nerve regeneration following RP are under investigation.

PATHOPHYSIOLOGY

- Pelvic Surgery/RP:
  - Injury to cavernosal nerves leading to neuropraxia and lethal axonal damage.
  - Apoptosis of smooth muscle and endothelium within the penis.
  - Potential end-organ failure with corporal smooth muscle fibrosis leading to cavernous venocclusive dysfunction over time.
  - Role of arterial injury is not well defined.
    - Data suggests preservation of accessory pudendal arteries may help prevent post-op ED.
- RT:
  - Endothelial cell and microvascular arterial injury leading to arterial insufficiency and ultimately ischemia.
  - Small likely role of cavernous nerve injury following RT.
  - RT-induced corporal tissue fibrosis leading to cavernosal vono-occlusive dysfunction (CVOD aka venous leak).

ASSOCIATED CONDITIONS

Treatment effects are generally dependent upon the modality used and are discussed elsewhere.

GENERAL PREVENTION

- Pelvic surgery/RP:
  - Cavernous nerve sparing surgery
  - Sparing of accessory pudendal arteries intraoperatively
- RT:
  - Reducing volume of tissue irradiated is postulated to reduce likelihood of ED
  - No definitive evidence supporting use of intensity-modulated radiation therapy (IMRT), BT, or proton beam RT to reduce ED
  - Treatment plans limiting RT to the corpora cavernosa may have a beneficial effect
- Penile rehabilitation:
  - Signals from studies suggesting early rehabilitation (phosphodiesterase Type 5 Inhibitors [PDE5i], intracavernosal injections) can impact posttreatment erectile status after RP and RT
  - Goals: Cavernosal oxygenation, preservation of endothelial function, prevention of corporal smooth muscle fibrosis
  - Optimal regimen for rehabilitation is not understood

DIAGNOSIS

HISTORY

- Medical history: Risk factors for general ED
  - Cardiovascular disease
  - Diabetes mellitus
  - Smoking
  - Peripheral neuropathy
  - Depression
  - Alcoholism
- Surgical history

  – Type and date of surgery
  – Nerve sparing status (if RP or radical cystectomy)
- Radiation history
  – Dose, template, radiation modality, and date
  – Use of ADT
- ED history
  – Validated questionnaires, ie, International Index of Erectile Function (IIEF)
  – Onset and severity of ED
  – Consistency of erectile quality
  – Presence of nocturnal erections
  – Prior use of therapy and response

PHYSICAL EXAM
- General physical exam
- Penile exam focusing on presence of tunical plaques and penile compliance
- Testicular volume and consistency as screening for hypogonadism

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Generally noncontributory.
- If evidence of hypogonadism, check early morning serum testosterone.

Imaging
- Duplex Doppler ultrasound of the penis
  – Can be used to evaluate for presence of vasculogenic ED
  – Peak systolic velocity <30 cm/s indicative of arterial insufficiency
  – End diastolic velocity >5 cm/s indicative of CVOD

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Hyperprolactinemia
- Medication induced: Antihypertensives, psychotropics, antiandrogens
- Neurogenic ED
- Profound hypogonadism
- Psychogenic ED
- Vasculogenic ED

TREATMENT

GENERAL MEASURES
- Perform cardiovascular risk assessment to evaluate fitness for sexual activity prior to treatment.
- Patient and partner should be informed of relevant treatment options, risks, and benefits.

MEDICATION

First Line

- PDE5i (2)[A]
  - Likely to be ineffective immediately after surgery given cavernosal nerve injury
  - Daily dosing frequently used in rehabilitation regimens
  - When used on-demand only, decreased response noted 2–3 yr after RT
  - Medications:
    - Sildenafil 50–100 mg: Onset 15–60 min, duration of action 4 hr
    - Vardenafil 10–20 mg: Onset 15–60 min, duration of action 2–8 hr
    - Tadalafil 10–20 mg: Onset 15–120 min, duration of action 24–36 hr
    - Avanafil 100–200 mg
  - Contraindications to PDE5i use:
    - Absolute contraindications: Use of nitrates
    - Sildenafil: Should be postponed for 4 hr after taking α-adrenergic antagonists
    - Vardenafil: Should not be taken with type 1A or type 3 antiarrhythmics or patient with long QT syndrome
  - Side effects: All associated with headache, dyspepsia, facial flushing
    - Tadalafil: Backache, myalgia
    - Sildenafil: Blurred/blue vision—reacts with PDE6 in retina

Second Line

- Intracavernosal injection therapy
  - Highly efficacious with up to an 89% response rate post-RP (3)[C]
  - Risks include priapism, penile pain, ecchymosis
  - Used in a variety of formulations
    - Single agent: Prostaglandin E_1
    - Bimix: Papaverine and phentolamine
    - Trimix: Papaverine, phentolamine, and prostaglandin E_1
- Intraurethral prostaglandin E_1 suppository (MUSE)
  - Variable efficacy
  - Penile pain frequently reported, especially in the immediate postoperative period

SURGERY/OTHER PROCEDURES

- Vacuum constriction devices
  - Low patient satisfaction given cumbersome application
  - Cooler, cyanotic appearance of vacuum-assisted erection appears “unnatural” to some
- Penile prosthesis implantation
  - Definitive therapy for patients failing or refusing 1st- and 2nd-line treatments
  - Generally, postponed until 2-yr post-RP as regeneration of cavernous nerves during this time may preclude need for surgical therapy
  - High patient satisfaction in appropriately selected population
  - Implant infection and malfunction risk must be discussed with patient preoperatively

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Limited data on combining modalities has been reported
  - Level 3 evidence: PDE5i + either transurethral or intracavernosal injection therapy generate better efficacy rates than either monotherapy alone
  - Level 4 evidence: Enhanced efficacy with the combination of vacuum-erection therapy + either PDE5i or transurethral PGE1 or intracavernosal injection therapy

Complementary & Alternative Therapies

- Data does not support use of trazodone, yohimbine, and herbal therapies. These medications are not recommended for use in ED by the American Urological Association
- Testosterone therapy
  - May be useful in aiding erectile function recovery only in patients with documented hypogonadism
  - Controversial; must discuss risks/benefits of androgen supplementation before initiating therapy, particularly in patients with a history of prostate cancer

ONGOING CARE

PROGNOSIS

- Improvement in erectile function can be noted after pelvic surgery, with maximal improvement noted between 18 and 24 mo postoperatively.
- Low likelihood of improvement in erectile quality after 2 yr postoperatively.
- Nadir of erectile function 3 to 5 yr after RT.
- Penile rehabilitation likely improves the prognosis of postsurgical/post-RT ED. Definitive data are pending.

COMPLICATIONS

- Significant effect on patient quality of life
  - Noted to be strongest predictor of patient satisfaction after prostate cancer therapy
- Depression

FOLLOW-UP

Patient Monitoring

- Variable dependent upon patient response to treatment.
- Close follow-up is recommended in patients on rehabilitation protocols to evaluate for erectile recovery.

Patient Resources

Mulhall JP. *Saving Your Sex Life: A Guide for Men with Prostate Cancer.* 1st ed. Chicago, IL: Hilton Publishing Company; 2008.

REFERENCES

1. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. *JAMA*. 2011;306(11):1205–1214.
2. Candy B, Jones L, Williams R, et al. Phosphodiesterase type 5 inhibitors in the management of erectile dysfunction secondary to treatments for prostate cancer: Findings

from a Cochrane systematic review. *BJU Int.* 2008;102(4):426–431.
3. Coombs, PG, Heck M, Guhring P, et al. A review of outcomes of an intracavernosal injection therapy programme. *BJU Int.* 2012;110(11):1787–1791.

ADDITIONAL READING

• Mendenhall WM, Henderson RH, Indelicato DJ, et al. Erectile dysfunction after radiotherapy for prostate cancer. *Am J Clin Oncol.* 2009;32:443–447.
• Mulhall JP, Bivalacqua TJ, Becher EF. SOP for the preservation of erectile function outcomes after radical prostatectomy. *J Sex Med.* 2013;10:195–203.

See Also (Topic, Algorithm, Media)

• Erectile Dysfunction/Impotence, General Considerations
• Penile Doppler Ultrasound, Indications and Parameters
• Penile Rehabilitation
• Reference Tables: International IIEF (Sex Function Survey)

CODES

ICD9

607.84 Impotence of organic origin

ICD10

• N52.31 Erectile dysfunction following radical prostatectomy
• N52.32 Erectile dysfunction following radical cystectomy
• N52.39 Other post-surgical erectile dysfunction

CLINICAL/SURGICAL PEARLS

• ED after pelvic surgery and RT is highly prevalent and frequently underestimated in physician marketing materials.
• ED after pelvic surgery is immediate in onset with 18- to 24-mo time to maximal recovery.
• ED after RT has an insidious onset, with nadir of erectile function at 3- to 5-yr post-RT.
• Data on penile rehabilitation is conflicting but increasingly shows an improvement in posttreatment erectile recovery.
• The majority of postpelvic surgery/RT ED patients are effectively treated with PDE5i ± intracavernosal injection therapy.

ERECTILE DYSFUNCTION/IMPOTENCE, GENERAL CONSIDERATIONS

Nathaniel Readal, MD
Trinity J. Bivalacqua, MD, PhD

BASICS

DESCRIPTION

Consistent or recurrent inability to attain and/or maintain an erection sufficient for satisfactory sexual activity

EPIDEMIOLOGY

Incidence

- Crude incidence: 26 cases/1,000 man years
  - Incidence increases with each decade above 40
    - 12 cases/1,000 man years: 40–49 yr
    - 30 cases/1,000 man years: 50–59 yr
    - 46 cases/1,000 man years: 60–69 yr

Prevalence

- Increases universally with age and medical comorbidities (cardiovascular disease, hypertension, smoking, inactivity, obesity)
  - Prevalence by age
    - Below age 40: 1–9%
    - 40–59 yr: 20–30%
    - 60–69 yr: 20–40%
    - >70 yr: 50–75%

RISK FACTORS

- Probability of ED increases with presence of each risk factor
  - Diabetes mellitus
    - Prevalence of ED 3 times higher in diabetic men
    - ED occurs at earlier age and increases with disease duration
    - Associated with 14 times increased risk of cardiovascular morbidity and mortality
  - Cardiovascular disease (hyperlipidemia, hypertension, peripheral vascular disease)
  - Lower urinary tract symptoms/Benign prostatic hyperplasia (BPH)
  - Chronic renal failure, chronic liver disease
  - Endocrinopathies (hypogonadism, Cushing disease)
  - Prior abdominal/pelvic/penile surgery, radiation or trauma
  - Priapism, Peyronie disease
  - Neurologic disease (Parkinson disease, dementia, prior stroke)
  - Depression/Psychological disorders
  - Long-distance cycling
  - Smoking

- Medications
  - Antihypertensives (thiazide diuretics, β-blockers, α_2-agonists)
  - ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers cause less ED/may improve erectile function
  - Psychotropics (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, lithium)
  - Antiandrogens
  - Miscellaneous (digoxin, cimetidine, spirolactone, marijuana)
  - Tobacco smoking

Genetics

- Several gene polymorphisms linked with ED
- Angiotensin-converting enzyme (ACE) polymorphisms may be risk factors for vasculogenic ED and endothelial nitric oxide synthase (eNOS) polymorphisms alone or in combination with other genetic polymorphisms implicated in ED

PATHOPHYSIOLOGY

- Mechanism of erection
  - Relaxation of cavernosal smooth muscle (contracted in flaccid state inhibiting inflow of blood)
    - Mediated by NO release from pelvic nerves and endothelial cells
    - Increased cyclic GMP (cGMP) and cyclic AMP (cAMP) trigger signaling pathways leading to decreased intracellular calcium causing smooth muscle relaxation, increased penile blood flow, and tumescence
    - Smooth muscle relaxation further promoted due to inhibition of Rho-kinase
    - Veno-occlusive mechanism prevents outflow of blood from penis and maintains erection
    - cGMP degraded by phosphodiesterase type 5 (PDE5)
- Organic ED
  - Vasculogenic
    - Arteriogenic—atherosclerotic lesions decrease arterial inflow to penis
    - Venogenic—failure of corporal vasoocclusion
  - Neurogenic—Alzheimer disease, Parkinson disease, injury to central nervous system, spinal cord, or peripheral nerves
  - Anatomic
  - Endocrinologic (hyperprolactinemia, hyper or hypothyroidism, adrenal disorders/Cushing syndrome)
- Psychogenic ED
  - Only accounts for 10% of ED
  - More common in men <35 yr old
    - May result from lack of interest in partner, performance-related anxiety, negative mood, life stressors

ASSOCIATED CONDITIONS

- Atherosclerosis
- Diabetes mellitus
- Hypertension, stroke

- Depression
- Parkinson disease, multiple sclerosis
- Priapism
- Peyronie disease
- Prostate cancer

GENERAL PREVENTION
- Avoidance of tobacco use
- Optimal medical management of commonly associated conditions
- Increase exercise/weight loss
- Split bicycle seat for long-distance cycling

DIAGNOSIS
HISTORY
- Medical history—comorbid conditions, medications, alcohol, tobacco, recreational drug use, history of cycling
- Surgical history
- Psychosexual history
  - Status of current relationship
  - Level of libido/interest in sex
  - Quality of erection
  - Duration of ED
  - Onsent of ED (sudden vs. gradual)
  - Presence of nocturnal/early morning erections
  - Presence of penile curvature, plaque, pain
  - International Index of Erectile Function Questionnaire (IIEF-5)
    - 5 questions scored individually from 0–5 (maximum of 25 points, higher score indicated better function)
    - Classifies ED into severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25)

PHYSICAL EXAM
- Neurologic: Stroke, CNS disease, visual field defects, neuropathy, perineal sensation
- Endocrinologic: Atrophic testes, gynecomastia, loss of secondary sexual characteristics
- Cardiovascular: Blood pressure, femoral/pedal pulses, lower extremity ischemia
- Penile: Curvature, Peyronie disease plaques
- Rectal exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Complete blood count
- Serum chemistries
- Fasting glucose level, hemoglobin A1C
- Lipid profile
- Serum total testosterone
- Thyroid function tests (optional)

- PSA (suspect prostate pathology)
- Urinalysis (glucose as indicator of diabetes)

Imaging

- Duplex penile ultrasound—most reliable and least invasive modality for assessing ED
- Provides imaging evaluation and quantification of penile blood flow

Diagnostic Procedures/Surgery

ALERT

A trial of oral pharmacotherapy is warranted prior to an invasive procedure/test

- Specialized testing indicated for:
  - Young men < 40 yr old
  - Men with previous perineal/pelvic trauma
    - Combined intracavernosal injection and stimulation (CIS) with duplex ultrasound (US): Intracavernosal injection of vasodilator with genital/audiovisual sexual stimulation and measurement of erection/blood flow—provides objective measurement of vascular parameters
    - Penile angiography: Reserved for young patient with ED secondary to traumatic arterial disruption/compression to evaluate for revascularization
    - Nocturnal penile tumescence (RigiScan®): Automated, portable measurement of presence of nocturnal erections—can confirm integrity of neurovascular axis, diagnose psychogenic ED

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

Psychogenic erectile dysfunction, depression, possible early sign of cardiovascular disease

TREATMENT

GENERAL MEASURES

- Treatment choice should be made among physician, patient, and partner after evaluation of risk/benefits of all treatment choices
- Cardiovascular risk assessment should be performed before initiating therapy
  - Low risk: Asymptomatic, < 3 risk factors—may proceed with treatment
  - Intermediate risk: Asymptomatic, ≥ 3 risk factors, stable angina, or mild heart failure—requires full cardiovascular assessment to reclassify as high vs. low risk
  - High risk: Unstable angina, recent myocardial infarction, uncontrolled hypertension, advanced heart failure or valvular disease—defer until cardiac condition stabilized

MEDICATION

First Line

- PDE5 inhibitors (PDE5i): Inhibit breakdown of smooth muscle cGMP promoting smooth muscle relaxation. > 50% of patients will respond
  - Drugs:
    - Sildenafil 50–100 mg : Onset 15–60 min, duration of action 4 hr

- Vardenafil 10–20 mg: Onset 15–60 min, duration of action 2–8 hr
- Tadalafil 10–20 mg: Onset 15–120 min, duration of action 24–36 hr
- Avanafil 100–200 mg

– Contraindications to PDE5i use:
- Absolute contraindications: Use of nitrates
- Sildenafil: Should be postponed for 4 hr after taking α-adrenergic antagonists
- Vardenafil: Should not be taken with type 1A/type 3 antiarrhythmics or with long QT syndrome

– Side effects: All associated with headache, dyspepsia, facial flushing
- Tadalafil: Backache, myalgia
- Sildenafil: Blurred/blue vision—reacts with PDE6 in retina

Second Line

• Intracavernous injection therapy
– Mechanism: Self-injection of vasoactive agent into corpora cavernosa producing rapid erection
– Drugs:
- Alprostadil (PGE1)
- Bimix: Papaverine and phentolamine
- Trimix: Papaverine, phentolamine, and prostaglandin E_1

– Side effects: Fibrosis, priapism, painful erection, hematoma
– Contraindications: Monoamine oxidase medication usage, decreased manual dexterity
– Efficacy: 80–90% effective in wide range of patients

• Intraurethral therapy
– MUSE:Medicated urethral system for erection
– Mechanism: Insertion of alprostadil containing pellet into distal urethral, absorbed into corpora cavernosa production erection within 30 min
– Side effects: Penile/vaginal pain, dysuria
– Contraindications: Priapism risk
– Efficacy: $<50\%$ effective

• Vacuum constriction device
– Effective 2nd-line treatment and represents an alternative/adjunct to pharmacotherapy
– Pursued prior to surgical intervention
– Produces negative penile pressure, engorging corpora with blood
– Constrictive ring at the base of penis maintains tumescence
– Side effects: Penile ischemia when duration of use >30 min, pain, abnormal color of penis

SURGERY/OTHER PROCEDURES

• IPP
– Indications: Failed 1st- and 2nd-line pharmacotherapy or vacuum erection device
– Mechanism: Definitive ED treatment with placement of inflatable cylinders into corpora cavernosa
– Complications: Infection (1–3%), erosion ($<5\%$), mechanical malfunction (5–10%)

• Penile revascularization
– Reserved for select young patients with clearly documented arterial occlusion

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Psychosexual therapy: Referral for sex therapy in patients with psychogenic ED. Cognitive behavioral intervention identifies sexual stressors and refocus maladaptive thought processes

Complementary & Alternative Therapies

No FDA-approved dietary supplements or herbal medications for ED but gingko biloba, red ginseng, yohimbine reportedly improve ED

ONGOING CARE

PROGNOSIS

Excellent if reduction of cardiovascular risk factors, weight loss, exercise, smoking cessation

COMPLICATIONS

N/A

FOLLOW-UP

Patient Monitoring

- Patients to be reevaluated periodically with following considerations:
  - Response to initial therapy
  - Need for dose titration
  - Patient education on proper medication use (specific PDE5i on empty stomach, use of local injection therapy)
  - Need for progression to 2nd-line therapy/surgery based on therapeutic effectiveness and patient satisfaction

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=60

REFERENCES

1. Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders-Elsevier; 2012.
2. Carson CC, Lue TF. Phophodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int*. 2005;96:257–280.
3. Burnett AL. Evaluation and management of erectile dysfunction. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders-Elsevier; 2012.

ADDITIONAL READING

Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: An AUA update. *J Urol*. 2005;174(1):230–239.

See Also (Topic, Algorithm, Media)

- Erectile Dysfunction Algorithm

- Erectile Dysfunction, Following Pelvic Surgery or Radiation
- Erectile Dysfunction/Impotence, General Considerations Image
- Penile Rehabilitation

CODES

ICD9

- 302.72 Psychosexual dysfunction with inhibited sexual excitement
- 607.84 Impotence of organic origin

ICD10

- F52.21 Male erectile disorder
- N52.9 Male erectile dysfunction, unspecified
- N52.39 Other post-surgical erectile dysfunction

CLINICAL/SURGICAL PEARLS

- ED is a symptom of multiple underlying diseases that affect the following: penile nerve, artery, endothelial or smooth muscle function.
- Cardiac risk assessment should occur prior to initiation of therapy.
- Surgical therapy (penile prosthesis) is an essential therapy when medical treatment has failed or is contraindicated.

EXSTROPHY, BLADDER (CLASSIC EXSTROPHY)

Grahame H.H. Smith, MBBS

BASICS

DESCRIPTION

- Classic bladder exstrophy is a major genitourinary anomaly characterized by the bladder laying open on the abdominal wall with an associated lower midline abdominal wall hernia. The defect extends from the umbilicus to the distal end of the phallus, resulting in coexistent epispadias in males and a bifid clitoris in females.
- Classic exstrophy is considered midway in severity between cloacal exstrophy and epispadias, as part of exstrophy–epispadias complex.

EPIDEMIOLOGY

Incidence

- 1 in 10,000–50,000
- Male > Female (2:1)

Prevalence

N/A

RISK FACTORS

Genetics

- Multifactorial etiology without definite genetic link (1)
  - May be associated with p63 gene dysregulation
  - Chromosomal regions 4q31.21–22, 19q13.31–41, and 22q11.21 may harbor genes associated with exstrophy
- Risk in sibling is 1 in 100; risk in offspring is 1 in 70

PATHOPHYSIOLOGY

- Incompletely understood, 2 predominant theories
- 1st theory postulates that an incomplete ingrowth of mesoderm is unable to reinforce cloacal membrane, which results in premature rupture and subsequent failure to develop ectoderm and mesoderm. The timing of the rupture determines cloacal (earlier) vs. classic exstrophy vs. epispadias (later)
- 2nd theory describes an overgrowth of cloacal membrane preventing medial migration of mesenchymal tissue. Bladder smooth muscle cells in exstrophy patients show lower intracellular calcium concentrations and enhanced migration

ASSOCIATED CONDITIONS

- Usually healthy without any other major organ system defects
- Subsequent inguinal hernia common
- Rarely may be associated with duplication of bladder or urethra, colorectal abnormalities (2%), cleft lip and palate, subsequent testis tumors
- In contrast, cloacal exstrophy has much more extensive anomalies

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY
Any family history of exstrophy

PHYSICAL EXAM
- Bladder exposed on abdominal wall
- Bladder plate size
- Lateral ureteric orifices
- Males have an open bladder neck and prostate, the short and broad phallus is open dorsally with dorsal chordee
- Females have an open bladder neck and urethra, bifid clitoris lateral to urethra and anteriorly situated vagina
- Low-set umbilicus with foreshortened distance to pubis
- Pubic diastasis with external rotation of pelvis

DIAGNOSTIC TESTS & INTERPRETATION
- Antenatal
  - May be diagnosed on antenatal ultrasound study due to absence of the bladder (1st trimester) or reduced umbilical to pubic length (2nd trimester)

Lab
- Full blood count, electrolytes, creatinine
- Blood type and cross-match in preparation for surgery

Imaging
- Renal ultrasound
- Pelvic x-ray to document pubic diastasis

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
- Exstrophic bladders may have more type III collagen and fewer myelinated nerve fibers
- If left untreated and exposed, the urothelium undergoes squamous metaplasia as a response to acute and chronic inflammation

DIFFERENTIAL DIAGNOSIS
- Cloacal exstrophy
- Omphalocele
- Gastroschisis
- Epispadias

TREATMENT

GENERAL MEASURES

- Antenatal
  - Consider MRI assessment and *karyotyping*. Options for termination may be discussed
- Immediate postnatal care:
  - 2-0 silk suture on umbilical cord as close to abdominal wall as possible
  - Cover bladder with a nonadherent dressing (eg, Saran Wrap) to prevent excoriation
  - Irrigate with normal saline and apply a new dressing with each diaper change

MEDICATION

First Line

No medical treatment is available to close the bladder wall

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Ideally the extrophy is closed on next elective list with two senior staff in attendance:
  - Requires an adequate bladder plate but the minimum size is not defined
  - If unable to easily approximate pubis, then may need pelvic osteotomy
  - Pelvic osteotomy may reduce the incidence of dehiscence and subsequent prolapse in females
- Avoid latex exposure to prevent latex allergy
- 3 contemporary closures (2)
- Classic repair involves 3 stages:
  - Immediate bladder closure
  - Epispadias repair at 6 mo
  - Bladder neck repair at 5 yr:
    - Requires >100-cc bladder capacity and motivation for continence
- Complete primary repair of bladder exstrophy (CPRE):
  - Epispadias repaired along with bladder as neonate with penile disassembly (if male)
- Kelly repair:
  - Soft tissue mobilization away from pelvic sidewall with midline closure without the need for pelvic osteotomy
- Associated surgery
  - Prophylactic inguinal hernia repair in males is advised
  - Ureteric reimplantation may be required subsequently

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Delayed closure in the case of a late presentation
- All need osteotomy with option of external fixation
- Inadequate bladder plate:
  - Delay closure with osteotomies, once adequate
  - If remains inadequate consider augmentation at time of closure
- Postoperative:

- Ensure maximal urinary drainage with ureteric stents, suprapubic tube, and urethral catheter
- With our without pelvic immobilization (traction, Buck, Bryant; Mermaid dressing; spica cast)
  - Optimal duration of immobilization not established
- Remove stents one at a time; suprapubic only removed after ensuring appropriate bladder emptying

Complementary & Alternative Therapies

N/A

ONGOING CARE

- Subsequent operative treatment options:
  - Bladder neck plasty (failure rate 50%)
  - Bladder neck closure (failure rate 2%) with augmentation and Mitrofanoff conduit
  - Ureterosigmoidostomy (plus or minus Mainz II pouch)
  - Umbilicoplasty
  - Radial forearm flap phalloplasty (males)
  - Vaginoplasty, clitoroplasty (females)

PROGNOSIS

- Life expectancy normal
- Urinary continence in 50–90%; definition of continence disputed; most common definition of continence is dry with voiding or catheterization every 3 hr (3)
- May require multiple surgeries
- Quality-of-life scores are less than the normal. Functional results seem to be the most likely predictive factor of health-related QOL score

COMPLICATIONS

- Failure of primary closure; 10%
- Failure to store (urinary incontinence secondary to incompetent outlet plus or minus poor bladder compliance)
- Failure to empty (after closure or after bladder neck procedure)
- Upper tract damage and renal failure due to high bladder pressures and or high outlet resistance
- Developmental psychopathology
- Male: Infertility, retrograde ejaculation, urethrocutaneous fistula, loss of phallus (complete penile disassembly, Kelly repair), inadequate phallus, testis tumors
- Female:
  - Vaginal stenosis, requiring vaginoplasty
  - Degree of diastasis association with risk of uterine prolapse
  - Enterocystoplasty may lead to false-positive pregnancy test
  - Normal fertility possible, Cesarean delivery suggested
- Increased risk of adenocarcinoma of bladder
- Increased risk of colonic adenocarcinoma after ureterosigmoidostomy

FOLLOW-UP

Patient Monitoring

- After discharge:
  - Antibiotic prophylaxis to prevent urinary tract infections
  - Regular ultrasound to assess for hydronephrosis, residual volume, and bladder volume
  - Yearly colonoscopy starting 10 yr after ureterosigmoidostomy

Patient Resources

The Association of Bladder Exstrophy. Community. http://bladderexstrophy.com/

REFERENCES

1. Mahfuz I, Darling T, Wilkins S, et al. New insights into the pathogenesis of bladder exstrophy-epispadias complex. *J Pediatr Urol*. 2013;9(6 Pt B):996–1005.
2. Mahajan JK, Rao KL. Exstrophy epispadias complex - Issues beyond the initial repair. *Indian J Urol*. 2012;28:382–387.
3. Lloyd JC, Spano SM, Ross SS, et al. How dry is dry? A review of definitions of continence in the contemporary exstrophy/epispadias literature. *J Urol*. 2012;188(5):1900–1904.

ADDITIONAL READING

- Palmer B, Frimberger D, Kropp B, et al. http://www.pediatricurologybook.com/bladder_exstrophy.html
- Reiner WG. A brief primer for pediatric urologists and surgeons on developmental psychopathology in the exstrophy-epispadias complex. *Semin Pediatr Surg*. 2011;20(2):130–134.

See Also (Topic, Algorithm, Media)

- Epispadias
- Exstrophy, Cloacal
- Exstrophy–Epispadias Complex
- Exstrophy, Bladder (Classic Exstrophy) Images

CODES

ICD9

753.5 Exstrophy of urinary bladder

ICD10

- Q64.11 Supravesical fissure of urinary bladder
- Q64.19 Other exstrophy of urinary bladder

CLINICAL/SURGICAL PEARLS

- Achieving normal urinary continence with normal voiding after repair is uncommon. It is almost always possible to achieve continence if the patient is willing to undertake clean intermittent catheterization.
- Males will tend to be unhappy about the length of their penis. However, what they lack in length they gain in width.

- For the inexperienced clinician it is sometimes difficult to identify the gender of a newborn baby with bladder exstrophy. Boys almost always have bilateral palpable gonads.

EXSTROPHY, CLOACAL

Jason C. Fisher, MD
Harry P. Koo, MD, FAAP, FACS

BASICS

DESCRIPTION

- Cloacal exstrophy, or vesicointestinal failure, is a congenital abnormality of the infraumbilical abdominal wall. Its presentation is highly variable, but key features include an exomphalos with an exstrophied cecum flanked by two hemibladders
- Ureteral orifices present on each hemibladder. Cecal plate has orifices to three structures:
  - Appendix
  - Blind-ending hindgut (colonic remnant)
  - Ileum, often prolapsed elephant-trunk deformity
- Most severe anomaly along epispadias–exstrophy complex (EEC) spectrum
- When neurospinal defects and omphalocele occur with cloacal exstrophy, it is termed OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects)

EPIDEMIOLOGY

Incidence

- One of the rarest urologic anomalies
- Widely quoted historic incidence of 1:200,000 to 1:400,000 based on statistical estimates
- More accurate and contemporary international registries now estimate 3:100,000 to 8:100,000.
- Male ≥ Female (1:1–2:1)

RISK FACTORS

- No well-defined causative factors; statistical analysis of large registries identifies the following:
  - Bimodal risk of maternal age: <20 year old or >30 year old
  - Intrauterine fet al demise of twin pregnancy
  - In vitro fertilization

Genetics

- Most cases are sporadic
- Some cases reported with genetic causation:
  - Unbalanced translocation of 9q and Yq
  - Homeobox mutations at HLXB9 and HOX

PATHOPHYSIOLOGY

- Traditionally postulated embryologic theories:
  - Premature cloacal membrane rupture (8 wk)
  - Failed cloacal partition by lateral folds of Rathke
  - Incomplete descent of a cloacal septum
- Current understanding of cloacal exstrophy embryogenesis (1)[B]:

– Disrupted cellular proliferation and apoptosis of dorsal cloacal wall and infraumbilical mesenchyme—this disrupts the infraumbilical body wall, everts the cloacal cavity, and wedges the pubic bones and genital tubercles apart

ASSOCIATED CONDITIONS

- Upper genitourinary anomalies:
  - Unilateral renal agenesis (33%)
  - Pelvic kidney (33%)
  - Hydronephrosis (33%)
  - Horseshoe kidney
  - Fusion anomalies
  - Ureteral anomalies
- Lower genitourinary anomalies:
  - Separation or absence of clitoral/phalic halves
  - Separation of scrotum or labia
  - Undescended testicles/bilateral hernias
  - Uterine and vaginal duplication anomalies
- Gastrointestinal anomalies:
  - Omphalocele (88–100%)
  - Short-gut (25%; source of major morbidity)
  - Intestinal malrotation
  - Intestinal duplication
  - Imperforate anus/anal atresia
- Central nervous system anomalies:
  - Tethered spinal cord
  - Myelomeningocele
  - Aberrant pelvic autonomic nerve anatomy
  - Impaired continence, ambulation, erectile function
- Musculoskelet al anomalies:
  - Symphysis pubis diastasis
  - Sacral dysplasias and vertebral anomalies
  - Scoliosis
  - Hip subluxation and acetabular dysplasia
  - Lower limb anomalies
- Serious cardiovascular and pulmonary anomalies are uncommon with cloacal exstrophy

DIAGNOSIS

Cloacal exstrophy is a major congenital anomaly. Prompt referral and coordination with a variety of specialists including pediatric urology, pediatric general surgery, pediatric orthopedics, neonatology, pediatric gastroenterology, pediatric neurosurgery, endocrinology, genetics, and social work is needed.

HISTORY (ANTENATAL)

- Major diagnostic criteria (2)[A]:
  - Nonvisualization of the bladder (91%)

  - Large midline infraumbilical anterior abdominal wall defect or cystic anterior abdominal wall structure (82%)
  - Omphalocele (77%)
  - Lumbar myelomeningocele (68%)
- Prolapsed ileal segment can be pathognomic

PHYSICAL EXAM

- The classic collection of findings include:
  - Exstrophy of the bladder
  - Complete phallic separation
  - Wide pubic diastasis
  - Cecal plate everted between 2 hemibladders
  - Blind-ending hindgut; no well-formed colon
  - Omphalocele
- Thorough assessment for associated anomalies (see "Associated Conditions"):
  - Spinal and vertebral defects
  - Lower extremity malformations
  - Patency and position of anus
  - Presence of descended testicles
- Detailed exam of exstrophy:
  - Males: Divided corpus cavernosum and glans
  - Females: Divided clitoris, duplicated vagina
  - Additional müllerian anomalies
  - Identification of ureteral orifices: Two exstrophied hemibladders are on either side of the exstrophied intestinal segment. Each half usually drains the ipsilateral ureter
  - Identification of intestinal orifices: Appendix, hindgut, ileum (often prolapsed)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Karyotype
- CBC, basic metabolic panel:
  - At risk for nongap metabolic acidosis due to absorption of urine chloride by intestinal mucosa
  - Type and cross blood for surgery

Imaging

- Plain CXR, sacral and spinal x-rays
- Ultrasounds of abdomen, kidneys, head, spine
- Consider MRI to detect occult spinal lesions if no obvious dysraphism and US nondiagnostic
- Skelet al and bony films of pelvis and lower extremities as needed
- Echocardiogram: Low incidence of associated cardiac lesions, but advisable in the preop setting

DIFFERENTIAL DIAGNOSIS

- Unique appearance makes it unlikely to confuse with other conditions
- Exists along EEC spectrum
- Consider isolated bladder exstrophy, giant isolated omphalocele, large epispadias

TREATMENT

GENERAL MEASURES

- Assessment of newborn with anomaly:
  - Immediate cardiopulmonary stabilization
  - Neonatology management of prematurity
  - IV access: UA and UV lines not possible
- Protection and prevention maneuvers:
  - Ligate umbilical cord with silk tie (avoid plastic clip which will irritate bladder mucosa)
  - Lower half of infant in bowel-bag initially
  - Cover exstrophic tissue with plastic wrap
  - Protect omphalocele: Minimal handling
  - Assess for open spinal cord defects
  - Place nasogastric tube for decompression
  - Prophylactic antibiotics (ampicillin and gentamicin)
- Contact specialists (see under “diagnosis" heading above) immediately.
- Detailed exam to assign gender
  - Identification of phallus, labia/scrotum, testes
  - Consistent with the karyotype if possible

MEDICATION

First Line

- IVF support: Adjust for fluid losses across exstrophied mucosa
- At risk for hyperchloremic metabolic acidosis
- Generally not candidates for epidural anesthesia due to spinal dysraphism

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Open spinal anomaly: Prompt neurosurgical repair required before addressing exstrophy.
- Exstrophy repair at 48–72 hrs of life if stable
  - Combined pediatric urology and general pediatric surgery
  - Usually staged approach vs. single stage
- Multistage approach (3)[B]: Creates classic bladder exstrophy anatomy at conclusion of initial surgery described above; preferred for most cases. General principles of Stage 1:
  - Separate hemibladders from cecal plate
  - Revert any prolapsed terminal ileum
  - Mobilize, rescue, and preserve any hindgut
  - Tubularize the cecum to bring terminal ileum, cecum, and hindgut into closed continuity
  - Create end colostomy from distal hindgut
  - Assess and preserve müllerian anatomy
  - Excise and close omphalocele if possible
  - Anastomose hemibladders in midline
- Single-stage approach (4)[B]: In highly select patients, can proceed with bladder and abdominal wall closure and phallic reconstruction which may avoid osteotomies, minimize

bladder scarring. Otherwise, Stage 2 is performed in late infancy, mirroring a classic bladder exstrophy repair:
  – Mobilize bladder plate and posterior urethra deep into pelvis: Yields incontinent bladder.
  – Orchiopexy with repair of inguinal hernias
  – Reconstruct gender-based external genitalia
  – Pubic reapproximation +/– pelvic bone osteotomies with fixation and traction for 4–6 wk
- Stage 3 involves procedures aimed at continence and genital cosmesis and is addressed in older children, often involving bladder augmentation and catherizable conduits
- Surgical pitfalls to avoid:
  – Injury to ureteral orifices: Place stents
  – Overaggressive closure of a large omphalocele defect leading to compartment syndrome
  – Excising/discarding diminutive male phalic remnants and assigning female gender: Controversial and still occurs with unclear long-term consequences
  – Excising/discarding the hindgut even if short
  – Primary perineal pull-through of the hindgut (can be performed in highly select patients)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Large omphaloceles not amenable to primary closure can be treated with Silvadene-mediated epithelialization of sac followed by delayed closure, or by excision of sac and placement of a silo with gradual staged reduction of viscera
- Consider gastrostomy tube placement and/or tunneled central line during initial repair if patient appears at risk for short-gut syndrome

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Survival >90% over last 20 yr
- Nutrition and growth is the most important determinant of early survival and morbidity
  – 30–50% will have failure to thrive before age 5
  – Important to avoid using any bowel for GU reconstruction procedures until child is thriving
- After 3 yr, quality-of-life issues outweigh nutritional concerns
  – Urinary continence: Rarely achieved; dependent on a compliant reservoir and continent catherizable conduit
  – Fecal continence: Usually managed by enema regimen, rarely are perineal pull-through maneuvers associated with any continence
  – Gender assignment and reconstruction, especially for genetic males raised as females
  – Ambulation impairments
  – Gynecologic issues after onset of menarche
  – Psychosexual problems

COMPLICATIONS

- Infection and breakdown of repair
- Abdominal compartment syndrome
- Short-gut syndrome
- Vesicoureteral reflux and hydronephrosis
- Hirschsprung-type enterocolitis in the dysmotile hindgut, even after colostomy formation

FOLLOW-UP

Requires a multidisciplinary team (see "Diagnosis") to coordinate regular follow-up through all stages of surgical repair, with careful attention to nutrition and growth in infancy, and both surgical and psychological support for the multiple quality of life issues which begin in childhood and persist into adulthood

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=91

REFERENCES

1. Vermeij-Keers C, Hartwig NG, van der Werff JF. et al. Embryonic development of the ventral body wall and its congenital malformations. *Semin Pediatr Surg*. 1996;5:82–89.
2. Austin PF, Homsy YL, Gearhart JP, et al. The prenatal diagnosis of cloacal exstrophy. *J Urol*. 1998;160:1179–1181.
3. Stolar CH, Randolph JG, Flanigan LP. Cloacal exstrophy: Individualized management through a staged surgical approach. *J Pediatr Surg*. 1990;25:505–507.
4. Zderic SA, Canning DA, Carr MC, et al. The CHOP experience with cloacal exstrophy and gender reassignment. *Adv Exp Med Biol*. 2002;511:135–147.

ADDITIONAL READING

- Mathews R, Jeffs RD, Reiner WG, et al. Cloacal exstrophy: Improving the quality of life: The Johns Hopkins Experience. *J Urol*. 1998;160:2452–2456.
- McHoney M, Ransley PG, Duffy P, et al. Cloacal exstrophy: Morbidity associated with abnormalities of the gastrointestinal tract and spine. *J Pediatr Surg*. 2004;39:1209–1213.
- Reiner WG. Psychosexual development in genetic males assigned females: The cloacal exstrophy experience. *Child Adolesc Psychiatric Clin N Amer*. 2004;13:657–674.
- Soffer SZ, Rosen NG, Hong AR, et al. Cloacal exstrophy: A unified management plan. *J Pediatr Surg*. 2000;35:932–937.

See Also (Topic, Algorithm, Media)

- Epispadias
- Exstrophy–Epispadias Complex
- Exstrophy, Bladder (Classic Exstrophy)
- Exstrophy, Cloacal Images ☼

CODES

ICD9

753.5 Exstrophy of urinary bladder

ICD10
Q64.12 Cloacal extrophy of urinary bladder

CLINICAL/SURGICAL PEARLS

- Meticulous assessment of associated anomalies can prevent early clinical and surgical mishaps, particularly with regard to spinal defects.
- A multidisciplinary team is critical to the short- and long-term outcomes of these children.
- A staged surgical repair remains the preferred approach for most children with cloacal exstrophy.
- Do not underestimate the impact of early gender assignment: Avoid irreversible surgical resection of structures that may be useful for genital reconstruction.
- Save as much bowel as possible, especially the short hindgut, to maximize nutritional capability.

FERTILITY AND CANCER THERAPY, UROLOGIC CONSIDERATIONS

James M. Hotaling, MD, MS
Craig S. Niederberger, MD, FACS

BASICS

DESCRIPTION

- 2006 ASCO Guidelines recommend that all patients in their reproductive years undergoing cancer therapy be offered fertility preservation options (1)
- Mainstay of fertility preservation in men is referral to a reproductive specialist and sperm cryopreservation
- Sperm cryopreservation is often not covered by insurance but Livestrong Foundation and Fertile Hope offer financial support (2)

EPIDEMIOLOGY

Incidence

- 1.4 million people are diagnosed with cancer every year
- 10% of those diagnosed with cancer are <44 yr old (3)
- Testicular cancer is one of the most common cancers seen by men in their reproductive years and typically presents to urologists

Prevalence

Advances in cancer treatment have led to increased survival rates of 75–80% for those diagnosed <50 yr old (4)

RISK FACTORS

Men with male factor infertility (azoospermia) are significantly more likely to develop testis cancer

Genetics

N/A

PATHOPHYSIOLOGY

- Men presenting with cancer often have reduced semen quality (3)
- Radiation at doses of 2.5 Gy to the testis causes prolonged azoospermia
- Radical pelvic surgery can cause erectile and ejaculatory dysfunction
- Certain common chemotherapeutic agents cause prolonged azoospermia (1)
  - Cisplatin (500 mg/m^2)
  - Chlorambucil (1.4 g/m^2)
  - Cyclophosphamide (19 g/m^2)
  - Procarbazine (4 g/m^2)
  - Melphalan (140 mg/m^2)
  - Others shown to be gonadotoxic:
    - Busulfan, carmustine, cytarabine, ifosfamide, lomustine, nitrosoureas

ASSOCIATED CONDITIONS

- Hematologic malignancies
  - Whole-body radiation used before bone marrow transplant usually causes life-long infertility
- Prostate cancer can directly impact fertility through sperm impairment and indirectly through erectile dysfunction (5)
  - Radical prostatectomy and its effect on fertility should be disclosed to the patient preoperatively
  - Brachytherapy does not give a large dose of radiation to the testicles, and most men will remain fertile or recover sperm production
  - External radiation is more likely to cause permanent infertility, even if the testicles are shielded
- Testicular cancer
  - More than half of the patients with testicular germ cell cancer showed impaired fertility
  - Retrograde ejaculation following retroperitoneal lymphadenectomy

GENERAL PREVENTION

- Radiation to the testicles can cause permanent loss of sperm production
- Unless the cancer is in the testicles, attempt to protect them from radiation by using a shield called a clam shell (5)

DIAGNOSIS

HISTORY

- Thorough reproductive history
  - Gonadotoxin exposure?
  - Previous difficulty with conception?
  - Use of exogenous steroids?
  - Varicocele surgery?
  - Diagnosis of cystic fibrosis?
- Discussion of desire for future paternity
- Assessment of onset of puberty in adolescent patients
  - Nocturnal emissions?
  - Sexually active?

PHYSICAL EXAM

- Assessment of Tanner stage in adolescent males
- Focused testicular exam
  - Longitudinal testicular axis
  - Presence of vas deferens
  - Presence of epididymis

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Evaluation of baseline FSH, LH, estradiol, total testosterone, sex hormone binding globulin (SHBG), and albumin (to calculate bioavailable T)
- Values for optimal spermatogenesis

  - Bioavailable T >155 ng/dL
  - FSH <4.5
  - Total testosterone:estradiol ratio > 10:1
- Semen analysis by a high-volume lab: WHO 5th edition lower limits of normal
  - Sperm concentration >39 million/mL
  - Motility >40%
  - Total motile count >15 million
  - Morphology >4% normal by Kruger strict criterion

Imaging

N/A

Diagnostic Procedures/Surgery

If men are found to be azoospermic on semen analysis consider microsurgical testicular sperm extraction (microTESE)

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

N/A

TREATMENT

GENERAL MEASURES

- Semen analysis with cryopreservation of ejaculated sperm by a high-volume lab
  - Men with testis cancer or Hodgkin disease should bank multiple times given known lower recovery rates (3,6)
  - Any sperm obtained from semen analysis should be banked
  - Patients should abstain from ejaculation for 2 days before banking sperm but not more than 3 days
  - At least 2–3 samples should be banked for each patient
  - A frank discussion with the patient regarding the ongoing costs of cryopreservation and methods for patient contact in the future is vital
- Attempts to obtain and bank seminiferous tubules from prepubertal males for use in future-assisted reproductive technologies should only be done under an IRB-approved research protocol (4)
- All discussions for adolescents and children should involve both the patient and their parents
- Electroejaculation or vibratory stimulation may be used for patients with a spinal cord injury

MEDICATION

First Line

- To convert a retrograde ejaculation to an antegrade ejaculation
  - In the United States, ephedrine is most often used
  - In Europe, imipramine is also used
- α-adrenergic agents (dosing highly variable)

– Pseudoephedrine 60 mg
– Ephedrine 25–50 mg
– Imipramine 25–50 mg (may cause dizziness and nausea); commonly used in Europe
– Frequency ranges from QD to QID
– Duration ranges from 2 to 14 days
– Side effects: HTN, tachycardia

Second Line
N/A

SURGERY/OTHER PROCEDURES
In men who are azoospermic, aspiration of seminiferous tubules from the testis, sperm from the epididymis or microTESE with extraction of sperm and cryopreservation is a viable option and should be offered

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Roughly 30% of men who receive gonadotoxic chemotherapy or radiotherapy will remain azoospermic permanently

COMPLICATIONS
N/A

FOLLOW-UP
Patient Monitoring
- Men should have a repeat interrogation of their male endocrine axis and another semen analysis by a reproductive health specialist when they desire paternity
- Some men may be hypoandrogenic after completion of treatment and referral to a reproductive health specialist is essential to ensure that they are offered medication other than testosterone for androgen repletion

Patient Resources
- Oncofertility Consortium: http://oncofertility.northwestern.edu/
- Fertile Hope: www.fertilehope.org
- ASRM Cancer and Fertility Preservation: http://www.asrm.org/Cancer_and_Fertility_Preservation/

REFERENCES
1. Lee SJ, Schover LR, Partridge Ah, et al. American Society of Clinical Oncology

recommendations on fertility preservation in cancer patients. *J Clin Oncol.* 2006;24:2917–2931.
2. Woodruff TK. The Oncofertility Consortium–addressing fertility in young people with cancer. *Nat Rev Clin Oncol.* 2010;7:466–475.
3. Hotaling JM, Lopushnyan NA, Davenport M, et al. Raw and test-thaw semen parameters after cryopreservation among men with newly diagnosed cancer. *Fertil Steril.* 2013;99:464–469.
4. Trost LW, Brannigan RE. Oncofertility and the male cancer patient. *Curr Treat Options Oncol.* 2012;13:146–160.
5. http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/radia therapy-principles-side-effectsof-radiationto-specific-areas (accessed June 14, 2014).
6. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. *N Engl J Med.* 2009;360:902–911.

ADDITIONAL READING

WHO laboratory manual for the examination and processing of human semen, 5th edition, http://whqlibdoc.who.int/publications/2010/9789241547789_eng.pdf

See Also (Topic, Algorithm, Media)

- Kruger Strict Sperm Morphology
- Retrograde Ejaculation
- Semen Analysis, Abnormal Findings, and Terminology
- Semen Analysis, Technique, and Normal Values
- Tanner Stage

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 606.8 Infertility due to extratesticular causes
- V26.82 Encounter for fertility preservation procedure

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- N46.024 Azoospermia due to radiation
- Z31.84 Encounter for fertility preservation procedure

CLINICAL/SURGICAL PEARLS

- <10% of men who bank sperm retrieve it for use in assisted reproductive technologies.
- Referral to a reproductive specialist and sperm cryopreservation prior to initiation of gonadotoxic chemotherapy, radiation, or radical oncologic surgery is essential.
- Cost of sperm cryopreservation typically ranges from $200 to $500 initially usually with an annual maintenance fee.

FILLING DEFECT, UPPER URINARY TRACT (RENAL PELVIS AND URETER)

Scott G. Hubosky, MD

BASICS

DESCRIPTION

- Radiographic diagnosis of a radiolucent entity occupying the confines of the upper urinary tract including the intrarenal collecting system or ureter, as seen against contrast within the intraluminal space
- The finding itself is nonspecific but may represent malignant or benign processes
- Ureteroscopic evaluation is the gold standard to establish definitive diagnosis

EPIDEMIOLOGY

Incidence

- Difficult to define given the nonspecific nature of the radiographic finding
  - Upper tract urothelial carcinoma (UTUC)
    - Estimated 5,900–7,300 new cases in USA in 2014 (1)[C]

Prevalence

- Nephrolithiasis
  - Reported prevalence of kidney stones in USA between 1976 and 1994 was 13% in men and 7% in women (2)[C]

RISK FACTORS

- For UTUC
  - History of smoking
  - History of urothelial carcinoma of the bladder
  - Gene carrier or family history of Lynch syndrome (hereditary nonpolyposis colorectal cancer)
- For nephrolithiasis
  - Previous stone history
  - Chronic dehydration
  - Dietary factors
    - Elevated sodium intake
    - Purine gluttony
- For sloughed papilla
  - NSAID overuse
  - Sickle cell disease or trait
  - History of diabetes
- For fungus ball
  - Immunosuppression

Genetics

N/A

PATHOPHYSIOLOGY
Depends on underlying etiology

ASSOCIATED CONDITIONS
- Hematuria
  - Gross
  - Microscopic
- Flank pain

GENERAL PREVENTION
- Depends on underlying etiology
  - UTUC
    - Smoking cessation/avoidance
  - Nephrolithiasis
    - Adequate hydration
    - Diet and lifestyle modification to prevent future stone formation

DIAGNOSIS
HISTORY
- Flank pain or renal colic
- Hematuria
  - Gross
  - Microscopic
- Pre-existing malignancy
- History or urinary diversion
- Prior urinary tract manipulation (stent, stone treatment, etc.)

PHYSICAL EXAM
- Costovertebral angle tenderness
- Patient may by asymptomatic

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
- Urine cytology may suggest malignancy
- Urine culture including fungal cultures
- Serum creatinine/BUN

Imaging
- Filling defects are found in imaging modalities which utilize contrast that fills the intrarenal collecting system
  - Intravenous injection of contrast
    - CT urogram
    - MR urogram
    - IVP
    - Invasive arteriograms (cardiac catheterization, aortogram, etc.)
  - Intraluminal administration of contrast

- Retrograde pyelogram
- Antegrade nephrostogram
- Cystogram (if reflux present)

Diagnostic Procedures/Surgery

Ureteroscopic evaluation is required to obtain definitive diagnosis and provides for direct visual inspection with relatively low morbidity (3)[C]

Pathologic Findings

Depends on underlying etiology

DIFFERENTIAL DIAGNOSIS

- Malignant lesions
  - UTUC
  - Rare primary cancers of the upper urothelial surface
    - Squamous cell carcinoma (often associated with chronic untreated infected staghorn calculi)
    - Adenocarcinoma
    - Inverted papilloma (about 15% have malignant components)
    - Sarcoma
    - Leiomyosarcoma
    - Angiosarcoma
    - Small cell carcinoma
  - Metastatic carcinoma
    - Melanoma
    - Renal cell carcinoma
- Benign lesions
  - Air: Iatrogenic, infectious, fistula
  - Blood clot
  - Fibroepithelial polyp
  - Fungus ball
  - Hemangioma
  - Inflammatory lesions: Granuloma, malakoplakia, TB
  - Inverted papilloma
  - Calculus (usually radiolucent)
  - Benign tumors (rare): Leiomyoma, neurofibroma, cholesteatoma
  - Extrinsic compression of the ureter
  - Mucous (urinary diversion patients)
  - Protein matrix
  - Ureteritis or pyelitis cystica
  - Vascular impression
  - Fibroepithelial polyp
  - Papilla
    - Prominent papilla (ectopic or end on; normal anatomic variant)
    - Sloughed papilla (may cause obstruction or hematuria)
  - Foreign body

- Stent fragment (retained)
- Staple/clip (more likely with urinary diversion)

TREATMENT

GENERAL MEASURES

- If any doubt exists about the etiology of the filling defect then diagnostic ureteroscopy is indicated
- Prominent papilla may appear as filling defects in the very peripheral aspect of renal calyces in an "end on" position

MEDICATION

First Line

- For stones composed purely of uric acid manifesting as filling defects, alkalization of the urine can be attempted and if pH of 6.5 or greater is achieved then uric acids may dissolve over time
  - Potassium citrate
  - Sodium bicarbonate

Second Line

N/A

SURGERY/OTHER PROCEDURES

- UTUC
  - For low-grade UTUC which can be reached ureteroscopically and completely ablated, 5-yr survival is equal to radical nephroureterectomy (4)[C]
    - After complete ablation, local recurrence can be seen in up to 75% of patients if followed for at least 5 yr.
    - Progression of low-grade to high-grade disease occurs in about 15% of cases
    - These points should be stressed to patients when counseling on the management of UTUC
  - For high-grade UTUC or very large-volume low-grade UTUC, radical extirpative surgery is considered the gold standard for cancer control
    - Nephroureterectomy (open or laparoscopic)
    - Segmental ureterectomy
- Nephrolithiasis
  - Ureteroscopy with laser lithotripsy
  - ESWL with or without retrograde pyelogram to assist with localization or with ultrasound guidance
  - PCNL
- Sloughed papilla
  - Ureteroscopy confirms diagnosis
    - Papilla can be removed primarily with ureteroscopic grasper or basket
    - Coagulation with cautery or laser will achieve hemostasis
    - Avoid overuse of NSAIDs
- Fibroepithelial polyp

  - Can be removed with ureteroscopy using laser or grasper
- Fungus ball
  - Can be removed with ureteroscopy or percutaneous approach
  - Antifungals

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- UTUC
  - Neoadjuvant chemotherapy is currently under investigation for suspected high-stage disease with preliminary data suggesting down staging on pathologic specimens

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Depends on underlying etiology
  - Prognosis usually excellent for benign conditions
  - UTUC (prognosis depends on pathologic staging) (5)[C]. TNM pathologic staging and prognosis is as follows:
    - pTo, pTa, and pTis have 93% and 89% cancer-specific survival at 5 and 10 yr
    - pT1 has 91% and 85% cancer-specific survival at 5 and 10 yr
    - pT2 has 75% and 70% cancer-specific survival at 5 and 10 yr
    - pT3 has 54% and 45% cancer-specific survival at 5 and 10 yr
    - pT4 has 12% and 6% cancer-specific survival at 5 and 10 yr

COMPLICATIONS

N/A

FOLLOW-UP

Patient Monitoring

- UTUC
  - For those undergoing ureteroscopic conservative treatment, regular surveillance including cystoscopy and ureteroscopy is required given high chance of local recurrence
  - Cross-sectional imaging (CT or MRI) is recommended to check for locally advancing disease
  - For those undergoing radical nephroureterectomy (NU), surveillance cystoscopy and cross-sectional imaging are also needed on a regular basis
- Nephrolithiasis
  - Renal ultrasound, serum electrolyte testing
  - For patients at high risk for stone recurrence, 24-hr urine electrolyte evaluation

Patient Resources

N/A

REFERENCES
1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(1):9–29.
2. Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int.* 2003;63:1817.
3. Conlin MJ. Diagnostic ureteroscopy. In: Smith AD, et al. *Smith's Textbook of Endourology*. 3rd ed. Chichester: Wiley and Blackwell, 2012.
4. Grasso M, Fishman AI, Cohen J, et al. Ureteroscopic and extirpative treatment of upper urinary tract urothelial carcinoma: A 15-year comprehensive review of 160 consecutive patients. *BJU Int.* 2012;110:1618–1626.
5. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: A series from the upper tract urothelial carcinoma collaboration. *Cancer*. 2009;115:1224–1233.

ADDITIONAL READING

- Hubosky SG, Boman BM, Charles S, et al. Ureteroscopic management of upper tract urothelial carcinoma (UTUC) in patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome). *BJU Int.* 2013;112(6):813–819. doi: 10.1111/bju.12008
- Matin SF, Margulis V, Kamat A, et al. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract urothelial cell carcinoma. *Cancer.* 2010;116:3127–3134.
- Stower MJ, MacIver AG, Gingell JC, et al. Inverted papilloma of the ureter with malignant change. *BJU*. 1990;65:13.
- Xu AD, Ng CS, Kamat A, et al. Significance of upper urinary tract urothelial thickening and filling defect seen on MDCT urography in patients with a history of urothelial neoplasms. *Am J Roentgenol.* 2010;195:959–965.

See Also (Topic, Algorithm, Media)
- Fibroepithelial Polyp, Genitourinary
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter) Image
- Fungal Infections, Genitourinary
- Reference Tables: TNM: Renal Pelvis and Ureter Cancer
- Ureter and Renal Pelvic Tumors, General Considerations
- Ureter and Renal Pelvis, Squamous Cell Carcinoma
- Ureter and Renal Pelvis, Urothelial Carcinoma
- Urolithiasis, Ureteral

CODES

ICD9
- 189.1 Malignant neoplasm of renal pelvis
- 189.2 Malignant neoplasm of ureter
- 793.5 Nonspecific (abnormal) findings on radiological and other examination of genitourinary organs

ICD10
- C65.9 Malignant neoplasm of unspecified renal pelvis
- C66.9 Malignant neoplasm of unspecified ureter

- R93.4 Abnormal findings on diagnostic imaging of urinary organs

CLINICAL/SURGICAL PEARLS

- Up to 40% of patients with an upper tract urothelial carcinoma will develop urothelial carcinoma of the bladder.
- Ureteroscopy can be both diagnostic and therapeutic.

FLANK PAIN, GENERAL

Taylor B. Vaughan, MD
James S. Rosoff, MD

BASICS

DESCRIPTION

- Flank pain refers to pain or discomfort in the side of the abdomen between the last rib and the hip.
- Sometimes referred to as loin pain, it is often associated with urologic conditions, although not exclusively.

EPIDEMIOLOGY

Incidence

True incidence is difficult to ascertain, as it is a common symptom associated with many medical conditions.

Prevalence

- Many medical conditions can cause flank pain, the prevalence is high.
- Up to 12% of the adult US population will suffer from urolithiasis at some point.

RISK FACTORS

Risk factors are dependent upon etiology

Genetics

NA

PATHOPHYSIOLOGY

- Flank pain caused by urologic pathology is usually due to sudden stretch of the renal capsule, generally from inflammation or distal obstruction.
- The severity of the pain is directly related to the acuity of the obstruction and not to its degree.
- Flank pain from renal inflammation has a gradual onset and is often not as severe as renal colic due to acute obstruction.
- Flank pain from chronic obstruction is generally less severe, or may be absent.

ASSOCIATED CONDITIONS

Pregnancy Considerations:

- Flank pain during pregnancy may be a symptom of an obstructing ureteral stone or pyelonephritis, as well as hydronephrosis of pregnancy which may be present in 60–100% of women (more commonly on the right).

GENERAL PREVENTION

- Strategies depend on the etiology of the pain.
- Preventive strategies for calculous disease may include dietary modification and medical management to reduce recurrent stone formation.
  – Dietary modifications include increasing fluid intake, and reducing intake of sodium,

animal protein, and oxalate-rich foods.
  – Drugs such as citrate, allopurinol, and thiazide diuretics may be necessary depending on the underlying metabolic abnormality.
  – Calcium reduction has not been shown to affect the likelihood of recurrent stone formation in most patients.

DIAGNOSIS

HISTORY

- Age and sex of patient
- Pain characteristics
  – Location: Flank(s)/abdomen
  – Quality: Dull/sharp
  – Duration: How long have symptoms been present
  – Severity: Use visual analog pain scales
  – Timing: Constant/intermittent, onset (sudden vs. gradual)
  – Radiation: Pain radiating from the flank down into the testicle or labia may suggest renal colic caused by passage of stone or clot down the ureter
  – Moderating factors: Medications, rest, position
  – Aggravating factors: Movement, cough
  – Associated symptoms: Fever, chills, dysuria, nausea, vomiting
- Prior medical history
  – History of nephrolithiasis (stone recurrence rates: 10%, 1 yr; 35%, 5 yr; 50%, 10 yr)
  – Diabetes mellitus, patients have higher predisposition to papillary necrosis and infections, including xanthogranulomatous pyelonephritis (XGP) and emphysematous pyelonephritis
  – GYN history (pregnancy/STDs)
  – History of trauma (penetrating vs. blunt)
- Prior surgical history
  – General surgical, urologic, and gynecologic abdominal and pelvic procedures involving a potential risk of ureteral injury and obstruction (TAH/BSO, vascular bypass, AAA repair, colectomy, ureteral manipulation)
- Social history
  – Smoking is a risk factor for development of urothelial carcinoma
- Family history
  – Polycystic kidney disease
  – Renal cell carcinoma

PHYSICAL EXAM

- Vital signs
  – Temperature: Fever is usually associated with infectious etiologies
  – Blood pressure
    ◦ Hypotension: Suspect sepsis or hemorrhage (eg, ruptured angiomyelolipoma (AML), aortic aneurysm), may need immediate intervention
    ◦ Hypertension: May reflect response to pain. Rule out renal parenchymal, renal cystic, or vascular disease
- Abdominal exam

  - Inspect for scars, skin changes, or signs of trauma
  - Bruit with aneurysm
  - Palpate abdomen and flanks to evaluate for masses, organomegaly, or tenderness
  - Fist percussion of flank: CVA tenderness suggests renal etiology
- Peripheral pulses with aneurysm

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Initial diagnostic step in the management of flank pain. Ensure proper specimen collection: Clean catch or catheterized specimen.
  - Dipstick test is performed to evaluate for the presence of blood and/or infection. If abnormal, it should be followed by microscopic analysis and sent for culture and sensitivities.
  - Presence of epithelial cells suggests a contaminated sample.
  - Hematuria suggests insult to the urologic system.
  - Urinary pH: >7.6 should raise suspicion for the presence of urea-splitting organisms.
  - A pH <5 is often associated with the formation of uric acid calculi.
  - Nitrite and/or LE positivity: Indicates presence of infection or inflammation. Nitrite positivity is more specific for infection than LE positivity.
- Urine and blood cultures: Collect prior to administration of antibiotic therapy.
- CBC: Elevated WBC suggests infectious or inflammatory process. Low Hgb/Hct may suggest hemorrhage.
- Chemistry profile: Assess renal function and electrolytes; elevated BUN/creatinine and reduced creatinine clearance suggest renal insufficiency/failure.
- Liver function panel: Rule out malignant hepatic processes.
- Other tests may be ordered depending on clinical presentation and judgment.

Imaging (1)

- Plain radiograph. Historically, a kidney ureter bladder abdominal flat plate plain film (KUB) was the initial radiograph done for the evaluation of flank pain to rule out urolithiasis. However, KUB may be unable to demonstrate small or radiolucent (eg, uric acid, indinavir) calculi. May show nephrocalcinosis. Overall sensitivity for stone detection is 59%.
- Excretory urogram/IVP
  - Once the standard for urologic evaluation of flank pain, IVP is very accurate, with the diagnosis of calculous disease able to be established in 96% of cases.
  - Aids in quantifying severity of obstruction.
  - Contraindications to the use of IV contrast media include renal insufficiency and previous reaction to contrast media.
  - Limitations include the complexity and length of time needed to perform the series of images.
- CT
  - Low-dose, noncontrast-enhanced CT has largely replaced KUB and IVP as the standard imaging modality for the workup of acute flank pain from suspected urolithiasis. It has been shown to be very sensitive and specific (97% and 96%, respectively) in detecting calculi.

- It can detect secondary signs of obstruction (hydronephrosis, renal enlargement, perinephric stranding), and can also be used to assess nonrenal causes of flank pain (appendicitis, pancreatitis, tubal pregnancy, etc.).
- Renal/ureters/bladder US
  - Can diagnose hydronephrosis with a sensitivity of 85–94% and a specificity of 100%.
  - Disadvantages: Sensitivity for detecting stones only 24–57%, limited in obese patients, and operator-dependent.
- Nuclear scan: Helps to evaluate differential renal function, degree of obstruction, and presence of renal scarring.
- MRI: Not usually indicated for initial workup unless CT is contraindicated. It may be helpful for evaluation of renal masses or in the evaluation of suspected spinal cord pathology.

Diagnostic Procedures/Surgery

These are dependent upon etiology

Pathologic Findings

These are dependent upon etiology

DIFFERENTIAL DIAGNOSIS

- There are many causes of flank pain. It is useful to differentiate between urologic and nonurologic causes. Renal/ureteral etiologies are the most common and those that usually require urologic intervention. Some of the most common causes are listed below (2).
  - Urologic
    - Calculi: Mostly ureteral; however, renal pelvic and calyceal stones (obstructing infundibulum) can cause flank pain
    - Acute cortical necrosis
    - Acute papillary necrosis
    - Ptotic kidney
    - Polycystic kidney disease
    - Acute/chronic pyelonephritis
    - Renal infarction (renal artery thrombus or dissection)
    - Renal cyst (especially hemorrhagic; benign cysts rarely cause flank pain)
    - Renal neoplasm
    - Renal trauma
    - Renal vein thrombosis
    - Retroperitoneal bleed or mass
    - Ureteropelvic junction obstruction
    - Calyceal diverticulum
    - Medullary sponge kidney
    - Other ureteral obstruction (extrinsic compression, blood clot, necrotic material, etc.)
  - Nonurologic
    - Appendicitis
    - Abdominal aortic aneurysm
    - Diabetes
    - Diverticulitis
    - Herpes zoster

- Musculoskelet al (muscle spasm, costochondritis, strain)
- Myocardial infarction
- Ovarian torsion
- Pancreatitis
- Peripheral nerve compression or trauma
- Peripheral neuropathy
- Pleuritis
- Tubal pregnancy
- Vertebral or spinal cord/nerve root irritation (herniated disc, sciatica, vertebral body fracture, or collapse)

TREATMENT

GENERAL MEASURES (3)

- Treatment varies based on etiology.
  - Rest and physical therapy may be recommended for flank pain cause by muscle spasms.
  - NSAIDs are excellent 1st-line agents to control pain secondary to inflammation, but caution must be used in the presence of acute ureteral obstruction or in patients with advanced renal disease as they can decrease intrarenal blood flow.

MEDICATION

First Line

- Acute pain control (NSAIDs, opioids)
- Antiemetics, antipyretics, antibiotics as appropriate
- IV fluids if sepsis/hypovolemia. May also help with passage of stones

Second Line

α-antagonists and calcium channel blockers may help with expulsion of ureteral stones.

SURGERY/OTHER PROCEDURES

- Prior to any diagnostics or intervention, the patient must be stabilized.
- Surgical management may be required in some cases depending on the etiology and the patient's medical condition.
- Examples of surgical management: If the collecting system is infected and obstructed or renal abscess is present, percutaneous drainage and antibiotics are the mainstays of treatment. If dealing with a ruptured AML, embolization should be considered. Renal tumors should be treated on an elective basis. Emergent nephrectomy for ruptured AML or XGP/emphysematous pyelonephritis may be necessary.

ADDITIONAL TREATMENT

Radiation Therapy

NA

Additional Therapies

NA

Complementary & Alternative Therapies

NA

ONGOING CARE

- Follow-up for flank pain will also be dictated by the etiology and acuity of the clinical presentation. Repeat imaging or other lab studies may be required depending on response to initial therapy.
- If clinical picture fails to improve or worsens, a change in therapy should be instituted (ie, different antibiotic, PCN, surgical intervention).

PROGNOSIS

In general, for nephrolithiasis, the prognosis is good but this may vary for other etiologies.

COMPLICATIONS

Longstanding ureteral obstruction can cause permanent loss of renal function.

FOLLOW-UP

Patient Monitoring

Periodic renal imaging, urinalysis, or 24-hr urine may be indicated for patients with stone disease. Follow-up may be more or less intensive based on etiology.

Patient Resources

MedlinePlus http://www.nlm.nih.gov/medlineplus/ency/article/003113.htm

REFERENCES

1. Carter MR, Green BR. Renal calculi: Emergency department diagnosis and treatment. *Emerg Med Pract.* 2011;13(7):1.
2. Coursey CA, Casalino DD, Remer EM, et al. ACR Appropriateness Criteria acute onset flank pain–suspicion of stone disease. *Ultrasound Q.* 2012;28(3):227–233.
3. Marx JA, Hockberger RS, Walls RM, et al. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 7th ed. St Louis, MO: Mosby; 2010.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Calcifications, Abdominal and Pelvic
- Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Adult
- Renal Mass
- Urolithiasis, Adult, General
- Urolithiasis, Pediatric, General Considerations

CODES

ICD9

- 592.9 Urinary calculus, unspecified
- 788.0 Renal colic
- 789.09 Abdominal pain, other specified site

ICD10

- N20.9 Urinary calculus, unspecified

- N23 Unspecified renal colic
- R10.9 Unspecified abdominal pain

CLINICAL/SURGICAL PEARLS

- Flank pain associated with fever and chills may represent urinary tract infection (pyelonephritis).
- Abdominal aortic aneurysm is a potentially life-threatening cause of flank pain.

FOLEY CATHETER PROBLEMS (INSERTION AND REMOVAL)

James Kearns, MD

BASICS

DESCRIPTION

- The terms "urethral catheter" and "Foley catheter" are often used interchangeably. Urethral catheter is a general description of a tube that traverses the urethra whereas a Foley catheter refers to a urethral catheter with a retention balloon.
- Common types of urethral catheter include:
  - Foley: rounded tip with balloon
  - Council: hole at distal tip to allow for passage over wire or on the end of a stylette
  - Coude': angulated distal tip to allow for navigating past large prostates or elevated bladder necks
- 2-way catheters have a single drainage port and a balloon port
- 3-way catheters have a drainage port, an infusion port, and a balloon port
  - NOTE: Drainage channel is larger in a 2-way catheter than 3-way catheter of the same size
- Size measured in Charrier or French (Fr) scale
  - Fr = D × 3, where D = diameter in mm
  - Common sizes include 5–10 Fr in the pediatric population and 16–24 Fr in the adult population
- Common materials include latex and silicone
  - Latex appropriate for short-term (< 1 mo)
  - Silicone better for longer-term or latex allergy
- Hydrophilic coatings may facilitate easier passage of catheter
- Problems can occur with insertion, drainage, or removal

EPIDEMIOLOGY

Incidence

Unknown but very common in hospitalized patients

Prevalence

N/A

RISK FACTORS

Hospitalized patient requiring strict documentation of urine output, BPH, urethral stricture disease, bladder neck contracture, previous urethral or prostate surgery, trauma, immobility, obesity

Genetics

N/A

PATHOPHYSIOLOGY

Indications for urethral catheterization include need for bladder decompression, need for accurate monitoring of urine output, immobility during postoperative setting, diversion of urine from wounds, instillation of therapeutic agents, and facilitation of certain diagnostic

studies (eg, urodynamics, VCUG, cystogram)

ASSOCIATED CONDITIONS

- BPH
- Balanitis xerotica obliterans (BXO)
- UTI
- Urinary retention
- Neurogenic bladder
- Liver failure, heart failure—edema

GENERAL PREVENTION

- Minimization of unnecessary urethral catheterization
- Removal of urethral catheter as soon as clinically indicated
- Proper insertion technique prevents false passages and potential bladder neck or urethral strictures
  - Catheter should always be placed without undue force, using copious lubrication
    - Excess force may lead to false passage creation

ALERT

Do not inflate foley balloon unless the catheter is confirmed in the bladder.

- Look for urine return and insert catheter until "hub" reaches urethral meatus.
- If no urine return with "hubbed" catheter, irrigate normal saline into the bladder with a catheter-tipped syringe; 120 mL is often necessary before fluid can be aspirated.
- Inflation in urethra or prostate may lead to significant hematuria or future urethral stricture as well as inability to place another catheter:
  - Always inflate balloon with water as saline may crystallize and is usually not necessary to test balloon prior to insertion

DIAGNOSIS

HISTORY

- Previous difficulty with catheterization
- Urethral instrumentation in the past
- Episodes of urethral catheterization
- Prior pelvic radiation or brachytherapy
- History of urinary symptoms
  - Quality of urinary stream, urinary frequency, sensation of emptying, history of urinary retention
- Circumcision may lead to meatal stenosis

PHYSICAL EXAM

- Abdominal examination for palpable bladder, dullness to percussion over lower abdomen
- DRE feels for evidence of prostate cancer (nodularity or hardness), prostatic abscess (tender prostate), urethral disruption (high-riding or nonpalpable prostate)
- Bimanual examination to evaluate for bladder or pelvic masses
- Palpate penis for strictures
  - Both location and length of stricture important

- Blood at meatus suggests trauma/urethral disruption

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Electrolytes and creatinine to evaluate for renal function
  - Decreased renal function in an obstructed patient is risk factor for postobstructive diuresis

Imaging

- Generally unnecessary
- Retrograde urethrogram can demonstrate urethral disruption, injury, or stricture
- Cystourethroscopy, if needed

Diagnostic Procedures/Surgery

- Catheterization is both diagnostic and therapeutic
  - See treatment section

Pathologic Findings

If performed in OR, may consider biopsy of strictures

DIFFERENTIAL DIAGNOSIS

- Difficulty placing catheter
  - Urethral sphincter spasm
  - BPH
  - Urethral stricture
  - Bladder neck contracture
  - Urethral disruption
  - Urethral false passage
  - Phimosis
  - Meatal stenosis
  - Penile/foreskin edema
  - Obesity/buried penis
  - Retracted meatus in women
  - Urethral stone or foreign body
- Problems with drainage
  - Clot retention
  - Bladder debris (tumor or stone)
- Difficulty removing catheter
  - Improper coupling of syringe to balloon port
  - Obstructed balloon port
  - Encrustation of balloon or catheter
  - Catheter sutured in place

TREATMENT

GENERAL MEASURES

- Assess need for urethral catheterization
- For difficult placement, start with an 16–18-Fr Foley and note location of difficulty
  - If stricture suspected, attempt 1 pass with 12–16-Fr Foley

- If BPH suspected, attempt 1 pass with 18–22-Fr coude
- Choose proper catheter size for pediatric population
  - Newborns/neonates based on body weight (no retention balloon)
    - <1000 gm: 3.5 Fr
    - 1000–1800 gm: 5 Fr
    - 1800–4000 gm: 6.5 Fr
    - >4000 gm: 8 Fr
  - Children
    - Age <5 yr, 5–8 Fr
    - Age 5–10 yr, 8–10 Fr
    - Age 10–14 yr, 10 Fr
    - Age >14 yr, 10–14 Fr

MEDICATION

First Line

Intraurethral lidocaine jelly may be useful in difficult catheter placement

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Urethral sphincter spasm
  - Provide reassurance and ask patient to relax and take slow, deep breaths
  - Intraurethral lidocaine jelly may not decrease pain (1)
  - Instruct patient to attempt to void when encountering the sphincter
- BPH
  - Use a coude catheter to help navigate the prostate
    - Bend of catheter always facing up toward ceiling (often matches a raised area on balloon port)
  - Larger (ie, 20–22 Fr) preferable because less likely to bend on itself
- Urethral stricture/bladder neck contracture
  - If unable to pass 14 Fr or larger catheter, dilation likely necessary
  - General principle is to place catheter over a wire into the bladder using Seldinger technique
  - Flexible cystoscopy is ideal
    - Advance scope to level of stricture
    - Pass 0.038” wire through stricture into bladder
  - If cystoscope unavailable, consider filiforms with followers, or blindly pass 0.038” soft-tip wire into bladder and confirm location of wire in bladder
    - Portable pelvic x-ray
    - Insert 5-Fr open-ended catheter over wire and aspirate; presence of urine indicates bladder location of wire

ALERT

Never dilate urethra unless wire in bladder.

- Wire rigid enough to potentially undermine bladder neck or enter rectum:
  - Dilate over wire using serial Amplatz-type renal dilators to 1 size larger than desired

catheter (ie, 22 Fr for 20-Fr catheter)
- If dilators unavailable, serial silicone catheters may be rigid enough for dilation:
  - Insert Council catheter over wire until return of urine and inflate balloon
- If Council unavailable, use 14-gauge Angiocath to thread wire into Foley.

- Urethral disruption
  - Retrograde urethrogram generally necessary for diagnosis, but consider blind passage of catheter in trauma patient without pelvic fracture or signs of urethral injury (ie, blood at meatus, perineal hematoma, high-riding prostate) (2)
  - Consider cystoscopically inserting catheter
  - Low threshold for suprapubic catheter
- Urethral false passage
  - False passage generally down, so use coude with tip pointed up
  - If unable to pass coude, use cystoscope to place wire in bladder and place catheter over wire
- Phimosis
  - Attempt to retract foreskin
  - If able to visualize meatus, attempt to place Foley through meatus normally
  - If unable to visualize meatus, perform dorsal slit in foreskin under local anesthesia
- Meatal stenosis
  - Inject lidocaine gel
  - Serial dilation with Van Buren sounds
- Penile/foreskin edema
  - Manually compress edematous skin to minimize edema
  - Place catheter once meatus visible
- Retracted female meatus
  - Inserting a finger into the vagina may bring meatus forward
  - Manually direct catheter into meatus
- Urethral stone or foreign body
  - Cystoscopically remove stone/foreign body
- Clot retention with no catheter output
  - Ensure at least 20-Fr 2-way catheter in place
  - Manually irrigate catheter
  - If urine does not remain clear after irrigation, consider placing 3-way catheter (22 or 24 Fr) for continuous irrigation

ALERT
If outflow from catheter stops while on continuous bladder irrigation (CBI), immediately stop inflow.
- Decreased catheter output from bladder debris:
  - Manually irrigate
  - Consider insertion of larger catheter
- Inability to remove catheter:
  - Place syringe on balloon port for 30 min
  - Cut balloon port and wait for fluid output
  - Insert stiff end of wire through balloon port to attempt to unclog the port

– If still unable to remove catheter:
  ◦ Under US guidance, spinal needle may be inserted into balloon percutaneously
  ◦ In women, transvaginal US and needle placement may be preferable
  ◦ If balloon palpable in bulbar or pendulous urethral, transcutaneous placement of a 22-gauge needle may decompress balloon
– If catheter sutured in place and suture resorbable, consider waiting before removing catheter
– Open cystotomy with retrograde removal is a final resort

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

If unable to place urethral catheter, suprapubic catheterization may be necessary

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

N/A

COMPLICATIONS

- False passage
- Hematuria
- Catheter-associated UTI
  – Many catheters have antimicrobial coatings, which may not be beneficial (3)

FOLLOW-UP

Patient Monitoring

- Before removing difficult Foley, ensure no foreseeable indication for recatheterization
- Consider removing catheters at midnight so a failed voiding trial can be managed early during the day

Patient Resources

N/A

REFERENCES

1. Gordetsky J, Bendana E, O'Brien J, et al. (Almost) painless surgery: A historical review of the evolution of intraurethral anesthesia in urology. *J Urology*. 2010;77:12–16.
2. Lückhoff C, Mitra B, Cameron PA, et al. The diagnosis of acute renal trauma. *Injury*. 2010;42:913–916.
3. Siddiq D, Darouiche RO. New strategies to prevent catheter-associated urinary tract infections. *Nat Rev Urol*. 2012;9:305–314.

ADDITIONAL READING

Hollingsworth M, Quiroz F, Guralnick ML. The management of retained Foley catheters. *Can J Urol.* 2004;11(1):2163–2166.

See Also (Topic, Algorithm, Media)

- Benign Prostatic Hyperplasia
- Foley Catheter Problems (Insertion and Removal) Images
- Foley Catheter Problems (Insertion and Removal) Algorithm
- Postobstructive Diuresis
- Urethral Stricture Disease

CODES

ICD9

- 996.64 Infection and inflammatory reaction due to indwelling urinary catheter
- 996.76 Other complications due to genitourinary device, implant, and graft
- V53.6 Fitting and adjustment of urinary devices

ICD10

- T83.51XA Infect/inflm reaction due to indwell urinary catheter, init
- T83.89XA Other specified complication of genitourinary prosthetic devices, implants and grafts, initial encounter
- Z46.82 Encounter for fitting and adjustment of non-vascular catheter

CLINICAL/SURGICAL PEARLS

- Proper initial catheter placement will prevent many subsequent problems.
- A calm patient and proper equipment are critical for success.
- If dilation is necessary, always confirm wire in bladder before dilating.
- Perform voiding trials at times that allow for reinsertion of difficult catheter at a convenient time.
- Suprapubic catheterization is a reliable method of bladder drainage, if needed.
- Remove catheter as soon as possible to reduce risk of catheter-associated UTI.

FOURNIER GANGRENE

Brad Figler, MD
Bryan Voelzke, MD, MS

BASICS

DESCRIPTION

- Necrotizing soft tissue infection arising in the genitalia and/or perineum
- Rapidly progressive and life-threatening with a high mortality rate
- Much more common in men than women

ALERT
Fournier gangrene is a urologic emergency, causing progressive tissue destruction with significant potential for soft tissue loss, sepic shock, and death. Prompt debridement is mandatory.

EPIDEMIOLOGY

Incidence

- 1.1 per 100,000 patients are admitted for treatment of Fournier gangrene nationally (1)
- Most common in 5th and 6th decades of life
- Male > Female (10:1)
- Limited to 60 case reports in children

Prevalence

Unknown

RISK FACTORS

- Alcoholism
- Diabetes mellitus
- Genital skin trauma
- Impaired immunity
- IV drug abuse
- Recent penile, perineal, or perirectal surgery
- Urethral stricture

PATHOPHYSIOLOGY

- Primary insult is a breach in the integrity of the GI or urethral mucosal lining
- Infection is frequently polymicrobial (aerobic and anaerobic, gram-positive and gram-negative)
- Pathogens differs from nonnecrotizing infection: Higher frequency of virulent organisms such as group A streptococci, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), and Clostridium spp (2)
- Obliterative endarteritis leads to thrombosis, ischemia, and necrosis, which allows for further bacterial proliferation
- Process extends along Dartos and Colles fascia, potentially involving perineum, abdomen, thighs, ischiorectal fossa, and retroperitoneum

- Rates of spread as high as 2–3 cm/h have been reported
- Deep structure (corpus cavernosum, corpus spongiosum, and testicles) are typically not affected

ASSOCIATED CONDITIONS
- Perianal/scrotal abscess
- Immunosuppression
- Obesity
- Urethral stricture
- Paraplegia
- Malignancy
- Septic abortions, vulvar abscesses, and episiotomy (in women)

GENERAL PREVENTION
- Early recognition/treatment of infection
- Early and aggressive management of underlying immunosuppressive conditions

DIAGNOSIS

HISTORY
- Presentation is typically abrupt with severe pain in the perineum, abdominal wall and thighs, however a prodrome of several days of fever and lethargy can be seen
- Perineal or genital trauma (including bites)
- Urethral instrumentation
- Perirectal/scrotal/perineal abscess or wound
- Urinary tract infection or STD
- Urethral stricture disease
- Anal fissure, fistulae, or hemorrhoids
- Alcohol or IV drug abuse
- Malignancy
- Diabetes mellitus
- Steroid use
- HIV

PHYSICAL EXAM
- Altered mental status
- Pain out of proportion with physical exam
- Tachycardia and tachypnea
- Fever or hypothermia
- Cellulitis
- Dusky, erythematous or frankly necrotic, skin
- Foul odor described as strong or feculent
- Crepitus
- Edema of the involved skin
- Purulent drainage
- Rectal exam essential. Assess for:
  – Tumor

– Perirectal abscess

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC: Leukocytosis/leukopenia, anemia
- Serum chemistry: Hyponatremia, hypocalcemia, elevated serum creatinine, hyperglycemia, metabolic acidosis
- Myonecrosis may elevate CK levels
- Coagulopathy
- Glucosuria and pyuria
- Wound culture (aerobes, anaerobes, fungi)
  – Aspiration of subcutaneous skin at the point of demarcation for Gram stain and culture may be useful
  – Deep tissue cultures at the time of surgery should be obtained
- Urine and blood culture. In spite of severe clinical findings blood cultures are rarely positive

Imaging

- Plain radiography or ultrasound may show subcutaneous emphysema; less sensitive than CT
- CT helpful in identifying nidus of infection and/or subcutaneous emphysema
- MRI can be used to define affected areas, but should not delay prompt surgical intervention

Diagnostic Procedures/Surgery

- Immediate surgical debridement
- Incision should be extended until normal appearing tissue is encountered
- Infection presumed present as far peripherally as swelling, erythema exist, watery pus, or necrotic fascia are found

Pathologic Findings

- Intact epidermis with dermal necrosis
- Vascular thrombosis
- Acute PMN infiltrate

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Balanitis
- Epididymitis/orchitis
- Hidradenitis suppurativa
- Pyoderma gangrenosum
- Strangulated inguinal hernia
- Testicular torsion

TREATMENT

GENERAL MEASURES

- Immediate and aggressive surgical therapy with debridement of necrotic tissue
- Aggressive fluid resuscitation (isotonic fluid)
- Inotropic support is frequently necessary
- Correct coagulopathy

- Quadruple antibiotics
- ICU support until clinically stable

MEDICATION

First Line

- Antibiotics should include gram-positive, gram-negative, and anaerobic coverage in full therapeutic dosages
- Modify antibiotics as needed, based on Gram stain, culture, and sensitivity
- Appropriate empiric therapy typically consists of:
  - Penicillin G 3–5 million international units IV q6h (Gram-positive coverage)
  - Imipenem 500–1,000 mg IV q6h (polymicrobial coverage)
  - Clindamycin 600–1,200 mg/d, divided dose (anaerobic coverage)
  - Vancomycin 1 g IV BID (MRSA)

Second Line

- Potential single-agent regimens include:
  - Imipenem/cilastatin
  - Meropenem
  - Ertapenem
  - Piperacillin/tazobactam
  - Ticarcillin/clavulanic acid
  - Tigecycline
- Intravenous immunoglobulin may be a useful adjunct in treatment of staphylococcal or streptococcal infections with signs of toxic shock syndrome (TSS)

SURGERY/OTHER PROCEDURES

- Immediate and aggressive wide surgical debridement and irrigation with bacteriocidal solution minimizes progression of necrosis.
- All affected tissues should be debrided; questionable involvement can be treated with incision and drainage and observation.
- Repeat exam under anesthesia and possible debridement at 24-48 hr
- Fascia and muscle are rarely involved and do not typically require wide resection.
- Testicles and tunica vaginalis are rarely involved; when possible, tunica vaginalis should be left intact to facilitate future application of skin graft
- Consider cystoscopy if there is concern for urethral nidus
- Consider proximal urinary diversion (suprapubic tube, percutaneous nephrostomies) if the penis is extensively involved
- If perirectal disease is identified, exam with proctoscopy under anesthesia is necessary
- Postoperative care
  - If a vacuum assist closure (VAC) dressing is not used, wet-to-dry dressing changes are performed BID-TID
  - EUA after 24–48 hr to assess for and debride newly necrotic tissue
  - Follow cultures for sensitivities and adjust antibiotic therapy accordingly
  - Nutritional support (preferably enteral) should be instituted early to correct the negative nitrogen balance associated with profound sepsis

ADDITIONAL TREATMENT

- VAC may result in earlier wound granulation compared to simple wet-to-dry dressing changes, but may be difficult to apply to the perineum and genitalia (Level I) (4)
- If a VAC closure is not possible, the wound should be packed with fine-mesh gauze soaked in normal saline, Dakin (25%) solution, or Clorpactin
- Diverting colostomy may help keep perineal or peri-anal wounds clean
- Reconstruction can be performed after the patient has stabilized and the wound demonstrates adequate granulation
- When health of graft bed is uncertain, xenograft is an inexpensive and useful method for temporary wound coverage and is helpful in assessing suitability of graft bed for autologous skin grafting. Xenograft should be removed within 2 wk
- If $<50\%$ of scrotum is resected, can be reconstructed primarily
- Split-thickness skin grafts (meshed or unmeshed for penis; meshed for scrotum) are useful for covering small or extensive wounds, with excellent long-term results (4)
- Thigh pouches for testicles are effective, but can cause pain and interfere with testicular exam

Complementary & Alternative Therapies
- Whirlpool therapy for micro-debridement
- Hyperbaric oxygen may be helpful if used early as an adjunct to radical debridement (3)
- Dakin's solution, Sulfamylon solution, or Silvadene cream can be applied during each dressing change

ONGOING CARE

PROGNOSIS
- Historically, Fournier gangrene carried a $>50\%$ mortality rate
- Modern mortality rates average 5–20%, which is highly dependent on prompt diagnosis and tight coordination of definitive care (1)

COMPLICATIONS
- Coagulopathy
- Death from sepsis
- Disfiguring skin and soft tissue loss
- Infertility
- Multi system organ failure
- Renal failure
- Urethral stricture

FOLLOW-UP
Patient Monitoring
Prolonged critical care may be required.

Patient Resources
http://www.mayoclinic.com/health/gangrene/DS00993

REFERENCES
1. Sorensen MD, Broghammer JA, Rivara FP, et al. Fournier's gangrene: Contemporary

population-based incidence and outcomes analysis: A HCUP database study. *J Urol.* 2008;179(4):13.
2. May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect (Larchmt)*. 2009;10(5):467–499.
3. Mindrup SR, Kealey GP, Fallon B. Hyperbaric oxygen for the treatment of Fournier's gangrene. *J Urol.* 2005;173:1975–1977.
4. Black PC, Friedrich JB, Engrav LH, et al. Meshed unexpanded split-thickness skin rafting for reconstruction of penile skin loss. *J Urol.* 2004;172(3):976–969.

ADDITIONAL READING

Vick R, Carson CC, 3rd. Fournier disease. *Urol Clin North Am,* 1999;26(4):841–849.

See Also (Topic, Algorithm, Media)

- Diabetes Mellitus, Urologic Considerations
- Urosepsis (Septic Shock)
- Fournier Gangrene Images

CODES

ICD9

- 608.83 Vascular disorders of male genital organs
- 616.89 Other inflammatory disease of cervix, vagina and vulva

ICD10

- N49.3 Fournier gangrene
- N76.89 Other specified inflammation of vagina and vulva

CLINICAL/SURGICAL PEARLS

- Signs of local infection with pain out of proportion to physical exam is highly suspicious for a diagnosis of Fournier Gangrene.
- Prompt and radical debridement is mandatory.
- Infections are typically polymicrobial, so broad-spectrum antibiotics are critical.

FUNGAL INFECTIONS, GENITOURINARY

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BASICS

DESCRIPTION

- Primary fungal infection of the genitourinary (GU) tract is common with Candida, but uncommon with other fungi.
- Other fungal infections are found in the GU tract but are seen more commonly with immunocompromised patients or in setting of systemic disease.

EPIDEMIOLOGY

Incidence

- Difficult to determine because most cases are not reportable
  - Estimated 1–2 new cases per 100,000 population per year involving the GU tract

Prevalence

Difficult to estimate as cases are not reportable

RISK FACTORS

- Urinary tract drainage catheter
- Prior antibiotics
- Diabetes/glucosuria
- Urinary tract pathology
- Malignancy
- Increased age
- Neonates
- Female sex
- Prior surgical procedures
- Immunosuppression

Genetics

No heritable form of transmission

PATHOPHYSIOLOGY

- Funguria to fungemia:
  - Can occur with obstruction, reflux, or instrumentation
- Fungemia to funguria:
  - Disseminated disease seeds GU tract
    - Multiple microabscesses develop in the renal cortex, with subsequent penetration into the glomeruli and shedding into the urine from the proximal tubules

ASSOCIATED CONDITIONS

- Immunocompromised state:
  - Diabetes

  - AIDS
- Anatomic GU abnormalities:
  - Strictures
  - Prostatic hypertrophy
  - Diverticula
  - Indwelling tubes
  - Stones

GENERAL PREVENTION

- Remove unnecessary catheters/tubes
- Narrow antibiotic coverage
- Improve nutritional status
- Control hyperglycemia

DIAGNOSIS

HISTORY

- Immunocompromised state:
  - Fungi are ubiquitous in the environment and can overwhelm those with weakened immune systems
  - Those receiving chemotherapy, with AIDS, or afflicted with diabetes
- Recent antibiotic use:
  - Risk of candiduria is 6× after use of broad-spectrum antibiotics
- Indwelling GU tubes or prosthesis:
  - Risk of candiduria 12× with catheterization
- GU tract abnormalities:
  - Risk of candiduria 6× with abnormalities (1)[A]
- Occupation:
  - Exposure to aerosolized soil; spelunkers; bird handler
- Recent travel or recreation (see image):
  - Blastomycosis found in Ohio, Missouri, and Mississippi river basins; Great Lakes; Canada
  - Coccidioidomycosis found in semiarid regions of the Western US, Mexico, Central and South America
  - Histoplasmosis found in Midwestern and Southern US in areas of high-nitrogen soil such as chicken coops and bat caves
  - *Cryptococcus* thrives with birds
- UTI symptoms:
  - Only 4–14% with symptomatic candiduria

PHYSICAL EXAM

- CVA tenderness
- Abdominal tenderness
- Boggy or firm prostate
- Firm testicular or epididymal masses
- GU tubes present
- Manifestations of disseminated disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Candida:
  - No studies have established the importance of pyuria or quantitative urine culture in diagnosing *Candida* UTI (2)[A]
  - Presence of pyuria helpful in those without catheter, however, up to 25% with candiduria also have bacteriuria/pyuria
  - Urine cultures positive for candiduria in otherwise asymptomatic patients should be repeated with a clean catch sample to rule out contamination (2)[B]
  - >10,000 CFU/mL could mean infection; 10,000–100,000 CFU/mL could mean colonization
  - Check urine microanalysis looking for casts containing yeast: Very specific, not sensitive
- Aspergillosis:
  - Culture in Sabouraud medium or stain tissue with methenamine silver or Periodic acid–Schiff stain (PAS); can PCR
- Cryptococcosis:
  - Culture; stain tissue with India ink, PAS, methenamine silver; perform latex agglutination
- Phycomycosis:
  - Stain tissue
- Blastomycosis:
  - Stain tissue and visualize secretions
- Coccidioidomycosis/histoplasmosis:
  - Culture and stain tissue

Imaging

CT abdomen with contrast and delayed imaging vs. US may elucidate bezoars, perinephric pathology, renal destruction

Diagnostic Procedures/Surgery

- Cystoscopy/retrograde urogram
- Urine culture
- Tissue biopsy

Pathologic Findings

Positive histology staining for fungi in tissue

DIFFERENTIAL DIAGNOSIS

- Blood clots in collecting system
- Cystitis
- GU TB
- Nephrolithiasis
- Squamous cell carcinoma (SCC)
- Urothelial carcinoma (transitional cell carcinoma)

TREATMENT

GENERAL MEASURES

- Infectious Diseases Society of America recommends treatment of candiduria in (3)[A]:
  - Infants with low birth weight
  - Patients who will have GU procedures
  - Neutropenic patients
  - Symptomatic patients
- Treat UTI symptoms empirically for funguria only if the patient is unable to vocalize or perceive symptoms
- Asymptomatic candiduria: Assess for risk factors (3)[A]

MEDICATION

First Line

- Aspergillosis:
  - Amphotericin B 1–1.5 mg/kg/d for 10 wk
- Blastomycosis:
  - Itraconazole 200 mg PO BID for 6–12 mo
- Candidiasis:
  - Clotrimazole, miconazole, tioconazole, terconazole topical for 1 wk
- Candidemia (treat for 2 wk after afebrile and Cx negative):
  - Fluconazole 400–800 mg/d IV, then PO
- Candiduria:
  - Fluconazole 200 mg/d IV/PO for 1–2 wk
- Coccidioidomycosis:
  - Itraconazole 200 mg PO BID. for 1 yr
- Cryptococcosis:
  - Amphotericin B 0.5–1 mg/kg/d IV + flucytosine 100 mg/kg/d PO for 2 wk
    - Then fluconazole 400 mg/d PO for 8 wk OR
    - Then Itraconazole 200 mg PO BID for 8 wk
  - For cryptococcal suppression:
    - Fluconazole 200 mg/d PO OR
    - Amphotericin B 0.5–1 mg/kg IV every week
- Histoplasmosis:
  - Itraconazole 200 mg PO BID for 6–18 mo
  - For histoplasmosis suppression:
    - Itraconazole 200 mg/d PO BID OR
    - Amphotericin B 0.5–1 mg/kg IV every week
- Mucormycosis:
  - Amphotericin B 1–1.5 mg/kg/d IV for 6–10 wk

Second Line

- Aspergillosis
  - Voriconazole 6 mg/kg q12h for 2 days, then 4 mg/kg q12h (IV or oral) for 10 wk OR
  - Itraconazole 200 mg IV BID for 4 days, then 200 mg/d IV for 12 days, then 200 mg PO BID for 10 wk OR
  - Itraconazole 200 mg PO TID for 9 days, then 200 mg PO BID for 10 wk
- Blastomycosis

  – Amphotericin B 0.5–1 mg/kg/d for 6–12 wk OR
  – Fluconazole 400–800 mg/d PO for 6–12 mo
- Candidiasis
  – Fluconazole 150 mg in 1 dose
- Candidemia (treat until 2 wk after afebrile and Cx negative):
  – Caspofungin 70 mg/d IV in 1 dose, then 50 mg/d OR
  – Amphotericin B 0.5–1 mg/kg/d
- Candiduria:
  – Amphotericin B 0.3–0.5 mg/kg/d IV for 1–2 wk OR
  – Flucytosine 25 mg/kg/d PO for 1–2 wk
- Coccidioidomycosis:
  – Fluconazole 400–800 mg/d PO for 1 yr OR
  – Amphotericin B 0.5–0.7 mg/kg/d IV for 1 yr
- Histoplasmosis:
  – Fluconazole 400–800 mg/d PO for 6–18 mo OR
  – Amphotericin B 0.5–1 mg/kg/d IV for 10–12 wk

SURGERY/OTHER PROCEDURES
- Obstructions from fungal bezoars require drainage.
- Access to upper tracts can facilitate drainage, antifungal irrigation, and extraction if needed.
- Perinephric abscess can be drained percutaneously, but may require operative drainage if multiple loculations are present.
- Severe aspergillus kidney infections may require nephrectomy.
- Treatment of fungal prostatitis may require surgical intervention for prostate resection or drainage of abscess in addition to medical therapy (4)[B].

ADDITIONAL TREATMENT

Radiation Therapy

None

Additional Therapies
- Irrigation may be necessary in aggressive infections when systemic medication is not excreted into the urine
  – Amphotericin B GU tract irrigation
    - 50 mg in 1,000-mL water at 40 mL/hr (over 24 hr) for 5–7 days
  – In children, renal irrigation with 10–24 mg/d
- Removing catheter may eradicate funguria in 40% of cases

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS
- Candiduria does not predict development of candidemia in most people
  – Rates 1.3–10.5%
  – No different in renal transplant population: 5%

- Aspergillosis mortality 40–90% with treatment
- Phycomycosis (mucormycosis, zygomycosis) mortality 90% if untreated, 24% with nephrectomy and amphotericin B

COMPLICATIONS
- Bezoar formation
- Emphysematous pyelonephritis
- Obstruction, fungemia, death
- Papillary necrosis
- Perinephric abscess
- Renal scarring

FOLLOW-UP

Patient Monitoring
- Surveillance cultures can be obtained to document clearance of infection.
- Prostate can be fungal reservoir for recurrent infection.

Patient Resources

CDC Fungal Infections Fact Sheet http://www.cdc.gov/ncezid/dfwed/PDFs/fungal-factsheet-508c.pdf

REFERENCES

1. Achkar JM, Fries BC. Candida infections of the genitourinary tract. *Clin Microbiol Rev*. 2010;23:253–273.
2. Kauffman CA, Fisher JF, Sobel JD, et al. Candida urinary tract infections—diagnosis. *Clin Infect Dis*. 2011;52:452–456.
3. Fisher JF, Sobel JD, Kauffman CA, et al. Candida urinary tract infections—treatment. *Clin Infect Dis* 2011;52:S457–466.
4. Wise GJ, Shteynshlyuger A. How to diagnose and treat fungal infections in chronic prostatitis. *Curr Urol Rep*. 2006;7:320–328.

ADDITIONAL READING

- Kauffman CA. Candiduria. *Clin Infect Dis*. 2005;41:S371–S376.
- Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. 2000;30:14–18.
- The Medical Letter: Antifungal drugs. Treatment Guidelines from The Medical Letter 2005;30:7–14.
- Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004;38:161–189.

See Also (Topic, Algorithm, Media)
- Candidiasis, Cutaneous, External Genitalia
- Candiduria Algorithm ↕
- Cryptococcus, Genitourinary
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Fungal Infections, Genitourinary Algorithm ↕

- Fungal Infections, Genitourinary Image
- Histoplasmosis, Genitourinary
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

- 112.1 Candidiasis of vulva and vagina
- 112.2 Candidiasis of other urogenital sites
- 116.0 Blastomycosis

ICD10

- B37.3 Candidiasis of vulva and vagina
- B37.4 Candidiasis of other urogenital sites
- B40.89 Other forms of blastomycosis

CLINICAL/SURGICAL PEARLS

- When fungal infections are found in the GU tract in patients without risk factors, a search for systemic disease is warranted.
- Disseminated fungal disease can seed the GU tract through the development of renal microabscesses.
- Fungal infections are encountered in varying geographic locales based on type.
- Treat candiduria in infants with low birth weight, those undergoing GU procedures, neutropenic patients, and symptomatic patients.
- Surgical drainage of fungal infections is indicated in cases of urinary tract obstruction.

GLOMERULONEPHRITIS, ACUTE

Christopher E. Keel, DO
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BASICS

DESCRIPTION

- Inflammation of the glomerulus mediated through humoral and cell-mediated immune mechanisms including immunoglobins, complement, and circulating T cells usually in response to an infection (typically streptococcal).
- The inflammation and immunologic response results in immune deposits in the glomerulus.
- Onset of symptoms is usually acute and includes oliguria, hypertension, hematuria, proteinuria, and renal impairment.
- Poststreptococcal acute GN is the onset of GN after a preceding group A β-hemolytic streptococcal infection, most commonly of the pharynx or skin.
  – Most common glomerulonephritis affecting children.
- Synonym(s): Acute nephritic syndrome; Postinfectious glomerulonephritis.

EPIDEMIOLOGY

Incidence

- Poststreptococcal GN, the most common form, occurs most frequently in children between 2 and 10 yr of age but can occur at any age with a slight predominance of males over females
  – 10% cases are in adults >40 yr of age
  – 20/100,000/yr

Prevalence

- Most patients have a complete recovery, with resolution of clinical signs within a few weeks.
- The reported incidence of chronic renal insufficiency is 0–20%.

RISK FACTORS

- Occurs with infection of specific types of group A β-hemolytic streptococci, and these vary by site of infection. It occurs more commonly after pharyngitis than pyoderma:
  – Pharyngitis is associated with types 1, 3, 4, 12, 25, 49 with the more common sporadic variety following infection with type 12.
  – Pyoderma is associated with types 2, 49, 55, 57, 60.

Genetics

N/A

PATHOPHYSIOLOGY

- Tends to occur with impetigo in the late summer and with streptococcal pharyngitis in the winter.
- Note that cases of postinfective GN have also been reported from other bacteria (Pneumococcus, Staphylococcus, Meningococcus) and after viral infections (chickenpox, hepatitis).
- The exact mechanism of renal injury from poststreptococcal GN is not clear. IgG and C3

deposits are found at the capillary wall and in the mesangium. It is unclear if the inflammatory response is due to circulating immune complexes, complexes in situ, or both.
  – The antigen or antigens activate the alternative complement pathway and result in renal damage.

ASSOCIATED CONDITIONS
- Pharyngitis
- Hematuria
- Hypertension
- UTI
- Acute renal failure
- Rapid decrease in renal function heralds the syndrome of rapidly progressive glomerulonephritis

GENERAL PREVENTION
No specific prevention measures; prompt treatment of strep infections may reduce risk

DIAGNOSIS
HISTORY
- Recent episode of pharyngitis or skin infection.
- Pharyngitis usually precedes renal disease by 8–14 days.
- Time between purulent skin disease and acute nephritis is widely variable.
- Severity varies from asymptomatic microhematuria to anuric renal failure.
- Gross hematuria occurs in 30–50%.
- Volume overload occurs in up to 2/3 of patients and may be severe enough to cause congestive heart failure and pulmonary edema.
- Hypertension occurs in up to 80%. Severity may not correlate with the degree of volume overload.
- Hypertensive encephalopathy (seizures, confusion, coma) is the presenting feature in 5%.
- Often patient has contact with individuals complaining of similar symptoms.

PHYSICAL EXAM
- Patients may have periorbital edema, peripheral edema, HTN
- Transient oliguria will be present in half of patients

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Throat swabs are rarely positive.
- Urinalysis (1):
  – Hematuria may be microscopic or gross and is present in all cases.
  – Microscopic analysis shows dysmorphic red blood cells and red cell casts.
  – >30% of red blood cells having dysmorphic features is a highly sensitive test for glomerular disease.
  – Red blood cell cast present after acute pharyngitis episode is pathognomic for poststreptococcal GN.
- Proteinuria may also be present and is usually mild (no more than 2+ on dipstick), but

some may have proteinuria to the nephrotic range.
- Evaluate proteinuria with a spot urine protein-to-creatinine ratio:
  – Normal <0.2.
  – Nephrotic range proteinuria being >2.0.
- Basic chemistry profile may reveal elevated BUN and creatinine consistent with ARF.
  – Urea can be raised disproportionately to creatinine.
- Mild normochromic, normocytic anemia due to hemodilution.
- Hyponatremia may be present due to volume overload.
- Acidemia and hyperkalemia may occur in those with severely depressed renal function.
- ESR will be elevated.
- Serum complement levels, in particular, C3 will be depressed early in the disease in 90%:
  – Normalizes 2–6 wk after onset.
  – Prior penicillin therapy may attenuate the fall in C3.
  – If C3 remains depressed beyond this interval, look for other causes.
- Antistreptolysin-O and antihyaluronidase titers may be obtained and may be elevated in poststreptococcal GN (2).
- Not all strains of streptococci will cause these elevations and site of infection may affect which is present.

Imaging
- No imaging is indicated to identify poststreptococcal GN.
- CXR may identify fluid overload.

Diagnostic Procedures/Surgery
- Renal biopsy *not* indicated in poststreptococcal GN unless symptoms persist or renal function deteriorates due to progressive disease
- Renal biopsy, thus, indicated if:
  – Persistently low C3 beyond 8 wk
  – Persistent heavy proteinuria after 6 mo
  – Atypical presentation—nephrotic syndrome, severe acute renal failure with estimated GFR <30 mL/min/1.73 m^2
  – Atypical course—failure of renal function to improve after initial improvement during the acute phase which usually lasts no more than 2 wk

Pathologic Findings
- IgG and C3 deposits are found at the capillary wall and in the mesangium on renal biopsy.
- Rapidly progressive GN is characterized pathologically by crescents forming from the cells of Bowman capsule.
- Typically $>50\%$ of glomeruli should have crescents to be called rapidly progressive GN. This may result from any of the immunologically mediated types of GN, but most frequently occurs with antiglomerular basement membrane disease, antineutrophil cytoplasmic antibody GN, and Henoch–Schönlein purpura nephritis.

DIFFERENTIAL DIAGNOSIS
- Anaphylactoid purpura
- IgA nephropathy
- Alport's disease

- Membranoproliferative glomerulonephritis
- Other postinfective glomerulonephritis
- Infective endocarditis
- Rapidly progressive glomerulonephritis
- Systemic lupus erythematosus

TREATMENT

GENERAL MEASURES
- Supportive care and reassurance.
- Monitor weight and serum sodium daily during acute phase.
- Bed rest does not influence rate of recovery.
- Antibiotics do not change the course of illness once established but should be given to reduce infection-related morbidity.
- Restrict protein until azotemia clears.

MEDICATION
First Line
- Treatment is supportive for this condition and directed at the effects of renal insufficiency and HTN.
- Sodium and water restriction is indicated in patients who show signs of fluid overload (400 $mL/m^2/d$).
- Loop diuretics, calcium channel blockers, and vasodilators are mainstays in the treatment of resultant HTN.
  - Furosemide 2–4 mg/kg/dose IV
    - Titrate dose based on clinical response.

Second Line
- Patients should be treated with a 10-day course of penicillin antibiotics to prevent the spread of the nephritogenic organisms. This will not alter the course of the disease.
- Erythromycin is substituted if penicillin allergic.
- Family members of patients with acute GN should be cultured for group A β-hemolytic streptococci and treated if positive.

SURGERY/OTHER PROCEDURES
Renal biopsy if indicated (see evaluation)

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

- Most patients have a complete recovery, with resolution of clinical signs within a few weeks.
- The reported incidence of chronic renal insufficiency is 0–20%.
- Microscopic hematuria may persist for months up to 2 yr, and mild proteinuria may persist for years following an episode of poststreptococcal GN.

COMPLICATIONS

- Rarely does poststreptococcal GN progress to crescentic or rapidly progressive GN resulting in ESRD. Most cases resolve with no sequelae. Chronic renal failure or marked decline in glomerular filtration rate is very rare
- It is rare to result in severe HTN, seizures, anuria, hyperkalemia, or death.
- Hypertensive retinopathy or encephalopathy
- Rapidly progressive glomerulonephritis
- Microhematuria may persist for years
- Nephrotic syndrome (10%)
- Obesity may increase risk for residual renal injury

FOLLOW-UP

Patient Monitoring

- Subsequent urinalysis to ensure hematuria has resolved
- Periodic BP monitoring

Patient Resources

- National Kidney Foundation website http://www.kidney.org/atoz/content/glomerul.cfm
- MedlinePlus http://www.nlm.nih.gov/medlineplus/ency/article/000484.htm

REFERENCES

1. Tu WH, Shortliffe LD. Evaluation of asymptomatic, atraumatic hematuria in children and adults. *Nat Rev Urol.* 2010;7(4):189–194.
2. Lee MN, Shaih U, Butani L. Effect of overweight/obesity on recovery after post-infectious glomerulonephritis. *Clin Nephrol.* 2009;71(6):632–636.

ADDITIONAL READING

- http://kidney.niddk.nih.gov/kudiseases/pubs/glomerular/index.htm
- Kliegman RM. *Nelson Textbook of Pediatrics*. 18th ed. New York, NY: Saunders, 2007.
- Lau KK, Wyatt RJ. Glomerulonephritis. *Adolesc Med Clin.* 2005;16(1):67–85.
- Wong W. Starship Children's Health Clinical Guidelines on Glomerulonephritis – Acute, 2009 – http://www.adhb.govt.nz/starshipclinicalguidelines/_Documents/Glomerulonephritis.pdf

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Acute Kidney Injury, Pediatric (Renal Failure, Acute)
- Glomerulonephritis, Chronic

CODES

ICD9

- 446.21 Goodpasture's syndrome
- 580.4 Acute glomerulonephritis with lesion of rapidly progressive glomerulonephritis
- 580.9 Acute glomerulonephritis with unspecified pathological lesion in kidney

ICD10

- M31.0 Hypersensitivity angiitis
- N00.9 Acute nephritic syndrome with unsp morphologic changes
- N01.9 Rapidly progr nephritic syndrome w unsp morphologic changes

CLINICAL/SURGICAL PEARLS

- Dysmorphic RBC on microscopic urinalysis suggest the diagnosis.
- Prior pharyngitis or skin infection suggests diagnosis of acute glomerulonephritis.
- With supportive care, recovery is usually rapid and complete with an excellent prognosis.

GLOMERULONEPHRITIS, CHRONIC

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BASICS

DESCRIPTION

- Chronic glomerulonephritis is the loss of renal function caused by damage to glomeruli
- Often mediated by inflammation and cellular proliferation
- Frequently associated with hematuria and proteinuria
- Many forms of glomerulonephritis (GN) present acutely. Progression from acute to chronic GN is variable
- IgA nephropathy is the most common type of GN

EPIDEMIOLOGY

Incidence

- 4/100,000 people in the United States (US)
- 20–50% of patients with acute GN will develop chronic GN

Prevalence

- GN is the 3rd leading cause of end-stage renal disease (ESRD) in the United States after diabetes mellitus and hypertension (1)
  – Accounts for about 10% of dialysis patients

RISK FACTORS

- The cause of many forms of chronic GN is unknown
- Acute GN (focal segmental glomerulosclerosis, hemolytic uremic syndrome, IgA nephropathy, membranous GN)
- Autoimmune diseases (systemic lupus erythematosus (SLE), Goodpasture's syndrome, systemic vasculitis)
- Infections (β-streptococci, human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C)
- Other systemic diseases (diabetes mellitus, multiple myeloma, amyloidosis, Henoch–Schönlein purpura, polyarteritis nodosa, Wegener's granulomatosis)
- Family history of hereditary GN (Alport syndrome, thin basement membrane disease)

Genetics

Some cases of hereditary GN or nephritis (Alport syndrome caused by a mutation of *COL4A5* gene, usually X-linked and more severe in men; thin basement membrane disease)

PATHOPHYSIOLOGY (2)

- Damage to glomeruli, often mediated through immune/inflammatory mediators, leads to decreased filtering surface and nephron mass
- Remaining glomeruli are subjected to increased filtering pressure. This results in hyperfiltering by remaining glomeruli.
- Increased glomerular pressure causes progressive sclerosis of glomeruli and interstitial fibrosis and progressive loss of functioning glomeruli

ASSOCIATED CONDITIONS
See Risk Factors

GENERAL PREVENTION
- Early nephrology consultation can improve outcomes
- Treat active GN, eg, immune suppressing/modulating agents for active lupus nephritis
- Control blood pressure
  - Target <125/75 in patients with >1 g proteinuria
  - Target <130/80 in patients with <1 g proteinuria
- Treat comorbid conditions
  - Dyslipidemia
  - Diabetes
  - Infectious disease
  - Malignancy
- Dietary protein restriction
  - Must balance protein restriction with risk of malnutrition
- Avoid NSAIDs, aminoglycosides, and contrast media as they may further impact on the renal insufficiency

DIAGNOSIS

HISTORY
- Often asymptomatic
- Past acute kidney disease
- Symptoms of uremia
  - Decreased energy
  - Met allic taste in mouth
  - Poor appetite
  - Pruritus
  - Slowed cognition

PHYSICAL EXAM
- May be unremarkable
- Weight loss
- Hypertension
- Volume overload
  - Elevated jugular venous pressure, pulmonary rales, pedal edema
- Signs of uremia
  - Asterixis
  - Pericardial rub

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Elevated plasma creatinine from loss of renal function (3)
  - Prior plasma creatinine values may help determine rate of renal function deterioration
- Serologies may help identify etiology
  - Antistreptolysin O, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody

(ANCA), C3, C4, HIV, Hep B, Hep C
- Urinalysis
  - Proteinuria
  - RBC casts
    - Considered diagnostic for GN or vasculitis
  - Dysmorphic RBC
    - Isomorphic RBCs appear similar to erythrocytes in the circulation (small, anucleated cells; biconcave discs)
    - Dysmorphic RBC criterion varies; membrane protrusions such as seen with peripheral acanthocytes are 1 described criterion
- Urine protein measurement
  - 24-hr urine (normally <100 mg)
  - Random urine microalbumin/ creatinine ratio (normally <20 μ/mg)
  - Random urine protein/creatinine ratio (normally <0.2)
- With significant chronic kidney disease
  - Anemia from decreased erythropoietin production
  - Hyperkalemia from decreased potassium clearance
  - Hyperphosphatemia from decreased phosphorous excretion
  - Acidemia from decreased acid buffering

Imaging
- Renal ultrasound to assess kidney size and cortical volume
  - Advanced disease is associated with decreased renal size, increased echogenicity, and cortical thinning
  - Kidneys usually normal sized with diabetic nephropathy

Diagnostic Procedures/Surgery
- Renal biopsy can potentially diagnose different glomerular diseases
  - Biopsy may not be helpful in advanced disease

Pathologic Findings
- Renal biopsy may determine type of glomerular disease by pattern of injury and immune complex staining
  - With advanced disease and small kidneys on ultrasound, biopsy frequently shows advanced sclerosis/scarring and may not be able to determine etiology

DIFFERENTIAL DIAGNOSIS
- Aristocholic acid (for weight control)
- Chronic interstitial nephritis
- Diabetic nephrosclerosis
- Diuretic abuse
- Hypertensive nephrosclerosis
- Nephrotoxin exposure
- Obstructive uropathy
- Prerenal disease
- Renal artery stenosis

TREATMENT

GENERAL MEASURES

- See GENERAL PREVENTION
- Referral to nephrology
- Treat specific glomerular disease (eg, prednisone or other immunosuppressive agents)
- Control blood pressure (4)
- Renal replacement therapy may be necessary long term

MEDICATION

First Line

- Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) slow the decline of the glomerular filtration rate (GFR) in patients with diabetic and nondiabetic proteinuric nephropathies
  - ACEIs: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, others
  - ARB: Candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan
  - Use may be limited by drug-induced hyperkalemia, increased plasma creatinine due to decreased glomerular pressure, or anemia

Second Line

- Diuretics to treat volume overload
- Additional antihypertensive agents to reach blood pressure goals
  - β-Blockers, calcium channel blockers, central α2-agonists (eg, clonidine), α1-antagonists, and direct vasodilators

SURGERY/OTHER PROCEDURES

- Access for dialysis
  - AV fistula or graft
  - Hemodialysis access or peritoneal dialysis catheter
- Renal transplantation
  - Preemptive transplantation before dialysis results in better survival than transplantation after the initiation of dialysis

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Oral calcium supplements (1 g/d) and vitamin D (400–800 IU/d) for prophylaxis against osteoporosis.
- Sodium bicarbonate has been shown to slow progressive kidney damage.

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Progression of glomerular disease to ESRD is variable and dependent upon cause and response to treatment
- Prognosis has negative correlation with higher blood pressure and degree of proteinuria

COMPLICATIONS

- ESRD
  - Uremia
  - Volume overload
  - Hyperkalemia
  - Anemia
  - Acidosis
- Increased risk of cardiovascular disease
- Increased risk of mortality

FOLLOW-UP

Patient Monitoring

- Lab monitoring
  - Estimate glomerular filtration rate (eGFR): BUN, plasma creatinine
  - Basic metabolic panel + phosphorous
  - Random urine protein/creatinine ratio
  - 24-hr urine protein
- Blood pressure
- Signs or symptoms of uremia

Patient Resources

www.kidney.org/patients

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1–S266.
2. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med*. 1998;339(20):1448–1456.
3. Appel GB. Glomerular disorders and nephrotic syndromes. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23rd ed. Philadelphia, PA: Saunders Elsevier; 2007; Chapter 122.
4. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med*. 1995;123(10):754–762.

ADDITIONAL READING

Kopp JB. Glomerular disease in 2012: More mechanistic insights, but translational progress is slow. *Nat Rev Nephrol*. 2013;9(2):67–68.

See Also (Topic, Algorithm, Media)

Glomerulonephritis, Acute

CODES

ICD9

- 582.1 Chronic glomerulonephritis with lesion of membranous glomerulonephritis
- 582.89 Chronic glomerulonephritis with other specified pathological lesion in kidney
- 582.9 Chronic glomerulonephritis with unspecified pathological lesion in kidney

ICD10

- N03.2 Chronic nephritic syndrome w diffuse membranous glomrlneph
- N03.9 Chronic nephritic syndrome with unsp morphologic changes
- N11.9 Chronic tubulo-interstitial nephritis, unspecified

CLINICAL/SURGICAL PEARLS

- Many cases of acute GN can progress to chronic GN.
- ACEIs and ARB can slow the decline of the GFR in patients with proteinuric nephropathies.

GONORRHEA

Arpeet Shah, MD
Ahmer V. Farooq, DO

BASICS

DESCRIPTION

- A sexually transmitted disease (STD) caused by the gram-negative diplococcal bacteria *Neisseria gonorrhea*
  - Clinical manifestations range from asymptomatic disease to disseminated infection
  - In men, can cause urethritis, prostatitis, and epididymitis
  - In women, can cause cervicitis, salpingitis, endometritis, and pelvic inflammatory disease
  - Anorectal and pharyngeal infections may also occur depending on sexual practices
  - *Pediatrics:* Vertical transmission to newborn may result in infection of conjunctiva, rectum, or respiratory tract; rule out sexual abuse in infections of young children
  - Disseminated gonococcal infection may occur secondary to distinct strains or host factors and may result in a variety of clinical manifestations including skin lesions, arthritis, pericarditis, endocarditis, and meningitis

EPIDEMIOLOGY

Incidence

- In the United States, gonorrhea remains the 2nd most commonly reported bacterial STD
- The Center for Disease Control and Prevention (CDC) estimates 820,000 new cases per year with over half occurring in young adults ages 15–24
- In 2011, CDC reported the rate of gonorrheal infections to be 104.2/100,000 persons
- Rates in the United States have drastically declined since the 1970s due to the public health measures
- More recently, the rate decreased 11.7% during 2007–2011

RISK FACTORS

- Multiple sexual partners
- Unsafe sexual practices
- Alcohol and substance abuse
- Men have a 20–30% chance and women have a 70–80% chance after having 1 exposure

Genetics

Individuals with inherited or acquired deficiency of complement components C5–C9 are more susceptible to local and systemic gonorrheal infections

PATHOPHYSIOLOGY

- *N. gonorrhea* is not part of the normal flora of the genitourinary tract (1)
- Bacteria are introduced to the mucosal epithelial surface after direct contact with an infected individual
- Attachment of the bacteria to the mucosal epithelium is mediated by pili (PilC1 and PilC2) and Opa proteins

- Penetration of the organism into submucosal tissue usually takes 24–48 hr
- Invasion of the epithelial triggers a strong response by neutrophils causing sloughing of epithelium, submucosal microabscesses, and purulent drainage

ASSOCIATED CONDITIONS
- Always recommend testing for other STDs
- Commonly associated with concomitant infection with *Chlamydia trachomatis*

GENERAL PREVENTION
- Delaying onset of sexual activity and reducing the number of new partners
- Consistent condom use

DIAGNOSIS
HISTORY
- Obtain detailed history of sexual activity and partners
- Incubation period of 3–14 days
- Approximately 50% of infections in men are asymptomatic or minimally symptomatic; most common symptoms include dysuria and mucopurulent discharge
- Approximately 50% of women have asymptomatic infection; most common symptoms include vaginal/cervical discharge, dysuria, urinary frequency, abdominal pain, and abnormal menstrual bleeding
- Pregnancy does not change clinical presentation, but does lower incidence of pelvic inflammatory disease (PID)
- Anorectal infection is usually asymptomatic but can produce symptoms of pruritus, tenesmus, rectal bleeding, and discharge
- Pharyngeal infection is usually asymptomatic but can cause sore throat
- Approximately 50–75% of those with disseminated gonococcal infection (DGI) have skin lesions characterized by papules and pustules with surrounding erythema

PHYSICAL EXAM
- In men, mucopurulent urethral discharge may be seen; other signs include testicular/epididymal tenderness
- In women, pelvic exam with speculum may demonstrate mucopurulent cervical discharge; other signs include cervical erythema, edema, and friability as well as cervical motion and adnexal tenderness
- If suspecting anorectal infection, external inspection may reveal few or no signs of infection and anoscopy may be indicated with collection of specimens for culture
- Pharyngeal cases may demonstrate exudative pharyngitis and cervical adenitis
- Conjunctival cases demonstrate severe purulent discharge with crusting and lid edema

DIAGNOSTIC TESTS & INTERPRETATION
Lab (2)
- Gram stain of urethral or endocervical discharge with a swab.
  - Considered positive if neutrophils with intracellular gram-negative diplococci are visualized. Sensitivity and specificity of the Gram stain varies depending on the site of infection and the presence of symptoms.

- Culture has long been considered the gold standard for diagnosis.
  - Advantages include high specificity and the ability to test for antibiotic sensitivity.
  - Disadvantages include strict transport and storage requirements, specific environmental variables needed for growth (Thayer–Martin agar in CO_2 incubator), and delays in obtaining results. Culture is the test of choice for extragenital sites of infection.
- Nucleic acid amplification test (NAAT) use molecular techniques to amplify specific DNA and RNA sequences.
  - Optimal specimens are urine samples for males and vaginal swabs for females.
  - Advantages include higher sensitivities and comparable specificities of culture, minimal delay in results, noninvasive and self-collected samples, and identification of coinfections.
  - Disadvantages include inability to screen for antimicrobial sensitivity. CDC now recommends NAAT as the 1st-line diagnostic test for uncomplicated urogenital gonorrheal infection.

Imaging

- Not indicated in uncomplicated cases
- Computed tomography or pelvic ultrasound if pelvic inflammatory disease (PID) or pelvic abscess suspected
- Retrograde urethrogram if urethral stricture suspected

Pathologic Findings

Gram stain demonstrates gram-negative diplococci found inside of polymorphonuclear cells

DIFFERENTIAL DIAGNOSIS (3)

- Other genitourinary infections including *C. trachomatis, Trichomonas vaginalis, Mycoplasma genitalium, and Ureaplasma urealyticum*, herpes simplex virus, bacterial vaginosis, and candidiasis
- Also consider noninfectious sources such as foreign body, chemical irritation, allergic reaction, trauma, carcinoma, and leukorrhea of pregnancy
- For women who present with suspected PID, must rule out ectopic pregnancy and other intra-abdominal processes such as appendicitis

TREATMENT

GENERAL MEASURES

- Patients with suspected active infection should abstain from sex until diagnostically excluded or adequately treated
- All sexual partners who have contacted the infected patient within 60 days of diagnosis should also be evaluated
- Treatment with penicillins and tetracycline are not effective due to the high level of penicillinase-producing bacteria and plasmid-mediated high-level tetracycline-resistant bacteria
- Over the last decade, increasing mean minimum inhibitory concentrations of selective cephalosporins have indicated decreasing susceptibility and have impacted current treatment recommendations
- Fluoroquinolone resistance has impacted treatment options and is most prevalent in the

states of California and Hawaii
- Macrolide resistance has also been reported

MEDICATION

First Line (4)

- For uncomplicated cases of urethral and endocervical gonorrheal infection, patients must also be treated for concomitant chlamydia infection unless diagnostically excluded
- Ceftriaxone 250 mg IM in 1 dose PLUS azithromycin 1 g PO in 1 dose is the current gold standard
- Ceftizoxime 500 mg IM in 1 dose, cefotaxime 500 mg IM in 1 dose, or cefoxitin 2 g IM with probenecid 1 g PO in 1 dose are alternatives for ceftriaxone
- If an injectable cephalosporin is not an option, alternatives include cefixime 400 mg PO in 1 dose or cefpodoxime 400 mg PO in 1 dose. However, patients who receive these options should return in 1 wk for microbiologic test of cure with culture
- Doxycycline 100 mg BID PO for 7 days is an alternative for azithromycin

Second Line

- The management of those with a penicillin allergy depends on clinical suspicion of true allergy and the severity of the allergy. Most patients with documented penicillin allergy are not found to have an allergy after further testing and only 2% of those with a penicillin positive skin test cross react with cephalosporins. Thus, the physician must decide whether to give a cephalosporin vs. an alternative therapy
- Azithromycin 2 g PO in 1 dose monotherapy treats gonorrhea and chlamydia; however, due to GI side effects and growing macrolide resistance, it is not a preferred regimen unless the patient has a severe penicillin allergy
- Spectinomycin 2 g IM in 1 dose is a safe and effective alternative therapy for those with severe penicillin allergies, but is only available outside the United States
- Quinolones were once a 2nd-line therapy, but due to drug resistance in 10–100% of strains depending on location, they are no longer recommended for the treatment of gonorrhea

SURGERY/OTHER PROCEDURES

- Chronic gonorrheal infection may lead to bulbar urethral strictures requiring urologic intervention
- Gonorrheal abscesses may require incision and debridement procedures

ADDITIONAL TREATMENT

- Patient counseling regarding safe sex practices and abstinence for 7 days following treatment initiation
- Patients should also be offered additional STD testing and pregnancy testing
- Pregnancy considerations
  - 1st line still remains ceftriaxone 250 mg IM in 1 dose PLUS azithromycin 1 g PO in 1 dose
  - Doxycycline should be avoided during pregnancy
  - If the patient has a penicillin allergy, desensitization procedures or 2nd-line treatments such as azithromycin monotherapy are alternatives
  - Microbiologic test of cure with culture is recommended
- Ophthalmia neonatorum
  - Prevented by routine screening for endocervical infection during pregnancy and

prophylactic use of erythromycin ophthalmic solution

ONGOING CARE

PROGNOSIS

>95% of uncomplicated genitourinary gonorrheal infections are cured by 1 course of treatment

COMPLICATIONS

- In males, may lead to bulbar urethral stricture and sterility
- In females, can cause PID leading to chronic pelvic pain, ectopic pregnancy, and sterility
- Genital abscesses may occur in either sex requiring surgical intervention
- Fitz–Hugh–Curtis Syndrome – perihepatitis characterized by acute right or bilateral upper quadrant tenderness – may occur in either sex
- Ocular infection with gonorrhea in adults may lead to corneal scarring and vision loss
- The most common complication of DGI is septic arthritis and arthritis–dermatitis syndrome; extreme cases may lead to destruction of articular surfaces
- Hematogenous spread may lead to endocarditis and meningitis

FOLLOW-UP

- All patients diagnosed with gonorrhea should be tested to rule out repeat infection 3–4 mo after treatment
- All patients who undergo PO cephalosporin therapy and all pregnant patients should undergo microbiologic test for cure using a Gram stain and culture 7 days after treatment

REFERENCES

1. Klausner J, Hook III E. *Current Diagnosis and Treatment of Sexually Transmitted Diseases*, 1st ed. New York, NY: McGraw-Hill Medical, 2007.
2. Leone PA. Epidemiology, pathogenesis, and clinical manifestations of neisseria gonorrhoeae infection. In: *UpToDate*, Basow DS, ed. UpToDate. Waltham, MA; 2013.
3. Mandel G, et al. *Bennett's Principles and Practice of Infectious Diseases*. 7th ed. New York, NY: Churchill Livingstone; 2010.
4. Swygard H, et al., Diagnosis of Gonococcal Infections. In: *UpToDate*, Basow DS, ed. UpToDate, Waltham, MA; 2013.

ADDITIONAL READING

www.cdc.gov/std/Gonorrhea/STDFact-gonorrea.htm

See Also (Topic, Algorithm, Media)

- Epididymitis
- Gonorrhea Image
- Pelvic pain, Female
- Sexually Transmitted Infections (STIs) STDs, General
- Urethra, Discharge
- Urethritis

CODES

ICD9

- 098.0 Gonococcal infection (acute) of lower genitourinary tract
- 098.11 Gonococcal cystitis (acute)
- 098.12 Gonococcal prostatitis (acute)

ICD10

- A54.00 Gonococcal infection of lower genitourinary tract, unsp
- A54.01 Gonococcal cystitis and urethritis, unspecified
- A54.22 Gonococcal prostatitis

CLINICAL/SURGICAL PEARLS

- Maintain a high degree of suspicion for gonorrhea, especially in patients who are in their 20s.
- Most common symptoms include mucopurulent discharge and dysuria.
- Culture has been the gold standard for diagnosis, however, NAAT is now being widely used as a 1st-line diagnostic modality.
- 1st-line treatment includes ceftriaxone 250 mg IM in 1 dose PLUS azithromycin 1 g PO in 1 dose.
- Antibiotic susceptibilities continue to change and vary by geographical location.
- Always council patients regarding safe sex practices.

GROIN/INGUINAL MASS, MALE AND FEMALE

Edouard J. Trabulsi, MD, FACS

BASICS

DESCRIPTION

- A palpable bulge in the groin region that can be benign or malignant. The groin has 2 distinct anatomic areas:
  - Inguinal canal
  - Femoral triangle

EPIDEMIOLOGY

Incidence

- Hernia:
  - Estimated that ~5% of population will develop hernia at some point in their lifetime.
- Cryptorchidism:
  - 3–5% in newborn and 0.7–1% by the end of 1st yr.

Prevalence

N/A

RISK FACTORS

- Hernia:
  - Low birth weights (<1,500 g)
  - Incidence increases with aging as well as complications.
  - Full-term newborn has 3.5–5% chance
- Cryptorchidism:
  - Low birth weights (<2,500 g)
  - Prematurity 30%
  - Factors that may lead to late testicular descent include black or Hispanic ethnicity; a family history, low birth weight, and preterm birth delivery; and cola consumption during pregnancy

Genetics

Some connective tissue disorders are inherited and can be associated with a groin hernia (see "Groin Hernia, Adult and Pediatric")

PATHOPHYSIOLOGY

- The contents of the groin include skin, subcutaneous tissue, the inguinal canal and contents, femoral triangle and contents (including vessels, nerves, and lymph nodes), and musculoskelet al structures (1)
- Lymphadenopathy:
  - Infection with STD, skin infection in the lower extremities
  - Malignancy such as melanoma, lymphoma, other
- Hernia:
  - Persistence of patent processus vaginalis

  - Chronic increased intra-abdominal pressure
  - Connective tissue disorder altering collagen formation can predispose to hernia
  - Prematurity
- Cryptorchidism:
  - Endocrine abnormality
  - Absence or abnormalities of the gubernaculum
  - Reduced intra-abdominal pressure
  - Pronounced impairment in germ cell development

ASSOCIATED CONDITIONS
- Chronic increased intra-abdominal pressure.
- STDs associated with lymphadenopathy
- Penile cancer

GENERAL PREVENTION
- Avoid chronic increase in intra-abdominal pressure that may encourage hernia formation.
- Avoid STIs.

DIAGNOSIS
HISTORY
- Onset of the mass (age, activity) and any associated symptoms
- Family history of cryptorchidism
- Symptoms of malignancy (fevers, weight loss)
- Birth history: Premature or low birth weight (for congenital hernia and cryptorchidism)
- History of presence or absence of testes in the scrotum, contralateral testis
- Alteration in the size of the mass with cough or abdominal straining suggests hernia or varicocele.
- Fever, a lesion on genitalia or lower extremity, and weakness may suggest infection and lymphadenitis.
- Surgical history of previous hernia repair

PHYSICAL EXAM
- General:
  - Evidence of adenopathy elsewhere, to suggest more systemic disease such as lymphoma
- Groin:
  - Patient should be examined in standing position as well as supine, and Valsalva maneuver should be done during exam
    - A cough impulse usually suggests an inguinal hernia. Erythematous skin suggests infection or strangulated hernia. Pulsatile mass may suggest arterial aneurysm
    - A finger in the external ring can help to differentiate direct and indirect hernias
    - Groin tenderness: Likely infection is the etiology
- Genitalia:
  - Evaluate for masses, lesions, ulcers
    - Malignancy may result in groin adenopathy
    - Ulceration may suggest a sexually transmitted infection
- Scrotum:

- Absent testis suggests undescended testes
- Tender testis suggests epididymitis, testicular torsion, and epididymitis
- Transillumination test, if positive, may suggest a hydrocele/hydrocele of the spermatic cord

• Lower extremity exam:
- Any source of infection or malignancy such as melanoma

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Blood tests:
- Full blood count and ESR
- Renal function tests and electrolytes
- Syphilis serology, if indicated
- HIV serology, if indicated
- LGV (lymphogranuloma venereum) serologic test, if suspected

• Swab and culture the base of any lesions to diagnose genital herpes, syphilitic ulcer, chancroid (*Haemophilus ducreyi*)

Imaging (2)

• US can confirm hernia and can help to see the testes within the inguinal canal. Not sensitive for intra-abdominal testis.
• Doppler US for vascular conditions (Valsalva maneuver should be performed during exam).
• CT/MRI can help to diagnose obscure hernias. Also can identify related lymphadenopathy.
• Arteriography may help diagnose femoral artery aneurysm.
• Venography or Doppler US will help diagnose saphenous varix.

Diagnostic Procedures/Surgery

• Laparoscopy: Can be diagnostic and therapeutic for hernia and intra-abdominal testes.
• Exploratory surgery is necessary in many cases for both diagnosis and treatment.
• Lymph node biopsy or fine needle aspiration (FNA) for definitive diagnosis of lymphadenopathy.
• Chromosomal and hormonal analysis in situation with bilateral undescended testes.

Pathologic Findings

• Cryptorchidism:
- Decreased number of Leydig and Sertoli cells
- Failure to develop primary spermatocyte
- Peritubular fibrosis

• Lymphadenopathy:
- Can identify neoplastic or inflammatory cause

DIFFERENTIAL DIAGNOSIS

• The mnemonic "**MINT**" can be used to remember the possibilities (Malformations, Inflammatory, Neoplasms, Trauma):
- **M**alformations:
  - Hernia (inguinal or femoral), usually presents with a mass
  - Hydrocele

- Hydrocele of the canal of Nuck
- Cryptorchidism (undescended, maldescended, or retractile testicles)
- Testicular torsion
- Femoral artery aneurysm
- Varicocele
- Spermatocele

• **I**nflammatory Lesions:
  – Inguinal lymphadenitis (a mass found during exam):
    - Acute secondary to venereal disease (chancroid, gonorrhea herpes, or syphilis) or skin disease, infection in the groin area, drug reaction, and viral infections
    - Chronic secondary to TB
  – Cellulitis
  – Psoas abscess secondary to TB
  – Thrombophlebitis of the saphenous or femoral vein (especially postpartum)
  – Osteomyelitis
• **N**eoplasms:
  – Lymphadenopathy (penile cancer, melanoma, lymphoma, or metastatic tumor)
  – Paratesticular tumors
  – Skin tumor, lipoma and sarcoma of the bone
• **T**rauma:
  – A perforation of the femoral vein or artery
  – Contusion and fracture, or dislocation of the hip

TREATMENT

GENERAL MEASURES

Management is based on the cause of the mass and can vary from antibiotic therapy, biopsy, or further imaging for more extensive adenopathy.

MEDICATION

First Line

• Lymphadenopathy:
  – Infection requires treatment with specific antibiotics.
  – For STD-related adenopathy, see specific chapter.
  – Malignancy with either requires chemotherapy or lymph node dissection based on the etiology.
  – For penile cancer with lymphadenopathy, a course of antibiotics is indicated.

Second Line

N/A

SURGERY/OTHER PROCEDURES

• Cryptorchidism:
  – Treatment started at 6–12 mo
  – Hormonal treatment efficacy is $<20\%$ and is dependent on testis location
  – Surgery is the gold standard for management

- Hydrocele:
  - Communicating hydrocele with patent processus vaginalis will require surgery
- Testicular Torsion:
  - Manual detorsion followed by orchiopexy
- Hernias:
  - Congenital hernias are repaired by ligating the processus vaginalis at the internal inguinal ring (60% chance of having a contralateral defect)
  - Strangulated, incarcerated hernias require emergency intervention
  - Elective surgical repair for hernia is recommended based on surgeon preference

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

- Lymphadenopathy: Requires follow-up for chronic infection, response to treatment.
- Cryptorchidism: Requires follow-up for:
  - Malignancy: Increased risk of malignancy in undescended testis, and patient is required to perform monthly self-exam for any abnormality (corrective surgery does not reduce the chances of malignancy).
  - Increased risk of trauma and torsion.
  - Requires follow-up for fertility.
- Hernia: Follow for recurrences and possible occurrence on the other side in young children.

PROGNOSIS

Depends on the etiology of the mass

COMPLICATIONS

- Cryptorchidism:
  - Infertility
  - Malignancy
  - Increased risk of trauma and torsion
  - Hernia
- Hernia:
  - Nonreducible and incarceration
  - Obstruction
  - Strangulation
- Lymphadenopathy can erode into femoral vessels and cause exsanguination and death

FOLLOW-UP

Patient Monitoring

- Cryptorchidism:
  – Requires follow-up for fertility
  – Self-exam for testicular masses
- Hernia, for recurrence

Patient Resources
N/A

REFERENCES

1. van den Berg JC, Rutten MJ, de Valois JC, et al. Masses and pain in the groin: a review of imaging findings. *Eur Radiol.* 1998;8(6):911–921.
2. Shadbolt CL, Heinze SBJ, Dietrich BB, et al. Imaging of groin masses: Inguinal anatomy and pathologic conditions revisited. *Radiographics.* 2001;S261–S271.

ADDITIONAL READING

- Baskin LS, Kogan BA. *Handbook of Pediatric Urology*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005;20:51.
- Brunicardi FC, Andersen DK, Billiar TR, et al., eds. *Schwartz's Principles of Surgery*, 8th ed. New York, NY: McGraw-Hill, 2005.

See Also (Topic, Algorithm, Media)
- Cryptorchidism
- Groin Hernia
- Groin Inguinal Mass Image ☼
- Penis Cancer, General
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General

CODES

ICD9
- 550.90 Inguinal hernia, without mention of obstruction or gangrene, unilateral or unspecified (not specified as recurrent)
- 752.51 Undescended testis
- 789.39 Abdominal or pelvic swelling, mass, or lump, other specified site

ICD10
- K40.90 Unil inguinal hernia, w/o obst or gangr, not spcf as recur
- Q53.9 Undescended testicle, unspecified
- R19.09 Other intra-abdominal and pelvic swelling, mass and lump

CLINICAL/SURGICAL PEARLS
- The differential diagnosis varies greatly by the age of the patient.
- If the mass is reducible, strongly suggests a hernia.

GYNECOMASTIA

Samuel Walker Nickles
James S. Rosoff, MD

BASICS

DESCRIPTION

- Gynecomastia (GM) is benign enlargement of the male breast due to proliferation of ductal elements.
- Pseudogynecomastia/lipomastia is an increase in breast adipose tissue. This can be distinguished by careful physical exam of subareolar tissue and comparison to adjacent adipose tissue.

EPIDEMIOLOGY

Incidence (1)

Approximately 2,000 cases of male breast cancer are diagnosed in the United States annually

Prevalence

- 30–65% of men have palpable breast tissue and at autopsy 40–55% of men have histologic evidence of GM
- Age related: Asymptomatic GM is 60–90% in neonates, 50–60% in adolescents, and up to 70% in men aged 50–69 yr

RISK FACTORS

- Alcoholism
- Endocrinopathies
- Medications
- Obesity
- Renal failure

Genetics

- Klinefelter syndrome (47, XXY) is strongly associated with GM
- An increased risk of male breast cancer has been reported in families with a BRCA2 mutation

PATHOPHYSIOLOGY

- Male breast tissue has both androgen and estrogen receptors.
- Androgens inhibit breast development and estrogens stimulate it. GM develops when there is an imbalance of these two influences (ie, androgen deficiency or excess estrogen) or lack of tissue response to them.

ASSOCIATED CONDITIONS

- Prostate cancer
- Testicular tumors
- Cirrhosis
- Renal failure

GENERAL PREVENTION
With hormonally induced GM, prophylactic breast irradiation may reduce GM

DIAGNOSIS

HISTORY
- Age of patient and onset of symptoms (pubertal, GM of aging)
- Associated fevers or chills, breast trauma, nipple discharge
- Medical conditions (cirrhosis, chronic kidney disease, HIV, hyperthyroidism)
- Medications/drugs
- History of cryptorchidism
- Sexual history: Sexual maturation, changes in libido, erectile dysfunction, infertility

PHYSICAL EXAM
- General appearance, weight, amount of adipose tissue (contains aromatase capable of peripheral conversion of androgens to estrogen)
- Secondary sexual characteristics such as body hair distribution and phallus size
- Thyroid exam
- Breast exam: Special attention should be paid to distinguish true GM from pseudogynecomastia; unilateral vs. bilateral (if unilateral should be concerned for potential male breast cancer), firm and mobile vs. fixed, skin dimpling, any nipple discharge, palpation of axillary lymph nodes
- Genitourinary exam with special attention to the testicular exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Basic studies: Creatinine, LFTs, thyroid function tests, serum testosterone
- Further testing as needed:
  - Serum estrogens (estradiol, estrone)
  - LH, FSH, prolactin
  - Tumor markers: AFP, β-hCG
  - Adrenal androgens, serum DHEA, urinary 17-ketosteroids

Imaging
- Testicular US if abnormal tumor markers
- CT of the abdomen and pelvis/chest if abnormal levels of adrenal androgens
- Mammography if cancer suspected

Diagnostic Procedures/Surgery
Breast biopsy for suspected breast cancer

Pathologic Findings
- Proliferation of ductules embedded in a connective tissue stroma
- Over about 12 months, the breast tissue evolves into a quiescent stage, in which the amount of stroma and fibrosis increasesand the ductules become less prominent. glandular acini are rare (2)

DIFFERENTIAL DIAGNOSIS
- Physiologic GM: Normal in neonatal boys secondary to maternal estrogen exposure.

  - Occurs in 60–90% of neonatal boys and resolves within several weeks after delivery.
  - Pubertal GM results from the earlier rise of estrogens in early puberty. As the normal ratio of estrogen to testosterone is restored later in puberty the GM resolves.
  - 50–70% of boys develop GM during puberty.
  - 20% of men still have GM at 20 yr of age.
- GM of aging:
  - The hypothalamic–pituitary–testis axis is variable in age-related decline. Some men will have elevated gonadotropins while others will be normal.
  - Adiposity increases with age which leads to increasing peripheral conversion.
  - Sex hormone–binding globulin (SHBG) levels rise with age and decreasing bioavailable testosterone.
  - Medications may also play a part in GM in older men.
- Estrogen secreting tumors:
  - Leydig cell tumors are rare tumors of the testis; 85–90% are benign, most are nonpalpable. Some Leydig cell tumors can directly secrete estradiol. This increases estrogen levels and inhibits LH secretion, suppressing testicular production of testosterone.
  - Sertoli cell tumor: Converts androgens to estrogens leading to a direct increase in circulating levels of estrogens.
  - Feminizing adrenal cortical tumors are generally malignant and poorly differentiated. These cancers directly secrete estrogens as well as steroid precursors that may be aromatized to estrogens in peripheral tissues. Increased estrogen suppresses LH-mediated production of testosterone as well.
- hCG-secreting tumor such as choriocarcinoma stimulates Leydig cells to preferentially secrete estradiol. Many HCG-secreting tumors also will take up steroid precursors such as DHEA and convert them to active estrogens.
- Increased peripheral aromatization to estrogens: Familial aromatase excess syndrome. The enzyme aromatase (P450 aroma or CYP19A1) catalyzes the conversion of steroid precursors to estrogens.
- Estrogen receptor agonists:
  - Therapeutic administration of estrogens such as DES (diethylstilbestrol) may be used to treat men with prostate cancer and can lead to GM. Estrogens may also be used to stimulate breast development in male-to-female transsexuals.
  - Unintentional exposure may occur transcutaneously by sexual intercourse with a partner that uses topical estrogen. Occupational exposure is also possible. Estrogens can be found in hair creams, embalming creams, and in the production of medicinal estrogen products.
  - Marijuana smoke, digitoxin, testosterone, or other aromatizable androgens.
- Androgen deficiency or resistance:
  - Primary or secondary hypogonadism: Testicular failure from any cause may result in GM. Testosterone deficiency leads to elevated LH, which increases estradiol production by remaining Leydig cells. Increased estrogens lead to elevated levels of SHBG, further decreasing free testosterone.
  - Klinefelter syndrome is the most common genetic disorder associated with hypogonadism and infertility in men. GM is present in 50–70% of cases. Klinefelter syndrome is the only cause of GM with an established risk of breast cancer (20-fold increase).

  - Defects in genes critical for testosterone production may also lead to decreased testosterone production.
- Androgen resistance disorders:
  - In both partial and complete androgen insensitivity syndrome, cellular response to androgens is inadequate (elevated gonadotropins and increased serum testosterone) due to lack of negative feedback.
- Refeeding associated GM:
  - Recognized after WWII when imprisoned men resumed normal diets and developed tender GM. Starvation is associated with hypogonadotrophic hypogonadism. With resumption of a healthy diet and regaining weight the hypothalamic–pituitary–testis axis returns to normal, resulting in transient estrogen excess. May also explain GM associated with several chronic diseases.
- Renal failure:
  - Many men with chronic kidney disease develop GM upon initiation of hemodialysis. Before initiation of dialysis men are often nauseated, anorexic, and on protein-restricted diets. The pathogenesis is thought to be similar to refeeding GM.
- Cirrhosis:
  - Studies have shown that the prevalence of GM in cirrhotics is no different than hospitalized age-matched controls. Hormonal changes in chronic liver disease may increase the risk of GM.
  - Patients with cirrhosis have decreased clearance of androstenedione, which provides more substrate for peripheral conversion via aromatase.
  - SHBG may also be increased, decreasing free testosterone.
  - Alcohol has a direct toxic effect on gonadal function, and cirrhotics may have testicular atrophy and hypogonadism.
- Hyperthyroidism:
  - 10–40% of men with thyrotoxicosis may have GM. Due to the increased peripheral conversion of androgens to estrogens. There is also an increase in SHBG in hyperthyroidism. Restoration of euthyroid state resolves associated GM in 1–2 wk.
- HIV:
  - Multifactorial. Use of illicit drugs (heroin or marijuana) may also be seen in this group. Other chronic disease states may also be present such as Hep C, Hep B, and alcoholic liver disease. Some men on HAART therapy have hypogonadotropic hypogonadism.
- Diabetes Mellitus:
  - Diabetic mastopathy presents as a discrete lump or diffuse nodularity. The lesions are composed of B-cell infiltration of mammary ducts and lobules with fibrosis and vasculitis. Can be seen in Hashimoto thyroiditis and lupus.
- Medications:
  - Androgen deprivation therapy (ADT) in prostate cancer is often associated with breast pain, tenderness, and enlargement.
  - Rates of GM in men treated with ADT vary depend on the type employed.
- Miscellaneous medications may be responsible for as much as 25% of new cases of GM in adults.
  - Destruction of Leydig cells: Chemotherapy with cytotoxic agents.

  - Decreased testosterone or DHT production: Spironolactone, ketoconazole, metronidazole, finasteride, dutasteride.
  - Androgen receptor blocker: Flutamide, bicalutamide, nilutamide, cimetidine, marijuana, spironolactone.
  - Increased serum prolactin: Antipsychotic agents, metoclopramide.
  - Possible: Refeeding GM, isoniazid, digoxin.
  - Unknown: HAART, human growth hormone, amiodarone, calcium channel blockers, amphetamines, diazepam, antidepressants (tricyclics and SSRIs).
- Breast cancer:
  - Rare in men; symptoms are similar to those of female breast cancer.
  - A hard fixed mass, ulceration, bloody nipple discharge, or lymphadenopathy should raise suspicion.
  - Suspicious lesions should be biopsied.
  - Except in the setting of Klinefelter syndrome, GM does not increase the risk of breast cancer.

TREATMENT

GENERAL MEASURES

Removal of the offending drug or exogenous source of estrogen if possible

MEDICATION

First Line

- SERMs have been used to block the effects of estrogen excess on breast tissue. Tamoxifen, 10 and 20 mg/d, for 3–9 mo with 90% resolution. Additionally, raloxifene and clomiphene citrate have also been used.

Second Line

- Aromatase inhibitors such as testolactone and anastrazole have been used but not proven as effective as tamoxifen.
- Testosterone replacement therapy in androgen-deficient men may result in partial regression of GM, especially if breast enlargement is of recent onset.

SURGERY/OTHER PROCEDURES

- With longstanding GM, or those that refuse medical treatment, cosmetic surgical excision and reconstruction may be performed
- Testicular cancer: Orchiectomy
- Adrenal tumors: Adrenalectomy

ADDITIONAL TREATMENT

Radiation Therapy

- Prophylactic breast irradiation has been used prior to initiation of estrogens or androgen blockade for blockade for prostate cancer patients
  - Dose: 12 Gy in 2 fractions to 20 Gy in 5 fractions

Additional Therapies

Radioactive iodine ablation or propylthiouracil for hyperthyroidism

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Generally favorable prognosis.
- Patient main concerns: Ruling out breast cancer and cosmetic correction

COMPLICATIONS
Psychological stress

FOLLOW-UP
Patient Monitoring
No regular follow-up is necessary for patients who have physiologic GM and are untroubled by their symptoms and do not have symptoms suggestive of malignancy.

Patient Resources
N/A

REFERENCES

1. Braunstien GD. Gynecomastia. *N Engl J Med*. 1993;328:490–495.
2. Bembo SA, Carlson HE. Gynecomastia: Its features, and when and how to treat it.*Cleveland Clinic Journal OF Medicine*. 2004;(6):511–517.
3. Narula HS, Carleson HE. Gynecomastia. *Endocinol Metab Clin North Am*. 2007;36:497–519.

ADDITIONAL READING

Melmed S, et al. *Williams Textbook of Endocrinology*. Elsevier; Phialdephia, 2013;766–769, 1180–1181.

See Also (Topic, Algorithm, Media)
- Gynecomastia Algorithm
- Gynecomastia Image
- Infertile Male Syndrome
- Testis, Leydig Cell Tumor
- Testosterone, Decreased (Hypogonadism)
- XXY Syndrome (Klinefelter Syndrome)

CODES

ICD9
- 278.00 Obesity, unspecified
- 611.1 Hypertrophy of breast
- 758.7 Klinefelter's syndrome

ICD10
- E66.9 Obesity, unspecified
- N62 Hypertrophy of breast

- Q98.4 Klinefelter syndrome, unspecified

CLINICAL/SURGICAL PEARLS

- Breast cancer is rare in males, representing $<1\%$ of all cases of breast cancer.
- Klinefelter syndrome is the only cause of gynecomastia with an established risk of breast cancer.

HEMATOSPERMIA

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BASICS

DESCRIPTION

- Hematospermia (sometimes referred to as hemospermia) as the presence of visible blood (fresh or altered) in the ejaculate (not specified with regard to how many episodes or overall duration).
- Semen can be described as bright red, coffee-colored, rusty, or darkened; appearance may change as blood ages.
- May occur as a single episode or persist chronically.
- Usually a self-limited and benign condition.

EPIDEMIOLOGY

Incidence

- Accounts for 0.02% (1/5,000) new patient visits to a urology clinic; seen in 0.5% of men presenting for prostate cancer screening (1)
- Mean presenting age of 37 yr old
- Mean duration is 1–24 mo
- In men <40 yr old, cause is always almost due to an inflammatory or infectious process.
- Only 2.4–3.5% of cases of hematospermia result in the diagnosis of a malignancy, typically >40 yr old.

Prevalence

Not truly known

RISK FACTORS

- Recent genitourinary trauma, surgery (prostate biopsy), infection
- Prostatitis, bacterial
- Prolonged abstinence from or frequent ejaculation
- Use of anticoagulant medication
- Systemic coagulopathy/bleeding disorder
- Renal agenesis (associated with seminal vesicle [SV] cysts)

Genetics

None

PATHOPHYSIOLOGY

- Often occurs in isolation
- Pathophysiologic causes include:
  - Inflammation and infection
  - Ductal obstruction and cysts of the accessory sexual glands
  - Neoplasms
  - Vascular abnormalities

- Systemic factors
- Iatrogenic factors

ASSOCIATED CONDITIONS
- Nonmalignant prostatic disease (26%)
- Hypertension (HTN) (5%)
- Genital tuberculosis (TB) (1%)
- Prostate cancer (1%)

GENERAL PREVENTION
None known

DIAGNOSIS
HISTORY
- Duration and amount of bleeding
- Sexual history/frequency
  - Hematospermia often associated with long periods of abstinence or after frequent ejaculation
- Associated voiding disorders
  - Hematuria
  - Dysuria
  - Urethral discharge
  - Lower urinary tract symptoms (LUTS)
- Pain (pelvic, perineal)
- Systemic symptoms:
  - Fever
  - Weight loss
- Travel history to endemic areas:
  - TB
  - Schistosomiasis
  - Hydatid disease (Echinococcus)
- Medications
  - Aspirin
  - Oral anticoagulants
  - Atomoxetine (approved for the treatment of attention deficit hyperactivity disorder [ADHD])
- Recurrent trauma, surgery, or infection:
  - Transrectal ultrasound (TRUS) biopsy
  - Brachytherapy
  - Microwave hyper thermia
  - Cryoablation
  - Radiation therapy
  - High-intensity focused ultrasound (HIFU)
  - Sexually transmitted infection
  - Vasectomy

- Medical conditions
  - HTN
  - Liver disease
  - Bleeding disorders
  - Hyperuricemia in one series
- Rule out partner as a source (ie, vaginal bleeding)
  - If uncertainty exists, consider having the patient ejaculate into a condom for objective verification

PHYSICAL EXAM

- Assess blood pressure (BP)
- Abdominal exam for masses
- Penis/urethra
  - Meatal lesions/masses
  - Discharge
  - Condylomata
  - Meatus should be checked for bloody discharge after rectal exam
- Scrotum, epididymides, and testes:
  - Palpate vas deferens:
    - Induration may indicate TB
    - Absence may explain infertility
  - Assess for masses/fluctuance or tenderness
- Prostate
  - Nodularity: Tenderness, masses
  - Palpate for midline cystic structures
  - SV fullness can be associated with schistosomiasis (egg burden)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and cultures:
  - Urine culture (for acid-fast bacilli and parasites if indicated)
- Serum white cell count and coagulation profile (platelets/PT/PTT)
  - Complete blood count (CBC) if blood dyscrasia
- Suspected
  - INR for patients on coumadin
- Tuberculin skin test should be considered, particularly in patients with exposure history or if originate from or recent travel to endemic areas.
- Semen analysis can be used to confirm diagnosis of true hematospermia and, in cases of schistosomiasis, eggs may be noted. If performed, semen culture should also be sent.
- Urethral swabs/urine studies for the diagnosis of sexually transmitted infection if indicated
- In patients >40 yr or with risk factors for prostate or bladder malignancy:
  - Prostate serum antigen (PSA)
  - Urine cytology

Imaging

- Trans rectal ultrasound (TRUS) of the prostate:

  - To evaluate the prostate, seminal vesicles (SV's), and possible Müllerian duct remnants
  - Identifies etiology in ~95% of cases
    - Prostatic calcifications (43%)
    - Ejaculatory duct calculi (39%)
    - SV calcifications (11%)
    - Dilated SV (22%)
    - Ejaculatory duct cyst (11%)
  - Facilitates diagnostic procedures such as biopsy, puncture
  - Should be 1st imaging study for hematospermia
- Magnetic resonance imaging (MRI)
  - Abnormal signal intensity may represent hemorrhage
  - Should be used if TRUS is not diagnostic or if TRUS is equivocal
  - Cross-sectional or endorectal coil MRI may be obtained

Diagnostic Procedures/Surgery
- Prostate biopsy
  - Indicated if clinical suspicion of prostate cancer is high
- Cystourethroscopy
  - Allows visualization of urethral inflammation and opening of ejaculatory ducts
  - Critical for ruling out urothelial carcinoma

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Inflammation/infection
  - Calculi of SVs, prostate, or urethra
  - Prostatitis
  - Urethritis
  - Seminal vesiculitis
  - Viral:
    - Herpes simplex
    - Cytomegalovirus
    - Human papilloma virus/condylomata
  - Bacterial:
    - TB
    - Chlamydia trachomatis
    - Gonorrhea
    - Syphilis
  - Parasitic:
    - Schistosomiasis
    - Hydatid disease (Echinococcus)
- Ductal obstruction and cysts of accessory glands:
  - Ejaculatory duct cyst
  - SV diverticulum
  - Urethral stricture

  - Utricular cysts
  - Wolffian duct cysts
  - Prostatic cysts
- Neoplasms:
  - Benign
    - BPH
    - Leiomyoma of the SV
    - Urethral adenoma
  - Malignant
    - Bladder: Urothelial carcinoma
    - Prostate: Adenocarcinoma, ductal adenocarcinoma, sarcoma, stromal tumor, lymphoma, malakoplakia
    - SV: Adenocarcinoma, sarcoma, squamous cell carcinoma, malakoplakia, metastases to prostate or SVs (metastatic melanoma to the SVs or prostate, may result in melanospermia)
    - Urethra
    - Testis
    - Epididymis: Mesothelioma
- Vascular abnormalities
  - Arteriovenous malformations
  - Prostatic varicosities
  - Hemangioma
- Systemic factors
  - Hematologic conditions
  - Hemophilia
  - Von Willebrand disease
  - HTN
  - Chronic liver disease
  - Amyloidosis of the SVs
- Iatrogenic causes
  - Prostate biopsy (most common)
  - Genitourinary (GU) instrumentation
  - Extracorporeal shock wave lithotripsy (ESWL) of distal ureteral stones
  - Brachytherapy (occurs in 28% of seed cases)
  - Prostate radiation
  - HIFU
  - Postvasectomy (vasovenous fistula)
  - Postorchiectomy

TREATMENT

GENERAL MEASURES

- If an underlying cause is identified (ie, bleeding disorder, GU TB, schistosomiasis), initiate appropriate medical management.
- Patients should be made aware that this is very common after prostate biopsy

- Spontaneous hematospermia is rarely associated with malignancy
- Most commonly a benign condition that resolves spontaneously and reassurance is appropriate

MEDICATION

First Line

- In men < 40 yr old without an obvious cause of hematospermia after workup (normal physical exam, negative urine studies):
  - Reassurance and expectant management
  - Empiric antibiotic therapy with doxycycline or fluoroquinolone
  - Trial of 5α-reductase inhibitor (finasteride, dutasteride) for 3 mo (3)[C]
- While a similar approach can be taken in men > 40 yr old, diagnostic workup should be more exhaustive and prostate biopsy should be considered if PSA or DRE indicates.

Second Line

None

SURGERY/OTHER PROCEDURES

- Prostatic calculi: Transurethral incision
- Cystoscopic resection of any lesions seen on exam
- Cyst puncture and drainage should be considered in selected cases when indicated
  - Can be performed via TRUS guidance, transperineal or transurethral approaches
- Transurethral cannulation of ejaculatory ducts to perform seminal vesiculoscopy with a ureteroscope and perform therapeutic interventions (dilation, stone extraction, biopsy) has been described (2)[C]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Patients should be reassured, as should their partners.
- A significant number of cases remain idiopathic even after a full workup.
- Hematospermia following prostate biopsy may take several months to clear.

COMPLICATIONS

N/A

FOLLOW-UP

Patient Monitoring

Follow PSA in older patients, as per prostate cancer screening recommendations

Patient Resources
N/A

REFERENCES
1. Ahmad I, Krishna NS. *Hemospermia. J Urol.* 2007;177:1613–1618.
2. Xing C, Zhou X, Xin L, et al. Prospective trial comparing transrectal ultrasonography and transurethral seminal vesiculoscopy for persistent hematospermia. *Int J Urol.* 2012;19:437–442.
3. Badawy AA, Abdelhafez AA, Abuzeid AM. Finasteride for treatment of refractory hemospermia: Prospective placebo-controlled study. *Int Urol Nephrol.* 2012;44:371–375.

ADDITIONAL READING
• Kumar P, Kapoor S, Nargund V. Haematospermia—a systemic review. *Ann R Coll Surg Engl.* 2006;88:339–342.
• Leocadio DE, Stein BS. Hematospermia: Etiological and management considerations. *Int Urol Nephrol.* 2009;41:77–83.
• Szlauer R, Jungwirth A. Haematospermia: Diagnosis and treatment. *Andrologia.* 2008;40:120–124.

See Also (Topic, Algorithm, Media)
Prostate Biopsy, Infections and Complications

CODES

ICD9
• 286.9 Other and unspecified coagulation defects
• 601.9 Prostatitis, unspecified
• 608.82 Hematospermia

ICD10
• D68.9 Coagulation defect, unspecified
• N41.9 Inflammatory disease of prostate, unspecified
• R36.1 Hematospermia

CLINICAL/SURGICAL PEARLS
• Hematospermia is usually a benign and self-limited condition, particularly in men < 40 yr old.
• Will often resolve spontaneously in all age groups.
• Work-up only indicated if persistent or if other associated symptoms (such as hematuria).
• Expected symptom following prostate biopsy and can last for several weeks.
• Treatment should be directed toward underlying cause if identified.

HEMATURIA, GROSS AND MICROSCOPIC, ADULT

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BASICS

DESCRIPTION

- Hematuria may be gross (GH) (visible) or microscopic (MH)
- It can originate from any part of the urinary tract

ALERT

- Hematuria of any degree should not be ignored, as it may be a sign of serious renal or urologic disease, including malignancy.
- Urologic malignancy associated with microscopic hematuria in 1–3% (1).
- GH has a 5 times higher incidence of serious urologic disease compared to MH (2).

EPIDEMIOLOGY

Incidence

- Incidence of various disorders in patients who present with MH or GH: (3)
  - No diagnosis – 60.5%
  - UTI – 13%
  - Bladder cancer – 12%
  - Renal disease – 9.8%
  - Stone disease – 3.6%
  - Renal cancer – 0.6%
  - Prostate cancer – 0.4%
  - Upper tract cancer – 0.1%

Prevalence

Prevalence of asymptomatic MH varies with age and gender, and ranges from 0.19–21% (4).

RISK FACTORS (5)

- Age >35
- Male gender
- Current or past smoking history
- Recent trauma
- Urinary tract surgery or instrumentation
- Prostatic enlargement (BPH or BPE)
- Chronic indwelling Foley
- Family history of renal disease
- Renal calculi
- Pelvic radiation
- Recent febrile illness
- History of irritative voiding symptoms
- UTI

- Occupational exposure to chemicals or dyes
  - Benzenes or aromatic amines
- Medications
  - Cyclophosphamide
  - Analgesic abuse

Genetics

Familial hematuria (Alport syndrome or hereditary nephritis)—glomerulonephritis (GN), end-stage kidney disease, and hearing loss (2)

PATHOPHYSIOLOGY

- Macroscopically:
  - Blood clots that have a vermiform (worm-like) appearance suggest the origin of hematuria to be the upper tract
  - Blood clots that are amorphous suggest the origin to be the lower urinary tract—bladder or prostate
- On microscopic analysis: (2)
  - RBCs in the urine that are isomorphic and have smooth, round membranes and even hemoglobin distribution suggests urologic disease
  - RBCs that are dysmorphic with irregular shapes and uneven hemoglobin distribution suggests glomerular disease

ASSOCIATED CONDITIONS

- Neoplasms
- UTI
- Urolithiasis
- Glomerulonephritis
- Anatomic abnormalities of urinary tract (eg, UPJ [uretero-pelvic junction obstruction])
- Benign prostatic enlargement

GENERAL PREVENTION

- Adequate fluid intake, especially for patients with history of calculi
- Smoking cessation
- Treat/prevent underlying cause

DIAGNOSIS

HISTORY

- Age and sex: Age >35, bladder cancer is the most common cause of hematuria, urologic cancer is more common in males; females may have vaginal bleeding (4)
- Timing of GH during urinary stream:
  - Initial hematuria—anterior urethral pathology
  - Terminal hematuria—bladder neck, prostate, or urethra inflammation/pathology
  - Hematuria throughout—vesical or upper-tract origin
- Associated pain:
  - Painless hematuria suggests bladder cancer
  - Flank pain, GH, and abdominal mass is pathognomonic of renal cell carcinoma

  - Ureteral colic/flank pain can be caused by calculi (most common), tumor, or blood clot
  - UTI/prostatitis can cause hematuria associated with dysuria, urgency, and frequency
- Presence of clot—indicates significant degree of hematuria and higher probability of significant pathology
  - Amorphous clots—bladder/prostate origin
  - Vermiform clots—upper tract origin
- Lower urinary symptoms (frequency, urgency, etc.):
  - BPH can cause hematuria
  - Incomplete bladder emptying can predispose to bladder stones and infection
  - Straining to urinate or spraying of urinary stream can indicate a urethral stricture
- Activity/exercise-induced hematuria should be excluded
- Trauma—significant crush injury or burn may result in myoglobinuria; abdominal or pelvic trauma may cause urinary tract injury
- Recent upper respiratory infection—associated with GN or immunoglobulin A (IgA) nephropathy
- Medical or surgical history:
  - Renal or urologic disease or surgery
  - Recent urethral instrumentation (including catheterization)
  - Sexually transmitted diseases (STDs)
  - History of tuberculosis (TB)
  - History of pelvic radiation
  - History of autoimmune diseases and bleeding disorders
- Current medications
  - Anticoagulants
  - Analgesic abuse
  - Cyclophosphamide
- History of smoking tobacco
- Menstrual history: Vaginal bleeding can be mistaken for hematuria
- Family history
  - Primary renal disease
  - Hypertension (HTN)
  - Adult polycystic kidney disease
  - Alport syndrome
  - Urolithiasis
  - Urologic malignancy
- Occupational risk factors:
  - Exposures to chemicals or dyes (aromatic amines, benzenes) in rubber, petroleum, and dye industries—risk of urothelial carcinoma

PHYSICAL EXAM

- Vital signs
  - If hypertensive evaluate for renal parenchymal disease, chronic kidney disease (CKD) or renal failure, renal cystic disease or renal vascular disease; may be hypotensive if hematuria persistent/severe
- Pallor

  – Anemia may be associated with SLE, hemolytic anemia, and CKD or renal failure
- Rashes
  – Consider Henoch–Schönlein purpura, SLE, and vasculitis
- Generalized edema
  – Associated with nephrotic syndrome or renal failure
- Hearing loss: Alport syndrome
- Heart murmurs: Subacute bacterial endocarditis
- Palpable abdominal or flank masses
  – Hydronephrosis, renal cystic disease, renal tumors, distended bladder
- Flank tenderness:
  – Pyelonephritis or urolithiasis
- Flank lacerations, contusions or rib fractures—underlying renal injury
- Pelvic exam:
  – Urethral caruncle or vaginal prolapse, vaginal bleeding
- Digital rectal exam (DRE)
  – Boggy, tender, warm prostate suggests acute prostatitis
  – Nodularity suggest cancer
  – High-riding prostate suggests urethral disruption in presence of pelvic fracture

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: Must include standard urine dipstick and microscopic evaluation:
  – MH is defined as ≥3 RBCs/high-powered field (hpf) in urinary sediments from 2 of 3 properly collected urine specimens (catheterized sample if vaginal contamination or phimosis) (5)[C]
  – Color
    ◦ Bright red: Suggests recent or ongoing bleeding with urologic/anatomic origin
    ◦ Brown (tea-colored): Suggests old blood/clots or medical renal disease (GN)
  – Dipstick (4)
    ◦ Specific gravity: Poorly concentrated urine—low specific gravity (<1.007) suggests hydronephrosis with renal impairment or intrinsic renal disease
    ◦ Proteinuria: Heavy (3–4+) suggests GN or renal disease
    ◦ Leukocyte esterase and/or nitrite positive (pyuria) suggests infection
    ◦ False-positive dipsticks for blood: Oxidizing agents (betadine, bacterial peroxidases), myoglobinuria, hemoglobinuria (microscopic analysis is negative)
    ◦ False-negative dipsticks for blood: Reducing agents (high-dose vitamin C), urine pH <5.1
  – Microscopy
    ◦ Pyuria – suggests infection
    ◦ Red cell casts – pathognomonic of glomerular bleeding
    ◦ Crystalluria – suggests urolithiasis
- Phase-contrast microscopy or urinary sediment: Differentiates glomerular (renal) and nonglomerular bleeding based on the presence of distorted RBCs (80%) in glomerular bleeding; sensitivity of 95% and specificity 100% (2)
- Urine culture:

- If urinalysis suggests infection
- Urinary cytology
  - Recommended for all patients with risk factors or irritative voiding symptoms. Not recommended as part of routine evaluation for asymptomatic MH (5)[C].
  - Sensitivity for detecting bladder cancer 40—76% (1) (Better at detecting high-grade urothelial carcinoma and CIS)
    - Negative result does not rule out malignancy
    - Atypical cells can be seen with calculi or inflammation
  - NMP22, BTA stat, and UroVysion are alternatives; not considered standard of care but can be useful in some cases of bladder cancer
- Renal function tests (creatinine and BUN)
- CBC – anemia may be due to GH or chronic renal disease. Elevated white blood cell count (WBC) with a left shift suggests infection
- Coagulation profile studies (PT, PTT, INR) to identify coagulopathy
- Other lab tests as clinically indicated
  - Streptozyme (antistreptolysin O titer), serum complement, and antinuclear antibody (ANA), total serum proteins, and albumin: Globulin ratios for GN
  - Urinary calcium: Creatinine ratio (for hypercalciuria), peripheral smear (for sickle cell disease/trait), TB skin test, and urinary mycobacterial cultures (for TB)
  - If in bone marrow transplant patient, consider cytology to look for typical changes associated with polyoma virus

Imaging

- Plain abdominal imaging: Limited utility in initial evaluation of hematuria, may be useful in long-term follow-up of radiopaque stones
- Intravenous pyelography (excretory urography)
  - Traditional imaging for the detection of stones, masses, or obstruction, largely replaced by CT urogram (CTU)
  - Has utility for papillary necrosis and medullary sponge kidney
- Computerized tomographic urogram (CTU) (with and without IV contrast)
  - The current gold standard for surveying the genitourinary (GU) tract for causes of hematuria; can detect stones (on noncontrast imaging), hydronephrosis and other anatomic abnormalities, renal masses, collecting system filling defects, lower urinary tract pathology (contraindicated in serum creatinine >2 mg/dL) (5)[C]
  - Noncontrast CT scanning is the procedure of choice to evaluate kidney stones but should not be used in the initial evaluation of hematuria.
- MRI
  - Alternative imaging modality when CT scanning is not advised (contrast allergy, renal insufficiency, met allic implants)
  - Provides excellent visualization of small renal masses and arteriovenous malformations but has less utility for stones
  - Gadolinium contrast is avoided in patients with creatinine >2 mg/dL (eGFR <30 mL/min), due to risk of progressive systemic fibrosis (nephrogenic systemic fibrosis [NSF])
- Renal US

- Detects renal cystic disease, renal masses, hydronephrosis
- Less sensitive for detecting stone disease but useful in children and pregnancy, when radiation is contraindicated
- Operator dependent, large body habitus can limit utility

• Bladder US
- Useful to assess postvoid residuals, can detect larger bladder tumors, bladder calculi and diverticuli, although less sensitive than CT scan

• VCUG
- Not routinely performed in work-up of hematuria in adults
- May be done in children if hematuria is felt to be in conjunction with febrile UTI, concern for urethral obstruction, or other lower urinary tract abnormalities

• Nuclear renal scans
- Limited utility in the initial evaluation of hematuria

• Renal arteriography and venography
- Useful for renal artery stenosis and renal vein thrombosis and preoperative elucidation of anatomy for surgical planning

• Retrograde urethrogram (RUG), cystogram as clinically indicated

Diagnostic Procedures/Surgery

• Cystoscopy (5)[C]
- Should be performed in all patients >35 yr old with MH or GH
- Patients <35 yr; cystoscopy performed if significant risk factors for urologic malignancies present (irritative voiding symptoms, tobacco history, chemical exposures, etc.)

• Retrograde pyelograms +/− ureteroscopy to evaluate the upper tract when IV contrast is contraindicated (ie, contrast allergy/elevated creatinine) or when upper tract pathology is suspected but not seen on less invasive imaging

• Renal biopsy
- As directed by nephrologist when suspected glomerulonephritis (GN)

Pathologic Findings

Based on primary cause

DIFFERENTIAL DIAGNOSIS

• Pseudohematuria
- Drugs:
  - Reddish color: Pyridium, doxorubicin, phenytoin, salicytes, senna, others
  - Brown color: Cascara, iron supplements, nitrofurantoin, others
- Vegetables: Beets
- Dyes or pigments
- Myoglobin and free hemoglobin
- Menstrual period contamination
- Dysfunctional uterine bleeding

• Congenital/inherited:
- Cystic renal disease
  - Polycystic kidney disease
  - Medullary sponge kidney

    - Medullary cystic disease
  - Benign familial hematuria or thin basement membrane nephropathy
  - Alport syndrome
  - Inherited renal tubular disorders that can lead to urolithiasis
    - Renal tubular acidosis type I
    - Cystinuria
    - Oxalosis
- Hematologic abnormalities
  - Bleeding dyscrasias
  - Sickle hemoglobinopathies
- Anatomic causes
  - Urethral and ureteric strictures
  - Phimosis
  - Posterior urethral valves
  - Urethral caruncle
  - Diverticula
  - UPJ obstruction
  - Obstructive uropathy: Hydronephrosis
  - Vesicoureteric reflux
- Vascular malformations: Hemangiomas
- Traumatic
  - Abdominal and pelvic injury
  - Degree of hematuria is a poor indicator of injury severity
  - Iatrogenic trauma after abdominal, pelvic, or urinary tract surgery
- Exercise-induced hematuria
- Foreign bodies: Catheters, stents, self-introduced, etc.
- Inflammatory
  - UTI/prostatitis and specific infections (schistosomiasis, TB, etc.)
  - GN: IgA nephropathy most common (4%)
  - Radiation: Radiation cystitis and nephritis
- Metabolic
  - Urinary calculi
  - Hypercalciuria
  - Hyperuricosuria
- Neoplastic: Any benign or malignant GU lesion
- Drug-induced
  - Nephrotoxic drugs
  - Analgesic abuse
  - Cyclophosphamide
  - Overanticoagulation
- Miscellaneous
  - BPH
  - Renal vessel disease
    - Arterial emboli or thrombosis

- Renal vein thrombosis
- Endometriosis of the urinary tract—female with cyclic hematuria
- Benign essential hematuria

TREATMENT

GENERAL MEASURES

- The standard urologic evaluation should include urinalysis, urine culture, cytology if risk factors, CTU and cystoscopy as outlined above (See also "Hematuria Algorithm")
- Treatment depends on etiology
- Consider and rule out pseudohematuria or medical causes of hematuria based on presentation, history, lab data, or if evaluation for anatomic lesion is negative
- Gross hematuria
  - If patient is urinating without difficulty and has no blood clots can treat conservatively—increase oral fluid intake
  - For patients with clots/urinary retention: Place a large-bore 3-way Foley catheter (large-bore 2-way or rigid catheter may be more effective to clear clots) and hand irrigate out all clots, followed by continuous bladder irrigation (CBI) with sterile saline or water
  - More severe hematuria or hemodynamic instability may require surgery—cystoscopy with clot evacuation/fulguration
- Microscopic hematuria
  - Work-up can be done in the office setting and usually requires no immediate monitoring or treatment unless associated with trauma

MEDICATION

First Line

- Not treated primarily by medications.
- Aminocaproic acid (Amicar)—for intractable gross hematuria (6)
  - Inhibitor of fibrinolysis
  - Rare but serious side effects of thrombotic events and renal failure
- Finasteride may be effective for prostatic hemorrhage

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Transfuse RBCs if indicated for extreme acute blood loss
- Continuous bladder irrigation (CBI) with normal saline for persistent hematuria with clots
- Consider bladder irrigation with 1% Alum if GH persists (6)
- Cystoscopy, clot evacuation, fulguration if conservative treatment fails
- If intractable GH despite all other measures consider formalin bladder instillation (6)
  - Performed under anesthesia
  - Must rule out vesicoureteric reflux 1st—contraindicated if positive
  - Side effects: Renal failure, bladder contracture/decreased capacity, incontinence, ureteral stenosis
- For life-threatening hemorrhagic cystitis or recurrent/refractory hemorrhagic cystitis

stabilize patient then consider
– Unilateral selective arterial embolization
– Urinary diversion with or without cystectomy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Hyperbaric oxygen therapy (HBO) has been shown to be effective in hematuria caused by radiation-induced cystitis if delivered within 6 mo of initiation of hematuria

ONGOING CARE

PROGNOSIS

Based on etiology of the hematuria

COMPLICATIONS

Hypotension and anemia may result on degree and chronicity of blood loss

FOLLOW-UP

Patient Monitoring

- Monitor hemodynamic status if severe gross hematuria persists or if associated with trauma
  – Serial hemoglobin and hematocrit

Patient Resources

- Hematuria: Blood in the Urine – National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). http//kidney.niddk.nih.gov/kudiseases/pubs/hematuria
- Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=113

REFERENCES

1. Grossfeld GD, Litwin MS, Wolf JS Jr. Evaluation of asymptomatic microscopic hematuria in adults: The American Urological Association best practice policy–part II: Patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. *Urology*. 2001;57:604–610.
2. Sutton JM. Evaluation of hematuria in adults. *JAMA*. 1990;263:2475–2480.
3. Khadra MH, Pickard RS, Charlton M, et al. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol.* 2000;163:524–527.
4. Grossfeld GD, Litwin MS, Wolf JS. Evaluation of asymptomatic microscopic hematuria: The American Urological Association best practice policy – part I: Definition, detection, prevalence, and etiology. *Urology.* 2001;57:599–603.
5. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol.* 2012;188:2473–2481.
6. Abt D, Bywater M, Engeler DS, et al. Therapeutic options for intractable hematuria in advanced bladder cancer. *Int J Urol.* 2013;20:651–660.

ADDITIONAL READING

- Corman JM, McClure D, Pritchett R, et al. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. *J Urol.* 2003;169:2200–2202.
- Sieber PR, Rommel FM, Huffnagle HW, et al. The treatment of gross hematuria secondary to prostatic bleeding with finasteride. *J Urol.* 1998;159:1232–1233.

See Also (Topic, Algorithm, Media)

- Cystitis, Hemorrhagic (Infectious, Noninfectious, Radiation)
- Glomerulonephritis, Acute
- Glomerulonephritis, Chronic
- Hematuria, Athletic (Runner's Hematuria)
- Hematuria Adult Algorithm ↕
- Hematuria, Gross and Microscopic, Pediatric
- Hematuria, Traumatic Algorithm ↕
- Hematuria-Dysuria Syndrome
- Hematuria-Loin Pain Syndrome
- Urine, Abnormal Color

CODES

ICD9

- 599.0 Urinary tract infection, site not specified
- 599.71 Gross hematuria
- 599.72 Microscopic hematuria

ICD10

- R31.0 Gross hematuria
- R31.2 Other microscopic hematuria
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- Gross or microscopic hematuria in any patient should be evaluated, especially when significant risk factors are present (age >35, smoking history, exposure to chemicals/dyes, irritative voiding symptoms).
- Risk of urologic malignancy is 5 times higher in patients who present with gross hematuria.
- Cytology is recommended for patients with risk factors; however, a negative result does not rule out malignancy.
- CTU is the imaging test of choice for evaluating hematuria from the upper tract.
- Cystoscopy should be performed on any patient >35 yr of age presenting with unexplained MH or GH.

HEMATURIA, GROSS AND MICROSCOPIC, PEDIATRIC

Douglas W. Storm, MD, FAAP, FACS
Christopher S. Cooper, MD, FAAP, FACS

BASICS

DESCRIPTION

- Hematuria can be macroscopic or microscopic
  - Macroscopic: Grossly red/pink-tinged urine
  - Microscopic: >5–10 RBC/hpf
  - Common pediatric urology referral
  - Approach is different in children compared to adults
    - Low risk of malignancy as cause in children
    - Medical causes more frequent than surgical

EPIDEMIOLOGY

Incidence

- Microscopic hematuria more frequently encounte-red than gross hematuria (1,2)[A]
- Microscopic hematuria
  - 0.41% (41 in 1,000 pediatric visits)
  - 0.32% school-aged girls
  - 0.14% school-aged boys
- Macroscopic hematuria
  - 0.13% (1.3 in 1,000 pediatric visits)
  - 80% of cases involve males; 20% females

Prevalence

Exact prevalence is unknown

RISK FACTORS

- Alport syndrome
- Anaphylactoid purpura
- Benign familial hematuria
- Dysfunctional voiding
- Glomerular bleeding
- Glomerulonephritis (GN)
- Hemophilia
- Henoch–Schönlein purpura (HSP)
- Genitourinary anatomic anomaly
- Kidney stones
- Medications
- Recent upper respiratory illness
- Recent strep throat
- Renal papillary necrosis

- Sexual abuse
- Sickle cell disease or trait
- Systemic lupus erythematosus (SLE)
- Trauma
- UTI
- Vigorous exercise

Genetics
- Benign familial hematuria: Autosomal dominant
- Sickle cell anemia: Autosomal recessive
- Alport syndrome: X-linked

PATHOPHYSIOLOGY
- Depends on source of the bleeding:
  - Glomerular source (most common)
  - Renal tubular source
  - Interstitial source
  - Vascular source
  - Urinary tract

ASSOCIATED CONDITIONS
Depends on the bleeding source

GENERAL PREVENTION
Must understand the source of the bleeding and tailor prevention accordingly

DIAGNOSIS

HISTORY
- Age of child and timing of onset:
  - Poststreptococcal GN occurs 14–28 days after the sore throat
  - IgA nephropathy hematuria occurs at the time of or shortly after the respiratory illness
  - HSP hematuria occurs 1–3 mo after the rash
- Characterize the pattern of hematuria
  - Gross pink/red urine suggests a urologic cause
    - Initial or terminal hematuria suggests lower urinary tract source
    - Total hematuria suggests upper tract source
    - Idiopathic urethrorrhagia seen in prepubertal boys with blood spotting at the end of urinary stream
  - Gross brown, tea-colored, or cola-colored suggests glomerular origin
  - Microscopic suggests nephrologic cause
- Any precipitating events
  - Recent viral illness, strep throat, skin rash
  - Trauma, strenuous exercise, foreign bodies, sexual abuse, or bleeding/coagulation disorders
- Associated lower urinary tract symptoms (urgency, frequency, dysuria) and/or flank and abdominal pain suggests UTI, stone disease, or dysfunctional voiding component

- Family history of renal disorders, stones, end-stage renal disease, neurosensory hearing loss, HTN, or coagulopathy
- Current medications

PHYSICAL EXAM

- Blood pressure (BP)
  - High BP is suggestive of glomerular disease, especially when accompanied with edema
- Presence of fever and costovertebral angle (CVA) tenderness suggests stone and/or pyelonephritis
- Presence of palpable abdominal or flank mass, bruit, or abdominal tenderness
- Skin rashes and arthritis may suggest HSP and SLE
- Hearing loss suggests Alport disease
- Examine the genitalia for meatal stenosis, urethral prolapse, ureterocele, trauma, sexual abuse
- Edema suggestive of nephrotic syndrome

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Microscopic hematuria considered clinically significant if >5–10 RBC/hpf
  - Recommend that 2 of 3 urinalyses show microscopic hematuria over 2–3 wk before work-up initiated (1,2)[A]
    - False-negative results occur with high urine specific gravity or with high ascorbic acid concentration
    - False-positive results occur in presence of myoglobin, medications (eg, rifampin, pyridium, etc.), bile pigments, and oxidizing agents (eg, household bleaches)
- Urinalysis
  - Proteinuria
    - If 1+– or 2+ child should be evaluated for postural proteinuria
    - 2+ or greater proteinuria child should be evaluated for glomerulonephritis and nephrotic syndrome
  - RBC casts are highly specific for glomerulonephritis
  - Dysmorphic RBCs predict glomerular bleeding with a sensitivity of 93–95% and a specificity of 95–100%
  - WBCs, bacteria, leukocyte esterase, nitrates suggest UTI
    - Recommend urine culture to verify UTI and identify bacteria causing the infection
- Other blood tests:
  - Serum creatinine, BUN, electrolytes (if renal insufficiency noted)
  - Complete blood count CBC)
  - antistreptolysin O titer/streptozyme panel (indicative of poststreptococcal GM)
  - C3/C4 levels (may be lowered in cases of SLE and GN)
  - plasma IgA levels (may be increased with IgA nephritis and HSP)
- Other urine tests:
  - urine calcium to creatinine ratio (varies by age, but generally <0.18; if >0.18 suggests high 24-hr excretion of calcium >4 mg/kg/d)
- Other lab tests:

- throat culture (to rule out strep throat)

Imaging

- Renal and bladder sonography
  - Evaluates for renal parenchymal disorders, stones, tumors, renal artery stenosis, and anatomic abnormalities
- Voiding cystourethrogram (VCUG)
  - Not routinely performed in work-up of hematuria
  - May be done if hematuria is felt to be in conjunction with febrile UTI, concern for urethral obstruction, or other lower urinary tract abnormalities
- CT
  - Selectively used in pediatrics secondary to radiation exposure
  - May be used to evaluate for stone disease or anatomic abnormality or after recent trauma

Diagnostic Procedures/Surgery

- Renal biopsy
  - Heavy proteinuria and worsening renal function are the main indications for biopsy. Only performed if the results will alter therapy.
- Cystoscopy
  - Rarely performed in children
  - Performed if bleeding source thought to originate from the lower urinary tract
  - May inspect efflux of urine from each ureteral orifice to lateralize source of bleeding
  - May perform retrograde ureteropyelogram to look for upper tract source (eg, fibroepithelial polyp)
- Hearing test
  - Alport syndrome

Pathologic Findings

Dependent on the cause of the bleeding

DIFFERENTIAL DIAGNOSIS

- Divided into categories, based on the source of the bleeding
  - Glomerular sources
  - Interstitial and tubular sources
  - Urinary tract source
  - Vascular source
- Glomerular source
  - IgA nephropathy or Berger disease (recurrent gross, painless hematuria, often following a mild fever, upper respiratory illness, viral illness, or exercise)
  - Benign familial hematuria (usually microscopic hematuria also found in parent without hearing loss or renal insufficiency)
  - Alport syndrome (usually microscopic hematuria, proteinuria, progressive renal insufficiency, high-frequency hearing loss, family history of renal disease)
  - Acute poststreptococcal glomerulonephritis (PSGN) (usually acute onset edema, tea-colored urine, history of antecedent illness 2–4 wk prior, elevated BP, urinalysis with RBC casts, and proteinuria)
  - Membranoproliferative glomerulonephritis

  - SLE
  - Rapidly progressive glomerulonephritis (pediatric nephrology emergency, presents with signs and symptoms similar to PSGN, renal function though shows renal insufficiency, may progress to end-stage renal disease in a few weeks)
  - Henoch–Schönlein purpura (rash on dependent parts of the body, renal manifestations may include: No involvement, HTN, active glomerulonephritis, nephrotic syndrome, and acute renal failure)
  - Goodpasture syndrome (pulmonary hemorrhage associated with severe and progressive glomerulonephritis)
- Interstitial and tubular source
  - Acute pyelonephritis
  - Renal tuberculosis
  - Sickle cell disease or trait
  - Acute interstitial nephritis
  - Nephrocalcinosis
  - Metabolic (eg, Fabry disease)
  - Nephrotoxins (eg, analgesics, NSAIDs)
  - Renal cystic disease
  - Acute tubular necrosis
- Urinary tract source
  - Dysfunctional voiding and elimination
  - Papillary necrosis
  - HIV, hepatitis
  - Infestations (eg, schistosomiasis)
  - Nephrolithiasis
  - Anatomic abnormality (eg, ureteropelvic junction obstruction, fibroepithelial polyp)
  - Hemorrhagic cystitis (eg, viral, chemical, radiation)
  - UTI
  - Urethritis
  - Hypercalciuria
  - Tumor
  - Drug-induced cystitis (eg, chemotherapy, antibiotics, Coumadin, etc.)
  - Menstruation
  - Foreign bodies (eg, urinary catheter)
  - Exercise
  - Trauma
- Vascular source
  - Trauma
  - Sickle cell disease/trait
  - Renal vein thrombosis
  - Renal artery thrombosis (20% of gross hematuria in 1st months of life)
  - Arteriovenous malformation
  - Nutcracker syndrome
  - Vasculitis (eg, C3 arteriolar deposition)

– Coagulopathy
– Thrombocytopenia

TREATMENT

GENERAL MEASURES

- Establish diagnosis and treat any underlying medical problems causing the hematuria
- Prompt evaluation must be provided to a child with any of the following in addition to the hematuria (1,2)[A]
  – HTN
  – Edema
  – Oliguria
  – Significant proteinuria (2+ or greater)
  – RBC casts

MEDICATION

Based on underlying cause of hematuria

OTHER PROCEDURES

Based on clinical diagnosis and etiology of the hematuria

ADDITIONAL TREATMENT

Additional Therapies

Based on clinical diagnosis and etiology of the hematuria

Complementary & Alternative Therapies

Based on clinical diagnosis and etiology of the hematuria

ONGOING CARE

PROGNOSIS

Based on underlying cause of the hematuria (3)

COMPLICATIONS

Based on the underlying cause of the hematuria and any interventions delivered

FOLLOW-UP

Patient Monitoring

- Current recommendation of American Academy of Pediatrics is screening urinalysis at age 5 yr
- Annual measurements of height, weight, and BP measurements after age 3 yr

Patient Resources

- http://www.uptodate.com/contents/evaluation-of-microscopic-hematuria-in-children
- http://www.uptodate.com/contents/evaluation-of-gross-hematuria-in-children
- www.chop.edu/healthinfo/hematuria.html
- http://www.childrenshospital.org/az/Site1000/mainpageS1000P1.html

REFERENCES

1. Meyers KE. Evaluation of hematuria in children. *Urol Clin North Am*. 2004;31:559–573.
2. Patel HP, Bissler JJ. Hematuria in children. *Pediatr Clin North Am*. 2001;48:1519–1537.
3. AAP Committee on Practice and Ambulatory Medicine. Recommendations for preventive pediatric health care. *Pediatrics*. 2000;105:645–646.

ADDITIONAL READING

• Feld LG, Waz WR, Pérez LM, et al. Hematuria. An integrated medical and surgical approach. *Pediatr Clin North Am*. 1997;44:1191–1210.
• Quigley R. Evaluation of hematuria and proteinuria: How should a pediatrician proceed? *Curr Opin Pediatr*. 2008;20:140–44.

See Also (Topic, Algorithm, Media)

• Cystitis, Hemorrhagic (Infectious, Noninfectious, Radiation)
• Hematuria, Gross and Microscopic, Pediatric Images
• Hematuria, Pediatric Macroscopic (Gross) Algorithm
• Hematuria, Pediatric Microscopic/Isolated Asymptomatic
• Hematuria, Gross and Microscopic, Adult
• Hematuria-Loin Pain Syndrome
• Urine, Abnormal Color

CODES

ICD9

• 599.0 Urinary tract infection, site not specified
• 599.71 Gross hematuria
• 599.72 Microscopic hematuria

ICD10

• N39.0 Urinary tract infection, site not specified
• R31.0 Gross hematuria
• R31.2 Other microscopic hematuria

CLINICAL/SURGICAL PEARLS

• Prompt evaluation must be provided to a child with any of the following in addition to the hematuria:
  – HTN, edema, oliguria, significant proteinuria, RBC casts
  – Unstable BP, renal insufficiency, fevers

HEMORRHAGE FOLLOWING TURP OR TURBT

Frank M. Nezu, MD
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BASICS

DESCRIPTION

Significant gross hematuria with or without clot retention that occurs following transurethral resection of the prostate (TURP) or transurethral resection of bladder tumor (TURBT)

EPIDEMIOLOGY

- Occurs in up to 11% of patients, typically within the 1st 3 mo after TURP (1)[B]
- TURP is associated with a 2.9% transfusion rate (2)[B]
- 2.2–3.3% of patients require recatheterization, clot evacuation, or return to OR for bleeding after TURP (3)[A]

RISK FACTORS

- Excessive Valsalva/straining/constipation
- Inadequate hemostasis/coagulation of bleeding vessels
- Infection
- Medications: Warfarin, heparin, low molecular weight heaprins, aspirin, thienopyridine (clopidogrel), etc.
- Trauma
- Undermining of bladder neck

Genetics

Patients with deficiencies in the clotting cascade (eg, hemophilia) or other coagulopathies are more prone to hemorrhage.

GENERAL PREVENTION

- Obtain sufficient hemostasis intraoperatively
- Stop anticoagulants or other blood-thinning medications prior to surgery
- Delay starting anticoagulant medications postoperatively if possible, although this practice has been questioned (4)[B]
- Gentle postoperative catheter traction
- 5α-reductase inhibitors, taken pre operatively reduce surgical blood loss intraoperatively (5)[A]
- 5α-reductase inhibitors, do not decrease rates of postoperative clot retention (6)[A]

PATHOPHYSIOLOGY

- Anesthetic technique (regional or general) appears to have no impact on TURP-related bleeding
- Inadequate hemostasis/coagulation of bleeding vessels
- Narcotics may cause constipation and increased intra-abdominal pressure
- NSAIDs are not contraindicated after TURP, they do not increase risk of postoperative

adverse events (7)[A]

- Due to the sloughing of necrotic tissue in prostatic fossa or bleeding at the bladder neck
- Size of tissue resected, duration of resection, or presence of prostate cancer does not correlate with the incidence of hematuria post-TURP (1)[B]
- Studies suggest that there is transient change in platelet count, prothrombin time, and fibrinogen and serum sodium concentrations postoperatively, which can be explained on the basis of dilution of the blood
- Prostate cancer is known to trigger disseminated intravascular coagulation (DIC), and this should be kept in mind when performing resection in the face of known advanced prostate cancer
- In the absence of prostate cancer, up to 6% of patients undergoing TURP may develop mild subclinical intravascular coagulopathy
- Urinary fibrinolysis is a normal physiologic process. Plasminogen is converted to plasmin by plasminogen activators
- The presence of a clot in the bladder causes the release of additional plasminogen activators. Evacuation of clot in the bladder is essential to stopping the bleeding

ASSOCIATED CONDITIONS

- BPH
- Bladder cancer
- Prostate cancer

DIAGNOSIS

HISTORY

- Color of urine, presence of clots
- Patient is not able to void (clot retention)
- History of TURP TURBT—timing, complications, catheter removal
- Use of anticoagulation or similar medications
- Excessive straining or trauma; last bowel movement
- History of clotting disorder
- History of prostate cancer

PHYSICAL EXAM

- General: Pallor, dehydrated, acutely ill
- Vitals: Hypotensive or tachycardic
- Abdomen: Bladder distended or palpable
- Genitalia: Edematous; ecchymotic

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC to assess for anemia
- Creatinine level for obstruction
- Urinalysis, urine culture
- Coagulopathy screen (platelets, PT/PTT) particularly if there is suggestion of bleeding from other sites

Imaging
Bladder US or pelvic CT to evaluate for large organized clot within bladder

Diagnostic Procedures/Surgery
Bladder drainage and irrigation with large-caliber hematuria catheter

DIFFERENTIAL DIAGNOSIS
- Bleeding from lower GU tract source: Urethra, prostate, bladder
- Bleeding from upper GU tract source: Ureter, renal pelvis, kidney

TREATMENT

GENERAL MEASURES
- Limit physical activity, encourage bed rest
- Limit Valsalva and avoid constipation through stool softeners
- Adequate hydration; IV fluid resuscitation
- Bladder drainage and clot evaluation with large-caliber hematuria catheter
- Continuous bladder irrigation (CBI) via 3-way Foley catheter to clear clots and prevent new clots from forming in the bladder
- Foley traction, additional inflation of Foley balloon
- Cessation of anticoagulants or blood-thinning medications
- Check CBC and coagulation profile
- PRBC transfusions if necessary, vitamin K and/or FFP if coagulopathic
- CBI with intravesical alum or silver nitrate
- These are reported but rarely necessary:
  - Hyperbaric oxygen
  - Aminocaproic acid (Amicar) antifibrinolytic
  - Hormonal manipulation: LHRH agonists
  - Urinary diversion with bilateral PCNs
  - Salvage radical prostatectomy
  - Selective arterial prostatic embolization (SAPE) (8)[A]

MEDICATION
First Line
- Antibiotics if infected
- Stool softeners
- 5α-reductase inhibitors such as finasteride or dutasteride (although will not have an acute effect)

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Transurethral clot evacuation with fulguration and cauterization (laser or electrocautery) of prostate if bleeding does not subside within a reasonable time frame
  - Typical Findings: Visible bleeding arterial vessel or discrete/nondiscrete venous bleeding
- Post-TURBT hemorrhage, more expeditious clot evacuation and fulguration

ONGOING CARE

PROGNOSIS

- The mortality rate for hemorrhage after TURP and TURBT is unknown
- Whether hemorrhage after TURP increases the risk of future prostatic bleeding has not been described in the literature
- Use of stool softeners and avoidance of constipation for several weeks after TURP and TURBT seems advisable

COMPLICATIONS

Severe anemia and/or hypovolemic shock can lead to syncope and/or MI

FOLLOW-UP

Patient Monitoring

- Can be managed on the floor setting with staff who are accustomed to managing catheters and CBI
- Serial CBCs, blood transfusions as necessary
- Monitor coagulation profile, FFP if needed

Patient Resources

N/A

REFERENCES

1. Normand G, Guignet J, Briffaux R, et al. Macroscopic haematuria after transurethral resection of the prostate. *Prog Urol.* 2006;16(4):461–463.
2. Reich O, Gratzke C, Bachmann A, et al. Morbidity, mortality and early outcome of transurethral resection of the prostate: A prospective multicenter evaluation of 10,654 patients. *J Urol.* 2008;180(1):246–249.
3. Roehrborn CG. The Agency for the Health Care Policy and Research. Clinical guidelines for the diagnosis and treatment of benign prostatic hyperplasia. *Urol Clin North Am.* 1995;22(2):445–453.
4. Ehrlich Y, Yossepowitch O, Margel D, et al. Early initiation of aspirin after prostate and transurethral bladder surgeries is not associated with increased incidence of postoperative bleeding: A prospective randomized trial. *J Urol.* 2007;178(2):524–528.
5. Pastore AL, Mariani S, Barrese F, et al. Transurethral resection of prostate and the role of pharmacological treatment with dutasteride in decreasing surgical blood loss. *J Endourol.* 2013;27(1):68–70.
6. Hahn RG, Fagerström T, Tammela TL, et al. Blood loss and postoperative complications associated with transurethral resection of the prostate after pretreatment with dutasteride. *BJU Int.* 2007;99:587–594.
7. Kara C, Resorlu B, Cicekbilek I, et al. Analgesic efficacy and safety of nonsteroidal anti-Inflammatory drugs after transurethral resection of prostate. *Int Braz J Urol.* 2010;36(1):49–54.
8. Rastinehad AR, Caplin DM, Ost MC, et al. Selective arterial prostatic embolization (SAPE) for refractory hematuria of prostatic origin. *Urology.* 2008;71:181–184.

ADDITIONAL READING

- Kavanagh LE, Jack GS, Lawrentschuk N, et al. Prevention and management of TURP-related hemorrhage. *Nat Rev Urol.* 2011;8:504–514.
- Mebust WK, Holtgrewe HL, Cockett AT, et al. Transurethral prostatectomy: Immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol.* 1989;141:243–247.

See Also (Topic, Algorithm, Media)

- Hematuria, Gross and Microscopic, Adult
- Hemorrhage, Postop, Urologic Considerations
- Hemorrhagic Cystitis
- Urine, Abnormal Color

CODES

ICD9

- 599.71 Gross hematuria
- 998.11 Hemorrhage complicating a procedure

ICD10

- N99.820 Postproc hemor/hemtom of a GU sys org fol a GU sys procedure
- R31.0 Gross hematuria

CLINICAL/SURGICAL PEARLS

- Proper patient selection, identify patients at risk for bleeding with attention to medications.
- Attention to detail at the end of TURP/TURBT, complete hemostasis and evacuation of specimen.
- Avoid constipation postoperatively.
- In patient with clot retention a large-bore catheter is used to evacuate all clots and start continuous bladder irrigation (CBI) immediately.

HERPES SIMPLEX, GENITAL

Michael Perrotti, MD

BASICS

DESCRIPTION

- Herpes simplex is a common sexually transmitted virus infection
- Herpes simplex virus (HSV)
  - HSV-2 is the most common cause of genital herpes
  - Can be caused by HSV-1 (oral sex during HSV-1 outbreak)
- An increasing proportion of anogenital herpetic infections in some populations has been attributed to HSV-1 infection

EPIDEMIOLOGY

Incidence

0.5–1 million new cases of genital herpes per year in US

Prevalence

~45 million people in US have genital herpes

RISK FACTORS

- Sexual contact with an infected person
- Unprotected sexual intercourse
- Multiple sexual partners

PATHOPHYSIOLOGY

- Transmission can occur by anal, vaginal, or oral sex
- Primary infection if patient was HSV-seronegative for both HSV-1 and HSV-2
- Secondary infection if patient with pre-existing HSV-1 immunity
- Most persons infected with HSV-2 have not been diagnosed with genital herpes. Many have mild or unrecognized infections and shed virus intermittently in the genital tract. As a result, the majority of genital herpes infections are transmitted by persons who are unaware that they have the infection or who are asymptomatic when transmission occurs (2).
- Asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 infection and is most frequent during the first 12 mo after acquiring HSV-2.

ASSOCIATED CONDITIONS

- HIV
- Other STDs

GENERAL PREVENTION

- Monogamous seronegative partner
- Condom use
- Randomized trials have demonstrated that male circumcision (MC) reduces heterosexual acquisition of various STI/STD including HSV type 2, and it reduces genital ulcer disease among female partners (1)

DIAGNOSIS

HISTORY

- Patients may experience a prodrome before the appearance of lesions
  - Tingling, pruritus, paresthesias
- Fever
- Malaise
- Headache
- Painful genital lesions
- Dysuria

PHYSICAL EXAM

- Multiple shallow genital ulcers that may be vesicular
  - However, these classical painful multiple vesicular or ulcerative lesions may be absent in some.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Viral culture
- Polymerase chain reaction
- Direct fluorescence antibody
- Type-specific serology testing
  - Both lab-based assays and point-of-care tests that provide results for HSV-2 antibodies from capillary blood or serum.
    - The sensitivities of these glycoprotein G type-specific tests for HSV-2 antibody vary from 80–98%, are false-negative at early stages of infection. The specificities are ≥96%. False-positive results can occur, especially in patients with a low likelihood of HSV infection

Imaging

MRI in suspected CNS disease

Diagnostic Procedures/Surgery

- Unroofing of vesical to obtain fluid for viral culture
- Lumbar puncture in meningitis

DIFFERENTIAL DIAGNOSIS

- Acute UTI
- *Neisseria gonorrhoeae*
- Treponema pallidum
- Drug eruption
- Behçet's disease

TREATMENT

GENERAL MEASURES

- No cure is available
- Encourage safe sex practices to reduce transmission (ie, condom use); however, lesions can

sometimes spread outside of the coverage area
- Common concerns regarding genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. The misconception that HSV causes cancer should be dispelled.
- Avoidance of sexual activity during recurrences
- Antiviral medications can prevent or shorten outbreaks.
- Daily suppressive therapy can reduce recurrences and the likelihood of transmission to partners.
- Topical therapy with antiviral drugs offers minimal clinical benefit.
- Treatment guidelines based on most current CDC recommendations (2)
- Acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients in the doses recommended for treatment of genital herpes.

MEDICATION

First Line

- Recommended regimens for 1st episode (extend treatment if healing is incomplete after 10 days of therapy).
  - Acyclovir 400 mg PO TID for 7–10 days OR 200 mg PO 5 times a day for 7–10 days
  - Famciclovir 250 mg PO TID for 7–10 days
  - Valacyclovir 1 g PO BID for 7–10 days

Second Line

- Suppressive therapy for recurrent genital herpes
  - Acyclovir 400 mg PO BID (3)[A]
  - Famciclovir 250 mg PO BID
  - Valacyclovir 500 mg or 1,000 mg PO once daily
    - Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (ie, ≥10 episodes per year).
- Episodic therapy for recurrent genital herpes (2)
  - Requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks.
  - Provide patient with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
    - Acyclovir 400 mg TID for 5 days OR 800 mg PO BID for 5 days OR 800 mg PO TID for 2 days
    - Famciclovir 125 mg PO BID for 5 days OR 1,000 mg PO BID for 1 day OR 500 mg once, followed by 250 mg BID for 2 days
    - Valacyclovir 500 mg PO BID for 3 days OR 1 g PO QD for 5 days

SURGERY/OTHER PROCEDURES

- Sitz baths
- Foley catheter for retention of urine associated with sacral nerve root involvement

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- In complicated HSV infection (central nervous system disease, disseminated HSV), the Centers for Disease Control recommend intravenous acyclovir (5–10 mg/kg) every 8 hr for 2–7 days or until clinical improvement
- Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among HIV-positive persons.

Complementary & Alternative Therapies

None noted to be effective

ONGOING CARE

PROGNOSIS

- Symptoms may last 2–4 wk if untreated
- Symptoms less severe in nonprimary compared to person without pre-existing HSV immunity
- Treatment during primary infection lessens morbidity (1)[A]

COMPLICATIONS

- Aseptic meningitis
- Encephalitis
- Transverse myelitis
- Hepatitis
- Pneumonitis
- Disseminated HSV
- HIV transmission
  - When the sores come into contact with the mouth, vagina, or rectum during sex, they increase the risk of HIV transmission if either partner is HIV-infected.
- Some HSV-infected persons might express anxiety concerning genital herpes that does not reflect the actual clinical severity of their disease; the psychological effect of HSV infection frequently is substantial.

FOLLOW-UP

Patient Monitoring

- Patient's education concerning the natural history of the disease, potential for recurrent episodes, asymptomatic viral shedding, and the risks of sexual transmission.
- At 1st episode of genital herpes, advise the patient that suppressive therapy is available and effective in preventing symptomatic recurrent episodes
- Encourage patients to inform their current sex partners that they have genital herpes and to inform future partners before initiating a sexual relationship.
- The risk for HSV-2 sexual transmission can be decreased by the daily use of valacyclovir by the infected person. Episodic therapy does not reduce the risk for transmission and its use should be discouraged for this purpose among persons whose partners might be at risk for HSV-2 acquisition (4).
- Symptomatic sex partners should be evaluated and treated in the same manner as patients

who have genital lesions. Asymptomatic sex partners of patients who have genital herpes should be questioned concerning histories of genital lesions and offered type-specific serologic testing for HSV infection.

Patient Resources

http://www.cdc.gov/STD/Herpes/

REFERENCES

1. Tobian AA, Kacker S, Quinn TC. Male Circumcision: A globally relevant but under-utilized method for the prevention of HIV and other sexually transmitted infections. *Annu Rev Med*. 2014;65:293–306.
2. MMWR. December 17, 2010, Vol 59, no. RR-12. Available at http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf. Accessed January 3, 2014.
3. Bryson YJ, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: A randomized double-blind controlled trial in normal subjects. *N Engl J Med*. 1983;308:916–921.
4. Mattison HR, Reichman RC, Benedetti J, et al: Double blind placebo controlled trial comparing long term suppressive with short term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med*. 1988;85:20–25.

ADDITIONAL READING

Hofstetter AM, Rosenthal SL, Stanberry LR. Current thinking on genital herpes. *Curr Opin Infect Dis*. 2014;27(1):75–83.

See Also (Topic, Algorithm, Media)

- Aphthous Ulcer, External Genitalia
- Genital Ulcers
- Genital Ulcers Algorithm
- Herpes Simplex, Genital Image
- Penis, Cutaneous Lesion
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General

CODES

ICD9

- 054.10 Genital herpes, unspecified
- 054.11 Herpetic vulvovaginitis
- 054.19 Other genital herpes

ICD10

- A60.00 Herpesviral infection of urogenital system, unspecified
- A60.04 Herpesviral vulvovaginitis
- A60.9 Anogenital herpesviral infection, unspecified

CLINICAL/SURGICAL PEARLS

- It is estimated that 1 in 5 adults in US is infected with HSV, but that many are asymptomatic and do not know that they are infected with the virus.
- Most infected individuals have recurrent episodes of painful genital ulcers.
- The 1st episode usually occurs a few weeks following initial infection with the virus and may last 2–3 wk.
- HSV recurrences generally decrease in frequency over time.

HESITANCY AND INTERMITTENCY

Patricia Lewandoski, MD
Akhil Das, MD, FACS

BASICS

DESCRIPTION

- Hesitancy is the delay in the start of micturition.
- Intermittency is the involuntary stopping and starting of the urinary stream during voiding.
- Hesitancy and intermittency are commonly characterized as obstructive (emptying) symptoms. These spectrum of symptoms also include:
  - Postvoid dribbling
  - Straining to void
  - Decreased force of stream
  - Incomplete bladder emptying

EPIDEMIOLOGY

Incidence

- Obstructive urinary symptoms and age are highly correlated.
- Patient symptom reporting is influenced by sociodemographic and cultural factors.
- Hesitancy and intermittency is primarily related to BPH and occurs mostly in men.

Prevalence

- Age-stratified prevalence of moderate-to-severe Lower Urinary Tract Symptoms (LUTS) in men:
  - 40–50 yr old: ~20%
  - 50–60 yr old: ~30%
  - 60–70 yr old: ~40%
  - 70–80 yr old: ~56%

RISK FACTORS

- Bladder outlet obstruction:
  - In men, primarily related to benign prostatic hypertrophy (BPH), bladder neck contracture, bladder stones, urethral valves, urethral stricture disease, and prostate cancer.
  - In women, primarily caused by pelvic floor prolapse/large cystocele, bladder stones, and urethral stricture disease (rarely)
- Detrusor underactivity:
  - Idiopathic
  - Neurogenic: Diabetes, Parkinson disease, etc.
  - Non-neurogenic: Dysfunctional voiding
- Obesity is associated with a higher incidence of LUTS

Genetics

N/A

PATHOPHYSIOLOGY

- Bladder outlet obstruction: Increased resistance to urinary flow due to various etiologies (BPH, stricture, etc.) requires the bladder to generate higher voiding pressures which delays the initiation of micturition and may cause intermittency.
- Inadequate detrusor contraction due to various etiologies delays the start of voiding and may cause intermittency.

ASSOCIATED CONDITIONS
BPH and erectile dysfunction in men

GENERAL PREVENTION
Adequate treatment of LUTS

DIAGNOSIS
HISTORY
- Quantification of lower urinary tract symptoms
  - AUA/IPSS symptom index should be used.
  - Other obstructive voiding symptoms should be assessed.
  - Consider voiding diary if history is unclear.
- Assess for irritative voiding symptoms:
  - Cystitis/prostatitis: Can present with acute, severe obstructive symptoms.
- History of hematuria:
  - Urethral stricture
  - Bladder/kidney stones
  - Bladder mass
- Certain pelvic procedures can result in detrusor underactivity.
  - Other medical conditions:
    - Certain neurologic conditions and diabetes can cause detrusor underactivity.
    - Prior pelvic irradiation can affect bladder contractility.
- History of STD may predispose patients to urethral stricture disease.
- Medications:
  - Certain over the counter (OTC) medications for colds or sinusitis may contain phenylephrine which may exacerbate LUTS.
  - Antimuscarinics may lead to obstructive symptoms.

PHYSICAL EXAM
- Abdominal exam: Palpate for a distended bladder.
- Focused neurologic exam should be performed. The following should be assessed:
  - General mental status
  - Ambulatory status
  - Lower extremity neuromuscular function
  - Anal sphincter tone
- Digital rectal exam (DRE) should be performed:
  - Prostatic nodularity, if present, may be a sign of prostate cancer and should be worked up accordingly
  - Size should be assessed, although DRE tends to underestimate size
  - Bogginess or tenderness: Consistent with prostatitis

- In men, circumcision status, assess for urethral stenosis
- In women:
  - Pelvic exam should be performed to assess for masses, pelvic floor prolapse, and/or cystocele.
  - Urethral lesions should also be assessed.
- Pediatric considerations:
  - Meatal stenosis should be considered in young boys who present with hesitancy and intermittency

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis by dipstick testing or microscopic exam of the sediment should be performed to screen for hematuria and UTI.
  - If UTI suspected: Urine culture.
- Serum PSA should be assessed in men with at least a 10-yr life expectancy.
- Renal function tests (BUN and creatinine) are NOT recommended in the initial evaluation of men with LUTS, such as hesitancy or intermittency according to the AUA guidelines for BPH.

Imaging

- Upper tract evaluation (CT scan, IVP, or US) is not recommended as part of the initial work-up of hesitancy and intermittency unless warranted by history, exam, or lab evaluation.
- If urethral stricture disease is suspected, retrograde urethrography (RUG) may be helpful
- Transrectal US should be reserved for patients with an increased suspicion of prostate cancer undergoing prostate needle biopsy

Diagnostic Procedures/Surgery

- Urinary flow rate should be considered:
  - May be helpful in patients with complex medical history.
  - Should be performed in patients who are to undergo invasive therapy, as this may predict response to surgery.
- Catheterized or scanned PVR should also be considered:
  - Will indicate which patients need immediate catheterization for acute urinary retention.
  - Helps in diagnosis of voiding dysfunction or in patients with neurologic disease.
- Cystourethroscopy should be considered in patients with possible urethral stricture.
- Urodynamics (pressure flow) study should be considered in certain patients with complicated histories that imply neurologic disease.

Pathologic Findings

BPH findings on pathologic exam include proliferation of the stroma and epithelium.

DIFFERENTIAL DIAGNOSIS

- Bladder outlet obstruction
  - BPH—common cause of hesitancy and intermittency in men
  - Bladder neck contracture (ie, after prostate surgery)
  - Urethral stricture disease
- Bladder stone

- Foreign body
- Cancer (prostate, bladder, urethral)
- Prostatitis
- UTI
- Bladder neck dyssynergia
- Detrusor-sphincter dyssynergia
- Pelvic organ prolapse
- Detrusor underactivity (more common cause of hesitancy and intermittency in women):
- Diabetes mellitus
- Parkinson disease
- Multiple sclerosis
- Interstitial cystitis
- Radiation cystitis
- Spinal cord injury/lumbosacral disk disease
- Medications: Noradrenergic drugs are less likely than selective serotonin reuptake inhibitors (SSRIs) to cause sexual dysfunction but more likely to cause urinary hesitancy

TREATMENT

GENERAL MEASURES

- When the effect of LUTS on quality of life was studied, most important factors for seeking treatment were the severity and degree of bother.
- Treatments are tailored to the degree of bother and the severity of the disease
- Review medications (anticholinergics, sympathomimetics, and opioids) to determine if any are potential cause; consider alternatives
- Mild symptoms: Watchful waiting and conservative measures
  - Limit fluid intake
  - Avoid diuretics
  - Avoid coffee, tea, alcohol which may irritate the bladder

MEDICATION (2)

First Line

- For patients with evidence of infection, appropriate antibiotic therapy should be initiated.
- For men with hesitancy and intermittency presumably due to BPH/BOO:
  - α-adrenergic antagonists (alfuzosin, doxazosin, tamsulosin, terazosin, silodosin) reduce resistance at the bladder outlet and provide symptom relief.
  - At maximal doses, all agents are felt to be equally effective.
  - Side effect profiles may include syncope, orthostatic hypotension, retrograde ejaculation, asthenia, and nasal congestion.
- 5α-reductase inhibitors (5ARIs) (finasteride 5 mg/d and dutasteride 0.5 mg/d) reduce prostate volume, prevent progression of BPH, and improve symptoms in clinical trials.
  - These drugs can cause decreased libido, sexual dysfunction, and reduce PSA by ~50% and are of little use in men without evidence of clinical BPH.
- Combination therapy: MTOPS study showed a 67% 5-yr risk reduction in BPH progression in men on combination therapy (doxazosin and finasteride) compared to placebo and better

than either agent alone (39% and 34%, respectively).

Second Line

- Combination therapy combining an 5ARI with an α-blocker may be useful
- If ED and BPH/BOO coexist daily tadalafil (2.5–5 mg PO QD) can be used

SURGERY/OTHER PROCEDURES

- Urethral stricture disease and/or bladder neck contractures should be addressed using appropriate endoscopic or open procedures.
- Cystocele and/or pelvic floor prolapse in women should be addressed surgically if indicated.
- For men with hesitancy and intermittency presumably due to BPH/BOO who do not respond to medical management:
  - Transurethral resection of the prostate (TURP) remains the gold standard surgical approach in patients who do not respond to medical management to BPH.
    - Can be combined with various laser techniques to facilitate tissue hemostasis and removal
- Transurethral laser vaporization or enucleation.
- Transurethral microwave heat treatment (TUMT): Minimally invasive therapy is somewhat effective in the treatment of LUTS due to BPH.
  - Simple open prostatectomy is often reserved for patients with large prostates (>100 cc) who are not candidates for TURP.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Behavioral interventions, such as timed voiding or double voiding

Complementary & Alternative Therapies

Saw palmetto (*Serenoa repens*) has been reported to improve LUTS due to BPH/BOO. Randomized clinical studies have produced contradictory results.

ONGOING CARE

PROGNOSIS (3)

- 25% of untreated patients with moderate-to-severe LUTS presumably due to BPH/BOO experience clinical progression of symptoms within 5 yr.
- Randomized clinical trials of patients receiving α-blocker therapy indicate that >1/2 will report a >25% improvement in symptoms within 3 mo of initiating treatment.
- 5–10% of men with moderate-to-severe LUTS will fail medical therapy and will require surgical intervention for their condition.

COMPLICATIONS

- Patients with disease progression who do not receive appropriate treatment may experience the following complications:
  - Renal insufficiency
  - UTI

– Stone formation
– Acute urinary retention
– Secondary bladder dysfunction

FOLLOW-UP

Patient Monitoring

- After appropriate treatment has been initiated and patients report improvement, annual follow-up should include:
- History and physical exam, urinalysis, PSA
  – Uroflowmetry and postvoid residual urine as needed

Patient Resources

MedlinePlus. http://www.nlm.nih.gov/medlineplus/ency/article/003143.htm

REFERENCES

1. Rosenberg MT, Staskin DR, Kaplan SA, et al. A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. *Int J Clin Pract.* 2007;61:1535–1546.
2. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387–2398.
3. Takeda M, Araki I, Kamiyama M, et al. Diagnosis and treatment of voiding symptoms. *Urology.* 2003;62:11–19.

ADDITIONAL READING

McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol.* 2011;185(5):1793–1803.

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Lower Urinary Tract Symptoms (LUTS)
- Prostate, Benign Hypertrophy
- Prostatitis, General

CODES

ICD9

- 788.61 Splitting of urinary stream
- 788.64 Urinary hesitancy
- 788.69 Other abnormality of urination

ICD10

- R39.11 Hesitancy of micturition
- R39.13 Splitting of urinary stream
- R39.19 Other difficulties with micturition

CLINICAL/SURGICAL PEARLS

- Hesitancy and intermittency is often associated with BPH and generally represents LUTS associated with an obstruction.
- Increasing hesitancy may be seen before an episode of retention.
- In men, the incidence increases with age.
- Pressure-flow studies are helpful in determining obstruction vs. detrusor underactivity.

HIV/AIDS, UROLOGIC CONSIDERATIONS

Daniel C. Parker, MD
Michael A. Pontari, MD

ALERT
The American Urological Association (AUA) policy statement now considers circumcision to be of a health benefit, citing a50–60% risk reduction in HIV transmission in some African nations.

BASICS

DESCRIPTION
- HIV disease results from the acquired deficiency of cellular immunity caused by the human immunodeficiency virus (HIV).
  - Hallmarks
    - Reduction of the helper T-lymphocytes in the blood and the lymph nodes
    - Development of opportunistic infections (*Pneumocystis carinii* pneumonia, cytomegalovirus infections, tuberculosis, candida infections, cryptococcosis, others)
    - Development of malignant neoplasms (non-Hodgkin lymphoma and Kaposi sarcoma)
- A spectrum of HIV infections range from asymptomatic seropositivity to AIDS
- Urologic manifestations of HIV/AIDS
  - Bacterial and nonbacterial infections
  - Urolithiasis
  - Increased risk of malignancy
  - Renal impairment
  - Voiding dysfunction

EPIDEMIOLOGY
Incidence
40–50,000 new cases per year in US

Prevalence
- 0.5% of US adults <50 are infected
  - 2.6% of African American men and 1.5% of African American women were HIV positive from 1999 to 2006
- 33.2 million people worldwide with HIV/AIDS
- 2.1 million deaths due to HIV/AIDS in 2007

RISK FACTORS
- Unprotected intercourse, anal or oral sex
- IV drug abuse and needle sharing
- Transfusion of blood products
- Concomitant STD/STI
- Uncircumcised phallus

- Transmission of mother to infant at birth or via breast milk
- Health care workers
  - Risk for HIV after percutaneous exposure to HIV infected blood is 0.3%; after mucous membrane exposure 0.09%.

Genetics

- 3 groups of HIV viruses: M, N, and O
  - Most infections are by class M
    - 9 subtypes of M exist
  - 15–20% genetic variation between viruses

PATHOPHYSIOLOGY

- HIV-1 binds to cells expressing CD4, leading to decline in CD4 cells and immune function.
- Immunosuppression allows opportunistic/unusual infections, decreases host defense against malignancy.

ASSOCIATED CONDITIONS

- UTI
  - Greater if CD4 count $<500/mm^3$
  - Associated with typical bacteria (*Escherichia coli*, *Enterococcus*) and atypical pathogens such as fungi, mycobacteria, and viruses
- Epididymitis/orchitis
  - Chlamydia, gonorrhea, salmonella, toxoplasmosis
- Fournier gangrene
- Prostatitis
  - Up to 14% in patients with AIDS
  - Greater risk in AIDS patients for developing prostatic abscess
- Urolithiasis
  - Risk with use of indinavir or from metabolic abnormalities
- Hepatitis B virus (HBV)
- Malignancies
  - Non-Hodgkin lymphoma
    - Usually B cell
    - May involve kidneys in 6–12% of AIDS patients
  - Kaposi sarcoma
    - Up to 20% of untreated patients
  - Testicular tumors
    - Usually seminoma
    - Up to 50 times more common
  - Renal cell carcinoma
    - Up to 8-fold increased risk vs. noninfected individuals
- HIV associated nephropathy (HIVAN)
  - Proteinuria >3.5 g/d, edema, and HTN
  - Associated with focal segmental glomerulosclerosis (FSGS) on renal biopsy
  - Progression to dialysis in <10 mo.
- Voiding dysfunction

– Can be retention, detrusor overactivity, and sphincter dyssynergia

GENERAL PREVENTION

- Barrier protection during sex (male and female condoms)
  – Lab studies indicate that the female condom is an effective mechanical barrier to viruses, including HIV, and to semen.
- Avoid high-risk sexual behavior
- Male circumcision
  – Although male circumcision should not be substituted for other HIV risk-reduction strategies, it has been shown to reduce the risk for HIV and some STDs in heterosexual men.
  – Despite these data, male circumcision has not been demonstrated to reduce the risk for HIV or other STDs among men who have sex with men.
- Use of precautions by health workers
- Treating STDs

DIAGNOSIS

HISTORY

- Voiding history (1)[A]
  – Dysuria
  – Frequency
  – Incontinence
  – Urethral discharge
  – Pelvic or testicular pain
  – Flank pain
- Neurologic history
  – Numbness
  – Dysesthesias
- Social history
  – Sexual history
  – IV drug use
  – Blood product transfusions
- Generalized lymphadenopathy, fever, weight loss, and chronic diarrhea are common symptoms.
- Review of systems (ROS): Constitutional symptoms, skin lesions, confusion, urticaria

PHYSICAL EXAM

- General: Skin lesions, adenopathy
- Neurologic exam: Numbness, alterations in sensation
- GU exam: Urethral discharge, testicular/epididymal exam for masses, prostate exam for nodule or tenderness
- Penile lesions of Kaposi sarcoma present as red/brown/purple nodules, macules, or patches

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- HIV testing

- Screening HIV-1 antibody titer
  - If positive, need confirmation by Western blot or immunofluorescence.
  - Need separate consent for HIV testing.
- UA, urine C + S
  - May show rectangular crystals from indinavir
  - Common bacterial pathogens in HIV-infected patients are *E. coli, Enterobacter* (enterococci), *Pseudomonas aeruginosa*, *Proteus* spp., *Klebsiella, Acinetobacter, Staphylococcus aureus*, group D *Streptococcus, Serratia*, and *Salmonella* spp.
  - If UTI suspected and C&S negative, consider atypical organisms: Fungi, parasites, viruses
- CBC
- BUN/creatinine
- Specific testing for STD if urethral discharge present

Imaging

- With flank pain: Noncontrast CT
  - Indinavir stones may not show on CT: Consider contrast study or retrograde pyelogram if renal impairment.
- Scrotal US for palpable lesions
- Prostate abscess: CT scan

Diagnostic Procedures/Surgery

- Measure PVR urine
- Urodynamics for voiding dysfunction or retention.
  - Distinguishes bladder outlet obstruction from acontractile bladder if in retention
    - Bladder hypocontractility was seen in 35–45% at time of urinary retention (2)[A]
  - Common urodynamic findings:
    - Hypo- and hyperreflexia
    - Acontractile hypoactive bladder
    - Detrusor-sphincter dyssynergia

Pathologic Findings

- Testicular tumors: Usually seminoma
- Lymphoma: B-cell non-Hodgkin lymphoma (NHL)
- Penile lesions: Kaposi sarcoma from lymphatic endothelial cells vs. squamous cell carcinoma

DIFFERENTIAL DIAGNOSIS

- Other systemic disease that cause fatigue: Chronic fatigue syndrome, others
- *Salmonella* epididymitis pathognomonic for HIV

TREATMENT

GENERAL MEASURES

- Refer to neurology, nephrology, infectious diseases when appropriate
- Patient education about risk factors, transmission

MEDICATION

First Line

- Highly active antiretroviral therapy (HAART)
  - Combination therapy to combat the ability of HIV to generate drug-resistant mutants (3) [A].
  - 10 million people now on antiretroviral therapy according to the WHO
  - HIV therapy should be started in patients with:
    - AIDS
    - New WHO guidelines recommend starting therapy when CD4 count $<500/mm^3$ (previous guidelines were $<350/mm^3$)
    - Pregnant women
    - Patients with HIV nephropathy
    - Coinfection with HBV regardless of CD4 count.
    - New WHO guidelines also call for some people to begin treatment as soon as they test positive for HIV, regardless of CD4 count

Second Line

- General urologic conditions such as UTI, voiding symptoms, calcium stones treat as per general practice.
  - *Salmonella* epididymitis
    - 2–4 wk of doxycycline 100 mg PO BID plus Cipro 500 mg PO BID
    - If difficult to eradicate may need lifelong suppression.
- Kaposi sarcoma
  - If focal, local radiation, cryosurgery, or retinoids.
  - If disseminated use chemotherapy (doxorubicin) or immunotherapy with interferons

SURGERY/OTHER PROCEDURES

- Indinavir and other protease inhibitor (PI) stones
  - Stop indinavir
  - Hydration
  - Stent if necessary
    - Stones are soft and may pass after stenting.
- Surgical drainage of prostatic abscess
- Stenting for ureteral obstruction from retroperitoneal NHL

ADDITIONAL TREATMENT

Radiation Therapy

Indicated in some cases of focal Kaposi sarcoma

Additional Therapies

- For health care worker exposure
- Post-Exposure Prophylaxis (PEP)
  - Occupational PEP (“oPEP”), healthcare worker potentially exposed to material infected with HIV
  - Non-occupational PEP (“nPEP”), someone is potentially exposed to HIV outside the workplace (eg, from sexual assault, unprotected sex, needle-sharing injection drug use).
  - begin within 72 hrs of exposure; 2–3 antiretorviral medications for 28 days
- Pre-Exposure Prophylaxis (PrEP)

– For people who are HIV-negative and at substantial risk for HIV infection (relationship with HIV infected partner, gay or bisexual man who has had sex without a condom or been diagnosed with a sexually transmitted infection within the past six months, others
– Along with other prevention methods like condoms, PrEP can offer good protection against HIV if taken daily

Complementary & Alternative Therapies
None

ONGOING CARE

PROGNOSIS
Much improved prognosis leading to longer life expectancies, primarily due to newer drug combination therapies

COMPLICATIONS
- Antiretroviral therapy
  – Risk of nephrotoxicity, crystal precipitation leading to stones, hypocalcemia
  – Erectile dysfunction and decreased libido (caused by increased estradiol) may be associated with HAART therapy
- Drugs used for the treatment of HIV-infected patients have become the most frequent cause of drug-containing urinary calculi.
  – Among these agents, PIs are well known to induce kidney stones, (indinavir, atazanavir, darunavir).

FOLLOW-UP
Patient Monitoring
- CD4 counts
- Serum creatinine

Patient Resources
- CDC HIV/AIDS Fact Sheets. http://www.cdc.gov/hiv/library/factsheets/index.html

REFERENCES

1. Breyer BN, Van den Eeden SK, Horberg MA, et al. HIV status is an independent risk factor for reporting lower urinary tract symptoms. *J Urol.* 2011;185(5):1710–1715.
2. Lebovitch S, Mydlo JH. HIV-AIDS: Urologic considerations. *Urol Clin North Am.* 2008;35(1):59–68.
3. von Wyl V, Yerly S, Böni J, et al. Emergence of HIV-1 drug resistance in previously untreated patients initiating combination antiretroviral treatment: A comparison of different regimen types. *Arch Intern Med.* 2007;167:1782–1790.

ADDITIONAL READING

- Cohen MS, Hellmann N, Levy JA, et al. The spread, treatment and prevention of HIV-1: Evolution of a global pandemic. *J Clin Invest.* 2008;118:1244–1254.
- Izzedine H, Lescure FX, Bonnet F, et al. HIV medication-based urolithiasis. *Clin Kidney J.* 2014;7(2):121–126.

- Millett GA, Flores SA, Marks G, et al. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: A meta-analysis. *JAMA*. 2008;300:1674–1684.
- www.aidsinfo.nih.gov (Accessed August 11, 2014)
- www.cdc.gov/hiv/resources/factsheets/index.htm (Accessed August 11, 2014)

See Also (Topic, Algorithm, Media)

- HIV/AIDS, Urologic Considerations Image
- Kaposi Sarcoma, Urologic Considerations
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General
- Tuberculosis, Genitourinary, General Considerations
- Urolithiasis, Indinavir, and Other Protease Inhibitors

CODES

ICD9

- 042 Human immunodeficiency virus [HIV] disease
- 599.0 Urinary tract infection, site not specified
- 592.9 Urinary calculus, unspecified

ICD10

- B20 Human immunodeficiency virus [HIV] disease
- N20.9 Urinary calculus, unspecified
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- Urologic considerations in patients with HIV/AIDS include bacterial infections, urolithiasis, malignancy, renal impairment, and voiding dysfunction.
- Urolithiasis is associated with patients taking indinavir and other protease inhibitors (PI's).
- HIV associated nephropathy (HIVAN) increases the patient's risk of dialysis.
- Salmonella epididymitis is pathognomonic for HIV.
- Highly active antiretroviral therapy (HAART) increases estradiol and can lead to symptoms of erectile dysfunction and decreased libido.

HOT FLUSHES/VASOMOTOR INSTABILITY IN MALES

Tara K. Ortiz, MD
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BASICS

DESCRIPTION

- Hot flushes are typically described as a feeling of intense heat with associated flushing, sweating, rapid heart rate, and anxiety
- Sometimes called "hot flashes"
- Common side effect of androgen ablation therapy in men with metastatic or locally advanced prostate cancer
- Flushing can be associated with wide ranges of other conditions and medications
- This section primarily discusses this condition in males

EPIDEMIOLOGY

Incidence

Occurs in 50–80% of men on androgen deprivation therapy (1)

Prevalence

N/A

RISK FACTORS

- Age, race and ethnicity, educational level, smoking, cardiovascular risk including body mass index, and genetics
- Prostate cancer

Genetics

N/A

PATHOPHYSIOLOGY

- Exact mechanism unknown; majority of theories based on studies in postmenopausal women
- Hot flushes in prostate cancer patients result from decreased feedback of testosterone to the hypothalamus.
- Central control of thermoregulation is preoptic/anterior area in the brain
- Increases in internal and/or skin temperature sensed in the anterior pituitary results in cutaneous vasodilatation (flushing) and sweating.
- Thermoregulatory zone is disrupted:
  - Reduced thermoneutral zone between an upper threshold for sweating and a lower threshold for shivering
- Alterations in glucose transport across blood–brain barrier theorized to be a trigger:
  - Hot flushes are counterregulatory attempts to increase cerebral blood flow and cerebral glucose levels.
- Decreased plasma sex hormones results in loss of negative feedback, thus increasing hypothalamic norepinephrine (NE) levels
- NE decreases thermoneutral zone

– Thermoregulatory center in hypothalamus is anatomically close to the GnRH-secreting neurons
– These neurons are stimulated by NE to secrete GnRH
– Increased GnRH stimulation, by being in close proximity to the thermoregulatory center, might activate heat-losing mechanisms (flushing, sweating).

ASSOCIATED CONDITIONS
- Osteopenia, osteoporosis
- Erectile dysfunction/loss of libido
- Metabolic syndrome (insulin resistance, unfavorable lipid profile, increased fat mass)
- Gynecomastia
- Normocytic, normochromic anemia
- Fatigue

GENERAL PREVENTION
- Identification of triggers
  – Avoid hot beverages, spicy foods, alcohol, abrupt change in ambient temperature
- Keep environment cool

DIAGNOSIS
HISTORY
- Abrupt onset of warmth, frequently followed by profuse sweating requiring change of clothes
- More likely to occur at night
- Sensation typically affects the face and trunk
- Attacks normally last 1–5 min, but can persist for up to 20 min
- Can occur occasionally or multiple times daily:
  – Majority of patients have daily episodes
- Frequently experienced at night
- Onset is typically seen within the 1st yr after androgen ablation:
  – 1/3 of men will develop symptoms within the 1st mo

PHYSICAL EXAM
- During acute episode, facial flushing common
- Perspiring frequently present
- Mild tachycardia secondary to vasodilation or anxiety
- Slight increase in oral and forehead temperature
- Usually normal exam in between hot flush episodes
- May have gynecomastia, increased fat mass secondary to androgen deprivation

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- No routine lab evaluation indicated
- No pattern of characteristic changes in testosterone, follicle-stimulating hormone (FSH), leuteinizing hormone (LH), or prolactin

Imaging

N/A

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Febrile states or hyper thermia
- Emotional blushing
- Systemic illness:
  - Carcinoid syndrome
  - Pheochromocytoma
  - Medullary thyroid tumors
  - Pancreatic islet cell tumors
  - Renal cell carcinoma
- Other illness:
  - Rosacea
- Neurologic disorders
- Medications:
  - Phosphodiesterase 5 inhibitors (sildenafil, vardenafil, tadalafil, avanafil),
  - Any vasodilatory agent (nitroglycerine, etc.)
  - Nicotinic acid
  - Calcium channel blockers most commonly nifedipine, nisoldipine, amlodipine
  - Opiates
  - Tamoxifen
  - Antibiotics (vancomycin, amphotericin B)
  - IV contrast media
- Dietary
  - Ethanol ingestion
  - Monosodium glutamate or other food additives

TREATMENT

GENERAL MEASURES
- For flushing related to androgen deprivation therapy
  - Reassurance if symptoms mild
  - Attempt to identify and avoid lifestyle triggers
  - Keep environment cool
  - Many men will experience resolution after several years without therapy

MEDICATION
First Line
- For androgen deprivation therapy related hot flushes most are hormonal agents
- Megestrol acetate (Megace) 20 mg/d:
  - Synthetic derivative of progesterone

- 1 study demonstrated complete resolution of symptoms in 90% of patients, >50% improvement in 25% (2)[B]
- Side effects include chills, weight gain, nausea, carpal tunnel–like syndrome, disease progression

• Medroxyprogesterone acetate (Depo Provera) 400 mg/d IM:
- 91% with symptomatic improvement (1)[B]
- 46% have complete response as defined as total elimination of hot flushes.
- Side effects could include weight gain, congestive heart failure exacerbation, loss of bone mineral density, disease progression

• Transdermal estrogen patch 0.05 or 0.1 mg/d (1,3)[B]:
- 3 studies with over 70% of men reporting complete resolution
- Side effects include breast swelling, nipple tenderness

• Diethylstilbestrol (DES): 0.30–1 mg/d:
- 70–90% of men achieve excellent results (1)[B]
- Side effects include painful gynecomastia.
- At low doses, thromboembolic events are not a significant problem.
- Generic drug, inexpensive though difficult to obtain in US.

• Cyproterone acetate (Androcur) 100 mg/d
- Not approved for use in US
- Steroidal antiandrogen, antigonadotropin with progestin-like activity
- May interfere with ADT regimen
- 1 study demonstrated resolution of symptoms in 84% of patients, >50% improvement in 37% (2)[B]
- Side effects include fatigue, increased risk of thrombosis, anemia, potential hepatotoxicity, gynecomastia

Second Line (Nonhormonal Therapy)

• Venlafaxine (Effexor) 12.5 mg/d PO:
- Antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) type
- Median weekly hot flush scores decreased 54% from baseline after 1 mo (2)[B]
- Side effects include lack of sexual desire, delayed orgasm, and increase in suicidal ideation.

• Paroxetine (Paxil-CR) 12.5–37.5 mg/d:
- Antidepressant of the selective serotonin reuptake inhibitor (SSRI) class
- In 1 study, daily hot flushes decreased from 6.2–2.5. (4)[B]
- Side effects include sexual dysfunction, somnolence

• Ergotamine/belladonna/phenobarbital (EBP): 1 tablet PO BID:
- Ergot alkaloid used primarily to treat migraine headache
- Use with caution with patients on monoamine oxidase inhibitors (MAOIs), central nervous system (CNS) depressants, anticholinergic agents
- Generally not recommended for the treatment of hot flushes in men

• Gabapentin (Neurontin) 900 mg/d (300 mg TID, titrated) (5)[B]
- Anticonvulsant/treatment of neuropathic pain

– Modest 46% reduction in hot flush symptom score at target dose of 900 mg
– Side effects include nausea, vomiting, dizziness, and somnolence

- Clonidine (Catapres) 0.1–1 mg/d (PO or patch formulations):
  – Centrally acting α-adrenergic agonist used for treatment of hypertension (HTN)
  – 1/3 of men will report a partial response although similar to placebo (1)[B].
  – Side effects include hypotension, dry mouth, skin irritation from patches.

SURGERY/OTHER PROCEDURES

N/A

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Behavioral therapy: Slow, deep breathing may reduce frequency of hot flushes

Complementary & Alternative Therapies

- Acupuncture:
  – 10–12 wk (twice weekly × 2 wk then once weekly × 8–10 wk)
  – 43–78% reduction in frequency of flushes, average 9-mo duration of effect (1)[B]
- Vitamin E:
  – 30% reduction vs. 22% of women receiving placebo in 1 study *(not studied in men)*
  – May increase the risk of prostate cancer; unclear effect on existing cancer (1)[B]
- Soy products:
  – Contain phytoestrogens which might decrease severity of hot flushes (1)[C]
  – Also have shown benefit with regard to cardiac and bone health
- Black cohosh:
  – Has been used in some postmenopausal women for treatment of hot flushes
  – Mechanism is unknown
  – In 1 trial, no difference found with men taking placebo (1)[C]

ONGOING CARE

PROGNOSIS

- Most men have symptom improvement with medical or complementary therapy.
- At 8 yr of treatment with ADT over 40% of men still had flashes.
- In 1 study, 72% of patients noted that hot flashes interfered with sleep and 59% reported they interfered with the quality of life.

COMPLICATIONS

Some men have side effects from medications taken to alleviate hot flushes (bloating, weight gain, hypertension)

FOLLOW-UP

Patient Monitoring

- Ask patients on androgen deprivation at each follow-up clinical evaluation about the presence and severity of hot flushes:

– Inquire about side effects from therapy
– Intermittent cessation of treatment can be used if side effects become bothersome.
  ○ May have positive effect on quality of life, but may decrease survival

Patient Resources
N/A

REFERENCES

1. Jones JM, Kohli M, Loprinzi CL, et al. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl.* 2012;14(2):193–197.
2. Irani J, Salomon L, Oba R, et al. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: A double-blind, randomised trial. *Lancet Oncol.* 2010;11:147–154.
3. Langenstroer P, Kramer B, Cutting B, et al. Parenteral medroxyprogesterone for the management of luteinizing hormone releasing hormone induced hot flashes in men with advanced prostate cancer. *J Urol.* 2005;174:642–645.
4. Naoe M, Ogawa Y, Shichijo T, et al. Pilot evaluation of selective serotonin uptake inhibitor antidepressants in hot flash patients under androgen-deprivation therapy for prostate cancer. *Prostate Cancer Prostatic Dis.* 2006;9(3):275–278.
5. Moraska AR, Atherton PJ, Szydlo DW, et al. Gabapentin for the management of hot flashes in prostate cancer survivors: A longitudinal continuation study—NCCTG Trial N00CB. *J Support Oncol.* 2010;8:128–132.

ADDITIONAL READING

- Baum NH, Torti DC. Managing hot flashes in men being treated for prostate cancer. *Geriatrics.* 2007;62:18–21.
- Engstrom CA, Kasper CE. Physiology and endocrinology of hot flashes in prostate cancer. *Am J Men Health.* 2007;1:8–17.
- Sharifi N, Gulley JL, Dahut WL, et al. Androgen deprivation therapy for prostate cancer. *JAMA.* 2005;294:238–244.

See Also (Topic, Algorithm, Media)
- Andropause (Late-Onset Hypogonadism)
- Menopause, Urologic Considerations
- Testosterone, Decreased (Hypogonadism)

CODES

ICD9
- 780.2 Syncope and collapse
- 780.8 Generalized hyperhidrosis
- 782.62 Flushing

ICD10
- R23.2 Flushing

- R55 Syncope and collapse
- R61 Generalized hyperhidrosis

CLINICAL/SURGICAL PEARLS

- Symptoms are usually reversible with cessation of ADT usually within 3–4 mo of stopping treatment.
- Most effective treatment is hormonal therapy with estrogen or progesterone derivatives.
- There are limited data to support alternative/complementary therapies.

HYDROCELE, ADULT & PEDIATRIC

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BASICS

DESCRIPTION

- A hydrocele is a collection of serous fluid in some part of the processus vaginalis, usually in the tunica. Can be congenital or acquired
- Translucent swelling in the scrotum or inguinal canal or both
- Aside from congenital hydrocele, it is possible to get examining fingers above the swelling realted to a hydocoele.
- Demonstrated fluctuation in size in congenital hydrocele (also called communicating hydrocele)

EPIDEMIOLOGY

Incidence

- More common in childhood
- 1% of adult males; prevalence: 1,000 in 100,000
- No racial predilection

Prevalence

N/A

RISK FACTORS

- The hydrocele is produced by:
  - Connection with the peritoneal cavity (PPV); also known as congenital hydrocele
  - Defective absorption of fluid by tunica vaginalis; eg, primary hydrocele (common in adults)
  - Excessive production of fluid within the sac; (eg, secondary hydrocele) due to epididymitis, orchitis, testicular torsion causing a “reactive” hydrocele
  - Trauma with bleeding (technically a hematocele)
  - Lymphatic obstruction; eg, filariasis, scrotal surgery (varicocele), renal transplantation, pelvic radiation, malignancy
  - Migration of ventriculoperitoneal (VP) shunt
- Prematurity, low birth weight are risk factors

Genetics

N/A

PATHOPHYSIOLOGY

- Congenital: The PV does not close after testicular descent.
  - 80–90% of newborns have patent processus vaginalis with most closing by age 2
- 4 anatomic variants:
  - Vaginal (PV around the testis)
  - Infantile (PV around testis and cord)

  – Congenital communicating (PV communicates with the peritoneal cavity)
  – Hydrocele of the cord (PV patent with obliteration above and below)
- Acquired: Can be primary (idiopathic) or secondary to disease of the testis. Secondary hydroceles may present acutely or chronically.
- The hydrocele of the canal of Nuck is comparable in females. The cyst is in relationship with the round ligament and located in the inguinal canal.
- Hydrocele fluid characteristics:
  – Amber colored; specific gravity of 1.022–1.024
  – Components: Water, inorganic salts, 6% albumin, and fibrinogen
  – Nonclotting, unless a drop of blood added
  – Chronic hydrocele: Cholesterol-rich
  – Occasionally, tyrosine crystals are present

ASSOCIATED CONDITIONS
- Ehlers–Danlos syndrome
- Exstrophy of the bladder
- Indirect inguinal hernia
- Hydrocephalus (with VP shunt)
- Peritoneal dialysis
- Testicular tumors or epididymo-orchitis in secondary hydrocele
- Undescended testicle with patent procesus vaginalis (PPV)
- Varicocele surgery

GENERAL PREVENTION
None other than repair of indirect hernia defect in infants/children

DIAGNOSIS
HISTORY
- Symptoms of epididymitis, UTI, or acute pain:
  – Secondary hydrocele with infection, torsion, and trauma usually painful
- Usually not painful
- Sensation of heaviness or discomfort in the scrotum
- Change in size of the swelling (ie, size varies throughout day):
  – Suggests congenital communicating hydrocele
- Birth history:
  – Hydrocele more common in premature and low–birth-weight infants
- Medical or surgical history:
  – Varicocelectomy, renal transplant, VP shunt, trauma to the genitalia can be causes
  – Recent inguinal hernia repair (1)

PHYSICAL EXAM
- Transilluminate scrotum:
  – If transilluminates, favors simple hydrocele, but is *not* diagnostic
- Palpation of testes bilaterally:
  – Especially in children, need to rule out undescended testicle. Adults, attempt to feel for testicular mass

- Spermatoceles are always located superior to the testis and are palpated as distinct from the testis, which differentiates them from hydroceles.
- Positive pinch test in a secondary hydrocele (ability to pinch the tunica)
- Examine the groin for inguinal hernia.
- Lymphedema of external genitalia or lower extremities:
  – Tissue edema can be mistaken for the hydrocele.
- On abdominal exam, concomitant presence of a mass may indicate an abdominoscrotal hydrocele

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture if epididymo-orchitis suspected
- Tumor markers (bhCG, AFP) if tumor suspected

Imaging

- Transscrotal US in adults with hydrocele to detect underlying testicular abnormality (ie, tumor) and confirm the nature of the mass as a hydrocele.
- Nuclear scan or Doppler US exam in cases of torsion

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

Fibrous wall lined by mesothelial single layer cuboidal or flattened mesothelial cells; may contain benign mesothelial proliferations

DIFFERENTIAL DIAGNOSIS

- Cord lipoma
- Epididymo-orchitis
- Hydrocele of the spermatic cord
- Inguinal/femoral hernia
- Lymphedema of the external genitalia
  – Retroperitoneal process with obstruction of lymphatics (ie, malignancy, lymphatic filiariasis)
  – Nephrotic syndrome
  – Anasarca (protein-loosing enteropathy, cirrhosis)
- Spermatocele
- Testicular or paratesticular tumors
- Torsion (testis or appendix testis)
- Traumatic injury to the testis (hematocele)
- Varicocele (large)

TREATMENT

GENERAL MEASURES

- Adults:
  – No treatment is necessary unless the hydrocele causes discomfort or cosmetic concerns or there is a significant underlying cause present, such as a tumor.

– Communicating hydroceles in older patients may have increased risk of incarceration
- Children:
  – Most will resolve in 1st yr of life.
  – For newborns and children <1 yr supportive care is indicated
  – Persistence beyond age 1 suggests the presence of a patent indirect hernia sac that should be repaired.

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Children:
  – Inguinal incision between internal and external rings.
  – High ligation of the processus vaginalis and excision of the sac.
  – In hydrocele of the cord, the sac can be completely removed. It is imperative that the hydrocele sac be opened when the anatomy is confusing or the sac is very thickened. Failure to do so may result in disastrous consequences if bowel, bladder, or ovary is contained in the sac and not recognized.
- Adults:
  – Scrotal approach with drainage of the hydrocele and resection of the tunica vaginalis; scrotal drain for 24–48 hr
    - Bottle procedure (thin hydrocele sac): Also called Andrews procedure; incise anteriorly, wrap sac back around testicle
    - Jaboulay–Winkelmann procedure (thick hydrocele sac): Hydrocele sac resected and edge wrapped posteriorly around cord structures (resected edges can also simply be oversewn)
    - Lord procedure (thin hydrocele sac): Radial sutures used to gather sac posterior to testis

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Aspiration of the hydrocele, with or without the injection of sclerosing agents is not usually recommended
- Nonseptated hydrocele aspiration and sclerotherapy with doxycycline has been reported to have an 84% success rate with a single treatment (2)
- Aspiration may have a role in postoperative hydroceles such as after inguinal hernia repair.

Complementary & Alternative Therapies

Scrotal support may provide relief of discomfort

ONGOING CARE

PROGNOSIS

Many hydroceles do not enlarge and can be observed if confirmed that there is no underlying pathology (based on ultrasound confirmation).

COMPLICATIONS

- Rupture: Usually traumatic
- Hernia of the hydrocele sac: Tension causes herniation through the Dartos muscle.
- Calcification of the wall: May occur with longstanding cases
- Hematocele: Following trauma or aspiration, or presents chronically simulating a neoplasm
- Infection
- Postoperative:
  - Testicular atrophy or infarction after repair due to damage to vascular supply to the testicle
  - Infection
  - Recurrence

FOLLOW-UP

Patient Monitoring

- Periodic follow-up (baseline US) suggested if managed by observation; return for any acute changes in symptoms
- Parents of a newborn with a hydrocele should be instructed in the natural history of the condition in children.
- Following surgical repair, edema may take several weeks to resolve.

Patient Resources

N/A

REFERENCES

1. Gulino G, Antonucci M, Palermo G, et al. Urological complications following inguinal hernioplasty. *Arch Ital Urol Androl.* 2012;84(3):105–110.
2. Francis JJ, Levine LA. Aspiration and sclerotherapy: A nonsurgical treatment option for hydroceles. *J Urol.* 2013;189(5):1725–1729.

ADDITIONAL READING

- Lord PH. A bloodless operation for the radical cure of idiopathic hydrocele. *Br J Surg.* 1964;51:914–916.
- Skoog SJ, Conlin MJ. Pediatric hernias and hydroceles: The urologist's perspective. *Urol Clin North Am.* 1995;22:119–130.
- Szabo R, Kessler R. Hydrocele following internal spermatic vein ligation: A retrospective study and review of the literature. *J Urol.* 1984;132:924–925.

See Also (Topic, Algorithm, Media)

- Canal of Nuck Hydrocele and Cyst (Female Hydrocele)
- Groin/Inguinal Mass, Male and Female
- HIV/AIDS, Urologic Considerations Image
- Hydrocele of the Spermatic Cord
- Scrotum and Testicle, Mass

- Spermatocele

CODES

ICD9

- 603.8 Other specified types of hydrocele
- 603.9 Hydrocele, unspecified
- 778.6 Congenital hydrocele

ICD10

- N43.2 Other hydrocele
- N43.3 Hydrocele, unspecified
- P83.5 Congenital hydrocele

CLINICAL/SURGICAL PEARLS

- Tenderness, fever, or other symptoms such as nausea, vomiting, abdominal pain associated with an acute hydrocele requires immediate evaluation to rule out other scrotal pathology.
- The inability to transilluminate a hydrocele could be due to a thick-walled or septated hydrocele, another cause of an enlarged scrotum such as tumor or hematocele or the presence of bowel in a large hernia defect.

HYDROCOLPOS AND HYDROMETROCOLPOS, PEDIATRIC

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BASICS

DESCRIPTION

- Hydrocolpos and hydrometrocolpos are congenital anomalies of the female reproductive tract due to an imperforate hymen or less commonly due to a transverse vaginal septum.
  - Hydrocolpos: Gross distension of the vagina with fluid
  - Hydrometrocolpos: Gross distension of vagina and uterus with fluid. May also be associated with vaginal or cervical atresia, stenosis, urogenital sinus, or cloacal anomalies
- Hematocolpos: bloody fluid in vagina
- Hematometrocolpos: bloody fluid in vagina and uterus
- Can be an infrequent cause of an abdominal mass in a newborn female

EPIDEMIOLOGY

Incidence

0.1–3.8% of live female births

Prevalence

N/A

RISK FACTORS

- Imperforate hymen
- High/low transverse vaginal septum
- Urogenital sinus/cloacal abnormality

Genetics (1)

- *McKusick*–Kaufman syndrome
  - Autosomal recessive multiple malformation syndrome
  - Characterized by vaginal atresia with hydrometrocolpos, polydactyly, congenital heart defects, nonimmune hydrops fet alis
- Bardet–Biedl syndrome
- Langer–Giedion syndrome
- Herlyn-Werner-Wunderlich (HWW) syndrome

PATHOPHYSIOLOGY

- Hydrocolpos: Congenital obstruction of the female genital tract leading to accumulation of vaginal secretions and distension of the vagina
- Hydrometrocolpos: Same as hydrocolpos but the pressure now is transmitted past the cervix into the uterus causing distention of both vagina and uterus.
  - The most frequent cause of hydrometrocolpos is the presence of imperforate hymen due to failure of partial resorption of this membrane during the embryonic development
  - Hymen fails to rupture during the 8th wk of gestation

ASSOCIATED CONDITIONS
- Vaginal atresia
- Cloacal anomalies
- Urogenital sinus
- Other malformations, such as imperforate anus, bifid clitoris, polycystic kidney.
- Pediatric considerations:
  – The diagnosis should be considered in the pubertal female with amenorrhea.

GENERAL PREVENTION
Early diagnosis may prevent urinary retention, hydronephrosis, and upper urinary tract complications.

DIAGNOSIS
HISTORY
- Sonolucent mass on prenatal ultrasound (US)
- Stranguria due to bladder outlet obstruction
- Intestinal obstruction with larger mass
- Amenorrhea in pubertal females if the problem was not diagnosed before menarche. In these rare cases, chronic cyclic lower abdominal pain may be present.

PHYSICAL EXAM
- Imperforate hymen with bulging cystic vaginal introitus. The hue is typically bluish if there is trapped blood.
- Palpable suprapubic mass due to distended bladder if associated with outlet obstruction
- Lower extremity lymphedema due to decreased venous return
- Examine for stigmata of Mckusick–Kaufman syndrome (see above)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Electrolytes and creatinine if significant bilateral upper urinary tract dilation

Imaging
- Abdominal US:
  – Large sonolucent cystic mass displacing bladder anteriorly and rectum posteriorly
  – May see layering of debris
  – Hydronephrosis or ureteral ectasia may be present
  – Prenatal sonogram can detect Hydrometrocolpos as an antenatal diagnosis but usually cannot identify the etiology
- IVP:
  – May see hydroureteronephrosis and a distended bladder
- VCUG:
  – May see an anteriorly displaced bladder
- MRI/MRU:
  – Maybe useful for further delineation of pelvic anatomy when US is equivocal
  – MR urography provides dynamic images that may identify underlying etiologies such as ureteral ectopia

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS (2)
- Dermoid cyst
- Hematometrocolpos:
  – Accumulation of menstrual blood products in vaginal and uterus
- Mucocolpos
- Ovarian cyst
- Periurethral cyst:
  – Eccentric smooth mass displacing urethral meatus
- Prolapsed ureterocele:
  – May see necrotic tissue, asymmetric urethral meatus
- Prolapsed urethra:
  – Donut-shaped urethral meatus in the center of a normal vaginal introitus
- Rhabdomyosarcoma:
  – Cluster of grapelike masses protruding from vaginal introitus

TREATMENT

GENERAL MEASURES (3)
- Incision of the hymen if due to imperforate hymen. If an imperforate hymen is present and no mass or hydronephrosis is present, surgical correction is sometimes delayed until tissues become more estrogenized. However, the correction of the imperforate hymen must take place before there is development of hydrocolpos.
- Address vaginal or cervical issues as the anatomic pathology presents

MEDICATION
First Line
N/A

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Simple incision of the imperforated hymen. A cruciate incision with resection of excess tissue tags as necessary
- Cloacal anomalies require a coordinated surgical team and planned intervention.
- Vaginal septum if present needs to be incised either endoscopically or through open surgery

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Excellent, especially with early diagnosis and treatment

COMPLICATIONS
- Renal compromise or acute kidney injury with severe hydronephrosis
- Abdominal ascites
- Urinary retention and voiding difficulty
- Reports of increasing rates of infertility based upon level of obstruction
- Respiratory compromise in neonates due to massive abdominal distension
- At menarche, retrograde flow may predispose patient to endometriosis

FOLLOW-UP
Patient Monitoring
Usually none necessary. Follow for resolution of hydronephrosis if present.

Patient Resources
N/A

REFERENCES

1. Ameh EA, Mshelbwala PM, Ameh N. Congenital vaginal obstruction in neonates and infants: Recognition and management.*J Pediatr Adolesc Gynecol*. 2011;24(2):74–78.
2. Nazir Z, Rizvi RM, Qureshi RN, et al. Congenital vaginal obstructions: Varied presentation and outcome. *Pediatr Surg Int*. 2006;22:749–753.
3. Puhl AG, Steiner E, Krämer WW, et al. Fet al urogenital sinus with consecutive hydrometrocolpos because of labial fusion: Prenatal diagnostic difficulties and postpartal therapeutic management. *Fet al Diagn Ther*. 2008;23:287–292.

ADDITIONAL READING

Parlakgumus A, Yalcinkaya C, Kilicdag E. Prenatal diagnosis of McKusick-Kaufman/Bardet-Biedl syndrome. *BMJ Case Rep*. 2011;2011.

See Also (Topic, Algorithm, Media)
- Hydrocolpos and hydrometrocolpos Image
- Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Pediatric
- Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Prenatal

CODES

ICD9
- 623.8 Other specified noninflammatory disorders of vagina
- 752.42 Imperforate hymen
- 752.46 Transverse vaginal septum

ICD10

- N89.8 Other specified noninflammatory disorders of vagina
- Q52.3 Imperforate hymen
- Q52.11 Transverse vaginal septum

CLINICAL/SURGICAL PEARLS

The diagnosis should be considered in the pubertal female with amenorrhea.

HYDRONEPHROSIS/HYDROURETERONEPHROSIS (DILATED URETER/RENAL PELVIS), ADULT

Kelly A. Healy, MD
Demetrius H. Bagley, MD, FACS

BASICS

DESCRIPTION

- Hydronephrosis includes dilation of the renal pelvis and calyces while hydroureteronephrosis is dilation of the renal pelvis, calyces, and ureter
- Both can result from obstructive and nonobstructive causes
- Intrinsic and extrinsic obstructive process can affect the entire urinary tract
- Obstructive uropathy indicates impedance of urinary flow anywhere along the urinary tract, upper or lower and damage to the renal parenchyma due to obstruction at any site

EPIDEMIOLOGY

Incidence

Asymptomatic, unilateral hydronephrosis occurs in ~3% of population

Prevalence

- 3.1% prevalence in historic autopsy series of 59,000 patients
  - Age 20–60 more common in women, secondary to pregnancy/gynecologic conditions
  - Age >60 yr obstruction more common in men (6.2% vs. 2.9%) attributed to prostatic diseases
- A similar 2.5% prevalence of asymptomatic unilateral hydronephrosis in radiologic series among potential renal donors
  - More women than men (86% vs. 14%)
  - No association with potential donor age

RISK FACTORS

- Urolithiasis is most common cause of upper urinary tract obstruction, prevalence between 10–15% by age 70 yr
- Ureteropelvic junction (UPJ) obstruction can occur from anatomic-crossing vessel, high insertion, or secondary conditions (impacted stone)
- Lower urinary tract disorders can result in hydroureteronephrosis, often bilateral
- Benign prostatic enlargement is the most common affecting 70% of men by age 70
- Hydronephrosis can develop with obstructive lesions at essentially any level.
- Kidney:
  - Benign lesions including peripelvic cysts
  - Malignant neoplasms with renal cell carcinoma and urothelial carcinoma
  - Renal pelvic calculi
  - UPJ obstruction
  - Infection tuberculosis
  - Renal artery aneurysm

  - Hilar lymphadenopathy
- Ureter:
  - Neoplasms: Benign papilloma, fibroepithelial polyp, ureteritis cystica; malignant urothelial carcinoma
  - Ureteral calculi or stricture
  - Ureterocele or congenital megaureter
  - Infection (tuberculosis, schistosomiasis)
  - Retroperitoneal lymphadenopathy (lymphoma, other malignancy)
  - Inflammatory (retroperitoneal fibrosis and arterial aneurysms)
  - Gynecologic: Ovarian vein syndrome, endometriosis, GYN malignancy, pregnancy
  - Pelvic lipomatosis
  - Retrocaval ureter
- Bladder/urethra:
  - Malignant neoplasms: eg, urothelial carcinoma locally advanced carcinoma of the prostate
  - Bladder neck contracture
  - Prostatic obstruction
  - Detrusor dysfunction
  - Increasing intravesical storage pressure
  - Urethral stricture; meatal stenosis
  - Phimosis

Genetics

Nonobstructive hydronephrosis occurs with several congenital syndromes, usually diagnosed in infancy (see “Hydronephrosis/Hydroureteronephrosis, Pediatric”)

PATHOPHYSIOLOGY

- Effective hydroureteronephrosis on renal function depends on whether it is totally or partially obstructive and unilateral or bilateral
- Effects of obstruction of the kidney are time dependent. Within several hours, changes are evident but (1)
  - 1–2 wk—glomerular destruction, tubular atrophy, and interstitial fibrosis occur
  - By 6–8 wk irreversible damage occurs

ASSOCIATED CONDITIONS

Numerous causal conditions can be associated. See “Risk Factors” above.

GENERAL PREVENTION

Hydronephrosis may be disease related and prevention then must be individualized

DIAGNOSIS

HISTORY

- Signs and symptoms vary dependent on the etiology and chronicity of the condition
- Acute obstruction can cause abdominal flank and/or back pain; may be associated with anorexia, nausea, vomiting
- Gradual ureteral obstruction more typically presents with vague complaints or may be asymptomatic

- Insidious obstruction of solitary kidney or bilateral can present with symptomatic obstructive uropathy or evidence of renal compromise
- Complete urinary history is essential
- Site of obstruction, upper vs. lower urinary tract may relate to presentation
  - Upper urinary tract—flank pain and costovertebral angle tenderness with acute obstruction
  - Lower urinary tract maybe associated with obstructive voiding symptoms

PHYSICAL EXAM

- General condition—pain or localized symptoms
- Hypertension can be related to obstruction
- Abdominal, flank, or pelvic mass
- Flank tenderness can occur with acute obstruction and with calculi or infection (pyelonephritis, pyelonephrosis, retroperitoneal abscess)
- Vaginal exam
  - Ureteral prolapse
  - Ureterocele through urethra
- Digital rectal exam
  - Enlarged prostate, nodularity suggestive of prostate cancer

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis for hematuria, pyuria, crystalluria
- Urine culture
- Renal function studies:
  - BUN & creatinine
- CBC
  - Anemia—associated with chronic renal insufficiency
  - Elevated white blood cell count with infection
- Serum chemistries, special attention to potassium
- Serum prostatic-specific antigen (PSA)
- Urine cytology for urothelial carcinoma

Imaging (2)

- Several modalities are available. They differ in their degree of anatomic and functional information and may distinguish the presence and extent of obstruction.
- Renal ultrasound: Inexpensive, widely available, no ionizing radiation, and no contrast (3)
  - Excellent to define hydronephrosis
  - Should include imaging through the bladder to assess for distal hydroureter, ureteral jets, bladder wall thickening, and postvoid residual
  - Renal cortex can be evaluated
- Color Doppler renal ultrasound (4):
  - Help distinguish obstructive vs. nonobstructive hydronephrosis
  - Resistive index (RI) = (PSV – EDV)/PSV (peak systolic velocity end diastolic velocity)/peak systolic velocity
    - RI $\geq$0.7 suggested of obstruction (92%) sensitivity and (88%) specificity

- RI is time dependent and decreases >48 hr after obstruction. Thus, less useful for chronic vs. acute obstruction

- Noncontrast CT scan:
  - Imaging of choice for acute renal colic
  - Visualizes entire urinary tract and adjacent structures; best for urolithiasis and may not detect soft tissue masses or filling defects
  - Secondary signs of acute obstruction include perinephric stranding and nephromegaly
  - Normal ureter on unenhanced CT is considered to be 3 mm in adults
- CT urogram
  - Good for incidental hydronephrosis
  - Noncontrast phase for ureterolithiasis
  - Contrast phase-delayed nephrogram suggested obstruction
  - Defined parenchymal masses, evaluate for crossing vessels with UPJ obstruction
  - Delayed (excretory) phase may look like site of obstruction and rule out filling defect depending on degree of renal impairment
- Excretory urogram:
  - Generally replaced by CT urogram
- Magnetic resonance imaging (MRI)
  - Lack of ionizing radiation advantageous for children, pregnant patients, and those with renal insufficiency or contrast allergy
  - More time consuming, expensive, does not effectively image urolithiasis
- Pyelography: Antegrade or retrograde
  - Can be used with ultrasound or noncontrast CT in patients with contrast allergies or renal insufficiency; but invasive
- Functional studies to differentiate obstructive vs. nonobstructive uropathy
  - Whitaker test: 1st described in 1980
    - Indwelling percutaneous nephrostomy tube
    - Percutaneous puncture renal pelvis
    - Upper urinary tract is perfused at a rate of 5–10 mL per minute with saline or contrast media
    - Serial pressure recording is made in renal pelvis and bladder; spot films aid in evaluation
    - Pressure gradient: Obstruction >22 cm H_2O; equivocal 15–22 cm H_2O; normal <15 cm H_2O
  - Nuclear renography:
    - Primary noninvasive study to distinguish obstructive vs. nonobstructive uropathy
    - DTPA: Freely filtered by glomerulus. Neither secreted nor resorbed by renal tubules
    - MAG-3: Almost exclusively limited by proximal tubule secretion without resorption distally
    - Preparation of patient, maintain hydration, place a Foley catheter if concern for lower urinary tract dysfunction or obstruction
    - Furosemide 20–40 mg given 20 min after radiotracer administration to induce diuresis
    - Half time ($T_{½}$ clearance). Time it takes to eliminate 50% of radiotracer: Obstruction >20 min; equivocal >10–20 min; normal <10 min; false positives: More commonly with severe dilation or poor function

- Endoluminal ultrasound (ELUS):
  - Evaluate periureteral anatomy, vessels of high insertion and UPJ obstruction, define ureteral stricture
  - Study of choice for submucosal calculi
- Voiding cystourethrogram (VCUG):
  - Evaluate for reflux
  - Patients with recurrent urinary tract infections, flank pain, nonobstructive hydronephrosis

Diagnostic Procedures/Surgery

Cystoscopy, retrograde ureteropyelogram

Pathologic Findings

Nephropathy related to obstruction (see above)

DIFFERENTIAL DIAGNOSIS

- Obstructive vs. nonobstructive hydroureteronephrosis
- See also “Risk Factors”

TREATMENT

GENERAL MEASURES

- Management is highly dependent on underlying condition and the timing (acute vs. chronic)
- Urgent decompression is needed with:
  - Severe pain
  - Active urinary tract infection and acute kidney insufficiency
  - Retrograde ureteral stent or percutaneous nephrostomy can provide equally effective drainage
- Hydronephrosis lower urinary tract etiology is typically bilateral and patients may be asymptomatic
- May warrant catheter drainage or endoscopic treatment

MEDICATION

First Line

- Patients with infection and hydronephrosis require antibiotic therapy and drainage
  - Renal failure and electrolyte abnormalities should be corrected in conjunction with drainage

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Catheter drainage of obstructed system with percutaneous nephrostomy or ureteral stent is guided by the severity of the illness
  - Hydronephrosis and fever may be ominous signs requiring early drainage
  - Other surgical procedures can be guided by the findings on imaging studies

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
Hemodialysis may rarely be needed in the acutely ill patient

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Cause specific

COMPLICATIONS
- Progressive renal deterioration
- With vesicoureteral reflux, scarring and hypertension can occur
- Postobstructive diuresis seen only with bilateral obstruction or solitary functioning kidney

FOLLOW-UP
Patient Monitoring
- The etiology for hydronephrosis will determine the appropriate surveillance regimen
- Consider renal ultrasound and renal scan at 3 mo after treatment
- Postoperative imaging may demonstrate the dilatation persists despite relief of obstruction

Patient Resources
N/A

REFERENCES

1. Arena S, Magno C, Montalto AS, et al. Long-term follow-up of neonatally diagnosed primary megaureter: Rate and predictors of spontaneous resolution. *Scand J Urol Nephrol.* 2012;46:201–207.
2. Patatas K, Panditaratne N, Wah TM, et al. Emergency department imaging protocol for suspected acute renal colic: Re-evaluating our service. *Br J Radiol.* 2012;85:1118–1122.
3. Jandaghi AB, Falahatkar S, Alizadeh A, et al. Assessment of ureterovesical jet dynamics in obstructed ureter by urinary stone with color Doppler and duplex Doppler examinations. *Urolithiasis.* 2013;41:159–163.
4. Piazzese EM, Mazzeo GI, Galipò S, et al. The renal resistive index as a predictor of acute hydronephrosis in patients with renal colic. *J Ultrasound.* 2012;15:239–246.

ADDITIONAL READING

Shapiro SR, Wahl EF, Silberstein MJ, et al. Hydronephrosis Index: A new method to track patients with hydronephrosis quantitatively. *Urology.* 2008;72:536.

See Also (Topic, Algorithm, Media)
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult Image
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric
- Ureter, Obstruction
- Urolithiasis, Ureteral

CODES

ICD9

- 591 Hydronephrosis
- 592.0 Calculus of kidney
- 600.00 Hypertrophy (benign) of prostate without urinary obstruction and other lower urinary tract symptom (LUTS)

ICD10

- N13.2 Hydronephrosis with renal and ureteral calculous obstruction
- N13.30 Unspecified hydronephrosis
- N40.0 Enlarged prostate without lower urinary tract symptoms

CLINICAL/SURGICAL PEARLS

- Hydronephrosis and fever especially sepsis may require immediate drainage.
- Hydronephrosis may be nonobstructive.
- Generally hydronephrosis in an adult can be considered a sign of a process that must be defined and possibly treated.

HYDRONEPHROSIS/HYDROURETERONEPHROSIS (DILATED URETER/RENAL PELVIS), PEDIATRIC

Ahmad H. Bani-Hani, MD, FAAP, FACS

BASICS

DESCRIPTION

- Refers to dilatation of any part of the collecting system, single or combined:
  - Pelviectasis (renal pelvis)
  - Caliectasis (calyces)
  - Pelvocaliectasis (both renal pelvis and calyces)
  - Ureterectasis (ureter)
  - Hydroureteronephrosis (entire collecting system is dilated)
- Society of Fet al Urology (SFU) grading of infant hydronephrosis (1)[A]:

SFU grade	Pattern of renal sinus splitting on renal ultrasound
0	No splitting
1	Urine in pelvis barely splits sinus
2	Urine fills *intrarenal* pelvis and/or urine fills *extrarenal* pelvis *major* calyces dilated
3	SFU Gr 2 *and minor* calyces uniformly dilated *and* parenchyma preserved
4	SFU Gr 3 *and* parenchyma thin

EPIDEMIOLOGY

- Prenatal hydronephrosis is detected in about 1.4% of total prenatal ultrasound performed in US
- The true incidence is difficult to determine secondary to many asymptomatic, undetected cases

RISK FACTORS

- Family history of hydronephrosis, maternal type I diabetes mellitus (associated with infant sacral agenesis)
- Genetic syndromes: Downs, trisomy 13, trisomy 18, CHARGE, Ehlers–Danlos, Menkes, Prune belly, etc
- Horseshoe kidney/pelvic kidney
- Duplication renal anomalies
- Neurogenic bladder secondary to tethered spinal cord, myelodysplasia, sacral agenesis

Genetics

No specific genetic abnormalities except if associated with specific genetic syndromes as outlined above

ALERT

Hydronephrosis is not a specific diagnosis but a finding or sign. The cause of the

hydronephrosis is the diagnosis and indicates the appropriate treatment.

PATHOPHYSIOLOGY

- Physiologic hydronephrosis: Unclear etiology but typically improves with serial renal ultrasound monitoring
- Pathologic hydronephrosis
  - Vesicoureteral reflux: Reflux can be primary or secondary to conditions that raises the intravesical pressures (eg, bladder outlet obstruction and neurogenic bladder)
  - Ureteropelvic junction (UPJ) obstruction (2)[A]:
    - Defined as obstruction to the flow of urine from the renal pelvis to the proximal ureter
    - Considered to be the commonest cause of prenatal hydronephrosis
    - Obstruction can be caused by an intrinsic narrowing at the UPJ or by an extrinsic compression by a lower pole anteriorly crossing vessel
    - Examples of intrinsic obstruction can include: Narrow segment with muscular discontinuity, ureteral valves, mucosal folds, or ureteral polyps
  - Ureterovesical junction (UVJ) obstruction:
    - Primary: Called primary obstructive megaureter. The most common finding is a distal adynamic ureteral segment that affects the free efflux of urine resulting in a functional obstruction
    - Secondary: Distal stone, hypertrophy of the distal ureter and trigone in neurogenic bladder or posterior urethral valves
  - Ureterocele:
    - Defines as cystic dilatation of the distal ureteral segment
    - More common in females and can cause obstruction to the distal urine flow
    - Often associated with duplication anomalies of the kidneys particularly involving the upper pole moiety
  - Ectopic ureter:
    - Occurs when the distal opening of the ureter is not in the normal location at the corner of the trigone
    - Ureter can enter the bladder neck, urethra, and, in female, the vestibule, vagina, and rarely the uterus
    - Ectopic ureters opening outside the bladder or urethra tend to be obstructed and often associated with nonfunctioning renal moiety
    - Commonly involves the upper pole moiety in duplicated renal anomalies
  - Posterior urethral valves:
    - The most common cause of congenital lower urinary tract obstruction in males (1/4,000 to 1/7,500 births)
    - Varies in severity and can result in deterioration of fet al renal function, and progressive oligohydramnios, which may lead to pulmonary hypoplasia with a high risk of perinatal morbidity and mortality
  - Other causes:
    - Anterior urethral valves
    - Urethral atresia
    - Nonneurogenic neurogenic bladder (Hinman syndrome)

ASSOCIATED CONDITIONS

Hydronephrosis can by physiologic or pathologic associated with many condition as noted above

DIAGNOSIS

HISTORY

- Detailed prenatal history of:
  - Timing of 1st detection of hydronephrosis in relation to gestational age
  - Unilateral vs. bilateral
  - Gender of the baby
  - Maternal diabetes mellitus, particularly type I (associated with fet al sacral agenesis)
  - Family history of renal anomalies
  - Amniotic fluid volume
  - Paternal allergy to penicillin
- Detailed postnatal history:
  - Circumcision status
  - Birth weight
  - Jaundice
  - Urinary tract infections
  - Progression with potty training
  - Incontinence
  - Hypertension, failure to thrive

PHYSICAL EXAM

- Vital signs, particularly blood pressure
- Weight
- Jaundice
- Abdominal masses
- Is bladder palpable?
- Cutaneous manifestations of spina bifida occulta (hairy patch, sacral dimple, lipoma, asymmetric or short gluteal fold)
- Genital/anorectal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Basic metabolic panel
- Urine analysis and culture if indicated

Imaging

- Renal and bladder ultrasound (RUS):
  - Should be 1st-line imaging study
  - Will give excellent idea about the laterality and severity of hydronephrosis, associated bladder pathology such as ureterocele, are ureters dilated too?
  - Bladder pathology such as abnormal bladder wall thickness, key hole sign in posterior urethral valves
  - Indirect way to assess overall renal function by looking at echogenicity and thickness of

renal parenchyma
- Abdominal kidney-ureter-bladder (KUB) x-ray:
  – Displaced bowel pattern from hydronephrosis or bladder distension
  – Stool load and distribution to help in management
- Voiding cystourethrogram:
  – Assess presence of reflux
  – During early filling, a ureterocele can be identified
  – Assess the entire urethra for evidence of posterior or anterior urethral valves
- Diuretic renal scan (MAG-3 with Lasix):
  – Evaluates differential renal function and drainage curves from each kidney.
  – Very useful for the diagnosis and evaluation of possible UPJ/UVJ obstruction
- MR urogram:
  – Can provide useful information such as renal function and anatomic details when evaluating conditions such as ectopic ureter location

Diagnostic Procedures/Surgery
- Usually reserved for treatment of certain conditions such as posterior urethral valve ablation
- Cystoscopy and retrograde pyelogram can be used to define the anatomy of the collecting system and placement of a drainage stent

Pathologic Findings
Depends on the underlying pathology responsible for the hydronephrosis

DIFFERENTIAL DIAGNOSIS
- Prominent extrarenal pelvis
- Multicystic dysplastic kidney
- Polycystic renal disease
- Renal cysts

TREATMENT

GENERAL MEASURES
Depends on underlying pathology responsible for the hydronephrosis

MEDICATION
First Line
- Antibiotic prophylaxis may be needed in severe cases of hydronephrosis and/or presence of reflux
  – Prophylactic daily antibiotics to keep urine sterile, preferentially given at bedtime to maximize urinary retention
    - < 2 mo age: Amoxicillin 20 mg/kg/d
    - ≥ 2 mo of age: Trimethoprim–sulfamethoxazole 2 mg/kg/d (concentrates in urine); nitrofurantoin is an alternative, but liquid is expensive and bad-tasting

Second Line
- Anticholinergics in cases of an overactive bladder and/or raised intravesical pressures
- β-blockers in some cases of bladder outlet obstruction

SURGERY/OTHER PROCEDURES

- Vesicoureteral reflux: Antibiotic prophylaxis vs. surgical correction
- UPJ obstruction: Pyeloplasty
- UVJ obstruction: Distal ureterectomy and ureteral reimplant
- Ureterocele: Several options available including observation, intravesical puncture, ureteroureterostomy, and partial nephrectomy
- Ectopic ureter: Several options available including heminephrectomy and ureteroureterostomy
- Posterior urethral valves: Endoscopic ablation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Clean intermittent catheterization in cases of neurogenic bladder
- Biofeedback in some patients with voiding dysfunction

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Varies and depends on underlying pathology and its severity (3)[A]

COMPLICATIONS

- Hypertension
- Kidney/bladder stones
- Multiple UTIs
- Reflux
- Renal insufficiency
- Renal scarring
- Urinary incontinence

FOLLOW-UP

Patient Monitoring

- Patients need meticulous follow-up once hydronephrosis is diagnosed before and after treatment
- Referral to pediatric urology/nephrology for full assessment and treatment

Patient Resources

National Kidney Foundation. http://www.kidney.org/atoz/content/hydronephrosis.cfm

REFERENCES

1. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: Introduction to the system used by the Society for Fet al Urology. *Pediatr Radiol.* 1993;23(6):478–480.
2. Koff SA. Pathophysiology of ureteropelvic junction obstruction. Clinical and experimental

observations. *Urol Clin North Am*. 1990;17:263–272.
3. Liu HY, Dhillon HK, Yeung CK, et al. Clinical outcome and management of prenatally diagnosed primary megaureters. *J Urol*. 1994;152:614–617.

ADDITIONAL READING

Mesrobian HG, Mirza SP. Hydronephrosis: A view from the inside. *Pediatr Clin North Am*. 2012;59(4):839–851.

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Prenatal
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric Images
- Megaureter
- Posterior urethral valves
- Ureterocele
- Ureteropelvic junction obstruction

CODES

ICD9

- 591 Hydronephrosis
- 596.54 Neurogenic bladder NOS
- 753.3 Other specified anomalies of kidney

ICD10

- N13.30 Unspecified hydronephrosis
- N31.9 Neuromuscular dysfunction of bladder, unspecified
- Q63.1 Lobulated, fused and horseshoe kidney

CLINICAL/SURGICAL PEARLS

- Hydronephrosis is not a diagnosis but a sign.
- Renal ultrasound, VCUG, and diuretic renal scan can establish the underlying etiology of hydronephrosis.

HYDRONEPHROSIS/HYDROURETERONEPHROSIS (DILATED URETER/RENAL PELVIS), PRENATAL

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BASICS

DESCRIPTION

- In utero dilation of fet al renal collecting system
- May represent a normal developmental variant or a pathologic anomaly
- Prenatal hydronephrosis (PN) may be observed early in pregnancy but the diagnosis usually cannot be made with certainty until 18wk of gestation
- Severity based on anterior–posterior renal pelvis diameter (APD) (1)
  - Mild: 4 to <7 mm (2nd trimester); 7 to <9 mm (3rd trimester)
  - Moderate: 7 to ≤ 10 mm (2nd trimester); 9 to ≤ 15 mm (3rd trimester)
  - Severe: >10 mm (2nd trimester); >15 mm (3rd trimester)

EPIDEMIOLOGY

Incidence

- 1–5% of fetuses are observed to have PN (2)
  - Mild: 57–88%
  - Moderate: 10–30%
  - Severe: 2–13%
- Risk of clinically significant PN increases with severity. Risk of undergoing surgery $<10\%$ with mild and $>50\%$ with severe.

Prevalence

None

RISK FACTORS

- Family history of renal abnormalities or vesicoureteral reflux
- Previous fet al loss due to urinary tract causes

Genetics

None

PATHOPHYSIOLOGY

- Transient hydronephrosis (most common, physiologic dilation of the ureter is seen in 41–88% of cases of PN)
  - $\sim 90\%$ of mild PN will be transient
- Ureteropelvic junction (UPJ) obstruction (most common pathophysiology)
- Ureterovesical obstruction (megaureter, obstructed and nonobstructed)
- Bladder outlet obstruction (posterior urethral valves (PUVs), urethral atresia)
- Nonobstructive processes: Vesicoureteral reflux, nonrefluxing nonobstructed megaureter, and prune belly syndrome

- Severe PN with oligohydramnios may cause pulmonary hypoplasia

ASSOCIATED CONDITIONS
Congenital hydronephrosis is associated with many syndromes.

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Timing of prenatal detection; earlier detection implies more severe condition.
- Presence of calyectasis and renal cortical thinning indicate more severe condition.
- Presence of cortical cysts may indicate dysplasia.
- Unilateral vs. bilateral renal involvement is a critical determination for diagnosis and prognosis.
- Change in dilation in relation to bladder filling may indicate vesicoureteral reflux.
- Presence of oligohydramnios important: Suggests severe comprise of renal function.
  - Associated with severe obstructive uropathy due to PUVs, congenital urethral stricture, or ureterocele obstructing bladder outlet
  - Associated with pulmonary hypoplasia and fet al or neonatal death

PHYSICAL EXAM
N/A

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Maternal α-feto protein may be elevated in some cases of fet al renal anomalies
- Assessment of pulmonary maturity in patients with oligohydramnios (lecithin-to-sphingomyelin ratio)
- Amniotic fluid studies:
  - Volume: Composed mostly (90%) of fet al urine after the 16th wk of gestation
  - Correlates with fet al renal function
- Fet al karyotype (may indicate gender or important genetic information)
- Assessment of fet al urinary electrolytes:
  - Generally only done with oligohydramnios
  - Good prognosis: Sodium <100 mg/dL; osmolarity <210 mOsmol/dL; chloride <90 mg/dL (remember dilute urine is better in the fetus)
- Postnatal serum electrolyte assessment:
  - Nadir creatinine (<0.7 mg/dL in 1st yr holds good prognosis)
  - CO_2: Acidosis has a poor prognosis.
- Urinalysis and urine culture as needed

Imaging
- Prenatal US in 3rd trimester: Based upon severity of PN in 2nd trimester(1)
  - Mild: Consider 3rd trimester US
  - Moderate: 3rd trimester US
  - Severe: US in 3–4 wk

- Additional prenatal US in 3rd trimester: Based upon severity of PN in 3rd trimester (1)
  - Mild: Postnatal evaluation
  - Moderate: Postnatal evaluation
  - Severe: US in 2–3 wk
- Postnatal evaluation: Controversial. Society of Fet al Urology (SFU) recommendations based on severity of PN (1)
- Unilateral mild PN
  - Postnatal US at 2–4 wk
  - Consider VCUG at 2–4 wk if hydro present on postnatal US
  - Consider diuretic nuclear renal scan (MAG-3) at 4 wk if hydro present on postnatal US
- Unilateral moderate-severe PN
  - Postnatal US at 2–4 wk
  - VCUG at 2–4 wk if hydro present on postnatal US
  - Consider diuretic nuclear renal scan (MAG-3) at 4 wk of hydro present on postnatal US
- Bilateral moderate-severe PN
  - 1st postnatal US 1–3 days after birth
  - VCUG 1–7 days after birth
  - Males: Early VCUG to rule out PUVs
  - Consider diuretic nuclear renal scan (MAG-3) at 4 wk
- Special situations: Bladder/urethral abnormalities, decreased amniotic fluid
  - Early evaluation similar to severe bilateral PN
- Postnatal US within 48–72 hr after birth may underestimate degree of hydronephrosis
- Rare cases of pulmonary compromise from mass effect require emergent drainage

Diagnostic Procedures/Surgery

Fet al urinary electrolyte bladder aspiration in cases of oligohydramnios

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Urinary conditions:
  - Autosomal recessive polycystic kidney disease
  - Duplication anomalies
  - Ectopic ureter
  - Megacystis-megaureter microcolon syndrome
  - Multicystic dysplastic kidney
  - PUVs
  - Prune belly syndrome
  - Transient hydronephrosis
  - UPJ obstruction
  - UVJ obstruction
  - Vesicoureteral reflux
- Intestinal disorders:
  - Cloacal exstrophy
  - Duodenal atresia

  - Imperforate anus
  - Intestinal duplication
  - Mesenteric cysts
  - Ovarian cysts
  - Persistent cloaca
- Tumors:
  - Congenital mesoblastic nephroma
  - Neuroblastoma

TREATMENT

GENERAL MEASURES

- Prenatal management: Assessment of hydronephrosis, oligohydramnios:
  - Unilateral cases: Serial prenatal US if severe; deliver at term
  - Bilateral cases
    - No oligohydramnios: Observation, deliver at term
    - Oligohydramnios: Termination, early delivery, prenatal treatment for pulmonary immaturity
- Postnatal management:
  - Pulmonary support if respiratory compromise
  - Antibiotic prophylaxis if moderate-severe unilateral or bilateral PN
  - Bilateral hydronephrosis with dilated bladder: Place catheter to drain bladder
  - All hydronephrosis: US, VCUG, MAG-3 renal scan as indicated (see above for SFU recommendations)

MEDICATION

First Line

- No specific antenatal medications exist
- Prophylactic antibiotics controversial.
  - Recommended by SFU with moderate-severe PN, bladder/urethral abnormalities, dilated ureter, oligohydramnios(1)
  - Amoxicillin (20 mg/kg/d—1 dose per day)
- Surfactant to assist lung function after birth with pulmonary hypoplasia

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Fet al intervention (cases with oligohydramnios only):
  - Controversial(3)
  - Tapping of fet al bladder
  - Percutaneous shunting: Vesicoamniotic drain
- Surgery is seldom necessary in the neonatal period with the exception of severe bilateral obstruction due to bladder outlet obstruction or severe UPJ or UVJ obstruction.
- Need for postnatal surgery based upon diagnosis and correlated with severity of PN
  - Mild: $<10\%$

– Severe: ~50%

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most neonates have an excellent prognosis. Prognosis depends on etiology of the dilated system and other associated anomalies.
- Severe bilateral hydronephrosis is associated with obstruction and oligohydramnios early in gestation predicts an adverse outcome.
- Fetuses with bilateral hydronephrosis, a distended bladder, and oligohydramnios are at highest risk of neonatal demise or pulmonary complications.
- Risk of UTI correlated with severity of PN
  – Mild: ~10%
  – Moderate-severe: ~30%

COMPLICATIONS

- Pulmonary hypoplasia with severe oligohydramnios
- Renal impairment
- UTIs

FOLLOW-UP

Patient Monitoring

- Based on initial evaluation, subsequent imaging may be necessary (1)
- Most centers employ serial renal US every 3–6 mo for the 1st yr of life
- If febrile UTI, consider VCUG and/or MAG-3 renal scan

Patient Resources

- http://urology.ucsf.edu/patient-care/children/Hydronephrosis
- http://urology.ucsf.edu/patient-care/children/urinary-tract-obstruction/ureteropelvic-junction-obstruction
- http://urology.ucsf.edu/patient-care/children/additional/megaureter
- http://urology.ucsf.edu/patient-care/children/urinary-tract-obstruction/posterior-urethral-valves

REFERENCES

1. Nguyen HT, Herndon CD, Cooper C, et al. The Society for Fet al Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *J Pediatr Urol.* 2010;6:212–231.
2. Lee RS, Cendron M, Kinnamon DD, et al. Antenatal hydronephrosis as a predictor of

postnatal outcome: A meta-analysis. *Pediatrics*. 2006;118:586–593.
3. Morris RK, Malin GL, Khan KS, et al. Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. *BJOG*. 2010;117:382–390.

ADDITIONAL READING

Davenport MT, Merguerian PA, Koyle M. Antenatally diagnosed hydronephrosis: Current postnatal management. *Pediatr Surg Int*. 2013;29(3):207–214.

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Pediatric
- Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Prenatal Image
- Megaureter, Congenital

CODES

ICD9

- 753.6 Atresia and stenosis of urethra and bladder neck
- 753.20 Unspecified obstructive defect of renal pelvis and ureter
- 753.29 Other obstructive defects of renal pelvis and ureter

ICD10

- Q62.0 Congenital hydronephrosis
- Q64.31 Congenital bladder neck obstruction
- Q62.39 Other obstructive defects of renal pelvis and ureter

CLINICAL/SURGICAL PEARLS

- Majority of prenatal/fet al hydronephrosis (especially mild) is transient with no clinical significance.
- VCUG is not recommended for unilateral mild hydronephrosis.
- Prophylactic antibiotics have not been shown to be effective. Not recommended in mild cases.
- Emergent evaluation by urologist should occur with:
  - Severe bilateral prenatal hydronephrosis
  - Severe unilateral prenatal hydronephrosis in solitary kidney
  - Prenatal hydronephrosis with dilated bladder consistent with posterior urethral valves
  - Severe prenatal hydronephrosis with pulmonary compromise from mass effect (rare)

HYPERALDOSTERONISM, PRIMARY (ALDOSTERONISM, CONN SYNDROME)

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BASICS

DESCRIPTION

- Primary hyperaldosteronism or Conn syndrome is characterized by HTN, hypokalemia, hypernatremia, alkalosis, and suppressed renin, due to excess production of aldosterone.
- It classically refers to an aldosterone-producing adenoma (APA) of the adrenal gland that is usually small (< 3 cm), unilateral, and renin-unresponsive.
- APA subtype of primary hyperaldosteronism accounts for 30–60% of primary hyperaldosteronism.
- Secondary hyperaldosteronism is usually related to HTN and/or edematous state disorders such as CHF, cirrhosis, and nephrotic syndrome.
- Pseudohypoaldosteronism can be due to ingestion of large amounts of licorice or Liddle syndrome

EPIDEMIOLOGY

Incidence

Incidence data is lacking.

Prevalence

- 5–13% of hypertensive population (recent increased prevalence of primary aldosteronism due to improved diagnostic testing)
- Peak incidence during 4th and 5th decades
- 20% primary aldosteronism in resistant hypertensives (elevated BP despite 3 antihypertensive medications)
- Adrenal adenoma is more common in women.

RISK FACTORS

No known risk factors for primary hyperaldosteronism

Genetics

- Hereditary pattern for more common APAs unclear
- A rare form of autosomal dominant primary hyperaldosteronism is glucocorticoid-remediable aldosteronism (GRA).
- Gene for aldosterone synthase (CYP11B2) recently identified

PATHOPHYSIOLOGY

- The biochemical hallmark of the disease is increased aldosterone after sodium (Na) loading and low plasma renin activity (PRA) during Na depletion
- Autonomous aldosterone secretion leads to inappropriate Na and water reabsorption from the cortical collecting tubule:

  - Electrical gradient created favors secretion of potassium (K), resulting in hypokalemia.
  - Extracellular fluid volume (ECF) volume causes mild hypertension (HTN).
- Renal escape limits Na retention and prevents significant edema:
  - Occurs after ~1.5 kg of extracellular fluid (ECF) is absorbed, or a weight gain of ~3 kg.
  - Spontaneous diuresis then occurs, lowering the ECF.
  - Increased Atrial natriuretic peptide (ANP), decreased thiazide-sensitive Na-Cl cotransporter, and pressure natriuresis are factors that may contribute to renal escape.

ASSOCIATED CONDITIONS
- Adrenal cancer (rare)
- Essential HTN

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- HTN, often refractory to medical therapy
  - Headaches secondary to HTN
- Symptomatic hypokalemia:
  - Muscle cramps, paresthesias, tetany, nocturia, polyuria

PHYSICAL EXAM
- No specific findings
- Mild-to-moderate HTN, not usually distinguishable from essential HTN
- Malignant HTN rare
- Lack of edema

DIAGNOSTIC TESTS & INTERPRETATION
- Consider screening the following patients (1):
  - Hypertensive and hypokalemic:
    - HTN with K <3 highly suspicious of an aldosterone-producing adenoma (APA).
    - Hypokalemia is thought to be a late manifestation of aldosterone excess.
    - If patient is on restricted Na diet, severe hypokalemia often absent; only test patients if adequately salt loaded.
    - Hypokalemia can be induced with oral Na loading.
    - 20% of patients with hyperaldosteronism are normokalemic; more often seen in adrenal hyperplasia.
  - Inappropriate kaliuresis on initiation of diuretic
  - HTN resistant to multidrug treatment
  - Family history of early HTN or stroke
  - Adrenal incidentaloma
- Diagnosis may be difficult in those with normal serum K levels and those being treated with antihypertensives or diuretics

Lab
- Hypernatremia, hypokalemia, metabolic alkalosis, impaired glucose tolerance

- Plasma renin activity (PRA) low in primary hyperaldosteronism; if plasma renin >1, diagnosis unlikely
- Screening: Plasma aldosterone concentration (PAC)/plasma renin activity (PRA) in the upright position; obtain when K is corrected. Positive if:
  - PAC/PRA >20 with PAC ≥15 ng/dL *OR*
  - PAC/PRA >40 with PRA >0.2 ng/mL/h
  - Diuretics, ACE inhibitors, ARBs can falsely elevate PRA.
- Confirmatory studies:
  - Na-loading test with:
    - Saline infusion: PAC at baseline and 4 hr (positive test PAC >10 ng/dL)
    - Oral Na: 24-hr urine Na and aldosterone on days 3 and 4 (positive if aldosterone <12 mg/d) and (Na >200 mmol/d)
    - Fludrocortisone suppression
- All confirmatory tests should be used with care in patients with compromised left ventricular cardiac function.

Imaging

- CT with thin cuts through the adrenals is the preferred noninvasive test:
  - Used to identify surgically curable disease and differentiate the subtypes once primary aldosteronism is confirmed
  - aldosterone-producing adenomas (APA's) usually uniform, round, and hypodense with Hounsfield unit ≤10
  - 6% probability of identifying an adrenal mass on CT
  - Lacks overall accuracy to distinguish between unilateral and bilateral disease:
    - Bypass adrenal vein sampling only if clear adrenal mass (>1 cm) is identified in the younger patient (<40) with highly suspicious biochemical findings
- MRI is not more sensitive than CT
- Adrenal scintigraphy using Iodine-131-6-iodomethyl-19-nor-cholesterol is rarely available in US, cumbersome to perform, and depends heavily on the size of the adenoma.

Diagnostic Procedures/Surgery

- Adrenal vein sampling (AVS) for aldosterone is the gold standard in localizing the site of excess production:
  - Aldosterone and cortisol samples obtained from peripheral veins, IVC, right and left adrenal veins after corticotrophin infusion
  - 44% of patients with bilateral renal masses had a unilateral source of aldosterone secretion.
  - Cure also reported after adrenalectomy in patients with AVS-proven unilaterality despite normal adrenals on CT scan.
- Postural tests, historically used to distinguish adenoma from bilateral hyperplasia have become less useful with the discovery of angiotensin-responsive APAs.

Pathologic Findings

- Solitary, well-demarcated mass with the typical mottled yellow color of adrenal cortex
- Without diffuse thickening of the zona glomerulosa or hyperplastic nodules
- May compress the nonneoplastic uninvolved adrenal gland

• Histopathology: Foamy lipid-laden clear cells, in sheets or nests

DIFFERENTIAL DIAGNOSIS

• Other causes of HTN. In Cushing disease, aldosterone and renin will both be low. In renal artery stenosis, there will be high renin and high aldosterone.
• Other causes of HTN and hypokalemia, such as:
  – Overingestion of licorice
  – Use of chewing tobacco
  – Hyperdeoxycorticosterones
• Other subtypes of primary hyperaldosteronism:
  – Bilateral adrenal hyperplasia: Idiopathic
  – GRA due to aldosterone-producing, renin-responsive adenoma. Familial hyperaldosteronism type I, autosomal dominant
  – Familial occurrence of APA or bilateral idiopathic hyperplasia or both
  – Adrenal cancer producing aldosterone: Extremely rare
• Liddle syndrome: Autosomal dominant disorder. Mimics hyperaldosteronism and involves problems with excess resorption of Na and loss of K.

TREATMENT

GENERAL MEASURES

• Treatment selected based on etiology of hyperaldosteronism
• Control HTN

MEDICATION

First Line (2)

• Mineralocorticoid receptor antagonist used in those with bilateral adrenal hyperplasia and unilateral hyperplasia or APA who are not surgical candidates:
  – Spironolactone: Limited due to affinity for androgen and progesterone receptors. Can cause gynecomastia, sexual dysfunction, menstrual irregularities
  – Eplerenone: No active metabolites, shorter half-life than spironolactone, 50–75% as potent as spironolactone but less adverse effects
• Thiazide diuretics, ACE inhibitors, calcium channel antagonists, angiotensin blockers

Second Line

Amiloride, an epithelial Na channel blocker and K-sparing diuretic, may also be used, especially if spironolactone or eplerenone are intolerable. More often used in conjunction with the above.

SURGERY/OTHER PROCEDURES

• Unilateral adrenalectomy is indicated in patients with hyperaldosteronism due to an adenoma.
• HTN is cured or improved significantly in up to 90% of such cases. Usually takes 3–6 mo to see an effect.
• Adequate control of BP (see “Medications”) for several weeks and correction of metabolic abnormalities should be done before surgery.
• Obtain PAC after surgery to confirm cure

- Monitor K closely postoperatively

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Emerging therapies include developing drugs that inhibit actions of aldosterone synthase enzyme, encoded on the CYP11B2 gene

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Patients with primary hyperaldosteronism have higher rates of prior stroke (12.9% vs. 3.4%) compared to those with essential HTN.
- Nonfatal MI (4% vs. 0.6%)
- Atrial fibrillation (7.3% vs. 0.6%)

COMPLICATIONS

- Related to HTN (left ventricular hypertrophy, coronary artery disease, heart failure, stroke, intracerebral hemorrhage, etc.)
- Related to low K (tetany, headache, arrhythmias, etc.)

FOLLOW-UP

Patient Monitoring

BP and serum electrolytes should be evaluated postoperatively and following medical therapy.

Patient Resources

Hyperaldosteronism - primary and secondary MedlinePlus.
http://www.nlm.nih.gov/medlineplus/ency/article/000330.htm

REFERENCES

1. Mantero F, Mattarello MJ, Albiger NM. Detecting and treating primary aldosteronism:Primary aldosteronism. *Exp Clin Endocrinol Diabetes.* 2007;115:171–174.
2. Young WF Jr. Minireview: Primary aldosteronism–changing concepts in diagnosis and treatment. *Endocrinology.* 2003;144(6):2208–2213.

ADDITIONAL READING

- Calhoun DA. Aldosteronism and hypertension. *Clin J Am Soc Nephrol.* 2006;1:1039–1045.
- Conn JW. Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med.* 1955;45:3–17.
- Lim PO, Young WF, MacDonald TM. A review of the medical treatment of primary aldosteronism. *J Hypertens.* 2001;19(3):353–361.
- Mattsson C, Young WF Jr. Primary aldosteronism: Diagnostic and treatment strategies. *Nat Clin Pract Nephrol.* 2006;2(4):198–208.

- Plouin PF, Amar L, Chatellier G. Trends in the prevalence of primary aldosteronism, aldosterone-producing adenomas, and surgically correctable aldosterone-dependent hypertension. *Nephrol Dial Transplant.* 2004;19:774–777.
- Wheeler MH, Harris DA. Diagnosis and management of primary aldosteronism. *World J Surg.* 2003;27:627–631.

See Also (Topic, Algorithm, Media)

- Adrenal Mass
- Aldosteronism (Hyperaldosteronism, Conn Syndrome) Algorithm
- Hypertension, Urologic Considerations

CODES

ICD9

- 255.10 Hyperaldosteronism, unspecified
- 255.12 Conn's syndrome
- 255.14 Other secondary aldosteronism

ICD10

- E26.01 Conn's syndrome
- E26.1 Secondary hyperaldosteronism
- E26.09 Other primary hyperaldosteronism

CLINICAL/SURGICAL PEARLS

- Hypertension (HTN) with serum K < 3 meq/L is highly suspicious of an aldosterone-producing adenoma (APA).
- Treatment selection is based on etiology of hyperaldosteronism.
- Surgical excision provides excellent control of hypertension in aldosterone-producing adenoma (APA).
- Control of the adrenal vein is the most important step during adrenalectomy.

HYPERPROLACTINEMIA, UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Hyperprolactinemia (HPRL) refers to serum prolactin levels that exceed the normal range <25 mg/L (~ 500 mIU/L) in women and <20 mg/L (~ 400 mIU/L) in men.
- It is the most common endocrine abnormality due to hypothalamic–pituitary disorders.
- It may result in hypogonadism, erectile dysfunction, infertility, galactorrhea, and osteoporosis.
- Most common causes are pregnancy, medications, hypothyroidism, and prolactin-secreting pituitary tumors (prolactinomas)

EPIDEMIOLOGY

Incidence

- Peak incidence occurs in women of age 25–34, at 23.9/100,000/yr.
- Incidence data in men is lacking

Prevalence

- Lifetime prevalence of prolactinoma is 30/100,000 in woman and 10/100,000 in men.
- Pituitary microadenomas are found in 10.9% of autopsies, with 44% prolactinomas.
- In men with sexual dysfunction, $\sim 1\%$ have HPRL.
- 90% of prolactinomas occur in women of reproductive age.
- 40% of pituitary adenomas are prolactinomas

RISK FACTORS

- Female sex
- Pregnancy
- Prolactinomas
- Medications (antipsychotics, antidepressants, verapamil, opiates, GI motility drugs, estrogens)
- MEN-1 syndrome

Genetics

- Most prolactinomas are sporadic (1)
- Present in about 20% of adults with MEN-1, who have an autosomal dominant mutation in the MEN-1 tumor suppressor gene on chromosome 11
- Can rarely occur as part of familial isolated pituitary adenomas

PATHOPHYSIOLOGY

- Prolactin is produced in the anterior pituitary
- Secretion is pulsatile and increases with stress and sleep
- Tonically suppressed by dopamine via D2 receptors
  – Medications that inhibit dopamine secretion raise prolactin levels

- Elevated prolactin suppresses GnRH, with subsequent reductions in LHRH, FSH, and sex steroid levels.
  - Low testosterone can cause decreased libido, erectile dysfunction, infertility, and gynecomastia in men.
  - Low estrogen can cause oligomenorrhea, decreased libido, anovulation, and galactorrhea in women
  - Decreased bone mineral density can occur in both sexes secondary to low sex steroid levels.
- Prolactinomas: Pituitary microadenomas (<10 mm) and macroadenomas (>10 mm) can be seen in some patients as the cause of the elevated levels.
  - Macroadenomas can have mass effect symptoms, including headache and visual disturbance by optic nerve compression
- Rarely, chest wall injury can increase prolactin levels.
- Macroprolactinemia is caused by an abnormal binding of the molecule to circulating IgG.

ASSOCIATED CONDITIONS

- Amenorrhea and/or galactorrhea in women
- Hypogonadism and/or ED in men
- Hypothyroidism: Increased thyrotropin-releasing hormone can stimulate prolactin secretion.
- Renal failure can result in reduced clearance.
- Cirrhosis
- Herpes zoster (particularly involving the chest wall)

GENERAL PREVENTION

Discontinuation of medication causing symptomatic HPRL (asymptomatic prolactin elevations need not be treated)

DIAGNOSIS

HISTORY

- Women: Often presents early in disease course.
  - Infertility (including pregnancy history)
  - Amenorrhea/menstrual irregularities
  - Galactorrhea
- Men: Often presents late in disease course.
  - Complaints of sexual dysfunction
    - Decreased libido
    - Erectile dysfunction (ED)
  - Gynecomastia
- General
  - Headache
  - Visual field defects
- Psychiatric history and antipsychotic medication use
- Alcohol abuse
- Medication use:
  - Antipsychotics: Butyrophenones (eg, haloperidol), phenothiazines (eg, chlorpromazine),

thioxanthenes (eg, thiothixene), risperidone and others: Metoclopramide, sulpiride, pimozide, methyldopa, reserpine
  - Others reported: Antiandrogens, cimetidine, cyproheptadine, danazol, estrogens, INH, tricyclic antidepressants, opiates, verapamil

PHYSICAL EXAM
- Breast exam for gynecomastia, galactorrhea
- Evidence of chest wall trauma or herpetic lesions
- Signs of hypogonadism
- Signs of hypothyroidism
- Visual field abnormalities

DIAGNOSTIC TESTS & INTERPRETATION

Lab (2)
- A single serum measurement > upper limit of normal makes the diagnosis of HPRL
- Serum PRL >500 µg/L is diagnostic of a macroprolactinoma
- Women of reproductive age should have a pregnancy test.
- In men presenting with ED, a testosterone level should be checked. If low, further evaluation of prolactin should be performed.
- With medication-induced HPRL, prolactin levels are usually <50 mg/L and almost always <100 mg/L.
- After stopping suspected medication, prolactin levels usually return to normal within 4 days.

Imaging
- Pituitary MRI is the test of choice. Should be obtained in all cases where prolactin is persistently elevated and no cause is apparent.
- DEXA scanning to evaluate for possible bone mineral density problems
- In women, pelvic US to assess for uterine or ovarian pathology

Diagnostic Procedures/Surgery

Formal visual field assessment should be done in patients with macroadenomas.

Pathologic Findings

Prolactinoma: Glands composed of cuboidal cells. May be either eosinophilic or chromophobic.

DIFFERENTIAL DIAGNOSIS
- Hypothyroidism
- Lab error or macroprolactinemia (abnormal prolactin molecule)
- Medication-induced
- Nonprolactin-secreting pituitary or hypothalamic tumor
- Polycystic ovary syndrome (PCOS)
- Pregnancy
- Prolactinoma
- Renal failure

TREATMENT

ALERT
Do not treat women until pregnancy is excluded.

GENERAL MEASURES (3)

- Women of reproductive age should have a pregnancy test 1st.
- Treat underlying cause or stop offending drug if possible
- Asymptomatic HPRL secondary to medication use does not require treatment.

MEDICATION

First Line

- Cabergoline or bromocriptine (dopamine agonists):
  - Usually will lower prolactin levels, regardless of cause, and shrink prolactinomas
  - In general, both cabergoline and bromocriptine are effective. Cabergoline is usually better-tolerated, more convenient, and more effective than bromocriptine, whereas bromocriptine is less expensive and has been used longer.
  - Use dopamine agonists with caution in patients on psychotropic drugs that inhibit dopamine action.
    - Cabergoline dosing (0.5-mg tablets): Start with 0.25–0.5 mg once or twice weekly and increase the dose at monthly intervals until prolactin normalizes (>3 mg/wk is rarely needed).
    - Bromocriptine dosing (2.5-mg tablets): Start with 0.625 or 1.25 mg with food before bedtime and gradually increase at weekly intervals until prolactin level is controlled (usually 2.5 mg BID–TID).
  - Side effects include nausea and postural hypotension
- Pregnancy considerations
  - More experience with bromocriptine.
  - Neither bromocriptine nor cabergoline has been associated with teratogenicity.
  - Nevertheless, either drug is usually stopped at the 1st evidence of pregnancy, except in patients with macroadenomas in whom previous mass effects may recur if tumor enlarges.
  - Significant enlargement of microadenomas is uncommon during pregnancy.
  - Lactation: Dopamine agonists will inhibit lactation.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Often performed transsphenoidally
- For microadenomas, generally reserved for patients intolerant of drug therapy. Tumors may recur.
- Only indicated for pituitary macroadenomas when medical therapy is ineffective, including persistent visual field abnormalities:
  - Usually not curative

ADDITIONAL TREATMENT

Radiation Therapy

Usually only indicated for pituitary macroadenomas that have failed medical therapy, and where response to surgery is inadequate or surgery is contraindicated.

Additional Therapies
Men with ED or persistent hypogonadism may require additional therapies.

Complementary & Alternative Therapies
Vitex agnus-castus extract can be tried in cases of mild HPRL

ONGOING CARE

PROGNOSIS
- 90–95% of prolactin-secreting pituitary microadenomas will not grow further, even without medical therapy.
- Medical therapy is usually successful in normalizing prolactin levels, normalizing menses, reducing or stopping galactorrhea, inducing ovulation, and shrinking pituitary tumors.
- >90% of microadenomas do not grow significantly during pregnancy, even after medical therapy is stopped.
- Some microadenomas disappear with time (especially after menopause) or do not recur after medical therapy.
- Pituitary macroadenomas usually do not disappear completely with medical therapy and require continuous medical therapy.

COMPLICATIONS
- Dopamine agonists can worsen underlying psychiatric problems in patients taking psychotropic medications.
- Pituitary macroadenomas can secrete other hormones or become resistant to medical therapy.

FOLLOW-UP
Patient Monitoring
- Drug-induced HPRL:
  - Prolactin should normalize after switching medications and no further follow-up is needed.
- Microadenomas:
  - Some microadenomas resolve spontaneously.
  - Measure prolactin every 6–12 mo to ensure continued drug efficacy.
  - No need for repeat pituitary MRI unless prolactin increases markedly on therapy.
  - Consider stopping dopamine agonist after at least a year of successful therapy; some microadenomas do not recur
- Macroadenomas:
  - If prolactin normalizes, repeat pituitary MRI after 3–6 mo to ensure tumor shrinkage and establish new baseline.
  - No consensus on frequency of further MRIs in patients whose prolactin is well-controlled medically.
  - Repeat prolactin measurements every 3–6 mo.
  - Follow visual fields in patients who have visual field defects at baseline.
  - Some macroadenomas resolve spontaneously.

Patient Resources

Patient guide to hyperprolactinemia diagnosis and treatment. *J Clin Endocrinol Metab.* 2011;96:35A–36A.

REFERENCES

1. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–288.
2. Klibanski A. Clinical practice. Prolactinomas. *N Engl J Med.* 2010;362(13):1219–1226.
3. Casanueva FF, Molitch ME, Schlecte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)*. 2006;65:265–273.

ADDITIONAL READING

- Klibanski A. Clinical practice. Prolactinomas. *N Engl J Med.* 2010;362(13):1219–1226.
- Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. *Endocrinol Metab Clin North Am*. 2008;37:67–99.
- Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–288.
- Molitch ME. Drugs and prolactin. *Pituitary*. 2008;11:209–218.
- Schlecte JA. Long-term management of prolactinomas. *J Clin Endocrinol Metab*. 2007;92:2861–2865.
- Zeitlin S, Rajfer J. Hyperprolactinemia and erectile dysfunction. *Rev Urol.* 2000;2(1):39–42.

See Also (Topic, Algorithm, Media)

- Erectile Dysfunction
- Gynecomastia

CODES

ICD9

- 253.1 Other and unspecified anterior pituitary hyperfunction
- 256.39 Other ovarian failure
- 257.2 Other testicular hypofunction

ICD10

- E22.1 Hyperprolactinemia
- E28.39 Other primary ovarian failure
- E29.1 Testicular hypofunction

CLINICAL/SURGICAL PEARLS

- Women present early in the disease course, while men present late.
- Dopamine agonists are the 1st-line treatment of prolactinomas.
- Surgical excision is reserved for refractory cases.
- All women should be screened for pregnancy before initiating treatment.

HYPOSPADIAS

Steve J. Hodges, MD
Anthony Atala, MD

BASICS

DESCRIPTION

- Common congenital disorder of male external genitalia characterized by a ventrally displaced urethral meatus
  - Associated conditions may include:
    - Ventral chordee
    - Incomplete foreskin with dorsal hood and ventral deficiency
  - May be an isolated defect or may be associated with a significant underlying abnormality
  - Classification:
    - Anterior (distal) 50%: Glandular, coronal, subcoronal, megameatus intact prepuce
    - Middle (midshaft) 30%
    - Posterior (proximal) 20%: Penoscrotal, scrotal, perineal

EPIDEMIOLOGY

Incidence

- 1 in 250–300 live male births
- 1 in 80–100 in family history of hypospadias

Prevalence

Prevalence in US for hypospadias ranges between 2.01 and 56.17 per 10,000

RISK FACTORS

- 5× incidence in IVF births compared to controls
- Environmental:
  - Because of increases in rates in certain areas an association with chemicals with estrogenic or antiandrogenic effects has been suggested
  - Examples include environmental chemicals such as bisphenol A (BPA) and hormones used during pregnancy such as progesterone.
  - Genetics (see below)

Genetics

- <5% of cases have genetic cause (2)
- Can be seen in isolated and syndromic genetic abnormalities
- Caused by mutations of genes controlling development of male gonads or penis (eg, homeobox, FGF, and Sonic hedgehog genes)
- 5α-reductase mutations
- Familial propensity
  - 10% have affected 1st–3rd degree relative
  - 14% of male siblings affected
  - 27% concordance in monozygotic twins

PATHOPHYSIOLOGY

- Normal penile development:
  - Urogenital folds form on either side of the cloacal membrane, and fuse anteriorly at the genital tubercle
  - Lateral labioscrotal folds fuse posteriorly and separate the urogenital and anal membranes
  - Under influence of testosterone and DHT, phallus elongates and the genital folds fuse in the midline to enclose urethral proximally to distally
  - Canalization of the glans occurs distally, fusing with urethra
  - Process complete by 20th wk of gestation
- Glandular hypospadias likely represents failure of distal canalization
- Proximal hypospadias due to failure of fusion of genital folds
- Scrotal or perineal variants result in cleft scrotum

ASSOCIATED CONDITIONS

- Growth restriction (low birth weight and length, small head circumference) has been associated with hypospadias
- Associated anomalies are more common in cases of severe hypospadias
  - Cryptorchidism (7–9%)
  - Inguinal hernia/hydrocele (9–16%)
  - Syndromes:
    - 49 described in which hypospadias is frequent or occasional (Aniridia-Wilms tumor association, Beckwith–Wiedemann, Smith–Lemli–Opitz, Trisomy syndromes [4p, 9p, 13, 18], VACTERL association, XXY, Zellweger, and many others)
    - 78% of these have associated micropenis, cryptorchidism, and/or scrotal anomaly
    - In presence of hypospadias and cryptorchidism must rule out intersex condition (15% with palpable undescended testicle, 50% with nonpalpable)
- 2–12% have upper tract anomalies (horseshoe kidney, renal ectopia, duplicated ureters, others)
- Enlarged prostatic utricle can be associated with severe cases and may increase risk of UTI or prostatic utricle stone formation

GENERAL PREVENTION

Not possible except by avoidance of environmental agents or medications with estrogenic effects by pregnant women (see “Risk Factors”)

DIAGNOSIS

HISTORY

- Family history of hypospadias
  - Any associated congenital anomalies
    - Exposure of mother to hormonally active agents during pregnancy
- IVF may increase risk of hypospadias

PHYSICAL EXAM

- Determine location of urethral opening
- Evaluate for chordee
- Evaluate foreskin

- Evaluate presence of inguinal hernia, hydrocele, or cryptorchidism
- Severely proximal hypospadias may be associated with bifid scrotum and/or penoscrotal transposition
  – Look for other congenital anomalies

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Karyotype and hormonal evaluation to rule out intersex is needed in cases of severe hypospadias and cryptorchidism

Imaging

- No routine imaging necessary for routine hypospadias evaluation
  – In setting of intersex evaluation, genitogram or pelvic US may be performed
  – VCUG in proximal hypospadias may demonstrate prominent prostatic utricle

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- In cases of proximal hypospadias associated with an undescended testicle differential should include:
- Congenital adrenal hyperplasia
- Mixed gonadal dysgenesis
- Partial androgen insensitivity
- True hermaphroditism

ALERT

Do not perform circumcision in the setting of hypospadias. Hypospadias in the presence of cryptorchidism may signal an intersex disorder.

TREATMENT

GENERAL MEASURES (3)

The general tenets of repair are to move the urethral meatus to an orthotopic location, straighten the penis (repair chordee), and either remove or modify the foreskin to give the appearance or a normal circumcised or uncircumcised penis

MEDICATION

First Line

- There is no specific medical therapy for hypospadias
  – Preoperative hormonal therapy (testosterone injections or creams, or HCG injections) may be used to enlarge penile size to aid in repair in cases of small phallus (4)
  – However, although a preference for the use of preoperative hormonal therapy is observed in the literature, the exact protocol and benefit is not conclusively determined
  – 25–50 mg of testosterone propionate given IM weekly for 3 wk preoperatively is one such approach

SURGERY/OTHER PROCEDURES

- Indications of repair (1):
  - Goals are to create a cosmetically normal appearing penis with orthotopic meatus, and straight phallus so the child can in the future void while standing, have sexual intercourse, and effectively inseminate.
  - Timing of repair is ideal at 4–6 mo of age, surgeries should be complete by 2 yr (the age of genital awareness)
  - Techniques dictated by meatal location, degree of chordee, and skin availability
  - Chordee should be repaired 1st (orthoplasty)
  - Distal hypospadias: MAGPI, Thiersch–Duplay, tubularized incised plate urethroplasty, Mathieu (perimeatal-based flap)
  - Midshaft hypospadias: Tubularized incised plate urethroplasty, Mathieu, onlay island flap
  - Proximal hypospadias: 1 stage—Thiersch–Duplay, incised plate urethroplasty, onlay island flap; 2 stage—1st stage repair chordee, second stage 6 mo after 1st (Thiersch–Duplay, incised plate urethroplasty)
    - In cases of lack of skin may use buccal mucosal graft
    - Hypospadias revision: Meatoplasty, fistula repair

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Patient may need revisions for chordee, meatal issues, or recurrent chordee at later dates

Complementary & Alternative Therapies

Psychosocial support for patient and family if needed long term

ONGOING CARE

PROGNOSIS

Most patients have normal penile function for voiding, sexual performance, and insemination

COMPLICATIONS

- Early:
  - Bleeding/hematoma—treated with compression or surgical exploration; infection—treated with antibiotics or incision and drainage;
  - UTI—treated with appropriate antibiotics;
  - Wound dehiscence—requires reoperation 6 mo later
- Late:
  - Residual/recurrent chordee—treated with reoperation,
  - Meatal stenosis—treated with meatal dilation or meatoplasty
  - Urethral stricture—treated with dilation or urethroplasty;
  - Urethrocutaneous fistula or urethral diverticulum—treated with excision and repair;
  - Hair in urethral repair—treated with endoscopic laser or cauter or excision and repair;
  - Lichen sclerosis or balanitis xerotica obliterans—treated with complete excision and buccal graft

FOLLOW-UP

Patient Monitoring

- Follow-up for observation of penile development and complications noted above
  - Children may present after toilet training or even as late as adolescence with newly diagnosed complications from repair as an infant

Patient Resources

Urology Care Foundation http://www.urologyhealth.org/urology/index.cfm?article=130

REFERENCES

1. Subramaniam R, Spinoit AF, Hoebeke P. Hypospadias repair: An overview of the actual techniques. *Semin Plast Surg.* 2011;25(3):206–212.
2. Akre O, Boyd HA, Ahlgren M, et al. Maternal and gestational risk factors for hypospadias. *Environ Health Perspect.* 2008;116(8):1071–1076.
3. Bhat A. General considerations in hypospadias surgery. *Indian J Urol.* 2008;24(2):188–194.
4. Netto JM, Ferrarez CE, Schindler Leal AA, et al. Hormone therapy in hypospadias surgery: A systematic review. *J Pediatr Urol.* 2013;9(6 Pt B):971–979.

ADDITIONAL READING

Macedo A Jr, Rondon A, Ortiz V. Hypospadias. *Curr Opin Urol.* 2012;22(6):447–452.

See Also (Topic, Algorithm, Media)

- Bifid Scrotum
- Disorder of Sexual Development (DSD)
- Hypospadias Image ☼
- Penoscrotal Transposition

CODES

ICD9

- 752.61 Hypospadias
- 752.63 Congenital chordee
- 752.69 Other penile anomalies

ICD10

- Q54.0 Hypospadias, balanic
- Q54.1 Hypospadias, penile
- Q54.9 Hypospadias, unspecified

CLINICAL/SURGICAL PEARLS

- More severe cases (proximal) more likely to be associated with an intersex disorder.
- All members of the health care team must clearly understand that circumcision should not be performed if hypospadias is present.

IMMUNOCOMPROMISED PATIENTS, UROLOGIC CONSIDERATIONS

Nathan Roberts, MD
Patrick J. Shenot, MD, FACS

BASICS

DESCRIPTION

- Immunocompromised patients have attenuated immune responses caused by:
  - Immunosuppressive drugs (chemotherapy)
  - Radiation (bone marrow irradiation)
  - Hematopoietic stem cell transplant
  - Malnutrition
  - Disease processes (HIV, lymphoma, congenital immune deficiencies, autoimmune disorders)
- Immunocompromised patients are at risk for opportunistic infections
- Hematopoietic stem cell transplant
  - Need preparative regimens to prevent rejection of transplanted graft: Complete myeloablative, Nonmyeloablative or +/– chemotherapy
- Miliary tuberculosis
  - Hematogenous dissemination of Mycobacterium tuberculosis
  - HIV coinfection is common; 38% with military TB patients also have HIV

EPIDEMIOLOGY

Incidence

- HIV infections
  - 2.7 million new HIV infections worldwide
- Tuberculosis
  - 11,182 reported cases in US in 2010
  - 22% of cases were extrapulmonary
  - 2.7% were miliary TB

Prevalence

HIV/AIDS: 1.2 million Americans

RISK FACTORS

- Hemorrhagic cystitis (HC) (1)
  - Increased degree of immunosuppression
    - BK virus Hemorrhagic cystitis (HC)
  - Early onset Hemorrhagic cystitis (HC)
    - Conditioning regimen used for Hematopoetic stem cell transplant (HSCT) with cyclophosphamide, busulfan, or with antithymocyte globulin (4)
    - Donor–recipient gender mismatch
  - Late onset Hemorrhagic cystitis (HC)

- Allogenic HSCT transplant
- Graft versus host disease (GVHD)
  - Use of corticosteroids or cyclosporine for GVHD
- Use of T-cell depleted grafts
- Need for blood transfusions

- HIV/AIDS
  - Unprotected high-risk sexual contact
  - Blood transfusion
  - Uncircumcised Men
  - Occupational exposure
- Tuberculosis
  - HIV infections: 14% of TB patients have HIV

PATHOPHYSIOLOGY

- Cyclophosphamide/busulfan
  - Metabolized in the liver to acrolein
    - toxic to urothelium; prolonged exposure in the bladder causes increased inflammatory mediators: Bladder mucosal edema, vascular dilation, and increased capillary fragility
    - Long-term increased bladder cancer risk
- Polyoma virus–related hematuria (see Polyoma virus [BK, JC]), urologic considerations
- HIV/AIDS
  - Virus targets CD4+ T cells
    - Virus targets CCR5 expressing CD4+ cells; with decreased CD4 lymphocyte count. Mucosal tissues preferentially targeted, leads to immunosuppression
- TB genitourinary involvement
  - Hematogenous spread → renal capillaries → renal cortex → immune response → chronic inflammation → granuloma with central caseous necrosis → inflammation into renal tubules and medulla → renal papilla sloughing → calyceal ulceration → fibrosis from healing → calyceal infundibular narrowing or UPJ scarring → hydronephrosis
  - Tubercles can also form in distal ureter leading to stricture

ASSOCIATED CONDITIONS

- HIV/AIDS; indinavir calculus
- TB
- Any cause requiring bone marrow transplant
- Urethritis: Reiter syndrome, arthritis

GENERAL PREVENTION

- HIV/AIDS: Protection during sexual activity; universal precautions for healthcare professionals
- Miliary tuberculosis: Treatment of latent TB can prevent miliary TB

DIAGNOSIS

HISTORY

- HC

  - Ranging from pink urine to clot retention
  - Can also have bladder pain and or lower urinary tract symptoms (LUTS)
- HIV/AIDS (2)
  - Increased risk of transmission and acquisition of sexually transmitted infections
    - Atypical and prolonged course; genital lesions do not respond to normal treatments
    - Can present with symptomatic genitourinary tract infections
    - Testicular pain: Epididymitis/orchitis are common findings
    - Can be positive for LUTS with prostatitis
    - Cystitis: Increased risk of bladder infections
    - Urolithiasis: Can present with typical complaints of ureteral calculus (flank pain, nausea, vomiting, dysuria, increased frequency, urgency)
    - Can present with voiding dysfunction
    - Commonly present with urinary retention
    - Detrusor hyperreflexia, LUTS for bladder outlet syndrome
- Miliary tuberculosis
  - Failure to thrive, fever of unknown origin and night sweats, anorexia, weight loss
    - Subacute or chronic presentation more common; can have dysfunction of one or more organ system
    - 50% have pulmonary disease with dyspnea or cough
  - Genitourinary involvement
    - Hematuria; small percentage may be passing material in urine (caseous material)
    - Flank pain, symptoms of cystitis, LUTS (storage symptoms), scrotal pain, male infertility workup; hematospermia

PHYSICAL EXAM

- HC
  - May present with palpable bladder if in clot retention
- HIV/AIDS
  - Most common intrascrotal pathology in AIDS is testicular atrophy
    - Secondary to endocrine imbalances, febrile episodes, malnutrition, testicular infections, and toxic effects of therapeutic agents
  - Prostatitis
    - Boggy prostate
  - Scrotal swelling/testicular pain
    - Epididymitis/orchitis caused by common and uncommon organisms (Candida, CMV, toxoplasmosis)
  - Voiding dysfunction
    - May have enlarged prostate
- Miliary tuberculosis
  - Pulmonary: Course breath sounds on auscultation, may have lymphadenopathy
  - Genitourinary involvement
    - Possible costovertebral angle tenderness
    - Epididymal/prostate tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- HIV/AIDS
  - HIV ELISA for anti-HIV-1 and 2
    - >99% sensitivity; Western blot to exclude false-positive but also to confirm HIV diagnosis
  - Plasma HIV RNA
    - Detectable by day 12; antibodies detected day 21
    - Used to assess treatment response/failure HIV-associated nephropathy: Proteinuria-increased creatinine
- Tuberculosis
  - PPD; may be false negative
  - Mycobacterial blood cultures
    - Urinalysis: Sterile pyuria, possible hematuria
    - Urine acid fast bacilli (AFB) culture

Imaging

- HC
  - CT with and without contrast: Can show clot, filling defect, calculus
- HIV/AIDS
  - Urolithiasis
    - CT non contrast may be associated with minimal findings with indinavir calculus
  - Kidney infection
    - CT scan: Can see striated nephrogram in pyelonephritis, abscess
- Tuberculosis
  - Chest radiograph (miliary disease)
    - Faint, reticulonodular infiltrate distributed fairly uniformly throughout the lungs
  - GU findings: Disparity in renal size. Larger may indicate caseous lesions or shrunken and fibrotic from autonephrectomy
    - Autonephrectomy: Diffuse, uniform, extensive parenchymal, putty-like calcification, a lobar cast of the kidney
    - Calcifications in 30–50% of cases (seen in caseating lesions)
    - Calculi may also be seen in the collecting system or ureter secondary to stricture formation
    - Ureteral calcifications are rare and are characteristically intraluminal
    - Bladder wall calcifications are not very common except in late cases of bladder contraction
    - Calcifications of the prostate and seminal vesicles are seen in 10% of cases
  - Contrast-enhanced computed tomography
    - Renal parenchymal masses and scarring
    - Thick urinary tract walls
    - Tuberculoma: Renal mass coalescing caseating granulomas
    - Can see hydronephrosis
    - Sensitive in seeing the calcifications
    - Contrast can evaluate function of the kidney
  - Ultrasound: Limited in diagnosis, Can be used for monitoring disease progression

Diagnostic Procedures/Surgery

- HC
  - Cystoscopy, possible ureteroscopy
- HIV/AIDS
  - Kidney biopsy: Help to diagnose HIV-associated nephropathy (HIVAN)
  - Voiding dysfunction
    - May warrant UDS, may uncover neurogenic voiding dysfunction
    - Post-void residuals, cystoscopy
- Tuberculosis
  - Biopsy of the following can demonstrate granulomas and be used for culture: lung, bone marrow, lymph nodes, bones, joints, liver, brain, and other tissues
  - Cystoscopy/retrograde pyelograms
    - Limited in diagnosis: Stricture, acute UO inflammation, acute tuberculous ulcer. Golf hole ureter: Circular and often excessively lateral ureteral orifice

Pathologic Findings

- Tuberculosis
  - Granulomatous inflammation
    - Contain epithelioid macrophages, Langhans giant cells, and lymphocytes
    - Contain caseation necrosis
    - Organisms may or may not be seen with acid fast staining
- HIV
  - HIV-associated nephropathy (HIVAN)
    - Collapsing form of focal segmental glomerulosclerosis
    - Dilated tubules and interstitial inflammation

DIFFERENTIAL DIAGNOSIS

- HC
  - Infectious source
    - Bacterial
    - Viral BK vs. adenovirus, CMV, JC, and herpes
- HIV
  - Voiding dysfunction
    - Patient may have underlying neurologic opportunistic infection

TREATMENT

GENERAL MEASURES

- Reduction of immunosuppression (if possible) can help to reduce clinical sequelae
- HIV patients have higher risk of bladder infections than non-HIV patients
  - Associated with typical uropathogens
  - Salmonella is of particular concern due to high-risk fatal recurrence (may need chronic suppression)

MEDICATION

First Line

- HC

- Increased hydration
- Catheter placement with clot evacuation
- Continuous bladder irrigation (CBI)

• HIV/AIDS
- Antiretroviral therapy (ART)

• Miliary TB (3)
- Standard pulmonary therapy
- Often directly observed therapy
- Isoniazid (INH), rifamycin (rifampin), pyrazinamide, and ethambutol for 2 mo
- Isoniazid and rifamycin for additional 4 mo

Second Line

• HC
- Conjugated estrogens
  - Act by stabilization of microvasculature
  - Oral vs. intravenous administration
- Intravesical instillation of Alum
  - An astringent precipitates protein over bleeding surface
  - 1% Alum solution in continuous bladdder irrigation (CBI)
  - Can be used in presence of vesico ureteral reflux (VUR)
- Intravesical instillation of silver nitrate
  - Chemical coagulation and eschar at bleeding sites
  - 0.5–1% instilled for 10–20 min
  - VUR may lead to renal failure due to precipitation and obstruction of upper tracts
- E-aminocaproic acid
  - Inhibits fibrinolysis preventing activation of plasminogen to plasmin
  - Given orally, parenterally, or intravesically
  - Patients can form hard clots that are difficult to flush from the bladder
- Intravesical instillation of prostaglandin
  - PGE2: May encourage platelet aggregation and induce vasoconstriction
  - PGE2: 0.75 mg in 200 mL of normal saline and left indwelling
  - May cause bladder spasms
- Intravesical instillation of formalin (40% formaldehyde)
  - Hydrolyzes proteins and coagulates tissue on superficial level
  - Painful and needs to be done with general anesthesia
  - Should not be done with VUR. Can fibrose the ureters, cause obstruction, hydronephrosis and also papillary necrosis
  - Can result in small contracted bladder

• HIV/AIDS
- Urinary tract infection (UTI)
  - Can treat with prolonged 7–10-day course of antibiotics
  - If patients do not respond to empiric antibiotics attention should be turned and patients screened for atypical and opportunistic infections (ie, fungi, parasites, TB, and viruses)
- Prostatitis/Epididymitis/Orchitis
  - Should be treated with antibiotics

- Opportunistic infections should be suspected if not resolving
- Voiding dysfunction
  - Individualized for the patient
  - Males: α-blockers possibly 5α-reductase inhibitors
  - Irritative symptoms: Anticholinergics if low PVR's

Surgery

- HIV/AIDS
  - Kidney infection abscess (Aspergillus and toxoplasma)
    - Percutaneous or open drainage
    - Nephrectomy
  - Prostatic abscess
    - Percutaneous (transperineal vs. transrectal aspiration)
    - Transurethral unroofing (TUR)
  - Testicular and epididymal infections
    - If intractable pain may warrant epididymectomy or orchiectomy
- Tuberculosis
  - Often will proceed 3–6 wk after medications
    - Abscess drainage
    - Ureteral stenting for strictures (41% successful)
    - PCN: TB fistula can form
    - Nephrectomy: If kidney is nonfunctioning, there is extensive disease involving the whole kidney, coexisting renal carcinoma
    - Partial nephrectomy
    - Epididymectomy: Caseating abscess that has not responded to medical therapy or firm swelling that has remained unchanged or increased in size with medial therapy
    - Augmentation cystoplasty (<100 cc capacity) vs. orthotopic bladder substitution (20 cc capacity)

SURGERY/OTHER PROCEDURES

- HC
  - Hyperbaric oxygen therapy
    - 100% oxygen in a hyperbaric chamber at 2.5 atmospheres absolute for 90 min 5 days a week.
  - Cystectomy if refractory life-threatening cases
  - Selective embolization
    - Vesical or internal iliac artery

ADDITIONAL TREATMENT

Additional Therapies

- Oxazaphosphorine (cyclophosphamide)-induced HC
  - Mesna
    - Binds to acrolein and inactivates it
  - Supra hydration
  - Prophylactic Continuous bladder irrigation (CBI)
    - Often occurs within 72 hr

ONGOING CARE

PROGNOSIS

- HIV/AIDS
  - Greatly improved in the era of HAART therapy
  - Cancer
    - Penile: 8-fold higher incidence
    - Testicular cancer: 2-fold increase in seminoma
- Miliary tuberculosis
  - Greatly improved with the introduction of antibiotics
  - Mortality previously 100% (preantibiotics) now 20%

COMPLICATIONS

- Increased risk for malignancy in immunosuppressed patients
- HIV/AIDS
  - 3.5% of HIV-infected patients will experience HIV-associated nephropathy
    - Caucasian patients 12:1 risk
    - Intravenous drug use and men who have sex with men association
- Tuberculosis
  - Percutanous nephrostomy (PCN)
    - Tuberculosis fistula formation
  - Ureteral stenting
    - Limit high-pressure contrast injection during retrograde pyelogram may disseminate infection

FOLLOW-UP

Patient Monitoring

- Hemorrhagic cystitis (HC)
  - Cyclophosphamide
    - 9-fold increase in urothelial carcinoma
    - 10-yr latency period

REFERENCES

1. Manikandan R, Kumar S, Dorairajan LN. Hemorrhagic cystitis: A challenge to the urologist. *Indian J Urol.* 2010;26:159–166.
2. Shindel AW, Akhavan A, Sharlip ID. Urologic aspects of HIV infection. *Med Clin North Am.* 2011;95(1):129–151.
3. Cek M, Lenk S, Naber KG, et al. EAU guidelines for the management of genitourinary tuberculosis. *Eur Urol.* 2005;48(3):353–362.
4. Gyurkocz B, Rezvani A, Storb RF. Allogeneic hematopoietic cell transplantation: the state of the art. *Expert Rev Hematol.* 2010;3(3):285–299.

ADDITIONAL READING

Lee SH, Hong SH, Lee JY, et al. Asymptomatic hematuria associated with urinary polyomavirus infection in immunocompetent patients. *J Med Virol.* 2014;86(2):347–353.

See Also (Topic, Algorithm, Media)

- Cystitis, Hemorrhagic (Infectious, Non-Infectious, Radiation)
- HIV/AIDS, Urologic Considerations
- HIV/AIDS, Urologic Considerations Image
- Polyoma Virus (BK, JC), Urologic Considerations
- Tuberculosis, Genitourinary, General Considerations
- Tuberculosis, Kidney and Ureter

CODES

ICD9

- 279.9 Unspecified disorder of immune mechanism
- 279.49 Autoimmune disease, not elsewhere classified
- 279.50 Graft-versus-host disease, unspecified

ICD10

- D89.9 Disorder involving the immune mechanism, unspecified
- D89.813 Graft-versus-host disease, unspecified
- M35.9 Systemic involvement of connective tissue, unspecified

CLINICAL/SURGICAL PEARLS

- Recurrent UTI in the absence of infections in other organ systems, is not a typical presentation of an immunocompromised patient.
- Most common intrascrotal pathology in AIDS is testicular atrophy.

INCONTINENCE, URINARY, ADULT FEMALE

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BASICS

DESCRIPTION

- Incontinence is broadly defined as the loss of urine that is objectively demonstrable and is of social and hygienic concern
- Stress urinary incontinence (SUI): Involuntary loss of urine on effort of physical exertion
- Urgency incontinence (UI): Involuntary loss of urine associated with urgency
- Mixed incontinence (MI): Lost of urine associated with urgency and also with effort
- Overflow incontinence (OI): High residual or chronic urinary retention leads to urinary spillage from bladder overdistention
- Functional incontinence: Loss of urine due to deficits of cognition and mobility
- Coital incontinence: leakage urine during intercourse
- Continuous incontinence: Continuous involuntary loss of urine

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Affects 30–50% of adult women
- Stress urinary incontinence is the most common (49%), followed by mixed (29%) and urge (21%) incontinence

RISK FACTORS

- Advanced age
- Cognitive impairment
- COPD
- Menopause
- Obesity
- Pelvic organ prolapse
- Pelvic surgery or radiation
- Pregnancy
- Smoking
- Vaginal childbirth

Genetics

Evolving data to support genetic predisposition

PATHOPHYSIOLOGY

- Stress incontinence: Occurs with increased intra-abdominal pressure without detrusor contraction. 2 types:
  – Anatomic: Due to urethral hypermobility from lack of pelvic support

- Hammock theory: Normally, the suburethral support contributed by the endopelvic fascia and anterior vaginal wall provides a stable backboard against which the urethra is compressed while intra-abdominal pressure rises. When this suburethral support layer is lax and mobile, any effective compression is not achieved, causing leakage
  - Intrinsic sphincter deficiency (ISD): Impairment of urethral mucosal seal and inherent closure from collagen, fibroelastic tissue, smooth and striated muscles. May be lost secondary to surgical scarring, radiation, or hormonal and senile changes
- Urge incontinence: Detrusor overactivity (may be secondary to detrusor myopathy or neuropathy)
- OI: Urinary retention (usually from lower motor paralytic neurogenic bladder in women)
- Total incontinence: Constant loss of urine. Ectopic ureters in females usually open in the urethra distal to the sphincter or in the vagina, causing continuous leakage
  - Suspect fistula if pneumaturia or fecaluria in history of radiation
- Coital incontinence: Up to 60% of women who report incontinence appear to leak urine during intercourse

ASSOCIATED CONDITIONS

- Pelvic organ prolapse
- Diabetes
- Neurologic disease (ie, multiple sclerosis, Parkinson)

GENERAL PREVENTION

- Weight loss
- Optimization of medical health (ie, diabetes)
- Smoking cessation

DIAGNOSIS

HISTORY

- Parity: Weakness of the pelvic floor is more likely in multiparous women leading to SUI
- Amount and frequency of leakage
- Continuous slow leakage in between regular voiding indicates ectopic ureter, urinary fistula, etc.
- Pain: Suprapubic pain with dysuria implies urinary infection, interstitial cystitis, etc.
- Medical history:
  - Cerebrovascular accidents, Parkinsons disease, multiple sclerosis, myelodysplasia, diabetes, spinal cord injury
  - Radiation to pelvic and vaginal areas: Causes ISD, urgency, and low bladder compliance
- Medications
- Surgical history: Pelvic and vaginal surgeries can weaken the pelvic floor support

PHYSICAL EXAM

- General neurologic exam:
  - Mental status, speech, intellectual performance
  - Motor status: Gait, generalized or focal weakness, rigidity, tremor
  - Sensory status: Impairment of perineal-sacral area sensation helps localize the level of neurologic deficit

  - Reflex: A bulbocavernous reflex implies contraction of the anal sphincter in response to squeezing the clitoris. This reflex tests the integrity of S2–S4 spinal cord segments
- Urologic exam:
  - Abdomen: Scars of previous surgeries
  - Suprapubic tenderness: May indicate cystitis
  - Palpable bladder: Chronic urinary retention
- Pelvic exam:
  - The patient is asked to cough or strain to reproduce incontinence or demonstrate urethral hypermobility (Q-tip test positive if >30 degrees)
  - Assess for atrophic vaginitis
  - Examine vaginal for cystocele, enterocele, rectocele, or uterine descensus

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis
- Urine culture: Assess for infection

Imaging

- CT urogram: Determines status of upper urinary tract, duplicated systems for ectopic ureters, and associated pathologies (indicated only when upper tract issues are suspected)
- Voiding cystourethrogram: Preferably done in combination with videourodynamic studies

Diagnostic Procedures/Surgery

- 24-hr voiding diary to assess frequency, timing, volume of symptoms
- Cystoscopy: If concern for fistula or malignancy
- Urine cytology: If hematuria and urgency (concern for carcinoma in situ)
- Urodynamic studies:
  - Filling cystometry: Pressure/volume relationship during bladder filling
    - Assess 1st sensation, desire to void, strong desire to void, capacity, detrusor overactivity
    - Assess Valsalva leak point pressure: Determines the intra-abdominal pressure at which leakage is observed at the meatus or by fluoroscopy; low leak point pressure (<60 mm H_2O) implies ISD
    - Assess detrusor leak point pressure: Lowest detrusor pressure at which leakage of urine occurs in absence of detrusor contraction and increase abdominal pressure (>40 cm H_2O risk or renal deterioration)
  - Voiding cystometry: Pressure/volume relationship during micturition
    - Assess urinary flow rate, postvoid residual, detrusor sphincter synergy
  - Videourodynamic studies: Combination of fluorocystourethrography and urodynamic studies mentioned above
    - Most useful in patients at risk for neurogenic bladder to assess for detrusor sphincter dyssynergia which is risk for renal deterioration

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Stress incontinence: Due to urethral hypermobility or ISD, although in the majority it is

mixed or due to both of the factors
- Urgency incontinence: Can be due to urinary infection, interstitial cystitis, carcinoma in situ, bladder calculi, detrusor overactivity, or neurogenic detrusor overactivity. Most often idiopathic
- Nocturnal enuresis: Idiopathic, neurogenic, cardiogenic, or obstructive causes
- Continuous leakage: Ectopic ureter, urinary fistulas, exstrophy–epispadias complex
- Postvoid dribbling: Urethral diverticulum, idiopathic or iatrogenic
- Mobility or cognitive impairment post stroke
- Coital or mixed incontinence

TREATMENT

GENERAL MEASURES (1)
- Nonsurgical management (helps ~50–65% patients with milder symptoms)
- Treat correctable causes (Atrophic vaginitis, constipation, UTI, fistula, etc.)
- Encourage weight loss in obese patients
- Biofeedback and pelvic floor exercises (Kegel exercise) (3)
- Behavioral therapy: Voiding at progressively increasing predetermined intervals

MEDICATION
First Line (2)
- Stress incontinence: Activation of α-adrenergic receptors in the internal urethral sphincter increases the urethral resistance to urinary flow with sympathomimetic drugs, estrogen, and tricyclic agents (not used commonly due to side effects and interaction concerns and potential-limited efficacy)
- Urge incontinence: Anticholinergic, antispasmodic, and tricyclic antidepressant medications have been used to treat overactive bladder symptoms
  - Mirabegron is a 1st in class β_3-agonist for treatment of urge incontinence. When compared to anticholinergic medications much less dry mouth and constipation, but risk of hypertension
    - Mirabegron (25–50 mg/d)

Second Line
Other antichlonergic agents oxybutynin, ect.

SURGERY/OTHER PROCEDURES
- Stress urinary incontinence
  - Vaginal pessary
  - Surgical management: Provides more successful and sustained outcome (5)
    - Periurethral injection of bulking agents: Calcium hydroxylapatite/sodium carboxymethylcellulose and hyaluronic acid
    - Pubovaginal sling suspension: Used for coaptation and compression of the incontinent urethra, using autologous fascia or xenograft or allograft materials
    - Midurethral sling: Controversial as to if retropubic (TVT) or transobturator (TOT) better for urethral hypermobility and ISD patients
      - Postoperative de novo urgency, urge incontinence, voiding difficulty, and urinary

retention, necessitating intermittent self-catheterization or take-down of the suspension, remain as concerns in up to ~20% of patients
  - Artificial urinary sphincter (not FDA approved for female incontinence)
- Refractory overactive bladder (failed 1st- and 2nd-line therapies including anticholinergics):
  - Sacral neuromodulation: Efficacy ~50% of patients who have failed other treatments
  - Percutaneous tibial nerve stimulation
  - Intravesical botulinum toxin for neurogenic detrusor overactivity or refractory UI
    - Efficacy: Up to ~75% improved/cured in those refractory to other medical treatment
    - Side effects: UTI (~25%), Urinary retention (~10%) (patients must be counseled about possible need for postoperative intermittent catheterization)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Reduction or avoidance of spicy foods, citrus, or chocolate; limiting excessive fluid intake and caffeine can improve symptoms of urinary incontinence (especially if overactive bladder)

Complementary & Alternative Therapies

No high-level data to support

ONGOING CARE

PROGNOSIS

Excellent prognosis for many patients with awareness of this condition, combined with advances in diagnosis and management to minimize associated morbidity of this condition.

COMPLICATIONS

- Prolonged exposure to urine causes skin breakdown and dermatitis, which may lead to ulceration and secondary infection (4)
- Catheter-related complications can result from long-term indwelling catheters, such as recurrent UTIs, skin infections, and urethral erosion

FOLLOW-UP

Patient Monitoring

- Initial postoperative assessment after midurethral sling: Evaluate voiding function with estimation of postvoid residual and need for intermittent catheterization
- Periodic long-term follow-up with validated outcome-based questionnaire surveys

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
http://kidney.niddk.nih.gov/kudiseases/pubs/uiwomen/

REFERENCES

1. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188:2455–2463. [B]
2. Madhuvrata P, Cody JD, Ellis G, et al. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev*. 2012;1:CD005429. [A]

3. Dumoulin C, Glazener C, Jenkinson D, et al. Determining the optimal pelvic floor muscle training regimen for women with stress urinary incontinence. *Neurourol Urodyn*. 2011;30(5):746–753. [B]
4. Shamliyan T, Wyman JF, Ramakrishnan R, et al. Benenefits and harms of pharmacologic treatment for urinary incontinence in women: A systematic review. *Ann Intern Med*. 2012;156(12):861–874. [A]
5. Schierlitz L, Dwyer PL, Rosamilia A, et al. Three-year follow-up of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency. *Obstet Gynecol*. 2012;119(2 Pt 1):321–327. [A]

ADDITIONAL READING

• Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA Guideline on the surgical management of female stress urinary incontinence. *J Urol*. 2010;183(5):1906–1914.
• Jha S, Strelley K, Radley S. Incontinence during intercourse: myths unravelled. *Int Urogynecol J*. 2012;23(5):633–637.
• Winters JC, Dmochowski RR, Goldman HB, et al. Urodynamic studies in adults: AUA/SUFU guideline.*J Urol*. 2012;188(Suppl6):2464–2472. https://www.auanet.org/common/pdf/education/clinical-guidance/Adult-Urodynamics.pdf (Accessed April 7, 2014)

See Also (Topic, Algorithm, Media)

• Coital Incontinence (Coital leakage/Intercourse Incontinence)
• Ejaculation, Female
• Incontinence, Urinary, Adult Female Image
• Overactive Bladder
• Pelvic Organ Prolapse
• Urethral Sling, Indications and Anatomic Positions
• Urethral Sling, Materials

CODES

ICD9

• 625.6 Stress incontinence, female
• 788.30 Urinary incontinence, unspecified
• 788.31 Urge incontinence

ICD10

• N39.3 Stress incontinence (female) (male)
• N39.41 Urge incontinence
• R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

• Recent FDA Alerts regarding vaginal mesh applies to prolapse repair and not midurethral sling. Mesh for stress incontinence has been supported in multiple randomized controlled trials.

- Consider reduction of pelvic organ prolapse as part of evaluation for incontinence.
- Consider referral to neurologist in young patients with refractory idiopathic overactive bladder as 1st presenting symptom of multiple sclerosis is isolated urinary urgency in ~15%.

INCONTINENCE, URINARY, ADULT MALE

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BASICS

DESCRIPTION

Defined by International Continence Society, urinary incontinence is the involuntary loss of urine that presents a social or hygienic problem

EPIDEMIOLOGY

Incidence

No published reports on incidence

Prevalence

- 3–11% overall prevalence rate of incontinence in male population
- NOBLE study
  - Urge incontinence
    - 2.6% American men of all ages
  - After age 64, prevalence rose sharply
    - ~10% in men ≥75 (1)
  - Reaches 31% in men ≥85 (2)
- Stress incontinence in men is rare
  - Unless attributable to prostate surgery, neurologic disease, or trauma
- Incontinence after prostatectomy ranges from 1% after transurethral resection to 2–57% after radical prostatectomy
- Incontinence in male of all ages is ~1/2 as prevalent as it is in women

RISK FACTORS

- Age
- Neurologic disease
- Prostate surgery
- Pelvic trauma

Genetics

N/A

PATHOPHYSIOLOGY

- Incontinence secondary to bladder abnormalities
  - Detrusor overactivity results in urge urinary incontinence (UUI)
    - Associated with bladder outlet obstruction from benign prostatic hyperplasia (BPH)
- Incontinence secondary to outlet abnormalities
  - Sphincteric damage
    - Secondary to pelvic surgery or radiation
  - Sphincteric dysfunction
    - Secondary to neurologic disease

- Mixed incontinence is due to abnormalities of both bladder and the outlet

ASSOCIATED CONDITIONS
- Neurologic disease
  - Parkinson disease, multiple sclerosis
- Pelvic radiation
- Pelvic trauma
- BPH
- Prostate surgery

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Voiding symptoms
  - Duration and characteristics of incontinence
  - Stress, urge, total
  - Precipitants and associated symptoms
  - Use of pads, briefs, diapers
  - Fluid intake
  - Alteration in bowel habits
  - Previous treatments and effect on incontinence
- Diabetes mellitus
- Associated conditions
  - Neurologic disease
- Medication use
  - Diuretics
- Alcohol and drug use including caffeine
- Radical pelvic surgery or radiation
  - Abdominoperineal resection
  - Radical prostatectomy

PHYSICAL EXAM
- Abdominal exam
  - Suprapubic mass
    - Suggests retention
  - Suprapubic tenderness
    - Suggests UTI
  - Surgical scars suggesting pelvic surgery
  - Skin lesions associated with neurologic disease
    - Neurofibromatosis and café au lait spots
- External genitalia
- Prostate
- Spine/back
- Skelet al deformities

- Scars from previous spinal surgery
- Sacral abnormalities may be associated with neurologic bladder dysfunction
  - Cutaneous signs of spinal dysraphism
    - Subcutaneous lipoma
    - Vascular malformation, tuft of hair, or skin dimple on lower back
  - Cutaneous signs of sacral agenesis
    - Low, short gluteal cleft
    - Flattened buttocks
    - Coccyx not palpable
- Focal neurologic exam
  - Motor function
    - Inspect muscle bulk for atrophy
    - Tibialis anterior (L4–S1): Dorsiflexion of foot
    - Gastrocnemius (L5–S2): Plantar flexion of foot
    - Toe extensors (L5–S2): Toe extension
- Sensory function
- Reflexes
  - Anal reflex (S2–S5)
    - Gently stroke mucocutaneous junction of circumanal skin
    - If visible contraction (wink) absent, suggests peripheral nerve or sacral (conus medullaris) abnormality
  - Bulbocavernosus reflex (BCR) (S2–S4)
    - Elicited by squeezing glans to cause reflex contraction of anal sphincter
    - Absence of BCR suggests sacral nerve damage

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Creatinine
  - If significant retention suspected
- Urinalysis
  - Glucosuria, infection

Imaging

None usually indicated

Diagnostic Procedures/Surgery

- Urodynamics
  - Useful for confirming bladder outlet obstruction as a possible cause of detrusor overactivity

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Urge incontinence
  - Loss of urine accompanied by urgency; often related to triggers such as sounds of running water, cold weather, passing a restroom

- Stress incontinence
  - Urinary leakage associated with exertion, lifting, coughing, sneezing
- Mixed incontinence
  - Urinary leakage associated with both stress and urge incontinence
- Low bladder compliance resulting in overflow incontinence
- Continuous urinary incontinence is the continuous loss of urine
- Post micturition dribble
  - The involuntary loss of urine immediately after he has finished passing urine, usually after leaving the toilet
- Mobility or cognitive impairment post stroke

TREATMENT

GENERAL MEASURES

- Bladder diaries are invaluable
  - Help patients understand patterns of incontinence
- Time voiding
  - Avoids significant bladder distention
- For postradical prostatectomy incontinence see Section I: Incontinence, urinary, following radical prostatectomy

MEDICATION

First Line

- Urge incontinence
  - Antimuscarinics: Inhibit the effect of acetylcholine at postjunctional muscarinic receptors on detrusor muscle cells
    - Tolterodine (2–4 mg/d)
    - Trospium XR (60 mg/d)
    - Darifenacin (7.5–15 mg/d)
    - Solifenacin (5–10 mg/d)
    - Oxybutynin (IR 7.5–20 mg/d, XL 5–30 mg/d, patch twice weekly)
    - Fesoterodine (4–8 mg/d)
  - β_3-adrenergic agonist agent: Promotes detrusor muscle relaxation
    - Mirabegron (25–50 mg/d)
- Stress incontinence
  - No generally accepted drug therapy
  - Tricyclics sometimes used
    - Imipramine 10–25 mg PO BID-TID

Second Line

- Urge incontinence
  - Tricyclic antidepressants
    - Imipramine 10–25 mg PO BID-TID
  - DDAVP for nocturnal symptoms
    - 0.1–0.5 mg PO or intranasal QHS (off label)
    - Avoided in patients with cardiac disease and older patients

- Risk of significant hyponatremia
- Intradetrusor botulinum toxin injections

SURGERY/OTHER PROCEDURES

- Urge incontinence
  - Sacral neuromodulation
  - Augmentation cystoplasty
- Stress incontinence
  - Urethral bulking agent
  - Male sling procedure
    - Promising short-term results
    - No long-term studies (3)[B]
  - Artificial urinary sphincter
    - Excellent long-term continence rates (4)[A]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Pelvic floor exercise (Kegels)
  - Significantly improve SUI/UUI
- Biofeedback
- Timed voiding in UUI
- Overflow incontinence due to poor bladder contractility with urinary retention
  - Indwelling catheter
  - Intermittent catheterization
  - Evaluate for outlet obstruction

Complementary & Alternative Therapies

- Penile clamps, condom catheters, and pads are occasionally used
- They should be reserved for minor degrees of incontinence or in patients who have multiple other comorbidities in whom surgery may be thought inappropriate (5)
- Penile compression clamps
  - Applied externally to the penis to exert nonsurgical compression of the urethra, thereby preventing leakage of urine
  - 3 types of commercially available penile incontinence clamps (C3, U-Tex Male Adjustable Tension Band and Cunningham clamp) have been studied in a small trial (6)
  - No device completely eliminated leakage when applied at a comfortable pressure
  - Complications of penile clamps can include edema, pain, urethral erosion, and obstruction
  - Penile clamps should not be used for more than 4 hrs at a time
- Absorbent products (pouches, absorbant pants, small pads) were evaluated in a multi-center, multi-crossover study (7)
  - The conclusion was that no one product suits every patient although small pads came closest
  - Washable absorbant pants for men with light incontinence have economic advantages

ONGOING CARE

PROGNOSIS

Continence can be improved in almost all patients

COMPLICATIONS

- Candidiasis
- Dermatitis
- Skin breakdown

FOLLOW-UP

Patient Monitoring

Monitor post-void residual in patients on anticholinergic medications

Patient Resources

Urology Care Foundation. Surgical Management of Urinary Incontinence http://www.urologyhealth.org/urology/index.cfm?article=33, Accessed April 2013.

REFERENCES

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the US. *World J Urol.* 2003;20:327–336.
2. Anger JT, Saigal CS, Stothers L, et al. Urologic Diseases of America Project. The prevalence of urinary incontinence among community dwelling men: Results from the National Health and Nutrition Exam survey. *J Urol.* 2006;176(5):2103–2108.
3. Comiter CV. The male sling for stress urinary incontinence: A prospective study. *J Urol.* 2002;167:597–601.
4. Elliott DS, Barrett DM. Mayo Clinic long-term analysis of the functional durability of the AMS 800 artificial urinary sphincter: A review of 323 cases. *J Urol.* 1998;159:1206–1208.
5. Moore, KC, Lucas, MG. Management of male urinary incontinence. *Indian J Urol.* 2010;26(2):236–244.
6. Moore KN, Schieman S, Ackerman T, et al. Assessing comfort, safety, and patient satisfaction with three commonly used penile compression devices. *Urology*. 2004;63:150–154.
7. Fader M, Macaulay M, Pettersson L, et al. A multi-centre evaluation of absorbent products for men with light urinary incontinence. *Neurourol Urodyn*. 2006;25:689–695.

ADDITIONAL READING

Burden H, Warren K, Abrams P, et al. Diagnosis of male incontinence. *Curr Opin Urol.* 2013;23(6):509–514.

See Also (Topic, Algorithm, Media)

- Bladder Areflexia (Detrusor Areflexia)
- Cunningham Clamp
- Incontinence Clamps
- Incontinence, Urinary, Adult Male Image ☼
- Incontinence, Urinary, Following Radical Prostatectomy
- Incontinence, Urinary, with Orgasm (Climcaturia)

• Lower Urinary Tract Symptoms (LUTS)

CODES

ICD9

• 788.30 Urinary incontinence, unspecified
• 788.31 Urge incontinence
• 788.32 Stress incontinence, male

ICD10

• N39.3 Stress incontinence (female) (male)
• N39.41 Urge incontinence
• R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

• Prevalence of incontinence in males is 50% that of women.
• Continence can be improved in almost all patients.
• An Artificial urinary sphincter has excellent long-term continence rates.

INCONTINENCE, URINARY, FOLLOWING RADICAL PROSTATECTOMY

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BASICS

DESCRIPTION

- Post-prostatectomy incontinence (PPI) is a well-recognized complication of radical prostatectomy (RP) whether performed openly (perineal retropubic) or laparoscopically with or without robotic assistance.
- The definition of continence following RP in the literature varies widely, with the strictest definition of continence being no pads used.

EPIDEMIOLOGY

Incidence

- The incidence of PPI depends on the interval of time following surgery, the definition and methodology for assessing continence, and the experience of the surgeon.
- The overwhelming majority of men have some degree of PPI immediately after catheter removal.
- If PPI is defined as no pads/small protective pad or total control/occasional dribbling, experienced surgeons consistently report continence rates exceeding 95% at 1–2 yr after RP.
- Recent evidence suggests that PPI may improve after 2 yr.

Prevalence

Approximately 6% of men will undergo a procedure for the management of PPI at a median of 20 mo after RP (1)

RISK FACTORS (2)

- Body mass index (BMI) ≥ 25
- Compromised sexual potency (IIEF-EF < 10)
- Enlarged prostate volume
- Increasing age (> 65 yr)
- Nerve-sparing status (non vs. unilateral vs. bilateral)
- Presence of preoperative incontinence/lower urinary tract symptoms (LUTS)
- Previous TURP
- Surgeon inexperience

Genetics

N/A

PATHOPHYSIOLOGY

- PPI results primarily from injury to the rhabdosphincter resulting in SUI.
- Pre-existing detrusor instability (DI) is a less likely etiology of PPI.
- An anastomotic stricture may be the cause, or exacerbate PPI.

ASSOCIATED CONDITIONS
- Anastomotic stricture/bladder neck contracture
- Detrusor Instability (DI)/Overactive bladder (OAB)
- Sphincteric incompetence

GENERAL PREVENTION
- Achieving a bloodless surgical field following anatomic ligation of the dorsal venous complex is required to meticulously divide the prostatourethral junction.
- Maximal preservation of the rhabdosphincter is felt to minimize PPI.
- Encourage Kegel exercises—may accelerate continence recovery.
- Preoperative pelvic floor muscle training with biofeedback has not resulted in improved postoperative continence recovery (3)

DIAGNOSIS
HISTORY
- Assess the severity of LUTS and incontinence preoperatively.
  – The International Prostate Symptom Score (IPSS).
- Inquire about the use of α-blockers because these agents may exacerbate PPI.
- Ascertain if the PPI is exacerbated by physical activity.
- Determine the severity of PPI by: Number of pads, degree of bother, and frequency of incontinence episodes.
- Assess the severity of LUTS.
- Inquire if PPI is improving, stable, or deteriorating:
  – Deterioration of continence together with increasing voiding symptoms suggests an anastomotic stricture.

PHYSICAL EXAM
- Observe for skin excoriation secondary to PPI.
- Observe degree of pad saturation.
- Observe degree of incontinence when transferring from the sitting to standing position.
- Observe caliber of urinary stream.

DIAGNOSTIC TESTS INTERPRETATION (C)
Lab
Urinalysis to exclude urinary tract infection

Imaging
Sonographic post-void residual (PVR)

Diagnostic Procedures/Surgery
- Uroflowmetry
- 24-hr pad test to quantify PPI
- Urodynamics evaluation with or without fluoroscopy will help define the etiology for PPI
- Pressure flow study is useful for evaluating a possible obstructive anastomotic stricture

Pathologic Findings
None

DIFFERENTIAL DIAGNOSIS

- Anastomotic stricture
- Detrusor Instability (DI)/Overactive bladder (OAB)
- Stress urinary incontinence (SUI)
- Urge incontinence
- Overflow incontinence
- Mixed incontinence

TREATMENT

GENERAL MEASURES

- Kegel exercises should be encouraged as soon as urinary catheter removal
- Discontinue α-blockers
- Limitation of fluid intake
- Timed voiding
- Voiding before strenuous activity
- Counsel patient that incontinence following RP is the norm and that with time most patients will improve

MEDICATION

First Line

- α-Agonists generally not effective for SUI
- Imipramine (a tricyclic antidepressant) promotes external urethral sphincter muscle tone and may improve mild SUI (off-label use)
  - Typical off-label starting dose is 25–50 mg PO QHS
- Anticholinergic agents may improve PPI secondary to DI
  - Options include: Oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, trospium

Second Line

Periurethral bulking agents (bovine glutaraldehyde cross-linked collagen polydimethylsiloxane elastomer) are costly; they require multiple injections and have limited durable success in this setting.

SURGERY/OTHER PROCEDURES

- Surgical intervention should not be pursued until at least 1 yr post-prostatectomy because of the temporal improvements in the condition
- Surgical intervention should not be contemplated at 1–2 yr if there is evidence of progressive improvement
- Imperative to exclude anastomotic stricture and DI before embarking on surgical correction of SUI
- Surgical options:
  - The specific surgical procedure is dictated by severity of PPI.
  - More severe cases best managed with an artificial urinary sphincter (AUS)
  - In many cases, surgery achieves marked improvement in PPI but some degree of SUI may persist
    - Male slings

- Artificial urinary sphincter (AUS)

ADDITIONAL TREATMENT

Radiation Therapy

Although there is no role in the treatment of PPI, data suggest that radiation administered in the adjuvant setting following RP may not worsen incontinence but may limit resolution of continence particularly if the radiation is administered before continence returns.

Additional Therapies

- Urethral dilation should be performed if evidence of bladder outlet obstruction and anastomotic stricture.
- Transurethral incision of the stricture may be required if stricture reoccurs despite multiple dilation(s).
- In Europe duloxetine, a serotonin-norepinephrine reuptake inhibitor is approved for stress incontinence (US approval is only for neuropathic pain and depression).

Complementary & Alternative Therapies

Biofeedback may have a role in selected patients in strengthening pelvic musculature.

ONGOING CARE

PROGNOSIS

- The overwhelming majority of men will spontaneously regain urinary continence following RP.
- The small subset of men with persistent SUI will improve, providing the appropriate surgical procedure is performed.
- The worst prognosis exists for cases with severe refractory anatomic strictures (bladder neck contractures) who must 1st be made totally incontinent with subsequent placement of an AUS.
- PPI secondary to DI likely to improve with anticholinergic agents.

COMPLICATIONS

- Dermatitis
- Diminished self-esteem:
  - Limitation of physical activity
  - Withdrawal from sexual activity
  - Complications of treatment for PPI

FOLLOW-UP

Patient Monitoring

- Pad use
- Impact of PPI on quality of life

Patient Resources

http://www.webmd.com/urinary-incontinence-oab/mens-guide/urinary-incontinence

REFERENCES

1. Kim PH Pinheiro LC, Atoria CL, et al. Trends in the use of incontinence procedures after radical prostatectomy: a population based analysis. *J Urol.* 2013;189(2):602–608.

2. Abdollah F, Sun M, Suardi N, et al. A novel tool to assess the risk of urinary incontinence after nerve-sparing radical prostatectomy. *BJU Int.* 2013;111(6):905–913.
3. Geraerts I, Van Poppel H, Devoogdt N, et al. Influence of Preoperative and Postoperative pelvic floor muscle training (PFMT) compared with postoperative PFMT on urinary incontinence after radical prostatectomy: A randomized controlled trial. *Eur Urol.* 2013;64(5):766–772.

ADDITIONAL READING

• Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted \radical prostatectomy. *Eur Urol.* 2012;62:405–417.
• Gacci M, Ierardi A, Rose AD, et al. Vardenafil can improve continence recovery after bilateral nerve sparing prostatectomy: Results of a randomized, double blind, placebo-controlled pilot study. *J Sex Med.* 2010;7:234–243.
• Healy KA, Gomella LG. Retropubic, laparoscopic, or robotic radical prostatectomy: is there any real difference? *Semin Oncol.* 2013;40(3):286–296.

See Also (Topic, Algorithm, Media)

• Bulking Agents, Injectable
• Incontinence, Urinary, Adult Male
• Stress Urinary Incontinence, Male

CODES

ICD9

• 788.39 Other urinary incontinence
• 997.5 Urinary complications, not elsewhere classified

ICD10

• N39.498 Other specified urinary incontinence
• N99.89 Oth postprocedural complications and disorders of GU sys

CLINICAL/SURGICAL PEARLS

• Post prostatectomy incontinence (PPI) is very common, with the vast majority (95%) resolving 6–12 mo postoperatively.
• Kegel exercises should be instituted immediately after catheter removal postoperatively.
• It is crucial to determine the exact pattern of urinary leakage.
• If conservative measures fail, treatment for bothersome SUI requires surgery.
• Type of surgery is dictated by severity of SUI.

INCONTINENCE, URINARY, PEDIATRIC

Steve J. Hodges, MD
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BASICS

DESCRIPTION

- Incontinence: Involuntary leaking of urine due to any cause
- A "wet" child is the most common problem seen by pediatric urologists. Most wetting children will appear to no inciting cause, and some will improve spontaneously
- Enuresis: Involuntary leaking of urine while sleeping
  - "Nocturnal" enuresis implies night wetting alone, "diurnal" implies day and night, although these terms are outdated according to International Childrens Continence Society (ICCS)
  - Primary enuresis: Child was always wet at night
  - Secondary enuresis: Child has had a dry interval for at least 6 mo before wetting again

EPIDEMIOLOGY

Prevalence

- Day or night wetting occurs in up to 25% of 4–6 yr old children (daytime incontinence is present in approximately 5–10%)
- Resolution rates of approximately 15% a year
- At 12 yr of age 4% of children are enuretic at least once a week, at 15 yr old it is 2%
- Enuresis is 3× more common in boys than girls, however daytime incontinence is more common in females in all age groups

RISK FACTORS

- Spinal dysraphism
- Urinary tract anomalies
- Developmental delay
- Family history of enuresis
- Attention deficit disorder
- Urinary tract infection
- Constipation

Genetics

- Children whose parents were not bed-wetters have a 15% incidence of bedwetting. When one or both parents were bed-wetters, the rates jump to 44% and 77%, respectively.
- Genetic research shows that bedwetting is associated with the genes on chromosomes 13q and 12q (possibly 5 and 22 also).

PATHOPHYSIOLOGY

- Daytime control attained before nighttime
- Constipation plays a major role in urinary continence
- Normal bladder control involves 3 basic components: Intact neurologic system, normal

anatomy, and a mature, motivated child
- Normal urinary control occurs in stages:
  - Infantile voiding (0–6 mo) low-pressure filling, reflex detrusor contractions, simultaneous relaxation of external sphincter, complete emptying, uninhibited voids
  - Transitional voiding (1–2 yr) conscious sensation of bladder filling, continence achieved by controlling external sphincter, increasing bladder capacity (60 cc at birth + 30 cc/yr till 12 yr old)
  - Adult voiding: Supraspinal inhibition of voiding reflex, voluntary inhibition/initiation of voiding
- Delayed voiding/defecation lead to bladder overactivity, constipation
- Bladder overactivity/constipation compounded by dyssynergy of pelvic floor, with failure to relax pelvic floor completely with emptying

ASSOCIATED CONDITIONS
See risk factors

GENERAL PREVENTION
- Aggressively prevent and treat constipation
- Ensure an environment where children are not delaying micturition or defecation

DIAGNOSIS

ALERT
Incontinence in the presence of an abnormal back exam may signal a neurologic abnormality.

HISTORY
- Child's age—more common in young
- Child's sex—bedwetting is more common in boys, daytime wetting more common in girls
- When did the symptoms begin? What is the pattern? Severity?
- Primary enuresis is highly associated with constipation
- Secondary nocturnal enuresis implies an acquired cause or stressor
- Dribbling upon standing or activity in girls may imply vaginal voiding
- Determine associated daytime symptoms (urgency, frequency, weak or intermittent stream, or infrequent voiding)
- History of UTI? Functional constipation?
- History of large or firm bowel movements, or encopresis, may signify constipation even in setting of normal frequency of bowel movements
- Does child show holding behavior? (curtsey or squatting in girls, holding genitals in boys)
- History of neurologic disorder?
- Family history of incontinence? UTIs? Enuresis?

PHYSICAL EXAM
- Level of physical and emotional development
- Abdominal exam—rule out masses, constipation
- Back exam—rule out signs of occult spinal dysraphism (dimples, short sacrum, spinal defect, hairy patches)

- Flattened buttocks, low gluteal cleft, or nonpalpable coccyx suggest sacral agenesis
- GU exam, rule out genital or perineal sensation disorders, signs of abuse, hypospadias, or epispadias
- Rule out urine in vaginal vault or labial adhesions in girls
- Ectopic perineal ureteral orifice can be cause of constant wetness in girls
- Rectal exam to rule out rectal stool, evaluate normal sensation and tone
- Neurologic exam
- Measure or observe urinary stream for force, caliber, straining, duration (may obtain flow/PVR)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Rule out UTI, microhematuria, proteinuria, glucosuria
- If any of above discovered, require thorough evaluation and treatment
- Urine culture if UA shows signs of infection

Imaging

- KUB to rule out spinal anomalies and rule out occult constipation
- Renal US to evaluate for normal GU anatomy
- VCUG only needed in the setting of febrile UTI (or any UTI in boys), hydronephrosis; allows evaluation of urethra in males
- MR urography may be needed when concerned for ectopic ureter
- Renogram rarely needed to evaluate for urinary obstruction, renal function

Diagnostic Procedures/Surgery

- Urodynamics indicated in setting of known neurologic disorder
- Cystoscopy only needed if evaluation demonstrated anatomic abnormality such as posterior urethral valves

Pathologic Findings

- Incontinence classified as structural, neurogenic, complicated, or uncomplicated
- Structural—anatomic cause of incontinence (eg, ectopic ureter in girls)
- Neurogenic—incontinence due to spinal dysraphism or other neurologic cause
- Uncomplicated—nocturnal enuresis in appropriate age group in the presence of no obvious causes on diagnostic and physical exam (least common—almost all cases have cause if look closely)
- Complicated—functional voiding disorders; significant incontinence without anatomic or neurologic cause
- Need KUB and renal/bladder US, urodynamics optional
- Other pediatric bladder disorders:
  - Lazy bladder syndrome (infrequent voider)—rare voids, 2–3× a day, may have infections, associated with constipation
  - Bladder overactivity—typically associated with delayed voiding and constipation, typified by uninhibited bladder contraction with no neurologic lesion
  - Hinman-Allen syndrome—nonneurogenic neurogenic bladder, may be due to constipation as well

- Daytime frequency syndrome—frequent urination in a child with no other identifiable abnormalities, usually do have constipation on KUB
- Giggle Incontinence—rare form of incontinence where wetting only occurs with laughing, may be centrally mediated (brain), treated with Ritalin

DIFFERENTIAL DIAGNOSIS

- Structural incontinence:
  - Ectopic ureter
  - Exstrophy-epispadias complex
  - Fibrotic bladder (postoperatively or postradiation)
  - Imperforate anus
  - Labial adhesions
  - Posterior urethral valves
  - Urethral duplication
  - Urogenital sinus
  - Vesical fistula
- Neurogenic:
  - Anterior sacral meningocele, caudal tumor
  - Intradural lipoma, diastematomyelia
  - Myelodysplasia
  - Occult dysraphism
  - Sacral agenesis, spinal cord trauma, myelitis cerebral palsy
  - Tight filum terminale, dermoid cyst/sinus
  - Isolated nocturnal enuresis: Constipation, sleep arousal disorder, nocturnal polyuria
- Complicated incontinence:
  - Giggle incontinence
  - Hinman-Allen syndrome
  - Lazy bladder syndrome
  - Overactive bladder

TREATMENT

GENERAL MEASURES

- Behavioral measures—timed voiding, constipation therapy
- Biofeedback—physical therapy to relax external sphincter
- Diet—avoid bladder irritant, caffeine
- Perineal hygiene—voiding positioning

MEDICATION

First Line

- Treat UTI if present
- Overactive bladder
  - Anticholinergic medications
    - Oxybutynin: Safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 yr of age and older
    - Tolterodine (off label in children)

- Consider β_3-agonist (mirabegron off label in children)

- Constipation
  - PEG 3350, enemas or suppositories, Senna laxatives, fiber supplements

SURGERY/OTHER PROCEDURES

- Structural—alleviate structural cause of incontinence
  - Neurogenic—low compliance bladder may require enterocystoplasty, urethral dilation, neural stimulation, or botulinum toxin injection
  - Overactive bladder—may benefit from neural stimulation, botulinum toxin injection in bladder or sphincter, rarely urethral dilation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Aggressive constipation management for severe cases may require chronic enemas or antegrade continence enema (ACE) creation

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most patients do resolve over time as they grow, and gain more mature toileting habits
- Severe cases may lead to pelvic floor disorders (such as pelvic pain syndrome, dyspareunia) in future, so aggressive therapy indicated

FOLLOW-UP

Patient Monitoring

- Follow-up for observation of progress, adjusting medications as needed
  - Structural and neurogenic causes need routine evaluations to rule out upper tract injury and monitor progress

Patient Resources

- National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
  http://kidney.niddk.nih.gov/kudiseases/pubs/uichildren/

REFERENCES

1. Feldman A, Bauer S. Diagnosis and management of dysfunctional voiding. *Curr Opin Pediatr*. 2006;18:139–147.
2. Humphreys MR, Reinberg YE. Contemporary and emerging drug treatments for urinary incontinence in children. *Pediatr Drugs*. 2005;7(3):151–162.
3. Hodges SJ. Overactive bladder in children. *Curr Bladder Dysfunct Rep*. 2012;7(1):27–32.

ADDITIONAL READING

Dave S, Salle JL. Surgical management of pediatric urinary incontinence. *Curr Urol Rep*. 2013;14(4):342–349.

See Also (Topic, Algorithm, Media)
- Dysfunctional Elimination Syndrome
- Giggle Incontinence (Enuresis Risoria)
- Hinman Syndrome
- Incontinence, Urinary, Adult Male
- Incontinence, Urinary, Adult Female
- International Children's Continence Society (ICCS), Terminology
- Overactive Bladder (OAB)
- Sacral Agenesis
- Spinal Dysraphism
- Vincent curtsey

CODES

ICD9
- 788.30 Urinary incontinence, unspecified
- 788.36 Nocturnal enuresis
- 788.91 Functional urinary incontinence

ICD10
- F98.0 Enuresis not due to a substance or known physiol condition
- N39.44 Nocturnal enuresis
- R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS
- Aggressive constipation therapy is needed.
- Enemas are most effective in treating incontinence.
- Incontinence in children is never normal and is a sign of treatable pathology.

INFERTILITY, UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Infertility is the inability to achieve pregnancy after 1 yr of regular unprotected intercourse
- Couples achieve pregnancy by intercourse at a rate of approximately 20–25% per month, 75% by 6 mo, and 90% by 1 yr

EPIDEMIOLOGY

Incidence

- 15% of couples have infertility
- In approximately 30%, infertility is due to a significant male factor alone
- An additional 20% of couples have both male and female factors present

Prevalence

N/A

RISK FACTORS

- Anatomic: Varicocele; bilateral cryptorchidism; hypospadias; testicular trauma; testicular torsion; thermal exposure (hot baths, saunas); spinal, inguinal, or retroperitoneal surgery
- Medications: Cancer and cancer treatments (chemotherapy, radiation); recreational drugs (marijuana, cocaine); prescription meds (exogenous testosterone [T], GnRH agonists/antagonists, α-blockers, antibiotics, sulfasalazine, cimetidine, spironolactone, Ca channel blockers, colchicine, opioids, psych meds)
- Others: Heavy alcohol use; GU infections; chromosomal abnormalities; neurologic disease; endocrine disorders

Genetics

- Most common defects and % of men with nonobstructive azoospermia (NOA) or obstructive azoospermia (OA) with each:
  - Klinefelter syndrome 47,XXY (10% NOA)
  - Cystic fibrosis transmembrane conductance regulator protein (CFTR) found abnormal in 80% of patients with congenital bilateral absence of the vas deferens (CBAVD) (6% OA)
  - Azoospermia factor (AZF) a, b, and c:
    - AZFa (1% NOA) predictive of testicular sperm extraction (TESE) failure
    - AZFb (1–3% NOA) predicts TESE failure
    - AZFc (13% NOA) best prognosis, can be oligospermic, if azoospermic 2/3rds have sperm on TESE

PATHOPHYSIOLOGY

3 categories:

- Pretesticular: Endocrine abnormality
- Testicular: Abnormal sperm production

- Posttesticular: Abnormal sperm transport

ASSOCIATED CONDITIONS

- Pretesticular:
  - Hypogonadotropic hypogonadism: Low follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) with normal prolactin
  - Hypothyroidism
  - Medication use: See Risk Factors
  - Elevated estradiol from morbid obesity, tumors, or hepatic dysfunction
  - Kallmann syndrome: X-linked, absent GnRH secretion, absent puberty, anosmia
  - Pituitary/cranial trauma, infection, or tumor
  - Hyperprolactinemia: Prolactin inhibits LH action on Leydig cells. Brain MRI to evaluate for macroadenoma (>1 cm)
    - Macroadenoma: Refer for possible resection
    - Microadenoma: May respond to dopamine agonist (1st line: Cabergoline, 2nd: Bromocriptine)
- Testicular:
  - Varicocele: 15% of all men, 35–40% of men with primary infertility, 70–80% of men with secondary infertility
  - Bilateral cryptorchidism
  - Testicular cancer—pretreatment sperm density and motility are significantly decreased
  - Gonadotoxins: Radiation, chemotherapy, medications, environmental endocrine disrupting chemicals (eg, phthalates used in plastics)
  - Immunologic: Antisperm antibodies; febrile infections can decrease sperm production for 3 mo; postpubertal mumps orchitis
  - Sertoli-cell only syndrome: Absent germ cells
  - Maturation arrest: Spermatogenesis halted at a certain stage
  - Genetic/chromosomal factors:
    - Klinefelter: 47,XXY; small, firm testes; often azoospermic, however, mosaicism (47,XXY/46,XY) allows spermatogenesis. Up to 69% have sperm found from TESE
    - Y microdeletions: AZFa, b and c: See Genetics
    - Androgenization disorders: Defects in synthesis of T, androgen receptor, and 5α reductase
    - 47,XYY: Usually fertile due to mosaicism with XYY cells arresting in meiosis and XY cells producing mature sperm
    - 46,XX with male phenotype: No spermatogenesis, donor sperm/adoption
    - Primary ciliary dyskinesia (Kartagener syndrome): Immotile sperm; frequent respiratory infections; situs inversus
    - Globozoospermia (round-headed sperm): Severe teratospermia in which sperm lack acrosomes giving the heads a round appearance
- Posttesticular:
  - Obstruction of epididymis or vas deferens: Congenital or acquired (eg, vasectomy)
  - CBAVD: 80% have CFTR mutations—genetic testing must be performed for male and female
  - Ejaculatory dysfunction:

- Anejaculation: Caused by retroperitoneal surgery, neuropathic disorders, α-blockers and psychiatric medications
- Retrograde ejaculation: Transurethral prostate and bladder neck procedures as well as the same causes of anejaculation (above)

– Ejaculatory duct obstruction (EDO): Low-volume azoospermia; causes include previous infection, iatrogenic trauma, and congenital

GENERAL PREVENTION

See “Risk Factors”

DIAGNOSIS

HISTORY

• Mnemonic **TICS:**

– **Toxic:** Varicocele, chemotherapy, radiation exposure, thermal exposure to testes, testicular injury, heavy alcohol use, recreational drugs (marijuana, cocaine), surgical history, medications, and other medical illnesses

– **Infectious:** Sexually transmitted disease, urinary tract infections, epididymitis, recent febrile illness, and postpubertal mumps

– **Congenital:** Bilateral cryptorchidism, testicular torsion, family history of difficulty conceiving or miscarriages, family history of cystic fibrosis

– **Sexual:** Length of time attempting to conceive, previous pregnancies with current or previous partner, frequency of intercourse, lubricant use, erectile dysfunction, age at puberty, libido, exogenous T use, energy level

PHYSICAL EXAM

• General: Degree of virilization, Tanner stage

• Penile exam: Location of urethral meatus, buried penis

• Scrotal exam:

– Measure testicles by long access length or orchidometer volume (nL ≥4 cm or 20 mL)

– Testicular consistency, including careful evaluation for testicular masses

– Epididymal exam—note presence of caput, corpus, and cauda as well as possible induration or fullness suggestive of obstruction

– Cord structures: Evaluate for varicocele in standing position, note presence or absence of vasa deferentia as well as continuity or malunion

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Semen analysis:

– Minimum of 2 specimens due to variability

– World Health Organization (WHO) 2010 5th edition reference values:

- Volume >1.5 mL normal, if low, obtain post ejaculatory urinalysis to distinguish between retrograde ejaculation and EDO
- Concentration >15 million/mL
- Total sperm count >39 million/mL
- Total Motility >40%
- Morphology >4%

  - Azoospermia:
    - Distinguish between obstructive and NOA
    - If FSH <7.6 mIU/mL and testicular long axis >4.6 cm then 96% probability of OA
    - If FSH ≥ 7.6 and testicle ≤ 4.6 cm then 89% probability of NOA (1)[B]
- Further specialized semen testing may aid decision-making but not routinely obtained
- Endocrine workup obtained if abnormal semen analysis, impaired sexual function or findings indicative of endocrine abnormality:
  - Obtain T, sex hormone binding globulin (SHBG), albumin to calculate bioavailable T and FSH, LH estradiol for all patients needing workup
  - Consider prolactin and others as indicated
- Genetic testing
  - CBAVD: Patient and partner should have genetic counseling and CFTR mutation testing
  - Karyotyping is indicated in patients with NOA or severe oligospermia (<5 million sperm/mL)
  - Consider Y chromosome microdeletion testing if azoospermic

Imaging

- Transrectal ultrasound—use in azoospermic patients with palpable vasa and low-volume ejaculate. Seminal vesical dilatation (normal <2 cm) indicative of EDO
- Scrotal ultrasound—only used in patients with difficult or inadequate scrotal exams
- Renal ultrasound—recommended if unilateral absent vas or CBAVD with no CFTR mutations to evaluate for renal abnormalities

Diagnostic Procedures/Surgery

Testicular biopsy is typically unnecessary

Pathologic Findings

- Seminiferous tubules findings include:
  - Normal spermatogenesis—indicative of OA
  - Maturation arrest ($\sim 20\%$ of NOA)—can be “early” or “late”
  - Sertoli-cell-only syndrome ($\sim 60\%$ of NOA)—germinal cell aplasia
  - Hypospermatogenesis ($\sim 20\%$ of NOA) or germ cell hypoplasia
  - Tubular hypoplasia—possible hypogonadotropic hypogonadism
  - Seminiferous tubule sclerosis
  - Testis cancer

DIFFERENTIAL DIAGNOSIS

See “Associated Conditions”

TREATMENT

GENERAL MEASURES

- The goal is to address the underlying problem to allow natural conception, if possible.
- Female evaluation by a reproductive specialist and coordinated care is crucial for optimal outcomes.

MEDICATION

First Line

- Clomiphene citrate 50 mg every other day: Used for hypoandrogenism. Stimulates GnRH resulting in increased T and spermatogenesis. Less than 10% of men with azoospermia and hypoandrogenism have return of sperm to ejaculate after T normalizes using clomiphene citrate (2)[B]. Note: Exogenous T decreases fertility
- Pseudoephedrine 60 mg 1–2 hr prior to sex: For retrograde ejaculation
- Anastrozole 1 mg daily: Men with abnormal semen parameters and low testosterone to estradiol ratio (<10:1)

Second Line

- hCG and/or recombinant FSH: If hypoandrogenism unsuccessfully treated with clomiphene citrate
- Alternatives for retrograde ejaculation: Imipramine 25 mg, ephedrine 25 mg

SURGERY/OTHER PROCEDURES

- MicroTESE: Performed for NOA, superior to other sperm-retrieval techniques with 20–30% improvement in yield up to 67%
- Vasectomy reversal: Time since vasectomy is the best predictor of success (3)[B]
- MicroTESE, vasovasostomy, or vasoepididymostomy should be performed by microsurgical specialist
- OA, if patient does not desire reconstruction or it is not possible: TESE, testicular sperm aspiration (TESA), percutaneous or microsurgical epididymal sperm aspiration (PESA or MESA)
- Varicocelectomy: Recommended for men with infertility, palpable varicocele, abnormal semen parameters, elevated FSH, and female partner with normal/potentially correctable infertility (4)[A]
- Transurethral resection of ejaculatory ducts: For EDO
- Neurostimulatory ejaculation: Men with spinal cord injury may be able to retrieve sperm via ejaculate with penile vibratory stimulation or, electroejaculation or via microTESE

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Assisted Reproductive Technologies (ARTs), Intrauterine insemination (IUI), In Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI)

Complementary & Alternative Therapies

Coenzyme Q10 is used

ONGOING CARE

PROGNOSIS

- Pregnancy rates are highly dependent on the age of the female partner
- MicroTESE for NOA: 67% sperm-retrieval rate
- IUI: ~15% pregnancy rate per cycle

- IVF: ~30% pregnancy rate per cycle
- IVF with ICSI: ~35–45% pregnancy/per cycle

COMPLICATIONS
- Scrotal surgery: Hematoma, bruising, pain
- ART: Multiple gestations, passing genetic defects to offspring

FOLLOW-UP

Patient Monitoring

Spermatogenesis takes approximately 64 days; semen analysis 3 mo after starting treatment

Patient Resources
- UrologyCare Foundation http://www.urologyhealth.org/urology/index.cfm?article=102
- Maledoc.com

REFERENCES

1. Schoor RA, Elhanbly S, Niederberger CS, et al. The role of testicular biopsy in the modern management of male infertility. *J Urol.* 2002;167:197–200.
2. Hussein A, Ozgok Y, Ross L, et al. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: A multicentre study. *BJU Int.* 2013;111(3 Pt B):E110–E114.
3. Belker AM, Thomas AJ Jr, Fuchs EF, et al. Results of 1469 microsurgical vasectomy reversals by the vasovasotomy study group. *J Urol.* 1991;145:505–511.
4. Agarwal A, Deepinder F, Cocuzza M, et al. Efficacy of varicocelectomy in improving semen parameters: New meta-analytical approach. *Urology.* 2007;70:532–538.

ADDITIONAL READING

Lipshultz LI, Howards SS, Niederberger CS. *Infertility in the Male.* 4th ed. New York, NY: Cambridge University Press; 2009.

See Also (Topic, Algorithm, Media)
- Assisted Reproductive Techniques (ARTs)
- Azoospermia, Oligospermia
- Ejaculatory Disturbances
- Infertility, Urologic Considerations Image
- Semen Analysis, Abnormal Findings, and Terminology
- Semen Analysis, Technique, and Normal Values
- Varicocele

CODES

ICD9
- 606.1 Oligospermia
- 606.8 Infertility due to extratesticular causes
- 606.9 Male infertility, unspecified

ICD10
- N46.029 Azoospermia due to other extratesticular causes

- N46.129 Oligospermia due to other extratesticular causes
- N46.9 Male infertility, unspecified

CLINICAL/SURGICAL PEARLS

Testis biopsy is rarely indicated in the evaluation of male infertility.

INTERSTITIAL CYSTITIS (IC)/PAINFUL BLADDER SYNDROME (PBS)

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BASICS

DESCRIPTION

- Interstitial cystitis (IC) or Painful Bladder Syndrome (PBS) is an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the bladder, associated with lower urinary tract symptoms (LUTS) for more than 6 wk duration, and in the absence of other identifiable causes (1,2)
- 92% of patients also complain of frequency (>10–12× daily); nocturia is common
- 84% complain of constant/persistent urgency
- Dysuria is uncommon
- Symptoms can be associated with a wide range of diseases (see "Differential Diagnosis")
- Two forms of IC/BPS:
  - "Classic": Associated with Hunner lesions on cystoscopy (formerly known as Hunner ulcer)
  - "Nonclassic": No inflammatory lesions identified upon cystoscopy
- Nomenclature change from IC to IC/PBS due to the lack of gross inflammatory bladder wall changes found in most patients
- Median age of onset 30–40 yr
- Female: Male ~ 5:1
- 5–10% of patients have Hunner lesions

EPIDEMIOLOGY (3)

Incidence and prevalence vary widely

Incidence

0.6–1.6 per 100,000 people

Prevalence

Ranges from 1.6 to 2,600 per 100,000 people

RISK FACTORS

No known risk factors beyond a possible genetic predisposition

Genetics

Adult female 1st-degree relatives of IC patients have a prevalence 17× greater than that of the general population

PATHOPHYSIOLOGY

- Multifactorial etiology with a number of proposed mechanisms
  - Epithelial permeability
  - Antiproliferative factor

  - Mast cell activation
  - Neurogenic inflammation
  - Infectious
  - Autoimmunity
  - Urinary abnormality: Toxic, allergic, immunologic

ASSOCIATED CONDITIONS

- Myalgia of pelvic floor: Most commonly identified comorbid condition
- Irritable bowel syndrome
- Fibromyalgia
- Chronic fatigue syndrome
- Multiple allergies
- Sjögren syndrome
- Chronic headaches
- Depression/anxiety/panic disorder
- In females: Vulvodynia, endometriosis
- In males: Chronic prostatitis/chronic pelvic pain syndrome, BPH, prostate cancer

GENERAL PREVENTION

No definitive prevention strategies, although dietary changes and medical therapy may mitigate symptom flares

DIAGNOSIS

HISTORY

- IC patients 10× more likely to have childhood bladder problems
- Symptoms unrelated to any identifiable cause (infection, STD, cancer, radiation, overactive bladder (OAB), diverticula, vaginitis, stones)
- Chronic pelvic pain, pressure
- Abdominal/supra-pubic pain
- Pain associated with bladder filling and/or emptying
- Premenstrual flares
- Urinary frequency, urgency, nocturia
- Urinary frequency based upon need to decrease level of pelvic discomfort/pain
- Helpful evaluation/monitoring tools:
  - Symptom evaluation with voiding diary
  - O'Leary-Sant Symptom and Problem Score
  - Visual analog scale (pain score)
  - PUF (Pelvic Pain & Urgency/Frequency) Questionnaire
  - Bladder Pain/Interstitial Cystitis Symptom Score

PHYSICAL EXAM

- General:
  - Abdominal exam to assess for supra-pubic tenderness
  - Focused neurologic exam
- Females:
  - Q-tip test to assess for vulvodynia

  - Bimanual exam with palpation of bladder, urethra, and pelvic floor muscles to assess presence of muscle tenderness/banding
- Males:
  - Digital rectal exam with palpation of prostate and pelvic floor musculature
  - External genitalia exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture
- Urine cytology in high-risk groups

Imaging

No recommended imaging for the diagnosis of IC/PBS

Diagnostic Procedures/Surgery

- Urodynamics:
  - Normal detrusor function on cystometry; may have increased sensitivity (pain) on filling and decreased capacity.
  - Late stages of "classic" IC/PBS may be associated with significant decrease in capacity and bladder compliance
- Cystoscopy:
  - Used selectively to exclude other bladder pathology and identify Hunner lesions
- Cystoscopy with hydrodistention under general/spinal anesthesia:
  - Findings may include: Glomerulations (small foci of hemorrhage), Hunner lesions, decreased anesthetic capacity, mucosal tears; low sensitivity and specificity
  - Hunner lesion (ulcer) is described as circumscript, reddened area with small vessels radiating toward a central scar. Fibrin deposit/coagulum can be attached to this area. With bladder distention the site ruptures with petechial blood oozing from the lesion and mucosal margins (5)
- Potassium sensitivity testing (KCl test):
  - Low sensitivity and specificity; positive result provokes pain
- Residual urine/flow in males

Pathologic Findings

- Histologic findings can vary widely and none are truly pathognomonic
- Bladder biopsy
  - Indicated only to rule out other disease processes
  - Hunner lesions demonstrate pan-mural inflammation

DIFFERENTIAL DIAGNOSIS

- Bacterial cystitis
- Bladder cancer (including CIS)
- Bladder effects of chemotherapy
- Bladder outlet obstruction/urinary retention
- Bladder/lower ureteral stone
- Genital herpes
- Overactive bladder

- Pelvic floor muscle dysfunction
- Pudendal nerve entrapment
- Radiation cystitis
- Females:
  - Cervical/uterine/ovarian cancer
  - Urethral diverticulum
  - Pelvic organ prolapse
  - Endometriosis
  - Vaginal candidiasis
- Males: BPH, prostate cancer, prostatitis

TREATMENT

GENERAL MEASURES

(Adapted from AUA guidelines 2011) (6)

- Patients should be aware that no single treatment has been found effective
- 1st line
  - Stress reduction
  - Exercise
  - Warm baths
  - Stool softeners
  - Biofeedback
  - Avoidance of spicy foods, caffeine, alcohol, artificial sweetener, acidic beverages
- 2nd line
  - Pelvic floor physical therapy/massage
  - Multimodal pain management
  - Amitriptyline
  - Cimetidine
  - Hydroxyzine
  - Pentosan polysulfate
  - Intravesical instillation: Author's preferred "cocktail": Lidocaine, gentamicin, heparin, triamcinolone
  - Intravesical: 50% DMSO
  - Intravesical: 4% alkalinized lidocaine
- 3rd line
  - Cystoscopy with hydrodistention (low pressure/short duration)
  - Fulguration of Hunner lesions
  - Submucosal injection of Hunner lesions with triamcinolone
- 4th line
  - Neuromodulation (InterStim, etc.)
- 5th line
  - Cyclosporine A
  - Intradetrusor botulinum toxin A
- 6th line
  - Urinary diversion +/– cystectomy: May eliminate urinary frequency but does not

necessarily eliminate the pain component

MEDICATION

First Line

See above

Second Line

See Above

SURGERY/OTHER PROCEDURES

See above

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

See General Measures

Complementary & Alternative Therapies

See General Measures; myofascial physical therapy may help (4)

ONGOING CARE

PROGNOSIS

Spontaneous remission rate of 50% at mean of 8 mo

COMPLICATIONS

N/A

FOLLOW-UP

Patient Monitoring

Follow symptoms

Patient Resources

Interstitial Cystitis Association http://www.ichelp.org/

REFERENCES

1. Hanno P, Lin AT, Nordling J, et al. Bladder pain syndrome. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence*. Paris, France: Health Publication Ltd; 2009. pp. 1459–518.
2. Van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/ interstitial cystitis: An ESSIC proposal. *Eur Urol*. 2008;53:60–67.
3. Suskind AM, Berry SH, Ewing BA, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial Cystitis Epidemiology male study. *J Urol*. 2013;189(1):141–145.
4. FitzGerald MP, Payne CK, Lukacz ES, et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome

and pelvic floor tenderness. *J Urol*. 2012;187(6):2113–2118.
5. Hillelsohn J, Rais-Bahrami S, Friedlander JI, et al. Fulguration for Hunner ulcers: Long term clinical outcomes. *J Urol*. 2012;188(6):2238–2241.
6. Hanno P, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol*. 2011;185(6):2162–2170.

ADDITIONAL READING

- Friedlander JI, Shorter B, Moldwin RM. Diet and its role in interstitial cystitis/bladder pain syndrome and comorbid conditions. *BJU Int*. 2012;109(11):1584–1591.
- The Interstitial Cystitis Survival Guide: Your guide to the latest treatment options and coping strategies. Moldwin RM. New Harbinger Publications, Oakland CA, Oct 2000.
- Understanding the IC/PBS Diet. Beyer J, Gordon B, Laumann B, Osborne J, Shorter B. ichelp.org.

See Also (Topic, Algorithm, Media)

- Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) Image
- Lower Urinary Tract Symptoms (LUTS)
- Pelvic Pain, Female
- Pelvic Pain, Male
- Prostatitis, General

CODES

ICD9

- 595.1 Chronic interstitial cystitis
- 599.70 Hematuria, unspecified
- 788.41 Urinary frequency

ICD10

- N30.10 Interstitial cystitis (chronic) without hematuria
- N30.11 Interstitial cystitis (chronic) with hematuria
- R35.0 Frequency of micturition

CLINICAL/SURGICAL PEARLS

- IC/PBS is more common in women than in men.
- This is primarily a clinical diagnosis based upon the presence of characteristic symptoms and the exclusion of other causes.

LATEX ALLERGY, UROLOGIC CONSIDERATIONS

Ahmad H. Bani-Hani, MD, FAAP, FACS

BASICS

DESCRIPTION

- Localized or systemic reaction to latex, a natural substance from the sap of the rubber tree, *Hevea brasiliensis* (1)[A].
- Latex is a common ingredient in many medical and dental products (eg, bladder catheters, blood pressure cuffs, face mask, gloves, endotracheal tubes, IV infusion sets, etc.)
- Patients with spina bifida or congenital urogenital abnormalities have the highest risk.
- Mild forms include pruritus and swelling. The most severe form of allergic reaction is anaphylaxis: A severe, life-threatening, generalized or systemic hypersensitivity reaction characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes.

ALERT

All patients with neurogenic bladder should be considered for latex precautions.

EPIDEMIOLOGY

Incidence

- Latex sensitivity (assessed by serum latex IgE or skin prick test) in the general population is <1%
  - Spina bifida population is 18–72%
- Latex allergy (eg, anaphylactic symptoms) is rare in healthy population.
- Healthcare community: Up to 12.1% which fell to 4% with the introduction of powder-free gloves
- Exposure to multiple surgeries: 1/3–2/3 of children who underwent surgeries in the 1990s developed latex sensitivity; this risk decreased dramatically since the implementation of latex avoidance in hospitals and products

Prevalence

N/A

RISK FACTORS

- Occupational exposure:
  - Healthcare
  - Food handlers/restaurant workers
  - Hairdressers
  - Construction workers
  - Painters
  - First responders
  - Security personal
  - Gardeners
- Atopic disease

- People with food allergies mainly to kiwi, strawberry, banana, avocado, chestnut
- Multiple surgeries at young age
- Children with anorectal or urologic malformations (5)[A].
  - Spinal dysraphism
  - Bladder exstrophy/cloacal anomalies
  - Patients on clean intermittent catheterization

Genetics

- Genetic factor might be indicated.
- Latex allergy is less frequent in adults with spinal cord injury and multiple surgical procedures than in children with similar conditions.
- Interleukin-13 (IL-13) and IL-18 promoter polymorphisms more likely to be found in healthcare workers in comparison to nonatopic controls or patients with anorectal/urologic malformations.

PATHOPHYSIOLOGY

- Presensitization with Hevea latex allergens is prerequisite to initiate an allergic response.
- A number of proteins found in the cytoplasm of *H. brasiliensis* are known potent allergens that can elicit human IgE antibody, leading to sensitization in exposed patients and a spectrum of allergic reactions upon subsequent exposure (4)[A].
- Symptoms of delayed (type IV) hypersensitivity usually develop within 1–2 days of exposure. Immediate (type I) hypersensitivity causes symptoms within minutes of exposure.
- Immediate hypersensitivity reactions to latex (type I) are caused by cross-linking of latex protein-specific IgE antibody with mast cells and basophils.
- Cross-reactivity between various proteins is responsible for the clinical associations between latex allergy and allergic responses to a number of fruits and vegetables.
- Type IVc (T-cell–mediated type), delayed hypersensitivity reaction can occur and usually manifest as contact dermatitis 24–96 hr after exposure.

GENERAL PREVENTION

- Facility:
  - Avoidance is the most effective and least expensive method.
  - Establishment of a latex-safe environment should be a priority for institutions by replacing all Hevea latex–containing products with non–Hevea-based synthetic products or powder-free latex products.
  - Synthetic alternatives to rubber include butyl rubber, a petroleum-based product with no allergenic protein, neoprene, and copolymers of butadiene and acrylonitrile.
  - Non-Hevea source of natural rubber is the guayule plant (Yulex). Yulex-based products pose no risk to individuals allergic to Hevea latex and is approved by the Food and Drug Administration (FDA).
- Individuals with latex allergy:
  - Should wear a medical alert bracelet indicating latex allergy
  - Should be encouraged to have self-injectable epinephrine if they have a clinical history of systemic reaction to latex
  - Should avoid latex-containing products
  - Should report their allergies prior to any medical or surgical procedure

DIAGNOSIS

HISTORY

- Detailed clinical history of allergic reactions that are temporarily associated with exposure to Hevea latex–containing products (eg, prior history to anaphylaxis and/or intraoperative shock, itching, redness, or swelling following dental, rectal, or pelvic exam; itching or swelling with condoms, diaphragms, or latex sexual aids)
- Detailed history of associated risk factors: Healthcare workers, hair dressers, rubber handling, eczema/hay fever, multiple surgeries, food allergies, etc.
- 30–80% of patients with latex allergy also have food allergy
- Allergic symptoms can include the following symptoms:
  - Dizziness
  - Dyspnea
  - Pruritus
  - Rhinitis
  - Tearing
  - Swelling at the site of contact
  - Abdominal cramps
- In the most extreme cases, anaphylaxis can develop

ALERT
Use caution when examining any child for dysfunctional voiding especially if the child has neurologic symptoms or suspected spina bifida.

PHYSICAL EXAM

- Use nonlatex exam gloves
  - Mucocutaneous manifestations:
    - Erythema
    - Edema
    - Papules, macules, urticaria
    - Allergic rhinitis
    - Allergic conjunctivitis
    - Angioedema
  - Cardiopulmonary manifestations:
    - Tachypnea
    - Stridor, wheezing
    - Tachycardia
    - Hypotension
    - Shock

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Routine resuscitation lab studies (blood gas, etc.) if during acute anaphylaxis

Imaging

N/A

Diagnostic Procedures/Surgery

- These are performed on a routine basis and not during an acute event
- Prick skin test:
  - Extracts of Hevea latex, at least 3
  - Commercial extracts are available
  - Test involves performing a puncture with a lancet device through a drop of latex extract at sequential concentrations ranging from 0.001–1 mg/mL of protein
  - Results are read after 15 min and compared with the positive histamine and negative saline controls
  - Small risk of anaphylaxis
- Serology:
  - An alternative test for confirming sensitization when commercial skin test reagents are not available
  - Involves measuring serum Hevea latex–specific IgE antibodies
  - Diagnostic sensitivity and specificity: 80% and >95%, respectively

Pathologic Findings

- Biopsy of skin lesions (type IV hypersensitivity):
  - Perivascular cuffing of CD4 cells identified using anti-CD4 antibody staining
  - Vesicular dermatitis with dermal and epidermal mononuclear infiltrates

DIFFERENTIAL DIAGNOSIS

- Systemic allergic reaction to another allergen, including medications or food products.
- Mild allergic manifestations:
  - Allergic rhinitis
  - Asthma
  - Atopic dermatitis (ie, eczema)
  - Conjunctivitis
  - Contact dermatitis to other allergens (ie, nickel products)
- Severe life-threatening manifestations:
  - Anaphylactic shock
  - Cardiogenic shock
  - Septic shock
  - Hypovolemic shock

TREATMENT

GENERAL MEASURES

- Latex avoidance is by far the most-effective method of prevention (2,3)[A].
- Institutional policy changes in the use of Hevea products are needed to reduce occupational and patient exposure.
- Always seek the use of nonlatex alternative products (eg, silicone urethral catheters)
- Synthetic and Yulex, non-Hevea rubber, are safe alternatives in Hevea-sensitized individuals.
- Additional measures recommended for patients with latex allergy include carrying nonlatex gloves, wearing medical alert bracelets, and having auto-injectable epinephrine available.
- For acute anaphylaxis, standard shock management.

MEDICATION

First Line

- For the management of anaphylaxis
  - Remove latex source
  - Basic life support principles (Airway, Circulation, Breathing)
  - Injectable epinephrine in severe anaphylaxis
    - 0.3–0.5 mL of a 1:1000 solution IM (adult)
    - 0.15–0.3 mL of a 1:000 solution IM (children)
  - Epinephrine autoinjectors:
    - EpiPen, Adrenaclick (0.3 mg) in adults
    - EpiPen Jr., Adrenaclick (0.15 mg) in children
- Supportive medications cannot be substituted for epinephrine in the emergent management of anaphylaxis because they do not prevent or relieve respiratory failure or shock, but can be useful after initial resuscitation
  - Antihistamines (diphenhydramine)
  - Bronchodilators (albuterol)
  - Steroids (hydrocortisone)
  - H_2 blockers (ranitidine)

Second Line

N/A

SURGERY/OTHER PROCEDURES

N/A

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Most healthcare facilities have banned latex helium–filled balloons and are striving to become latex-free.
- There is no desensitization available, but several including sublingual and other immunotherapies are under study.

ONGOING CARE

PROGNOSIS

- Depends on severity of symptoms and timely identification of responsible agents.
- High index of suspicion and immediate treatment are essential to good outcome.
- Individuals with severe latex allergy should be provided with epinephrine autoinjections.
- Patients with type I hypersensitivity: Risk of fatal anaphylaxis and/or respiratory compromise

COMPLICATIONS

- Death can result from anaphylactic shock
- Secondary bacterial wound infections in cases of severe contact dermatitis

FOLLOW-UP

Patient Monitoring

- Some patients experience a biphasic or late stage reaction several hours after the initial anaphylactic event. Patients should be observed for at least 4 hr after the initial event.
- Avoidance should extend outside of the hospital to items such as latex balloons, rubber bands, toys, etc.
- Inpatient admission may be necessary until cardiopulmonary risk is reduced.
- Allergy identification band, “MedicAlert" bracelet
- Avoid foods with latex cross-reactivity:
  – Banana, kiwi, chestnut, avocado

Patient Resources

- http://www.latexallergyresources.org/
- http://www.aaaai.org/conditions-and-treatments/allergies/latex-allergy.aspx
- http://www.nlm.nih.gov/medlineplus/latexallergy.html

REFERENCES

1. Bernstein DI. Management of natural rubber latex allergy. *J Allergy Clin Immunol*. 2002;110:S111–S116.
2. Blumchen K, Bayer P, Buck D, et al. Effects of latex avoidance on latex sensitization, atopy and allergic diseases in patients with spina bifida. *Allergy*. 2010;65:1585–1593.
3. Cusik C. A latex-safe environment is in everyone’s best interest. *Mater Manag Health Care*. 2007;16:24–26.
4. Accetta D, Kelly KJ. Recognition and management of the latex-allergic patient in the ambulatory plastic surgerical suite. *Aesthet Surg J*. 2011;31:560–565.
5. Brown RH, Hamilton RG, McAllister MA; Johns Hopkins Latex Task Force. How health care organizations can establish and conduct a program for latex-safe environment. *Jt Comm J Qual Saf*. 2003;29:113–123.

ADDITIONAL READING

- Bernardini R, Novembre E, Lombardi E, et al. Prevalence of and risk factors for latex sensitization in patients with spina bifida. *J Urol*. 1998;160:1775–1778.
- Reddy S. Latex allergy. *Am Fam Physician*. 1998;57(1):93–100.

See Also (Topic, Algorithm, Media)

Myelodysplasia (Spinal Dysraphism), Urologic Considerations

CODES

ICD9

- 596.54 Neurogenic bladder NOS
- 753.9 Unspecified anomaly of urinary system
- V15.07 Allergy to latex

ICD10

- N31.9 Neuromuscular dysfunction of bladder, unspecified
- Q64.9 Congenital malformation of urinary system, unspecified
- Z91.040 Latex allergy status

CLINICAL/SURGICAL PEARLS

- Natural rubber latex allergy is caused by sensitization to proteins found in *H. brasiliensis*, the rubber tree.
- The highest prevalence of latex allergy (up to 68%) is in patients with spina bifida or congenital urogenital abnormalities.
- The mainstay of management of latex allergy is avoidance of latex products as there is no cure for latex allergy.

LIBIDO, DIMINISHED, FEMALE

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Sandip P. Vasavada, MD, FACS

BASICS

DESCRIPTION

- Diminished libido, low sexual drive, or hyposexuality are defined by a lack of desire for sexual activity.
- Hypoactive sexual desire disorder or subjective sexual arousal disorder may be implicated.

EPIDEMIOLOGY

Incidence

- More common with advancing age and especially following menopause
- A congenital syndrome may be causative at a young age.

Prevalence

Estimated prevalence of 25–75% of women varies by study sample and assessment

RISK FACTORS (1)

- Low testosterone (physiologic or iatrogenic)
- Advanced age
- Menopause (physiologic or iatrogenic)
- Pelvic floor disorder (incontinence or prolapse)
- Physical or psychological trauma (sexual assault, physical abuse, or verbal abuse)
- Pregnancy (multifactorial per hormonal, emotional, and physical changes)

Genetics

Early onset menopause may be implicated

PATHOPHYSIOLOGY (2,3)

- Testosterone drops 50% from age 30 to 60 years and is linked to low libido as are other androgens.
- Estrogen can increase sex hormone–binding globulin concentrations and lower free testosterone.
- Progesterone may lower mood and decrease sex drive as seen with some contraceptives.
- Follicle-stimulating and luteinizing hormone reduction by contraceptives lowers androgen creation.
- Serotonin level alterations from certain antidepressants can decrease sex drive.

ASSOCIATED CONDITIONS

- Vaginal atrophy
- Congenital syndromes
- Posttraumatic stress disorder (prior physical or psychological trauma)

GENERAL PREVENTION

Exercise, balanced diet, healthy lifestyle

DIAGNOSIS

HISTORY

- Details of low libido
  - Acquired or lifelong problem
  - Always or intermittently present
  - With only specific sexual partners
  - After a new diagnosis or procedure
  - Following use of a new medication
  - Association with life events
- Reproductive information
  - Age of menarche or onset of menses
  - Pregnancies and deliveries
  - Contraception use and type
  - Infertility and treatment
- Other sexual information
  - Sexually transmitted infection
  - Pain or discomfort with sexual activity
  - Problems with sexual function of the partner
- Current or prior abuse
  - Sexual
  - Verbal or physical
- Symptoms of androgen insufficiency
  - Dysphoria, fatigue, low sense of well-being
  - Reduced sexual receptivity and pleasure
  - Decreased vaginal lubrication despite estrogen treatment
- Signs of androgen insufficiency
  - Bone loss, decreased muscle mass, less strength
  - Memory changes and altered cognitive function
- Other endocrine disorders
  - Hypothyroidism
  - Cushing syndrome
  - Diabetes
- Urogenital conditions
  - Urinary incontinence or fecal incontinence
  - Pelvic organ prolapse
- Medications
  - Oral contraceptives, estrogens, progestins, gonadotropin-releasing hormone agonists
  - Antidepressants, amphetamines, anticonvulsants, antiepileptics, psychotropics
  - Antihypertensives, antilipidemics, antiarrhythmics
  - Steroids, narcotics
- Chronic medical conditions
  - Psychiatric conditions
  - Substance abuse

PHYSICAL EXAM

- Assessment of nongenital sexual characteristics
  - Breast development
  - Axillary hair
- Signs of endocrinologic disorder
  - Cushingoid appearance
  - Hypothyroid skin and hair changes
  - Diabetic neuropathy
- Visual inspection of the external genitalia
  - Distribution of pubic hair
  - Ulcerations, pustules, discharge, or bleeding
  - Prolapsed urethra, vagina, or cervix
- Speculum exam
  - Mucosal rugae, moisture, thinning, or excoriation
  - Ulcerations, pustules, discharge, or bleeding
  - Cystocele, rectocele, or enterocele
  - Vaginal wall masses
- Palpation of the external genitalia, vaginal sidewalls, pelvic floor muscles, cervix, and ovaries
  - Urethral or vaginal sidewall masses
  - Surgically placed foreign bodies
  - Pelvic floor muscle tension, spasm, or tenderness
  - Cervical motion, ovarian, or adnexal tenderness
  - Vaginal cul-de-sac mass or tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Estrogens: Estradiol and estrone
- Androgens: Dehydroepiandrosterone, androstenedione, testosterone, and dihydrotestosterone
- Proteins: Sex hormone–binding globulin (SHBG) with free testosterone and total testosterone
- Adjunctive: Thyroid-stimulating hormone, glycosylated hemoglobin

Imaging

Brain magnetic resonance imaging to assess the hypothalamus and pituitary gland

DIFFERENTIAL DIAGNOSIS

- Hormonal
  - Decreased free testosterone or increased sex hormone–binding globulin
  - Decreased androgen
  - Hypogonadotropic hypogonadism
  - Adrenal insufficiency or adrenal suppression
  - Adrenal suppression or glucocorticoid excess
  - Hypothyroidism or hyperthyroidism
- Psychological
  - Hypoactive sexual desire disorder, subjective sexual arousal disorder, sexual aversion disorder

  – Sexual dysfunction in a partner
• Iatrogenic
  – Medication side effect
• Gynecologic
  – Dyspareunia, pelvic organ prolapse, sexually transmitted infection
• Urologic
  – Urinary incontinence
• Colorectal
  – Fecal incontinence
• Congenital syndrome

TREATMENT

GENERAL MEASURES (1)

• Behavioral
  – Identify and eliminate any libido-reducing behaviors, habits, or addictions
  – Psychological counseling, couples therapy, or sex therapy as indicated
  – Encourage a healthy lifestyle with balanced diet, exercise, work, and sleep

MEDICATION

First Line

• Testosterone alone or in combination has been used off-label to increase drive
  – Postmenopausal women with decreased libido who are not receiving estrogen therapy have modest success using an experimental testosterone patch delivering 300 µg/d testosterone
• If possible elimination or replacement of medications that may reduce libido
• Adjunctive treatment of vaginal atrophy with topical estrogen can be helpful
• Also consider appropriate goal-directed treatment of other medical conditions

Second Line

N/A

SURGERY/OTHER PROCEDURES

Appropriate treatment of possibly causative medical (ie, endocrine tumor) conditions

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

• Results vary with etiology and treatment for many is long-term

- Multimodal approach to any etiology should be most beneficial

COMPLICATIONS

Loss of libido can result in depression, infertility

FOLLOW-UP

Patient Monitoring

- Frequent follow-up with initiation of new therapy is best with regular lab work if hormones are used.
- If using testosterone, monitor for signs of testosterone excess (acne, hirsutism, male pattern baldness, hyperlipidemia)

Patient Resources

N/A

REFERENCES

1. Maclaran K, Panay N. Managing low sexual desire in women.*Womens Health*. 2011;7(5):571–581.
2. Brotto LA, Petkau AJ, Labrie F, et al. Predictors of sexual desire disorders in women. *J Sex Med*. 2011;8(3):742–753.
3. Clayton AH. The pathophysiology of hypoactive sexual desire disorder in women. *Int J Gynaecol Obstet*. 2010;110(1): 7–11.

ADDITIONAL READING

McDougal WS, Wein AJ, Kavoussi LR, et al. Female Sexual Function and Dysfunction. In: Moore CK, ed. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier; 2012:823–833.

See Also (Topic, Algorithm, Media)

- Dyspareunia
- Female Hypoactive Sexual Desire Disorder
- Urinary Incontinence
- Vaginal Atrophy

CODES

ICD9

- 799.81 Decreased libido
- 627.2 Symptomatic menopausal or female climacteric states
- 302.71 Hypoactive sexual desire disorder

ICD10

- F52.0 Hypoactive sexual desire disorder
- N95.1 Menopausal and female climacteric states
- R68.82 Decreased libido

CLINICAL/SURGICAL PEARLS

- A good social history is essential.

- Sexual dysfunction in partners can cause this.
- Overall physical health helps maintain libido.

LIBIDO, DIMINISHED, MALE

Daniel Box, MD
Anish K. Shah, MD

BASICS

DESCRIPTION

- Diminished libido (hyposexuality) is the lack of desire to engage in sexual experience.
- Hypoactive sexual desire disorder is characterized by reduced libido and interest in sexual activity causing distress in women.
- This section primarily focuses on decreased libido in men.

EPIDEMIOLOGY

Incidence

- 10–15% of men
- 20–25% of women

Prevalence

N/A

RISK FACTORS

- Therapy for prostate cancer
- Congenital absence of the testicles
- Inflammatory insults to the testicles
- Surgical injury or removal of the testicles
- Metabolic syndrome

Genetics

- Loss of libido may be associated with some of the genetic disorders/syndromes, listed below:
  - 17α-Hydroxylase deficiency
  - Autoimmune polyendocrine syndrome
  - Klinefelter syndrome
  - Inactivation of the luteinizing hormone (LH)-receptor gene
  - Mutations of steroid 5α-reductase gene

PATHOPHYSIOLOGY

- Psychological causes of diminished libido
  - Libido (sexual drive) is mediated by the cerebral cortex.
  - Psychological disturbances of all degrees, from anxiety to major psychiatric disorders
  - May be secondary to medical conditions (ie, congenital anomaly, disfiguring injury, etc.)
  - Erectile dysfunction may cause loss of libido
- Hormonal causes of diminished libido
  - Hypogonadism: Androgen deficiency, particularly testosterone, whether primary (testicular defect) or secondary to hypothalamic–pituitary dysfunction, Cushings syndrome
  - Hyperprolactinemia with or without pituitary lesion (1)[B]
  - Thyroid: Both hyper- and hypothyroidism can lead to diminished sexual desire

- Drugs: β-blockers, clonidine, diuretics, lithium, major tranquilizers, methyldopa, sedatives, ketoconazole, α-blockers, dihydrotestosterone inhibitors, cimetidine, antiandrogens, androgen analogs, selective serotonin reuptake inhibitors
- Temporal lobe epilepsy
- Prostatitis
- Chronic and serious diseases can lead to loss of libido through psychological or physiologic effects

ASSOCIATED CONDITIONS

- Erectile dysfunction (ED) and infertility may be associated with loss of libido and vice versa (2)[B].
- Hypothyroidism
- Alcoholism
- Syndromes, listed above in the Genetics section

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Sexual history:
  - Frequency and level of sexual desire
  - Difficulty in achieving or maintaining an erection
  - Evidence of ejaculation disorder, overall satisfaction with sexual life
  - If semen volume is normal, it is unlikely that endocrine factors are responsible for loss of libido
  - Sexual Health Inventory of Men (SHIM) score
- History of psychiatric illness
- Symptoms to suggest decreased testosterone: ED, increased irritability or depression, fatigue, reduced muscle mass and strength, inability to concentrate, decreased bone density/osteoporosis
- Previous/current medication
- History of endocrine disorder
- Therapy for prostate cancer
- Chronic alcoholism may result in decreased serum testosterone, testicular atrophy, and decreased libido.

PHYSICAL EXAM

- Assessment of secondary sexual characteristics.
  - Absence of secondary sexual characteristics suggests hormonal etiology.
- Detailed exam of external genitalia for abnormalities
- Assessment of testicular volume and atrophy

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum testosterone

- Serum prolactin
- If any disturbances of the above, then serum follicle-stimulating hormone and LH
- Serum-free T4 and TSH
- Serum GH and IGF-1 (primarily in children)
- Evlauation for increased cortisol if Cushing's is suspected

Imaging

MRI of the brain if prolactin is elevated

DIFFERENTIAL DIAGNOSIS

- Psychiatric disturbances
- Hormonal disturbances
- Drug induced
- Chronic and serious diseases

TREATMENT

GENERAL MEASURES

- Determine the cause and correct, if possible.
- Identify potential medications causing libido issues.
- Psychiatric consultation/sexual function therapist
- Endocrinology consultation

MEDICATION

First Line

- Decreased testosterone (3)[B]
  - Hormonal supplementation. For replacement dosing, see chapter on "Testosterone, decreased (hypogonadism)."
- Patients interested in sustaining fertility: Avoid exogenous testosterone; stimulate with human chorionic gonadotropin.
- If sexual dysfunction is identified as the cause: Phosphodiesterase inhibitors (sildenafil, tadalafil, etc.) are potentially useful 1st-line therapies
- Bromocriptine for prolactin-secreting tumors

Second Line

N/A

SURGERY/OTHER PROCEDURES

Only useful for pituitary adenomas causing hyperprolactinemia or in cases of Cushing's disease

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

L-arginine and yohimbine are touted but not proven

ONGOING CARE

PROGNOSIS

The prognosis is good when there is a treatable underlying cause for loss of libido. Otherwise it can be permanent.

COMPLICATIONS

Loss of libido can result in depression, infertility, and erectile dysfunction.

FOLLOW-UP

Patient Monitoring

Men treated with androgens should be followed closely with digital rectal exam and prostate-specific antigen every 6 mo

Patient Resources

- http://www.merckmanuals.com/home/mens_health_issues/sexual_dysfunction_in_men/decre
- http://men.webmd.com/mens-libido-directory

REFERENCES

1. Shimon I, Benbassat C. Male prolactinomas presenting with normal testosterone levels. *Pituitary*. 2014;17(3):246–250.
2. Malavige LS, Jayaratne SD, Kathriarachchi ST, et al. Erectile Dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. *J Sex Med*. 2008;5(9):2125–2134.
3. Aydogan U, Aydogdu A, Akbulut H, et al. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy. *Endocr J*. 2012;59(12):1099–1105.

ADDITIONAL READING

- Carey JC. Pharmacological effects of sexual function. *Obstet Gynecol Clin North Am*. 2006;33(4):599–620.
- Swerdloff R, Wang C, Goldman. *Cecil Medicine*. 23rd ed. Philadelphia, PA: WB Saunders; 2007.
- Wilson B. The effect of drugs on male sexual function and fertility. *Nurse Pract*. 1991;16(9):12–17, 21–24.

See Also (Topic, Algorithm, Media)

- Andropause (Late Onset Male Hypogonadism)
- Erectile Dysfunction
- Female Hypoactive Sexual Desire Disorder
- Testosterone, Decreased (Hypogonadism)

CODES

ICD9
- 302.71 Hypoactive sexual desire disorder
- 752.89 Other specified anomalies of genital organs
- 799.81 Decreased libido

ICD10
- F52.0 Hypoactive sexual desire disorder
- Q55.0 Absence and aplasia of testis
- R68.82 Decreased libido

CLINICAL/SURGICAL PEARLS
- Decreased libido can be from a number of causes (medications, hormonal or psychiatric disorders, etc.).
- A thorough history (including sexual history and SHIM score) and physical exam (assessment of secondary sex characteristics and testicular volume) are critical and can often point to a diagnosis.
- It is very important to distinguish decreased libido from other disorders of sexual function (arousal, erectile dysfunction, premature ejaculation, orgasm, and sexual pain disorders) but patients can often have multiple issues simultaneously.
- Surgery is usually designated for pituitary adenomas (ie, prolactinomas), which can be found on brain MRI.

LOWER URINARY TRACT SYMPTOMS

Matthew J. Resnick, MD
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BASICS

DESCRIPTION

- The lower urinary tract infection (LUTS) complex includes both obstructive and storage urinary symptoms.
  - Obstructive urinary symptoms include urinary hesitancy, intermittency, post-void dribbling, and straining to void.
  - Storage urinary symptoms include urinary frequency, nocturia, and urinary urgency.
- While benign prostatic hyperplasia (BPH) frequently contributes to the development of LUTS, there are numerous other etiologies that must be considered in patients presenting with new urinary symptoms.
- LUTS may result from structural or functional abnormalities of the genitourinary tract.

EPIDEMIOLOGY

Incidence

- There is a well-described relationship between age and the development of LUTS.
- A few data specifically address the incidence of LUTS, given the basically negligible low case-fatality rate and the often slow onset of symptoms.

Prevalence

- Disease prevalence is highly variable due to differences in disease definition.
- The Olmsted County Study revealed age-dependent increases in the prevalence of moderate-to-severe LUTS from 26% (40–49 yr) to 46% (70–79 yr)
- 21.1% of patients in the National Health and Nutrition Examination Survey (NHANES) reported at least one symptom of LUTS.
- Various community-based studies estimate the age-stratified prevalence of moderate–to-severe LUTS in men as follows:
  - 40–50 yr old: ~20%
  - 50–60 yr old: ~30%
  - 60–70 yr old: ~40%
  - 70–80 yr old: ~50–60%

RISK FACTORS

- Bladder outlet obstruction (BOO; male)
  - Benign prostatic hyperplasia
  - Urethral stricture disease/bladder neck contracture
  - Prostate/bladder cancer
  - Bladder calculi
- BOO (female)
  - Pelvic organ prolapse
  - Bladder calculi

  - Urethral stricture disease
- Bladder (detrusor) hypocontractility
  - Idiopathic
  - Neurogenic
- Obesity, diabetes, and caffeine intake all have been associated with increased risk of LUTS

Genetics
- Increased risk of moderate-to-severe LUTS in men with a family history of BPH.
- The precise contribution of genetic and environmental factors to the development of LUTS remains largely unknown.

PATHOPHYSIOLOGY
- BOO necessitates generation of higher bladder pressures to overcome outlet resistance.
- Bladder "remodeling" secondary to longstanding outlet obstruction results in overactive bladder syndrome, storage symptoms, and over time, decreased contractility.
- LUTS may result from numerous conditions of the central and peripheral nervous systems.
- Result in either detrusor overactivity (storage symptoms) or detrusor hypocontractility (urinary retention/inadequate emptying).

ASSOCIATED CONDITIONS
Erectile dysfunction

GENERAL PREVENTION
NA

DIAGNOSIS

HISTORY
- Essential to quantify LUTS for both diagnosis and treatment planning
  - Use the validated AUA Symptom Score (AUASS) often referred to a the AUA Symptom Index [AUA-SI]) or International Prostate Symptom Score (I-PSS) (1–7 mild; 8–19 moderate; 20–35 severe)
  - Attention should be paid to nature (obstructive/storage) and duration of LUTS
- Consider voiding diary (frequency/volume charts) if the patient is unable to elaborate the nature of his or her symptoms
- Elicit history of prior urinary tract infection or prostatitis
- Elicit history of prior hematuria (gross or microscopic)
- Elicit history of prior urologic/pelvic surgery
  - Prior lower urinary tract intervention predisposes to stricture/bladder neck contracture
  - Disruption of pelvic plexus with pelvic surgery may result in detrusor hypocontractility
- Elicit history of other medical conditions
  - Neurologic disease—overactivity or bladder hypocontractility
  - Diabetes—bladder hypocontractility
  - History of sexually transmitted infection(s)—urethral stricture disease
  - History of pelvic radiation—urethral stricture disease or bladder hypocontractility
- Elicit family history of genitourinary disease (BPH/LUTS, prostate cancer, prostatitis)
- Review medications as certain antihistamines, antimuscarinics, sympathomimetics, and

bronchodilators may exacerbate LUTS.
- Elicit history of sexual dysfunction
- Evaluate overall fitness to undergo invasive procedure(s)

PHYSICAL EXAM
- Abdominal exam to assess suprapubic region for bladder distension
- Focused neurologic exam should be performed with particular attention to:
  - General mental status
  - Ambulatory status
  - Motor and sensory function of the lower extremities and perineum
  - Anal sphincter tone
- In men:
  - Inspection of the urethral meatus should be performed to rule out meatal stenosis
  - Digital rectal exam (DRE) should be performed to evaluate for:
    - Prostatic enlargement
    - Nodularity or firmness suggestive of prostate cancer
    - Bogginess or tenderness suggestive of prostatitis
    - Anal sphincter tone, abnormalities of which suggest neurologic disease
- In women:
  - Speculum exam should be performed to evaluate for mass, prolapse, and urethral abnormalities

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis should be performed to evaluate for urinary tract infection or hematuria.
- Serum PSA should be considered as a diagnostic test (as opposed to a screening test).
- Serum creatinine is not recommended in the evaluation of routine LUTS associated with BPH.

Imaging
- Imaging with CT or ultrasound (US) is not recommended as routine procedure.
- Upper tract imaging with either CT or US may be considered in the context of:
  - Acute symptom onset
  - History of upper urinary tract infection or stone disease
  - History of renal insufficiency
  - Recent onset of nocturnal enuresis
- Prostate imaging with transrectal or transabdominal US may provide information for treatment planning and is considered optional

Diagnostic Procedures/Surgery
- Assessment of post-void residual urine with US imaging or catheterization is optional.
  - May aid in the noninvasive assessment of bladder function
- Assessment of urinary flow rate is optional that may predict response to invasive therapy.
- Pressure flow urodynamic studies are not indicated in the evaluation of the uncomplicated patient with LUTS
  - May be useful in patients with mixed symptoms or neurologic disease to develop a therapeutic strategy

- Cystourethroscopy is not recommended for the uncomplicated patient with LUTS.
  - May be helpful to assess prostate configuration as it relates to invasive therapies
  - May be useful in patients with mixed symptoms or neurologic disease to develop a therapeutic strategy
  - May be useful in patients with a history suggestive of urethral stricture/bladder neck contracture

Pathologic Findings

Histopathology of BPH reveals proliferation of both stromal and glandular prostatic elements.

DIFFERENTIAL DIAGNOSIS

- BOO:
  - Urethral Stricture/bladder neck contracture
  - Bladder stone
  - Cancer (prostate, bladder, urethral)
  - Prostatitis
  - Urinary tract infection
  - Detrusor-sphincter dyssynergia
  - Pelvic organ prolapse
- Detrusor hypocontractility
  - Diabetes mellitus
  - Parkinson disease
  - Multiple sclerosis
  - Radiation cystitis
  - Spinal cord injury
  - Lumbosacral disc disease
  - Bladder stone

TREATMENT

GENERAL MEASURES (1,2)

- Treatment should be offered to men with moderate to severe symptoms (AUASS or IPSS ≥ 8) who are bothered enough to consider therapy.
- Men with demonstrable sequelae of BPH/BOO (renal failure secondary to obstruction, bladder calculi, etc.) should be counseled on benefits of treatment.
- Treatment is tailored to symptom type (obstructive, storage, mixed).

MEDICATION

First Line

- α-Adrenergic blockers: relax prostatic/bladder neck smooth muscle tone and improve symptoms (all appear to have equal effectiveness)
  - Alfuzosin 10 mg/d
  - Doxazosin start 1 mg/d to max. 8 mg
  - Silodosin 8 mg/d
  - Tamsulosin start 0.4 mg to max. 0.8 mg
  - Terazosin start 1 mg/d to max. 20 mg

  - Side effects include syncope, orthostasis, retrograde ejaculation, asthenia, and nasal congestion
- 5α-Reductase inhibitors: reduce prostatic volume
  - Finasteride or dutasteride
  - Side effects include decreased libido and sexual dysfunction
  - Reduce PSA by ~50% and correction should be used when evaluating risk for cancer
- Combination therapy (α-adrenergic blocker + 5α-reductase inhibitor) should be considered in men with moderate to severe symptoms and prostatic enlargement.
- Tadalafil 2.5–5 mg/d can treat combined LUTS and erectile dysfunction (ED).
- Antimuscarinic agents can be used alone or in combination for overactivity/storage symptoms

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Urethroplasty or directly visualized incision of urethral stricture (DVIU) should be considered for stricture/bladder neck contracture
- Prolapse repair should be considered for women with urinary symptoms and prolapse
- Numerous surgical options exist for men with BPH/BOO. Some of these include:
  - Transurethral resection of the prostate (TURP)
  - Transurethral microwave therapy (TUMT)
  - Transurethral laser vaporization of the prostate
  - Transurethral laser enucleation of the prostate
  - Simple open or laparoscopic prostatectomy (generally reserved for men with prostate volume > 80–100 cc)
- There are a few high-quality comparative-effectiveness data upon which clinical decisions can be based
  - Patients and physicians must weigh potential benefits and harms of treatments.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Behavioral interventions including timed voiding, double voiding, and biofeedback may improve symptoms.

Complementary & Alternative Therapies

Saw palmetto is widely used to treat LUTS with little benefit in randomized trials (CAMUS trial) (3).

ONGOING CARE

PROGNOSIS

- 20% of men with untreated LUTS experience progression within 5 yr (MTOPS trial). Options for men with BPH/BOO include:
  - Combination therapy reduces risk of progression by 66% (2).

• 5–10% of men with moderate-to-severe LUTS will require surgical intervention (MTOPS).

COMPLICATIONS

• Complications of BPH/LUTS include:
  – Recurrent UTIs
  – Renal insufficiency
  – Bladder stone formation
  – Urinary retention
  – Secondary bladder dysfunction

FOLLOW-UP

Patient Monitoring

• Monitoring with serial AUASS or IPSS to quantify symptom intensity and bother
• Urinalysis, serum PSA, urinary flow rate, and post-void residual as clinically indicated

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=59&display=1

REFERENCES

1. AUA Guideline on the Management of Benign Prostatic Hyperplasia (BPH). 2012. http://www.auanet.org/content/clinical-practice-guidelines. Accessed November 23, 2013.
2. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387–2398.
3. Barry MJ, Meleth S, Lee JY, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial. *JAMA*. 2011;306:1344–1351.

ADDITIONAL READING

• McNicholas TA, Kirby RS, Lepor H. Evaluation and nonsurgical management of benign prostatic hyperplasia. In: Wein AJ, Kavoussi LR, Novick AC, et al. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2010.
• Roehrborn CG. Benign prostatic hyperplasia: etiology, pathophysiology, epidemiology, and natural history. In: Wein AJ, Kavoussi LR, Novick AC, et al. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2010.

See Also (Topic, Algorithm, Media)

• Bladder Outlet Obstruction (BOO)
• LUTS Algorithm ‡
• Prostate, Benign Hyperplasia/Hypertrophy (BPH)
• Reference Tables: AUA Symptom Index/International Prostate Symptom Score (I-PSS)

CODES

ICD9

• 788.41 Urinary frequency
• 788.64 Urinary hesitancy

- 788.99 Other symptoms involving urinary system

ICD10

- R35.0 Frequency of micturition
- R39.9 Unsp symptoms and signs involving the genitourinary system
- R39.11 Hesitancy of micturition

CLINICAL/SURGICAL PEARLS

- Quantification of symptoms is paramount in the management of LUTS.
- Treatment should be offered to men with moderate to severe symptoms (AUASS ≥ 8).
- Treatment should be tailored to symptoms and prostate volume and may include behavioral intervention, medical management, or surgical intervention.

LYMPHADENOPATHY, INGUINAL

Michael E. Woods, MD
Raj S. Pruthi, MD, FACS

BASICS

DESCRIPTION

- Clinically evident inguinal lymphadenopathy can be secondary to infection, inflammation, or malignancy.
- Lymph nodes (LNs) are generally considered enlarged if >1 cm.
- There is a <1% annual incidence of unexplained peripheral (including inguinal) lymphadenopathy.
- 14% of all abnormal lymphadenopathy present in inguinal region

EPIDEMIOLOGY

Incidence

- Malignancy
  - Penile cancer (1)[A]
    - 0.4–0.6% of male cancers in USA
    - Median age at diagnosis: 68 yr
    - 50% of enlarged LN secondary to cancer
  - Lymphoma: ~80,000 cases/yr in USA
- Infectious (STD/STI) (2)[A]
  - Approximately 15 million new Sexually Transmitted Infections (STI) cases/yr in USA
  - Chancroid (*Haemophilus ducreyi*)–24 cases reported to the CDC in 2010
  - Herpes simplex–775,000 cases/yr, 16% of 14–49-yr olds infected with HSV-2
  - Lymphogranuloma venereum (LGV)–relatively rare; rise in USA and UK associated with men who have sex with men and persons with HIV
  - Syphilis–In 2011, USA, men 8.2/100,000; women 1/100,000
  - HIV–1.1 million people in USA infected
  - Gonorrhea: 2nd commonest STI in USA
- Infectious (soft tissue of the leg/foot)
  - Common causes: β-hemolytic streptococci and *Staphylococcus aureus*

RISK FACTORS

- Penile Cancer
  - Circumcision (neonatal circumcision is protective)
  - Poor genital hygiene; phimosis
  - Number of sexual partners
  - Human papilloma virus (HPV) infection (type 16 and 18)
  - Incidence of LN metastases related to grade, stage, and lymphovascular invasion
- STI: High-risk sexual practices (ie, nonuse of condom, multiple partners, men who have sex with men)

PATHOPHYSIOLOGY

- Inguinal lymph nodes (ILNs) serve at the primary lymphatic drainage for the penis, scrotum, urethra, vulva, vagina, perineum, gluteal region, lower abdominal wall, lower anus, and lower extremities.
- ILNs lie within the femoral triangle (inguinal ligament, sartorius, and adductor longus) and are separated into superficial and deep groups by the fascia lata of thigh.
- Penile squamous cell carcinoma (SCC) cancer spreads by a relatively reliable pattern: From superficial pelvic LNs to deep pelvic LNs

ASSOCIATED CONDITIONS

- Balanitis
- Phimosis
- Additional sexuallt transmitted infections (STI's)

GENERAL PREVENTION

- Prepubertal circumcision is protective against penile cancer
- Good genital hygiene
- STD education and safe sexual practices
- Sun protection against melanoma
- HPV vaccination may reduce risk (unproven)

DIAGNOSIS

HISTORY

- Constitutional symptoms: Weight loss, night sweats
- Age: Penile cancer is more likely in older individuals, STI more common in younger patients
- Sexual history: Number and sex of partners, condom use
- Travel: International travel is common source of STI and other endemic diseases.
- Ethnicity: Higher penile cancer in South America
- History of other diseases, malignancy, lower extremity trauma, animal exposure

PHYSICAL EXAM

- Cachexia: Suggests systemic illness
  - HIV, lymphoma
- Generalized lymphadenopathy (neck, axilla)
  - Signs of systemic process (HIV, lymphoma)
- Abdominal exam
  - Palpable masses, splenomegaly
- Lower extremities bilaterally for lesions
- Inguinal exam
  - Size, fixation of LNs
  - Erythema, tenderness, warmth, drainage/purulence
- Genital exam
  - Penis, glans, foreskin, scrotum for lesions
  - Erythema, drainage, purulence, abscess
  - Ulcers (can be secondary to herpes, chancroid, granuloma inguinale, syphilis, neoplasias); vesicles with herpes

- Formal pelvic exam in women

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Suspected malignancy
  - CBC, basic metabolic panel, liver function testing (LFT's)
- Infectious/STD (2)
  - Gonococcus
    - Nucleic acid amplification testing (ie, polymerase chain reaction [PCR]) of vaginal samples, urine, urethral samples—98% sensitive
    - Culture–72–95% sensitive, perform if drug resistance is suspected
  - Syphilis
    - Darkfield microscopy of primary chancre, screen with nontreponemal test (RPR, VDRL) confirm with treponemal test (FTA-ABS)
  - Herpes simplex
    - Viral culture of active lesion (50% sensitive)
    - PCR of specimen from genital ulcer
    - Direct fluorescent antibody of specimen
    - Serology for HSV-1/2 (90% and 95% sensitivity and specificity, respectively)
  - LGV: Culture *Chlamydia trachomatis* from ulcer or LN aspirate
    - Serologic identification with complement fixation or microimmunofluorescence; PCR
  - Chancroid: *H. ducreyi* culture (75% sensitive)
    - PCR >95% sensitive/specific (non-FDA approved)
  - HIV: Serology for IgG antibody to HIV-1 antigens (positive test confirmed via western blot assays)

Imaging

- CT abdomen/pelvis: Extent of disease
  - Evaluates other sites of lymphadenopathy lymphoma
- CT chest/CXR: Staging in setting of malignancy
- Inguinal US: Evaluate solid vs. cystic lesions; identify abscess

Diagnostic Procedures/Surgery

- Excisional biopsy of abnormal LN or primary lesion (preferred)
- Percutaneous biopsy/aspiration of abnormal LN
- Bone marrow biopsy (lymphoma workup)

DIFFERENTIAL DIAGNOSIS

- Nonspecific lymphadenitis
- Malignancy: In a historic study of over 200 patients the order of malignancy in inguinal lymphadenopathy was: Cutaneous malignancy of lower extremity (melanoma), cervical, vulva, cutaneous malignancy of the trunk, rectum/anus, ovary, and penile cancer.
- Infectious
  - Soft-tissue infection of the lower extremity (ie, *Staphylococcus*)
  - STD (HIV, gonococcus, herpes simplex, chancroid, LGV, syphilis)
- With more generalized lymphadenopathy consider a systemic disease
  - Infections: Epstein–Barr, toxoplasmosis, cytomegalovirus, mycobacteria (TB, etc.),

mononucleosis
  - Lymphoma, lupus
- Medications: Cephalosporins, others

TREATMENT

GENERAL MEASURES

- Generalized lymphadenopathy should be referred for global evaluation.
- A period of observation for localized lymphadenopathy is reasonable if there are no other clinical findings.
- Penile cancer requires treatment of primary lesion (based on size and location), followed by inguinal lymphadenectomy if indicated.
- Infectious etiologies need to be accurately diagnosed so appropriate treatment can be initiated (see below).
- Gynecologic malignancies have a high predisposition for inguinal spread.

MEDICATION

First Line

- STD (2)[A]
  - Chancroid: Azithromycin 1 g PO ×1 or ceftriaxone 250 mg IM ×1 or ciprofloxacin 500 mg PO BID ×3 days or erythromycin base 500 mg PO TID ×7 days
  - Herpes simplex (primary): Acyclovir 400 mg PO TID ×7–10 days or acyclovir 200 mg PO 5×/day ×7–10 days or famciclovir 250 mg PO TID ×7–10 days or valacyclovir 1 g PO BID ×7–10 days
  - LGV: Doxycycline 100 mg PO BID ×21 days OR erythromycin base 500 mg PO QID ×21 days
  - Syphilis (primary and secondary): Benzathine penicillin G 2.4 million units IM ×1
  - Syphilis (late latent): Benzathine penicillin G 2.4 million units 1×/wk ×3 wk
  - Gonococcus: Ceftriaxone 400 mg IM ×1 plus azithromycin 1 g PO ×1 or doxycycline 100 mg PO BID ×7 days OR cefixime 400 mg PO ×1 plus azithromycin 1 g PO ×1 or doxycycline 100 mg PO BID ×7 days; if cephalosporin allergy: Azithromycin 2 g PO ×1
  - HIV: Antiretroviral drug regimens (see Section 1 “HIV/AIDS, Urologic Considerations” and latest CDC guidelines)

SURGERY/OTHER PROCEDURES

- Penile cancer (1)[A]
  - Management of primary lesion (local excision, partial penectomy, total penectomy)
  - Non-palpable ILNs
  - Up to 50% of all enlarged ILNs are benign in patients with newly diagnosed penile cancer. Treated with 6 wk of antibiotics (currently controversial) prior to consideration of inguinal lymph node dissection (ILND) or undergo a fine aspiration of the node in question if the primary tumor is low risk.
  - Occult metastases ~25%
    - TaG1-2/T1G1—surveillance
    - T1G2—surveillance vs. ILND or dynamic sentinel node biopsy (DSNB)
    - ≥T2 or any G3—ILND or DSNB

- Palpable ILNs
  - Low risk—consider fine-needle aspiration to confirm malignancy; Intermediate/high risk—ILND

- Inguinal lymphadenectomy techniques
  - Dynamic sentinel node biopsy (DSNB)
    - Use of blue dye + γ-emission (radio nuclide tracer)
    - False-negative 5%; expertise required
  - Superficial ILND
    - Removal of LN above fascia lata
    - If lymph positive on frozen section, then compete ILND needed
    - Option for prophylactic ILND
  - Modified ILND
    - Appropriate for prophylactic ILND
    - Decreased morbidity
    - Limited template (lateral border femoral artery, caudal border fossa ovalis)
    - Includes deep nodes medial to femoral vein
    - Smaller incision; preserve saphenous vein
    - Avoids transposition of sartorius muscle
    - Positive on frozen, then standard ILND
  - Radical/standard ILND
    - Indicated for patient with metastatic disease to the ILNs
    - Larger template including tissue lateral femoral artery and distally to apex of the femoral triangle
    - Routine division of saphenous vein and sartorius transposition; higher morbidity
- Infectious etiology
  - Fine-needle aspiration for culture
  - Incision and drainage of abscess
- Lymphoma
  - Excisional biopsy of ILN (may consider other site if generalized lymphadenopathy is present)

ADDITIONAL TREATMENT

Radiation Therapy

Penile Cancer: Palliation of bulky, unresectable inguinal lymphadenopathy

Additional Therapies

- Penile cancer
  - Patients with fixed ILN or pelvic LNs should receive cisplatin-based chemotherapy followed by consolidative surgery when appropriate (3)[C]
    - Paclitaxel, ifosfamide, cisplatin—50% complete response (CR) or partial response (PR) and ~75% underwent planned surgery

ONGOING CARE

PROGNOSIS

- Penile Cancer

– Node negative: 46–100% 5-yr survival (mean ~75%)
– Node positive: 0–86% 5-yr survival based on nodal burden (average ~60%)

COMPLICATIONS

- ILND
  – Seroma, lymphedema, wound infection, skin necrosis
  – 25–50% risk

FOLLOW-UP

Patient Monitoring

- Penile Cancer (1)[A]
  – Nx (surveillance)
    ◦ Q3mo yr 1–2 then Q6mo yr 3–5
  – N0, N1
    ◦ Q6mo yr 1–2 then Q12mo yr 3–5
  – N2, N3
    ◦ Q3–6mo yr 1–2 then Q6–12mo yr 3–5
- Infectious (2)[A]
  – Chancroid–3–7 days after initiating treatment
  – LGV–evaluate for clinical resolution, timing variable
  – Syphilis–clinical and serologic evaluation at 6 and 12 mo
  – Gonorrhea–none if symptoms resolve

Patient Resources

N/A

REFERENCES

1. Spiess PE, Horenblas S, Pagliaro LC, et al. Current concepts in penile cancer. *J Natl Compr Canc Netw*. 2013;11:617–624.
2. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–116.

ADDITIONAL READING

- Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: A phase II study. *J Clin Oncol.* 2010;28:3851–3857.
- Zaren HA, Copeland EM, III. Inguinal node metastases. *Cancer*. 1978;41(3):919–923.

See Also (Topic, Algorithm, Media)

- Chancroid
- Groin/Inguinal Mass, Male and Female
- Lymphadenopathy, Inguinal Image ☼
- Lymphadenopathy, Pelvic and Retroperitoneal
- Lymphogranuloma Venereum (LGV)
- Penis, Cancer, General Considerations
- Penis, Cancer, Lymphadenopathy

- Reference Tables: TNM Classification: Penis Cancer
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General

CODES

ICD9

- 187.4 Malignant neoplasm of penis, part unspecified
- 202.80 Other malignant lymphomas, unspecified site, extranodal and solid organ sites
- 785.6 Enlargement of lymph nodes

ICD10

- C60.9 Malignant neoplasm of penis, unspecified
- C85.90 Non-Hodgkin lymphoma, unspecified, unspecified site
- R59.0 Localized enlarged lymph nodes

CLINICAL/SURGICAL PEARLS

- Differentiate inguinal adenopathy from more generalized LN involvement.
- The viability of the skin flaps developed during an inguinal dissection are based on the anastomotic vessels within the superficial fatty layer of Camper's fascia which course lateral to medial along the skin lines. This is a key anatomic dissection plane as the lymphatic drainage of the penis lies beneath Camper's fascia allowing this superficial fatty layer to remain attached to the skin flaps.
- Use a modified technique in a clinically negative groin to decrease morbidity. The key components: Shorter incision (~10 cm), preserve saphenous vein, minimize dissection lateral to the femoral artery, and avoid transposition of the sartorius muscle.

LYMPHADENOPATHY, PELVIC AND RETROPERITONEAL

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BASICS

DESCRIPTION

- Enlarged nodal tissue in the pelvis and/or retroperitoneum
- Can be regional or generalized
- Definitions vary, but include solitary node ≥1–1.5 cm in short axis, any rounded node >8 mm or multiple nodes >1 cm (1).
- Pelvic lymph nodes (LNs) are generally considered abnormal if >1.3 cm.
- Often discovered incidentally or with imaging performed for tumor staging.
- Usually nonacute, but potentially life threatening.

EPIDEMIOLOGY

Incidence

- Lymphoma is the most frequent malignant tumor in the retroperitoneum. Non-Hodgkin lymphoma (93.7%) occurs more commonly than Hodgkin lymphoma (6.3%).
- Other common causes of retroperitoneal lymphadenopathy are malignancies, infections of retroperitoneal and pelvic organs and external genitalia.

Prevalence

No consistency in literature

RISK FACTORS

- Tumor-associated syndromes:
  - Renal cancer:
    - von Hippel–Lindau (VHL)
    - Hereditary papillary renal carcinoma (HPRC)
    - Hereditary leiomyomatosis and renal cell cancer (HLRCC)
    - Birt–Hogg–Dube (BHD)
    - Hereditary paraganglioma and pheochromocytoma (HPP)
    - Tuberous sclerosis complex (TSC)
- Adrenal cancer:
  - Gardner syndrome
  - Beckwith–Wiedemann syndrome (associated with hemihypertrophy)
  - Multiple endocrine neoplasia type 1
  - SBLA syndrome (Sarcoma, Breast, Lung, Adrenal carcinoma)
  - Li–Fraumeni syndrome
- Urothelial cancer
  - Hereditary nonpolyposis colorectal cancer (HNPCC)
  - Hereditary retinoblastoma
  - Costello syndrome
  - Possibly Apert syndrome

- **Prostate cancer**
  – Hereditary breast and ovarian syndrome (HBOS)
- Patients with primary tumors of GI, GU, and GYN tracts and associated risk factors for these malignancies
- Smoking, age, family history, HPV
- Immunosuppression (HIV, autoimmune)
- Lymphadenitis seen with inflammatory/infectious conditions of the pelvis

Genetics
- Ureteral obstruction
- IVC compression +/– lower extremity edema
- DVT
- Await genetics consult for others
- VHL: 3p25-26
- HPRC: 7q31
- HLRCC: Long arm of chromosome 1
- BHD: 17p11.2
- Hereditary paraganglioma and pheochromocytoma (HPP)
- Tuberous sclerosis complex: TSC, TSC1, 9q34.13; TSC2, 16p13.3

PATHOPHYSIOLOGY
- Most adenopathy incidental; may be regional or generalized
- Usually one of five causes: Malignant, infectious, autoimmune, inflammatory (reactive), iatrogenic

ASSOCIATED CONDITIONS
See risk factors

GENERAL PREVENTION
Resolution of primary source

DIAGNOSIS

HISTORY
- Constitutional: Weight loss, night sweats (especially with lymphoma), fatigue, fever
- Local compressive symptoms: Bowel obstruction, hydronephrosis/pyelonephritis/uremia, lower limb edema (vascular/lymphatic compromise)
- Severe infection on perineum/pelvis may result in inguinal/pelvic adenopathy
- History of primary GU, GI, or GYN tumor
- Paraneoplastic syndromes (ie, breast tenderness, anemia, etc.)
- Immunocompromised states raise risk of mycobacterial infection, lymphoma, or Kaposi sarcoma

PHYSICAL EXAM
- Evaluate for peripheral lymphadenopathy (neck, supraclavicular, inguinal, axillary)
- Chest: Clear breath sounds, breast tissue, or tenderness
- Abdominal/pelvic exam: Meta/menorrhagia, palpable mass, bruits, thrills
- GU/GI exam: Testicular mass, right-sided varicocele, penile lesions, digital rectal exam

(DRE), perineal cellulitis/abscess, fecal occult blood testing, hematuria, pelvic exam in females
- Skin: Rash, lesions (malignant, benign), ie, melanoma
- Lower extremity edema

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC, ESR, exam of peripheral smear
- Creatinine (for imaging and to check renal function)
- Urinalysis for hematuria
- Urine cytology
- Tumor markers:
  - PSA: Prostate cancer
  - AFP, β-hCG, LDH: Testicular cancer
  - CA-125: Ovarian cancer
  - CEA: Colon cancer

Imaging

- May diagnose cause of adenopathy (ie, renal mass)
- Ultrasound: Can pick up larger masses; false-negatives are significant
- CT/MRI: More sensitive than US (1)[A]
  - Nodes <7–10 mm considered reactive
  - CT generally considered best; use MRI if contrast contraindicated
- PET: Evaluate fibrosis from metabolically active nodes, ie, postchemotherapy testicular cancer, seminoma (2); expanding role (3)
  - Some studies show PET can define testicular relapse before CT.
- SPECT: Advances in lymphoscintigraphy have advanced opportunity for LN resection in select GU malignancies (1).
- Bipedal lymphangiography largely replaced by CT and MRI.

Diagnostic Procedures/Surgery

- Nodal tissue exam unless diagnosis is clear (ie, testicular or prostate tumor), then size or function and physiology becomes important (1).
- CT-guided biopsy best way to obtain nodal tissue.
  - Not always feasible (ie, proximity to major vessels), open/laparoscopic in select cases
- CT/MRI or SPECT imaging

Pathologic Findings

Numerous, depends on cause (see below)

DIFFERENTIAL DIAGNOSIS

- Tumor
  - Primary lymphatic: Lymphoma (non-Hodgkin, Hodgkin, others)
  - Secondary: Adrenal, renal, urothelial and nonurothelial bladder or upper tract cancer, prostate, urethral, penile, germ cell, cervical, ovarian, uterine, GI (carcinoid, lymphomas), colorectal, melanoma, Kaposi sarcoma
- Infectious/inflammatory

  - Granulomatous: TB, sarcoidosis, histoplasmosis, lymphogranuloma venereum, Castleman disease (angiofollicular LN hyperplasia associated with HIV and human herpesvirus 8 [HHV-8]).
  - Nongranulomatous: Viral, bacterial (if abscess in local areas), sinus histiocytosis, retroperitoneal fibrosis
- Other: Neoplastic, non-neoplastic, and cystic retroperitoneal masses (lymphocele, urinoma, hemorrhage) aneurysms

TREATMENT

GENERAL MEASURES
- Wide variety, based on diagnosis of primary disease
- Image-guided needle biopsy, as a 1st-line investigation, is useful in the diagnosis of space-occupying lesions of the retroperitoneum
- Routine lymphadenectomy usually indicated for GU malignancy

MEDICATION
First Line
Based on diagnosis of primary disease

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Open or laparoscopic nodal sampling may be required in select cases
- Lymphadenectomy at time of organ-specific resection indicated in many cases of GU, GYN, and GI malignancy

ADDITIONAL TREATMENT
- Underlying cause must be treated appropriately
- Benign reactive lymphadenopathy can be seen in the presence of malignancy and improves with appropriate treatment
- Lymphadenectomy for malignant lymphadenopathy does not always affect overall survival (4).

Radiation Therapy
For certain causes such as seminoma

Additional Therapies
- In select cases, reimaging for signs of growth or assessing therapeutic response, eg, hormonal therapy for prostate cancer, antibiotics for penile cancer
- Notification of partners if HIV-positive (3)[A]

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

Widely variable

COMPLICATIONS

- Severe lymphadenopathy can result in lower extremity edema, varicocele
- Potential surgical complications of retroperitoneal lymphadenectomy include vascular injury, lymphocele, chylous ascites, ejaculatory dysfunction, and GI complications (pancreatitis, bowel injury/obstruction)

FOLLOW-UP

Patient Monitoring

Based on primary disease

Patient Resources

N/A

REFERENCES

1. Chernyak V. Novel imaging modalities for lymph node imaging in urologic oncology. *Urol Clin North Am.* 2011;38:471–81.
2. Becherer A. PET in testicular cancer. *Methods Mol Biol.* 2011;727:225–241.
3. Bouchelouche K, Oehr P. Recent developments in urologic oncology: Positron emission tomography molecular imaging. *Curr Opin Oncol.* 2008;20:321–326.
4. Bochner BH, Coleman JA, Carver BS, et al. Role of lymphadenectomy in genitourinary cancer. AUA Update Series. 2009;28:205–209.

ADDITIONAL READING

Chen L, Kuriakose P, Hawley RC, et al. Hematologic malignancies with primary retroperitoneal presentation: Clinicopathologic study of 32 cases. *Arch Pathol Lab Med.* 2005;129(5):655–660.

See Also (Topic, Algorithm, Media)

- Groin/Inguinal Mass
- Lymphadenopathy, Inguinal
- Lymphadenopathy, Pelvic and Retroperitoneal Images ☼
- Retroperitoneal Mass and Cysts

CODES

ICD9

- 202.80 Other malignant lymphomas, unspecified site, extranodal and solid organ sites
- 567.9 Unspecified peritonitis
- 785.6 Enlargement of lymph nodes

ICD10

- C85.90 Non-Hodgkin lymphoma, unspecified, unspecified site
- K65.9 Peritonitis, unspecified
- R59.0 Localized enlarged lymph nodes

CLINICAL/SURGICAL PEARLS

- General malignancies (testis, penile) have predictable lymphadenopathy pattern of spread.
- Pelvic organ malignancies may have skip lesions to the retroperitoneum.
- Lymphadenectomy may be curative for many urologic and nonurologic malignancies.
- Urinary, bowel, and vascular obstruction possible with advanced lymphadenopathy.
- Inflammatory and infectious conditions may lead to reactive lymphadenopathy.

LYMPHOCELE, PELVIC

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BASICS

DESCRIPTION

- A lymphocoele is a localized encapsulated collection of lymphatic fluid created by disruption of lymphatic vessels.
- A collection of lymph fluid in a cavity that is not lined by epithelium
- Generally occurs following surgery such as pelvic or retroperitoneal lymphadenectomy or renal transplantation

EPIDEMIOLOGY

Incidence (1)

- Incidence: 0.6–18% after renal transplant
- Clinical incidence: 1–10% after pelvic lymphadenectomy
  - May be up to 20–25% if all patients were imaged postoperatively
- After robot-assisted laparoscopic lymphadenectomy (RA-PLND) is about 5%, half becoming symptomatic

RISK FACTORS

- Recent pelvic surgery (ie, PLND, open or laparoscopic), renal transplant, retroperitoneal lymph node dissection (RPLND), RA-PLND, gynecologic procedures:
  - Extended PLND > conventional PLND
  - Extraperitoneal > transperitoneal procedures
  - Risk increases linearly with the number of nodes retrieved.
- Prior radiation or chemotherapy
- Anticoagulation or antiplatelet therapy may increase risk
- Long-term use of steroids
- Presence of involved lymph nodes

PATHOPHYSIOLOGY

- Lymphatic fluid collects in the extraperitoneal space due to continued lymphatic leakage.
- Transperitoneal pelvic lymphadenectomy is less commonly associated with the development of a lymphocele but can occur.
- Fluid is chylous in nature.
- Occurs in up to 20% of kidney transplant recipientscaused by leakage from lymphatic vessels transsected during the transplant surgery

ASSOCIATED CONDITIONS

- Bladder cancer
- Gynecologic malignancy
- Penile cancer
- Prostate cancer

- Renal cancer
- Renal insufficiency with transplantation
- Retroperitoneal metastasis

GENERAL PREVENTION

- Meticulous lymphadenectomy with clips on proximal end of lymphatic vessels.
  - Monopolar electrocoagulation may not adequately seal lymph channels.
  - Bipolar or harmonic devices have been shown to be effective (bipolar devices created seals that were fivefold to 10-fold stronger than the harmonic devices)
    - These vessel-sealing devices (VSDs) may reduce risk.
  - Use of FloSeal or other hemostatic products after lymphadenectomy may reduce the number of symptomatic lymphoceles.
- Some reports that the use of anticoagulants (eg, subcutaneous heparin) postop may increase lymphocele risk.
  - Use of low-dose heparin in this setting when injected in the upper arm may reduce lymphocele risks.
- Use of suction drains does not appear to impact the development of lymphoceles.

DIAGNOSIS

HISTORY

ALERT

Lymphoceles can occur after transperitoneal laparoscopic, robot-assisted surgery.

- Recent pelvic surgery, particularly involving lymphadenectomy
- Prior chemotherapy or pelvic radiation
- Timing of onset of symptoms:
  - Urine leak (urinoma), hematoma, abscess, and peritonitis typically present early
  - Lymphocele can present early in the postop period, but may present several weeks or months after surgery
- Urinary frequency (if compressing bladder)
- Sensation of pelvic fullness
- Constipation
- Flank or abdominal pain (40%)
- Lower-extremity pain/swelling (37%)
- Ileus
- Fever (47%)

PHYSICAL EXAM

- Palpable abdominal mass or lower abdominal tenderness
- Lower-extremity edema
  - Painful leg swelling suggests deep venous thrombosis (DVT).
  - Lymphocele-related, lower-extremity swelling is usually not painful.
- Peno-scrotal or labial edema

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum creatinine, BUN (especially to follow renal function in transplant patient)
- Aspirated fluid creatinine and BUN, Gram stain and culture
- Lymphatic fluid typically contains protein, BUN, creatinine, electrolytes, and, occasionally, lipids as serum
- In contrast, urinoma has markedly elevated creatinine; lymphocele creatinine = serum creatinine

Imaging
- Key to diagnosis, but cannot distinguish between lymphocele and urinoma
- US: Imaging, lymphoceles appear as anechoic cystic structures that may contain thin septations and debris.
  - Pelvic: To identify fluid collection that is separate from the bladder, adjacent to renal allograft
  - Retroperitoneal: To evaluate hydronephrosis, if suspected
  - Ideal for follow-up of resolution
  - Duplex study of the lower extremities: To evaluate for DVT
- Pelvic CT: Best definition of size and location of lymphocele
  - Seen as thin-walled hypodense lesions
  - Negative Hounsfield units
  - Thickened, enhanced wall suggest infection
- IVP: May show displacement of ureter and compression of bladder, but is seldom necessary

Diagnostic Procedures/Surgery
- Lymphangiography/lymphoscintigraphy: If other studies unclear, historic value
- Diagnostic aspiration with count and cultures

Pathologic Findings
Lymph fluid in a fibrous cavity not lined by epithelium-containing lymphatic fluid.

DIFFERENTIAL DIAGNOSIS
- Abscess
- Cystic malignancy
- Hematoma
- Lymphocele
- Urinoma due to urinary leakage
- Seroma

TREATMENT

GENERAL MEASURES
- Treat DVT if present.
- Foley catheter if the patient has significant voiding dysfunction
- Asymptomatic small lymphoceles should be monitored (<100–150 mL volume). Many will resolve spontaneously.

MEDICATION
First Line
- Lymphocele management is primarily interventional with limited role for medications unless

associated with infection or sclerosis (see below) (2).
- Systemic antibiotics (with percutaneous drainage) if lymphocele is infected.

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Treatment of symptomatic or large lymphoceles is immediate percutaneous drainage (3).
  - Reported success rates with aspiration and drainage tube are approaching 80%, with a mean drainage duration ranging from a few days to several months.
  - Increased risk of infection, especially in immunocompromised (transplant) patients.
- Sclerosis therapy can be used to treat extraperitoneal lymphoceles
  - Sclerotherapy (povidone–iodine, 95% ethanol, tetracycline 0.5–2 g in 50 mL NS, bleomycin 1 U/mL, fibrin glue):
  - Cavity is aspirated, then filled gently with a sclerosing agent.
  - Sclerosis is usually contraindicated.
    - Multiseptated lymphoceles: Drainage, lack of access to all chambers
    - When the ureter is in close contact with a wall of the lymphocele (periureteral fibrosis, ureteral obstruction)
    - Incomplete lymphoceles should not be treated by sclerosis.
- Transperitoneal laparoscopic marsupialization (4)
  - If unsuccessful sclerosis or not amenable to percutaneous drainage
  - Three transperitoneal ports provide access for excision of the peritoneal window and optional omental wick placement to keep peritoneal window open.
  - Success: 77–100%
- Open marsupialization (internal drainage) into the peritoneum is the historic gold standard:
  - A window of peritoneum is excised, allowing the lymph to be reabsorbed by the peritoneum.
- Infected lymphoceles require percutaneous or open surgical drainage.
- Omentoplasty:
  - Placing a portion of omentum in the window decreases recurrence maintaining patency.
  - Success: 75–100%

ONGOING CARE

PROGNOSIS
- Most smaller asymptomatic lymphoceles resolve spontaneously.
- >90% success with marsupialization

COMPLICATIONS
- DVT/PE
- Lymphostasis of the lower extremity
- Infection
- Ureteral obstruction
- Bowel obstruction

FOLLOW-UP

Patient Monitoring
Repeat imaging: Ultrasound or CT in 2–4 mo after treatment to detect recurrence.

Patient Resource
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2498000

REFERENCES

1. Musch M, Klevecka V, Roggenbuck U, et al. Complications of pelvic lymphadenectomy in 1,380 patients undergoing radical retropubic prostatectomy between 1993 and 2006. *J Urol*. 2008;179:923–928.
2. Glass LL, Cockett AT. Lymphoceles: Diagnosis and management in urologic patients. *Urology*. 1998;51(5A):135–140.
3. Loeb S, Partin AW, Schaeffer EM, et al. Complications of pelvic lymphadenectomy: Do the risks outweigh the benefits? *Rev Urol*. 2010;12(1):20–24.
4. Hamilton BD, Winfield HN. Laparoscopic marsupialization of pelvic lymphoceles. *Tech Urol*. 1997;2(4):220–224.

ADDITIONAL READING

Taneja SS. Complications of lymphadenectomy. In: Taneja SS, ed. *Complications of Urologic Surgery: Prevention and Management*. 4th ed. Philadelphia, PA: Saunders/Elsevier; 2010.

See Also (Topic, Algorithm, Media)
- Edema, External Genitalia
- Lymphocele, Pelvic Images ☼
- Urinoma (Perinephric Pseudocyst)

CODES

ICD9
457.8 Other noninfectious disorders of lymphatic channels

ICD10
I89.8 Oth noninfective disorders of lymphatic vessels and nodes

CLINICAL/SURGICAL PEARLS
- Use of clips on identifiable lymphatic channels can minimize the occurrence of postoperative lymphoceles.
- A transperitoneal approach for lymphadenectomy is not protective against the formation of a lymphocele because loculation of lymphatic fluid can still occur.
- Symptomatic lymphoceles may require percutaneous or laparoscopic drainage.

MEDULLARY CYSTIC KIDNEY DISEASE (MCKD)

Scott G. Hubosky, MD

BASICS

DESCRIPTION

- Medullary cystic kidney disease (MCKD) is a rare congenital, cystic disease of the kidneys which results in progressive renal deterioration and to eventual end-stage renal disease (ESRD)
- Symptoms develop insidiously and diagnosis is not common until renal insufficiency is detected and initiates evaluation (1)[C]

EPIDEMIOLOGY

Incidence

Less than 1: 100,000

Prevalence

N/A

RISK FACTORS

Positive family history

Genetics

- Mode of inheritance is autosomal dominant (2)[C]
  - Medullary cystic kidney disease-1 (MCKD1)
    - Mutation in MCKD1 gene localized to chromosome 1q21
  - MCKD2
    - Mutation in MCKD2 gene localized to chromosome 16p12

PATHOPHYSIOLOGY

- Unlike other renal cystic diseases such as autosomal dominant polycystic kidney disease (ADPKD), there is no clear correlation between genetic mutation and identifiable protein product responsible for the MCKD phenotype (3)[C]

ASSOCIATED CONDITIONS

- Hyperuricemia and gouty arthritis are associated with MCKD2
- In contrast to juvenile nephronophthisis, MCKD does not have many extrarenal manifestations

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Polyuria
  - Usually the 1st clinical manifestation
  - Occurs due to reduced urinary concentrating ability of the kidney

- Polydipsia
- Family history of ESRD, or renal cysts

PHYSICAL EXAM

Hypertension may be noted with disease progression

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Proteinuria and hematuria are usually absent
- CBC
  - Anemia present in advanced cases due to lack of erythropoietin
- Serum electrolytes
  - Elevated creatinine
  - Hyperkalemia or metabolic acidosis in later stages due to renal insufficiency

Imaging

- Renal ultrasound
  - Kidneys may be atrophic depending on stage of disease
  - Cysts may be visible at the corticomedullary junction in later disease but are usually not detectable in early stages
  - Increased parenchymal echogenicity from tubulointerstitial fibrosis
- CT scan
  - Can detect cysts at the corticomedullary junction better than ultrasound
  - Need for IV contrast is suboptimal in patients with ESRD

Diagnostic Procedures/Surgery

Percutaneous renal biopsy confirms the diagnosis

Pathologic Findings

- Gross findings
  - Initially before disease progression, the kidneys are of normal size
  - Cortical atrophy with progression
  - Cysts develop at the corticomedullary junction and range in size from 1 to 10 mm.
  - With disease advancement the kidneys become very small and demonstrate a granular exterior surface
- Microscopic findings
  - Interstitial nephritis
  - Dilated, atrophic tubules
  - Inflammatory cell infiltrates

DIFFERENTIAL DIAGNOSIS

- Juvenile nephronophthisis
  - Clinically and anatomically similar to MCKD
  - Autosomal recessive inheritance
  - ESRD usually manifests as early as age 13 yr
  - Extrarenal manifestations are common
    - Retinal disorders (retinitis pigmentosa)

    - Hepatic fibrosis
    - Bardet–Biedl syndrome (obesity, retinitis pigmentosa, mental retardation, polydactyly)
- Polycystic kidney disease
  – Autosomal recessive polycystic kidney disease (infantile form)
  – Autosomal dominant polycystic kidney disease (adult form)
- Multicystic dysplastic kidney
- Benign multilocular cyst (cystic nephroma)
- Medullary sponge kidney

TREATMENT

GENERAL MEASURES

- Same as for any patient with renal insufficiency
  – Control hypertension if present
  – Monitor fluid balance/daily weights
  – Monitor serum electrolytes

MEDICATION

First Line

- None for primary treatment
- Antihypertensive regimens sometimes necessary

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Dialysis when ESRD develops
- Renal transplant
  – Allograft is not affected by MCKD after transplantation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- MCKD1 patients manifest with ESRD at median age of 62 yr
- MCKD2 patients manifest with ESRD at median age of 32 yr

COMPLICATIONS

Similar to any patient with renal insufficiency or ESRD

FOLLOW-UP

Patient Monitoring
Close nephrology follow-up is essential

Patient Resources
- National Kidney Foundation
  – www.kidney.org/patients

REFERENCES

1. Scolari F, Ghiggeri GM. Nephronophthisis-medullary cystic kidney disease: From bedside to bench and back again. *Saudi J Kidney Dis Transplant.* 2003;14:316–327.
2. Hildebrandt F, Omram H. New Insights: Nephronophthisis-medullary cystic kidney disease. *Pediatr Nephrol.* 2001;16:168–176.
3. Kim CM, Glassberg KI. Molecular mechanisms of renal development. *Cur Urol Rep.* 2003;4:164–170.

ADDITIONAL READING

Hildebrandt F, Otto E. Molecular genetics of nephronophthisis and medullary cystic kidney disease. *J Am Soc Nephrol.* 2000;11:1753–1761.

See Also (Topic, Algorithm, Media)
- Nephronophthisis (Juvenile, Infantile, and Adolescent)
- Renal Cysts (Intrarenal, Peripelvic, and Parapelvic)
- Renal Mass

CODES

ICD9
- 585.6 End stage renal disease
- 753.16 Medullary cystic kidney
- 788.42 Polyuria

ICD10
- N18.6 End stage renal disease
- Q61.5 Medullary cystic kidney
- R35.8 Other polyuria

CLINICAL/SURGICAL PEARLS
- MCKD has an insidious disease onset.
- Symptoms usually not present until patient has renal insufficiency documented on serum testing.
- Polyuria is commonly the 1st clinical manifestation.

MEDULLARY SPONGE KIDNEY (MSK)

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BASICS

DESCRIPTION

Medullary sponge kidney (MSK) consists of developmental abnormalities of the kidneys with ectatic or dilated terminal collecting ducts and associated medullary cysts

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Estimated at 1 in 5,000–20,000 in the general population
- Occurs more frequently in stone formers ranging from 5 to 20%
- Identification and therefore recognized incidence of MSK may be decreasing since it depends on radiographic contrast studies to detect the dilated collecting ducts

RISK FACTORS

N/A

Genetics

Many cases may be sporadic:

- Increasing evidence suggests inheritability of the disorder, possibly of an autosomal dominance based on familial studies
- Mutations in glial cell–derived neurotropic factor (GDNF) account for roughly 12% of MSK cases (1)[B]

PATHOPHYSIOLOGY

- Dilated collecting ducts and medullary pyramidal cysts which may actually represent ectatic ducts
- Dilated ducts may be filled with calcium apatite crystal
- Distal renal tubular acidosis (DRTA) (33–40%)
- Hypercalciuria (9–100%)
- Hypocitraturia (19–83%)

ASSOCIATED CONDITIONS

- Renal calculi
- Urinary tract infections (UTIs)
- Hypocitraturia and hypercalciuria (as noted above)
- Reduced bone density (2)[B]

GENERAL PREVENTION

- This developmental condition cannot be prevented
- Secondary complications (infections, urolithiasis) can be prevented by appropriate measures

DIAGNOSIS

HISTORY

- Many patients are asymptomatic and are diagnosed incidentally on contrast studies
- Pain associated with renal/ureteral calculi
- Pain without associated obstructing calculi
- Hematuria, microscopic or gross

PHYSICAL EXAM

- May be normal without associated findings
- May have flank tenderness, especially among those with episodes of pain

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum electrolytes usually are normal except with significant distal renal tubular acidosis (DRTA) in which serum bicarbonate and potassium may be low
- Urinary study
  - Urinalysis
    - Microhematuria or pyuria
  - 24-hr urine collections
  - May show hypercalciuria (9–100%)
  - Hypocitraturia in 19–83%
- Stone composition commonly calcium oxalate in 33% (pure) to 63% (mixed)
- Most common mineral
  - Calcium oxalate monohydrate
- Calcium phosphate predominate in 63–67%

Imaging

- Diagnosis based on blush or “paint brush” appearance of dilated collecting ducts after contrast administration
- Intravenous urogram (IVU) or excretory urogram (EXU)
  - Multiple calcifications may appear in dilated ducts as nephrocalcinosis. Often seen on scout film and appear to reside within renal parenchyma
  - Plain film may be useful to detect the appearance of new calcifications
  - Typically bilateral but can occur on one side or in a single renal pyramid
- CT
- Noncontrast CT (NCCT) has largely replaced contrast studies (IVU, EXU) in the diagnosis urinary calculus disease
  - May demonstrate multiple calcifications and possibly localize them to the renal pyramids (3)[B]
  - CT urogram (CTU) may be most useful imaging study
  - After the injection of contrast for CTU, a blush of the involved papillae may be seen
- Renal ultrasonography (RUS)
  - Nondiagnostic for MSK in adults
  - Does not accurately distinguish intraparenchymal from intraluminal calcifications
  - May be used to detect obstruction in the symptomatic patient

Diagnostic Procedures/Surgery

- Endoscopy, specifically ureteroscopy differentiates intraluminal from intraparenchymal calcifications (4)[B]
- 24-hr urine studies to identify metabolic abnormalities

Pathologic Findings

- Typical sponge appearance of the medulla results from the dilated intrapapillary collecting ducts and small medullary cysts
  - Calcifications may be found in the dilated collecting ducts

DIFFERENTIAL DIAGNOSIS

- Dent disease
- Other rare abnormalities of calcium phosphate metabolism
- Primary hyperparathyroidism
- RTA

TREATMENT

GENERAL MEASURES

- Majority of asymptomatic patients can be observed
- General stone clinic measures including high fluid intake should be maintained
- Alkalinization with potassium citrate appears to be of value
- Other abnormalities such as hypercalciuria which do not resolve should be treated specifically
- Treat UTIs as necessary

MEDICATION

- Potassium citrate is employed in patients with hypocitraturia (5)
- Thiazide diuretics are used in patients with stones and nonresponsive hypercalciuria
- Specific antibiotics are indicated for the treatment of UTIs
  - Suppressive antibiotics may be necessary in patients with persistent or multiply recurrent UTIs

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Shock wave lithotripsy has been utilized for treatment of collecting duct stones that can be distinguished from nephrocalcinosis as well as symptomatic intraluminal calculi
- Endoscopy with ureteroscopy or occasionally percutaneous nephrostolithotomy can treat collecting system stones and unroof mucosa to remove obvious and accessible collecting duct stones
- SWL and endoscopy have been advocated to reduce the frequency of symptomatic episodes but is unproven

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Urinary calculi are the most common risk but can be followed and also may be controlled with medical treatment
- Recurrent UTIs can usually be treated
- Development of renal failure is very uncommon

COMPLICATIONS
- Stone formation and subsequent obstruction
- Recurrent/chronic flank pain
- UTI

FOLLOW-UP
Patient Monitoring
- Imaging at every 6–12 mo in stone formers to evaluate for change in existing stones or appearance of new ones
- In some patients, renal ultrasound (RUS) can be used to monitor stones and avoid radiation
- 24-hr urine collections are used to monitor stone risk factors during treatment for urinary abnormalities
- Serum studies are used to monitor changes related to medication

Patient Resources
National Kidney and Urologic Diseases
Information Clearinghouse (NKUDIC)
http://kidney.niddk.nih.gov/kudiseases/pubs/medullaryspongekidney/

REFERENCES

1. Torregrossa R, Anglani F, Fabris A, et al. Identification of GDNF gene sequence variations in patients with medullary sponge kidney disease. *Clin J Am Soc Nephrol*. 2010;5:1205–1210.
2. Fabris A, Bernich P, Abaterusso C, et al. Bone disease in medullary sponge kidney and effect of potassium citrate treatment. *Clin J Am Soc Nephrol*. 2009;4:1974–1979.
3. Maw AM, Megibow AJ, Grasso M, et al. Diagnosis of medullary sponge kidney by computed tomographic urography. *Am J Kidney Dis*. 2007;50:146–150.
4. Miller NL, Humphreys MR, Coe FL, et al. Nephrocalcinosis: Re-defined in the era of endourology. *Urol Res*. 2010;38:421–427.
5. Fabris A, Lupo A, Bernich P, et al. Long term treatment with potassium citrate and renal stones in medullary sponge kidney. *Clin J Am Soc Nephrol*. 2010;5:1663–1668.

ADDITIONAL READING

• Fabris A, Anglani F, Lupo A, et al. Medullary sponge kidney: state of the art. *Nephrol Dial Transplant.* 2013;28:1111–1119.
• McPhail EF, Gettman MT, Patterson DE, et al. Nephrolithiasis in medullary sponge kidney: Evaluation of clinical and metabolic features. *Urology*. 2012;79:277–281.

See Also (Topic, Algorithm, Media)
• Dent Disease
• Distal Renal Tubular Acidosis
• Hypercalciuria
• Medullary Cystic Kidney Disease (MCKD)
• Medullary Sponge Kidney (MSK) Image ☼
• Nephrocalcinosis
• Polycystic Kidney Disease
• Urolithiasis, Adult

CODES

ICD9
• 588.89 Other specified disorders resulting from impaired renal function
• 592.0 Calculus of kidney
• 753.17 Medullary sponge kidney

ICD10
• N20.0 Calculus of kidney
• N25.89 Oth disorders resulting from impaired renal tubular function
• Q61.5 Medullary cystic kidney

CLINICAL/SURGICAL PEARLS

• Be suspicious of MSK in patients with multiple papillary calculi.
• Use contrast study for diagnosis.
• Search for metabolic defects.
• Treat metabolic factors in stone formers.
• Consider treatment of renal stones in patients with recurrent symptomatic stones.
• Significant benefit in endoscopic inspection and treatment.

MEGAURETER, CONGENITAL

Ahmad H. Bani-Hani, MD, FAAP, FACS

BASICS

DESCRIPTION

- Megaureter is a ureter that is dilated out of proportion to the rest of the urinary tract
- Most consider ureters measuring ≥7 mm in diameter by ultrasound a megaureter
- Four types of megaureter are described:
  - Refluxing megaureter
  - Obstructed megaureter
  - Refluxing and obstructed megaureter
  - Nonrefluxing-nonobstructed megaureter
- Each of the above groups further categorized as either primary (defect lies in the ureter itself) or secondary (another disorder leading to megaureter such as urethral obstruction)
- Primary megaureter represents the 2nd most common cause of hydronephrosis in the newborn, with ureteropelvic junction obstruction the most common cause

EPIDEMIOLOGY

Incidence

- Varies depending on etiology
  - Vesicoureteral reflux (VUR): 0.4–1.8% in children
  - Primary obstructive megaureter (POM): 1 per 10,000 population
  - VUR is more common in females
  - POM is more common in males with predilection for the left kidney
  - Bilateral involvement in up to 40%

Prevalence

N/A

RISK FACTORS

- Posterior urethral valves
- Neurogenic bladder
- Diabetes insipidus

Genetics

- No specific genetic factors can be identified in the majority of patients with megaureters
- VUR can be familial

PATHOPHYSIOLOGY

- Refluxing megaureters
  - Caused by congenital abnormality of the intravesical ureter secondary to abnormal insertion of the ureter into the bladder or the intravesical portion of the ureter is not long enough to enable closure of the ureter during bladder filling
- POM:
  - Exact etiology is unclear, however, the most common finding is a distal adynamic ureteral

segment that affects the free efflux of urine resulting in a functional obstruction
- Refluxing, obstructed megaureter:
  - This paradox of pathology was 1st reported by Weiss and Lytton. The muscle cells in the intravesical and juxtavesical sections of the distal ureter are so lacking that they become incapable of adequate transmission of urine. On VCUG, delayed emptying of the refluxing contrast/sharp cut-off distally is highly suggestive of the diagnosis
- Nonrefluxing, nonobstructed megaureter
  - Transient dilatation of the ureter and/or renal pelvis. Renal parenchyma is preserved. Can be primary (idiopathic) or secondary to urosepsis (bacterial toxins can paralyze the ureteral muscle and produce atonic ureter) or polyuric kidney that lost its concentration ability, eg, following ablation of posterior urethral valves

ASSOCIATED CONDITIONS
- Posterior urethral valves
- Prune belly syndrome

DIAGNOSIS
HISTORY
- Most megaureters are diagnosed currently prenatally with ultrasound (asymptomatic)
- For late diagnosis, patients may present with abdominal pain, UTIs, or kidney stones

PHYSICAL EXAM
- Abdominal mass
- Abdominal pain and costovertebral angle tenderness with pyelonephritis

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urine analysis and culture if UTI is suspected
- Serum electrolytes, BUN, and creatinine
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for pyelonephritis

Imaging
- Normally best to perform ultrasound imaging several days after birth to allow relative newborn dehydration to equilibrate
- Renal and bladder ultrasound:
  - Establishes the diagnosis of megaureter, assesses renal parenchyma and may provide clues on possible etiology eg, thickened bladder wall secondary to urethral valves
- Voiding cystourethrogram:
  - Will evaluate for the presence of VUR and urethral abnormalities such as anterior or posterior urethral valves
- Diuretic renal scan:
  - 99mTc-mercaptotriglycylglycine (MAG-3 scan)
  - Assesses renal function and presence of obstruction to the flow of urine
  - Furosemide washout correlates with the degree of obstruction
  - In general, a washout of >20 min after furosemide suggests obstruction

Diagnostic Procedures/Surgery

- Whitaker test (perfusion-pressure test):
  - More invasive as it requires percutaneous renal access
  - Will provide valuable information if the diuretic renal scan is equivocal
- Endoscopy: Invasive test as it requires anesthesia. Can be combined with transurethral resection of urethral valves if present

Pathologic Findings

- Varies with etiology
- With electron microscopy, the muscle population and the size of smooth muscle cells of megaureters can be measured
  - In obstructed megaureters, muscle hypertrophy and hyperplasia are expected. These changes are absent or minimal in refluxing megaureters and ureters associated with prune belly syndrome
  - Collagen fiber derangements can also be seen in primary obstructed megaureter (Increased collagen types I and III deposition)

DIFFERENTIAL DIAGNOSIS

- Bowel segment misinterpreted as dilated ureter
- Posterior/anterior urethral valves
- Prune belly syndrome
- Retrocaval/retroiliac ureter
- Ureteral stone
- Ureterocele
- Ureterovesical junction obstruction
- VUR

TREATMENT

GENERAL MEASURES

- Serial renal and bladder ultrasounds to monitor progress/resolution of megaureter is important
- Workup of megaureter to assess the presence or absence of reflux and/or obstruction will guide further treatment options
- Prenatally discovered megaureter
  - Unilateral obstructed megaureter has a good prognosis
    - These patients can be followed expectantly in the prenatal period, without further intervention or early delivery
    - Bilaterally obstructed megaureter findings require close monitoring for the development of oligohydramnios

MEDICATION

First Line

- Treat active UTI with culture appropriate antibiotics
- Consider prophylactic antibiotics in refluxing and obstructed megaureter variants (eg, Amoxicillin)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Refluxing megaureters:
  - Antibiotic prophylaxis and monitor progress with renal ultrasound (RUS) and VCUG
  - Ureteral reimplant in cases of breakthrough UTIs, renal scarring, or noncompliance with medications
- Primary obstructed megaureter (1)[A]:
  - Excision of the distal adynamic ureteral segment and ureteral reimplant. Ureteral tapering maybe required
- Refluxing, obstructed megaureter:
  - Excision of the distal ureteral segment and ureteral reimplant. Often requires ureteral tapering
- Nonrefluxing, nonobstructed megaureter: Observation with serial ultrasound is all that is needed

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- If the child is newborn or infant, temporizing the obstructing variant of megaureter can be achieved with:
  - Ureteral stent insertion
  - Cutaneous ureterostomy

ONGOING CARE

PROGNOSIS

- Depends on the baseline renal function (2)[A]
- Surgical correction of obstructing megaureters carries a high success rate
- Most nonobstructive, nonrefluxing megaureters will resolve with time
- Outcomes can be poor with concomitant renal anomalies such as renal hypoplasia and dysplasia

COMPLICATIONS

- UTIs
- Ureteral obstruction, mainly technical inattention to details during ureteral reimplant that will cause either:
  - Ureteral kinking at the bladder insertion site
  - Compromised blood supply to the distal ureter associated with excisional ureteral tapering
- Nephrolithiasis

FOLLOW-UP

Patient Monitoring

- Serial RUS (3)[A]
- Serial serum chemistry to monitor renal function

Patient Resources

Urology Care Foundation http://www.urologyhealth.org/urology/index.cfm?article=3

REFERENCES

1. Stehr M, Metzger R, Schuster T, et al. Management of the primary obstructed megaureter (POM) and indication for operative treatment. *Eur J Pediatric Surg*. 2002;12(1):32–37.
2. Liu HY, Dhillon HK, Yeung CK, et al. Clinical outcome and management of prenatally diagnosed primary megaureters. *J Urol*. 1994;152:614–617.
3. Shukla AR, Cooper J, Patel RP, et al. Prenatally detected primary megaureter: A role for extended follow-up. *J Urol*. 2005;173(4):1353–1356.

ADDITIONAL READING

Di Renzo D, Aguiar L, Cascini V, et al. Long-term followup of primary nonrefluxing megaureter. *J Urol*. 2013;190:1021–1026.

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Prenatal
- Megaureter, Congenital Image ☼
- Posterior Urethral Valves
- Prune Belly Syndrome
- Vesicoureteral Reflux

CODES

ICD9

753.22 Congenital obstruction of ureterovesical junction

ICD10

Q62.2 Congenital megaureter

CLINICAL/SURGICAL PEARLS

- Wide spread use of prenatal ultrasound helps identify patients with megaureters at an early stage, commonly prenatally.
- It is important to classify megaureters based on their refluxing and/or obstructing status with the aid of VCUG and diuretic renal scan.
- Long-term follow-up in patients with megaureter is important for best outcome.

MESOBLASTIC NEPHROMA, CONGENITAL (BOLANDE DISEASE)

Lauren N. Hendrix, MD
Stephen E. Strup, MD, FACS

BASICS

DESCRIPTION

- Congenital mesoblastic nephroma (CMN) is a renal tumor arising from nephrogenic mesenchyme
- Usually a solid lesion, but cystic varieties have been reported
- Majority are benign with a favorable prognosis
- First reported in 1967, referred to in older literature as Bolande's tumor or Bolande disease

EPIDEMIOLOGY

Incidence

- Most common real tumor in children <6 mo of age, usually diagnosed prior to 3 mo
- Accounts for 3–10% of all pediatric renal neoplasms (1)
- More common in males (1)
- Usually unilateral
- Often detected prenatally by ultrasound

Prevalence

N/A

RISK FACTORS

Genetics

- ETV6-NTRK3 gene fusion
  - Results from translocation t (12;15) (p13;q25)
  - Found only in the cellular variant
  - Also found in congenital fibrosarcoma (2,3)

PATHOPHYSIOLOGY

- Tumor classification
  - Stage I: Tumor limited to kidney without involvement of capsule or hilar vessels
  - Stage II: Tumor extends beyond capsule with invasion into perinephric fat or blood vessels, but margins of resection are negative
  - Stage III: Tumor not completely resectable, tumor spillage occurs at time of resection, or tumor was biopsied preoperatively
  - Stage IV: Hematogenous metastases or lymphatic spread outside of abdomen
  - Stage V: Bilateral tumors

ASSOCIATED CONDITIONS

- Polyhydramnios
- Hydrops fet alis

DIAGNOSIS

HISTORY

- History of prenatal ultrasound finding of unilateral renal mass
- History of polyhydramnios
- Neonate with abdominal mass
- Hematuria, jaundice, hypertension, anemia, hypercalcemia

PHYSICAL EXAM

- Palpable abdominal mass
- Hematuria
- Jaundice

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Complete blood count
- Basic metabolic panel
  - Serum creatinine
  - Serum calcium
- Urinalysis

Imaging

- Abdominal ultrasound
  - Preferred modality
  - "Ring pattern"
    - Hypoechoic mass with hyperechoic rim signifying vessels at the tumor periphery
    - Seen only in the classic variant
  - Homogeneous or heterogeneous solid mass seen in cellular variant
- CT
  - Homogeneous mass
  - May have peripheral enhancement or focal enhancement at sites of hemorrhage or necrosis
- MRI
  - Signal similar to normal parenchyma with exception of areas of hemorrhage (4)

Diagnostic Procedures/Surgery

- Biopsy
  - The role of biopsy in pediatric renal tumors is controversial as nephrectomy is the mainstay of treatment and preoperative biopsy upstages to stage III

Pathologic Findings

- Three histologic subtypes
  - Classic
    - 1/3 of cases
    - Similar macro- and microscopically to leiomyoma
    - Entrapped nephrons and blood vessels seen at the tumor periphery
    - Not associated with metastasis
  - Cellular

- 2/3 of cases
- More aggressive than classic with high mitotic index and atypical growth pattern
- Associated with local invasion/recurrence and metastasis

– Mixed (3)

DIFFERENTIAL DIAGNOSIS

- Solid renal mass
  – Wilms tumor
  – Rhabdoid tumor
  – Metanephric adenofibroma
  – Renal cell carcinoma
  – Angiomyolipoma
  – Clear cell sarcoma
  – Multilocular cystic nephroma
- Autosomal recessive polycystic kidney disease
- Cross-fused ectopia
- Renal vein thrombosis
- Solitary kidney with compensatory hypertrophy
- Beckwith–Weidemann syndrome
- Adrenal mass
- Retroperitoneal mass (3)

TREATMENT

GENERAL MEASURES

- Management of associated features
  – Hypertension
  – Hypercalcemia
  – Jaundice
  – Anemia
- Chemotherapy reserved for patients >3 mo with cellular variant, tumor spillage at resection, microvascular invasion, metastatic disease, and inoperable tumors

MEDICATION

First Line

- Vincristine, cyclophosphamide, and doxorubicin (VCD)
- Vincristine, doxorubicin, and actinomycin D (VDA)

Second Line

- Isophosphamide, carboplatin, etoposide (ICE)
  – Has considerable nephrotoxicity (3)

SURGERY/OTHER PROCEDURES

- Radical nephrectomy
  – Gold standard
  – Allows for appropriate staging
  – Decreased risk of local recurrence

- Partial nephrectomy
  - Has been reported with success in Wilms tumors but not CMN

ADDITIONAL TREATMENT

Radiation Therapy

No defined role

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Radical nephrectomy generally curative
- Classic variant favorable
- Metastases and local recurrence possible with cellular type, but rare
- Risk factors for recurrence: Cellular variant, older patient age, tumor spillage during resection, and positive surgical margins (3)

COMPLICATIONS

- Prenatally
  - Polyhydramnios
  - Hydrops fet alis
  - Intrauterine fet al demise
- After birth
  - Hypertension
  - Hemodynamic instability
  - Respiratory distress

FOLLOW-UP

Patient Monitoring

Regular abdominal ultrasound for 1 yr in classic variant and longer in cellular variant

Patient Resources

www.cancer.gov/cancertopics/pdq/treatment/wilms/Patient

REFERENCES

1. England RJ, Haider N, Vujanic GM, et al. Mesoblastic nephroma: A report of the United Kingdom's Children's Cancer and Leukaemia Group (CGLG). *Pediatr Blood Cancer.* 2011;56:744–748.
2. Mallya V, Arora R, Gupta K, et al. Congenital Mesoblastic Nephroma: A rare pediatric neoplasm. *Turkish J Path.* 2013;29:58–60.
3. Ahmed HU, Arya M, Levitt G, et al. Part II: Treatment of primary malignant non-Wilms' renal tumors in children. *Lancet Oncol.* 2007;8:842–848.
4. Sheth MM, Cai G, Goodman TR, et al. AIRP best cases in radiologic-pathologic correlation: Congenital mesoblastic nephroma. *Radiographics.* 2012;32:99–103.

ADDITIONAL READING

McKenna PH, Ferrer FA. Prenatal and postnatal urologic emergencies. In: Docimo SG, ed. *The Kelalis-King-Belman Textbook of Clinical Pediatric Urology*. 5th ed. London: Informa Healthcare, 2007.

See Also (Topic, Algorithm, Media)

- Renal Mass
- Wilms Tumor (Nephroblastoma)

CODES

ICD9

236.91 Neoplasm of uncertain behavior of kidney and ureter

ICD10

- D41.00 Neoplasm of uncertain behavior of unspecified kidney
- D41.01 Neoplasm of uncertain behavior of right kidney
- D41.02 Neoplasm of uncertain behavior of left kidney

CLINICAL/SURGICAL PEARLS

- Most common solid renal tumor <6 mo of age.
- Radical nephrectomy is generally curative.

MICROPENIS (MICROPHALLUS)

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BASICS

DESCRIPTION

- A micropenis refers to a stretched newborn penis that is <2.5 standard deviations below the normal mean in length (1)
- Full-term newborn micropenis would be <1.9 cm in length (1)
- Typical normal mean stretched penile length in a newborn is 3.5 cm
- The penis is normally formed but small, ie, no hypospadias (2)
- Scrotum usually normal but can be smaller
- Testicles usually descended but may not function normally
- A micropenis is generally not considered to be associated with ambiguous genitalia since the penis is normal in configuration, the scrotum is normal and the testes are usually descended.
- Micropenis is a finding with many causes

EPIDEMIOLOGY

Incidence

~1.5/10,000

Prevalence

None

RISK FACTORS

- Maternal exposure to antiandrogen medications during pregnancy
- Advanced maternal age: Nondisjunction during meiosis can lead to Down syndrome, Klinefelter syndrome, and polysomy X syndromes

Genetics

- X-linked recessive, autosomal recessive, autosomal dominant have all been identified
- Idiopathic spontaneous mutations noted
- Specific known genetic conditions:
  - Kallmann syndrome
  - Prader–Willi syndrome
  - Laurence–Moon–Biedl syndrome
  - Polysomy X (Klinefelter)
  - Translocation, deletion, trisomy of chromosome 8, 13, 18, and 21
  - Partial androgen-insensitivity syndrome (PAIS)
  - 5α-reductase deficiency
  - Noonan syndrome
  - Rud's syndrome

PATHOPHYSIOLOGY

- Normal penile growth and development is both androgen dependent and independent.
- 1st trimester: Maternal hCG stimulates testicle Leydig cells to produce Testosterone (T). T is converted to dihydrotestosterone (DHT) by 5α-reductase in genital tubercle. Penis and urethra are completely formed by end of 1st trimester by influence of DHT.
- 2nd trimester: Fet al hypothalamus and pituitary drive T production by fet al testis which causes penile growth.
- Micropenis believed to be due to inadequate fet al T production or action after the 1st trimester (1).

ASSOCIATED CONDITIONS

- Hypogonadotropic hypogonadism:
  - Most common cause of micropenis
  - Kallmann syndrome: Anosmia, deficit in GnRH secretion, autosomal dominant
  - Prader Willi syndrome: Short stature, hyperphagia, hypotonia, diabetes mellitus, behavior problems, hypogonadism
  - Laurence–Moon–Biedl syndrome
  - Rud's syndrome
- Primary testicular failure:
  - Gonadal dysgenesis
  - Anorchia
  - Klinefelter's and polysomy X syndromes
  - Luteinizing hormone (LH) receptor defects
  - Defects in T steroidogenesis
  - Noonan syndrome
  - Robinow syndrome
  - Laurence–Moon–Biedl syndrome
  - Trisomy 8, 13, 18, and 21
- Defects in T action
  - PAIS
  - 5α-reductase deficiency
- Idiopathic form:
  - Normal hypothalamic–pituitary–testicle axis
  - Hypothesized to be due to delayed onset of fet al gonadotropin stimulation

GENERAL PREVENTION

Avoid maternal exposure to antiandrogens

DIAGNOSIS

HISTORY

- History of genetic syndrome (eg, Kallman)
- Maternal history: Medications during pregnancy, antenatal US, prior stillbirths, decreased fet al activity, or hypotonia at birth
- Family history: Genitourinary anomalies, hypospadias, cryptorchidism, infertility, major congenital anomalies

PHYSICAL EXAM

- Facies suggestive of midline cranial defect, mental retardation:
  - Microcephaly, hypertelorism, low-set ears, small mouth, high-arched palate
- Weight and body habitus: Prader–Willi syndrome, growth hormone abnormality
- Skin: Nevi, ichthyosis
- Hearing: Deafness
- Smell: Anosmia suggests Kallmann syndrome
- Retinal pigment changes on funduscopic exam
- Penis:
  - Always depress fat pad during exam
  - Prepuce, meatus location, general appearance
  - Stretched penile length (SPL): Measure from tip of glans to pubic symphysis
  - Use physiologic age when comparing SPL with standard nomograms
  - Penile girth usually normal and proportional to length
  - Exclude other diagnoses such as hidden penis or buried penis (beware of a large suprapubic fat pad that may distort a normal penis)
- Scrotum: Size, symmetry, and appearance
- Gonads: Size, shape, and position

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Karyotype
- Genetic testing if history consistent with known syndromes such as Prader–Willi or Kallman
- Differentiate between hypogonadotropic hypogonadism and primary testicular failure
  - Pituitary assessment: ACTH, GH, TSH, LH, FSH. Low levels suggest hypogonadotropic hypogonadism
  - High prolactin suggests hypothalamus defect vs. low prolactin suggests pituitary defect
  - Elevated levels of LH, FSH, and T are normal during 1st 6 mo of life. Low T during this time suggests testicular failure. Confirm with hCG stimulation test. LH, FSH should elevate but T will remain low in testicular failure
  - hCG stimulation test: Assesses testicle for T biosynthesis: 1,000 U of hCG IV or IM for 3 days, measure serum T and DHT levels on days 0 and 4. If T at day 4 $>$100 ng/dL, response is normal. If no response, suggests primary testicular failure
  - From 6 mo to puberty, levels of LH, FSH, and T are low. LH, FSH elevate with hCG stimulation test but serum T low in testicular failure
  - For patients who have undergone or started puberty, LH and FSH are normally elevated as may be serum T. LH, FSH, and T are usually low in micropenis. Do hCG stimulation test and look for response; assess pubertal changes to be sure it is not constitutional pubertal delay
  - Antimüllerian hormone is produced by functional sertoli cells and can be used to detect functional testis tissue
- Identifying defects in T action
  - LH, FSH, T normal, or elevated with PAIS
  - PAIS diagnosis often given after excluding other diagnoses
  - Penis may grow with trial of T IM in PAIS
  - Increased T/DHT ratio with hCG stimulation test or postpubertal suggests 5α-reductase

deficiency
  – AR gene mutation only found in 20% of PAIS

Imaging

- MRI of head: Assess hypothalamus, pituitary, brain, craniofacial anomalies, optic chiasm, 4th ventricle, corpus callosum
- Renal imaging: Assess kidneys and bladder; VCUG and MAG3 renal scan if US suggest renal or bladder anomaly or ectopia

Diagnostic Procedures/Surgery

- Laparoscopy to assess nonpalpable undescended testicles, look for müllerian duct structures, biopsy any dysgenetic tissue
- Genitogram indicated if dysgenetic gonads, ovotestis, müllerian duct structures are found or if androgen insensitivity is suspected

Pathologic Findings

- Newborn penis is proportional but <1.9 cm
- Kallmann syndrome: Anosmia, GnRH deficiency: 10% KAL1 gene defect on Xp22.3, 10% KAL2 on 8p12, 70% autosomal dominant with no identified gene defect
- Prader–Willi syndrome: Short stature, hyperphagia, mental retardation, diabetes, hypotonia, behavioral problems; lacking expression of gene SNRPN or necdin on 15q of paternal origin
- Laurence–Moon–Biedl syndrome: Obesity, retardation, pigmented retinopathy, polydactyly

DIFFERENTIAL DIAGNOSIS

- Concealed penis: Large suprapubic fat pad
- Webbed penis: Prominent penoscrotal web
- Postcircumcision cicatrix:
  – Residual foreskin scarred above glans tip
- Hypospadias with and without chordee
- Chordee
- Disorders of sex differentiation:
  – Female DSD: Congenital adrenal hyperplasia, gonads not palpable in labia/scrotum
  – Male DSD
- Hypothalamic–pituitary axis dysfunction (50% of cases):
  – Syndromes: Kallmann, Prader–Willi, Laurence–Moon–Biedl, Rud's
- Isolated hormone deficiency:
  – GnRH deficiency without Kallmann syndrome
  – LH deficiency
  – GH deficiency or growth hormone receptor defect (Laron dwarfism)
- Primary testicular failure:
  – Hypergonadotropic hypogonadism (25% of cases)
  – Testicular dysgenesis (Klinefelter syndrome, 47XXY)
  – Laurence–Moon–Biedl syndrome
  – Polysomy X syndromes
  – Anorchia; intrauterine testicular torsion
- 5α-reductase deficiency: Rare
- PAIS (Partial androgen insensitivity syndrome)

- CNS abnormalities:
  - Anencephaly, congenital pituitary aplasia, agenesis of corpus callosum, malformation of fourth ventricle
- Chromosome defects:
  - Polysomy X syndromes
  - Translocation, deletion, and trisomy of chromosomes 8, 13, 18, and 21
- Rare syndromes: Rud, Robinow, Martsolf, Fanconi anemia, Smith–Lemli–Opitz syndromes
- Idiopathic: Normal hypothalamic pituitary axis:
  - Virilize normally at puberty

TREATMENT

GENERAL MEASURES

- Generally coordinated with an endocrinologist
- Correct any metabolic disturbances
- Specific treatment based upon cause
- Adrenal insufficiency: Treat with hydrocortisone supplementation and IV saline to correct hypovolemia

MEDICATION

First Line

- Testosterone therapy: Diagnostic and therapeutic: 25–50 mg testosterone enanthate IM Q monthly × 3 mo in infancy or prepubertal
- Long-term cortisol replacement, growth hormone, and thyroid hormone if pan-hypopituitarism present
- For gonadal deficiency: Induce puberty later in life with T IM injection or transdermal patch/gels
- For central deficiency: Administer hCG injection or GnRH therapy

Second Line

None

SURGERY/OTHER PROCEDURES

- Manage cryptorchidism with orchiopexy or orchiectomy (if dysgenetic) as needed
- Penile surgery for length or bulk has not been shown to be effective

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Familial genetic counseling and screening
- Prenatal care:
  - Amniocentesis or chorionic villous sampling for chromosomal anomalies and sex determination
  - Fet al US to look for genitourinary and central nervous anomalies

Complementary & Alternative Therapies

Gender reassignment: Generally not done any more for micropenis and is of only historical interest

ONGOING CARE

PROGNOSIS

- Overall good, but long-term effects depend on underlying cause
- Most have stable male gender identity
- Generally good response to 3-mo course of T IM with 100% increases in length seen (3)
- Final adult penis size with treatment usually < mean, but within 2.5 standard deviations (3)

COMPLICATIONS

- Relate to endocrine abnormalities if present
- Side effects of testosterone:
  - Premature closure of epiphyseal plates; limits long-bone growth
  - Behavioral changes: More aggressiveness
  - Early stimulation of penile growth does not affect ultimate penile length
- Psychosocial issues:
  - Most patients have a stable male gender identify but some dissatisfied with penis length

FOLLOW-UP

Patient Monitoring

- Psychological support and psychiatric therapy as needed:
  - Reassure concerns about penile size, function, gender, potency
  - Address behavioral and psychosocial problems
- Hormone biochemical monitoring:
  - Follow pituitary and gonadal hormone therapy
  - Assess growth, vital signs, electrolytes, serum glucose, renin, ACTH, GH, LH, FSH, and T.
- Physical monitoring: Serial penile measurements

Patient Resources

None

REFERENCES

1. Wiygul J, Palmer LS. Micropenis. *ScientificWorldJournal.* 2011;11:1462–1469.
2. Tsang S. When size matters: A clinical review of pathological micropenis. *J Pediatr Health Care*. 2010;4:231–240.
3. Bin-Abbas B, Conte FA, Grumbach MM, et al. Congenital hypogonadotropic hypogonadism and micropenis: Effect of testosterone treatment on adult penis size – why sex reversal is not indicated. *J Pediatr.* 1999;134:579–583.

ADDITIONAL READING

Baskin LS, Kogan BA. *Handbook of Pediatric Urology*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

See Also (Topic, Algorithm, Media)

- Androgen insensitivity syndrome (AIS; OR Androgen Resistance Syndrome), Complete

(CAIS) and Partial (PAIS)
- Disorders of Sexual Development (DSD)
- Micropenis (Microphallus) Image ☼
- Penis, Buried (Concealed, Trapped, or Hidden)
- Penis, Length, Normal
- Penis, Webbed

CODES

ICD9
752.64 Micropenis

ICD10
Q55.62 Hypoplasia of penis

CLINICAL/SURGICAL PEARLS

- Micropenis is a condition with many causes, most of which are either a form of hypogonadotropic hypogonadism or primary testicular failure.
- Thought to be due to deficient T synthesis or action after the 1st trimester.
- Watch out for large suprapubic fat pad leading to incorrect diagnosis.
- Surgery generally not indicated except for associated cryptorchidism.

MULTICYSTIC DYSPLASTIC KIDNEY

Ellen Shapiro, MD, FACS
Daniel Wollin, MD

BASICS

DESCRIPTION

- Multicystic dysplastic kidney (MCDK) is a congenital renal anomaly with a kidney comprised of cysts of varying sizes; no identifiable renal parenchyma—"bunch of grapes" with a paucity of stroma between cysts; no large central or medial cyst
- No reniform appearance of the involved kidney
- Usually unilateral; bilateral incompatible with life
- Most common type of renal cystic disease and 2nd most common cause of abdominal mass in neonates and infants after hydronephrosis

EPIDEMIOLOGY

Incidence

- 1 in 4,300 live births (unilateral)
- Slight male predominance
- Slightly greater occurrence on the left
- Bilateral MCDK
  - 1 in 10,000—fet al demise due to oligohydramnios or postnatal demise due to pulmonary hypoplasia

Prevalence

N/A

RISK FACTORS

- Possible association with in utero urinary obstruction
- Possible association with teratogens (in utero viral infections, medications such as maternal antiepileptics)
- Maternal diabetes

Genetics

- MCDK seen in disorders of known genetic etiology such as renal cysts and diabetes syndrome (RCAD) which involves mutations in hepatocyte nuclear factor-1β
- Genes such as PAX2, EYA1, SIX1, WNT, WT-1, GNF, and AT2 have an important role in ureteral bud formation and mutations have been identified in human syndromes such as:
  - Branchio-oto-renal (BOR) syndrome with mutations in the EYA1 or SIX1 genes
  - Renal-coloboma syndrome (RCS) with mutations in the PAX2 gene
- Linking genetic mutations with renal dysplasia suggest bud theory as the pathogenesis in MCKD

PATHOPHYSIOLOGY

- Ureteral bud theory:
  - If ureteral bud is atretic or connects abnormally with the metanephric blastema or forms

abnormal distal ureteral connections to the bladder, MCDK will result.
– Prerequisite is the normal reciprocal induction between a normal ureteral bud and normal metanephric mesenchyme.

ASSOCIATED CONDITIONS
- Prenatal hypertrophy of the contralateral kidney (24–46%)
- About 1/3 will have associated congenital anomalies of kidneys and urinary tract (CAKUT)
- Contralateral vesicoureteral reflux (~20%); of those with reflux, 40% will have grades III–V
- Contralateral UPJ obstruction (3–12%) and UVJ obstruction (6%)
- Dilated nonobstructed contralateral renal pelvis (common)
- Anomalies of the ipsilateral internal duct structures (15%) including seminal vesicle cyst, Gartner's cyst, obstructed hemivagina
- Large series show no increased incidence of Wilms tumor or hypertension (see Patient Monitoring)
- Ureterocele or ectopic ureter associated with single system or upper pole of duplex system
- Horseshoe kidney

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
At least 65% are detected prenatally

PHYSICAL EXAM
- Abdominal mass palpable in 13%
- Elevated BP (rare)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
- Urine microalbuminuria

Imaging
- US: Multiple noncommunicating cysts of variable size, scant, or no renal parenchyma
- Dilated renal pelvis in hydronephrotic form
- VCUG not absolutely recommended with normal contralateral kidney and bladder despite 20% having contralateral reflux
- Renal scan (DMSA): Confirms absence of function, or rarely minimal function especially in hydronephrotic form or in smaller more solid dysplastic kidneys

Diagnostic Procedures/Surgery
- VCUG: To evaluate for contralateral VUR if hydronephrosis or other contralateral upper tract abnormality on US
  – If the contralateral kidney is normal, performing a VCUG remains controversial

Pathologic Findings
- Renal maldevelopment with large cysts tend to have a small amount of stroma (thin septa of

fibrous tissue) and primitive dysplastic elements
  – Primitive ducts (a duct encircled by a collar of fibromuscular cells)
  – Immature cartilage and remnants of early metanephros can be present
- Kidneys with smaller cysts tend to have more solid components
- Hydronephrotic form
- Small to no vascular pedicle
- Ureter totally or partially atretic; renal pelvis may be absent
- Microscopic communication between cysts
- Often involute—circumscribed rims of calcifications may be seen in the renal fossa on plain film of adults

DIFFERENTIAL DIAGNOSIS
- Acquired renal cysts
- Autosomal dominant kidney disease
- Cystic congenital mesoblastic nephroma
- Cystic Wilms tumor
- Cysts of the medulla
- Hydronephrosis
- Multilocular cystic nephroma
- Neuroblastoma (calcifications)
- Renal cysts, isolated or associated with syndromes (tuberous sclerosis, von Hippel–Lindau, etc.)
- Ureteropelvic junction obstruction (UPJO)
- Vesico ureteral reflux (VUR)

TREATMENT

GENERAL MEASURES
- Educate parents about the signs and symptoms of UTI in infancy and childhood especially if reflux status unknown
- The use of nephrectomy to manage MCDK is controversial

MEDICATION
First Line
N/A

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Mostly nonoperative:
  – 25% totally involute
  – 60% regress
  – 15% remain stable
  – A very small number may increase in size
- Indications for nephrectomy:
  – Kidneys which remain large, increase in size, or show an increased amount of solid tissue

(especially with function)
  - Kidneys easily removed (especially laparoscopically) or cysts may be sequentially decompressed
  - Hypertension: Uncommon (5%) in childhood and not likely caused by MCDK
    - May persist after nephrectomy depending on the patient age at onset of hypertension and the presence of CAKUT (see Prognosis)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Usually excellent in unilateral disease
- KIMONO study (1) reports renal injury (hypertension, albuminuria and/or the use of renoprotective medication) present in 32% at young age (mean age 9.5 yr).
  - Increased renal injury in individuals with a solitary functioning kidney in later life when CAKUT present.
  - Study suggests long-term clinical follow-up for hypertension and microalbuminuria especially into puberty and adulthood.
  - These findings are supported by an early study (2).

COMPLICATIONS

- Malignant transformation extremely low with only 15 cases of tumors reported
- Rare hypertension; usually associated with contralateral renal injury

FOLLOW-UP

Patient Monitoring

- Renal US to document involution and contralateral renal growth
  - Every 6 mo in the 1st 3 yr and then every 1–2 yr to assure appropriate renal growth until puberty
  - Protocol personal preference of physician since there is no consensus; some follow patients every 3–12 mo. No frequency of follow-up has been shown to be beneficial or cost-effective
- As of 2012, the American Academy of Pediatrics states that contact-sport participation is generally OK for children who have only one functional kidney. In a very large published series, none of the kidney injuries were catastrophic or needed surgery
- Long-term follow-up for hypertension and microalbuminuria by informed pediatrician or family physician; referral to nephrology for renoprotective medications when indicated

Patient Resources

- National Kidney and Urologic Diseases
- Information Clearinghouse (NKUDIC)
  http://kidney.niddk.nih.gov/kudiseases/pubs/kidneydysplasia/

REFERENCES

1. Westland R, Schreuder MF, Bökenkamp A, et al. Renal injury in children with a solitary functioning kidney–the KIMONO study. *Nephrol Dial Transplant*. 2011;26(5):1533–1541.
2. Sanna-Cherchi S, Ravani P, Corbani V, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney Int*. 2009;76(5):528–533.

ADDITIONAL READING

- Abou Jaoudé P, Dubourg L, Bacchetta J, et al. Congenital versus acquired solitary kidney: Is the difference relevant? *Nephrol Dial Transplant*. 2011;26(7):2188–2194.
- Hains DS, Bates CM, Ingraham S, et al. Management and etiology of the unilateral multicystic dysplastic kidney: A review. *Pediatr Nephrol*. 2009;24(2):233–241.
- Hayes WN, Watson AR; Trent & Anglia MCDK Study Group. Unilateral multicystic dysplastic kidney: Does initial size matter? *Pediatr Nephrol*. 2012;27(8):1335–1340.
- Mansoor O, Chandar J, Rodriguez MM, et al. Long-term risk of chronic kidney disease in unilateral multicystic dysplastic kidney. *Pediatr Nephrol*. 2011;26(4):597–603.
- Psooy K. Multicystic dysplastic kidney in the neonate: The role of the urologist. *Can Urol Assoc J*. 2010;4(2):95–97.
- Schreuder MF, Westland R, van Wijk JA. Unilateral multicystic dysplastic kidney: A meta-analysis of observational studies on the incidence, associated urinary tract malformations and the contralateral kidney. *Nephrol Dial Transplant*. 2009;24(6):1810–1818.
- Thomas DF. Prenatally diagnosed urinary tract abnormalities: Long-term outcome. *Semin Fet al Neonatal Med*. 2008;13(3):189–195.

See Also (Topic, Algorithm, Media)

- Multicystic Dysplastic Kidney Image
- Potter Syndrome/Potter Facies
- Renal Cysts
- Renal Dysplasia, Hypodysplasia, and Hypoplasia

CODES

ICD9

- 593.70 Vesicoureteral reflux unspecified or without reflux nephropathy
- 753.15 Renal dysplasia
- 753.19 Other specified cystic kidney disease

ICD10

- Q61.4 Renal dysplasia
- Q62.7 Congenital vesico-uretero-renal reflux
- Q62.39 Other obstructive defects of renal pelvis and ureter

CLINICAL/SURGICAL PEARLS

- MCDK occurs as a result of renal maldevelopment due to possible mutation(s) in genes responsible for ureteral bud formation.
- Large cysts of varying sizes present with no identifiable parenchyma; ureter usually atretic.
- Most involute or become significantly smaller; rare enlargement.
- Almost none require nephrectomy; consider for functioning solid component or increasing size.
- Not associated with increased risk of hypertension during childhood or Wilms tumor in large series.
- Long-term follow-up recommended for hypertension and microalbuminuria especially at puberty and in adulthood.

MULTIPLE SCLEROSIS, UROLOGIC CONSIDERATIONS

Alana M. Murphy, MD

BASICS

DESCRIPTION

- Multiple sclerosis (MS) is a neurologic disease causing focal demyelination of white matter in the brain and spinal cord that can impact urinary tract functioning.
- Plaques visible on magnetic resonance imaging (MRI) are inflammatory and often lead to scar tissue deposition. They interfere with conduction of electrical signals resulting in loss of central inhibition of reflex activity and dysfunctional conduction of sensory and motor signals.
- Neurologic impairment can vary from mild to severe.
- Urologic manifestations include urinary frequency, urgency incontinence, voiding symptoms, urinary retention, and sexual dysfunction.
- Detrusor sphincter dyssynergia (DSD) and detrusor overactivity (DO) are common dysfunctions noted on urodynamic studies (UDS).

EPIDEMIOLOGY

Incidence

- Most commonly presents between ages 20 and 50 yr old
- Females have 1.5–3 times greater incidence than males

Prevalence

- 1 in 750 lifetime risk of developing MS in USA
- Marked variations in worldwide prevalence
- More common in Caucasians and above 40° latitude

RISK FACTORS

- Caucasian ethnicity
- Primary relative with MS
- Live about 40° latitude

Genetics

- Increased risk if MS is present in a 1st-degree relative
- Primary relative with MS confers 20 times risk
- Identical twin: 300 times increased risk if other twin develops MS
- Unknown pattern of inheritance

PATHOPHYSIOLOGY (1)

- Autoimmune attack on the central nervous system (CNS) myelin:
  - Focal demyelination with relative axon sparing
  - Histopathology shows perivenular lymphocytic infiltrates, macrophages within the white matter, gliosis, and scarring
- Urologic pathophysiology:
  - MS affects the cervical spinal cord in the pyramidal and reticulospinal tracts, affecting

innervation of the bladder and external urethral sphincter, causing DO and DSD
  – MS can affect the sacral cord and may lead to bladder areflexia and elevated post-void residual (PVR) volumes

ASSOCIATED CONDITIONS
- DSD leading to urinary retention, recurrent UTIs, and impairment in renal function
- Urolithiasis due to urinary stasis from incomplete bladder emptying and recurrent UTIs

GENERAL PREVENTION
No proven methods for prevention

DIAGNOSIS
HISTORY
- Presence of neurologic symptoms:
  – Vision changes, balance problems, discoordination, numbness, or paresthesias
- Urologic history: All patients with MS should be screened for urologic problems
  – Recurrent UTIs
  – Urinary frequency
  – Urgency incontinence
  – Voiding symptoms
  – Urinary retention

PHYSICAL EXAM
- Urologic exam:
  – Testicular and prostate exam in males to rule out neoplasm or infection
  – Pelvic exam in females to assess pelvic support and rule out urethral or vaginal pathology
- Focused neurologic exam:
  – Bulbocavernosus reflex to assess function of sacral nerves (absent in up to 30%)
  – Deep tendon reflexes, proprioception, Babinski reflex, and cranial nerve exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis: Concomitant infection or hematuria
- CSF for initial MS diagnosis (oligoclonal IgG bands)

Imaging (2,3)
- MRI:
  – The most useful tool for diagnosing MS; diagnostic in 70–95% of cases
  – Increased signal intensity on T2-weighted images in areas of demyelination
- Upper urinary tract imaging:
  – Rule out presence of hydronephrosis
  – Renal ultrasound (US) is a good screening test
  – Important in patients with known DSD or in patients with indwelling catheters
- Lower tract imaging less commonly performed:
  – Fluoroscopy during UDS can assess for bladder pathology (stones, trabeculation), vesicoureteral reflux, and DSD

Diagnostic Procedures/Surgery

- PVR
  - Large (>275–300 cc) PVR on 2 separate occasions should initiate clean intermittent catheterization
- UDS done by urologic specialists to assess bladder capacity, compliance, detrusor function, continence, and detrusor–sphincter coordination:
  - Routinely performed with fluoroscopy in MS patients
  - Absolutely necessary to characterize voiding dysfunction in MS patients
  - Assess risk for upper tract deterioration (elevated storage and voiding pressures)
  - May suggest diagnosis of MS in patient with few other neurologic symptoms
  - Need follow-up UDS with change in clinical symptoms

Pathologic Findings

Detrusor hypertrophy with trabeculation

DIFFERENTIAL DIAGNOSIS

- Idiopathic overactive bladder
- Dysfunctional voiding
- Detrusor underactivity or acontractile detrusor

TREATMENT

GENERAL MEASURES

- Remissions can occur spontaneously, making management difficult
- Physical therapy and exercise to help prevent muscle atrophy and loss of postural tone
- Avoid stressors
- Disease-modifying medications specific to MS can reduce relapses and control some symptoms: β interferons, glatiramer acetate, fingolimod, natalizumab, and teriflunomide
- Bladder emptying in cases of detrusor underactivity or DSD with urinary retention:
  - Intermittent catheterization preferred over indwelling catheter
  - Consider a suprapubic catheter if intermittent catheterization is not possible
  - Patients on intermittent catheterization or with an indwelling catheter should not be treated with antibiotics for asymptomatic bacterial colonization of the urinary tract
- Urinary frequency and urgency incontinence treatment should include behavioral modification with avoidance of bladder irritants and management of fluid intake

MEDICATION

First Line

- Medical therapy is primarily aimed at urinary frequency and urgency incontinence
  - Antimuscarinic medications: Most common side effects include dry mouth and constipation
    - Fesoterodine 4–8 mg QD
    - Hyoscyamine ER release 0.375 mg BID
    - Oxybutynin 5 mg BID-TID
    - Oxybutynin transdermal patch 3.9 mg/d
    - Oxybutynin XL 10–15 mg/d
    - Oxybutynin, topical gel 10% apply 1 sachet QD to dry skin

- Solifenacin 5–10 mg/d
- Tolterodine LA 1–2 mg BID
- Tolterodine LA 2–4 mg/d
- Trospium XR 60 mg/d

– β_3-agonist: Most common side effects include an increase in blood pressure and palpitations
- Mirabegron 25 mg/d increase to 50 mg/d after 8 wk PRN

Second Line (4)

• Botulinum toxin injection into the detrusor:
– Decreases the force and frequency of neurogenic DO
– Well-tolerated office-based therapy performed under local anesthesia
– Neurogenic DO treated with cystoscopic injection of 200–300 units botulinum toxin type A [onabotulinumtoxinA] into 10–25 sites within the bladder muscle
– Treatment effect lasts 3–9 mo
– Risk of temporary urinary retention requiring intermittent catheterization

SURGERY/OTHER PROCEDURES

• Suprapubic catheter placement:
– If unable to perform intermittent catheterization; avoids urethral erosion; reduces incidence of UTIs, epididymitis, and prostatitis
– Drawbacks include risk of bladder calculi and development of squamous cell carcinoma (usually in >10 yr).
• Augmentation cystoplasty: To address significantly impaired bladder compliance or when conservative management of incontinence from DO has failed
• Urinary diversion: Ileal conduit, ileovesicostomy, or catheterizable stoma

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Stress reduction therapies and acupuncture have been associated with symptom reduction

ONGOING CARE

PROGNOSIS

With proper urologic follow-up, renal function can be preserved in most patients

COMPLICATIONS

• Hydronephrosis and impairment in renal function due to elevated bladder storage or voiding pressure
• Urolithiasis due to urinary stasis, indwelling catheters and infection
• Recurrent UTIs
• Urethral erosion from indwelling catheters

FOLLOW-UP

Patient Monitoring

- Upper urinary tract screening is especially important in men, since men with MS often develop high bladder storage pressure and urinary stasis without developing overt urologic symptoms such as incontinence.
- Incontinence, especially in women, can become problematic as the severity of MS progresses.
- Patients with bladder dysfunction secondary to MS can be stratified into low- and high-risk:
  - High-risk patients: Incontinence, recurrent infections, DSD, elevated storage pressures >40 cm H_2O, indwelling catheters
    - Follow closely for upper tract deterioration, development of squamous cell carcinoma of the bladder, and other problems associated with long-term indwelling catheters.
  - Low-risk patients: Those with normal continence, no UTIs, and complete bladder emptying. These patients do not require frequent upper tract imaging.
- All patients should undergo periodic urodynamic testing, especially if there is a change in symptoms, an increase in infections, or an overall worsening of their MS.

Patient Resources

- http://www.nationalmssociety.org
- http://www.msfocus.org

REFERENCES

1. Carr LK. Lower urinary tract dysfunction due to multiple sclerosis.*Can J Urol*. 2006;Suppl1:2–4.
3. Lemack GE, Hawker K, Frohman E. Incidence of upper tract abnormalities in patients with neurovesical dysfunction secondary to multiple sclerosis: Analysis of risk factors at initial urologic evaluation. *Urology*. 2005;65(5):854–857.
4. Ukkonen M, Elovaara I, Dastidar P, et al. Urodynamic findings in primary progressive multiple sclerosis are associated with increased volumes of plaques and atrophy in the central nervous system. *Acta Neurologica Scand*. 2004;109(2):100–105.
5. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotuli-numtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol*. 2012;187(6):2131–2139.

ADDITIONAL READING

- Tremlett H, Zhao Y, Rieckmann P, et al. New perspectives in the natural history of multiple sclerosis. *Neurology*. 2010;74:2004–2015.
- Provider's Approach to Bladder Management in Multiple Sclerosis. http://www.va.gov/MS/articles/Provider_s_Approach_to_Bladder_Management_in_Multiple_Sc (Accessed February 13, 2014)

See Also (Topic, Algorithm, Media)

- Detrusor Overactivity
- Detrusor Sphincter Dyssynergia
- Neurogenic Bladder, General Considerations

CODES

ICD9

- 340 Multiple sclerosis
- 788.31 Urge incontinence
- 788.41 Urinary frequency

ICD10

- G35 Multiple sclerosis
- N39.41 Urge incontinence
- R35.0 Frequency of micturition

CLINICAL/SURGICAL PEARLS

- Medical therapy and behavioral modification remain the 1st-line treatment for urinary frequency and urgency incontinence.
- Cystoscopic injection of botulinum toxin should be used for refractory neurogenic detrusor overactivity.
- Adequate management of lower urinary tract function will lead to preservation of renal function.

MYASTHENIA GRAVIS, UROLOGIC CONSIDERATIONS

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Arthur L. Burnett, II, MD, MBA, FACS

BASICS

DESCRIPTION

- Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by weakness and early fatigability of the skelet al muscles due to antibody-mediated loss of nicotinic acetylcholine (Ach) receptors (1,2)
- Involvement of the external striated urethral sphincter is rare but may be vulnerable to dysfunction after transurethral resection of the prostate (TURP), explaining the relatively high incidence of post-TURP incontinence in this group (3)
- Although smooth muscle is generally not affected, there are rare reports of detrusor areflexia (4)
- Urologic complaints are uncommon but may include incontinence, urgency, retention, or erectile dysfunction

EPIDEMIOLOGY

Incidence

Published estimates of 2–21 cases per million people per year (1,2)

Prevalence

- In patients < 40 yr:
  – Female > Male (7:3)
- In the 5th decade, new cases of MG are evenly split between the genders
- After the 5th decade:
  – Male > Female (3:2) (1,2)

RISK FACTORS

- Thymic hyperplasia is observed in 65–75% of patients (1,2)
- MG has been described as a paraneoplastic syndrome related to renal cell carcinoma (RCC) (5), as well as other malignancies (thymoma, lymphoma, lung cancer, Kaposi's sarcoma) (6)

Genetics

- Congenital myasthenia syndromes, a subset of MG, stem from genetic mutations resulting in abnormal neuromuscular transmission (1,2)
- HLA types B8 and DR3 are associated with MG

PATHOPHYSIOLOGY

- Autoantibodies develop against Ach nicotinic postsynaptic receptors (1,2).
- The autoantibodies mechanically block the neuromuscular junction binding site and eventually destroy them.
- Cholinergic nerve conduction to striated skelet al muscle is thus impaired.
- Clinical symptoms begin to develop when the number of Ach receptors is reduced to ~30% of the normal level.

- Smooth and cardiac muscle are not affected.
- The role of the thymus in MG is unclear, but it is suspected to be a site of autoantibody formation.
- A majority of patients with MG have thymic hyperplasia or thymoma.
- Many patients improve clinically following thymectomy.

ASSOCIATED CONDITIONS
- Neonatal MG is a transitory disorder resulting from passive maternal antibody transfer to the fetus.
- Congenital myasthenic syndromes result from genetic mutations that lead to abnormal neuromuscular transmission.
- Ocular MG refers to weakness limited to the extraocular muscles and eyelids.

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Reduced exercise tolerance that improves with rest and worsens with warm temperature (eg, after a hot bath)
- The natural history of MG usually follows a characteristic pattern that initially involves weakness of eyelids and extraocular muscles.
- Difficulty climbing stairs is typical of generalized weakness in MG.
- Weakness is variable and fluctuating, but tends to be worse later in the day.

PHYSICAL EXAM
- Muscle fatigability can be tested for many muscles by repeated action: Ptosis, diplopia, dysphagia, and peripheral muscle weakness
- "Dropped head syndrome"

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serology tests demonstrate anti-ACh receptor antibodies in ~90% of patients
- ~50% of patients who test negative for anti-ACh receptor antibodies have antibodies against the MuSK protein.

Imaging
- Chest computed tomography (CT) to rule out thymoma
- If level of suspicion is high, CT abdomen to rule out RCC (5)

Diagnostic Procedures/Surgery
- Edrophonium chloride test: Positive for MG if IV administration unequivocally yields improved strength
- Repetitive nerve stimulation
- Single-fiber electromyography
- Complete urodynamic evaluation if urologic symptoms are present (4)
- Urodynamics:
  – If bladder dysfunction present, resembles lower motor neuron pattern with variable

areflexia or atonia
  – In one UDS series 63% failing to empty completely due to hypocontractile bladders and 6% had complete areflexia

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Acute inflammatory demyelinating polyradiculoneuropathy
- Botulism
- Lambert–Eaton syndrome

TREATMENT

GENERAL MEASURES
- Intermittent catheterization for rare cases of refractory detrusor areflexia (4)
- Adjust mealtimes to take advantage of daily periods of relative strength
- Install railing in household places where it will be needed for support in rising, such as adjacent to the bathtub and toilet
- Use electric toothbrushes and can openers to conserve strength
- Generalized muscle weakness in the acute setting should prompt careful attention to the possibility of respiratory failure
- Patients with MG have symptoms worsened with high core or ambient temperature; therefore, muscle strength will likely improve when a fever is treated with antipyretics
- Urinary tract symptoms, if present, may respond favorably to therapy for MG

MEDICATION
First Line
- Cholinesterase inhibitors (neostigmine, pyridostigmine) provide temporary strength improvement in patients with MG.
- Corticosteroids can produce rapid improvements in MG but are associated with numerous dose-dependent side effects

Second Line
- Plasmapheresis is reserved for short-term treatment in response to myasthenic exacerbations or crises.
- Intravenous immunoglobulin (IgG) also provides short-term improvements in strength during myasthenic exacerbations or crises as an alternative for patients who are poor plasmapheresis candidates because of vascular access issues.
- Immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, tacrolimus) for steroid-sparing protocols, or for refractory disease (6)

SURGERY/OTHER PROCEDURES
- If surgical intervention for bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH) is being considered, some advocate suprapubic prostatectomy to reduce risk of incontinence (3)
- Thymectomy results in complete remission in 35% of cases and clinical improvement in 85%

of patients
- If MG presents as paraneoplastic syndrome associated with RCC, effective treatment for RCC may resolve MG symptoms (5)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

β-Agonist and anticholinergic bronchodilators can reduce bronchospasm and respiratory distress resulting from cholinergic medications.

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most (96%) of patients have normal lifespan when appropriate medical care involving cholinesterase inhibitors, plasmapheresis, and immunosuppressive agents is given.
- Thymectomy results in complete remission in about 1/3 of patients, but the postsurgical prognosis is otherwise highly variable.

COMPLICATIONS

- Post-TURP incontinence
- Respiratory failure
- Cholinergic crisis from excessive use of cholinesterase inhibitors
- Multiple complicating effects may result from chronic steroid use, including poor wound healing and opportunistic infection

FOLLOW-UP

Patient Monitoring

Patients with MG should be followed by a neurologist with urology referral as needed.

Patient Resources

National Institute of Neurological Disorders and Stroke: Myasthenia Gravis Fact Sheet (http://www.ninds.nih.gov/disorders/myasthenia_gravis/detail_myasthenia_gravis.htm Accessed August 8, 2014)

REFERENCES

1. Phillips LH. The epidemiology of myasthenia gravis. *Ann NY Acad Sci.* 2003;998:407–412.
2. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet* 2001;357:2122–2128.
3. Wise GJ, Gerstenfeld JN, Brunner N, et al. Urinary incontinence following prostatectomy in patients with myasthenia gravis. *Br J Urol.* 1982;54:369–371.
4. Christmas TJ, et al. Detrusor failure in myasthenia gravis. *Br J Urol.* 1990;65:422.
5. Torgerson EL, Khalili R, Dobkin BH, et al. Myasthenia gravis as a paraneoplastic syndrome associated with renal cell carcinoma. *J Urol.* 1999;162(1):154–155.
6. van Sonderen A, Wirtz PW, Verschuuren JJ, et al. Paraneoplastic syndromes of the neuromuscular junction: Therapeutic options in myasthenia gravis, lambert-eaton

myasthenic syndrome, and neuromyotonia. *Curr Treat Options Neurol*. 2013;15(2):224–239.

ADDITIONAL READING

Mayo ME, Chetner MP. Lower urinary tract dysfunction in multiple sclerosis. *Urology*. 1992;39(1):67–70.

See Also (Topic, Algorithm, Media)

Neurogenic Bladder, General

CODES

ICD9

- 358.00 Myasthenia gravis without (acute) exacerbation
- 788.30 Urinary incontinence, unspecified
- 788.63 Urgency of urination

ICD10

- G70.00 Myasthenia gravis without (acute) exacerbation
- N39.41 Urge incontinence
- R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

- Patients with MG may develop voiding dysfunction, most commonly detrusor areflexia resulting in urinary retention.
- Urinary incontinence may develop after TURP.
- Urologic symptoms may be improved by systemic MG therapy, although specific therapy for urologic complications, such as urinary retention or incontinence, may need to be instituted.

MYELODYSPLASIA (SPINAL DYSRAPHISM), UROLOGIC CONSIDERATIONS

Blake A. Wynia, MD, MPH
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BASICS

DESCRIPTION

- Myelodysplasia (spinal dysraphism, neural tube defect) is a very broad term encompassing a large heterogeneous group of congenital vertebral column defects that result from defects that occur during neural tube closure.
- Group of developmental abnormalities that can be open (meningocele, myelomeningocele, lipomyelomeningocele) or closed (spinal bifida occulta, posterior meningoceles, lipomyelomeningocele, and myelocystocele).
- Primary functional deficits can be lower limb paralysis and sensory loss, bladder and bowel dysfunction, and cognitive dysfunction.
- Affected children often have varying degrees of neurogenic bladder dysfunction.

ALERT
Patients with myelodysplasia have a high incidence of latex allergy. From birth, parents need to be educated in latex precautions.

EPIDEMIOLOGY

Incidence

- Spinal dysraphism:
  - 1 per 1,000 births in USA previously
  - 2.5 times more common in Caucasians than blacks
  - Incidence decreasing over past 20 yr due to prenatal diagnosis and use of folic acid

Prevalence

- Open spinal dysraphism: 60,000 cases estimated in USA
- Spina bifida occulta: 5–10% of the general population; most cases are found incidentally

RISK FACTORS

- Maternal folate deficiency during pregnancy
- Family history: Incidence for mother with one affected child is 20–50/1,000 live births; also 2nd and 3rd degree affected relative
- Prepregnancy obesity or diabetes
- Exposure to high temperatures in early pregnancy (fever or hot tub)
- Intrauterine exposure to valproate or carbamazepine
- Low vitamin B-12 levels
- Chromosome trisomies 13 and 18, triploidy, and single-gene mutations.

Genetics

Genes involved in folate-homocysteine metabolism and transport (see Risk Factors)

PATHOPHYSIOLOGY

- Increased maternal blood AFP (α-feto protein) at 16 wk can indicate the presence of an NTD (neural tube defect).
- Spinal cord begins normal development on day 18 of gestation:
  - The canal closes in a cephalocaudal direction; complete closure day 35 of gestation
  - Exact mechanism of dysraphism undefined
- Myelodysplastic states can be subdivided:
  - Spina bifida occulta: The mildest form. No overt signs of spinal abnormality; may be associated with tethering of the spinal cord and often associated with a low-lying conus (below L2–L3); usually detected by plain x-ray, demonstrating open vertebral bodies
  - Posterior meningoceles, myelocystocele, and lipomyelomeningocele are closed defects associated with a skin-covered back mass
  - Meningocele: The meninges or dural sac, but no neural elements, extend beyond the vertebral canal. Mostly normal lower extremity
  - Myelomeningocele: The nerves and spinal cord are exposed through an opening in the spinal column, meninges, and skin. Significant neurologic defects (paralysis, urinary incontinence) are usually associated.
  - Lipomyelomeningocele: Fatty tissue along with cord structures extend with protruding sac.
- Myelomeningocele account for >90% of spinal dysraphism:
  - Arnold–Chiari malformation in 85% of children with myelomeningocele:
    - Cerebellar tonsils herniated through foramen magnum
    - The 4th ventricle is obstructed leading to hydrocephalus if shunting is not performed

ASSOCIATED CONDITIONS

- Cloacal anomalies/Cloacal exstrophy
- Hydrocephalus/Arnold–Chiari malformation
- Imperforate anus
- Latex allergy
- Sacral agenesis
- VACTERL syndrome (Vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities)

GENERAL PREVENTION

- Folic acid 0.4 mg/d in all women of childbearing age; 4.0 mg/d in women with previous NTD-affected pregnancy
  - Begin 2 mo before planned conception
- Prenatal surgery for meningomyelocele at special centers by 26 wk gestation.
  - Outcomes encouraging with shunt placement in only 68% vs. 98% who underwent postnatal repair; also results in improved mental development and motor function at 30 mo of age
  - Has not been shown to impact on urologic outcomes

DIAGNOSIS

HISTORY

- Review medical and developmental history
- Most patients now diagnosed prenatally
- Older patients commonly present with urinary and bowel incontinence:
- Change in bowel habits or gait, onset of leg or back pain, presence of seizures or other neurologic symptoms may suggest subsequent spinal cord tethering

PHYSICAL EXAM

- Assess general appearance, body habitus, gait, dexterity, muscular, and neurologic development
- Genitalia: Presence or absence of hypospadias, cryptorchidism, labiovulvar abnormalities
- Rectal exam: Perianal sensation, rectal tone, fecal impaction
- Back exam for open (obvious exposed neural tissues) or closed defects. Stigmata that may be associated with occult spinal dysraphism include:
  - Dimples or sinuses, subcutaneous mass, skin tags, hemangiomas, abnormal hair patches, pigmentation, or abnormal gluteal cleft.
- Neurologic exam:
  - Gait, balance, muscular development/tone

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Urinalysis, urine culture, basic metabolic panel with high-grade reflux or hydronephrosis

Imaging

- 15–20% of neonates have abnormality of upper tract when 1st studied
- Plain abdominal x-rays:
  - May show structural vertebral anomalies or evaluate for partial or complete sacral agenesis
  - May visualize stones or fecal impaction
- Renal US (ultrasound):
  - Determine baseline of urinary tract; should be performed shortly after birth; important to repeat after back closure prior to discharge
  - Assess for hydronephrosis, hydroureter, and PVR (postvoid residual) if patient voids spontaneously
- Voiding cystourethrogram (VCUG):
  - Assess for vesicoureteral reflux, bladder wall appearance, bladder capacity, PVR
- Dimercaptosuccinic acid (DMSA) renal scan in select cases including: High-grade reflux, renal scarring, and solitary functioning kidney
- Magnetic resonance imaging (MRI):
  - Assess spinal cord and vertebral anomalies in patients with suspected occult spinal dysraphism or a “closed” lesion. Spinal sonogram useful in children <3 mo of age prior to boney ossification.

Diagnostic Procedures/Surgery

- Urodynamic studies (UDS): Fill rate based on average bladder capacity in milliliters: (24.5 $\times$ age $+$ 62) divided by 10 is the rate of filling the bladder with warm saline
  - Often with video (video urodynamic studies or VUDS)
  - Performed 2–3 mo after back closure or at time of diagnosis of occult spinal dysraphism

– Assess bladder capacity, volume, and pressure at abdominal and detrusor leak points (compliance), pressure when reflux, if present, is observed, detrusor overactivity, detrusor sphincter dyssynergia (DSD)
– Findings: Synergic (26%), dyssynergic with or without poor detrusor compliance (37%) and complete denervation (36%)

Pathologic Findings
See Pathophysiology

DIFFERENTIAL DIAGNOSIS
- Other causes of neurogenic bladder (see Chapter on Neurogenic Bladder, general)
- Tethered cord syndrome

TREATMENT

GENERAL MEASURES (1,2,3)
- Urgent neurosurgical intervention is critical for open defects which may lead to hydrocephalus.
- Upper tract preservation is the primary goal with the achievement of continence at an appropriate age.
- Incomplete bladder emptying or significant upper tract hydronephrosis/high-grade reflux before and after repair of the back defect
- Clean intermittent catheterization (CIC) for detrusor filling pressures of >30–40 cm H_2O. May often require the addition of anticholinergic therapy (see Medication)
- Cutaneous vesicostomy or urethral dilation to lower emptying pressures not usually performed

MEDICATION
First Line
- Anticholinergics: Decrease detrusor overactivity, increases bladder compliance and functional capacity
  – Oxybutynin 0.2 mg/kg BID-TID; should be initiated early in life when indicated to prevent upper tract deterioration secondary to poor detrusor compliance and DSD
  – Tolterodine 0.01 mg/kg BID to a maximum of 0.4 mg/kg BID; long-acting forms when older
  – Almost always used in conjunction with CIC
  – Side effects: Headaches, dry mouth, flushing of skin, abdominal discomfort, blurred vision
- Prophylactic antibiotics considered for reflux

Second Line
- α-sympathomimetic, α-sympatholytic, β-sympatholytic, smooth muscle relaxants
- Imipramine 0.7 mg/kg BID with maximum dosing of 1.2 mg/kg TID; consider pretreatment EKG

SURGERY/OTHER PROCEDURES
- When pharmacotherapy and CIC do not result in favorable bladder dynamics and/or continence in older patients, consider:

  - Cystoscopy and botulinum-A toxin injection
  - Bladder augmentation usually with creation of continent catheterizable stoma since many of the children are wheelchair bound; wait until the child is 4–5 yr old for continence if upper tracts not deteriorating and bladder is not hostile
  - Anti-reflux procedure for high-grade reflux
  - Bladder neck reconstructions: Young-Dees-Leadbetter, Kropp, Pippi–Salle modification, bladder neck closure
  - Fascial sling or artificial urinary sphincters
- Bowel incontinence:
  - If oral laxatives, enemas/irrigation, and rectal suppositories do not result in social bowel continence consider MACE procedure selectively

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Neuromodulation of the bladder via intravesical electrical stimulation, sacral nerve stimulation, transcutaneous stimulation, and biofeedback; all of unproven efficacy
- Tissue-engineered bladder augmentation (experimental)
- Artificial somatic-autonomic reflex pathway procedure (experimental)

ONGOING CARE

PROGNOSIS

- Self-performance of CIC is likely in school-aged children with supervision.
- Regular monitoring for silent upper tract deterioration including renal sonogram and VUDs
- Erectile and ejaculatory dysfunction
- Delivery concerns especially at the end of gestation in myelodysplasia patients with bladder/bladder neck reconstruction

COMPLICATIONS

- Incontinence with resulting skin ulceration due to ammonia burns; consider delaying circumcision until continence program instituted since the prepuce provides protection for the glans
- Renal insufficiency
- Symptomatic UTIs
- Shunt failure or infections
- Seizure disorders
- Musculoskelet al problems (scoliosis, club foot, others)

FOLLOW-UP

Patient Monitoring

Close follow-up with pediatric urology and neurology from infancy and throughout childhood is required to avoid upper tract deterioration and achieve urinary and bowel continence.

Annual US and VUD when continent with stable upper tracts.

Patient Resources
Spina Bifida Association http://www.spinabifidaassociation.org

REFERENCES

1. Bauer SB, Austin PF, Rawashdeh YF, et al. International Children's Continence Society's recommendations for initial diagnostic evaluation and follow-up in congenital neuropathic bladder and bowel dysfunction in children. *Neurourol Urodyn*. 2012;31:610–614.
2. Rawashdeh YF, Austin P, Siggaard C, et al. International Children's Continence Society's recommendations for therapeutic intervention in congenital neuropathic bladder and bowel dysfunction in children. *Neurourol Urodyn*. 2012;31:615–620.
3. de Kort LM, Bower WF, Swithinbank LV, et al. The management of adolescents with neurogenic urinary tract and bowel dysfunction. *Neurourol Urodyn*. 2012;31:1170–1174.

ADDITIONAL READING

- Biencowe H, et al. Folic acid to reduce neonatal mortality from neural tube disorders. *Int J Epidemiol*. 2010;Suppl 1:110–121.
- De Jong T, Chrzan R, Klijn AJ, et al. Treatment of the neurogenic bladder in spina bifida. *Pediatr Nephrol*. 2008;23:889–896.
- Hopps C, Kropp K. Preservation of renal function in children with myelomeningocele managed with basic newborn evaluation and close followup. *J Urol*. 2003;169:305–308.
- Kochakarn W, Ratana-Olarn K, Lertsithichai P, et al. Follow-up for long-term treatment with clean intermittent catheterization for neurogenic bladder in children. *Asian J Surg*. 2004;27:134–136.
- Tarcan T, Bauer S, Olmedo E, et al. Long-term followup of newborns with myelodysplasia and normal urodynamic findings: Is followup necessary? *J Urol*. 2001;165(2):564–567.

See Also (Topic, Algorithm, Media)
- Latex allergy, Urologic Considerations
- Myelodysplasia (Spinal Dysraphism), Urologic Considerations Image
- Neurogenic Bladder, General Considerations
- Tethered Cord Syndrome

CODES

ICD9
- 238.75 Myelodysplastic syndrome, unspecified
- 596.54 Neurogenic bladder NOS
- 788.30 Urinary incontinence, unspecified

ICD10
- D46.Z Other myelodysplastic syndromes
- N31.9 Neuromuscular dysfunction of bladder, unspecified
- R32 Unspecified urinary incontinence

CLINICAL/SURGICAL PEARLS

- Affected children often have varying degrees of neurogenic bladder and bowel dysfunction.
- 1st-line treatment consists of CIC for elevated PVR and anticholinergics when VUD testing suggests poor detrusor compliance and/or detrusor overactivity with or without upper tract deterioration. Botulinum-A toxin injections, bladder augmentation, antireflux procedures and /or bladder neck procedures performed to protect upper tracts and achieve urinary continence.

NEPHROCALCINOSIS, ADULT

Jennifer E. Heckman, MD, MPH
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BASICS

DESCRIPTION

- Disorder characterized by deposition of calcium salts in the renal parenchyma
  - Calcium oxalate (CaOx)
  - Calcium phosphate (CaPhos)
- May be intratubular or interstitial
- May cause renal injury or be incidentally detected
- Associated with multiple conditions
  - Renal prognosis dependent on underlying cause
  - Often associated with severe metabolic defects
- Can be classified by location:
  - Renal medulla (medullary nephrocalcinosis)
  - Renal cortex (cortical nephrocalcinosis)
- Can also be classified as:
  - Molecular: Measurable increase in intracellular calcium concentration, but not visible microscopically or radiographically
  - Microscopic: Visible microscopically
  - Macroscopic: Visible radiographically
- Distinct entity from nephrolithiasis (calcifications in collecting system)
- Neonatal nephrocalcinosis is discussed in Section II "Nephrocalcinosis, Neonatal"

EPIDEMIOLOGY

Incidence

Unclear secondary to wide range of etiologies

Prevalence

- Primarily diagnosed in:
  - Adults
  - Low–birth-weight neonates (60% of preterm infants, frequently caused by loop diuretics)
- Medullary nephrocalcinosis (97–98%), cortical nephrocalcinosis (2–3%)

RISK FACTORS

- Disorders that cause:
  - Hypercalcemia
  - Hyperphosphatemia
  - Hypercalciuria
  - Hyperphosphaturia
  - Hyperoxaluria
  - Hypocitraturia

Genetics
Inherited disorders may lead to risk factors for nephrocalcinosis development (eg, autosomal dominant hypocalcemia, familial hyperoxaluria)

PATHOPHYSIOLOGY
- Caused by increase in urinary excretion of calcium, phosphate, and/or oxalate (1)
  - May occur with or without hypercalcemia
  - CaOx and CaPhos crystals result from urinary supersaturation
    - CaOx and CaPhos crystals precipitate, aggregate, and move to interstitium
    - May result in acute or chronic renal damage and/or lead to calculus formation
    - Renal ischemia or injury may augment nucleation of CaOx or CaPhos crystals

ASSOCIATED CONDITIONS
- Nephrolithiasis
- Hypercalciuric states:
  - Primary hyperparathyroidism (most common cause in adults)
  - Sarcoidosis
  - Vitamin D intoxication
  - Multiple myeloma
  - Tuberculosis
  - Milk-alkali syndrome
  - Distal renal tubular acidosis
  - Medullary sponge kidney
  - Inherited tubular defects (eg, Bartter syndrome)
  - Chronic hypokalemia (eg, primary aldosteronism)
  - Chronic immobilization
- Hyperphosphaturic states:
  - Tumor lysis syndrome
  - Inherited tubular defects
- Hyperoxaluric states:
  - Primary oxaluria
  - Secondary oxaluria (increased intake or enhanced absorption)
  - Fat malabsorptive disorders (eg, pancreatic insufficiency, inflammatory bowel disease)
- Chronic pain

GENERAL PREVENTION
- Avoid hypercalciuric, hyperphosphaturic, and hyperoxaluric states
- Avoid medications that enhance calcium loss (eg, loop diuretics)

DIAGNOSIS
HISTORY
- Most cases are asymptomatic (incidental finding on imaging)
- Occasionally present with symptoms related to underlying cause or associated condition
  - Nausea, decreased appetite, abdominal pain, myalgias, polydipsia, lethargy (hypercalcemia)
  - Fatigue, edema, mental status changes, seizures (renal failure)

  – Renal colic, hematuria (nephrolithiasis)
• Review past medical history and medications

PHYSICAL EXAM
• Nonspecific, many patients are asymptomatic
• Physical findings otherwise a manifestation of underlying disorder

DIAGNOSTIC TESTS & INTERPRETATION
Lab
• Used to identify underlying causative disorder
• Serum studies:
  – Calcium, phosphate, albumin
  – Electrolytes
  – BUN, Cr
  – Parathyroid hormone (PTH) levels
  – Thyroid-stimulating hormone (TSH) levels
  – CBC
• Urine studies:
  – Urinalysis with microscopy +/– urine culture (if indicated)
  – 24-hr urine collection

Imaging
• Can be detected on:
  – Abdominal radiograph
    ◦ Usually only if attenuation >100 Hounsfield units and size >2 mm
    ◦ Medullary nephrocalcinosis: Stippled calcifications in renal pyramids
    ◦ Cortical nephrocalcinosis: Thin peripheral band with perpendicular extension; thin, peripheral calcific tracts; or diffuse punctuate calcifications
  – Ultrasound
    ◦ Hyperechoic areas with or without acoustic shadowing
  – Computed tomography
    ◦ Most sensitive and specific
• Pattern and distribution may be suggestive of etiology
• Imaging extent of calcium deposition unrelated to renal functional impairment or prognosis
• Regardless of imaging modality, can be difficult diagnosis, with low levels of intra-observer concordance (2)[B]

Diagnostic Procedures/Surgery
• Radiographic diagnosis (usually incidental finding)
• Rarely, diagnosed on renal biopsy

Pathologic Findings
• Primary histologic finding on renal biopsy:
  – Tubular, intracellular, and interstitial basophilic calcifications
• (+) von Kossa stain of calcifications diagnostic of CaPhos

DIFFERENTIAL DIAGNOSIS
• Nephrolithiasis

- Renal calcifications, associated with:
  - Chronic ureteropelvic junction obstruction or ureterocele
  - Renal infarction
  - Renal mass
- Dystrophic calcifications, associated with:
  - Renal tuberculosis
  - Congenital cystic kidney
- Renal artery calcifications
- Calcification associated with spinal injury

TREATMENT

GENERAL MEASURES

- Treatment directed at underlying etiology
- No specific treatment prevents progression
- Early treatment of reversible causes of renal injury important
- Reduce urinary concentration and increase solubility of calcium, phosphate, and/or oxalate
  - Increase fluid intake
    - Goal urine output >2 L/d
  - If hypercalciuria:
    - Restrict animal protein intake (<0.7 g/kg)
    - Restrict sodium intake (<100 mEq/d)
  - If hypocitraturia and urine pH <7:
    - Potassium citrate (titrate to normal urinary citrate)

MEDICATION

First Line

Must be tailored to underlying etiology (eg, for hyperparathyroidism, resection of adenoma, treatment of renal tubular acidosis, etc.)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgical intervention may be required, particularly if calcification obstructs collecting system
  - Endourologic management
    - May use in diagnosis (direct visual inspection) (3)[C]
    - May treat with flexible ureteroscopy/nephroscopy with laser or electrohydraulic lithotripsy (4)[C]
    - Ureteroscopic laser papillotomy may be safe and effective in patients with chronic flank pain (5)[C]
  - Extracorporeal shockwave lithotripsy (ESWL)
    - Poor fragmentation and evacuation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Depends on underlying etiology
- Most do not progress to end-stage renal failure

COMPLICATIONS
- Nephrolithiasis
- Obstructive uropathy
  - May be associated with sepsis
- Renal infection
- Renal scarring
- Defects in renal tubular function
- Acute renal failure
- Chronic renal failure

FOLLOW-UP
Patient Monitoring
- Urinalysis, 24-hr urine collection
- Renal function testing
- Serum Ca
- Labs to monitor known metabolic abnormalities
- Imaging if symptomatic

Patient Resources
http://www.umm.edu/ency/article/000492.htm

REFERENCES

1. Sayer JA, Carr G, Simmons NL. Nephrocalcinosis: Molecular insights into calcium precipitation within the kidney. *Clin Sci (Lond)*. 2004;106:549–561.
2. Cheidde L, Ajzen SA, Tamer Langen CH, et al. A critical appraisal of the radiological evaluation of nephrocalcinosis. *Nephron Clin Pract.* 2007;106(3):c119–c124.
3. Miller NL, Humphreys MR, Coe FL, et al. Nephrocalcinosis: Re-defined in the era of endourology. *Urol Res.* 2010;38(6):421–427.
4. Kerbl K, Clayman RV. Endourologic treatment of nephrocalcinosis. *Urology*. 2000;56(3):508.
5. Gdor Y, Faddegon S, Krambeck AE, et al. Multi-institutional assessment of ureteroscopic laser papillotomy for chronic flank pain associated with papillary calcifications. *J Urol.* 2011;185(1):192–197.

ADDITIONAL READING

Monk RD, Bushinsky DA, Chapter 57. Nephrolithiasis and nephrocalcinosis. In: Floege J, Johnson RJ, Feehally J, eds. *Comprehensive Clinical Nephrology*. 4th ed. Philadelphia, PA: Mosby Elsevier; 2011.

See Also (Topic, Algorithm, Media)

- Calcifications, Renal
- Hypercalcemia, Urologic Considerations
- Hypercalciuria (Absorptive, Renal, and Resorptive)
- Hyperoxaluria
- Hyperparathyroidism, Urologic Considerations
- Hyperphosphatemia and Hypophosphatemia, Urologic Considerations
- Hypocitraturia
- Hypokalemia, Urologic Considerations
- Medullary Sponge Kidney
- Milk-alkali Syndrome
- Nephrocalcinosis, Adult Images
- Nephrocalcinosis, Neonatal
- Renal Tubular Acidosis
- Tumor Lysis Syndrome
- Urolithiasis, Adult, General Considerations
- Urolithiasis, Calcium Oxalate/Phosphate
- Urolithiasis, Pediatric, General Considerations

CODES

ICD9

- 275.3 Disorders of phosphorus metabolism
- 275.42 Hypercalcemia
- 275.49 Other disorders of calcium metabolism

ICD10

- E83.52 Hypercalcemia
- E83.59 Other disorders of calcium metabolism
- N29 Oth disorders of kidney and ureter in diseases classd elswhr

CLINICAL/SURGICAL PEARLS

- Important to distinguish nephrocalcinosis from nephrolithiasis.
- Management directed at underlying cause of disorder.
- Primarily a radiographic diagnosis, does not typically require surgical intervention.

NEPHROTIC SYNDROME

Michael Perrotti, MD

BASICS

DESCRIPTION

- Neoprotic syndrome refers to a specific renal disease with a distinct constellation of clinical and laboratory features:
  - Proteinuria (>3.5 g/d)
  - Hypoalbuminemia (<3 g/dL)
  - Peripheral edema
  - Hyperlipidemia and thrombotic disease frequently seen
- Nephrotic syndrome (NS) can be caused by specific renal diseases or systemic diseases such as diabetes, lupus and others.

EPIDEMIOLOGY

Incidence

- Uncommon Disease
  - Children: 2/100,000 new cases / year
  - Adult: 3/100,000 new cases / year

Prevalence

N/A

RISK FACTORS

- Primary renal disease (minimal change disease predominant cause in children)
- Underlying systemic disease in 30% of adults with NS including diabetes mellitus, amyloidosis, systemic lupus erythematosus
- Infection: Streptococcus, hepatitis, mononucleosis, syphilis, tuberculosis, HIV
- Medications: NSAIDs, interferons, bisphosphonates, lithium, gold, captopril, penicillamine, tyrosine kinase inhibitors
- Malignancy

Genetics

- Rare cause
  - 2–8% of cases are familial
  - Finnish type congenital nephritic syndrome is inherited as autosomal recessive

PATHOPHYSIOLOGY

- Severe proteinuria is due to abnormal permeability of the glomerular basement membrane (GBM) (1).
  - GBM normally restricts passage of proteins >70 kd.
- Signs/symptoms of NS worsen as serum albumin falls below 2.5 g/dL.
- Proteinuria can be selective or nonselective.
- Edema results from primary salt retention and secondary decreased plasma oncotic pressure.
- Hyperlipidemia is secondary to increased hepatic synthesis from low oncotic pressure and

urinary loss of regulatory proteins.
- Hypercoagulable state is likely due to loss of antithrombin III in urine.

ASSOCIATED CONDITIONS
- Membranous nephropathy (24%)
- Minimal change disease (15%)
- Lupus (14%)
- Focal segmental glomerulosclerosis (12%)
- Membranoproliferative glomerulonephritis (7%)
- Amyloidosis (6%)
- IgA nephropathy (6%)

GENERAL PREVENTION
- Avoidance of risk factors
- Treating conditions that may cause NS

DIAGNOSIS
HISTORY
- Symptoms of fluid/sodium retention:
  - Periorbital edema, especially on awakening
  - Peripheral edema, especially at end of day
  - Dyspnea/orthopnea secondary to pleural effusion
- Anorexia
- Oliguria, foamy urine
- Weight gain
- Foamy appearance of urine

PHYSICAL EXAM
- Along with signs of fluid retention, patients may have signs of systemic disease causing NS
- Vital signs: BP, temperature, weight
- Skin exam: Rash (eg, butterfly rash of SLE), pallor, edema, lymphadenopathy
- Ophthalmic exam: Uveitis in sarcoid, diabetic retinopathy
- Heart/lung exam: Endocarditis, pleural effusion
- Abdominal exam: Masses, ascites
- Neurologic exam: Diabetic neuropathy, CNS lesion, mononeuritis multiplex

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Blood chemistry: BUN, Cr, comprehensive metabolic panel, CBC
  - Hypoalbuminemia (<3 g/dL)
- Serum lipids: Cholesterol, triglycerides often elevated
- Urine analysis and microscopy
  - Marked proteinuria causes urine to foam.
  - Albuminuria detected by dipstick; all proteinuria detected by SSA; Protein is precipitated in urine by the addition of sulfosalicylic acid (SSA). Performed to confirm positive protein reactions seen on a urine dipstick.

  – Positive SSA and negative dipstick: Nonalbumin proteinuria (multiple myeloma)
  – Characteristic dipstick reading of 3+ to 4+ in NS patients
  – Glycosuria: Suggests diabetes mellitus as possible cause of NS
  – Hematuria common (usually microscopic)
  – Lipiduria: Maltese crosses seen microscopically
  – Microscopic: Oval fat bodies, fatty casts, hyaline casts, cellular casts
- 24-hr urine
  – Protein > 3.5 g/24 h, mostly albumin
- Additional testing as needed to rule out other nonrenal causes
  – Fasting blood sugar/glucose tolerance
  – Hepatitis B and C antibodies
  – Antinuclear antibody
  – Syphilis serology
  – HIV
  – Multiple myeloma

Imaging
- Renal ultrasound: Increased echogenicity of renal parenchyma
- Screening for underlying malignancy with CT scan

Diagnostic Procedures/Surgery
Renal biopsy

Pathologic Findings
- Minimal change glomerulopathy
- Membranous glomerulopathy
- Focal segmental glomerulonephritis
- Mesangioproliferative glomerulonephritis
- Membranoproliferative glomerulonephritis
- Diabetic glomerulosclerosis
- Fibrillary glomerulonephritis
- Light chain deposition disease

DIFFERENTIAL DIAGNOSIS
- Congestive heart failure
- Cirrhosis
- Malnutrition
- Protein losing enteropathy

TREATMENT

GENERAL MEASURES
- Sodium restriction (2 g/d)[A]
- Protein restriction
- BP control
- Maintenance of fluid balance

MEDICATION

First Line

- ACE inhibitors (captopril, enalapril, ramipril, others) or Angiotensin II receptor blockers (losartan, olmesartan, telmisartan others) (2)
  - Indicated with random protein to creatinine ratio >200 mg/G
  - Should not be used concurrently due to risk of hypotension and worsening renal function
  - Monitor for hypotension, hypokalemia, or worsening renal function
  - Common ACE-I side effects include cough, angioedema, or allergy
- Statin therapy
  - Goal LDL <100 and triglyceride <150
  - Side effects include myalgia, liver dysfunction, GI disturbance, and rash
- Corticosteroids for primary idiopathic or minimal change disease (3)[A]

Second Line

Cytotoxic agents (cyclophosphamide, chlorambucil, cyclosporine): Minimal change disease unresponsive to steroids, membranous glomerulonephritis with poor prognosis

SURGERY/OTHER PROCEDURES

- Dialysis
- Renal transplantation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Anticoagulation for thrombosis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prognosis depends on age, race, pathology, presence of HTN, underlying systemic disease, degree of renal dysfunction, and degree of proteinuria.
- Minimal change disease in children has an excellent prognosis.
- Prognosis of the other glomerulopathies much more variable.
- Prognosis of secondary NS depends on the systemic diseases causing the NS.

COMPLICATIONS

- Acute kidney failure
- Atherosclerosis, hyperlipidemia, cardiovascular disease
- Chronic kidney disease
- Congestive heart failure
- Heart disease
- Malnutrition
- Pneumococcal pneumonia and other infections

- Pulmonary edema
- Arterial and venous thrombosis (particularly deep vein and renal vein thrombosis)
- Pulmonary emboli

FOLLOW-UP

Patient Monitoring

- Assess response to treatment with 24-hr urine protein measurement
- Monitor BP and renal function
- Monitor for treatment toxicity

Patient Resources

- Medline Plus http://www.nlm.nih.gov/medlineplus/ency/article/000490.htm
- www.kidney.diddk.nih.gov

REFERENCES

1. Siddall EC, Radhakrishnan L. The pathophysiology of edema formation in the nephritic syndrome. *Kidney Int.* 2012;62:635–642.
2. Nakao N, Yoshimura A, Morita H, et al. Combination treatment of angiotensin II receptor blocker and angiotensin converting enzyme inhibitor in non-diabetic renal disease. A randomized controlled trial.*Lancet.* 2003;361:117–124.
3. Maas R, Hofstra JM, Wetzels JF. An overview of immunosuppressive therapy in idiopathic membranous nephropathy. *Minerva Med.* 2012;103:253–266.

ADDITIONAL READING

Cadnapaphornchai MA, Tkachenko O, Shchekochikhin D, et al. The nephrotic syndrome: Pathogenesis and treatment of edema formation and secondary complications. *Pediatr Nephrol.* 2014;29(7):1159–1167.

See Also (Topic, Algorithm, Media)

- Chronic Kidney Disease, Adult (Renal Failure, Chronic)
- Chronic Kidney Disease, Pediatric (Renal Failure, Chronic)
- Glomerulonephritis, Acute
- Nephropathy, Membranous
- Nephropathy, Minimal Change
- Proteinuria

CODES

ICD9

- 250.40 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
- 250.41 Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
- 581.9 Nephrotic syndrome with unspecified pathological lesion in kidney

ICD10

- E10.21 Type 1 diabetes mellitus with diabetic nephropathy
- E11.21 Type 2 diabetes mellitus with diabetic nephropathy

- N04.9 Nephrotic syndrome with unspecified morphologic changes

CLINICAL/SURGICAL PEARLS

- NS is a constellation of signs and symptoms caused by different disorders that damage the kidneys.
- The hallmark of NS is excess protein in the urine and edema.
- The most common cause in children is minimal change disease.
- The most common cause in adults is membranous glomerulonephritis.
- Treatment is directed toward the underlying disorder, symptom reduction, and prevention of complications and preservation of renal function.
- Most patients are given an ACE inhibitor or an angiotensin II receptor blocker to slow the loss of kidney function.

NEUROBLASTOMA

Nilay M. Gandhi, MD
Arthur L. Burnett, II, MD, MBA, FACS

BASICS

DESCRIPTION

- Heterogeneous malignancy arising from neural crest elements along the sympathetic chain with a broad spectrum of clinical behavior
- International Neuroblastoma Staging System (INSS) (1)
  - Stage 1: Localized tumor, completely excised, ipsilateral lymph nodes (LN) (–)
  - Stage 2a: Localized tumor, incompletely excised, ipsilateral LN (–)
  - Stage 2b: Localized tumor with/without complete excision, ipsilateral LN (+), enlarged contralateral LN (–)
  - Stage 3: Unresectable unilateral tumor crossing midline or localized unilateral tumor with contralateral LN (+)
  - Stage 4: Any primary tumor with metastasis to distant LN, bone, liver, skin, or bone marrow
  - Stage 4s: Localized primary tumor (stage 1, 2a, 2b) metastasis limited to liver, skin, and/or bone marrow in infant <1 yr

EPIDEMIOLOGY

Incidence

- 3rd most common childhood cancer (after leukemia and brain tumors)
  - Most common solid extra-cranial tumor in children
  - Most common cancer in infants <1 yr of age
- Comprises 6–10% of all childhood neoplasms
  - 1 in 7,000 live births
  - 750 new cases/yr
    - 50% incidence in children <2 yr of age (highest incidence in 1st yr of life)
    - Peak age 0–4 yr (median 18–24 mo)
    - More common in Caucasian male infants

Prevalence

- 10.5 per 1 million children <15 yr of age
- Accounts for 15% of all pediatric cancer fatalities

RISK FACTORS

- Risk in sibling or offspring is <6%
- Maternal factors:
  - Folate deficiency (increased incidence)
  - Gestational diabetes mellitus
- Environmental factors implicated but not confirmed (2)
  - Paternal exposure to electromagnetic fields
  - Prenatal exposure to alcohol, pesticides, or phenobarbital

  – Potential relationship with assisted pregnancies
- Genetic factors:
  – Increased incidence in Turner's syndrome

Genetics
- Majority are sporadic
  – 1–2% familial (autosomal dominant 20%)
    ○ 20% bilateral adrenal or multifocal tumors
    ○ Germline mutation in *ALK* gene
- Aneuploidy = favorable prognosis
- N-*MYC* amplification (20% patients), chromosome 1p deletion (25–35%), loss of 11q heterozygosity (35–45%) = adverse prognosis

PATHOPHYSIOLOGY
- Determined by tumor site origin, metastasis, and presence of paraneoplastic syndromes
- Likely failure of persistent primitive ganglion cells to respond to normal signals
- Spinal cord, sympathetic ganglia involvement:
  – Urinary retention, constipation, extremity paresis, Horner syndrome
- Presence of metastasis:
  – Fever, lethargy, weight loss, bony pain, pallor
- Bone metastasis (older children)
- Liver metastasis (younger children)
- Active biochemical products:
  – 90% produce catecholamines
    ○ Paroxysmal hypertension (HTN), palpitation, flushing, headache
  – Homovanillic acid (HVA) in poorly differentiated tumors
  – Vanillylmandelic acid (VMA) in well-differentiated tumors

ASSOCIATED CONDITIONS
- Other disorders of neural crest derived cells
  – Hirschsprung disease
  – Neurofibromatosis type 1
  – Congenital central hypoventilation syndrome

GENERAL PREVENTION
- Screening with urinary catecholamines is not effective (Japan, Canada, Germany)
  – Increased diagnosis, no impact on survival
  – Majority low-grade, spontaneously resolve
- Genetic counseling indicated if family history

DIAGNOSIS

HISTORY
- Early satiety, poor appetite, vomiting
  – Possible partial bowel obstruction due to intra-abdominal mass
- Unexplained weight loss, anorexia, fever, pallor, irritability suggests metastatic disease

- Urinary frequency/retention, constipation:
  - Extrinsic compression of pelvic organs/nerves from presacral mass
- Poor truncal balance, jerky muscle movements, or uncontrolled eye movement
  - Acute myoclonic encephalopathy (2%)
    - Toxic byproducts/autoimmune phenomenon
- Extremity weakness, sensory deficits
  - Paravertebral tumor compressing spinal cord
- Pain in skull and long bones from metastasis
- Pallor/anemia (bone marrow involvement in 50% of patients)
- Bleeding diathesis (from liver metastasis)
- Paroxysmal HTN, sweating, headaches, palpitations
  - $<5\%$ patients (catecholamines sequestered within intracellular vacuoles)
- Watery diarrhea, hypokalemia due to VIP secretion

PHYSICAL EXAM
- Abdominal mass
  - 65% retroperitoneal, 40% adrenal
- HTN (rare, due to catecholamine release)
- Metastasis present in 70% at diagnosis
  - Raccoon's eyes
    - Upper eyelid hemorrhage (periorbital metastasis)
  - Bluish/erythematous subcutaneous nodules
    - Skin metastasis, "blueberry-muffin" spots
- Acute myoclonic encephalopathy
  - Rapid eye movements (opsoclonus), jerky extremities (myoclonus)
  - Cerebellar ataxia, dysphasia, intellectual deficit
  - Autoimmune phenomenon
  - 70–80% with prolonged neurologic impairment (ACTH/steroid therapy)
- Unilateral Horner's syndrome
  - Ptosis, loss of papillary dilation, unilateral anhydrosis
  - Tumor compression on sympathetic ganglia
- Extremity paresis, sensory deficits
  - Paravertebral tumor compressing spinal cord

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- 24-hr urinary VMA and HVA
  - Elevated in 90–95% of patients
- CBC: Anemia suggests bone marrow involvement
- PT/PTT: Elevation suggests liver involvement
- Ferritin: Elevation in advanced disease
  - 40–50% of patients (must be >3 standard deviations)

Imaging
- Ultrasound (1st choice for children with palpable abdominal mass)
- Whole-body CT

  – Evaluate primary tumor, regional extent, distant metastasis
  – Intratumoral calcification and/or vascular encasement distinguishes from Wilms tumor
• Whole-body MRI
  – Evaluate intraspinal tumor extension, delineate major vessels
• Bone scan (radionuclide, not skelet al)
• Iodine^{123} MIBG
  – Determine extent of disease, assess tumor recurrence

Diagnostic Procedures/Surgery
• Open/laparoscopic biopsy for pathologic tissue diagnosis
• Bone marrow aspirate/biopsy
  – 2 marrow aspirates (bilateral iliac crests) + 2 core biopsies recommended
  – 70% positive aspirates
    ◦ Future research into neuroblastoma-specific immunocytology of marrow aspirates

Pathologic Findings
• Gross: Solid/cystic vascular, poorly encapsulated purple mass
• Histology:
  – Small round blue cells
    ◦ Mitosis-Karyorrhexis index is prognostic
  – Homer–Wright pseudorosettes
• Histopathologic markers:
  – N-*MYC*
  – DNA ploidy
  – Shimada classification (stroma poor/rich)
    ◦ Stroma-poor (based on age, histologic maturation, mitotic rate)
    ◦ Stroma-rich (nodular, intermixed, well differentiated)
• Neuron-specific enolase (NSE) staining is specific for neuroblastoma
• Periodic acid-Schiff (PAS) staining can distinguish sarcomas

DIFFERENTIAL DIAGNOSIS
• Ganglioneuroma (benign form)
• Ganglioneuroblastoma (intermediary between ganglioneuroma and neuroblastoma)
• Intra-abdominal mass in childhood:
  – Wilms tumor
  – Pheochromocytoma
  – Rhabdomyosarcoma
  – Lymphoma
  – Teratoma
  – Ewing sarcoma
  – Rare primary neoplasms of liver and pancreas

TREATMENT

GENERAL MEASURES
• Multimodal treatment approach involving surgery, chemotherapy, radiotherapy, and/or

bone marrow or stem cell transplantation
- Nearly all stage 4s patients spontaneously resolve (observation)
- INSS surgical stage and more recently the International Neuroblastoma Risk Group (INRG) pretreatment system dictates treatment (3)

MEDICATION

First Line (4)

- Low risk: None unless surgical failure
  – Cyclophosphamide, Adriamycin, and Cisplatin/VM-26 in low-dose cycles
- Intermediate risk: Induction with Cyclophosphamide and Adriamycin with or without radiotherapy
- High risk: Cyclophosphamide, Adriamycin, VM-26, Doxorubicin, Cisplatin, Etoposide in various combinations

Second Line

- Intermediate risk: Cisplatin/VM-26
- High risk: Alternative use of above-listed combinations

SURGERY/OTHER PROCEDURES

- Low risk (stages 1, 2, or 4s with age <1 yr or >1 yr with favorable pathology):
  – Surgery is curative
  – Chemotherapy indicated if recurrence, N-*MYC* amplification, or unfavorable histology
- Intermediate risk (stage 3 age <1 yr or >1 yr with favorable pathology, or stage 4 <1 yr):
  – Surgery + multiagent chemotherapy
- High risk (stage 2 with age >1 yr with unfavorable histopathology, or stage 3, 4, 4s with N-*MYC* amplification regardless of age):
  – Intensive chemotherapy with or without bone marrow ablation and repeated surgery

ADDITIONAL TREATMENT

Radiation Therapy

- Reserved for primary or secondary chemotherapy failures in low-risk patients
- Utilized for local control in bulky stage 3 or advanced stage 4
  – Avoid if spinal cord compression due to adverse effects on spine growth
- Intraoperative radiation therapy not better than external beam irradiation

Additional Therapies

Bone marrow transplantation

Complementary & Alternative Therapies (5)

- 13-cis-retinoic acid improves 5-yr overall survival (OS) in children with advanced stage disease after transplantation or intensive chemotherapy
- Iodine^{131} MIBG targeted delivery for metastatic disease
- Anti-GD2 antibodies (research pending)

ONGOING CARE

PROGNOSIS

- Dependent on risk status

  - Low risk: Resection is curative, 97% 5-yr OS
  - Intermediate risk: neoadjuvant chemo followed by >50% resection, 70–90% 5-yr OS
  - High risk: Neoadjuvant chemo 4 cycles (restage after 2 cycles), >50% resection, radiation, peripheral stem cell transplant, monoclonal Ab, 20–40% 5-yr OS
- Better survival in nonadrenal primary tumors
- Shimada classification
  - Stroma-poor: <10% survival

COMPLICATIONS

- Dumbbell neuroblastoma with spinal cord compression
  - Best treated with chemotherapy
  - Neurosurgical intervention only for emergent decompression
- Associated with tumor presentation and with treatment modalities

FOLLOW-UP

Patient Monitoring

- Low risk:
  - Imaging + lab markers 1–2 mo after therapy, every 6 mo for 5 yr, then annually after 5 yr
- Intermediate risk:
  - Imaging + lab markers 1–2 mo after therapy, every 1–3 mo for 1st yr, then every 4–6 mo for 2–5 yr, then annually after 5 yr
- High risk:
  - Imaging + lab markers 1–2 mo after therapy, every 1–3 mo for 5 yr, every 6 mo after 5 yr

Patient Resources

- National Cancer Institute (http://www.cancer.gov/cancertopics/types/neuroblastoma)
- National Cancer Comprehensive Network (http://www.nccn.com/living-with-cancer/265-neuroblastoma.html)

REFERENCES

1. Brodeur GM, Seeger RC, Barrett A. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol.* 1988;6(12):1874–1881.
2. Park JR, Eggert A, Caron H. Neuroblastoma: Biology, prognosis, and treatment. *Pediatr Clin North Am.* 2008;55(1):97–120.
3. Montclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: An INRG Task Force report. *J Clin Oncol.* 2009;27(2):298–303.
4. Maris JM. Recent advances in neuroblastoma. *NEJM.* 2010;362:2201–2211.
5. Wagner LM, Danks MK. New therapeutic targets for the treatment of neuroblastoma. *J Cell Biochem.* 2009;107(1):46–57.

ADDITIONAL READING

- Matthay KK, George RE, Yu AL. Promising therapeutic targets in neuroblastoma. *Clin Cancer Res.* 2012;18(10):2740–2753.
- Wylie L, Philpott A. Neuroblastoma progress on many fronts: The neuroblastoma research symposium. *Pediatr Blood Cancer.* 2012;58(4):649–651.

See Also (Topic, Algorithm, Media)

- Abdominal mass, newborn/child, urologic considerations
- Neuroblastoma Image ☼
- Pheochromocytoma
- Wilms tumor (nephroblastoma)

CODES

ICD9

- 194.0 Malignant neoplasm of adrenal gland
- 197.7 Malignant neoplasm of liver, secondary
- 198.5 Secondary malignant neoplasm of bone and bone marrow

ICD10

- C74.90 Malignant neoplasm of unsp part of unspecified adrenal gland
- C78.7 Secondary malig neoplasm of liver and intrahepatic bile duct
- C79.52 Secondary malignant neoplasm of bone marrow

CLINICAL/SURGICAL PEARLS

- Most common malignancy in infants <1 yr.
- INSS stage determines optimum treatment modality.
- Urine HVA and VMA are diagnostic.
- N-*MYC* associated with poor prognosis.
- Neuroblastoma requires a minimum of 5-yr follow-up.

NEUROGENIC BLADDER, GENERAL CONSIDERATIONS

Alana M. Murphy, MD

BASICS

DESCRIPTION

Neurogenic bladder (NGB) is a general term used to describe dysfunction of the urinary bladder due to disease of the central nervous system (CNS) or peripheral nerves involved in the control of urine storage and micturition

EPIDEMIOLOGY

Incidence

Difficult to determine incidence due to multiple etiologies

Prevalence

- Prevalence of voiding dysfunction by specific conditions:
  - Cerebrovascular accident: 20–50%
  - Parkinson disease: 35–70%
  - Multiple sclerosis: 50–90%
  - Diabetes mellitus: 5–60%

RISK FACTORS

- Neurologic disease, injury, or congenital malformation
- Diabetes mellitus
- Radical pelvic surgery

Genetics

Genetic diseases that may be associated with NGB include muscular dystrophy, hereditary spastic paraplegia, neurofibromatosis, and familial dysautonomia

PATHOPHYSIOLOGY

- CNS lesions (1):
  - Suprapontine:
    - Function: Inhibits sacral micturition center
    - Detrusor overactivity (DO) due to loss of inhibition of sacral micturition center
  - Pontine micturition center:
    - Function: Coordinates sphincter relaxation during bladder contraction
    - Lesions between pontine and sacral micturition centers are associated with DO and detrusor sphincter dyssynergia (DSD)
  - Sacral micturition center:
    - Function: Mediates reflex and voluntary bladder contraction
    - Detrusor underactivity or acontractility
- Peripheral lesions (1): Variable voiding dysfunction
  - Detrusor underactivity
  - Impaired bladder sensation
  - Impaired sphincteric function

ASSOCIATED CONDITIONS

- CNS diseases:
  - Cerebrovascular accident
  - Multiple sclerosis
  - Normal-pressure hydrocephalus
  - Parkinson disease
  - Spinal cord injury
  - Transverse myelitis
- Peripheral nerve disease:
  - Following radical pelvic surgery:
    - Abdominoperineal resection
    - Radical hysterectomy
  - Diabetes mellitus
  - Intervertebral disk disease
  - Spinal stenosis
  - Guillain–Barré syndrome
- Neural tube defects
- Cerebral palsy

GENERAL PREVENTION

- Tight glycemic control with diabetes mellitus
- Prevention aimed at preventing secondary complications
  - Infections
  - Incontinence
  - Skin breakdown
  - Urolithiasis

DIAGNOSIS

HISTORY

- Neurologic disease: Onset, duration
- Diabetes mellitus
- Congenital disorders:
  - Neural tube defects
  - Cerebral palsy
- History of radical pelvic surgery
- Voiding symptoms
- Storage symptoms
  - Urinary frequency
  - Incontinence
- Method of urinary management:
  - Volitional or reflex voiding
  - Condom catheter urinary collection
  - Intermittent self-catheterization
  - Indwelling urethral or suprapubic catheter
  - Credé or Valsalva voiding

- UTI:
  - Severity of infection: Febrile, hospitalization, IV antibiotics required
  - Frequency of recurrence
- Urolithiasis episodes, surgical intervention, calculus composition
- Autonomic dysreflexia (AD): Associated with spinal cord lesion at or above T6
  - Occurs with manipulation of the urinary or gastrointestinal tract

PHYSICAL EXAM

- Flank tenderness: Ureteral obstruction, pyelonephritis
- Abdominal mass: Distended bladder, urinary retention
- Incontinence of urine:
- Testicular exam:
  - Epididymo-orchitis/epididymitis; secondary abscess
- Digital rectal exam:
  - Prostate size: BPH may coexist with NGB
  - See neurologic exam
- Evaluate for sacral abnormalities:
  - Sacral dimple, skin tag, discoloration or tuft of hair may suggest occult spinal dysraphism
  - Sacral agenesis
- Focused neurologic exam:
  - Sacral root
  - Perianal sensation
  - Anal tone, sphincter control

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Blood studies:
  - Serum chemistry: Renal function, creatinine
  - CBC: Elevated WBC, secondary anemia due to decreased renal function or chronic infection
- Urinalysis:
  - Proteinuria: Renal dysfunction
  - Pyuria, nitrite, leukocyte esterase: Acute or chronic infection
  - Hematuria: Infection or urolithiasis

Imaging

- Imaging is most important in patients with risk factors for upper tract compromise:
  - DSD (especially males who void reflexively)
  - Impaired bladder compliance
- Renal ultrasound (US): To screen for calculus, hydronephrosis, or mass
- Excretory urography:
  - Delayed excretion of contrast with high urinary storage pressures
  - Hydroureteronephrosis:
    - Marked elevation of intravesical pressure or calculi
- Nuclear medicine renal scan:
  - Assess for obstruction

– Sequential studies detect deterioration of renal function

Diagnostic Procedures/Surgery

- Urodynamics (UDS): Necessary to determine effective urologic management for all patients with neurogenic lower urinary tract dysfunction
- Neurogenic DO (NDO):
  – Loss of CNS inhibition
- DSD (abnormal reflexive sphincter contraction during involuntary or voluntary detrusor contraction):
  – Functional bladder outflow obstruction with elevated intravesical pressure
  – Secondary damage: Pressure, infection, urolithiasis
  – 10–20% of patients have internal (bladder neck) sphincter dyssynergia with external sphincter dyssynergia.
  – Elevated intravesical pressure >40 cm H_2O responsible for sequelae of NDO–DSD
- Detrusor underactivity or acontractility:
  – Interruption of sacral reflex arc; no detrusor contraction
  – Typically low-pressure storage
  – Adrenergic overgrowth: May result in decreased bladder compliance, elevated storage pressure

Pathologic Findings

Bladder wall thickening with fibrosis and trabeculation

DIFFERENTIAL DIAGNOSIS

- Idiopathic overactive bladder
- Dysfunctional voiding

TREATMENT

GENERAL MEASURES (2)

- UDS is essential to determine lower urinary tract function/dysfunction and to plan urologic management.
- Maintaining low intravesical pressure protects upper urinary tracts
- Urinary drainage: Intermittent catheterization or external collection appliance
- Indwelling catheterization:
  – Associated with recurrent UTIs, urethral erosion, urolithiasis
- Intermittent self-catheterization: Most effective treatment; requires low storage pressure
- Surgical intervention is indicated when other therapies fail to protect the upper urinary tract or provide continence.

MEDICATION

First Line

- Antimuscarinics aimed at decreasing urinary storage pressure and reducing NDO. Most common side effects include dry mouth and constipation
  – Fesoterodine 4–8 mg QD
  – Hyoscyamine extended release 0.375 mg BID
  – Oxybutynin 5 mg BID-TID

  - Oxybutynin transdermal patch 3.9 mg/d
  - Oxybutynin XL 10–15 mg/d
  - Oxybutynin, topical gel 10% apply 1 sachet QD to dry skin
  - Solifenacin 5–10 mg/d
  - Tolterodine LA 1–2 mg BID
  - Tolterodine LA 2–4 mg/d
  - Trospium XR 60 mg/d
- β 3-agonist: Most common side effects include an increase in blood pressure and palpitations
  - Mirabegron 25 mg/d increase to 50 mg/d after 8 wk PRN
- *α*-Adrenergic blockers: Decrease internal sphincter resistance, lower voiding pressure; ineffective for DSD.
  - Alfuzosin 10 mg/d
  - Doxazosin start 1 mg/d to max 8 mg
  - Silodosin 8 mg/d
  - Tamsulosin start 0.4 mg to max 0.8 mg
  - Terazosin start 1 mg/d to max 20 mg

Second Line

- Botulinum toxin type A (onabotulinumtoxinA) injection into the external sphincter for DSD
  - Short-lived; requires repeat injections
- Botulinum toxin injection into the detrusor for NDO
  - Duration of action is 3–9 mo
  - Requires repeated injections

SURGERY/OTHER PROCEDURES

- Endoscopic sphincter ablation or stenting:
  - Only males with DSD; requires condom catheter
- Augmentation cystoplasty using an intestinal segment to enlarge the bladder
  - Goal is to increase bladder volume and decrease bladder pressure
  - Intermittent catheterization for urinary drainage
  - Limited dexterity mandates construction of a continent catheterizable stoma for the urinary reservoir, especially in females
- Ileovesicostomy
  - Useful for those unable to perform self-catheterization (ie, quadriplegia)
- Cystectomy with continent urinary reservoir
  - Ileal or colon pouch; continent catheterizable stoma (appendix or tapered ileum)
- Cystectomy with ileal conduit

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Neuromodulation, sacral nerve stimulation and posterior tibial nerve stimulation are not FDA approved for the treatment of NDO but may have some benefit.

Complementary & Alternative Therapies

Acupuncture has been reported to improve symptoms of neurogenic bladder.

ONGOING CARE

PROGNOSIS

Proper urologic management greatly improves quality of life in patients with NGB dysfunction.

COMPLICATIONS

- Recurrent UTIs
- Urinary retention
- Hydroureteronephrosis
- Neoplastic transformation: Associated with chronic catheter
- Urethral erosion

FOLLOW-UP

Patient Monitoring

- Annual evaluation in high-risk patients may include (3):
  - UDS
  - Imaging: Typically renal US
  - Serum creatinine

Patient Resources

- http://www.nationalmssociety.org
- http://www.spinalcord.org/
- http://www.parkinson.org/

REFERENCES

1. Fowler CJ, Dalton C, Panicker JN. Review of neurologic diseases for the urologist. *Urol Clin North Am.* 2010;37(4):517–526.
2. Abrams P, Agarwal M, Drake M, et al. A proposed guideline for the urological management of patients with spinal cord injury. *BJU Int.* 2008;101(8):989–994.
3. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol.* 2012;187(6):2131–2139.

ADDITIONAL READING

Tapia CI, Khalaf K, Berenson K, et al. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: a systematic review. *Health Qual Life Outcomes.* 2013;11:13–28.

See Also (Topic, Algorithm, Media)

- Bladder Areflexia (Detrusor Areflexia)
- Detrusor Overactivity
- Detrusor Sphincter Dyssynergia (DSD)
- Incontinence, Urinary, Adult Female
- Incontinence, Urinary, Adult Male

- Incontinence, Urinary, Pediatric
- Neurogenic Detrusor Overactivity (NDO)
- Overactive Bladder
- Spinal Cord Injury, Urologic Considerations
- Stroke (CVA), Urologic Considerations

CODES

ICD9

- 596.51 Hypertonicity of bladder
- 596.54 Neurogenic bladder NOS
- 596.59 Other functional disorder of bladder

ICD10

- N31.8 Other neuromuscular dysfunction of bladder
- N31.9 Neuromuscular dysfunction of bladder, unspecified
- N32.81 Overactive bladder

CLINICAL/SURGICAL PEARLS

Adequate management of lower urinary tract function is essential to avoid upper urinary tract compromise and preservation of renal function.

NOCTURIA

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BASICS

DESCRIPTION

- Nocturia is a symptom describing an individual who awakens at night one or more times to void. Each void is preceded and followed by sleep.
- Can negatively impact quality of life.
  - Can be associated with depression, daytime fatigue, and increased orthopedic morbidity among the elderly.
- Underlying etiologies of nocturia
  - Nocturnal polyuria:
    - The rate of urine output is excessive only at night and total 24-hr output is within normal limits.
  - Reduced bladder capacity
  - 24-hr polyuria
  - Sleep disorder

EPIDEMIOLOGY

Incidence

- The incidence of nocturia and total number of voiding episodes increases with age
  - Overall: 28%
  - Age >60: 41%
- Body mass index >29: 36%
- Black and Hispanic > White

Prevalence

- Higher prevalence in women than men among young adults
- Higher prevalence in men than women among elderly population groups

RISK FACTORS (1)

- Advanced age
- Diuretic usage
- Lower urinary tract dysfunction
- Cardiac disease
- Obesity, sleep apnea

Genetics

None

PATHOPHYSIOLOGY

- 24-hr polyuria:
  - Excessive total urine production where the total 24-hr urinary volume >40 mL/kg)
  - Diabetes mellitus:

    - Secondary to polydipsia and osmotic diuresis from hyperglycemia
  - Diabetes insipidus:
    - Under-secretion (central) or impaired response (nephrogenic) to ADH
  - Medications:
    - Lithium, diuretics, caffeine, nephrotoxic medications
  - Hypercalcemia: Can cause osmotic diuresis
  - Hyperaldosteronism
  - Psychogenic polydipsia
- Nocturnal polyuria
  - Relative increased production of urine at night that is often offset by lowered daytime urine production resulting in normal 24-hr urine volume.
  - Age-related loss of the normal diurnal secretion of vasopressin, resulting in increased nocturnal urine output.
  - Peripheral edema:
    - Fluid that accumulates in the lower extremities when upright during the day is mobilized when supine at night, due to an increase in GFR and excretion.
    - Conditions: CHF, liver disease, nephrotic syndrome, hypoalbuminemia, venous insufficiency, lymphedema, lower extremity injury/swelling.
  - Sleep apnea:
    - Transient periods of hypoxia lead to increased pulmonary vascular resistance and secretion of atrial natriuretic peptide, a potent diuretic.
  - Medications: Poorly timed/dosed diuretics that exert maximal effect during sleeping hours.
  - Excessive fluid intake prior to bedtime, resulting in a physiologic large volume excretion.
- Reduced bladder capacity
  - Nonneurogenic or Neurogenic OAB (over active bladder)
  - Inflammatory: UTI, radiation cystitis, bladder calculi, interstitial cystitis
  - Neoplastic: Bladder cancer, prostate cancer, extrinsic compression from pelvic masses
  - Traumatic: Spinal cord injury, urethral stricture, injury to pelvic nerves or bladder, foreign body within bladder
  - Obstructive; BPH, urethral stricture

ASSOCIATED CONDITIONS

- Bladder outlet obstruction
- OAB: Idiopathic and neurogenic
- Detrusor hyperactivity with impaired contractility
- Radiation cystitis
- Diabetes mellitus
- Psychogenic polydipsia
- Depression
- Obesity
- See also “Pathophysiology”

GENERAL PREVENTION

- Avoid excessive evening fluid intake, alcohol, and caffeine
- Closely monitor and control the underlying conditions that cause nocturia

DIAGNOSIS

HISTORY

- Number of times getting up at night to urinate from time of going to bed until time of waking in the morning
- Degree of bother assessment
- Differentiate between awakening due to the urge to void vs. awakening due to other sleep disturbances
- Fluid intake habits
- Timing, volume
- Caffeine and alcohol consumption
- Previous pelvic surgery or radiation
- Daytime fatigue and depression
- Review of medications known to contribute to nocturia: such as diuretics, excessive calcium supplementation, antacids, or lithium.
- Swelling of lower extremities

PHYSICAL EXAM

- Global or focal neurologic deficits
- Digital rectal: Assess anal tone, prostate exam in men
- Pelvic exam in women: Anterior prolapse causing retention, urethral diverticulum, atrophic vaginitis causing irritative urinary symptoms
- Lung auscultation for rales, crackles
- Dependent edema, pedal edema
- Suprapubic distension consistent with urinary retention
- Obesity and a wide neck circumference raises the possibility of sleep apnea

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: Low specific gravity (polyuria), RBCs (rule out stones, bladder cancer, foreign body, etc.), proteinuria (nephrotic syndrome), glucosuria (diabetes mellitus), pyuria (UTI)
- Urine culture: UTI
- Urine osmolality: Dilute low values suggest inappropriate excretion of ADH or excess intake of water
- PSA if indicated
- Serum electrolytes: Hypokalemia with diuretic use, CHF, or hyperaldosteronemia

Imaging

- Bladder US with PVR volume for suspected urinary retention, especially if considering antimuscarinics
- Renal US may demonstrate hydronephrosis in cases of urinary retention or poorly compliant bladders

Diagnostic Procedures/Surgery

- Voiding diaries
  - All voiding episodes and volumes should be recorded for a 24-hr period; the time the patient actually goes to sleep and awakens for the day should also be noted.

- Nocturnal urine volume (NUV) is the total volume of urine voided during the night (the 1st morning void is included in this sum since it represents urine excreted during sleep hours).
- Nocturnal polyuria index (NPi): NUV divided by the total volume voided over the 24-hr period:
  - NPi > 33% = nocturnal polyuria
- Nocturnal Bladder Capacity index (NBCi)
- NBCi = (NUV/Maximal volume per void)–1
  - NBCi > 0 suggests that the nocturnal bladder capacity cannot store the amount of urine made at night.

• Urodynamics
- Helpful when empiric treatment for overactive bladder (OAB) or bladder outlet obstruction has failed to improve nocturia

• Polysomnographic sleep studies: Differentiate between sleep disorder and true nocturia

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

• Sleep disorders:
- Most patients awaken due to the sleep disturbance, but recall this as an awakening to void.
- May need polysomnography

• Urologic
- Bladder outlet obstruction, OAB, incomplete bladder emptying.

• Nonurologic:
- Renal failure, idiopathic nocturnal polyuria, diabetes mellitus, central diabetes insipidus, nephrogenic diabetes insipidus, primary polydipsia, hypercalcemia, drugs, autonomic failure, obstructive sleep apnea.

TREATMENT

GENERAL MEASURES

• Nocturnal polyuria secondary to diuretics
- Change to afternoon dosing to induce an early evening diuresis rather than a nocturnal diuresis

• Treatment of underlying condition associated with nocturia

MEDICATION

First Line

• Antimuscarinics are appropriate for reduced voided volumes.

• Men only: α-blocker alone or combined with a 5-α-reductase inhibitor (only modest benefit) (2)[A].

Second Line

• DDAVP for nocturia associated with nocturnal polyuria (3)[B]:
- Dosing: 0.01 mg PO; titrate up to 0.04 mg.

– DDAVP has a high risk of hyponatremia.
– Greatest risk seen in men >65 yr old.

SURGERY/OTHER PROCEDURES

Sacral neuromodulation for nocturia secondary to reduced voided volumes is associated with refractory daytime frequency and urgency (4)[B].

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Behavioral training:
  - Pelvic floor muscle exercises, +/– biofeedback: More effective than both drug therapy and placebo in treatment of nocturia associated with daytime urgency and urge incontinence (5)[A]
- CPAP for obstructive sleep apnea

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS

Although it is often difficult to completely eliminate episodes of nocturia, characterizing nocturia according to cause-specific etiologies allows for cause-specific treatment.

COMPLICATIONS

- Traumatic falling accidents, including hip fractures, from rising from sleep to urinate
- DDAVP can lead to hyponatremia
- Urinary retention secondary to antimuscarinics

FOLLOW-UP

Patient Monitoring

- Bladder sonography with PVR as needed, particularly when treating men with antimuscarinics
- Repeat 24-hr voiding diaries
- Regular monitoring of serum electrolytes with DDAVP, starting 3 days after initiation of treatment

Patient Resources

- Medline Plus — Excessive Urination at Night
  http://www.nlm.nih.gov/medlineplus/ency/article/003141.htm

REFERENCES

1. Fitzgerald MP, Litman HJ, Link CL, et al. The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: Results from the BACH survey. *J Urol.* 2007;177:1385–1389.
2. Johnson TM 2nd, Burrows PK, Kusek JW, et al. The effect of doxazosin, finasteride and

combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol.* 2007;178:2045.
3. Mattiasson A, Abrams P, Van Kerrebroeck P, et al. Efficacy of desmopressin in the treatment of nocturia: A double-blind placebo-controlled study in men. *BJU Int.* 2002;89:855.
4. Van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: Outcomes of a prospective, worldwide clinical study. *J Urol.* 2007;78:2029.
5. Johnson TM 2nd, Burgio KL, Redden DT, et al. Effects of behavioral and drug therapy on nocturia in older incontinent women. *J Am Geriatr Soc*. 2005;53:846.

ADDITIONAL READING

- Cornu JN, Abrams P, Chapple CR, et al. A Contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management—a systematic review and meta-analysis. *Eur Urol.* 2012;62;877–890.
- Weiss JP, Blaivas JG, Bliwise DL, et al. The evaluation and treatment of nocturia: a consensus statement. *BJU Int*. 2011;108:6–21.

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction
- Diabetes Mellitus
- Incontinence, Adult Female
- Incontinence, Adult Male
- Neurogenic Bladder
- Nocturia Algorithm ‡
- Nocturnal Polyuria
- Overactive Bladder
- Urgency, Urinary (Frequency and Urgency)
- Urodynamics
- Voiding Diary (see Section VII: Reference Tables)

CODES

ICD9

- 596.59 Other functional disorder of bladder
- 788.42 Polyuria
- 788.43 Nocturia

ICD10

- N31.9 Neuromuscular dysfunction of bladder, unspecified
- R35.1 Nocturia
- R35.8 Other polyuria

CLINICAL/SURGICAL PEARLS

- The etiology of nocturia is not prostate or bladder related in the majority of men. Poor sleep

pattern and fluid consumption/mobilization need to be considered.

- A voiding diary is extremely helpful to determine the cause of nocturia.

ORCHITIS, GENERAL CONSIDERATIONS

James B. Angel, MD
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BASICS

DESCRIPTION

- Inflammatory reaction of the testes secondary to infectious or noninfectious etiology
  - Infectious (viral, bacterial, fungal)
  - Noninfectious (idiopathic, trauma, autoimmune)
- Can be acute or chronic if present for >6 weeks
- Untreated epididymitis can progress to epididymo-orchitis

EPIDEMIOLOGY

Incidence

- Dramatic decline in incidence following the development MMR vaccine (Measles-Mumps-Rubella)
- 4 out of 5 cases occur in prepubertal males (<10 years old) prior to widespread use of MMR vaccine
- Recent increase in incidence in postpubertal males corresponding to mumps outbreaks following national shortages of MMR vaccine as well as controversy related to MMR vaccine itself[1]
- Bacterial orchitis even more rare and usually associated with concurrent epididymitis

Prevalence

- ~20% prepubertal males with mumps develop orchitis
- Recent case reports of postpubertal vaccinated males with mumps developing orchitis in outbreaks[2]

RISK FACTORS

- Not being vaccinated against mumps virus
- Sexually transmitted diseases (STD) leading to epididmo-orchitis (i.e., *Neisseria*, *Chlamydia*, *Treponema*)
- Epididymitis or benign prostatic hypertrophy, BPH (ie, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Staphylococcus*, and *Streptococcus*)
- Fungal infections occasionally (i.e., candidiasis, aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis, actinomycosis)
- History of intravesical Bacillus Calmette Guerin (BCG) for bladder cancer
- Immunocompromised patients (i.e., *Mycobacterium*, *Tuberculosis*, *Cryptococcus*, *Toxoplasma*, *Haemophilus*, *Candida*)
- Case reports of mumps orchitis after immunization with MMR vaccine

Genetics

- There is no clearly defined genetic predisposition toward or familial disorders commonly associated with most cases of orchitis

- Autoimmune states have been implicated in truly noninfectious orchitis

PATHOPHYSIOLOGY

- Most commonly caused by hematogenous spread of mumps virus directly attacking testicular tissue resulting in parenchymal edema, congestion of seminiferous tubules, and perivascular infiltration of lymphocytes
  - Rare case reports of other viruses causing orchitis (mononucleosis, coxsackie virus, others)
- Cases of bacterial orchitis usually result from local spread from the ipsilateral epididymitis
- Truly noninfectious orchitis is usually idiopathic, trauma-related, or possibly autoimmune
- Orchitis is unilateral in 70% of cases
- Contralateral testis involvement can follow in 1–9 days
- Seminiferous tubules can experience necrosis from increased pressure and edema

ASSOCIATED CONDITIONS

- Mumps
- Epididymitis
- STD in sexually active men
- Urinary Tract Infections (UTI) in boys or elderly men
- BPH particularly in men >50
- Bladder cancer and history of intravesical BCG
- Immunocompromised states

GENERAL PREVENTION

- Vaccination against mumps virus limits mumps orchitis
- Protection from STD
- Treatment of epididymitis prior to progression to epididymo-orchitis

DIAGNOSIS

HISTORY

- Testicular pain and swelling
  - Mild discomfort to severe pain
  - Onset of scrotal pain and edema is acute
- History of recent scrotal trauma
- Systemic symptoms
  - Fatigue
  - Malaise
  - Myalgias
  - Fever and chills
  - Nausea, emesis
  - Headache
- Obtain vaccination history
- Mumps orchitis follows development of parotitis by 4–7 days
- Obtain sexual history as appropriate
- Evidence or history of immunocompromise
- History of BPH
- History of recent instrumentation (ie, catheterization, prostate biopsy, cystoscopy) increases

likelihood of epididymo-orchitis
- History of intravesical BCG therapy, may result in granulomatous orchitis

PHYSICAL EXAM
- Testicular exam:
  - Unilateral or bilateral involvement
  - Enlargement, induration, tenderness common
  - Erythema and edema of overlying scrotal skin
  - An enlarged epididymis is associated with epididymitis, typically unilateral
  - May find concurrent reactive hydrocele which transilluminates
- Rectal exam:
  - A soft, boggy prostate, which signifies prostatitis, can be associated with epididymitis
- Other:
  - Fever and/or chills
  - Urethral discharge
  - Abdominal masses or tenderness
  - Parotitis
  - Urethritis

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis and urine culture
- Urethral cultures if concern for urethritis
- Mumps: serum immunofluorescence antibody assay

Imaging
- Trans-scrotal color Doppler Ultrasound is considered required by many clinicians:
  - Can rule out testicular torsion or malignancy
- Additional imaging is unnecessary (i.e., CT Scan or MRI)

Diagnostic Procedures/Surgery

Usually not necessary

Pathologic Findings
- With viral infection, destruction of germ cells, edema and extensive inflammatory cell infiltrate is noted
- Later seminiferous tubules can experience necrosis from increased pressure and edema, with subsequent interstitial fibrosis.

DIFFERENTIAL DIAGNOSIS
- Epididymitis
- Granulomatous orchitis, infectious and noninfectious
- Reactive hydrocele
- Scrotal pyocele
- Testicular malakoplakia
- Testicular torsion
- Torsion of testicular appendage
- Testicular tumor

TREATMENT

GENERAL MEASURES

- Supportive in nature
  - Bed rest
  - Hot or cold packs for analgesia
    - Applied for 10–15 mins q.i.d or until pain subsides
  - Scrotal elevation and support with tight fitting underwear or athletic support Analgesics
  - Nonsteroidal anti-inflammatory drugs (NSAID)
  - Antiemetics
  - Counsel patient on safe sex practices if STD suspected

MEDICATION

First Line

- There are no targeted medications indicated the treatment of viral orchitis. Supportive care is essential.
- Bacterial orchitis requires coverage with appropriate antibiotic for suspected pathogen(1)[C]
  - < 35 years old, suspected STD as causative agent:
    - Ceftriaxone 125-250 mg IM once and either doxycycline 100 mg PO b.i.d. for 7 days or azithromycin 1-2 g PO once
  - > 35 years old, or epididymo-orchitis secondary to UTI:
    - Additional gram-negative coverage with a fluoroquinolone or trimethoprim-sulfamethoxazole (TMP-SMX)
- Tailor antibiotic prescription to local resistance patterns of most common UTI pathogens

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgical intervention is generally not indicated in the treatment of acute or chronic orchitis
- Associated scrotal pyocele or symptomatic hydrocele may require surgery
- Orchidectomy for chronic orchitis refractory to supportive measures is an option, but patients must be counseled surgery may not alleviate pain (2)[B]
- Consider microsurgical denervation of cord for chronic refractory orchitis/orchalgia following favorable response to spermatic cord block (3)[A]
  - 10 mL of 0.5% bupivacaine injected to cord for block

ADDITIONAL TREATMENT

Radiation Therapy

There is no role for radiation therapy

Additional Therapies

Interferon-α2B has been investigated in bilateral mumps orchitis, given that the mumps virus replicates with a virion-associated transcriptase

Complementary & Alternative Therapies

Patient specific referral for psychologic evaluation and support for chronic refractory orchitis

ONGOING CARE

PROGNOSIS

- Most cases of mumps orchitis are self-limited, resolving within 3-10 days
- With appropriate antibacterial coverage, most cases of bacterial orchitis resolve without complication

COMPLICATIONS

- Unilateral testicular atrophy in up to 60% with mumps orchitis
- Sterility is rarely a sequel of unilateral orchitis
- Impaired fertility reported rates of 7–13%
- No definitive evidence for increased risk of testicular tumor with history of orchitis

FOLLOW-UP

Patient Monitoring

- Most patients can be safely monitored in an outpatient setting
- A patient with a STD as the cause of orchitis should be tested for other STDs including Human immune deficiency virus (HIV)

Patient Resources

- http://www.mayoclinic.com/health/orchitis
- http://www.urologyhealth.org

REFERENCES

1. Nicholson A, Murray-Thomas T, Hughes G, et al. Management of epididymo-orchitis in primary care: results from a large UK primary care database. *Br J Gen Pract* 2010;579:407–422.
2. Nariculam J, Minhas S, Adeniyi A, et al. A review of the efficacy of surgical treatment for and pathological changes in patients with chronic scrotal pain. *BJU Int* 2007;99:1091–1093.
3. Larsen SM, Benson JS, Levine LA. Microdenervation of the spermatic cord for chronic scrotal content pain: single institution review analyzing success rate after prior attempts at surgical correction. *J Urol* 2013 189:554–558.

ADDITIONAL READING

- Zipprich J, Murray EL, Winter K, et al. Mumps outbreak on a university campus - California, 2011. *MMWR* 2012;61:986–989.
- Yapanoglu T, Kocaturk H, Aksoy Y, et al. Long-term efficacy and safety of interferon-alpha-2B in patients with mumps orchitis. *Int Urol Nephrol* 2010;42:867–871.

See Also (Topic, Algorithm, Media)

- Acute Scrotum
- Mumps Orchitis
- Orchitis, General Considerations Image
- Orchitis, Granulomatous
- Scrotum and Testicle, Mass
- Testis, Pain (Orchalgia)

- Testis, Tumor and Mass, Adult, General
- Testis

CODES

ICD9

- 604.90 Orchitis and epididymitis, unspecified
- 604.91 Orchitis and epididymitis in diseases classified elsewhere
- 604.99 Other orchitis, epididymitis, and epididymo-orchitis, without mention of abscess

ICD10

- N45.1 Epididymitis
- N45.2 Orchitis
- N45.3 Epididymo-orchitis

CLINICAL/SURGICAL PEARLS

- Most cases of orchitis are viral in nature and self-limited, other cases are bacterial and most commonly associated with epididymitis.
- Physical exam findings include tender, swollen testes with associated erythema of the scrotum with or without fever.
- Testicular ultrasonography is important to rule out torsion and malignancy.
- Medical therapy for orchitis is largely supportive; antibiotic coverage should be targeted to cover STDs in the young and sexually active and UTIs in the elderly.
- The role for surgical management of orchitis is limited.

OSTEITIS PUBIS, UROLOGIC CONSIDERATIONS

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Leonard G. Gomella, MD, FACS

BASICS

DESCRIPTION

- Osteitis pubis is a painful sterile inflammatory condition affecting the pubic symphysis
  - Most commonly seen in athletes
- First described with suprapubic surgery and remains a potential complication of pelvic procedures

EPIDEMIOLOGY

Incidence

- Overall incidence in nonathlete populations unknown
  - 0.16% in procedures using bone anchors

Prevalence

Overall prevalence in nonathlete populations unknown

RISK FACTORS

- Invasive pelvic procedures
  - Several urologic procedures implicated
    - Radical prostatectomy
    - Prostate cryotherapy
    - TRUS Bx of prostate
    - TURP
    - Retropubic urethropexy: Specifically Marshall–Marchetti–Krantz procedure
    - Sling procedures
    - Pelvic radiation
- Trauma
- Rheumatic disorders
- Pregnancy/parturition
- Overuse syndrome in athletes

Genetics

No known genetic predisposition

PATHOPHYSIOLOGY

- Symphysis pubis is a nonsynovial amphiarthrodial joint at the confluence of the two pubic bones, consisting of an intrapubic fibrocartilaginous disc between thin layers of hyaline cartilage
- Etiology unknown but may be related to periosteal trauma

ASSOCIATED CONDITIONS

- Ankylosing spondylitis

- Rheumatoid arthritis

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Inciting event such as a pelvic procedure or trauma
- Insidious onset of suprapubic pain
- Pain radiating to thigh adductors, lower abdomen, perineum
- Pain worse when walking or when rising from a seated position (1)[C]

PHYSICAL EXAM
- Point tenderness over pubic symphysis
- Waddling gait
- Low-grade fever
- Increased pain with coughing or Valsalva
- Painful hip abduction

DIAGNOSTIC TESTS & INTERPRETATION

ALERT
Must rule out osteomyletis, especially in postoperative patients.

Lab
- Not generally required to make diagnosis
- May see moderate leukocytosis and an increased erythrocyte sedimentation rate (2)[C]
  Raised levels of acute phase proteins (fibrinogen, C-reactive protein), and increased erythrocyte sedimentation rate are more suggestive of osteomyelitis

Imaging
- Pelvic radiograph
  – Typically normal in acute phase
  – Articular surface erosion, sclerosis, osteophyte formation
- Scintigraphy
  – Increased uptake around pubic symphysis
- Symphysogram of joint
  – Extravasation of contrast material
  – Diagnostic and therapeutic
- Magnetic resonance imaging (MRI) most sensitive and considered gold standard
  – Acute (<6 mo): Bone marrow edema, fluid in joint, periarticular edema
  – Chronic (>6 mo): Subchondral sclerosis/resorption, bony margin irregularities, osteophytes (3)[C]

Diagnostic Procedures/Surgery
- Symphysogram of joint
  – Pain on injection of contrast diagnostic (4)[C]
  – Generally replaced by MRI

- Aerobic/anaerobic culture of joint aspirate to rule out infection if clinically indicated

Pathologic Findings

Sclerotic changes in bony architecture and degeneration of hyaline cartilage with normal periosteum (5)[C]

DIFFERENTIAL DIAGNOSIS

- Osteomyelitis (the most critical)
- Neoplasia of pelvic rami
- Bony metastases
- Pubic osteolysis
- Sports hernia (athletic pubalgia, sportsman's hernia)
- Adductor strain
- Muscle tears
- Avulsion injuries
- Stress fractures
- Tears of acetabular labrum

TREATMENT

GENERAL MEASURES

- Rest, heat, or ice
- Physical therapy to strengthen pelvic girdle can be considered

MEDICATION

First Line

- Nonsteroidal anti-inflammatory
  - Ibuprofen 200–800 mg 2–4×/d (max dose 2.4 g/d)
  - Naproxen 250–500 mg 2×/d (max dose 1.5 g/d for limited time)
- Cyclooxygenase-2 (COX-2) inhibitor
  - Celecoxib 100–200 mg 1–2×/d
  - Adverse CV events noted with COX-2 inhibitors, use lowest effective dose for shortest duration possible

Second Line

- Oral glucocorticoids such as prednisone if local glucocorticoid injections fail
  - Typical short course (ie, 60 mg for 5 days)
  - Can use a taper dose

SURGERY/OTHER PROCEDURES

- Glucocorticoid injection in joint may be useful for cases refractory to rest and NSAIDs (4)[C]
  - Any steroid preparation can be used based on provider preference
    - Include an adjuvant anesthetic
- Various surgical techniques can be used for cases refractory to medical management
  - Curettage
  - Wedge resection
  - Wide resection
  - Arthrodesis

- If bone anchors are in place, their removal may be necessary

ADDITIONAL TREATMENT

Radiation Therapy

Has been attempted in the past with mixed results, but not recommended due to risk of neoplasia

Additional Therapies

- Cryotherapy, ultrasound therapy, laser therapy, and electric stimulation have been used with variable success in athletic osteitis pubis
  - No data on success of these modalities for nonathlete populations
- Anticoagulant therapy with heparin has been suggested as a possible treatment in a postoperative setting with some minimal success

Complementary & Alternative Therapies

Physical therapy

ONGOING CARE

PROGNOSIS

- Typically a drawn out and variable clinical course
  - Symptoms can last several months to several years
  - Operative procedures may be needed in 5–10% of cases

COMPLICATIONS

- Wedge or wide resection of pubic symphysis—risk of posterior instability of pelvic girdle leading to damage to sacroiliac joints
- Arthrodesis—risk of nonunion or death of bone graft site requiring additional surgery

FOLLOW-UP

Patient Monitoring

Follow-up depends on patient symptomatology and procedures obtained

Patient Resources

N/A

REFERENCES

1. Tibor LM, Sekiya JK. Differential diagnosis of pain around the hip joint. *Arthroscopy*. 2008;24(12):1407–1421.
2. Lentz SS. Osteitis pubis: A review. *Obstet Gynecol Surv*. 1995;50(4):310–315.
3. Kunduracioglu B, Yilmaz C, Yorobulut M, et al. Magnetic resonance findings of osteitis pubis. *J Magn Reson Imaging*. 2007;25(3):535–539.
4. O'Connell MJ, Powell T, McCaffrey NM, et al. Symphyseal cleft injection in the diagnosis and treatment of osteitis pubis in athletes. *AJR Am J Roentgenol*. 2002;179(4):955–959.
5. Mehin R, Meek R, O'Brien P, et al. Surgery for osteitis pubis. *Can J Surg*. 2006;49(3):170–176.

ADDITIONAL READING

- Pauli S, Willemsen P, Declerck K, et al. Osteomyelitis pubis versus osteitis pubis: A case

presentation and review of the literature. *Br J Sports Med*. 2002;36:71–73.
- Weber MA, Rehnitz C, Ott H, et al. Groin Pain in Athletes. *Rofo*. 2013;185(12):1139–1148.

See Also (Topic, Algorithm, Media)
- Suprapubic Pain, General Considerations
- Sports Hernia (Athletic Pubalgia, Sportsman's Hernia)
- Osteitis Pubic Images ☼

CODES

ICD9
733.5 Osteitis condensans

ICD10
M85.38 Osteitis condensans, other site

CLINICAL/SURGICAL PEARLS
- Osteitis pubis pain and osteomyelitis pain worse when walking or when rising from a seated position.
- Essential to rule out osteomyelitis as a more significant cause.
- Rarely osteitis pubis and osteomyelitis of the pubis can coexist.
- To distinguish between osteomyelitis and osteitis pubis, a biopsy and culture of the affected area are necessary.
- Suspect the condition in a urologic patient where the pubic symphysis has been involved in urologic surgical intervention such as bone anchors or sling procedures.

OVERACTIVE BLADDER (OAB)

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BASICS

DESCRIPTION

- OAB is defined as a symptom syndrome consisting of urinary urgency, with or without incontinence usually with urinary frequency and nocturia in the absence of causative factors or other identified pathologic conditions causing such symptoms.
- Urinary urgency is the key symptom.

ALERT
OAB is not synonymous with detrusor overactivity (DO, strictly a urodynamic term) and should be distinguished from bladder pain syndrome.

EPIDEMIOLOGY

Incidence

Overall 10.2–17.4% in adult males and 7.7–31.3% in adult females.

Prevalence

~16% of men and women over 40 suffer from OAB and the prevalence increases to 31% and 42%, respectively in patients >75 yr. OAB wet is more common in females.

RISK FACTORS

- Neurogenic: Stroke, Parkinson disease, multiple sclerosis, spinal injury, etc.
- Nonneurogenic: Caucasian, Insulin-dependent diabetes mellitus, Female gender, Depression, Aging associated with estrogen deficiency, Outflow obstruction, Arthritis, Increased BMI.

Genetics

For OAB a definite genetic link is not well established.

PATHOPHYSIOLOGY

- Not well established or understood.
- DO is found in some but not all patients with OAB.
- Urothelial afferent and efferent innervation, connective tissue, smooth muscle, pharmacologic (receptors, neurotransmitters, peptides, etc.), hormones, and other factors may contribute to OAB in individual patients.
- Ultimately, OAB results from either an afferent mechanism (underlying urgency), or a neurogenic or myogenic source or a combination of these.

ASSOCIATED CONDITIONS

- Pelvic floor disorders
- IBS
- High caffeine intake
- Depression/anxiety

- DM
- Smoking
- ADHD
- Obesity

GENERAL PREVENTION

Currently there are no known preventative measures to reduce the potential for development of OAB.

DIAGNOSIS

HISTORY

- Duration of symptoms
- Quantitative assessment of urinary frequency, nocturia, and incontinence (pad use)
- Documentation of urgency
- Quantitation of daily fluid intake
- Aggravating factors (caffeine, stress, etc.)
- Presence of dysuria, hematuria
- Response to prior therapy
- GU history including childhood voiding dysfunction, prior surgery (BPH, urethral stricture, dilation, etc.)
- History should include assessment of the impact of the disorder on daily life (I-QOL (1) and ICIQ (2) for urinary incontinence and OAB-q (3) for men and women with OAB specifically)
- Medical/surgical/OB-GYN history (especially if associated with the initial symptom onset):
  - Prior pelvic surgery: Prolapse, hysterectomy, anti-incontinence surgery, history of radiation therapy, etc.
  - Pregnancy especially vaginal delivery/episiotomy
  - UTI (frequency, urgency, dysuria)
  - Bowel function: Constipation
  - Neurologic history or events (eg, CVA/TIA, MS, Parkinson disease, trauma, back surgery, etc.)
  - Sexual function: Dyspareunia
  - Medical comorbidities: Congestive heart failure (CHF), diabetes, obesity, venous insufficiency, BPH, sleep apnea, etc.
  - Medications (diuretics, prescription, OTC)
  - Menopausal status and hormonal replacement: Contributes to atrophic vaginitis/urethritis
- Use of tobacco, alcohol, fluid intake, caffeine, etc.

PHYSICAL EXAM

- General exam:
  - Abdominal masses, bladder distention
  - Mental status/cognitive function
  - Neurologic exam including perineal sensation, anal wink, resting, and volitional sphincter tone, bulbocavernous reflex
  - Knee/ankle deep tendon reflexes: Sacral nerve compromise/injury
- Pelvic exam:

- Condition of vaginal mucosa: Atrophy (thinning, pallor), narrowing of introitus, inflammation
- Pelvic organ prolapse
- Pelvic floor tone
- Bimanual exam for mass or tenderness
- Cough stress test: Stress incontinence
- Rectal exam: Constipation and prostate evaluation for men

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis, urine cultures:
  - Infection, Glycosuria: Possible diabetes, Hematuria: Possible kidney/bladder pathology, Proteinuria: Kidney/chronic disease, Cytology: Atypia, urothelial carcinoma
  - The diagnosis and initial management of OAB does not require more than a history, physical exam, and urine analysis. Other diagnostic studies should be utilized selectively

Imaging

- These are optional studies usually reserved for complex patients or patients who have failed initial therapy
  - VCUG/Cystography/video urodynamic
  - Renal/bladder US

Diagnostic Procedures/Surgery

- 1–3-day frequency–volume chart (FVC) and/or bladder diary are helpful in documenting presence and severity of OAB
- Post-void residual volume (PVR) (catheterized or ultrasound)
  - PVR >100 is found in 10–19% women with OAB, 15.9% women with SUI, and 5% of asymptomatic women
  - Elevated PVR may be associated with urgency/frequency and nocturia
- Pressure flow urodynamics:
  - Provides functional information about bladder and urethral function
  - Assesses bladder filling and urinary storage as well as bladder emptying, contractility, voiding efficacy, and outlet obstruction
  - Can document presence of DO which is associated with OAB but is NOT required for the diagnosis
- Cystoscopy identifies lesions, tumors, trabeculation, and foreign bodies

ALERT
OAB is a clinical diagnosis and does not require UDS confirmation.

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Bladder calculi
- Bladder cancer/carcinoma in situ
- Bladder outlet obstruction/prostatic hypertrophy
- Congestive heart failure

- Detrusor-external sphincter dyssynergia
- Diabetes
- Interstitial cystitis/painful bladder syndrome
- Pelvic pain syndrome
- Medications
- Neurogenic bladder
- Pelvic organ prolapse
- Polyuria/polydipsia
- Sexually transmitted infection
- Stress incontinence
- Urethral diverticulum
- Urinary tract infection

TREATMENT

GENERAL MEASURES

- Lifestyle modifications and bladder/pelvic floor training in conjunction with pharmacotherapy are 1st-line therapy and are mainstays of treatment.
- Behavioral therapy:
  - Dietary and lifestyle modification (weight loss, reduce caffeine intake, EtOH, and nicotine cessation)
  - Bladder retraining (education, diaries, self-monitoring)
- Pelvic floor physiotherapy: To reestablish inhibitory control over bladder storage
  - Pelvic floor exercises (Kegel)
  - Adjunctive measures include biofeedback, electrical stimulation, vaginal weights/cones, magnetic therapy, etc.

MEDICATION

First Line

- Antimuscarinics: Inhibits the effect of acetylcholine at postjunctional muscarinic receptors on detrusor muscle cells. All used to treat OAB and all have level 1 evidence.
  - Tolterodine (2–4 mg/d)
  - Trospium XR (60 mg/d)
  - Darifenacin (7.5–15 mg/d)
  - Solifenacin (5–10 mg/d)
  - Oxybutynin (IR 7.5–20 mg/d, XL 5–30 mg/d, patch twice weekly)
  - Fesoterodine (4–8 mg/d)
- β_3-adrenergic agonist agent: Promotes detrusor muscle relaxation
  - Mirabegron (25–50 mg/d)

Second Line

- Urgent PC (PTNS): Tibial nerve stimulation: Office-based therapy requiring repetitive weekly therapy sessions over 3–4 mo and then periodic treatments thereafter
- InterStim (sacral neuromodulation): Implanted neurostimulation of sacral nerves: Modulates activities of bladder, sphincter, and pelvic floor muscles
- Intravesical botulinum toxin (onabotulinumtoxinA) injection:

– Addresses both motor efferent innervation and sensory afferent nerves that contribute to OAB. It is a transient effect requiring periodic retreatment at intervals of 4–12 mo.

surgery/other procedures (4)

- Augmentation enterocystoplasty: Using a portion of GI tract to increase bladder capacity. Usually involves use of ileum or colon
  – Auto-augmentation: Incision of detrusor muscle creating a pseudodiverticulum (most commonly performed in pediatric age group)
- Urinary diversion such as Bricker bilateral ureteroileostomy, rarely needed
- Clinical use of endoscopic bladder transection, bladder overdistension, or transvesical phenol injection is no longer recommended for nonneurogenic OAB

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Non-FDA approved:
  – Estrogens for females (topical or oral)
  – Tricyclic antidepressants (imipramine, etc.)
- For intractable OAB, options are appliances, catheters (urethral), and pads with careful attention to skin care

Complementary & Alternative Therapies

- Acupuncture
- Cognitive therapy

ONGOING CARE

PROGNOSIS

- Varies according to severity of disorder and compliance of the patient
- 50–80% of patients respond to combination of behavioral modification, pelvic floor therapy, and pharmacotherapy

COMPLICATIONS

- Antimuscarinic agents are contraindicated in narrow angle glaucoma and patients should be aware of side effects (dry mouth, constipation, etc.)
- Augmentation cystoplasty may lead to metabolic abnormalities and short bowel syndrome.
- SNS implant site complications include infection and pain.
- Botulinum toxin is associated with UTI, and urinary retention.

FOLLOW-UP

Patient Monitoring

Depending on treatment modality close follow-up with urologist or primary care physician is necessary

Patient Resources

- National Association for Continence 1-800-BLADDER (www.nafc.org)
- Simon Foundation (www.simonfoundation.org)

- National Institute of Diabetes and Digestive and Kidney Diseases (http://kidney.niddk.nih.gov/kudiseases/pubs/uiwomen/)

REFERENCES

1. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188(suppl 6):2455–2463.
2. Abrams P, Cardozo L, Khoury S, et al. Incontinence. 4th International consultation on incontinence, Paris July 5–8, 2008.
3. Voelzke BB. Overactive bladder; prevalence, pathophysiology, and pharmacotherapy. *Urol Rep*. 2007;1:16–22.
4. Wein AJ, Rackley RR. Overactive bladder: A better understanding of pathophysiology, diagnosis, and management. *J Urol*. 2006;175:S5–S10.

ADDITIONAL READING

- Avery K, Donovan J, Peters TJ, et al. ICIQ: A brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn*. 2004;23:322.
- Coyne K, Revicki D, Hunt T, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. *Qual Life Res*. 2002;11:563.
- Patrick DL, Martin ML, Bushnell DM, et al. Quality of life of women with urinary incontinence: Further development of the incontinence quality of life instrument (I-QOL). *Urology*. 1999;53:71.

See Also (Topic, Algorithm, Media)

- Detrusor Overactivity
- Incontinence, Urinary, Adult Female
- Incontinence, Urinary, Adult Male
- Nocturia
- Overactive Bladder (OAB) Image
- Posterior Tibial Nerve Stimulation (PTNS)
- Sacral Neuromodulation
- Urgency, Urinary (Frequency and Urgency)

CODES

ICD9

- 596.51 Hypertonicity of bladder
- 788.41 Urinary frequency
- 788.63 Urgency of urination

ICD10

- N32.81 Overactive bladder
- R35.0 Frequency of micturition
- R39.15 Urgency of urination

CLINICAL/SURGICAL PEARLS

- OAB is NOT synonymous with detrusor overactivity.
- The key symptom of OAB is urinary urgency.
- The diagnosis and initial management of OAB require only a history, physical exam, and normal urinalysis.

PAPILLARY NECROSIS, RENAL

Demetrius H. Bagley, MD, FACS
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BASICS

DESCRIPTION

- Renal papillary necrosis is ischemic necrosis of the papillae and occasionally the medullary pyramids.
- The clinical course may be acute and rapidly progressive or chronic
  - Acute forms are symptomatic and may present with hydronephrosis, pyelonephritis, and hematuria
  - Typically chronic forms are asymptomatic and discovered incidentally on radiographic studies
- Acute presenting symptoms include hematuria, flank or abdominal pain, and fever and chills

EPIDEMIOLOGY

Incidence

- Most cases occur after the 6th decade of life and papillary necrosis is uncommon in patients <40 yr
- Female > Male (1.1:1.0) (1)[B]

Prevalence

N/A

RISK FACTORS

- Include any condition causing ischemia that can predispose to the development of renal papillary necrosis. Many have >2 risk factors
- Diabetes mellitus
- Sickle cell trait or disease
- Analgesic abuse:
  - Most commonly phenacetin and NSAIDs
- Antiretroviral treatment:
  - Indinavir
- Urinary tract obstruction of any cause
- Pyelonephritis
- Systemic vasculitis
- Lupus nephritis
- Wegener granulomatosis
- Renal artery stenosis
- Systemic vasculitis
- Global ischemia:
  - Shock, hypoxia, dehydration

Genetics

N/A

PATHOPHYSIOLOGY

- The renal papilla normally exists in the state of hypoxia because of the blood flow in the vasa recta which can be affected further with conditions that reduce blood flow
  - Perfusion compromise in diabetes mellitus
  - Diminution in blood flow because of sickling of blood cells (sickle cell disease)
  - Infection that causes inflammation of the interstitium can lead to compression of the medullary vasculature
- Analgesic use causes COX inhibition and decreased prostaglandin production. This leads to decreased vascular perfusion, vasoconstriction and can cause ischemic necrosis
- Some medications can cause direct interstitial cell necrosis and decrease in prostaglandin production
- The necrotic, soft tissue can cause unilateral or bilateral ureteral obstruction

ASSOCIATED CONDITIONS

- Analgesic abuse
- Diabetes mellitus
- Pyelonephritis
- Sickle cell disease
- Urinary tract obstruction

GENERAL PREVENTION

- Treatment of underlying disorders including diabetes or sickle disease
- Avoidance of analgesic use

DIAGNOSIS

HISTORY

- May present with hematuria or obstruction with flank pain (2)
- With infection, fever, chills, dysuria, frequency, urgency, flank pain, and renal colic can occur
- Rarely, bilateral ureteral obstruction with necrotic tissue can present as acute oliguric renal failure

PHYSICAL EXAM

- Costovertebral angle tenderness
- Fever

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture:
  - Proteinuria, pyuria, bacteriuria, and low urine-specific gravity
  - Epithelial cells and casts may be present
- CBC may demonstrate leukocytosis
- Metabolic panel can demonstrate azotemia and elevated creatinine

Imaging

- CT has become the imaging modality of choice

- Contrast images show:
  - Ring shadows in the medullae
  - Contrast-filled clefts in the renal parenchyma
  - Renal pelvic filling defects
- Excretory urography has historically been the gold standard for diagnosis
  - Findings include shrinkage and irregularity of papilla defined by contrast materials as a ring shadow often in a triangular shape
  - A calix without a papilla
  - Filling defect in the renal pelvis or ureter
  - Contrast containing rice-grain–sized cavities in the papilla
- Retrograde pyelogram:
  - Useful in patients with azotemia, contrast sensitivity, or other situations where intravenous contrast is contraindicated
  - Findings may reveal a club-shaped calyx or a filling defect in the ureter

Diagnostic Procedures/Surgery

Patient presenting with hematuria needs a full urologic workup even if papillary necrosis is confirmed.

Pathologic Findings

- The cortex features depressed areas of cortical atrophy (3)
- Papilla shows various stages of necrosis, desquamation, and sloughing
  - Focal necrosis: Involves only the tip of the papilla
  - Diffuse necrosis: The entire papilla and portions of the medulla are involved
- Microscopically, changes of papilla may be a patchy appearance or complete coagulative necrosis. Glomeruli are typically unchanged

DIFFERENTIAL DIAGNOSIS

- Acute tubular necrosis
- Nephrolithiasis
- Carcinoma of the ureter or bladder
- NSAID abuse and/or overuse
- Pyelonephritis
- Renal trauma
- TB
- Ureteral stricture disease

TREATMENT

GENERAL MEASURES

- Hydration, oral or intravenous
- Glycemic control, if diabetic
- Definition and treatment of sickle disease

MEDICATION

First Line

- Cessation of any associated/causative medications including analgesics

- Treatment of underlying cause of ischemia
- Broad-spectrum antibiotics, if associated with pyelonephritis

Second Line
N/A

SURGERY/OTHER PROCEDURES
- When a patient presents with acute urinary obstruction, drainage is indicated with percutaneous nephrostomy, ureteral stent placement, or endoscopic/ureteroscopic removal of obstructing sloughed tissue
- In the nonacute case, renal pelvic or ureteral filling defect can be electively evaluated with ureteroscopy
- Nephrectomy is rarely warranted

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
Depends on the basis for the ischemia, the compounding factors, and the amount of necrosis

COMPLICATIONS
- Infection may develop in the desquamated necrotic papilla
- Calculi can develop on the base of the sloughed papilla
- Obstruction can develop along the ureter from multiple sloughed papilla

FOLLOW-UP
Patient Monitoring
- Monitoring includes the kidney itself for further necrosis and for changes in function
- Causes of ischemia should be closely monitored

Patient Resources
http://www.scripps.org/articles/1151-renal-papillary-necrosis

REFERENCES

1. Vijayaraghavan SG, Kandasamy SV, Mylsamy A, et al. Sonographic features of necrosed renal papillae causing hydronephrosis. *J Ultrasound Med*. 2003;22(9):951–956.
2. Gordon M, Cervellione RM, Postlethwaite R, et al. Acute renal papillary necrosis with complete bilateral ureteral obstruction in a child. *Urology*. 2007;69:575e11–575e12.
4. Amuluru K, Erickson BA, Okotie O, et al. Bilateral ureteral obstruction from papillary necrosis secondary to household cleaner ingestion. *Can J Urol*. 2009;16(3):4701–4703.

ADDITIONAL READING

Chung DC, Kim SH, Jung SI, et al. Renal papillary necrosis: Review and comparison of findings at multi-detector row CT and intravenous urography. *Radiographics*. 2006;26:1827–1836.

See Also (Topic, Algorithm, Media)

- Diabetes Mellitus, Urologic Considerations
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Hematuria, Gross and Microscopic, Adult
- Nephropathy, Analgesic
- Papillary Necrosis, Renal Image ☼
- Sickle Cell Disease, Urologic Considerations

CODES

ICD9

- 584.7 Acute kidney failure with lesion of renal medullary [papillary] necrosis
- 590.80 Pyelonephritis, unspecified
- 591 Hydronephrosis

ICD10

- N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
- N13.30 Unspecified hydronephrosis
- N17.2 Acute kidney failure with medullary necrosis

CLINICAL/SURGICAL PEARLS

Gross hematuria in a patient with sickle cell disease suggests papillary necrosis.

PARATESTICULAR TUMORS

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BASICS

DESCRIPTION

- Intrascrotal tumors involving the testicular tunic, epididymis, or cord structures. Can be benign (~70%) or malignant (~30%)
- The paratesticular region includes the contents of the spermatic cord, testicular tunics, epididymis, and vestigial remnants (appendices testis and epididymis)
- 90% of extratesticular tumors are found within the spermatic cord:
  - Of these, 30% are malignant
  - The majority represent benign lipomas
  - Mesenchymal tumors of the spermatic cord include rhabdomyosarcoma, leiomyosarcoma, liposarcoma, lipoma, fibrosarcoma, and myxochondrosarcoma
- The most common paratesticular tumor in children is rhabdomyosarcoma, which accounts for ~24–40% of all paratesticular tumors
- Adenomatoid tumor accounts for 30% of epididymis tumors and are benign:
  - Typically seen in 3rd and 4th decades of life
  - Rarely arise in testicular tunicae or spermatic cord (1)[C]
- Leiomyosarcoma is the most common type of paratesticular sarcoma in adults:
  - Incidence peaks in the 6th and 7th decades
  - Can be bilateral
  - May accompany a hydrocele or hernia
- Cystadenoma is a benign tumor that involves the epididymis in young adults:
  - Two-thirds associated with von Hippel–Lindau syndrome (2)[C]
  - Frequently bilateral
- Malignant mesothelioma presents in older patients (55–75 yr) and usually presents in association with a hydrocele
- Malignant lymphoma: Cord structures are frequently invaded by testicular lymphoma, but primary lymphomas do occur rarely
- Epididymal cysts occur in up to 40% of men
  - 75% of these are true cysts and contain lymphatic fluid (1)[C]

EPIDEMIOLOGY

Incidence

- The exact incidence of paratesticular soft tissue neoplasms is difficult to estimate
- Rhabdomyosarcoma
  - Occurs primarily in children and adolescents during the 1st 2 decades of life
- Racial differential: White > Black (3:1)
- Leiomyosarcoma: Exceedingly rare, ~110 reported cases in the literature

Prevalence

- Primary malignancies of the epididymis or paratesticular structures in adults extremely rare
- Rhabdomyosarcoma accounts for a large proportion of the paratesticular tumors in the pediatric population.

RISK FACTORS
- Marijuana and cocaine use in the parents is associated with rhabdomyosarcoma.
- Von Hippel–Lindau syndrome is associated with epididymal cystadenomas.
- Equestrians are prone to scrotal injury with up to 77% evidence of scrotal pathology (1)[C].

Genetics
- Partial monosomy of chromosome 11 often leads to embryonal rhabdomyosarcoma.
- Alveolar rhabdomyosarcoma is characterized by translocations t(2;13)(q35;q14) or t(1;13)(p36;q14); this subtype carries a poor prognosis.

PATHOPHYSIOLOGY
- Electron microscopy is very helpful in differentiating the type of sarcoma.
- Subtypes of sarcoma include rhabdomyosarcoma, leiomyosarcoma, liposarcoma, fibrosarcoma, malignant fibrous histiocytoma, and desmoplastic round cell tumor.
- Soft tissue sarcomas tend to infiltrate local tissues widely and have a tendency for local recurrence.
- Rhabdomyosarcoma:
  – 97% belong to the favorable histology group of embryonal cell tumors.

ASSOCIATED CONDITIONS
Renal cell carcinoma with von Hippel–Lindau

GENERAL PREVENTION
Testicular self-exam should be performed monthly.

DIAGNOSIS
HISTORY
- Patient complains of mass within his scrotum, distinct from the testicle
  – Typically painless
  – Delays in presentation due to embarrassment
- Obtain complete history to include accompanying symptoms, duration, and constitutional changes (2)[C]

PHYSICAL EXAM
- Palpation of the testes, epididymis, and cord structures bilaterally including the inguinal region:
  – Rhabdomyosarcoma reveals a firm mass that is usually distinct from the testis.
  – Adenomatoid tumor appears clinically as small solid lumps and is most commonly found at the head of the epididymis, testicular tunics, or spermatic cord.
  – Cystadenoma presents as asymptomatic cystic lumps and are bilateral in up to 1/3 of cases.
  – Leiomyosarcoma normally presents as a discrete nodular mass, frequently near the spermatic cord and entirely separate from the testicle.
  – Liposarcoma usually presents in an older patient as a large fatty-appearing mass.

  - Lymphoma presents as a hard, nontender mass, separate from the testis; seen in young adults. Transillumination suggests a fluid-filled lesion such as a hydrocele.
- Careful exam of the groin is necessary to rule out hernia and to evaluate for lymphadenopathy.
- Masses are occasionally accompanied by hydrocele.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis (midstream) and culture if epididymitis is suspected (1)[C].
- Tumor markers to include β-human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP), or lactic dehydrogenase (LDH) should be sent if the origin of the tumor is in question.

Imaging

- Gold standard: Scrotal ultrasound (US) (1)[C]
  - To evaluate location and characteristics of the lesion within the scrotum
  - Testicular vs. paratesticular
  - Solid vs. cystic (2)[C]
    - Solid lesions almost always require exploration
    - Simple cystic lesions are mostly benign
- Computed tomography (CT) of the abdomen and pelvis with and without contrast for staging
  - Paratesticular tumors may spread to retroperitoneal lymph nodes or hematogenously depending on the histology of the primary tumor
- Chest radiograph
- Chest CT
  - If abdominal or pelvic metastases are seen
- Clinical staging of retroperitoneal lymph nodes
- Radioisotope bone scan:
  - Especially for elevated alkaline phosphatase or symptoms with rhabdomyosarcoma

Diagnostic Procedures/Surgery

Surgery is often diagnostic and therapeutic

ALERT
Percutaneous biopsies are contraindicated due to the documented risk of seeding in the scrotal wall with malignancy.

- Bone marrow aspirate:
  - Routine part of staging at a time of diagnosis for rhabdomyosarcoma

Pathologic Findings

- Electron microscopy can help differentiate between the different types of sarcoma; these differences can be quite subtle.
- Leiomyosarcoma spreads 1st by lymphatics, then hematogenously, and last by local extension.

DIFFERENTIAL DIAGNOSIS

- Adenomatoid tumors

  – Most common benign paratesticular tumor
- Angiomyofibroblastoma
- Cystadenoma of the epididymis
- Epididymal cyst
- Epididymitis
- Fibrous pseudotumor of testicular tunic
- Fibrosarcoma
- Leiomyosarcoma
- Lipoma of the spermatic cord
- Liposarcoma
- Malignant fibrous histiocytoma
- Mesothelioma, benign, testicular tunic
- Mesothelioma, malignant, tunica vaginalis
  – Associated with asbestos exposure
- Postoperative changes
  – Sperm granuloma after vasectomy
- Spermatocele
- Testicular torsion
- Traumatic injury
- Tunica albuginea lesions
  – Cysts, fibrous pseudotumor
- Varicocele
- Hydrocele
- Hydrocele of the spermatic cord
- Inguinal hernia

TREATMENT

GENERAL MEASURES

- US suggests initial management.
- Lesions suggestive of a benign process can be observed with serial exams.
- Remove malignant or potentially malignant structures while minimizing effects on fertility, function, esthetics (2)[C].
- Benign lesions only require intervention if they become massive or cause pain (1)[C].
- Any concern about malignancy and the scrotum should be explored through a high inguinal incision.
- Transscrotal manipulation or biopsy is contraindicated.
- Rhabdomyosarcoma always requires primary surgical excision via inguinal orchiectomy.
- Leiomyosarcoma should also be treated with radical orchiectomy to be followed with adjuvant radiation therapy to reduce local recurrence.
  – No survival benefit has been demonstrated from the addition of radical pelvic lymph node dissection (RPLND) to radical orchiectomy.

MEDICATION

First Line

- Chemotherapy for malignant rhabdomyosarcoma
  - Vincristine, cyclophosphamide, and dactinomycin, and actinomycin D-based chemotherapy in patients with gross or microscopic residual disease

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Testicular or paratesticular lesions suspected to be malignant should be removed by radical inguinal orchiectomy with high ligation of the spermatic cord.
  - Early clamping of the cord limits hematogenous spread in leiomyosarcoma.
- Rhabdomyosarcoma:
  - Consider hemiscrotectomy for any degree of scrotal wall involvement.
  - The Intergroup rhabdomyosarcoma study group (IRS) recommended radical inguinal orchiectomy and routine RPLND in all males >10 yr and in boys <10 with metastasis noted on imaging.
- Complete surgical excision with a negative margin has significant impact on local recurrence and overall survival in soft tissue sarcomas.

ADDITIONAL TREATMENT

Radiation Therapy

- Rhabdomyosarcoma:
  - 4,000–6,000 centigray units of radiation (cGy) over 5 wk
  - Dose and port size determined by the tumor's primary site, patient age, and tumor burden

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Benign lesions—recurrence is rare
- Rhabdomyosarcoma—75% 5-yr survival when multimodal therapy is administered
- Leiomyosarcoma—50–80% survival with microscopic residual disease in 27% of cases
  - Adjuvant treatment via radiation is warranted.
- Malignant mesothelioma—high recurrence and mortality
- Larger tumor size, metastasis, higher-grade tumor, and incomplete primary resection lead to poorer overall prognosis.

COMPLICATIONS

- Disease associated death in ~10% of malignant cases
- Treatment-associated:
  - Retrograde ejaculation and intestinal obstruction if RPLND is performed
  - Hypogonadism and/or infertility secondary to chemotherapy
  - Hemorrhagic cystitis secondary to chemotherapy

– Growth abnormalities secondary to radiation therapy (spinal and renal) in children

FOLLOW-UP

Patient Monitoring

- Serial US for equivocal lesions, especially in the epididymis
- Benign lesions need patient-performed monthly testicular self-exams
- Rhabdomyosarcoma monitoring is provider dependent
  – Should be followed closely by a urologist

Patient Resources

N/A

REFERENCES

1. Montgomery JS, Bloom DA. The diagnosis and management of scrotal masses. *Med Clin North Am.* 2011;95(1):235–244.
2. Rosevear HM, Mishail A, Sheynkin Y, et al. Unusual scrotal pathology: An overview. *Nat Rev Urol.* 2009;6:491–450.

ADDITIONAL READING

- Ahmed HU, Arya M, Muneer A, et al. Testicular and paratesticular tumours in the prepubertal population. *Lancet Oncol.* 2010;11(5):476–483.
- Roman Birmingham PI, Navarro Sebastian FJ, Garcia Gonzalez J, et al. Paratesticular tumors. Description of our case series through a period of 25 years. *Arch Esp Urol.* 2012;65(6):609–615.

See Also (Topic, Algorithm, Media)

- Adenomatoid Tumors (Testis/Tunic/Epididymis)
- Epididymis, Mass (Epididymal Tumor and Cysts)
- Epididymis, Cystadenoma
- Fibrous Pseudotumor of Testicular Tunic
- Hydrocele of the Spermatic Cord
- IRS (Intergroup Rhabdomyosarcoma Study) Clinical Classification
- Mesothelioma, Benign, Testicular Tunic
- Mesothelioma, Malignant, Testicular Tunic
- Paratesticular Tumors Image ☼
- Rhabdomyosarcoma, Pediatric
- Scrotum and Testicle, Mass
- Spermatic Cord Mass and Tumors

CODES

ICD9

- 187.8 Malignant neoplasm of other specified sites of male genital organs
- 222.8 Benign neoplasm of other specified sites of male genital organs
- 239.5 Neoplasm of unspecified nature of other genitourinary organs

ICD10

- C63.7 Malignant neoplasm of other specified male genital organs
- D29.8 Benign neoplasm of other specified male genital organs
- D49.5 Neoplasm of unspecified behavior of other genitourinary organs

CLINICAL/SURGICAL PEARLS

- It is impossible to distinguish a benign from a malignant tumor based on physical exam.
- Can be indistinguishable from testicular masses.
- Percutaneous biopsies contraindicated due to documented seeding in scrotal wall with malignancy.

PARKINSON DISEASE, UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Parkinson disease (PD), also called paralysis agitans is a neurodegenerative disorder associated with loss of dopaminergic neurons.
- Three cardinal features are rest tremor, rigidity, and bradykinesia.
- Postural instability, sometimes deemed a cardinal feature, is nonspecific and usually absent in early disease.
- Autonomic dysfunction is manifested by urinary urgency and frequency, constipation, and orthostatic hypotension. Retention can also be seen.

EPIDEMIOLOGY

Incidence

- PD incidence increases with age, from 17.4 cases per 100,000 persons per year between 50–59 yr of age to 93.1 in 100,000 persons per year between 70–79 yr of age.
- Life risk of developing PD is 1.5%
- Voiding dysfunction occurs in 40–70% of patients with PD.

Prevalence

N/A

RISK FACTORS

- Men are about 1.5 times more likely than women to develop PD
- The median age of onset is 60 yr and the mean duration of the disease from diagnosis to death is 15 yr.
- Young-onset PD affects 5–10% of patients with the initial symptom arising before the age of 50 yr.

Genetics

- About 15% of patients with PD have a 1st-degree relative with the disease, typically without a clear mode of inheritance
- Mutations in two genes cause autosomal dominant forms of PD
  – α-Syn gene (*SNCA*): Located on chromosome 4q
  – Leucine-rich repeat kinase 2 (*LRRK2*): located on chromosome 12q
- To date, approximately 16 risk loci have been identified, some of which overlap with the genes known to contain disease-causing mutations

PATHOPHYSIOLOGY (1)

- Selective loss of dopaminergic projections from the substantia nigra pars compacta (a component of the basal ganglia) to the caudate nucleus and putamen
- Dopamine deficiency in the nigrostriatal pathways accounts for most of the clinical motor features of the disease

- The net effect of the basal ganglia on micturition is inhibitory, which is abolished due to cell loss in the substantia nigra
  - The bladder detrusor can thus become unstable and result in urgency and frequency with urge incontinence
- The smooth sphincter is synergic, however pseudodyssynergia, as well as delay in striated sphincter relaxation (bradykinesia) leading to urinary retention (2)
  - Impaired detrusor contractility may also occur
- PD can also be associated with bowel dysfunction (constipation) and sexual dysfunction
- Urinary symptoms tend to become worse in the course of the disease. Early on other correctable causes such as benign prostatic enlargement in men can cause similar symptoms
- Centrally acting anticholinergic drugs such as trihexyphenidyl and benztropine have been used to treat PD and can cause urinary retention

ASSOCIATED CONDITIONS

- Autonomic dysfunction
  - Constipation
  - Orthostatic hypotension
  - Urinary urgency/frequency/urge incontinence
- BPH
- Dementia
- Depression
- Sleep disturbance
- Erectile dysfunction
- Hyposmia
- Visual hallucination

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Urinary symptoms usually appear after the onset of neurologic symptoms
- Assess for LUTS:
  - Storage symptoms: Most common, include nocturia, urgency, frequency, and incontinence
  - Voiding symptoms: Difficulty initiating stream, weak FOS/prolonged urination, and straining
- Elevated PVRs are uncommon in PD patients
- Assess for concurrent urologic conditions:
  - BPH in men and SUI in women
- Assess for polypharmacy
  - Central acting anticholinergics listed below can be used in younger patients in whom tremor is the major symptom but may exacerbate incomplete emptying and urinary retention
  - Benztropine mesylate (Cogentin), trihexyphenidyl (Artane), biperiden (Akineton), orphenadrine (Norflex, Flexon)

PHYSICAL EXAM

- Cardinal features are rest tremor, rigidity, and bradykinesia.
- Slow, pill-rolling tremor of the hands (4–6 cycles/s) seen primarily at rest
  - Abolished by use of the affected hand
  - Aggravated by stress and cold weather
- Facial expressions can be immobile or rigid and speech slowed
- Slow, shuffling gait with loss of normal arm swing (rarely prominent early in the course of PD)
- Assessment of pelvic floor reflexes, motor and sensory
- Digital rectal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- No diagnostic test exists for PD as the diagnosis is clinical.
- Standard urologic evaluation (U/A, C&S) based on initial symptoms

Imaging

- Brain MRI is reserved for patients suspected of having PD who fail to respond to therapeutic doses of L-dopa administered for 12 wk, to exclude rare secondary causes and subcortical vascular pathology.
- Routine urologic imaging is not required.

Diagnostic Procedures/Surgery

- PD is a clinical diagnosis, although the definition of PD is a postmortem finding based on the neuropathologic examination.
- Urodynamics:
  - Detrusor overactivity is the most common cystometric abnormality.
  - Sporadic involuntary activity in the striated sphincter during involuntary bladder contraction is common, however, this does not cause obstruction.
  - Pseudodyssynergia may occur, as well as delay in striated sphincter (bradykinesia) relaxation at the onset of voluntary micturition, both of which can be misinterpreted as true dyskinesia.
  - Detrusor areflexia relatively rare in PD and when present may often be due to anticholinergic medications.
- Urodynamics is a useful tool for investigating concomitant obstruction secondary to BPH.

Pathologic Findings

Intraneuronal Lewy bodies and Lewy neurites are the pathologic hallmarks of PD.

DIFFERENTIAL DIAGNOSIS

- Parkinson
  - Multiple system atrophy
  - Normal aging
  - Vascular parkinsonism (multiple infarcts within the basal ganglia and subcortical white matter)
  - Parkinson plus syndromes
- Voiding dysfunction

TREATMENT

GENERAL MEASURES

- PD is a progressive neurodegenerative disorder despite treatment.
- Levodopa is the mainstay of therapy for PD and the gold standard against which new therapies are compared.
  - In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet).
  - Levodopa has been shown to have unpredictable effects on bladder function.
- Clinicians should offer behavioral therapies (eg, fluid management, clean intermittent catherization) as 1st-line therapy.
- Evaluate medications that may result in urinary symptoms (such as retention/hesitancy) with anticholinergic drugs such as trihexyphenidyl and benztropine used to treat some patients with PD.

MEDICATION

First Line

- For urologic symptoms of frequency, urgency, and urge incontinence, anticholinergics are commonly used but should be monitored closely in elderly as they may contribute to cognitive decline (3):
  - Oxybutynin 5 mg PO TID
  - Tolterodine LA 4 mg PO daily
  - Others (solifenacin, fesoterodine, darifenacin, trospium)
- β3-Adrenergic agonist agent: Promotes detrusor muscle relaxation and can also be considered for overactive bladder symptoms
  - Mirabegron (25–50 mg)

Second Line

- OnabotulinumtoxinA
  - While not specifically approved for PD, it is approved for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication
- The following are used but currently not FDA approved for urinary incontinence
  - Tricyclic antidepressants (TCA): Imipramine 10–25 mg PO BID–TID
  - Selective serotonin norepinephrine reuptake inhibitors (SSNRIs): Duloxetine 20–40 mg PO BID
- Nocturnal polyuria can be treated with desmopressin

SURGERY/OTHER PROCEDURES

Bladder outlet procedure: Consider if coexisting obstruction is found on urodynamic testing

ADDITIONAL TREATMENT

- PDE5 inhibitors for treatment of erectile dysfunction:
  - Sildenafil, tadalafil, vardenafil
- Deep brain stimulation of the subthalamic nucleus may decrease urinary symptoms

Additional Therapies

Incontinence aids may be necessary and are primarily chosen by the degree of absorbency

required and the ease of use. During the night, high absorbency pads are usually required.

Complementary & Alternative Therapies

Dietary fiber, laxatives, and prokinetic drugs (such as serotonergic agonists) are used to treat PD-related bowel dysfunction.

ONGOING CARE

PROGNOSIS

- PD is a progressive neurodegenerative disorder.
- Despite a variable disease course, the overall prognosis is poor with a mean duration of the disease from diagnosis to death of 15 yr.

COMPLICATIONS

- Urinary incontinence
  - Skin breakdown secondary to incontinence
- Urinary retention (often related to anticholinergics)

FOLLOW-UP

Patient Monitoring

Assess for elevated PVRs, specifically if taking anticholinergics

Patient Resources

National Parkinson Foundation: Urinary Problems in PD.
http://www.parkinson.org/NationalParkinsonFoundation/files/6c/6c980d82-f158-481c-97a9-0649ea6ba020.pdf

REFERENCES

1. Yeo L, Singh R, Gundeti M, et al. Urinary tract dysfunction in Parkinson's disease: A review. *Int Urol Nephrol.* 2012;44(2):415–424.
2. Sakakibara R, Tateno F, Kishi M, et al. Pathophysiology of bladder dysfunction in Parkinson's disease. *Neurobio Dis.* 2012;46(3):565–571.
3. Campeau L, Soler R, Andersson KE. Bladder dysfunction and parkinsonism: Current pathophysiological understanding and management strategies. *Curr Urol Rep.* 2011;12(6):396–403.

ADDITIONAL READING

- Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet.* 2009;373(9691):2055–2066.
- Wyndaele JJ, Kovindha A, Madersbacher H. Neurologic urinary incontinence. *Neurourol Urodyn.* 2010;29(1):159–164.

See Also (Topic, Algorithm, Media)

- Incontinence, Adult Female
- Incontinence, Adult Male
- Neurogenic Bladder, General

CODES

ICD9
- 332.0 Paralysis agitans
- 788.41 Urinary frequency
- 788.63 Urgency of urination

ICD10
- G20 Parkinson's disease
- N39.41 Urge incontinence
- R35.0 Frequency of micturition

CLINICAL/SURGICAL PEARLS
- Cardinal features are rest tremor, rigidity, and bradykinesia.
- Urinary incontinence is a common feature of PD due to symptoms of overactive bladder.

PELVIC ORGAN PROLAPSE (CYSTOCELE AND ENTEROCELE)

W. Stuart Reynolds, MD, MPH
Roger R. Dmochowski, MD, MMHC, FACS

BASICS

DESCRIPTION

- Pelvic organ prolapse (POP): The descent of one or more of the anterior vaginal wall, posterior vaginal wall, uterus/cervix, or apex of vagina (vaginal vault or cuff after hysterectomy)
- Cystocele: Anatomic defect of the anterior vaginal wall in which bladder prolapses into the vagina
- Enterocele: Anatomic defect of the vaginal apex typically; small intestine prolapses into the vagina
- Rectocele: Anatomic defect of the posterior vagina; the rectum prolapses into the vagina
- Defects in many or all vaginal compartments (anterior, posterior, apex) may occur together

EPIDEMIOLOGY

Incidence

Insufficient data to conclusively establish incidence rates

Prevalence

- Estimates vary, based on definitions, symptoms, and/or physical exam findings
  - 3% of US women report symptoms of vaginal bulging
  - 40% of US women have POP on exam
- Women have an 11% lifetime risk of undergoing surgery for POP and/or UI by age 80

RISK FACTORS

- Age
- Race/ethnicity (Hispanic > White > African American)
- Parity
- Obesity
- Hysterectomy
- Prior POP surgery
- Menopause
- Pelvic strain (high impact activity or work)

Genetics

- Increased familial risk (sisters and mothers)
  - 2.5 times more common if positive family history for POP
- Inheritable collagen disorders (eg, Ehlers–Danlos syndrome)
- Genome-wide studies ongoing with several potential candidate genes identified, most related to elastin and collagen metabolism (eg, *LAMC-1*)

PATHOPHYSIOLOGY

- Integrated support to the bony pelvis through the endopelvic fascial structures, suspensory

ligaments, levator ani muscles, and pelvic organs help maintain the pelvic organs in the proper anatomic position in the pelvis.
- Classically, three levels of vaginal support are described:
  - Level I: Uterosacral and cardinal ligaments support upper 1/3 of vagina, cervix, and uterus.
  - Level II: Pubocervical and rectovaginal fascia attach laterally to the arcus tendineus fascia pelvis to support midportion of vagina
  - Level III: Direct attachment of vagina to urethra, perineal body, and levator ani muscles
- Damage or weakness to the muscular and connective tissue supporting mechanisms, including innervation, contribute to POP

ASSOCIATED CONDITIONS
- Urinary incontinence
  - Stress urinary incontinence (SUI)
    - Present in 65% of POP
  - Occult SUI ("masked" or "latent" SUI)
    - SUI only observed after reduction of POP
    - Present in 25–80% of women with POP, especially with advanced stages
- Lower urinary tract symptoms
  - Overactive bladder
  - Voiding dysfunction
    - Advanced POP (stage III or greater) may result in urethral "kinking" resulting in bladder outlet obstruction
- Upper urinary tract obstruction
  - Advanced POP may result in bilateral ureteral obstruction with hydronephrosis
- Bowel dysfunction
  - Constipation
  - Fecal/anal incontinence
- Sexual dysfunction
  - Dyspareunia

GENERAL PREVENTION
- Weight management
- Protective role of elective cesarean section debatable

DIAGNOSIS

HISTORY
- Assess for prolapse symptoms
  - Vaginal bulging, including visualization or palpation of a "bulge" in the vagina
  - Pelvic pressure, heaviness, or dragging sensation
  - Vaginal mucosal irritation, bleeding, discharge, and/or infection
  - Splinting/digitation: Applying manual pressure to vagina or rectum to assist with voiding or defecation
  - Low backache, temporally associated with POP
- Assess for other pelvic floor symptoms

- Urinary incontinence and voiding dysfunction
- Constipation/anal incontinence
- Dyspareunia

PHYSICAL EXAM

- Useful to employ POP staging
  - POP quantification system (POPQ)
    - Stage 0: No prolapse is demonstrated
    - Stage I: Most distal portion of the prolapse is >1 cm above the level of the hymen
    - Stage II: Most distal portion of the prolapse is 1 cm or less proximal to or distal to the plane of the hymen
    - Stage III: The most distal portion of the prolapse is >1 cm below the plane of the hymen
    - Stage IV: Complete eversion of the total length of the lower genital tract is demonstrated
- Assessment of urinary incontinence
  - Provocative maneuvers (cough and Valsalva) to demonstrate urethral leakage; repeated with prolapse reduced to detect occult SUI

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture, as indicated
- Serum creatinine, BUN: May be abnormal in advanced POP with bladder outlet or ureteral obstruction

Imaging

- Routine imaging is not indicated; imaging may supplement exam with complex cases
- Defecography
  - Assesses defecatory dysfunction, including degree of rectocele and rectal emptying
- Voiding cystourethrogram
  - Assesses degree bladder prolapse and bladder neck function; may detect fistula, vesicoureteral reflux, or urethral diverticulum
- Pelvic ultrasound
  - Allows dynamic assessment of pelvic organs and bladder volume
- Magnetic resonance imaging (MRI)
  - Allows dynamic imaging of functional relationships among the pelvic floor viscera and supporting structures, and assesses pelvic pathology
  - Expensive; clinical utility over exam alone not established

Diagnostic Procedures/Surgery

- Postvoid residual (PVR) urine volume
- Urodynamic testing
  - Routine use not indicated; clinical utility not established
  - May detect voiding dysfunction or occult incontinence with POP reduction
  - Urethral function tests (leak point pressure, urethral pressure profilometry) assess urethral function and degree of SUI, if any

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS
- Uterovaginal prolapse
- Cystocele
- Enterocele
- Rectocele
- Soft tissue vaginal mass
- Urethral diverticulum

TREATMENT

GENERAL MEASURES
- Management is primarily surgical
- Bowel regimen for constipation
- Hormone replacement, topical vaginal, for atrophic vaginitis
  - Estrogen alone in postmenopausal with after hysterectomy; estrogen and progesterone if uterus present, even if postmenopausal

MEDICATION
First Line
N/A

Second Line
N/A

SURGERY/OTHER PROCEDURES

ALERT
The FDA has identified safety concerns with use of synthetic mesh materials for POP repair, specifically for transvaginal placement of synthetic mesh/prosthetics (See "Additional Reading").

- Transvaginal approach
  - Allows for concomitant repair of anterior, posterior, and apical compartment defects and anti-incontinence procedures
  - Augmentation of native tissue repairs with biologic or synthetic materials/grafts
    - Outcomes improved with augmented materials, but graft materials may pose safety concerns (1)[A]
    - Transvaginal "mesh kits": Prepackaged medical devices for transvaginal placement of mesh material
  - Anterior colporrhaphy or paravaginal repair
  - Posterior colporrhaphy, perineorrhaphy
  - Vaginal apical/vault suspension
    - Sacrospinous ligament fixation
    - Uterosacral ligament fixation
- Abdominal approach
  - Abdominal sacrocolpopexy (ASC)
    - Open, laparoscopic, or robotic approaches

- Vaginal apex fixation to the presacral fascia at S3–S4 using biologic or synthetic material
- Hysterectomy
  - Transvaginal or transabdominal approach
  - Complete vs. supracervical
    - Potential increased risk of vaginal mesh exposure after ASC in setting of hysterectomy; supracervical hysterectomy may be protective (2)[B]
- Colpocleisis
  - Closure or removal of the entire vagina
    - Reserved for those who are not candidates for more extensive surgery or do not plan future vaginal intercourse
    - Partial colpocleisis (Le Fort colpocleisis)
    - Total colpocleisis
- Concomitant anti-incontinence procedure
  - Retropubic colposuspension (Burch)
    - Prophylactic Burch procedure with ASC can decrease subsequent SUI by 50% (3)[A]
  - Suburethral sling, including midurethral (MUS) and pubovaginal, synthetic or biologic graft materials
    - Prophylactic, synthetic MUS at time of vaginal POP surgery reduces need for additional surgery in women at 12 mo (OR 0.48, 95% CI 0.30–0.77) (4)[A]
    - Number of slings needed to prevent 1 case of SUI at 12 mo is 6 (4)[A]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Vaginal pessary: Supportive and space-occupying devices for nonsurgical management of POP
  - Requires routine maintenance and care (removal, cleaning, vaginal inspection)

Complementary & Alternative Therapies

- Pelvic floor muscle training
  - Pelvic muscle strengthening can improve stage and symptoms, best with supervision of a physical therapist

ONGOING CARE

PROGNOSIS

- Recurrent POP
  - Historically 30% recurrence rate after surgery

COMPLICATIONS

- Mesh material complications occur in 10% of women (1)[B]
- Perioperative complications of bleeding, pelvic organ injury, bladder dysfunction, infection
- Postoperative complications include vaginal and pelvic pain, vaginal shortening or narrowing, dyspareunia

FOLLOW-UP

Patient Monitoring

- Evaluation for recurrent or de novo POP through history and exam
- Evaluation for urinary incontinence after POP surgery, if anti-incontinence procedure not performed
- Routine evaluation for complications related to synthetic mesh materials, if used in POP surgery
  - Patient history for vaginal symptoms, discharge, bleeding, dyspareunia
  - Physical exam for vaginal exposures
  - Cystoscopy for lower urinary tract perforations, as indicated

Patient Resources

Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). http://www.sufuorg.com/Patient-Education/Learn-About-Pelvic-Disorders.aspx

REFERENCES

1. Maher CM, Feiner B, Baessler K, et al. Surgical management of pelvic organ prolapse in women: The updated summary version Cochrane review. *Int Urogynecol J*. 2011;22:1445–1457.
2. Diwadker GB, Barber MD, Feiner B, et al. Complication and reoperation rates after apical vaginal prolapse surgical repair: A systematic review. *Obstet Gynecol*. 2009;113:367–373.
3. Brubaker L, Cundiff GW, Fine P, et al. Abdominal sacrocolpopexy with Burch colposuspension to reduce urinary stress incontinence. *N Engl J Med*. 2006;354:1557–1566.
4. Wei JT, Nygaard I, Richter HE, et al. A midurethral sling to reduce incontinence after vaginal prolapse repair. *N Engl J Med*. 2012;366:2358–2367.

ADDITIONAL READING

- FDA Safety Communication. Urogynecologic surgical mesh: Update on the safety and effectiveness of transvaginal placement for pelvic organ prolapse, 2011: www.fda.gov.
- Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29:4–20.

See Also (Topic, Algorithm, Media)

- Cystocele
- Cystocele Grading
- Incontinence, Urinary, Adult Female
- Pelvic Organ Prolapse (Cystocele and Enterocoele) Image ☼
- Pelvic Organ Prolapse Quantification System (POP-Q)
- Pelvic Organ Prolapse Terminology
- Prolapse, Staging Systems
- Urethra, Caruncle
- Urethrocele

CODES

ICD9

- 618.00 Unspecified prolapse of vaginal walls
- 618.6 Vaginal enterocele, congenital or acquired
- 618.9 Unspecified genital prolapse

ICD10

- N81.5 Vaginal enterocele
- N81.9 Female genital prolapse, unspecified
- N81.10 Cystocele, unspecified

CLINICAL/SURGICAL PEARLS

- Complete assessment of all vaginal compartments for POP staging is essential, including occult SUI.
- Nonsurgical treatments with pelvic floor muscle exercises and vaginal pessary should be offered prior to surgical intervention.
- Surgical repair with augmentation materials improves outcomes, but may pose serious safety risks.
- Patients must be informed of ongoing FDA concerns regarding safety of synthetic mesh materials used in POP surgery.
- Patient monitoring for recurrence and delayed mesh-related complications is imperative.

PELVIC PAIN, FEMALE

Kai-Wen Chuang, MD
Robert M. Moldwin, MD, FACS

BASICS

DESCRIPTION
- Chronic pelvic pain (CPP) is defined as discomfort below the umbilicus lasting ≥6 mo
- Etiology often unclear and symptom severity often out of proportion to objective findings
- Bears impact on physical, mental, emotional, and sexual well-being

EPIDEMIOLOGY
Incidence
N/A

Prevalence
- Difficult to ascertain due to varied definition
  - Affects ~1 in 7 women
  - 39% prevalence rate in primary care setting
  - Accounts for 10% of all gynecologic referrals

RISK FACTORS
- Depression, anxiety
- Personal history of abuse
- Prior sexually transmitted infections (STIs)
- Prior pelvic inflammatory disease (PID) increases risk 4-fold, prior STI/STD
- Substance dependence
- 1st-degree family with CPP

Genetics
- Twin studies and familial clustering do suggest genetic basis for increased nociception
- No established inheritance pattern

PATHOPHYSIOLOGY
- Exact mechanism unknown
- Complex and multifactorial, combining, biologic, psychological, and social factors

ASSOCIATED CONDITIONS
- Endometriosis, ectopic pregnancy, ovarian cysts, adhesions
- Urinary tract infections (UTIs), STIs, and PID
- Irritable bowel syndrome (IBS)
- Interstitial cystitis (IC)

GENERAL PREVENTION
- Prompt recognition
- Safe sex practices

DIAGNOSIS

HISTORY

- History of present illness
  - Onset/pallaition or provocation quality/radiation/severity/timing (OPQRST) of pain
  - Alleviating or aggravating factors
  - Ask if symptomatic during sexual intercourse
  - Menstrual history
- Past medical and surgical history
  - Check history of PID, STIs, ectopic pregnancy
  - Obtain history of trauma
  - Abdominal and pelvic surgeries contribute to adhesions
  - Check trigger points from incisional scars
- Family and social history
  - 1st-degree family with CPP
  - Inquire about physical and/or sexual abuse
  - Number of sex partners, method of contraception
  - Substance dependence, exposure to analgesics

PHYSICAL EXAM

- Vital signs
  - Fever, hypotension, and tachycardia suggest infectious etiology
- Abdominal exam
  - Search for trigger points
  - Assess peritoneal signs
  - Sensory evaluation of dermatomes
- Back and musculoskelet al exam
  - Evaluate posture and gait
  - Rule out scoliosis or lordosis
- Pelvic exam
  - Inspect vulva for skin lesions, signs of trauma, and irritation
  - Speculum exam to assess vaginal mucopurulent discharge and erythema
  - One-hand pelvic exam to identify muscular trigger points, cervical motion tenderness, urethral tenderness, and to delineate bladder base and vaginal fornix
  - Bimanual exam to assess uterine shape, direction, tenderness and mobility; assess adnexal masses and tenderness
- Rectal exam
  - Check rectal tone, rectovaginal septum, *cul-de-sac*, and uterosacral ligaments

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum
  - Complete blood count: Leukocytosis and left shift suggest infection
  - Erythrocyte sedimentation rate: Nonspecific markers of subacute or chronic inflammation
  - Cancer antigen-125: Marker for endometriosis, PID, and certain cancers
  - β-Human chorionic gonadotropin: Becomes positive 7 days after conception, a negative

test excludes ectopic pregnancy
- Urine
  - Urine pregnancy test
  - Urine analysis
  - Urine culture
  - Nucleic acid amplification test for gonorrhea and Chlamydia
  - Cytology, if hematuria to evaluate for bladder cancer
- Others
  - Cervical culture
  - Vaginal wet mount
  - PAP smear
  - Fecal occult blood test

Imaging
- Ultrasound
  - Transvaginal and/or pelvic ultrasound: Modality of choice in the initial evaluation of pelvic pain
  - Renal and bladder ultrasound: Assess hydronephrosis, renal stone disease, and bladder distension
- Plain films
  - Kidney, ureter, bladder x-ray (KUB): Assess urinary stone burden or dermoid cyst
  - Spinal and bony x-ray: Indicated when osseous and skelet al etiologies of pelvic pain are suspected
- Hysterosalpingography: Allow anatomic evaluation of the uterus and fallopian tubes
- Pelvic venogram: Assess pelvic vascular anatomy and venous congestion
- Axial imaging (CT, MRI)
  - Indicated when ultrasound negative or inconclusive
  - With intravenous and/or oral contrast
  - More sensitive evaluation of the gastrointestinal and genitourinary systems

Diagnostic Procedures/Surgery
- Diagnostic laparoscopy
  - Endometriosis most common (33%)
  - Adhesions (24%)
  - Negative 35–66% of the time
  - Negative findings do not exclude somatic cause and positive findings do not necessarily represent true etiology of CPP
- Barium enema or colonoscopy
- Urodynamics
- Cystoscopy, bladder biopsy, hydrodistension

Pathologic Findings
Based on diagnosis

DIFFERENTIAL DIAGNOSIS
- Gynecologic: Accounts for 20% of CPP
  - Cervical stenosis

  – Chronic PID (occurs after 30% of acute PID)
  – Endometriosis/chronic endometriosis
  – Gynecologic cancers
  – Pelvic congestion syndrome
  – Uterine fibroids
- Gastrointestinal
  – Colorectal cancers
  – Diverticulitis
  – IBS
  – Inflammatory bowel disease (IBD)
- Genitourinary
  – Bladder cancer
  – Cystitis, urinary retention
  – IC/painful bladder syndrome (PBS)
  – Kidney stones
  – Urethral diverticulum, urethritis
  – Urethral syndrome
- Others
  – Abdominal myofascial pain
  – Fibromyalgia
  – Pelvic floor muscular pain
  – Physical and/or sexual abuse
  – Psychiatric disorders
  – Radiculopathy
  – Surgical adhesions

TREATMENT

GENERAL MEASURES

- Goals of care for managing CPP
  – Symptomatic control
  – Patient education
  – Patient empowerment
- Multidisciplinary and individualized approach
  – Psychosocial counseling
  – Chronic pain management
  – Biofeedback
  – Physical therapy
  – Medications and surgery when needed
- Validated questionnaires and fluid diaries can help monitor progress

MEDICATION

First Line

- Target underlying condition, nerve block
- Nonsteroidal antiinflammatory drug (1)[B]

  – Superior to placebo
  – Can be given with acetaminophen
- Opioids (2)[A]
  – Oral, intramuscular, or transdermal
- Tricyclic antidepressants
  – More effective in neuropathic pain

ALERT
Common contraindications to antidepressants include recent infarction, arrhythmias, and severe hepatic/renal disease.

Second Line
- Selective serotonin reuptake inhibitors
- Anticonvulsants
  – Gabapentin (3)[A]
    - More effective in neuropathic pain
    - No place in acute pain

SURGERY/OTHER PROCEDURES
- Local injection of anesthetics
- Sacral neuromodulation (4)
- Surgical removal of endometriosis
- Hysterectomy
  – May be beneficial in women who have completed reproduction and whose CPP is believed to be due to uterine disorders such as adenomyosis or fibroids
- Presacral neurectomy

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Pelvic floor physical therapy
- Biofeedback and relaxation therapies
- Transcutaneous electrical nerve stimulation (TENS)
- Intravesical instillations or injections

Complementary & Alternative Therapies
- Acupuncture
- Massage and manipulations

ONGOING CARE

PROGNOSIS
Variable and dependent on underlying etiology and treatment modalities

COMPLICATIONS
- Risk of pharmacologic dependence, tolerance, and abuse associated with long-term

analgesia
- Surgical complications such as bleeding and infections are procedure specific

FOLLOW-UP

Patient Monitoring

- CPP is typically managed in outpatient setting
- Monitor serum hepatic/renal function and electrocardiogram when using antidepressants

Patient Resources

- The International Pelvic Pain Society
  – www.pelvicpain.org

REFERENCES

1. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhea. *Cochrane Database Syst Rev*. 2003:CD001751.
2. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. *Cochrane Database Syst Rev*. 2006:CD006146.
3. Wiffen P, Collins S, McQuay H, et al. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev*. 2005:CD001133.
4. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000;343:618–624.

ADDITIONAL READING

- Engeler DS, Baranowski AP, Dinis-Oliveira P, et al. The 2013 EAU guidelines on chronic pelvic pain: Is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol*. 2013;64(3):431–439.
- Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. *Eur Urol*. 2010;57(1):35–48.

See Also (Topic, Algorithm, Media)

- Chronic Pelvic Pain Syndrome (CPP) In Females Section II Table.
- Inflammatory Bowel Disease (Ulcerative Colitis and Crohn Disease), Urologic Considerations
- Interstitial Cystitis (IC)/Painful Bladder Syndrome
- Prostatitis, Chronic, Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B)

CODES

ICD9

- 338.29 Other chronic pain
- 617.9 Endometriosis, site unspecified
- 625.9 Unspecified symptom associated with female genital organs

ICD10

- G89.29 Other chronic pain
- N80.9 Endometriosis, unspecified
- R10.2 Pelvic and perineal pain

CLINICAL/SURGICAL PEARLS

- The pathophysiology of CPP is multifactorial, and the treatment for it is multidisciplinary.
- Initial evaluation for CPP aims to identify life- or organ-threatening conditions and rule out anatomic or structural abnormalities.
- Subsequent management of CPP focuses on symptomatic control and patient education.
- Treatment takes time, and cure may not be possible. Therefore, it is important to set patient-centered yet realistic goals of care.

PENILE PROSTHESIS PROBLEMS (INFECTION/EXTRUSION/MALFUNCTION)

Nelson Bennett Jr., MD

BASICS

DESCRIPTION

- While generally very reliable, penile prostesis can become infected, undergo extrusion and suffer form mechanical failure.
- 2 types of penile prosthesis, malleable (semirigid, noninflatable, nonhydraulic) and inflatable. Inflatables consist of 2-piece (pump and cylinders) and 3-piece (pump, cylinders, and reservoir).
- Implanted via suprapubic or penoscrotal approach.
- Meticulous sterility is required.
- Infections of any or all parts of the device components require removal of the entire device.
- Extrusion/erosion of the device may occur into or through the urethra, penile glans, proximal crura, bladder or bowel, or adjacent vascular structures.
- Mechanical breakdown may manifest as inability to inflate/deflate device, abnormal erectile morphology, or auto inflation.

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Overall infection rate: 1–8%
- Prosthesis revision infection rate: 10–13%
- Prosthesis revision through infected field infection rate: 18%
- Mechanical failure rate 2-piece: 5% @ 5 yr
- Mechanical failure rate 3-piece: 18% @ 15 yr

RISK FACTORS

- Infection: Diabetes, spinal cord injury, previous penile prosthesis, immunocompromised state, h/o UTI, obesity
- Extrusion/erosion: Previous surgery, previous pelvic radiation, penile fibrosis, aggressive dilation, lack of surgical experience, Peyronie disease, previous penile prosthesis, upsizing of cylinders
- Mechanical failure: Inadequate dilation of reservoir space

Genetics

N/A

PATHOPHYSIOLOGY

- Infection
  - 1–8% this percentage increases with number of revision surgeries

  - Most common bacteria – *Staphylococcus epidermidis*
  - Other bacteria: MRSA, Pseudomonas, Enterococcus, Prevotella, Morganella
  - Gram-negative bacteria may be associated with rapid infection
  - Biofilm plays important role in bacterial adherence and infection
- Extrusion/erosion
  - Erosion through skin is inherently infected
  - Pre-existing infection may hasten erosion
  - Iatrogenic-facilitated erosion may result from overaggressive dilation
- Malfunction
  - Mechanical failure rates are 15% at 5 yr and 30% at 10 yr
  - Common reasons include aneurysm, tubing breakage, reservoir leakage, and connector failure
  - Auto inflation is usually due to improperly positioned reservoir

ASSOCIATED CONDITIONS

- Conditions associated with erectile dysfunction
  - Adrenal disorders
  - AIDS-associated neuropathy
  - Alzheimer's
  - Cardiac arterial disease
  - CNS infections
  - CNS tumors
  - Diabetes mellitus (Type I and II)
  - History of kidney or liver transplant
  - History of myocardial infarction
  - History of prostatectomy, cystectomy, or colectomy
  - Hyperprolactinemia
  - Hypertension
  - Hyperthyroidism
  - Hypogonadism
  - Hypothyroidism
  - Liver failure
  - Multiple sclerosis
  - Peripheral vascular disease
  - Renal failure

GENERAL PREVENTION

- The preoperative assessment should include issues such as the patients' needs and expectations of the device (1,2)
  - Issues such as complications and the irreversibility of the procedure should be exhaustively discussed and documented through informed consent
- Infection
  - Ensure UTI or infectious skin rash is absent
  - Tight control of serum glucose and HbA1C
  - Preoperative parenteral antibiotic of vancomycin + aminoglycoside or imipenem
  - Meticulous adherence to sterile technique

  - Limit OR traffic
  - 10-min scrub of operative area
  - 10-min scrub for OR staff
  - Use of alcohol-based solution for final prep
  - Avoid having prosthesis contact skin
  - Use antibiotic-coated/antibiotic dripped prosthesis (3)
    - Postoperative oral antibiotics 7–10 days postoperatively
- Extrusion/erosion
  - Avoid aggressive corporal dilation
  - Avoid upsizing of cylinders
  - Avoid early/premature inflation of device
- Malfunction
  - Place corporotomy closing sutures before device insertion to avoid iatrogenic puncture
  - Demonstrate proper function and placement of the device prior to conclusion of surgery

DIAGNOSIS

HISTORY

Assess for fever, chills, pain, lethargy, fatigue, change in bowel or bladder function, dysuria, frequency, urethral discharge.

PHYSICAL EXAM

- Assess penis/scrotum for erythema, edema, induration, pain in palpation of penis/scrotum, presence of wound drainage, adherence of prosthesis components to skin.
- Erosion/extrusion of device through glans, urethral meatus, scrotal skin, or perineum.
- Assess functionality of device by inflation/deflation—if suboptimally rigid or deflated pump, consider fluid leak.
- Assess penile contour/morphology upon inflation:
  - Buckling of cylinder or S-shaped deformity suggests oversizing of cylinders.
  - Floppy glans (SST deformity) suggests undersized cylinders or inadequate corporal dilation.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
- Urine culture and sensitivity
- CBC with differential
- Metabolic profile
- Erythrocyte sedimentation rate

Imaging

- Usually not necessary
- Ultrasound scrotum—may reveal abscess
- MRI (with device inflated)—useful in assessment of corporal abnormalities.

Diagnostic Procedures/Surgery

Cystourethroscopy may reveal urethral erosion of cylinders or erosion of device component

into bladder.

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Intraoperative complications (4)
  - During corporal body dilation: Urethral perforation, cross over perforation of opposite crura during dilation
  - Reservoir position: Bladder perforation or improper positioning during the implant procedure
  - Component failure: Check device function before implantation; careful technique to avoid cylinder injury during corporal body closure
- Postoperative complications:
  - Infection
  - Erosion (oversized cylinder): Often associated with pain and buckling
  - Undersized cylinder ("concorde deformity" or "floppy glans") whereby there is excess mobility of the glans
  - Cylinder aneurysm
  - Fluid leak
  - Auto inflation/inability to deflate or inflate

TREATMENT

GENERAL MEASURES
- Broad-spectrum antibiotic should be started if infection is suspected.
- If sepsis is present, resuscitation is indicated prior to explanation of prosthesis.

MEDICATION
First Line
- AUA guidelines recommend the following antibiotic prophylaxis at the time of implantation (See Additional Reading)
  - Aminoglycoside (or aztreonam with renal insufficiency) plus
  - 1st/2nd-generation cephalosporin or vancomycin
  - Alternative regimens include:
    - Ampicillin/Sulbactam
    - Ticarcillin/Clavulanate
    - Piperacillin/Tazobactam

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Infection
  - Removal of prosthesis may be completed on a semiurgent basis (within 24 hr)
  - Immediate prosthesis salvage (replacement) may be possible in absence of frank purulence, erosion, necrotic tissue, poorly controlled diabetes, immunosuppression
  - Mulcahy protocol for prosthesis salvage (4):

- 1. Antibiotic solution (1 g vancomycin and 80 mg gentamicin in 1 L of normal saline)
- 2. ½ strength hydrogen peroxide
- 3. ½ strength betadine
- 4. Pressure washing with 1 g vancomycin and 80 mg gentamicin in 5-L irrigation
- 5. ½ strength betadine
- 6. ½ strength hydrogen peroxide
- 7. Antibiotic solution
- 8. Change instruments, gowns, drapes, and gloves immediately before prosthesis insertion

- Extrusion/erosion
  - Proximal erosion/extrusion managed by affixing RTE to the interior, proximal corpora with permanent suture
  - Alternatively, placing a purse-string suture in the corpora at tubing exit site
  - Distal extrusion/erosion (urethral) is best managed by immediately removing offending cylinder and prolonged Foley drainage. If contralateral cylinder has been placed, it may remain in place
- Malfunction
  - Floppy glans: Perform corporoplasty to reposition glans or dilate distal corpora
  - Cylinder aneurysm: Replace device
  - Fluid leak: Replace device
  - Auto inflation: Reposition, incise fibrotic capsule, or replace reservoir

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prosthesis satisfaction rates approach 95% for patients and partners
- Satisfaction rates for revision surgery is ~80%
- Infection rates have decreased with antibiotic coated or antibiotic dipped prosthetics

COMPLICATIONS

- Revision surgery may result in infection, extrusion/erosion, or malfunction
- Delay replacement of device may result in corporal fibrosis

FOLLOW-UP

Patient Monitoring

- In case of revision surgery, prolonged antibiotic treatment may be required.
- Biweekly follow-up is indicated until patient is cleared to use the device.

Patient Resources

AUA Foundation. http://www.urologyhealth.org/urology/index.cfm?article=11

REFERENCES

1. Akin-Olugbade O, Parker M, Guhring P, et al. Determinants of patient satisfaction following penile prosthesis surgery. *J Sex Med*. 2006;3(4):743–748.
2. Bettocchi C, Ditonno P, Palumbo F, et al. Penile prosthesis: What should we do about complications? *Adv Urol*. 2008;573560. Published online 2008 November 4.
3. Wilson SK, Salem EA, Costerton W. Anti-infection dip suggestions for the coloplast titan inflatable penile prosthesis in the era of the infection retardant coated implant. *J Sex Med*. 2011;8(9):2647–2654.
4. Mulcahy JJ. Penile prosthesis infection: Progress in prevention and treatment. *Curr Urol Rep*. 2010;11(6):400–404.

ADDITIONAL READING

- Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (2008). http://www.auanet.org/education/guidelines/antimicrobial-prophylaxis.cfm (updated February 2012. Accessed January 3, 2014)
- Bennett NE, Mulhall JP. Complication of surgery for erectile dysfunction and peyronie's disease. In: Taneja SS, ed. *Complications of Urologic Surgery Prevention and Management*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2010.

See Also (Topic, Algorithm, Media)

- Erectile Dysfunction (ED)
- Penile Prosthesis, Models and Descriptions
- Penile Prosthesis Problems (Infection/Extrusion/Malfunction) Images

CODES

ICD9

- 996.39 Other mechanical complication of genitourinary device, implant, and graft
- 996.69 Infection and inflammatory reaction due to other internal prosthetic device, implant, and graft
- 996.76 Other complications due to genitourinary device, implant, and graft

ICD10

- T83.6XXA Infect/inflm react d/t prosth dev/grft in genitl trct, init
- T83.89XA Other specified complication of genitourinary prosthetic devices, implants and grafts, initial encounter
- T83.420A Displacement of penile (implanted) prosthesis, initial encounter

CLINICAL/SURGICAL PEARLS

- Meticulous sterility is required during the implant in the operating room.
- Infections of any or all parts of the device components require removal of the entire device.
- Extrusion/erosion of the device may occur into or through the urethra, penile glans,

proximal crura, bladder or bowel, or adjacent vascular structures.

- Mechanical breakdown may manifest as inability to inflate/deflate device, abnormal erectile morphology, or auto inflation.

PENIS, CANCER, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Most common: Squamous cell carcinomas (SCCs)
  - SCC in situ or CIS: Erythroplasia of Queyrat (glans or prepuce), Bowen disease (shaft)
  - Low-grade noninvasive (eg, verrucous carcinoma)
  - Progression risk 5–33% if untreated
- Other penile cancer histology: Adeno- and adenosquamous carcinoma, basal cell carcinoma, melanoma, sarcomas, Kaposi sarcoma, neuroendocrine (small cell) undifferentiated carcinoma, sebaceous gland carcinoma, and rarely, metastases from other sites (prostate, bladder, colon, kidney, leukemia most common)

EPIDEMIOLOGY

Incidence

- In 2014 in the United States the American Cancer Society estimates that about 1,640 new cases of penile cancer will be diagnosed and 320 men will die of penile cancer
- In the United States
  - Hispanics (6.6 per million)
  - Blacks (4.0 per million)
  - Whites (3.9 per million)

Prevalence

- Rare in developed countries
- Most common genitourinary malignancy in Uganda
  - In Brazil 6–14/100,000 males (1)

RISK FACTORS

- Poor hygiene (2)
- Presence of foreskin and/or phimosis
- STD: HPV types 16, 18, and 33 or HIV
- Genital ultraviolet radiation, alone or combined with 8-methoxypsoralen
- Multiple partners, smoking
- Premalignant conditions:
  - Leukoplakia, Lichen sclerosus
  - Balanitis xerotica obliterans (BXO)
  - Giant condylomata

Genetics

Viral genes E6 & E7 expressed on high-risk HPV, E-cadherin (16q22) immunoreactivity correlates with increased risk of nodal metastases

PATHOPHYSIOLOGY

- Invasive SCC is thought to be preceded by superficial CIS (Bowen disease or erythroplasia of Queyrat). Invasive SCC grows into the skin locally before invading the corporal bodies and extending locally.
- Penile SCC spreads by a relatively reliable pattern: Form superficial pelvic lymph nodes to deep pelvic lymph nodes.
- SCC is found on the glans in 48%, prepuce in 21%, glans and prepuce in 9%, coronal sulcus in 6%, and shaft $<2\%$.

ASSOCIATED CONDITIONS
- Phimosis
- Balanitis
- Sexually transmitted infections (STIs)/STDs

GENERAL PREVENTION
- Good hygiene, avoid smegma accumulation
- Newborn circumcision more protective than circumcision later in life
- HPV vaccines may reduce the risk of HPV and, consequently, penile cancer (unproven)

ALERT
Presentation at advanced stage is not uncommon due to denial and poor hygiene.

DIAGNOSIS

HISTORY
- Persistent induration, erythema, nodularity of prepuce and/or glans. Usually has been treated with several agents, lotions
- Growth or sore on the penis that doesn't heal within 4 wk
- Patients often denies or ignores lesions and present at later stages
- Bleeding ulcer
- Penile pain—infection
  - New onset of priapism with a mass suggests metastatic corporeal body lesion (eg, melanoma)

PHYSICAL EXAM
- Induration, erythema, nodularity of prepuce and/or glans
- Bleeding ulcer
- Foul smell with purulence
- Phimosis
- Inguinal adenopathy

DIAGNOSTIC TESTS & INTERPRETATION
Lab
CBC, urinalysis, urine culture

Imaging
- Penile ultrasound
- CT pelvis—evaluate pelvic adenopathy
- Penile MRI—surgical planning

Diagnostic Procedures/Surgery

- Superficial lesion
  - Biopsy, preferably excisional
  - Circumcision
- Large or extensive
  - Partial penectomy

Pathologic Findings

- Most malignancies involve the epithelial surface of the penis
- CIS (erythroplasia of Queyrat, Bowen disease of the penis, bowenoid papulosis)
- Verrucous carcinoma, warty carcinoma, Buschke–Löwenstein tumor, and giant condyloma are terms used to describe infrequently seen rare tumors that may invade locally but do not metastasize. Mostly considered to be benign, but malignant degeneration has been reported
- Invasive cancer:
  - 95% are SCCs
  - Tongues of invasive atypical keratinocytes with multiple mitosis invade the lamina propria or deeper. Sites with foci of aberrant and ectopic keratinization called squamous pearls
  - SCCs are graded using the Broders System:
    - Grade I: Well-differentiated, keratin pearls, prominent intercellular bridges
    - Grade II–III: Greater nuclear atypia, increased mitotic activity, decreased keratin pearls
    - Grade IV: Cells deeply invasive, marked nuclear pleomorphism, nuclear mitoses, necrosis, lymphatic and perineural invasion, no keratin pearls

DIFFERENTIAL DIAGNOSIS

- BXO
- Erythroplasia of Queyrat; shiny red patches on mucosal surfaces (glans and prepuce if uncircumcised)
- Bowen disease (red, scaly patches on the keratinized skin of the penis typically penile shaft)
- Bowenoid papulosis (multiple flat, warty lesions, sometimes pigmented)
- Condyloma acuminatum, lata
- Giant condylomata
- Extramammary Paget disease: Adenocarcinoma of apocrine gland bearing skin, often pruritic
- Kaposi sarcoma: Friable nodular lesions of varying size and varying color (purplish, red, blue, dark brown black) often ulcerate/ bleed
- Lichen sclerosis
- Psoriasis
- Seborrheic keratosis
- Ulcer from STD
- Zoon balanitis

TREATMENT

GENERAL MEASURES

- 1st line is surgical excision of lesion on penis.
- Wound care issues are paramount after excision of the primary and after inguinal node

dissections.
- Surgical care should be taken to minimize the complications of penile deformity and/or meatal stenosis after excising the primary and diligent attention to avoiding infection, hematoma, and lymphocele after inguinal node dissection is necessary.
- Treatment based on extent of disease and specific tumor type. Recommendations below are for invasive SCC (3). For other tumor types, see specific sections.

MEDICATION

First Line

- Topical 5-fluorouracil for cases of CIS
- For invasive SCC of the penis, after resection of the primary tumor, inguinal adenopathy should be treated with 6 wk of broad-spectrum antibiotics (augmentin or cephalosporin such as keflex) to determine if the enlarged nodes resolve
  – Consideration to early fine-needle aspiration biopsy of enlarged nodes can be considered
- Some authors recommend immediate fine-needle aspiration of enlarged inguinal nodes

Second Line

- There is no established chemotherapeutic regimen for metastatic disease.
  – Potential active agents include 5-FU, bleomycin, methotrexate, and cisplatin.

SURGERY/OTHER PROCEDURES

- Initial dorsal slit may be necessary to assess the lesion in phimosis
- Circumcision, if preputial and noninvasive
- Laser ablation, if small and noninvasive
- Mohs micrographic surgery, if small and noninvasive or minimally invasive (4)
- Wide local excision for small lesions. A 2-cm margin considered necessary
- Partial or total penectomy should be considered in patients exhibiting adverse features for cure by organ preservation strategies, including tumors 4 cm or more, grade III lesions and tumors invading deeply into the glans urethra or corpora cavernosa
  – Partial penectomy must achieve a 2-cm safety surgical margin
- Inguinal lymphadenectomy is mandatory for persistent lymphadenopathy after antibiotics and control of the primary lesion
- Inguinal lymphadenectomy is controversial if inguinal nodes are palpably normal before and after eradication of the primary
- Lymph node sampling (either sentinel node biopsy or modified inguinal dissection) may be offered for patients with palpable normal inguinal nodes and T2 or above lesion:
  – Usually, bilateral dissections are recommended
  – A total inguinal and pelvic lymphadenectomy is necessary if metastases are noted on sentinel or modified dissection

ADDITIONAL TREATMENT

Radiation Therapy

- External radiation to primary lesion if patient refuses surgical excision
- Some advocate this as primary therapy with salvage surgery with recurrences
- Typical doses are 50–60 Gy over 4–6 wk
- Overall local control provided by interstitial brachytherapy appears superior to that provided by external beam radiation therapy with 5-yr local control rates of 70%–87%

Additional Therapies
Chemotherapy-based clinical trails

Complementary & Alternative Therapies
- Ketogenic diet
- Holistic approaches

ONGOING CARE

PROGNOSIS
- Depends on T-stage and nodal status
- AJCC staging
  - Stage I: Cancer is moderately or well-differentiated and only affects the subepithelial connective tissue
  - Stage II: Cancer is poorly differentiated, affects lymphatics, or invades the corpora or urethra
  - Stage IIIa: Deep invasion into the penis and metastasis in one lymph node.
  - Stage IIIb: Deep invasion into the penis and metastasis into multiple inguinal lymph nodes
  - Stage IV: The cancer has invaded into structures adjacent to the penis, metastasized to pelvic nodes, or distant metastasis is present
- 5-yr overall survival for men with node-negative disease is 80–90%.
- 5-yr survival for N+ men 30–40%
- Married or previously married men have better prognosis
- African Americans tend to present with more advanced disease and have a poorer prognosis

COMPLICATIONS
- Infections
- Erosion of lymphadenopathy into femoral artery
- After radiation or brachytherapy urethral fistula, stricture, or stenosis with or without penile necrosis, pain, and edema. Radical penectomy may be required

FOLLOW-UP
Patient Monitoring
- Close inspection for local recurrence usually every 3 mo for 5 yr
- Consider imaging for ambiguous findings on physical exam

Patient Resources
- http://www.cancer.gov/cancertopics/types/penile. Accessed 1/3/2014.
- The American Cancer Society: Penile Cancer: What is penile cancer? American Cancer Society. Last revised: 8/31/2013.
- http://www.cancer.net/cancer-types/penile-cancer. Last revised: 8/31/2013.

REFERENCES

1. Pow-Sang MR, Ferreira U, Pow-Sang JM, et al. Epidemiology and natural history of penile cancer. *Urology*. 2010;76(2 suppl 1):S2–S6.
2. Minhas S, Manseck A, Watya S, et al. Penile cancer–prevention and premalignant conditions. *Urology*. 2010;76(2 suppl 1):S24–S35.

3. McDougal WS, Kirchner FK Jr, Edwards RH, et al. Treatment of carcinoma of the penis: The case for primary lymphadenectomy. *J Urol*. 1986;136:38–41.
4. Mohs FE, Snow SN, Larson PO. Mohs micrographic surgery for penile tumors. *Urol Clin N Am*. 1992;19:291–304.

ADDITIONAL READING

- Pettaway CA, Davis JD. Contemporary management of penile cancer: Part I. *AUA Update Series*. 2012;31:15.
- Pettaway CA, Pagliaro L. Penile SCC Contemporary management of inguinal region: Part II. *AUA Update Series*. 2012;31:16.

See Also (Topic, Algorithm, Media)

- Balanitis Xerotica Obliterans (BXO)
- Bowen Disease and Erythroplasia of Queyrat
- Penis, Cancer, General Considerations Images
- Penis, Cancer, Lymphadenopathy
- Penis, Cutaneous Lesion
- Penis, Mass (Corporal Body Mass)
- Penis, Squamous Cell Carcinoma
- Penis, Squamous Cell Carcinoma Algorithm
- Reference Tables: TNM: Penis Cancer

CODES

ICD9

- 187.2 Malignant neoplasm of glans penis
- 187.3 Malignant neoplasm of body of penis
- 187.4 Malignant neoplasm of penis, part unspecified

ICD10

- C60.1 Malignant neoplasm of glans penis
- C60.2 Malignant neoplasm of body of penis
- C60.9 Malignant neoplasm of penis, unspecified

CLINICAL/SURGICAL PEARLS

- A painless lesion on the penis is the most common presentation.
- 40% of cases of penile cancer in the United States derive from HPV infections.
- 2-cm surgical margin is critical for a successful partial penectomy.
- Historically 6 wk of antibiotics are required to appropriate assessment of inguinal region adenopathy; consideration can also be given to early fine-needle biopsy.

PENIS, CANCER, LYMPHADENOPATHY

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BASICS

DESCRIPTION

- Penile cancer spreads systematically to inguinal lymph nodes (LNs) before spreading to the common iliac and para-aortic LNs and becoming metastatic disease
  - Drainage is bilateral in 81% of cases
- The inguinal LNs are classified as either superficial or deep
  - Superficial inguinal LNs (up to 25 nodes) are located under dermis and above the fascia lata in Scarpa's triangle
  - Deep inguinal LNs are located in the region of the fossa ovalis, medial to the femoral vein
- Extent of LN metastasis determines survival
- Lymphadenectomy (LAD) for penile cancer is associated with significant morbidity, but can improve long-term survival
- LAD is the primary form of treatment for localized lymphatic spread
  - Extent of LAD (radical vs. modified) remains controversial

EPIDEMIOLOGY

Incidence

1 in 100,000 men in the United States and Europe develop penile cancer

Prevalence

- LN spread occurs in 10–15% of patients with nonpalpable inguinal LNs
- LN spread occurs in 50% of patients with palpable inguinal LNs
  - Palpable inguinal LNs are present in 60% of presenting patients

RISK FACTORS

- Inguinal LN spread is correlated with an increase in clinical grade of primary tumor (0–29% in grade 1 vs. 33–50% in grade 3)
- Inguinal LN spread is correlated with an increase in local stage of primary tumor (<10% in pT1/pTis, 50–70% in pT2 disease, and 50–100% in pT3/pT4)

Genetics

HPV contributes to the development of penile cancer through interactions with tumor protein 53 (p53) and retinoblastoma (RB) tumor suppressor proteins

PATHOPHYSIOLOGY

- Inguinal LNs serve at the primary lymphatic drainage for the penis, scrotum, urethra, vulva, vagina, perineum, gluteal region, lower abdominal wall, lower anus, and lower extremities
- Inguinal LNs lie within the femoral triangle (inguinal ligament, sartorius, and adductor longus) and are separated into superficial and deep groups by the fascia lata of thigh

ASSOCIATED CONDITIONS

- Balanitis
- Phimosis
- STDs

GENERAL PREVENTION
- Prepubertal circumcision is protective against penile cancer
- Good genital hygiene
- STD education and safe sexual practices
- Sun protection against melanoma
- HPV vaccination may reduce risk (unproven)

DIAGNOSIS
HISTORY
- Circumcision
- Phimosis
- HPV infection
- Penile condylomata
- Penile cancer
- Sexual history (multiple partners, early age of initial intercourse)
- Smoking history
- Balanitis xerotica obliterans
- Treatment with sporalene and ultraviolet A phototherapy

PHYSICAL EXAM
Palpable inguinal LNs

DIAGNOSTIC TESTS & INTERPRETATION
Lab
No tissue parameters, including HPV and p53 status, are predictive of LN involvement

Imaging
- No imaging studies are currently utilized extensively in the diagnosis of LN involvement
- Ultrasound and PET-CT can be used to detect recurrences
- Chest x-ray and CT abdomen/pelvis can be used for staging

Diagnostic Procedures/Surgery
- Ultrasound-guided fine-needle aspiration cytology (FNAC)
  - Palpable LNs: Sensitivity of 93% and specificity of 91%
  - Nonpalpable LNs: Sensitivity of 39% and specificity of 100%
- Dynamic sentinel node biopsy (DSNB): Lymphoscintigraphy and blue dye staining for identification of positive LNs
  - False-negative rate of 5%
  - Should only be offered in experienced centers

Pathologic Findings
Squamous cell carcinoma accounts for 95% of penile cancers

DIFFERENTIAL DIAGNOSIS

- Reactive LNs
- Infections: Syphilis, herpes, chancroid, lymphogranuloma venereum, pedal fungal disease
- Malignant diseases: Metastatic melanoma, lymphoma
- Systemic diseases: Mononucleosis, rubella, human immunodeficiency virus, cytomegalovirus
- Autoimmune diseases: Sarcoidosis, lupus

TREATMENT

GENERAL MEASURES

- Tis, Ta primary tumors (1)
  - Nonpalpable inguinal LNs
    - Surveillance
  - Palpable inguinal LNs
    - Antibiotics for 1 mo to rule out infection vs. immediate fine-needle aspiration biopsy
    - If persistent LNs and either FNAC or excisional biopsy are positive, ipsilateral inguinal and pelvic LAD and contralateral superficial or modified inguinal LAD
- T1 grade 1 and grade 2 primary tumors
  - Nonpalpable inguinal LNs
    - Surveillance
  - Palpable inguinal LNs
    - If FNAC is negative and no resolution with antibiotics, excisional biopsy or inguinal LAD
    - If FNAC is positive, ipsilateral inguinal and pelvic LAD and contralateral superficial or modified LAD
- T2–T4 primary tumors
  - Nonpalpable inguinal LNs should undergo bilateral superficial inguinal LAD or DSNB
    - If frozen section is negative, surveillance
    - If frozen section is positive, that side should undergo ipsilateral inguinal and pelvic LAD
  - Palpable unilateral LNs should undergo ipsilateral inguinal and pelvic LAD and contralateral superficial or modified inguinal LAD
    - If contralateral frozen section is negative, surveillance
    - If contralateral frozen section is positive, deep inguinal or pelvic LAD
  - Palpable bilateral LNs should undergo FNAC to determine the extent of LAD
    - If FNAC is negative, at least bilateral superficial inguinal LAD or DSNB
    - If FNAC is positive, bilateral inguinal and pelvic LAD and chemotherapy is warranted
- Fixed or LNs >4 cm
  - Neoadjuvant chemotherapy potentially followed by surgery
- Pelvic LNs spread is more likely if (1) 2 or more inguinal node involvement, (2) extranodal metastasis, (3) Cloquet node involvement
- LAD should involve at least 8 LNs, as this improves 5-yr survival

MEDICATION

First Line

- Antibiotics
  - Use of antibiotics has become controversial for enlarged LNs
  - Historically, a 4–6-wk course of antibiotics (such as a cephalosporin or augmentin) was

recommended to rule out infection in Tis and Ta tumors with palpable LNs
  - Delay in LAD, a potentially curative treatment, has brought the use of antibiotics into question
  - FNAC can help determine if LNs are due to metastasis or infection

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical LAD (2,3)
  - Superior margin: Superior margin of the external ring to the anterior superior iliac spine (ASIS)
  - Lateral margin: ASIS to 20 cm inferiorly
  - Medial margin: Pubic tubercle to 15 cm inferiorly
  - Inferior margin: 20 cm inferior from the ASIS to 15 cm inferior from the pubic tubercle
- Modified LAD (after Catalona)
  - Excludes area lateral to the femoral artery and caudal to the fossa ovalis
  - Preservation of the saphenous vein
  - No transposition of the sartorius muscles
  - Conversion to radical LAD if there are positive LNs
- Techniques to minimize complications of LAD
  - Careful skin-flap management
  - Meticulous LN dissection
  - Prophylactic antibiotics: Cephalosporins for 2 mo
  - Vacuum drains
  - Elastic and/or pneumatic stocking
  - Early ambulation
- Endoscopic LAD (4)
  - Complete radical LAD can be completed through 3 endoscopic ports
  - Node yield is equivalent to open surgery
  - Decreased complications
- The viability of the skin flaps developed during an inguinal LN dissection are based on the anastomotic vessels within the superficial fatty layer of Camper's fascia which course lateral to medial along the skin lines. This is a key anatomic dissection plane as the lymphatic drainage of the penis lies beneath Camper's fascia allowing this superficial fatty layer to remain attached to the skin flaps during a groin dissection
- When performing an inguinal LN dissection for a clinically negative groin, a modified technique should be used to decrease morbidity. The key components of this technique include the following: Shorter incision (~10 cm), preservation of the saphenous vein, minimizing dissection lateral to the femoral artery, and avoiding transposition of the Sartorious muscle

ADDITIONAL TREATMENT

Radiation Therapy

- Adjuvant radiotherapy may improve locoregional control in patients with extensive metastases and/or extranodal disease

  – Side effects include edema and pain
• Radiotherapy in clinical N0 patients is not recommended

Additional Therapies
• Adjuvant chemotherapy
  – 3 courses of cisplatin and 5-fluorouracil for pN2–3
  – No adjuvant chemotherapy for pN1

Complementary & Alternative Therapies
None are effective

ONGOING CARE

PROGNOSIS
• 5-yr cancer-specific survivals:
  – 90–100% in pN0 disease
  – 70–80% in pN1 disease
  – <30% in pN2–pN3 disease
  – 15% in patients with positive pelvic LNs who had inguinal and pelvic LAD
• Predictors of cancer-specific survival: Pathologic stage of LNs, vascular and/or lymphatic involvement, primary tumor thickness

COMPLICATIONS
• LAD complications
  – Wound infection
  – Skin necrosis
  – Wound dehiscence
  – Thigh numbness
  – Lymphedema
  – Lymphorrhea
  – Scrotal swelling
  – Suprapubic swelling
  – Pulmonary embolism

FOLLOW-UP
Patient Monitoring
• Recurrences occur most often within 2 yr after inguinal LAD
• Nomograms available (5)
• Evaluation should include an exam and ultrasound-guided FNAC
• Maximum follow-up length of 5 yr
• Surveillance (patient did not have LAD)
  – Every 3 mo for yr 1 and 2
  – Every 6 mo for yr 3, 4, and 5
• LAD and pN0 disease
  – Every 6 mo for yr 1 and 2
  – Every 6 mo for yr 3, 4, and 5
• LAD and pN+ disease

– Every 3 mo for yr 1 and 2
– Every 6 mo for yr 3, 4, and 5

Patient Resources
National Cancer Institute: Penile Cancer Treatment (http://www.cancer.gov/cancertopics/pdq/treatment/penile/HealthProfessional)

REFERENCES

1. Pizzocaro G, Algaba F, Horenblas S, et al. EAU penile cancer guidelines 2009. *Eur Urol.* 2010;57:1002–1012.
2. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: The role and technique of lymph node dissection. *BJU Int.* 2001;88:473–483.
3. Johnson TV, Hsiao W, Delman KA, et al. Extensive inguinal lymphadenectomy improves overall 5-year survival in penile cancer patients: Results from the surveillance, epidemiology, and end results program. *Cancer.* 2010;116:2960–2966.
4. Master VA, Jafri SM, Moses KA, et al. Minimally invasive inguinal lymphadenectomy via endoscopic groin dissection: Comprehensive assessment of immediate and long-term complications. *J Urol.* 2012;188:1176–1180.
5. Kattan MW, Ficarra V, Artibani W, et al. Nomogram predictive of cancer specific survival in patients undergoing partial or total amputation for squamous cell carcinoma of the penis. *J Urol.* 2006;175:2103–2108; discussion 2108.

ADDITIONAL READING

Spiess PE, Horenblas S, Pagliaro LC, et al. Current concepts in penile cancer. *J Natl Compr Canc Netw*. 2013;11:617–624.

See Also (Topic, Algorithm, Media)
- Groin/Inguinal Mass, Male and Female
- Lymphadenopathy, Inguinal
- Penis, Cancer, General Considerations
- Penis, Cancer, lymphadenopathy Image ☼
- Penis Cutaneous Lesion
- Penis, Squamous Cell Carcinoma
- Reference Tables: TNM: Penis Cancer

CODES

ICD9
- 187.4 Malignant neoplasm of penis, part unspecified
- 196.5 Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
- 785.6 Enlargement of lymph nodes

ICD10
- C60.9 Malignant neoplasm of penis, unspecified
- C77.4 Sec and unsp malig neoplasm of inguinal and lower limb nodes

- R59.0 Localized enlarged lymph nodes

CLINICAL/SURGICAL PEARLS

- Penile cancer metastasizes to regional LNs before disseminating systemically.
- Treatment is dependent on the clinical presence of LNs, tumor stage, and tumor grade.
- Inguinal LAD is potentially curative and can improve long-term outcomes in penile cancer with nodal metastases.
- Careful tissue management, antibiotics, vacuum drains, and compression stockings can minimize the morbidities associated with LAD.

PENIS, CURVATURE, AND/OR PAIN

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BASICS

DESCRIPTION

- Penile pain could be a result of multiple etiologies and present in both a flaccid and erect penis
  - Penile pain: Flaccid penis
    - Usually secondary to inflammation of bladder and urethra with referred pain localized to meatus
    - Potentially secondary to paraphimosis
  - Penile pain: Erect penis
    - May be secondary to priapism or Peyronie disease (PD)
- Acquired penile curvature in men, known as PD, is an inflammatory condition of the tunica albuginea usually associated with painful erection with curvature. If severe, it can cause dyspareunia
  - Can be a result of complications of penile prosthesis implantation
  - Congenital chordee may present as penile curvature in infants due to a deficiency in formation of the urethra or the Buck fascia ventrally
  - Iatrogenic chordee secondary to circumcision or other penile skin procedures

EPIDEMIOLOGY

Incidence

- Common at all ages, but mean age: 53
- Mostly affects males 40–70 yr old, with 0.4–3.2% incidence

Prevalence

In general 5% of men have evidence of PD

RISK FACTORS

- Buckling erectile trauma
- Fracture of the tunica albuginea during sexual activity
- Intracavernous injection of vasoactive agents
- Priapism
- Urethral and penile surgery
- See also “Commonly Associated Conditions”

Genetics

- Associated with HLA (histocompatability B7) cross-reactive antigens
- PD less frequent in patients with Asian or African ancestry

PATHOPHYSIOLOGY

- Mechanical tunical stress forces causing microvascular hemorrhage and inflammation in the tunical wall or septum. The result is hypertrophic scar formation (plaque).

- Autoimmune components have been demonstrated in 38–75% of men with PD.
- Altered cell-mediated immunity and antielastin antibodies support an immunologic component.
- In the setting of erectile trauma, an altered immunologic response to wound healing may predispose a subpopulation to PD.

ASSOCIATED CONDITIONS
- Chronic intracavernous injection therapy
- Dupuytren contracture
- ED (venoocclusive dysfunction)
- Ledderhose disease (Plantar fasciitis)
- Paget disease
- Tympanic sclerosis
- Urethral stricture
- Hypospadias

GENERAL PREVENTION
Avoidance of penile trauma during intercourse

DIAGNOSIS
HISTORY
- Obtain a thorough medical, surgical, and sexual history (1)[A]
- It is critical to differentiate penile pain from urethral pain: History of voiding symptoms and/or recurrent UTIs
- Establish duration, degree, and location of curvature and pain
- Dyspareunia
- Painful erection (suggests PD)
- Painful ejaculation
- Nature of deformity: Curvature, indentation or instability (hinge effect)
- Condition causes distress to patient or partner
- Coexisting ED
- Palpable nodule
- History of penile prosthesis
- History of penile trauma
- History of penile surgery as a child
- Sickle cell disease suggests predisposition to priapism
- Insect bites

PHYSICAL EXAM
- Circumcised/uncircumcised; retractable foreskin
- Measurement of stretched penile length
- Palpation of stretched shaft to amplify plaque and determine its location and size
- Plaque tenderness
- Location of meatus for evidence of hypospadias
- Evidence of hematoma that suggests acute trauma
- Solitary or multiple plaques

- Erythema and crepitus with Fournier gangrene
- Eggplant sign with penile fracture

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Usually not useful unless for workup of infections
- Urinalysis with or without culture in cases of referred pain from other GU cause
- Serum-free testosterone (morning) and prolactin levels if erectile dysfunction coexists
- Corporal blood gas for priapism

Imaging

- Radiograph of penile shaft if calcification is suspected.
- Duplex Doppler US with intracavernous pharmacologic injection to assess cavernous arterial function, presence of venoocclusive dysfunction, and degree of erectile curvature, lateral indentation or circumferential wasting.
- Private self-photography of erect penis using instant (Polaroid) or digital film imaging is useful to classify the extent of the curvature.

Diagnostic Procedures/Surgery

- Uroflowmetry to rule out associated urethral stricture
- Bladder US for postvoid residual
- Retrograde urethrogram (if history and exam suggest urethral injury, such as blood at meatus. May be seen with penile fracture.)
- Urethroscopy for urethral pathology

Pathologic Findings

- PD is characterized by a fibrous noncompliant plaque within the tunica albuginea, which may calcify, preventing uniform expansion of the corpora cavernosa during erection.
  - Microscopy: Affected tunica albuginea demonstrates nonpolarized arrangement of collagen fibers and disordered arrangement of elastin fibers in PD.

DIFFERENTIAL DIAGNOSIS

- Balanitis, balanoposthitis, paraphimosis
- Cellulitis
- Chordee
- Congenital penile curvature
- Epispadius
- Erectile dysfunction
- Fournier gangrene
- Hypospadias
- Idiopathic urethralgia
- Insect bite
- Penile ischemia (embolic, atherosclerosis)
- Leukemic infiltration of the penile shaft
- Penile cancer
- Penile fracture, trauma, or contusion
- Penile pain syndrome

- Penile prosthesis problem: S-shaped or sigmoid curvature with buckling of prosthesis cylinders that are too long; pain also suggests infected prosthesis components
- Priapism
- Psychiatric causes of pain
- Pudendal neuralgia
- Referred pain, GI (rectum, hemorrhoids, fistula, fissures)
- Referred pain, GU (cystitis, urethritis, prostatitis, retention, urolithiasis, urethral calculus)
- Reiter syndrome
- STD (herpes, chancroid)
- Torn frenulum
- Trauma (GSW, penile fracture)
- Urethral foreign bodies
- Urethral shortening following urethroplasty
- Urethral stricture

TREATMENT

GENERAL MEASURES

Identify the specific cause of the penile pain and/or curvature and treat accordingly

MEDICATION

First Line

- PD
  - All oral agents yield insignificant therapeutic benefit:
    - Vitamin E (antioxidant), potaba (antifibrotic), colchicine (antifibrotic), tamoxifen (antifibrotic), L-carnitine (antioxidant), pentoxifylline
- Paraphimosis
  - Urgent manual reduction with firm pressure ± local anesthetic (see section on paraphimosis for details)
- Priapism
  - Irrigation and aspiration
  - Intracavernosal phenylephrine injection (100–500 mcg/mL)
- Referred pain to penis or urethra should be aimed at treating primary problem
- Treat infectious causes (cellulitis, STD) with antimicrobials

Second Line

- PD intralesional therapy
  - Collagenase clostridium histolyticum (CCH) (Xiaflex) (3)[A]
    - FDA approved curvature deformity of the penis due to the presence of a plaque in PD. Restricted distribution through Risk Evaluation and Mitigation Strategy (REMS) due to the risks of serious adverse reactions, including penile fracture and other serious penile injury
    - Maximum 4 treatment cycles. Each treatment cycle consists of 2 Xiaflex injection procedures (in which Xiaflex is injected directly into the collagen-containing structure of the penis) and 1 penile modeling procedure performed by the healthcare professional.
    - Breaks down collagen, promotes remodeling

- Other intralesional agents (off-label) Verapamil (antifibrotic), collagenase (antifibrotic), interferon-α (antifibrotic)
- Steroid therapy
  - Subcutaneous, nonintralesional injections of triamcinolone (50 mg) (2)[C]

SURGERY/OTHER PROCEDURES

- PD
  - Plication of the corporal body
  - Plaque incision with graft interposition
    - Synthetic (Dacron)
    - Autologous (buccal mucosa, dermis, tunica albuginea, tunica vaginalis)
    - Prepackaged biologic (porcine small intestine submucosa)
  - Penile prosthesis with manual molding, if necessary (4)[A]
- Paraphimosis
  - Dorsal slit or incision of constricting band
  - Circumcision may be necessary
- Chordee and epispadias
  - See specific topic for surgical correction
- Penile Fracture
  - See specific topic for surgical correction
- Priapism
  - Distal and/or proximal shunting procedures
  - See specific topic for surgical correction
- Penile reconstruction of scars, contractures, or other deformities
  - Z-plasty or other plastic operation

ADDITIONAL TREATMENT

Radiation Therapy

Ineffective in PD

Additional Therapies

N/A

Complementary & Alternative Therapies

- None have been shown to have convincing benefit
  - Vitamin E (α-tocopherol)
  - Potaba (potassium aminobenzoate)
  - L-carnitine
- Acupuncture

ONGOING CARE

PROGNOSIS

- Prognosis dependent on primary etiology of penile curvature and/or pain.
  - Surgical straightening of erection is predictably successful (>85%).
  - Shortened penile length and sensory loss may be noted postoperatively.

COMPLICATIONS

- Residual pain and curvature
- Dyspareunia
- Erectile dysfunction and loss of penile length due to PD or surgical repair

FOLLOW-UP

Patient Monitoring

Periodic monitoring of erectile function, penile length, and sensory function

Patient Resources

- The Peyronie Disease Society (www.peyroniessociety.org)
- Urology Care Foundation (http://www.urologyhealth.org/urology/index.cfm?article=115)

REFERENCES

1. Delavierre D, Rigaud J, Sibert L, et al. Symptomatic approach to chronic penile pain. *Prog Urol*. 2010;20:958–961.
2. Dickstein R, Uberoi J, Munarriz R. Severe, disabling, and/or chronic penile pain associated with Peyronie's disease: Management with subcutaneous steroid injection. *J Androl*. 2010;31:445–449.
3. Gelbard M, Mavuduru RM, Agarwal MM, et al. Clinical efficacy, safety, and tolerability of collagenase clostridium histoyliticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol*. 2013;190:199–207.
4. Segal RL, Burnett AL. Surgical Management for Peyronie's Disease. *World J Mens Health*. 2013;31:1–11.

ADDITIONAL READING

- AUA Guideline on the Management of Priapism 2003 (http://www.auanet.org/education/guidelines/priapism.cfm)
- www.urologyhealth.org

See Also (Topic, Algorithm, Media)

- Chordee
- Epispadias
- Penile Prosthesis, Models and Descriptions (Table)
- Penile Prosthesis Problems (Infection/Extrusion/Malfunction)
- Penis and Corporal Body Mass
- Penis, Curvature and or Pain Image
- Peyronie Disease
- Priapism, General

CODES

ICD9

- 605 Redundant prepuce and phimosis
- 608.89 Other specified disorders of male genital organs
- 752.63 Congenital chordee

ICD10

- N47.2 Paraphimosis
- N48.89 Other specified disorders of penis
- Q54.4 Congenital chordee

CLINICAL/SURGICAL PEARLS

- Focused history and physical exam allows for prompt diagnosis and effective treatment.
- High index of suspicion for emergent etiologies (Fournier gangrene, penile fracture, priapism, paraphimosis).
- New data suggests that CCH can significantly reduce the symptoms of Peyronie disease.

PENIS, CUTANEOUS LESION

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BASICS

DESCRIPTION
- 3 categories: Benign, premalignant, malignant
- May be male genitalia-specific (primary) or associated with other cutaneous lesions or systemic disease (secondary)
- May occur at any age

EPIDEMIOLOGY
Incidence
Varies widely by etiology

Prevalence
- Depends on etiology
  - Pearly penile papule found in 14–48% of postpubertal males
  - Genital warts found in 0.1–1% of men

RISK FACTORS
Systemic disease, irritant or allergen, sexual contact, trauma, uncircumcised penis, family history, inflammation, infections, medications, local skin hygiene, obesity, age, smoking

Genetics
- Reiter syndrome: Associated with HLA-B27 haplotype
- Hailey–Hailey disease: Autosomal dominant
- Penile cancer: Associated with altered expression of P53, P21, c-ras, myc, Ki-67 genes

PATHOPHYSIOLOGY
- Idiopathic, allergic, infectious, autoimmune, inflammatory, systemic, sexual transmission, genetic
- Lesions appear similar; biopsy often needed for diagnosis

ASSOCIATED CONDITIONS
- Lesler–Trélat syndrome: Increase in size and number of seborrheic keratosis lesions sometimes signaling internal malignancy
- Stevens–Johnson syndrome and toxic epidermal necrolysis: Prodromal upper respiratory illness followed by life-threatening desquamating lesions due to medications, infections, or cancers
- Psoriasis: Lesions under preputial skin, glans, or prepuce
- Reiter syndrome (reactive arthritis): Urethritis, arthritis, conjunctivitis. Circinate balanitis
- Behçet disease: Painful ulcers found in 57–93% of patients, mostly scrotum (90%), but glans and shaft also affected
- Inflammatory bowel disease: Arterial thrombosis of penis, penile swelling, and noncaseating

granulomas on biopsy; also pyoderma gangrenosum
- Hailey–Hailey disease: Vesiculobullous rash
- Diabetes: Phimosis
- HIV: Kaposi sarcoma, seborrheic dermatitis

GENERAL PREVENTION
- Circumcision helpful in some cases
- Proper hygiene
- Safe sex practices
- Avoid contact with allergens or irritants

DIAGNOSIS
HISTORY
- Age
- Symptoms: Pain, pruritus, burning, discharge
- Location: Scrotum, glans, shaft, preputial skin, urethral/bladder lining, other sites
- Duration
- Rate of onset: Acute or chronic
- Exposures: New bath/laundry soap, lotions, oils, travel (exotic plants, animals, insects, people), shared towels/clothes, new medications, industrial, chemical
- Sexual history: Sexual partner with lesions
- Trauma
- History of systemic diseases or cancers
- Allergies
- Family history
- Previous treatment

PHYSICAL EXAM
- Examine and describe lesion(s):
  - Elevated, nonelevated
  - Color of lesion
  - Morphology of lesion
  - Configuration of lesion (linear vs. serpiginous)
  - Degree of margination
  - Degree of firmness
  - Examine genitalia: Circumcised, uncircumcised, proper placement of foreskin
  - Describe primary lesion(s) (1)[A]:
    - Papule: ≤0.5 cm, solid, elevated
    - Plaque: >0.5 cm, solid, elevated
    - Nodule: >0.5 cm, solid, dome-shaped
    - Vesicle: ≤0.5 cm, fluid-filled, well-circumscribed
    - Bulla: >0.5 cm, fluid-filled, well-circumscribed
    - Pustule: Vesicle with purulent fluid, well-circumscribed
    - Wheal: Hive, edematous plaque
  - Describe secondary lesion(s) (1)[A]:

- Scale: Flakes on lesion surface
- Crust/scab: Collected cellular debris
- Atrophy: Thinning of skin causing depression
- Scar: Connective tissue collection
- Cyst: Lesion with wall and lumen
- Erosion: Defect with red/moist base
- Fissure: Thin linear defect
- Ulcer: Deep defect

• Full dermatologic exam:
  – Single or multiple lesions
  – Organ-specific or generalized
• Lymph node exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Urinalysis, Gram stain, culture
• Complete blood count
• Serum chemistry profile
• STD screening if suspected

Imaging

• If locally advanced lesion or internal lesions/tumors/malignancies suspected
• Workup for associated abnormalities

Diagnostic Procedures/Surgery

• Cytologic smears: Potassium hydroxide or periodic acid-Schiff staining for fungal infections
• Tzanck smear: Herpes, varicella, Molluscum contagiosum
• Microscopic exam: Scabies, pubic lice, pinworm, and other infections
• Gram stain, bacterial, and fungal cultures of lesion: Infections
• Excisional or incisional biopsy

Pathologic Findings

• Depth of lesion
• Exam of epidermis, dermis, and subcutaneous tissue and any changes noted
  – Infiltration with other cells or infectious agents

DIFFERENTIAL DIAGNOSIS

• Common benign lesions (1)[A]
  – Acrochordon: “Skin tag”
  – Angiokeratoma of Fordyce: Red papules on penis, scrotum; ectasia of dermal blood vessels
  – Epidermoid cysts: Most common cysts of genital area. Filled with keratin. Postsurgical after circumcision or hypospadias repair
  – Fordyce spots: Sebaceous glands on genitalia
  – Pearly penile papule: Small, white/flesh colored, multiple, on glans or corona
  – Seborrheic keratoses: “Stuck on” appearance
  – Vitiligo: Patchy depigmentation of skin
  – Zoon balanitis: Nonelevated, erythematous, glistening plaques on glans in uncircumcised

men. Biopsy to distinguish from SCC in situ
  - Sclerosing lymphangitis: Cordlike lesion of coronal sulcus; after vigorous sexual activity
- Allergic dermatitis, eczematous lesion with erythema, discharge, excoriations (1)[A]
  - Atopic dermatitis: Also known as lichen simplex chronicus, pruritic, red/scaly lesion on posterior scrotum. "Atopic triad" of eczema, allergic rhinitis, asthma
  - Contact dermatitis: Irritant or allergic. Scaly with crust. Direct cytotoxic effect of irritant or local type IV hypersensitivity reaction
  - Erythema multiforme: Red papules and target lesions, blisters. Minor or major. Major: Stevens–Johnson syndrome, toxic epidermal necrolysis
- Papulosquamous disorders, scaly lesion on erythematous base (2)[C]
  - Psoriasis: Thick plaque with silver scales. Corona and glans lesions in circumcised, underneath preputial skin in uncircumcised
  - Reiter syndrome: Circinate balanitis, urethritis, arthritis, ocular, oral, and skin lesions. History of infection with Chlamydia, Gonococcus, Ureaplasma, or GI bacteria
  - Lichen planus: Idiopathic autoimmune reaction against basal keratinocytes; small, flat, shiny, violaceous papules on glans
  - Lichen sclerosis: Pruritic pearly white papules and plaques on glans and inner prepuce that scar. Late stage called balanitis xerotica obliterans. Biopsy to exclude SCC
  - Fixed drug eruption: Hypersensitivity reaction to medication 1–2 wk after starting. Lesions occur in same location after challenge
- Vesicobullous disorders, autoimmune blisters and erosions (1)[A]
  - Pemphigus vulgaris: Extensive painful blisters and erosions. Difficult to treat and may be fatal
  - Bullous pemphigoid: LgG mediated, typically in patients older than 70 yr
  - Dermatitis herpetiformis: Associated with celiac disease; IgA mediated
  - Hailey–Hailey disease: Familial, seen in 20–30s, blisters in axilla, inguinal, perianal areas
- Noninfectious ulcers, lesions extending to dermis (1)[A]
  - Behçet disease: Painful oral and genital ulcers, uveitis and other systemic involvement
  - Pyoderma gangrenosum: Chronic painful ulcer associated with Crohn's, ulcerative colitis, collagen vascular disease
  - Traumatic ulcers: Direct impact, sexual activity, body piercings, cleansing techniques
- Infections and infestations (1)[A]
  - STDs: Herpes simplex, syphilis, chancroid, genital warts, granuloma inguinale, lymphogranuloma venereum, molluscum contagiosum, Chlamydia, gonorrhea, trichomoniasis
  - Genital warts: HPV 6 and 11.4 variants: Condylomata acuminate, common warts, flat-topped papules/plaques, Buschke–Löwenstein tumor (giant condyloma). Biopsy for flat-topped and giant condylomas to rule out SCC
  - Balanoposthitis: Inflammation of glans and foreskin in uncircumcised males. Can be due to bacteria, yeast, irritants, trauma
  - Cellulitis: Infection of deep dermis and subcutaneous tissues due to *Staphylococcus aureus* and *Streptococcus pyogenes*
  - Folliculitis: Infection of hair-bearing follicles
  - Furunculosis: "Boil"

- Hidradenitis suppurativa: Painful, firm, red nodules with draining sinuses; chronic inflammation of gland-bearing skin, superinfection possible
- Fournier's gangrene: Necrotizing fasciitis; progresses from cellulitis to blisters to foul-smelling necrotic lesions. Surgical emergency
- Infestation: Pubic lice (*Pediculosis pubis)* or scabies (*Sarcoptes Scabiei* mite); very pruritic

• Neoplastic lesions, see Section I "Bowen disease and Erythroplasia of Queyrat," "Penis, cancer, general considerations," "Penis, squamous cell carcinoma"

TREATMENT

GENERAL MEASURES

• Common benign lesions (1)[A]:
- No treatment if asymptomatic
- If inflamed or infected, treat with antibiotics
- Topical corticosteroids or emollient for symptomatic relief
- Recurrent infections or cosmetic reasons: Excise, remove with laser or cryotherapy
  - Zoon balanitis: Topical steroids for symptoms, circumcision for cure
  - Contact dermatitis: Remove offending agent
  - Psoriasis: Topical corticosteroids, clobetasol, or systemic treatment
  - Lichen sclerosis: Biopsy to exclude SCC. Long-term follow-up required. Circumcision curative.
  - Pemphigus vulgaris: Oral corticosteroids, immunosuppressive therapy
  - Behçet disease: Oral corticosteroids, immunosuppressive therapy
  - Genital warts: Topical 0.5% podofilox, 5% imiquimod, green tea polyphenol extract, 25% podophyllin or trichloroacetic acid, cryotherapy, electrosurgery, laser ablation, surgical excision
  - Balanoposthitis: Circumcision curative
  - Hidradenitis suppurativa: Skin care, topical clindamycin or oral clindamycin and rifampin. Surgical excision for recurrent lesions
  - Fournier's gangrene: Broad-spectrum intravenous antibiotic coverage and emergent surgical debridement
  - Infestation with scabies or pubic lice: 5% permethrin cream overnight and repeated a week later

MEDICATION

First Line

• Varies with etiology (see above) (3)[B]
- Low-potency topical corticosteroids for symptoms, eg, Hydrocortisone 1%, 2.5%
- Specific antibiotics aimed at pathogen

Second Line

• Varies with etiology (3)[B]
- High-potency or oral corticosteroids
- Immunosuppressive mediations
- Intravenous antibiotics

SURGERY/OTHER PROCEDURES
- Excision of lesion(s) and surrounding tissue
- Laser ablation, electrocautery, cryotherapy
- Circumcision
- More extensive surgeries if neoplastic lesion

ADDITIONAL TREATMENT
Radiation Therapy
Limited role in nonneoplastic lesions

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
- Most cutaneous lesions have a good prognosis but should be addressed promptly
- Widespread lesions difficult to control

COMPLICATIONS
- See "Differential Diagnosis" section
- If left untreated, lesions may progress locally or distally and cause symptoms

FOLLOW-UP
Patient Monitoring
Follow patients to monitor response to intervention and any change in lesion

Patient Resources
- http://www.cdc.gov/std/general/default.htm
- http://www.aad.org/skin-conditions/dermatology-a-to-z

REFERENCES

1. Choi JM. Common benign dermatologic genital lesions: Diagnosis and treatment. *AUA Update Series.* 2011;30:367–371.
2. Gogstetter D and Mercurio MG. Common penile lesions: Tips to the differential. *Med Aspects of Human Sexuality.* 2001;1(2):45–51.
3. Teichman JM, Sea J, Thompson IM, et al. Noninfectious penile lesions. *Am Fam Physician.* 2010;81(2):167–174.

ADDITIONAL READING

- Buechner SA. Common skin disorders of the penis. *BJU Int.* 2002;90:498–506.
- Köhn FM, Pflieger-Bruss S, Schill WB. Penile skin diseases. *Andrologia.* 1999;31(suppl 1):3–11.

See Also (Topic, Algorithm, Media)
- Balanitis and Balanoposthitis

- Bowen Disease and Erythroplasia of Queyrat
- Chancroid
- Condylomata Acuminata (Venereal Warts)
- Genital Ulcers
- Penis, Cancer, General Considerations
- Penis, Cutaneous Lesion Image ☼
- Penis, Squamous Cell Carcinoma
- Phimosis and Paraphimosis
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General

CODES

ICD9

- 078.11 Condyloma acuminatum
- 608.89 Other specified disorders of male genital organs
- 709.8 Other specified disorders of skin

ICD10

- A63.0 Anogenital (venereal) warts
- N48.89 Other specified disorders of penis
- R23.8 Other skin changes

CLINICAL/SURGICAL PEARLS

- Do a complete skin exam when genital cutaneous lesion found.
- Skin lesions appear similar and excisional or incisional biopsies are often necessary for diagnosis and to rule out cancer.
- Stevens–Johnson syndrome, toxic epidermal necrolysis, Fournier gangrene, pemphigus vulgaris can be life-threatening.

PENIS, SQUAMOUS CELL CARCINOMA

Michael A. Poch, MD
Philippe E. Spiess, MD

BASICS

DESCRIPTION

- The majority of penile carcinomas are squamous cell carcinoma (SCC) histology
- Can be SCC in situ (erythroplasia of Queyrat, Bowen disease of the penis, bowenoid papulosis), low-grade noninvasive (eg, verrucous carcinoma), or invasive carcinoma
- Other rare types of penile cancer histologies include adeno- and adenosquamous carcinoma, basal cell carcinoma, melanoma, sarcomas, Kaposi sarcoma, neuroendocrine (small cell) undifferentiated carcinoma, sebaceous gland carcinoma, and rarely, metastases from other sites (prostate, bladder, colon, kidney)
- Inguinal and pelvic lymph nodes are common sites of metastases

EPIDEMIOLOGY

Incidence

- Rare in developed countries. Approximately 1,640 new cases annually in US with approximately 320 deaths in 2014.
- Hispanics are more commonly affected than whites.
- Circumcision is protective.
- Accounts for up to 10% of cancers in men in South America.

Prevalence

Accounts for 0.4–0.6% of cancers in men

RISK FACTORS

- Human papilloma virus (HPV) types 16, 18, 31, and 33 (associated with 45–80%)
- Presence of foreskin and/or phimosis
- Poor hygiene
- Sexually transmitted disease (STD)
- HIV infection
- Chronic inflammation
- Lichen sclerosis
- Smoking

Genetics

N/A

PATHOPHYSIOLOGY

- HPV-associated DNA and chromosomal changes
- Smegma that forms from desquamated epithelial cells is thought to be a primary instigating factor in penile cancer; good hygiene and circumcision limit smegma accumulation
- Penile SCC spreads by a reliable pattern: Superficial inguinal lymph nodes to deep inguinal lymph nodes to pelvic lymph nodes

ASSOCIATED CONDITIONS
- Balanitis xerotica obliterans (BXO)
- Bowen disease
- Chronic inflammation
- Erythroplasia of Queyrat
- Giant condylomata
- Leukoplakia
- Phimosis
- Premalignant lesions that predispose to the development of invasive SCC of the penis and penile cancer
- STIs

GENERAL PREVENTION
- Good penile hygiene
- Newborn circumcision more protective than circumcision later in life

DIAGNOSIS
HISTORY
- Induration, erythema, nodularity of prepuce, glans, and/or shaft
- Bleeding ulcer on glans and/or penile shaft
- Inguinal adenopathy
- Penile pain if lesion infected
- Patients often deny or ignore symptoms resulting in presentation at advanced stage
- New onset priapism with a mass suggests a metastatic corporal body lesion
- Constitutional symptoms may suggest metastatic disease

PHYSICAL EXAM
- Induration, erythema, nodularity of prepuce and/or glans
- Fungating mass emanating from glans or shaft
- Bleeding ulcer on glans
- Purulence suggests concomitant infection
- Inguinal adenopathy
  - Location, number, unilateral, bilateral, mobility or fixation

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum CBC, electrolytes (including calcium), and liver function studies
- Urinalysis, urine culture

Imaging
- US or MRI of penis for local tumor (T) staging
- CT/MRI of pelvis and inguinal regional to evaluate for lymphadenopathy and metastatic disease

Diagnostic Procedures/Surgery
- Biopsy; punch, excisional, or incision
- Shave biopsy will not give adequate local tumor (T) staging

Pathologic Findings

- Most malignancies involve the epithelial surface of the penis
- Subtypes of SCC
  - Usual, papillary, verrucous, warty, basaloid, sarcomatoid
- CIS (erythroplasia of Queyrat, Bowen disease of the penis, bowenoid papulosis)
- Verrucous carcinoma, warty carcinoma, Buschke–Löwenstein tumor, and giant condyloma are terms used to describe infrequently seen rare tumors that may invade locally but do not metastasize. Mostly considered to be benign, but malignant degeneration has been reported
- Grade:
  - Broder's classification used
    - Keratinization, nuclear pleomorphism, number of mitosis
  - SCC grade classification: Grade strong predictor for metastatic nodal involvement
    - Grade I: Well differentiated, no evidence of anaplasia
    - Grade II: Moderately differentiated (<50% anaplastic cells)
    - Grade III: Poorly differentiated (>50% anaplastic cells)
    - Grade IV: Undifferentiated
- Vascular invasion is associated with prognosis

DIFFERENTIAL DIAGNOSIS

- BXO
- Bowen disease (red, scaly patches on the keratinized skin of the penis typically penile shaft)
- Erythroplasia of Queyrat; shiny red patches on mucosal surfaces (glans and prepuce if uncircumcised)
- Bowenoid papulosis (multiple flat, warty lesion sometimes pigmented)
- Condyloma acuminatum
- Condyloma lata
- Extramammary Paget disease
- Giant condylomata
- Kaposi sarcoma
- Lichen sclerosis
- Psoriasis
- Seborrheic keratosis
- Ulcer from STI
- Balanitis of Zoon

TREATMENT

GENERAL MEASURES

- Treatment typically based on grade and stage of primary tumor (1)
- Palpable lymphadenopathy
  - Fine-needle aspiration (FNA)
  - 6-wk course of oral antibiotics followed by repeat physical exam

MEDICATION

First Line

- Tis/Ta lesions

- Topical: Imiquimod 5% cream applied for 5 d/wk for 4–6 wk or 5-FU 5% cream every other day for 4–6 wk

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Primary lesions
  - Tis/Ta lesions
    - Laser ablation: CO_2 or neodymium
    - Circumcision (preputial lesions)
    - Wide local excision, Mohs surgery, glansectomy, glans resurfacing
  - T1 grade 1–2
    - Mohs, wide local excision
    - External beam radiation therapy
    - Brachytherapy (with interstitial placement)
    - Laser ablation
  - T1 grade 3–4 or ≥T2
    - Partial penectomy (with intraoperative frozen section)
    - Traditionally 2-cm margin is required
    - Total penectomy with perineal urethrostomy
- Regional nodes (2)
  - Sentinel node biopsy
    - High false-negative rate (25%)
  - Nonpalpable nodes
    - High-risk T2 or G3 and intermediate-risk cancer with lymphovascular invasion—inguinal node dissection (ILND)
  - Unilateral palpable nodes <4 cm
    - FNA or ILND if high risk
    - 6 wk of oral antibiotics less recommended
  - Palpable nodes ≥4 cm
    - Standard or modified ILND
    - Possible preoperative EBRTchemotherapy
- Pelvic lymph nodes
  - Pelvic Lymph node dissection if >2 inguinal nodes positive on frozen section at the time of ILND

ADDITIONAL TREATMENT

Radiation Therapy

- External radiation to primary lesion or inguinal lymph nodes
- Typical doses are 50–60 Gy over 4–6 wk
- Interstitial brachytherapy for clinically indicated lesions

Additional Therapies

- Neoadjuvant chemotherapy
  - TIP: Ifosfamide, paclitaxel, cisplatin
- Adjuvant for high-risk disease

  - Bilateral inguinal nodal disease
  - Pelvic lymph node involvement
  - Extranodal extension
  - >4 cm nodes
- Metastatic disease
  - TIP
  - Clinical trial
  - Supportive/palliative care

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Depends on T-stage and nodal status
- Overall survival for men with node-negative disease is 80–90%.
- 20–30% of men with inguinal lymph node metastasis will have pelvic lymph node metastasis
  - Pelvic nodal metastasis have a 10% 5-yr survival
- When applicable, ILND associated with improved disease-specific survival

COMPLICATIONS

- Infections
- Erosion of lymphadenopathy into femoral vessels
- Partial penectomy and total penectomy
  - Urethral stenosis
  - Loss of erective function
- ILND
  - Infection (43%)
  - Seroma (24%)
  - Wound breakdown (16%)
  - Lymphedema
  - Vascular injury

FOLLOW-UP

Patient Monitoring

- Close inspection for local recurrence usually every 3 mo for 5 yr (frequency depends on grade and stage)
- Consider imaging for ambiguous findings on physical exam

Patient Resources

National Cancer Institute. http://www.cancer.gov/cancertopics/types/penile

REFERENCES

1. National Comprehensive Cancer Network. Penile Cancer Version 1. 2013. http://www.nccn.org/professionals/physician_gls/pdf/penile

2. Johnson TV, Hsiao W, Delman KA, et al. Extensive inguinal lymphadenectomy improves overall 5-year survival in penile cancer patients: Results from the surveillance, epidemiology, and end results program. *Cancer*. 2010;2960–2966

ADDITIONAL READING

- Burgers JK, Badalament RA, Drago JR. Penile cancer: Clinical presentation, diagnosis, and staging. *Urol Clin N Am.* 1992;19:247–256.
- McDougal WS, Kirchner FK Jr, Edwards RH, et al. Treatment of carcinoma of the penis: The case for primary lymphadenectomy. *J Urol.* 1986;136:38–41.
- Mohs FE, Snow SN, Larson PO. Mohs micrographic surgery for penile tumors. *Urol Clin N Am.* 1992;19:291–304.
- Ornellas AA, Seixas AL, Marota A, et al. Surgical treatment of invasive squamous cell. *J Urol.* 1994;151(5):1244–1249.
- Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide and ciplatin chemotherapy for metastatic penile cancer. A phase II Study. *J Clin Oncol*. 2010;3851–3857.
- Pettaway CA, Pisters LL, Dinney CP, et al. Sentinel lymph node dissection for penile carcinoma: The MD Anderson Cancer Center experience. *J Urol.* 1995;154:1999–2003.

See Also (Topic, Algorithm, Media)

- Balanitis Xerotica Obliterans (BXO)
- Bowen Disease and Erythroplasia of Queyrat
- Genital Ulcer Algorithm
- Penis, Bowenoid Papulosis
- Penis, Lesion, General
- Penis, Leukoplakia
- Penis, Mass (Corporal Body Mass)
- Penis, Squamous Cell Carcinoma Algorithm
- Penis, Squamous Cell Carcinoma Images
- Reference Tables: TNM: Penis Cancer

CODES

ICD9

- 176.0 Kaposi's sarcoma, skin
- 187.4 Malignant neoplasm of penis, part unspecified
- 233.5 Carcinoma in situ of penis

ICD10

- C46.0 Kaposi's sarcoma of skin
- C60.9 Malignant neoplasm of penis, unspecified
- D07.4 Carcinoma in situ of penis

CLINICAL/SURGICAL PEARLS

- Grade and stage associated with prognosis FNA of palpable nodes is preferred over 6-wk course of oral antibiotics.

- Modified ILND is associated with improved morbidity.
- Bulky inguinal lymph node metastases should be managed by multimodal therapy consisting of neoadjuvant systemic chemotherapy followed by surgical resection (± radiotherapy).

PENIS, TRAUMA

Hunter Wessells, MD, FACS
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BASICS

DESCRIPTION

Acute traumatic injury to the penis may be due to blunt trauma (penile fracture to the erect penis), penetrating injury (stab wound, firearm, improvised explosive device [IED], or amputation), degloving (MVC, power takeoff injury), burns, human and animal bites, or constriction with reduced blood flow

EPIDEMIOLOGY

Incidence

- Penetrating trauma to genitals is relatively rare in civilian setting
- Gunshot wounds and penetrating injuries make up 40–60% of battlefield urologic injuries during times of war; likely due to lack of protection to external genitalia
- In the battlefield, use of fragmentation devices (mines, IED) and high-velocity missiles cause a significantly greater percentage of genitourinary injuries to involve the penis and genitalia
- Penile fracture infrequently seen in US, with incidence of 1 in 175,000 hospital admissions
- Penile fractures are common in Iran where it is a social practice (Taghaandan)

Prevalence

N/A

RISK FACTORS

- Occupational (military, farming, heavy machinery)
- Bicycling is leading sport associated with injury to the external genitalia

Genetics

N/A

PATHOPHYSIOLOGY

- Transfer of kinetic energy to the penis is most devastating due to penetrating mechanisms
- Blunt injuries to the flaccid phallus are much less likely to cause any damage
- Penis is very resistant to injury in flaccid state; in erect state, bending injury can lead to rupture of tunica albuginea (“penile fracture”)
  – Typically results from impact with partner’s pubic symphysis or perineum
- Redundant blood supply to the penis (dorsal, cavernosal, and bulbourethral arteries and superficial skin vasculature) all protect from ischemic loss of the penis
- Penile strangulation
  – Constricts blood flow, leading to edema, ischemia, constricted micturition
  – Pediatric patients: Hair or string causes constriction
  – Adult patients: Penile constricting devices designed for sexual enhancement
- Pelvic fracture can lead to avulsion of the crura of the corpora cavernosa with subsequent dysfunction

- Associated injuries are common due to the proximity to other pelvic organs
- Degloving injuries: Loss of superficial penile tissue (skin and Dartos fascia)

ASSOCIATED CONDITIONS

- Injury to scrotum, testicle, urethra, or rectum may accompany penile trauma
- Pelvic fracture

GENERAL PREVENTION

- Military services are developing devices for ballistic protection of the external genitalia
- Protective equipment during contact sports
- Proper safety training for industrial machinery
- Proper instruction in patients prescribed penile constriction devices for the management of erectile dysfunction
- Cautious sexual intercourse

DIAGNOSIS

HISTORY

- Type of injury
- Magnitude of force transmitted
- Type of object in penetrating injury
- Determine species of animal in bite injuries
- In cases of amputation history of method of preservation of amputated portion if available
  - Method of penile preservation
  - Self-inflicted amputation may occur in psychotic states
- Timing, severity, progression of pain, swelling, discoloration of penis, scrotum, and genitalia
- Circumstances and timing of penile constriction device
- Intercourse-related trauma to the penis may be reported as a “pop” or “snap” associated with swelling and immediate penile detumescence
- Intercourse-related trauma with “pop,” swelling but no immediate penile detumescence is suspicious for rupture of superficial dorsal vein
- Associated abdominal pain, nausea, emesis

PHYSICAL EXAM

- Pattern of erythema, ecchymosis
- Assess for injuries of adjacent organs
- Blood at meatus concerning for urethral injury
- Size of laceration, if present
- Transilluminate any palpable scrotal mass
  - Hydrocele will transilluminate
  - Hematocele or tumor will not transilluminate
- Penile fracture:
  - Penile swelling, ecchymosis with possible palpable defect in corpora cavernosa
  - “Eggplant sign”: Hematoma deep to Buck’s fascia
- “Butterfly hematoma”: Hematoma deep to Colles’ fascia
- Penile strangulation:
  - Penile edema, ischemic changes, gangrene

– Suprapubic fullness secondary to urethral constriction
• Gunshot wounds: Search for associated injuries especially injured femoral vessels, urethral injury, or rectal injury.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Urinalysis
• Urine culture if infection suspected
• CBC
• For delayed presentation with abscess formation, culture abscess

Imaging

• Suspicion of urethral injury warrants evaluation with retrograde urethrography to evaluate for the presence of injury and injury location.
• Penile fracture:
– MRI or US useful if rupture of superficial dorsal vein suspected
– Cavernosography historically described
• Scrotal ultrasound or CT scan may be useful if suspicious for associated injuries

Diagnostic Procedures/Surgery

Cystoscopy: Used to assess for urethral injury

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

• Burn
• Constriction injury (band or other device placed around base of penis) can include medically approved devices
• Fournier gangrene
• Human or animal bite
• Laceration
• Penetrating injury
• Penile “fracture”
• Rupture of superficial dorsal vein
• Penile amputation

TREATMENT

GENERAL MEASURES

• Ensure the overall stability of the patient (1)
• Recognize and appropriately manage injuries to the external genitalia
• Maintain high index of suspicion for urethral injury and assess with retrograde urethrogram or cystoscopy
• Association for the Surgery of Trauma (AAST) organ injury scale classification (2):
– I: Cutaneous laceration/contusion
– II: Buck’s fascia (cavernosum) laceration without tissue loss
– III: Cutaneous avulsion; laceration through glans/meatus; cavernosal/urethral defect < 2

cm
  - IV: Partial penectomy; cavernosal or urethral defect >2 cm
  - V Total penectomy
- For burns see section on “Burns, External Genitalia, and Perineum”

MEDICATION

First Line

- Appropriate fluid resuscitation based on severity of injury
- Broad-spectrum antibiotic prophylaxis for all penetrating genital injuries
- See section on Bites to penis (animal and human) for appropriate antibiotic coverage
- Tetanus prophylaxis for all penetrating injuries

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgical exploration is required in almost all cases of penile injury (3 – 5)
  - Exploration typically performed through a circumferential skin incision at coronal margin
  - Deeper injuries require penoscrotal or perineal incisions
- Hemostasis is achieved by closure of corporal defects due to fracture, gunshot, or stab wound
- The urethra should be directly inspected for appropriate identification of any urethral injuries which need to be identified and repaired
- Glans injuries are repaired by debridement and reduction in the size of the glans while maintaining its overall configuration
- Primary skin closure is appropriate unless significant contamination of wound is noted
- Penile amputation
  - Preservation of the amputated phallus
  - “2-bag method” (penis wrapped in saline gauze in inner bag; ice in the outer bag)
  - Cold ischemia >24 hr is acceptable if it allows transfer to a specialized center for microvascular replantation
  - Even at normal temperatures, replantation 16 hr after injury has been successful
  - Technique for microvascular replantation:
    - Single-layer urethral repair over catheter
    - Tunica albuginea reanastomosis (5-0 PDS)
    - Dorsal vein and dorsal artery microvascular reanastomosis (to preserve skin perfusion and venous drainage; 0-0 nylon)
    - Dorsal nerve reanastomosis for sensation, 10-0 nylon
  - If amputated segment cannot be reattached:
    - Close corporal bodies with 4-0 PDS
    - Spatulate urethral meatus to tunica
    - Can gain penile length later by cutting suspensory ligament, defatting pubis, or considering reconstruction with free flap
- Penile fracture:
  - Circumcising incision via subcoronal approach with evacuation of hematoma
  - Close cavernosal injuries with absorbable suture (5-0 PDS)

  – Explore for urethral injuries and, if present, repair (5-0 PDS)
- Penile strangulation:
  – Incision of offending agent if possible (cut hair, string, bands, soft rings with scissors)
  – Solid constricting devices: Attempt removal with lubrication; distal penile compression with manual pressure may decrease tissue edema long enough to remove foreign body
  – Some devices may require ring cutters, operative drills, industrial drills, various saws; protect phallus with tongue depressors, malleable retractors
  – Suprapubic tube may be needed for bladder decompression
- Avulsions (degloving injury):
  – Exposed surface should be immediately covered with sterile saline-soaked gauze and area re-examined in 24 hr to assess extent of injury
  – Penile shaft can be covered with split-thickness skin graft
  – Scrotum can be covered with meshed split-thickness skin graft
- Gunshot wounds:
  – If wound contaminated, then conservatively débride and allow healing by secondary intention
  – If wound clean, tunical margins can be reapproximated with absorbable suture; urethral injuries should be identified and repaired
- Human bites:
  – Should not be closed; antibiotic therapy includes oral dicloxacillin or cephalexin

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most penile injuries can be successfully repaired with low rate of erectile dysfunction when immediate reconstruction is performed.
- Delayed repair or nonoperative approach to penile injuries may lead to penile curvature and erectile dysfunction.
- Even after penile amputation, with successful replantation patients can have sensation with erectile function.

COMPLICATIONS

- Decreased sensation
- Impotence
- Penile curvature
- Skin loss (particularly with nonmicrovascular penile replantation)
- Urethral stricture

- Urethral stricture or fistula
- Wound infections

FOLLOW-UP

Patient Monitoring

- Patient monitoring is required for detection for complications.
- Traumatic injury may result in erectile dysfunction requiring additional therapy.

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=12

REFERENCES

1. Morey AF, Metro MJ, Carney KJ, et al. Consensus on genitourinary trauma: External genitalia. *BJU Int*. 2009;94:507–515.
2. American Association for the Surgery of Trauma. http://www.aast.org/library/traumatools/injuryscoringscales.aspx#penis (Assessed August 21, 2014)
3. Waxman S, Beekley A, Morey A, et al. Penetrating trauma to the external genitalia and Operation Iraqi Freedom. *Int J Impot Res*. 2009;21:145–148.
4. Wessells H, Long L. Penile and genital injuries. *Urol Clin North Am*. 2006;33:117–126.
5. Lewis EA, Pigott MA, Randall A, et al. The development and introduction of ballistic protection of the external genitalia and perineum. *J R Army Med Corps*. 2013;159(suppl 1):i15–i17.

ADDITIONAL READING

- Avery LL, Scheinfeld MH. Imaging of penile and scrotal emergencies. *Radiographics*. 2013;33(3):721–740.
- García Gómez B, Romero J, Villacampa F, et al. Early treatment of penile fractures: Our experience. *Arch Esp Urol*. 2012;65(7):684–688.
- Morey AF, Brandes S, Dugi DD, et al. Urotrauma: AUA Guideline (https://www.auanet.org/common/pdf/education/clinical-guidance/Urotrauma.pdf Accessed August 21, 2014)

See Also (Topic, Algorithm, Media)

- Bites to Penis (Animal and Human)
- Burns, External Genitalia and Perineum
- Penis, Strangulation
- Penis, Trauma Algorithm
- Penis, Trauma Images
- Scrotum and Testicle, Trauma
- Taghaandan
- Urethra, Trauma (Anterior and Posterior)

CODES

ICD9

- 878.0 Open wound of penis, without mention of complication
- 959.13 Fracture of corpus cavernosum penis
- 959.14 Other injury of external genitals

ICD10
- S31.20XA Unspecified open wound of penis, initial encounter
- S39.840A Fracture of corpus cavernosum penis, initial encounter
- S39.94XA Unspecified injury of external genitals, initial encounter

CLINICAL/SURGICAL PEARLS
- Penile injuries have high likelihood of associated injuries to the external and internal pelvic organs.
- Urethral injury must be excluded.
- With penile fracture there is 10–22% associated urethral injury; surgical repair is associated with lower rates of erectile dysfunction or curvature.
- Early surgical exploration and repair allows excellent preservation of function and cosmesis.
- Penile fracture characteristically causes ecchymosis, swelling, an associated popping or cracking sound during intercourse followed by immediate detumescence.

PEYRONIE DISEASE

Irvin H. Hirsch, MD

BASICS

DESCRIPTION

- An idiopathic, localized connective tissue disorder with increased collagen deposition in the tunica albuginea, resulting in a fibrous plaque that leads to pain and penile angulation (1)[C]
- Plaque (2)[C]:
  - Most commonly dorsal plaque on side of penis to which curvature directed
- Penile angulation may cause dyspareunia and even preclude sexual intercourse
- First described by French surgeon François Gigot de Peyronie
- Synonym(s): Acquired penile curvature, chronic inflammation of the tunica albuginea (CITA), penile induration, *Induratio penis plastica*

EPIDEMIOLOGY

Incidence

- Affects males 40–70 yr old, with 0.4–3.2% incidence (1)[C]
- 3–7% men 40–70 yr old have PD (3)[C]
- Mean age: 53

Prevalence

Estimated 388 in 100,000 men (1,2)[C]

RISK FACTORS

- Inherent tendency to produce abnormal fibrous tissue
- Erectile trauma or injury to the tunica albuginea of the penis may incite fibrotic reaction from repetitive microvascular injury and healing
- Intracorporal injection therapy and oral pharmacotherapy for ED not implicated as risk (2)[C]

Genetics

Association with Dupuytren contracture (in 9–39%) and HLA-B7 antigens (1)[C]

PATHOPHYSIOLOGY

- Idiopathic (1,2)[C]
- Origin of initial inflammatory process that leads to fibrosis, calcification, elastic fiber alterations, and plaque formation in tunica albuginea unknown, but likely predisposing genetic alteration with inciting trauma
- Acute phase:
  - Occurs in 1st 6–18 mo
  - Proliferation of fibroblasts, myofibroblasts, and collagen deposition
  - Pain with erections, slight penile curvature, and nodule formation
  - Medical therapy most effective in acute phase
- Chronic phase:

– Remodeling of connective tissue into a dense fibrotic plaque
– Stable plaque size, penile curvature possibly causing ED, erections less painful
• Natural history: Minority of patients (10%) will have spontaneous regression, yet most patients will not develop disease significant enough to require surgery

ASSOCIATED CONDITIONS
• ED: Occurs in 20% men with PD (1)[C]
– Comorbidities: Diabetes, hypertension, dyslipidemia, smoking, coronary disease
• PD is found in 10% men with ED
– Urethral stricture may coexist

GENERAL PREVENTION
Avoidance of penile trauma during intercourse

DIAGNOSIS
HISTORY
• Distress and depression resulting from Peyronie disease
• Duration and onset of symptoms, history of erectile trauma. Severe pain or snap or popping during intercourse
• Pain: With or without erection; during intercourse
• Penis: Induration; degree and direction of penile angulation; hourglass deformity; lateral indentation; shortening; sensory loss, partner's perception
• Erections: Quantify rigidity; sufficient for intercourse
• History of Dupuytren contractures or hand surgery for deformity

PHYSICAL EXAM
• Penile exam noting plaque size, tenderness and location
• Autophotography may be helpful in assessing degree of angulation
– Examine the palmar fascia for associated Dupuytren contracture

DIAGNOSTIC TESTS & INTERPRETATION
Lab
N/A

Imaging
No imaging necessary for diagnosis/medical therapy

Diagnostic Procedures/Surgery
• Preoperative assessment of stretched penile length and sensory threshold (Biothesiometry)
• Preoperative Doppler US with intracavernous vasoactive challenge: Assess plaque size, calcification, vascular hemodynamics of penis and erectile curvature
• Preoperative intracavernous injection of vasoactive agent and genital sexual stimulation with measurement of erectile curvature
• Photographic confirmation by the patient of degree of curvature is often helpful

Pathologic Findings
Excess collagen deposition and inflammatory infiltrate is found in the tunica albuginea

DIFFERENTIAL DIAGNOSIS

- Cancer: Primary or metastatic to corpora
- Chordee: Usually associated with hypospadias
- Kelami syndrome: Fibrosis of the corpus spongiosum that limits expansion of the ventral corpora cavernosa
- Penile fracture (hematoma)

TREATMENT

GENERAL MEASURES

- A small percent of men will undergo spontaneous remission.
- Surgery is not a common 1st-line option but ultimately offers definitive resolution of curvature and deformity.
- The lack of randomized, placebo-controlled trials makes evaluation of efficacy and comparison between any medical therapies for PD difficult.
- Patients most likely to respond to medical therapy: Young patients in acute phase. (1,2)[C]
- All medical therapies provide varying decrease in pain, curvature, or plaque size; complete resolution of curvature is uncommon.

MEDICATION

First Line

- Oral therapy (2):
  - No therapy has proven more or less effective than another
  - Vitamin E (tocopherol):
    - 800–1,000 U/d PO in divided doses
    - Antioxidant effects; may cause bleeding
  - Potassium aminobenzoate (Potaba):
    - 3 g PO q6h
    - May increase monoamine oxidase, decrease serotonin, or increase utilization of oxygen by tissues; Expensive, GI side effects
  - Colchicine:
    - 0.6 mg PO q8h
    - May decrease collagen synthesis and increase collagenase activity
  - Pentoxifylline:
    - Growth factor blocker and anti-inflammatory
    - 400 mg PO BID
  - Other reported oral therapy: Tamoxifen, acetyl-L-carnitine,
- Intralesional therapy (2):
  - Collagenase clostridium histolyticum (CCH (4)[C]:
    - Breaks down collagen, promotes remodeling
    - FDA approved for curvature deformity of the penis due to the presence of a plaque in PD. Restricted distribution through Risk Evaluation and Mitigation Strategy (REMS) due to the risks of serious adverse reactions, including penile fracture and other serious penile injury
    - A cycle consists of 2 CCH injection procedures and a penile modeling procedure
    - Induce a penile erection (eg, intracavernosal injection of 10–20 mcg of alprostadil)

- With the erection, identify and mark the target area in the Peyronie plaque
- The penis should be in a flaccid state before injecting CCH. Inject 0.58 mg CCH into the target plaque of a flaccid penis once on each of 2 days, 1–3 days apart
- Perform a manual penile modeling procedure 1–3 days after the 2nd injection of each treatment cycle. For each plaque causing the curvature deformity, up to 4 treatment cycles may be administered. Each treatment cycle may be repeated at approximately 6-wk intervals. If the curvature deformity is <15 degrees after the 1st, 2nd, or 3rd treatment cycle, or if further treatment is not indicated, then subsequent treatment cycles should not be administered
- 10,000 U in 0.25 cm^3 per injection

– No other intralesional therapy has proven more or less effective than another
– Verapamil (5)[C]:
- 12 injections (10 mg/10 mL) given once every 2–4 wk
- Calcium blockage inhibits extracellular transport of collagen; increases collagenase activity in vitro; must commit to full course
- Applicable for young patients in acute phase

– Interferon α2a or 2b (6)[C]:
- 5×10^6 U biweekly for 3–6 mo
- Inhibits fibroblast proliferation, diminishes collagen production, increases collagenase
- Applicable for young patients in acute phase
- Flu-like side effects

– Intralesional corticosteroids no longer recommended due to local side effects

Second Line
N/A

SURGERY/OTHER PROCEDURES
• Indications: Curvature or erectile dysfunction that precludes intercourse (2)[C]
• Patient must be in chronic phase with stable painless plaques
• Preoperative US with intracavernous vasoactive challenge is useful to evaluate vasculature and anatomy of penis, as described above
• Plication procedures:
– Candidates: Longer penis, mild, distal curvature, good erectile function
– Relative to corporal plaque, plication of opposite aspect of corpora cavernosa with a 12–24-point plication. A relaxing incision of plaque is rarely required
– Complications/side effects: Hematoma, stitch erosion/granuloma, penile shortening
• Plaque excision with grafting:
– Candidates: Shorter penis, proximal plaque, severe curvature, hourglass deformity, lateral indentation and good erectile function
– Plaque incised/excised and corporotomy defects grafted with small intestine submucosal graft (Surgisis, Cook Biotech)
– Complications: Loss of sensitivity, infection, hematoma, shortening, de novo venoocclusive erectile dysfunction
• Inflatable penile prosthesis placement:
– Candidates: Significant erectile dysfunction, severe curvature

- Modeling:
  - When prosthesis placement alone fails to straighten penis, manual modeling is recommended, with good outcomes
  - Forcible manual manipulation of penis ("modeling" over inflated prosthesis)
- Complications: Infection (1–3%), erosion (<5%), mechanical malfunction (5–10%), urethral injury

ADDITIONAL TREATMENT

Radiation Therapy

Mixed results reported; not recommended

Additional Therapies

Extracorporeal shockwave therapy: No good placebo-controlled studies to document efficacy; studies report decreased pain after ESWL therapy (2)

Complementary & Alternative Therapies

- Penile traction therapy may have utility when combined with other therapies
- Carnitine supplementation: Mixed results

ONGOING CARE

PROGNOSIS

See "Pathophysiology–Natural History"

COMPLICATIONS

- PD can impact quality of life and cause relationship difficulties
- Depression can be associated

FOLLOW-UP

Patient Monitoring

- Patients should be re-examined frequently to assess disease status and response to therapy.
- Recent studies suggest up to 48% of men with PD have clinically relevant signs of depression and should be considered for mental health screening. (7)

Patient Resources

- AUA Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=115
- The Peyronie Disease Society. www.peyroniessociety.org

REFERENCES

1. Hellstrom WJ, Bivalacqua TJ. Peyronie's disease: Etiology, medical, and surgical therapy. *J Androl.* 2000;21(3):347–354.
2. Wespes E, Eardley I, Giuliano F, et al. Guidelines on penile curvature. *Eur Urol.* 2012;62:543–552.
3. Sommer F, Schwarzer U, Wassmer G, et al. Epidemiology of Peyronie's disease. *Int J Impot Res.* 2002;14:379–383.
4. Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol.* 2013;190(1):199–

207.
5. Levine LA and Constabile RA. Is intralesional verapamil effective therapy for peyronie's disease? *J Urol.* 2012;188:704–706.
6. Hellstrom WJ, Kendirci M, Matern R, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon α-2b for minimally invasive treatment for Peyronie's disease. *J Urol.* 2006;176:394–398.
7. Nelson JN, Diblasio C, Kendirci M, et al. The chronology of depression in men with Peyronie's disease. *J Sex Med.* 2008;5:1985–1990.

ADDITIONAL READING

Abern MR, Larsen S, Levine LA. Combination of penile traction, intralesional verapamil, and oral therapies for Peyronie's disease. *J Sex Med.* 2012;9:288–295.

See Also (Topic, Algorithm, Media)

- Chordee
- Erectile Dysfunction/Impotence (ED)
- Penis, Curvature and/or Pain
- Penis and Corporal Body Mass
- Peyronie Disease Image ☼

CODES

ICD9

- 607.84 Impotence of organic origin
- 607.85 Peyronie's disease
- 608.89 Other specified disorders of male genital organs

ICD10

- N48.6 Induration penis plastica
- N52.9 Male erectile dysfunction, unspecified
- N53.12 Painful ejaculation

CLINICAL/SURGICAL PEARLS

- Diagnosis of Peyronie disease is exclusively based on history and physical exam.
- Patients with mild curvature and no evidence of erectile dysfunction should be observed.
- New data suggests that CCH can significantly reduce the symptoms of Peyronie disease.
- The ideal candidate for CCH is having Peyronie disease for at least 12 mo, has stable disease, and a curvature of 30 degrees or greater.

PHEOCHROMOCYTOMA

Shaun G.S. Grewal, MD
Gerald L. Andriole, MD, FACS

BASICS

DESCRIPTION

- Pheochromocytoma is a rare catecholamine-producing tumor arising chromaffin cells in the adrenal medulla
- Paragangliomas refer to lesions found in extra-adrenal sites arising from the sympathetic nervous system

ALERT
Hypertensive crisis and life-threatening complications can be seen with pheochromocytoma.

EPIDEMIOLOGY

Incidence

- 3–4 cases per million population yearly in US (1)
  - Average age in sporadic cases: 40–50 yr
  - Average age in hereditary cases: < 40 yr

Prevalence

- 0.005–0.1% of the general population
  - 01–0.2% of adult hypertensive patients
- > 50% of catecholamine-producing tumors undiagnosed until death

RISK FACTORS

- Familial tumors associated with MEN multiple endocrine neoplasia (MEN) syndromes:
  - MEN IIA (Sipple syndrome): Pheochromocytoma (50%), medullary carcinoma of the thyroid (50%), and parathyroid adenoma (25%):
  - MEN IIB (MEN III): Pheochromocytoma (50%), medullary carcinoma of the thyroid (100%), ganglioneuromatosis, multiple mucosal neuromas of eyelids, lips, tongue
- Neurofibromatosis Type I (von Recklinghausen syndrome): 1% has pheochromocytoma; 5% of patients with pheochromocytoma have neurofibromatosis.
- Von Hippel–Lindau disease (retinal cerebellar hemangioblastomatosis): 10% with pheochromocytoma

Genetics

- Germ-line mutations specific to each syndrome
- Syndromes are all autosomal dominant
  - Men IIA: Codon 634 of RET protein
  - Men IIB: Mutation in intracellular domain of RET protein
  - Von Hippel–Lindau: VHL tumor suppressor gene on chromosome 3p35
  - Von Recklinghausen syndrome: Neurofibromatosis type 1 gene
  - Familial nonsyndromic paraganglioma: Succinate dehydrogenase gene (1)

PATHOPHYSIOLOGY

- Tumors arise from chromaffin cells of neural crest origin in the sympathetic nervous system
- Rule of 10 (10% bilateral, 10% extra-adrenal, 10% familial, 10% malignant) no longer accurate:
  - 10% of sporadic tumors bilateral, 50% of familial tumors bilateral
  - Extra-adrenal up to 20%
  - Hereditary 20–30%
  - Malignant up to 5% in adrenal pheochromocytoma, 33% for extra-adrenal pheo
- Histologic determination of malignancy is not possible; diagnosed based on metastases
- Tumors contain enzymes necessary to convert tyrosine to catecholamines
- Clinical manifestations secondary to the release of these catecholamines, NE, and EPI
- Bladder pheochromocytomas account for $<1\%$ of bladder tumors and $<1\%$ of pheochromocytomas:
  - Can present with micturition syncope
  - Partial cystectomy is the treatment of choice. Transurethral excision is contraindicated because it may precipitate a hypertensive crisis

ASSOCIATED CONDITIONS

- MEN IIA
- MEN IIB
- Von Recklinghausen syndrome
- Von Hippel–Lindau disease

GENERAL PREVENTION

- No specific preventive measures exist.
- Screening of patients with familial pheochromocytomas allows earlier diagnosis and treatment.

DIAGNOSIS

HISTORY

- Most patients symptomatic
  - Paroxysmal HTN with severe headache, drenching, perspiration, and palpitations
  - Additional symptoms include nervousness, tremor, pallor, panic, pain in the chest and abdomen, nausea, fever, and flushing

PHYSICAL EXAM

- Hypertension: Most common sign
  - Sustained HTN: Children and MEN II
  - Paroxysmal HTNL dramatic attacks, 3–4 times a week
  - Sustained hypertension with superimposed paroxysms: 50% incidence
- Fine tremors, pallor, perspiration
- Palpable tumor (rare)
- Accelerated hypertensive retinopathy: Papilledema, exudate, A-V knicking
- Raynaud phenomenon
- Hyperhidrosis

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Plasma or urinary-fractionated metanephrines are the best screening tests:
  - Chromaffin cells metabolize NE to NMN and EPI to MN
  - Fractionated metanephrines refers to MN and NMN
  - Both plasma metanephrines and urine metanephrines are acceptable options; current recommendations do not recommend either test over the other
  - Plasma metanephrines have a high sensitivity (96–100%) but poor specificity, particularly in older patients (77–89%) (2)
- Urine test: 24-hr urine for NE, EPI, MN, NMN, and VMA:
  - VMA highly specific (95%) but not sensitive (64%)
  - If urinary values are >3 times normal, then proceed to localize the tumor
  - If urinary values are <3 times normal and suspicious, then repeat the test and proceed to pharmacologic testing
- Plasma metanephrine testing
  - No caffeine prior
  - No acetaminophen for 5 days prior
  - Rest supine for 20 min prior to draw
  - MN >96 pg/mL, NMN >130 pg/mL, or total metanephrines >200 abnormal (2)
- Pharmacologic testing:
  - Stimulation and suppression tests are generally not utilized
  - Provocative tests dangerous, with several reported deaths
- Clonidine suppression test:
  - Centrally acting α_2-agonist that suppresses sympathetic outflow
  - Normally results in decreased BP and lower levels of plasma catecholamines
  - Draw blood for NE/EPI before and 3 hr after administering clonidine (0.3 mg/70 kg)
  - Plasma catecholamines remain the same or elevated in patients with pheochromocytoma

Imaging

- Localization studies should be started only if clinical evidence for the tumor's existence is strong (hereditary predisposition or signs and symptoms with very high MN/NMN)
- CT or MRI for initial localization:
  - Neither CT nor MRI is recommended above the other
  - Pheochromocytoma characteristically hyperintense of T2-weighted images
  - Scan abdomen and pelvis 1st
  - If no tumor found, scan chest and neck
  - Metastases in long bones may be missed
  - Cannot reliably differentiate between types of adrenal tumors
- Iodine^{123}-labeled MIBG scintigraphy is more specific for localization of pheo:
  - Provides both anatomic and functional characterization of the tumor
  - Concentrated in sympathomedullary tissue through the catecholamine pump
  - Useful to evaluate for residual or multiple tumors, and MEN syndromes

Diagnostic Procedures/Surgery

ALERT

Biopsy of adrenal mass should not be performed until pheochromocytoma has been ruled out.

Pathologic Findings

- Sporadic tumors are solitary, well-circumscribed, and encapsulated.
- Malignant pheo cannot be differentiated from benign pheo by exam of primary tumor. Malignant pheo is defined by metastases.

DIFFERENTIAL DIAGNOSIS

- Essential HTN
- Renovascular disease
- Anxiety, tension states, psychoneurosis
- Hyperthyroidism
- Paroxysmal tachycardia
- Menopause
- Vasodilating headaches (migraine and cluster)
- Acute hypertensive encephalopathy
- Nephrologic diseases
- Cocaine, amphetamines

TREATMENT

GENERAL MEASURES

Surgical removal of the tumor is the only definitive method of treatment.

MEDICATION

First Line

- Appropriate antihypertensive drugs to manage HTN, control symptoms, and prepare for surgery
- α-Adrenergic blocking agents essential before surgery:
  - Phenoxybenzamine 0–40 mg BID or TID
  - Prazosin 1–10 mg BID
- β-Blocking agents contraindicated in the absence of established α-blockade:
  - Use only for concomitant cardiac arrhythmias or persistent tachycardia
  - Blockade of peripheral vasodilatory β-adrenergic receptors results in unopposed α-adrenergic stimulation with resultant hypertension
  - Can precipitate cardiomyopathy and pulmonary edema due to chronic catecholamine excess

Second Line

See “Additional Therapies”

SURGERY/OTHER PROCEDURES

- Preoperative adrenergic blockade is mandatory
- Volume expansion with high sodium diet (>5,000 mg/daily) recommended on day 2 or 3 of α-blockade due to catecholamine-induced volume contraction
- Laparoscopic surgical removal of the tumor is the preferred treatment for tumors <10 cm

(3):
  – Initial dissection aimed at early ligation and division of the adrenal vein before manipulation of the tumor
  – Malignant pheochromocytoma is slow growing
    ◦ Resection should be attempted
    ◦ Large masses can be debulked for palliation

ADDITIONAL TREATMENT

Radiation Therapy

An option for malignant pheochromocytoma

Additional Therapies

• Malignant pheochromocytoma
  – Iodine^{131}-MIBG radiation is the most effective treatment after surgery
  – Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine: 50–60% partial response
  – Local radiation or chronic blockade with metyrosine for symptomatic disease

Complementary & Alternative Therapies

No recommended complementary or alternative therapies exist.

ONGOING CARE

PROGNOSIS

• 10-yr survival for nonmalignant tumors: >80%
• 5-yr survival for malignant pheo: 34–60%:
  – Currently no cure for malignant pheo

COMPLICATIONS

• Retinopathy and nephropathy from persistent HTN
• Catecholamine-nduced cardiomyopathy
  – Cardiomyopathy reversible with α-blockade and β-methylparatyrosine
  – All patients should have preop cardiac evaluation including echocardiogram
• Cerebral vascular accident
• Hypertensive encephalopathy
• Renal insufficiency
• Hemorrhagic necrosis
• Dissecting aneurysm
• Ischemic enterocolitis
• Neurogenic pulmonary edema

FOLLOW-UP

Patient Monitoring

• Because of uncertainties about which tumors are malignant, measure urinary or plasma catecholamines 1–2 wk postoperatively and annually for 5 yr.
• BP should be monitored every month for the 1st 6 mo, then every 6 mo thereafter.
• 25% of patients have persistent HTN after surgery.

Patient Resources
www.pheochromocytoma.org

REFERENCES

1. Mittendorf E, Evans DB, Lee JE, et al. Pheochromocytoma: Advances in genetics, diagnosis, localization, and treatment. *Hematol Oncol Clin North Am.* 2007;21(3):509–525.
2. Lender JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: Which test is best? *JAMA*. 2002;287:1427–1434.
3. Vargas HI, Kavoussi LR, Bartlett DL, et al. Laparoscopic adrenalectomy: A new standard of care. *Urology*. 1997;49:673–678.

ADDITIONAL READING

- Karagiannis A, Mikhailidis DP, Athyros VG, et al. Pheochromocytoma: An update on genetics and management. *Endocrine-Related Cancer*. 2007;14:935–956.
- Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. *Lancet.* 2005;366:665–675.
- Pacak K, Eisenhofer G, Ahlman H, et al. Pheochromocytoma: Recommendations for clinical practice from the 1st International Symposium. *Nat Clin Pract.* 2007;3:92–102.

See Also (Topic, Algorithm, Media)

- Adrenal Mass
- Adrenal Mass, Algorithm
- Multiple Endocrine Neoplasia (MEN I and II)
- Pheochromocytoma Image

CODES

ICD9

227.0 Benign neoplasm of adrenal gland

ICD10

- D35.00 Benign neoplasm of unspecified adrenal gland
- D35.01 Benign neoplasm of right adrenal gland
- D35.02 Benign neoplasm of left adrenal gland

CLINICAL/SURGICAL PEARLS

- Hydration and adequate α-adrenergic blockade preop is mandatory.
- Laparoscopic adrenalectomy treatment of choice with early control and ligation of adrenal vein.

PHIMOSIS AND PARAPHIMOSIS

Michael A. Poch, MD
Philippe E. Spiess, MD

BASICS

DESCRIPTION

- Phimosis (preputial stenosis) is the inability to retract the foreskin.
- Can be seen in children and adults
  - Physiologic (congenital) phimosis: Foreskin (prepuce) is usually not retractile in a newborn. The majority can be retracted by 3–5 yr of age
  - Pathologic (acquired) phimosis: The prepuce cannot be retracted when previously possible or it has never been retractile and is associated with symptoms and/or complications
- Paraphimosis
  - The prepuce is retracted, left in position causing vascular engorgement of the glans preventing reduction.

EPIDEMIOLOGY

Incidence

- Phimosis
  - 10% nonretractile at age 3–5
  - <1% nonretractile at puberty
- Paraphimosis
  - 0.7% of uncircumcised boys

Prevalence

N/A

RISK FACTORS

- Poor hygiene
- Forced or traumatic retraction of foreskin
- Indwelling catheter
- Chronic balanitis
- Genital piercings

Genetics

N/A

PATHOPHYSIOLOGY

- Physiologic phimosis:
  - The foreskin is naturally adherent to the glans in infants.
  - Glandular secretions and keratin debris (smegma) and intermittent erections facilitates separation of preputial skin from glans
  - This is best simply observed; the newborn foreskin does not require manipulation or retraction.
- Pathologic phimosis:

  - Chronic irritation, often due to poor hygiene, leads to sclerosis of the preputial opening
    - Premature manipulation and trauma leads to scarring of the delicate prepuce.
    - Inadequate circumcision or postcircumcision care allows constriction of the circumcision line
- Paraphimosis
  - Retraction of the prepuce and leaving it in place behind the glans leads to vascular engorgement of the glans and subsequent inability to reduce the prepuce

ASSOCIATED CONDITIONS

- Penile cancer
- Balanitis (inflammation of the glans)
- Posthitis (inflammation of the prepuce)
- Balanoposthitis
- Balanitis xerotica obliterans (BXO)
- Diabetes mellitus

GENERAL PREVENTION

- Good hygiene
- Don’t prematurely manipulate the foreskin
- Circumcision

DIAGNOSIS

HISTORY

- Was foreskin previously retractile?
- Recent urethral manipulation (Foley catheter placement, cystoscopy)
- Circumcision status
- Dysuria and/or other voiding symptoms
- Penile discharge
- Cracking or bleeding from the foreskin
- Ballooning of the foreskin with voiding
- Postvoid dribbling
- Penile pain

PHYSICAL EXAM

- Evaluate for penile abnormalities such as hypospadias, chordee, webbed penis
- Local irritation and redness
- Appearance of foreskin:
  - Normal skin color
  - Erythema and inguinal adenopathy
  - Penile discharge
  - Circumferential white discoloration
  - Urethral meatus cannot be visualized
  - Crack in skin with attempted retraction
  - Severe scarring or BXO
  - Smegma (normal finding)
- Paraphimosis:

– Marked edema of inner prepuce distal to the constricting band
– Ulcerations if chronic
– Evaluate glans for ischemia/necrosis
– Glans tenderness
– Glans firm with flaccid penile shaft
– Rule out hair or foreign body in a circumcised male

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Usually not necessary unless symptoms of urinary tract infection (UTI) or sexually transmitted infection (STI) are present.

Imaging

Not usually performed

Diagnostic Procedures/Surgery

Physical exam is usually all that is necessary

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Phimosis:
  – Physiologic vs. pathologic
  – Trapped penis occurs when a dense cicatricial scar traps the penis under the prepubic or scrotal skin after neonatal circumcision.
  – BXO
- Paraphimosis:
  – Penile edema
  – Postcircumcision cicatrix
  – Hair/thread tourniquet:
    ○ Hair or thread wraps around a child's penis and causes penile edema or strangulation
- Balanitis

TREATMENT

GENERAL MEASURES

- In the elderly male undergoing bladder catheterization, failure to replace the foreskin to its normal reduced position may result in paraphimosis (1,2).
- Paraphimosis
  – Manual reduction should be attempted 1st prior to medication or surgical procedure
  – 1st attempt manual compression for 5 min to reduce edema and reposition foreskin
  – Manual reduction technique:
    ○ Place thumbs on the glans while stabilizing the foreskin in between the 2nd and 3rd fingers.
    ○ Apply pressure on the thumbs while attempting to pull the foreskin over the glans
- Physiologic phimosis:
  – Observation and reassurance

MEDICATION

First Line

- Physiologic phimosis:
  - Topical steroids (0.05% betamethasone) may allow atraumatic retraction (3)
  - Parents should be taught to never force back the foreskin but gradually retract it over time.
- Pathologic phimosis
  - Topical steroid
  - Aggressive retraction can cause worsening of preputial scarring
- Paraphimosis:
  - Immediate manual reduction should be attempted
  - Pain medication (eg, morphine, Demerol) or local anesthesia (lidocaine without epinephrine, infiltration, or penile block) may be necessary

Second Line

- Paraphimosis
  - Hyaluronidase injection
  - If manual reduction fails, a dorsal slit or incision of constricting band is indicated
  - Recurrent paraphimosis may need definitive circumcision to prevent recurrence.

SURGERY/OTHER PROCEDURES

- Phimosis:
  - Preputioplasty (dorsal slit with transverse closure) for patients wanting to maintain foreskin
  - Circumcision is curative; should be generally avoided in children unless for indications such as recurrent UTI, vesicoureteral reflux, or superficial infections
  - Circumcision is contraindicated in newborns with penile deformities (hypospadias, chordee, webbed penis, etc.) as foreskin may be needed for possible reconstructive surgery
- Paraphimosis
  - Dorsal or ventral slit urgently treats narrowing and preserves the foreskin
  - Immediate circumcision is occasionally necessary

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Paraphimosis
  - Compression wraps
  - Topical osmotic agents

ONGOING CARE

PROGNOSIS

- 95% of physiologic phimosis resolves by puberty, with the majority retractile by the age of 5

- Circumcision is curative.

COMPLICATIONS

- Complications of phimosis:
  - UTI
  - Postvoid dribbling
  - Chronic inflammation with recurrent balanitis or balanoposthitis
  - Calculi or pearls from smegma
  - Penile carcinoma (rarely)
- Complications of paraphimosis
  - Glans necrosis
- Complications of circumcision:
  - Hemorrhage
  - Persistent adhesions
  - Skin bridges
  - Inadequate skin removal
  - Insufficient skin removal
  - Inclusion cyst
  - Cicatrix/concealed penis
  - Meatal stenosis

FOLLOW-UP

Patient Monitoring

- Proper hygiene of uncircumcised males
- Foreskin reduction after procedures

Patient Resources

N/A

REFERENCES

1. Jordan GH, McCammon KA. Surgery of the penis and urethra. In: Wein AJ, ed. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier; 2011.
2. Pohlman GH, Phillips JM, Wilcox DT. Simple method of paraphimosis reduction revisited: Point of technique and review of the literature. *J Pediatr Urol*. 2013;9:104–107.
3. Palmer LS, Palmer JS. Efficacy of topical betamethasone for treating phimosis: A comparison of two treatment regimens. *Urology*. 2008;72:68–71.

ADDITIONAL READING

- Choe JM. Paraphimosis: Current treatment options. *Am Fam Physician.* 2000;62:2623–2626.
- Hamdy FC, Hastie KJ. Treatment for paraphimosis: The 'puncture' technique. *Br J Surg.* 1990;77(10):1186.
- Hutcheson JC. Male neonatal circumcision: Indications, controversies and complications. *Urol Clin North Am.* 2004;31:461–467.

See Also (Topic, Algorithm, Media)

- Circumcision, Adult Considerations
- Circumcision, Pediatric Considerations

- Penis, Cancer, General Considerations
- Phimosis and Paraphimosis Image

CODES

ICD9

- 605 Redundant prepuce and phimosis
- 607.1 Balanoposthitis

ICD10

- N47.1 Phimosis
- N47.2 Paraphimosis
- N48.1 Balanitis

CLINICAL/SURGICAL PEARLS

- In most cases physiologic phimosis will resolve.
- Aggressive retraction of phimosis can cause preputial scarring.
- Manual reduction of paraphimosis should be attempted 1st prior to surgical intervention.

PNEUMATURIA (GAS IN URINE)

Michael Perrotti, MD

BASICS

DESCRIPTION

Passage of gas in the urine

EPIDEMIOLOGY

Incidence

This is a rare disorder.

RISK FACTORS

- Diverticular disease
- Other disease of the colon
- Crohn disease
- Advanced age
- Diabetes

PATHOPHYSIOLOGY

- Most commonly there is an abnormal connection between the enteric and urinary system secondary to inflammation
- Much less common in gas-producing bacterial urinary tract infection (UTI) (*Escherichia coli*, *Klebsiella pneumoniae*) seen most frequently in elderly diabetic females

ASSOCIATED CONDITIONS

- Diverticulitis of sigmoid colon
- Colon cancer
- Crohn disease
- Diabetes
- Iatrogenic (radical prostatectomy, radiation)

GENERAL PREVENTION

- Colon health
- Prompt treatment of UTI

DIAGNOSIS

HISTORY

- Pneumaturia
- Dysuria
- Irritative urinary symptoms
- Fecaluria

PHYSICAL EXAM

- Depends upon etiology
- May have no significant findings if acute diverticular abscess has resolved

- In emphysematous cystitis there is frequently fever and abdominal tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis
- Urine culture
- Complete blood count
- Comprehensive metabolic profile

Imaging

- Computerized tomography scan identifies air or orally administered contrast in the bladder, colonic and bladder wall thickening, abscess (1)[A]
- Barium enema (definitive: 25%; suggestive: 100%)

Diagnostic Procedures/Surgery

- Colonoscopy may directly visualize the fistula, and is essential to inspect the remainder of the colon
- Cystoscopy may visualize the actual fistula, or identify suggestive localized inflammation and edema

Pathologic Findings

- Diverticular disease with abscess
- Colon malignancy
- Crohn disease
- Bladder malignancy
- Radiation or surgical induced fistula
- UTI

DIFFERENTIAL DIAGNOSIS

- Emphysematous cystitis
- Emphysematous pyelonephritis
- Urethral rectal fistula
- Vesical enteric fistula

TREATMENT

GENERAL MEASURES

- Antibiotic therapy
- Percutaneous drainage of gas and purulent material
- Relief of urinary obstruction

MEDICATION

First Line

- Parenteral antibiotic therapy for all patients with gas-producing UTI [A]
  - Ampicillin sulbactam 1.5 g IV q6h
  - Ticarcillin clavulanate 3.1 g IV q6h
  - Piperacillin tazobactam 3.375 g IV q6h
  - Meropenem 500 mg IV q8h

- Imipenem 500 mg IV q6h
- Doripenem 500 mg IV q8h

• Antibiotic therapy for acute diverticulitis
- Ciprofloxacin 500 mg PO BID with metronidazole 500 mg PO TID [A]
- Amoxicillin clavulanate 875 mg/125 mg PO BID
- Ampicillin sulbactam 3 g IV q6h
- Piperacillin tazobactam 3.375 g IV q6h
- Ticarcillin clavulanate 3.1 g IV q6h
- Ceftriaxone 1 g IV q24h with metronidazole 500 mg IV q8h

SURGERY/OTHER PROCEDURES
• Emphysematous UTI
- Percutaneous management of purulent material and gas
- Percutaneous nephrostomy placement for emphysematous pyelonephritis
- Emergent nephrectomy is associated with very high mortality

• Enterovesical fistula
- Enterovesical fistulae typically do not close spontaneously
- The portion of bowel responsible for the fistula is excised in a 1-stage procedure with resection and primary anastomosis
- Ureteral stent placement may be performed preoperatively to allow identification of the ureter intraoperatively
- Resection of the bladder is rarely necessary
- A small defect in the bladder can be managed with suture repair, indwelling Foley catheter, and closed suction drain in the pelvis

ONGOING CARE
PROGNOSIS
• Gas-producing UTI (2)[A]
- Parenteral antibiotic therapy is successful in the majority of patients with gas limited to bladder
- Patients with gas in the upper urinary tract are at increased risk of mortality and require percutaneous drainage with parenteral antibiotics
- Gas in the perinephric space and pararenal tissues are at increased risk of mortality

• Diverticular abscess and enteric vesical fistula
- Patients have an excellent prognosis after elective resection of the disease bowel segment
- In many cases this can be performed laparoscopically (3)[B]

COMPLICATIONS
• Patients with inflammatory disorders such as Crohn may have complex and recurrent fistulae
• Patients with fistulae following radiation therapy may have impaired healing and experience recurrence

FOLLOW-UP
Patient Monitoring

- Management of associated illness
- Prompt treatment of disease flare

Patient Resources
NA

REFERENCES

1. Jaret TW, Vaughan ED Jr. Accuracy of computerized tomography in the diagnosis of colovesical fistula secondary to diverticular disease. *J Urol*. 1995;153:44–46.
2. Huang JJ, Tseng CC. Emphysematous pyelonephritis: Clinicoradiological classification, management, prognosis and pathogenesis. *Arch Intern Med*. 2000;160:797–805.
3. Bartus CM, Lipof T, Sarwar CM, et al. Colovesical fistula: Not a contraindication to elective laparoscopic colectomy. *Dis Colon Rectum*. 2005;48:233–236.

ADDITIONAL READING

Golabek T, Szymanska A, Szopinski T, et al. Enterovesical fistulae: Aetiology, imaging, and management. *Gastroenterol Res Pract*. 2013;2013:617967.

See Also (Topic, Algorithm, Media)
- Cystitis, Emphysematous
- Fistula, Enterovesical
- Inflammatory Bowel Disease (Ulcerative Colitis and Crohn disease), Urologic Considerations
- Pneumaturia (Gas in Urine) Image
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male

CODES

ICD9
- 596.1 Intestinovesical fistula
- 599.0 Urinary tract infection, site not specified
- 599.84 Other specified disorders of urethra

ICD10
- N32.1 Vesicointestinal fistula
- N39.0 Urinary tract infection, site not specified
- R39.89 Other symptoms and signs involving the genitourinary system

CLINICAL/SURGICAL PEARLS
- Pneumaturia is the distinct sensation by the patient of passage of air from the urinary tract.
- Pneumaturia should be considered secondary to an enteric vesical fistula until proven otherwise.
- The CT scan finding of air in the bladder is abnormal and of high diagnostic value in the evaluation of the patient with suspected pneumaturia and is likely to reveal associated pathology.
- The most common cause of pneumaturia is diverticular disease.

POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL DOMINANT

Megan T. Bing, MD
James A. Brown, MD, FACS

BASICS

DESCRIPTION

- Inherited disease characterized by bilateral development of renal and extrarenal cysts with variable progression to ESRD, requiring either dialysis or transplantation
- Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of genetic kidney disease leading to chronic kidney disease

EPIDEMIOLOGY

Incidence

- 1–2:1,000 live births
  - Occurs worldwide and in all races
  - 4.4% of patients with renal replacement therapy have ADPKD

Prevalence

- 1:400 to 1:1,000
  - Renal volume increases 5.27% per year as cysts grow

RISK FACTORS

- Having a family member with ADPKD
  - Inherited in autosomal dominant fashion
  - Ages range from infant to elder

Genetics

- 1:1,000 carry mutant gene
- Autosomal dominant with 100% penetrance
- Genetically heterogenous: 2 genes
  - PKD1 (16p13.3) (Type 1 ADPKD)
    - Accounts for 85% of cases
    - More severe disease
    - Encodes polycystin-1 (PC1)
  - PKD2 (4q21) (Type 2 ADPKD)
    - Accounts for 15%
    - Less severe disease
    - Encodes polycystin-2 (PC2)

PATHOPHYSIOLOGY

- Loss of PC1 or PC2 results in inability of tubular cells to maintain polarity, increased rate of proliferation and apoptosis, increased cellular secretion and remodeling of extracellular matrix (ECM)
  - Epithelial cell growth
  - ECM remodeling

– Na^+-K^+ ATPase found apically which leads to abnormal flow of fluid

ASSOCIATED CONDITIONS
- Abdominal wall hernia
- Cardiac valvular abnormalities
- Colon diverticula
- Hepatic cysts from 29–73%
- Splenic and pancreatics in a small percentage
- Intracranial aneurysms
  – Only screen if patient has previous rupture
  – Saccular "berry" aneurysm of cerebral arteries in 3–13%
- Pancreatic cysts
- Polycystic liver disease

GENERAL PREVENTION
Genetic and prenatal counseling

DIAGNOSIS

HISTORY
- Typical presentation is 30- to 50-yr-old patient with HTN, hematuria, flank pain
- Calculi may also be present
- Family history: 3 generations with cystic renal disease

PHYSICAL EXAM
- HTN, hypertensive retinopathy
- Heart murmur
- Enlarged kidneys on abdominal exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum Cr may be elevated
- BUN may be elevated
- Hematuria on UA
  – In up to 50% and often the initial presenting symptom

Imaging
- Imaging is the main diagnostic tool
- Plain abdominal radiographs: Limited in early-stage disease; later may indicate displacement of organs with or without calcifications
- US
  – With unknown genotype, the presence of 3 or more (unilateral or bilateral) renal cysts establishes the diagnosis in 15–39 yo, 2 or more cysts in each kidney is sufficient if aged 40–59 yr, and 4 or more cysts in each kidney is required for individuals ≥ 60 yr
  – Conversely, < 2 renal cysts in at-risk individuals aged ≥ 40 yr are sufficient to exclude the disease
- CT and MRI methods have greater sensitivity compared to US for detecting cysts < 1 cm and in evaluating individual cysts for hemorrhage or malignancy

- Hemorrhagic renal cysts are fairly common
- On MRI uncomplicated cysts resemble simple cortical cysts
  - Homogeneous low signal intensity on T1 and high signal intensity on T2

• Echocardiography
- Evaluate for mitral prolapse

Diagnostic Procedures/Surgery

Cytogenetic analysis: May be needed when FH or imaging is equivocal

Pathologic Findings

• Gross pathology
- Bilaterally enlarged kidneys with multiple colored and fluid-filled cysts

• Histopathology
- Multicystic renal dysplasia in cortex and medulla
- Sclerosis

DIFFERENTIAL DIAGNOSIS

• Patients >10 yr old
- Simple cysts
  - Simple cyst not common <30 yr of age
  - >4 simple cysts in each kidney is rare
- Localized renal cystic disease
- Medullary sponge kidney
- Bilateral parapelvic cysts
- Autosomal recessive polycystic kidney disease (ARPKD)
- Tuberous sclerosis complex
- Von Hippel–Lindau disease
- Medullary cystic disease
- Orofaciodigital syndrome type I
- Autosomal dominant polycystic liver disease: Liver lesions predominate but also have renal cysts; genetic testing may be needed to differentiate

• Patients <10 yr of age
- Contiguous PKD1–TSC2 deletion syndrome
- ARPKD
- Meckel–Gruber syndrome

TREATMENT

GENERAL MEASURES

• Increase fluid intake
• Coordinated care with nephrology
• Protein-restricted diet is controversial
• Neurosurgery consult if intracranial aneurysm is present (1)

MEDICATION

First Line

• Hypertension:

  - Angiotensin-converting enzyme (ACE) inhibitors (ie, captopril, enalapril, lisinopril) or
  - Angiotensin II receptor blockers (ARBs) such as telmisartan, losartan, irbesartan, and candesartan
- Hyperlipidemia: Statin

Second Line
- Somatostatin (2)
- Inhibitors of mTOR

SURGERY/OTHER PROCEDURES
- Renal replacement therapy (2,4)
  - Renal transplantation
  - Hemodialysis/peritoneal dialysis
- Percutaneous cyst aspiration
  - < 200 mL
  - Sclerosing agent should be used
- Cyst decortication—typically for pain with large dominant cysts(s)
  - 95–100% success rate for relieving pain
  - Initial improvement in lowering HTN, but not sustained
- Nephrectomy
  - Disabling symptoms due to massively enlarged kidneys
  - Worsening or development of ventral (abdominal wall) hernias
  - Nephrectomy may be considered before renal transplant
    - Suspected malignancy
    - Recurrent infection
    - Extension of the polycystic kidney into the potential pelvic surgical transplant location

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies
- Infection: Lipid soluble antibiotic (sulfamethoxazole and trimethoprim or ciprofloxacin)
- Chronic pain: Avoid NSAIDs
- A small, randomized, placebo-controlled trial found that intramuscular octreotide slowed progression of renal cystic disease

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS
- Renal function usually normal until the 4th decade of life
- Disease diagnosed in utero carries a poor prognosis
- Patients on RRT carry the same or better prognosis than non-ADPKD patients on RRT
- Risk factors for progression:
  - Genetic factors (PKD1 vs. PKD2)

  – Hypertension
  – Early onset of symptoms including proteinuria and hematuria
  – Male gender
  – Increased kidney size (kidney size is greater with PKD1 mutations)
  – Increased left ventricular mass index
  – Dipstick detectable proteinuria
  – Low birth weight
  – Decreased renal blood flow
  – Increased urinary sodium excretion
  – Increased LDL cholesterol
  – Increased plasma copeptin (surrogate marker for vasopressin)
- With more advanced renal disease, ACE inhibitors and ARBs can cause hyperkalemia or worsen renal failure. Monitoring of serum chemistries is essential
- When screening family members with a family history of ADPKD data suggests that individuals >40 yr with a family history but without renal cysts are unlikely to develop ADPKD

COMPLICATIONS

- Cerebral hemorrhage
- Chronic kidney disease
- Renal cell carcinoma risk is not elevated; but when present is often bilateral and multicentric
  – Often present with fever
- Proteinuria
- Chronic pain
  – Nephrolithiasis in 25% of patients
- Pyelonephritis
- Cyst rupture
- Rarely portal HTN, cholangiocarcinoma

FOLLOW-UP

Patient Monitoring

- Follow BUN and Cr
- Prenatal testing for ADPKD is clinically available if the mutation has been identified in an affected family member or if linkage has been established in the family

Patient Resources

- www.pkdcure.org
- www.pkdinternational.org

REFERENCES

1. Agarwal MM, Hemal AK. Surgical management of renal cystic disease. *Curr Urol Rep*. 2011;12:3–10.
2. Caroli A, Perico N, Perna A, et al. Effect of long-acting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): A randomised, placebo-controlled, multicentre trial. *Lancet*. 2013;382(9903):1485–1495.

3. Harris PC, Torres VE. Polycystic kidney disease. *Ann Rev Med.* 2009;60:321–337.
4. Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: The last 3 years. *Kidney Int.* 2009;76:149–168.

ADDITIONAL READING

• Grantham JJ. The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: Recent advances. *Am J Kidney Dis*. 1996;28:788–803.
• Helal I, Reed B, Schrier RW, et al. Emergent early markers of renal progression in autosomal-dominant polycystic kidney disease patients: Implications for prevention and treatment. *Am J Nephrol*. 2012;36:162–167.
• Steinman TI. Polycystic kidney disease: A 2011 update. *Curr Opin Nephrol Hypertens*. 2012;21:189–194.

See Also (Topic, Algorithm, Media)

• Acquired Renal Cystic Disease
• Polycystic Kidney Disease, Autosomal Dominant Images ☼
• Polycystic Kidney Disease, Autosomal Recessive
• Renal Cysts (Intrarenal, Peripelvic, and Parapelvic)
• Renal Mass
• Retroperitoneal Mass and Cysts

CODES

ICD9

• 585.9 Chronic kidney disease, unspecified
• 753.13 Polycystic kidney, autosomal dominant

ICD10

• N18.9 Chronic kidney disease, unspecified
• Q61.2 Polycystic kidney, adult type

CLINICAL/SURGICAL PEARLS

• Lipid soluble antibiotics are needed for treatment of renal cyst infection.
• Abdominal pain and flank pain is common and may be due to infection, nephrolithiasis, or cyst hemorrhage.
• Cyst decortication is useful for large painful cysts.
• Patients with a personal or family history of cranial bleed need surveillance by neurosurgery.
• Acute cyst rupture usually best treated with pain control and observation.

POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE

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BASICS

DESCRIPTION

- A group of inherited disorders involving cystic dilatation of the renal collecting ducts and varying degrees of biliary dysgenesis and periportal fibrosis
- Formerly known as infantile polycystic kidney disease
- An overlap in the spectrum of renal and liver involvement precludes use of the Blyth and Orkenden classification (perinatal, neonatal, infantile, and juvenile subtypes)
- Best grouped as polycystic disease of newborn and young infant, polycystic disease of childhood, and congenital hepatic fibrosis

EPIDEMIOLOGY

Incidence

- Most common inherited cystic renal disease in infancy and childhood
- Incidence: 1–2 in 10,000 live births
- Males = females
- Severely affected neonates usually die hours after birth; overall survival is much improved if they live beyond the neonatal period

Prevalence

- Commonly discovered in perinatal period; can present early in childhood or adolescence
- Survival: For patients living to 1 mo: 86% alive at 1 yr, 67% alive at 15 yr

RISK FACTORS

- Definite risk factor: Heterozygous parents
- The cause of ARPKD remains poorly understood
- Genetic and/or epigenetic factors may promote aberrant epithelial hyperplasia that causes cystic expansion of the collecting ducts and fluid accumulation
- Less is known about hepatobiliary changes; however, epithelial hyperplasia may have role

Genetics

- Associated with mutations of the PKHD1 gene (1 – 3)
- Autosomal recessive, heterozygotes unaffected, gene locus at chromosome 6p21
- Gene located at 6p21 produces a protein called fibrocystin which has been identified at the renal collecting ducts and the hepatic bile duct; possible involvement in renal cilia function
- Multiple allelism is likely responsible for variable phenotypic presentation
- Offspring of heterozygotes: 25% risk of disease, 50% carriers

PATHOPHYSIOLOGY

- Clinical course (renal):
  - Severely affected neonates commonly die of pulmonary complications hours after birth
  - Patients surviving the neonatal period have a better prognosis; they can have some renal

maturation
  – Progressive renal cyst enlargement, fibrosis, and renal insufficiency
  – Eventually, most develop renal failure
  – Later presentation: Less severe renal component
• Clinical course (hepatobiliary):
  – Development of hepatosplenomegaly, portal HTN, extrahepatic bile duct dilation, gall bladder enlargement, occasional choledochal cyst formation, and hepatic dysfunction
  – Liver failure ultimately develops later in childhood

ASSOCIATED CONDITIONS
• Ehlers–Danlos syndrome
• Potter syndrome

GENERAL PREVENTION
Genetic counseling for families with proven ARPKD (linkage studies with polymorphic DNA markers)

DIAGNOSIS
HISTORY
• Age of the patient:
  – Other cystic renal disorders rarely present in the pediatric population:
    ○ Younger, more respiratory and renal issues;
    ○ Older, more hepatobiliary issues
  – ~1/3 are diagnosed before age 1; 1/3 between ages 1 and 20 yr; and 1/3 beyond 20 yr
• Prenatal care
  – Characteristic changes on prenatal US after week 30, abnormal uterine growth measurements, maternal α-fetoprotein levels, amniocentesis results, history of stillbirth
• Birth history:
  – Difficult delivery suggests possible flank or abdominal mass
• Family history:
  – Normal parents with a normal renal US suggests recessive disease
• Medical history:
  – For older patient, may suggest evolution of disease
• Present illness:
  – Polydipsia, polyuria, fatigue, unexplained fever, hematuria, pyuria, edema, difficult feeding, recent GI bleed or vague GI symptoms

PHYSICAL EXAM
• HTN, respiratory rate, temperature
• General appearance:
  – Potter phenotype, pallor
• Palpable kidneys: Hepatosplenomegaly
• Extremities: Joint contractures, edema

DIAGNOSTIC TESTS & INTERPRETATION
Lab

- Electrolytes, blood chemistry, urine analysis, urine culture
- CBC (exclude anemia, hypersplenism)
- Coagulation profile
- Liver function tests (usually normal)
- High maternal α-fetoprotein (associated with ARPKD), high amniotic fluid release (possible correlation)

Imaging

- Renal ultrasound is best initial test (4):
  - Prenatal: Enlarged kidneys, oligohydramnios, normal liver, no bladder filling (more reliable after 30-wk gestation)
  - Infancy: Enlarged reniform kidneys, cortical echogenicity
  - Older children: Macrocysts (< 2-cm diameter), decreased size, medullary echogenicity, hepatosplenomegaly
  - Loss of corticomedullary differentiation: The kidneys typically have a homogeneous appearance
- CT may be used in confusing cases: More sensitive to inhomogeneity of cysts

Diagnostic Procedures/Surgery

- Renal biopsy
- Liver biopsy

Pathologic Findings

- Renal
  - Bilateral enlarged kidneys with reniform shape
  - Pinpoint opalescent dots on capsule (cortical collecting duct cysts)
  - Cut surface with sponge-like quality due to linear distention of nephrons in radial pattern
  - Normal pelvicaliceal system and renal vessels
  - In neonates, kidneys at least 10% of body weight
  - Microscopic pathology: Fusiform cysts (< 2 mm + diameter) lined by low columnar or cuboidal epithelium
  - No normal parenchyma
- Hepatobiliary
  - All children with ARPKD have lesions in the periportal areas of the liver
  - Can have hepatosplenomegaly at presentation; frequently normal
  - Elongated, hyperplastic biliary ducts with ectasia
  - Periportal fibrosis with normal hepatocellular histology

DIFFERENTIAL DIAGNOSIS

- Autosomal dominant polycystic kidney disease (ADPKD)
- Bardet–Biedl syndrome
- Caroli disease
- Chondrodysplasia syndrome
- Congenital hypernephronia nephromegaly with tubular dysgenesis
- Glutaric aciduria type II
- Ivemark syndrome
- Jeune syndrome

- Juvenile nephronophthisis
- Meckel–Gruber syndrome
- Renal dysplasia
- Trisomy 9 and 13
- Zellweger syndrome

TREATMENT

GENERAL MEASURES

- No specific therapy for ARPKD. Treatments are supportive
- Pulmonary issues 1st priority initially; survival better with advances in perinatology
- Goals: Delay progression to renal failure, liver failure, and portal HTN
- Avoid nephrotoxic mediations
- Social support and respite care

MEDICATION

First Line

- Thiazides to help urine-concentrating defect
- Treatment of renal osteodystrophy with vitamin D and phosphate binders
- Recombinant human erythropoietin
- Growth hormone treatment

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Preemptive bilateral nephrectomy and peritoneal dialysis catheter (significant pulmonary distress)
- Unilateral nephrectomy (improve feedings, help with breathing)
- Gastrostomy tube placement (improve feedings)
- Splenorenal shunt or portocaval shunt procedures (portal HTN)
- Renal transplantation (ESRD)
- Liver transplantation (hepatic failure)
- Progressive liver fibrosis with portal hypertension may require combined liver and kidney transplantation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Adequate hydration
- Correct acid–base and electrolyte abnormalities
- Aggressive HTN control
- Peritoneal dialysis
- Enteral feedings
- Advanced pulmonary support as required

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

- Prenatal: Abnormal prenatal US (oligohydramnios, enlarged reniform kidneys, absent urine in bladder, seen after 30-wk gestation) (5)
- Neonates: If present at birth, the usual clinical course is death. Patients have feeding intolerance, respiratory distress
- Infants: Palpable flank masses, abdominal mass, respiratory distress, HTN, polydipsia, polyuria, edema, feeding intolerance, Potter phenotype, nonspecific GI complaints, failure to thrive, growth retardation, infection
- Older children: Palpable flank mass, abdominal mass, Potter phenotype, GI bleed, hematuria, pyuria, polydipsia, polyuria, HTN, nonspecific GI complaints, edema, growth retardation, fatigue, infection. Will eventually develop renal failure and HTN
- All patients with ARPKD have liver involvement. Those with severe ARPKD have mild congenital hepatic fibrosis and those with severe congenital hepatic fibrosis have milder ARPKD

COMPLICATIONS

- Renal: Renal failure (concentrating defect with polydipsia and polyuria), HTN, anemia, occasional metabolic acidosis, hyponatremia, osteodystrophy, growth failure, UTI
- Hepatobiliary: Hepatosplenomegaly, bleeding esophageal varices, portal thrombosis, hypersplenism, choledochal cysts, bacterial cholangitis
- Pulmonary: Respiratory failure, pulmonary hypoplasia, pneumothorax, atelectasis, poor diaphragmatic excursion
- GI: Feeding intolerance, failure to thrive

FOLLOW-UP

Patient Monitoring

- Progressive renal failure in most patients requiring ongoing renal assessments
- Blood pressure
- Liver functions and ultrasound at least annually
- Overall assessment of growth and nutritional status
- Parental counselling is critical as there is a 1 in 4 chance of another child having the disease

Patient Resources

PKD Foundation http://www.pkdcure.org/learn/arpkd

REFERENCES

1. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet.* 2002;30:259–269.
2. Adeva M, El-Youssef M, Rossetti S, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). *Medicine (Baltimore).* 2006:85:1–21. (Level II evidence)
3. Bergmann C, Senderek J, Küpper F, et al. PKHD1 mutations in autosomal recessive

polycystic kidney disease (ARPKD). *Hum Mutat.* 2004:5:453–463.
4. Levine E, Hartman DS, Mellstrup JW, et al. Current concepts and controversies in imaging of renal cystic disease. *Urol Clin North Am.* 1997;24:523–543. (Level III evidence)
5. Roy S, lon MJ, Trompeter RS, et al. Autosomal recessive polycystic kidney disease: Long-term outcome of neonatal survivors. *Pediatr Nephrol.* 1997;11:302–306. (Level II-3 evidence)

ADDITIONAL READING

Brinkert F, Lehnhardt A, Montoya C, et al. Combined liver-kidney transplantation for children with autosomal recessive polycystic kidney disease (ARPKD): Indication and outcome. *Transpl Int.* 2013;26(6):640–650.

See Also (Topic, Algorithm, Media)

- Acquired Renal Cystic Disease
- Meckel–Gruber Syndrome (Meckel Syndrome)
- Multicystic Dysplastic Kidney
- Nephronophthisis (Juvenile, Infantile, and Adolescent)
- Polycystic Kidney Disease, Autosomal Dominant
- Polycystic Kidney Disease, Autosomal Recessive Image
- Renal Cysts (Intrarenal, Peripelvic, and Parapelvic)
- Renal Dysplasia, Hypodysplasia, and Hypoplasia
- Renal Mass

CODES

ICD9

- 751.69 Other anomalies of gallbladder, bile ducts, and liver
- 753.14 Polycystic kidney, autosomal recessive
- 777.8 Other specified perinatal disorders of digestive system

ICD10

- P78.89 Other specified perinatal digestive system disorders
- Q44.5 Other congenital malformations of bile ducts
- Q61.19 Other polycystic kidney, infantile type

CLINICAL/SURGICAL PEARLS

- Renal and liver involvement is typical.
- Often fatal if present at birth.
- Treatments are supportive; no specific therapy.

POLYHYDRAMNIOS/OLIGOHYDRAMNIOS

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BASICS

DESCRIPTION

- Oligohydramnios is defined as an abnormally low amniotic fluid (AF) volume:
  - Associated with increased fet al morbidity and mortality
- Polyhydramnios is defined as an abnormally high AF volume:
  - Up to 20% of neonates will have a congenital anomaly
  - Associated with increase in aneuploidy, congenital malformations, preterm delivery, and perinatal death
- These conditions are diagnosed using prenatal US with strict criterion described below

EPIDEMIOLOGY

Incidence

- Oligohydramnios in 3–5% of pregnancies (1)
- Polyhydramnios in 1–3% of pregnancies (1)
- Usually discovered in 2nd trimester with 40% normal by term

Prevalence

N/A

RISK FACTORS

- Oligohydramnios:
  - Rupture of membranes
  - Some medications (eg, NSAIDs)
  - Maternal HTN
  - Maternal autoimmune disorders
- Polyhydramnios:
  - Maternal diabetes
  - Drug abuse

Genetics

Several genetic syndromes are associated with oligohydramnios or polyhydramnios

PATHOPHYSIOLOGY

- After 22–23 wk, most of AF is fet al urine
- Late in gestation AF averages ~700–800 mL
- Oligo- and polyhydramnios are due to an imbalance in the production and removal of amniotic fluid
- Production of amniotic fluid (2)
  - 600–1,200 mL/d fet al urine
  - 60–100 mL/kg/d tracheal secretions
- Removal of amniotic fluid (2)

- 200–1,500 mL/d fet al swallowing
- 200–500 mL/d removed across fet al placenta into fet al blood stream (intramembranous pathway)

• Oligohydramnios causes
- PROMs
  - Iatrogenic: Amniocentesis
  - Spontaneous/idiopathic
- Decreased fet al urine production
  - Prerenal: Placental insufficiency, umbilical cord compression, fet al demise, maternal hypotension or severe dehydration, chronic maternal HTN, autoimmune disorders, drugs (NSAIDs, ACE inhibitors)
  - Intrarenal: Renal dysplasia, renal agenesis
  - Obstructive: Posterior urethral valves (PUVs), prune belly syndrome, urethral atresia, bilateral ureteropelvic junction obstruction (UPJO), bilateral ureteral obstruction, bilateral ectopic ureters

• Effects of oligohydramnios
- Pulmonary hypoplasia: Correlated with fet al outcome and main cause of fet al death
- Intrauterine growth restriction
- Potter facies with severe oligohydramnios
- Better outcome if presents in 3rd trimester vs. 2nd trimester (3)
- Better outcome if cause is PROM vs. congenital anomaly (3)

• Causes of polyhydramnios
- Idiopathic: ~60%
  - Better outcomes
- Maternal causes: ~15%
  - Maternal diabetes
  - Infections: Syphilis, rubella, MV, toxoplasmosis, parvovirus, Rh isoimmunization
  - Drug abuse: Polyhydramnios in ~25–30% of drug-addicted women. Leads to decreased neurologic function of fetus and decreased swallowing
- Fet al causes:
  - Reduced fet al swallowing: Maternal drug use, fet al neurologic anomalies, aneuploidy
  - GI anomalies: T-E fistula, choanal atresia, facial cleft, esophageal atresia, imperforate anus
  - Cardiac failure with diuresis
  - Karyotype anomalies

ASSOCIATED CONDITIONS

• Oligohydramnios:
- Rupture of membranes
- Placental insufficiency
- Chronic maternal HTN
- Postdate gestation
- Multicystic dysplastic kidney or prune-belly syndrome
- Severe cardiac disease
- Pulmonary hypoplasia, limb abnormalities

  - Potter syndrome:
    - Characteristic appearance usually due to bilateral renal agenesis, obstructive uropathy, renal hypoplasia, autosomal recessive polycystic kidney disease
    - Less severe form referred to as Potter sequence
- Polyhydramnios
  - Anencephaly
  - Neural tube defects
  - GI obstruction (esophageal atresia, duodenal atresia)
  - Multiple gestation
  - Nonimmune hydrops fet alis
  - Maternal diabetes

GENERAL PREVENTION

- Oligohydramnios
  - Avoid known medications (NSAIDs, etc.)
  - Avoid unneeded amniocentesis
  - Avoid maternal dehydration
- Polyhydramnios
  - Control of maternal diabetes
  - Prevention of infections transmittable from mother to fetus
  - Avoid drug abuse

DIAGNOSIS

HISTORY

- Polyhydramnios:
  - Increased maternal weight
  - Maternal drug use
  - Maternal infectious exposure
- Oligohydramnios:
  - Poor weight gain
  - Medication history

PHYSICAL EXAM

- Polyhydramnios: Increased maternal fundal height
- Oligohydramnios: Decreased maternal fundal height
- Enlarged newborn urinary bladder due to obstruction
- Potters facies:
  - Characteristic of bilateral renal agenesis and other severe renal malformations
  - Ocular hypertelorism, low-set ears, receding chin, flattening of the nose

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Polyhydramnios:
  - Maternal testing for glucose, autoantibodies, TORCH screen, parvovirus, fet al karyotype
- Oligohydramnios:
  - General: Fet al karyotype, pulmonary maturity, maternal autoantibodies (lupus,

anticardiolipin, antinuclear)
  – Renal: Fet al urinary electrolytes
  – Better outcome associated with Na <100 mmol/L, Cl <90 mmol/L, and osm <210 mmol/L
  – Serial measurements may have better prognostic value
  – May also measure β2-microglobulin, α-microglobulin, and retinal-binding protein

Imaging

- US measurements of AF volumes are very operator-dependent and very variable (4)
- No perfect means to determine actual volume, but several surrogate markers are used:
  – Maximum vertical pocket: Polyhydramnios >8 cm, oligohydramnios <1 cm
  – AFI: Sum of largest volumes from each of 4 placental quadrants:
    ○ Oligohydramnios: <5 cm, polyhydramnios >25 cm
- Fet al MRI increasingly used for better anatomic detail

Diagnostic Procedures/Surgery

- Polyhydramnios
  – Remove excess fluid
- Oligohydramnios:
  – Amnioinfusion: Especially for premature PROM

Pathologic Findings

- Depends on cause (see pathophysiology)
- Renal dysplasia common finding in oligohydramnios

DIFFERENTIAL DIAGNOSIS

- Oligohydramnios
  – Premature rupture of membranes (PROM)
    ○ Iatrogenic: Amniocentesis
    ○ Spontaneous/idiopathic
  – Decreased fet al urine production
    ○ Prerenal: Placental insufficiency, umbilical cord compression, fet al demise, maternal hypotension or severe dehydration, chronic maternal HTN, autoimmune disorders, drugs (NSAIDs, ACE inhibitors)
    ○ Intrarenal: Renal dysplasia, renal agenesis
    ○ Obstructive: PUVs, prune belly syndrome, urethral atresia, bilateral UPJO, bilateral ureteral obstruction, bilateral ectopic ureters
  – Prolonged gestation can lead to oligohydramnios late in the pregnancy
- Polyhydramnios
  – Idiopathic: ~60%
    ○ Better outcomes
  – Maternal causes: ~15%
    ○ Maternal diabetes
    ○ Infections: Syphilis, rubella, MV, toxoplasmosis, parvovirus, Rh isoimmunization
    ○ Drug abuse: Polyhydramnios in ~25–30% of drug-addicted women. Leads to decreased neurologic function of fetus and decreased swallowing
    ○ Placental chorioangioma or arteriovenous fistula

– Fet al causes:
  - Reduced fet al swallowing: Maternal drug use, anencephaly, neural tube defects, muscular dystrophy syndromes, aneuploidy
  - GI anomalies: T-E fistula, choanal atresia, facial cleft, esophageal atresia, imperforate anus, gastroschisis, duodenal atresia/stenosis, diaphragmatic hernia
  - Cardiac failure: Congestive heart failure, severe anemia
  - Karyotype anomalies: Trisomy 21, etc.
  - Hydrops fet alis: Rh disease, severe anemia, infections in mother (eg, parvovirus, CMV), twin–twin transfusion syndrome, maternal hyperparathyroidism, disorders of glycosylation
  - Other: Sacrococcygeal teratoma, skelet al dysplasias, thoracic/mediastinal masses

TREATMENT

GENERAL MEASURES

- Polyhydramnios:
  – US every 3–4 wk
  – Follow pregnancy to 38 wk
  – Monitor for uterine hemorrhage
- Oligohydramnios:
  – US every 3–4 wk for fet al viability and BPP
  – Consider early delivery with steroids for pulmonary development
  – Newborn needs intensive care and urologic assessment

MEDICATION

First Line

- Maternal indomethacin has been used in cases of polyhydramnios
- Surfactant for the neonate with severe oligohydramnios and pulmonary hypoplasia

Second Line

None

SURGERY/OTHER PROCEDURES

In utero vesicoamniotic shunt in select cases of oligohydramnios due to bladder outlet obstruction

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Amnioinfusion of isotonic sodium chloride solution in the 2nd trimester may benefit some patients with oligohydramnios

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Polyhydramnios:
  - If idiopathic, the prognosis is usually good
- Oligohydramnios:
  - With renal agenesis, mortality rate is 100%
  - Fet al outcomes correlated to degree of pulmonary hypoplasia
  - Mild forms of obstructive uropathy may cause renal insufficiency
  - Better prognosis with presentation in 3rd vs. 2nd trimester (3)
  - Better prognosis with PROM as cause vs. congenital anomalies (3)

COMPLICATIONS

- Polyhydramnios can cause increased preterm labor
- Oligohydramnios can cause fet al distress before or during labor and severe respiratory distress and pneumothorax due to pulmonary hypoplasia

FOLLOW-UP

Patient Monitoring

Close monitoring by prenatal sonography

Patient Resources

- www.americanpregnancy.org
- www.acog.org/For_Patients

REFERENCES

1. Volante E, Gramellini D, Moretti S, et al. Alteration of the amniotic fluid and neonatal outcome. *Acta Bio Med*. 2004;75:71–75.
2. Sherer DM. A review of amniotic fluid dynamics and the enigma of isolated oligohydramnios. *Am J Perinatol*. 2002;19:253–266.
3. Shipp TD, Bromley B, Pauker S, et al. Outcome of singleton pregnancies with severe oligohydramnios in the second and third trimesters. *Ultrasound Obstet Gynecol*. 2996;7:108–113.
4. Harman CR. Amniotic fluid abnormalities. *Semin Perinatol*. 2008;32:288–294.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Polyhydramnios/Oligohydramnios Image
- Posterior Urethral Valves
- Potter Syndrome/Potter Facies

CODES

ICD9

- 657.00 Polyhydramnios, unspecified as to episode of care or not applicable
- 658.00 Oligohydramnios, unspecified as to episode of care or not applicable
- 761.2 Oligohydramnios affecting fetus or newborn

ICD10

- O40.9XX0 Polyhydramnios, unspecified trimester, not applicable or unspecified
- O41.00X0 Oligohydramnios, unspecified trimester, not applicable or unspecified
- P01.2 Newborn (suspected to be) affected by oligohydramnios

CLINICAL/SURGICAL PEARLS

- If anmiotic fluid (AF) levels are normal, the fetus is very likely to have adequate urine production even with bilateral hydronephrosis.
- In utero intervention with vesicoamniotic shunt is controversial.
- Idiopathic polyhydramnios has good outcomes.

POLYOMA VIRUS (BK, JC), UROLOGIC CONSIDERATIONS

Nathan Roberts, MD
Patrick J. Shenot, MD, FACS

BASICS

DESCRIPTION

- JC and BK viruses are 2 of 10 different human polyoma viruses
  - Small DNA viruses in the papovaridae family
  - JC and BK viruses named after 1st patients the viruses were isolated from in 1971
  - These viruses typically manifest clinical sequelae only in immunocompromised hosts
  - BK virus has a tropism for genitourinary epithelium
    - Clinical manifestations: Hemorrhagic cystitis (HC), ureteral stenosis, nephropathy, and rare GU-associated malignancies

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- BK virus has an 82–99% seroprevalence in adults of the United States, Italy, and Australia
  - 50% @ 2 yr of age; 90% @ 10 yr of age
- JC virus has a 39–81% seroprevalence in same regions
  - Clinically manifest only in immunocompromised subjects
- Ureteral stenosis due to BK virus infection among allograft recipients is approximately 3%
- BK-induced nephropathy:1–10% of transplants
- Hemorrhagic cystitis
  - Reported to cause hemorrhagic cystitis in 5.7–7.7% of bone marrow transplant recipients

RISK FACTORS

- Immunocompromised host
  - Degree of immunosupression
  - Transplant recipients
    - Solid organ (especially kidney), stem cell transplants
  - HIV/AIDS
    - Predilection toward hemorrhagic cystitis
  - Autoimmune disorders requiring immunosuppression
  - Multiple sclerosis
  - Systemic lupus erythematous

Genetics

- Small nonenveloped icosahedral particles of 40–45-nm diameter, with a nonenveloped, circular double-stranded DNA genome
- Polyoma viruses encode 6 proteins
- 3 structural capsid proteins

- 3 noncapsid regulatory proteins
  - Large and small T antigen (cell immortalization and latency), and agnoprotein (assembly of viral particles)
    - Proteins interact with cellular target proteins and impair pathways involved with cell cycle and DNA repair

PATHOPHYSIOLOGY

- Route of transmission is unknown but seems to occur early in life most likely oral/respiratory exposure (1,2)
- Hypothesized that subclinical infection leads to viremia that seeds the kidneys
- Pathology is postulated to occur from reactivation of latent infection and not reinfection
- Immuno-reconstitution inflammatory syndrome
  - Dominant inflammatory response to abundant polyoma virus antigen followed by brisk recovery of the cellular immune response
    - Seen in BKV-associated hemorrhagic cystitis after allogeneic stem cell transplantation
- Cytopathic-inflammatory polyomavirus pathology
  - High-level virus replication and a significant inflammatory response due to cytopathic lysis, necrosis, with infiltration of granulocytes and lymphocytes. Dominant inflammatory response to abundant polyoma virus antigen followed by brisk recovery of the cellular immune response
    - Seen in BKV-associated nephropathy in kidney allografts
- Oncogenic polyoma virus pathology
  - Early viral gene expression activating host cells but without sufficient late gene expression to cause rapid host cell lysis
    - Seen in rare BKV-associated urothelial and renal tubular cancers
    - There is conflicting evidence of BK virus involvement in these tumors
- Hemorrhagic cystitis
  - Another theory suggests 3 phases
    - Conditioning regimen for stem cell transplant damages the bladder mucosa providing environment for virus replication
    - Viral replication unchecked in the absence of functional immunity
    - Further damage to the bladder mucosa with immune reconstitution and return of anti-BK immunity

ASSOCIATED CONDITIONS

- BK virus has a tropism for genitourinary epithelium
  - Kidney transplant recipients
    - Tubulointerstitial nephritis
    - Ureteral stenosis
  - Stem cell transplant recipients
    - Hemorrhagic cystitis
- JC virus has a tropism for neural tissue
  - Causes progressive multifocal leukoencephalopathy
  - Not as common, but JC can also be related to genitourinary manifestations like BK virus and vice versa

GENERAL PREVENTION
- Route of transmission is unknown so difficult to prevent
- Competent immune system will prevent clinical sequelae

DIAGNOSIS
HISTORY
- Hemorrhagic cystitis
  - From pink colored urine to clot retention
  - Pt can also have bladder pain
  - Pt may have LUTS
- BK virus nephropathy
  - Typically occurs 10–13 mo after transplant
  - Often asymptomatic
  - May have hematuria
  - May have decreased urine output
- Transplanted ureteral stenosis (3)
  - Typically occurs 2–4 mo after transplant
  - Often asymptomatic
  - May have decreased urine output

PHYSICAL EXAM
- Hemorrhagic cystitis
  - May present with palpable bladder if in clot retention
- BK virus nephropathy
  - No significant findings on exam
- Ureteral stenosis of kidney transplant
  - May have no significant findings
  - Pelvic mass bulge from transplant hydronephrosis
  - Due to denervation of transplanted kidney, patient may not present with pain

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Virus culture mostly used in research setting
  - Takes weeks to months to grow
- Urine cytology
  - Detects virus shedding
  - Characteristic finding is an enlarged nucleus with a single large basophilic intranuclear inclusion (“decoy cells”)
    - Does not distinguish between various types of polyoma virus
- Urine quantitative PCR
  - Correlates with BK virus associated nephropathy
  - Can be positive in normal controls, elderly patients and HIV-infected patients without clinical manifestations
    - Difficult to assess clinical significance
- Plasma quantitative PCR

- Hemorrhagic cystitis
  - Urinalysis positive for blood/RBCs
- BK virus nephropathy
  - Elevated creatinine
  - Urinalysis
    - Pyuria, hematuria, and/or cellular casts of renal tubular cells and inflammatory cells
- Transplanted ureteral stenosis
  - Can have elevated creatinine

Imaging

- Hemorrhagic cystitis
  - Ultrasound or CT can show bladder thickening and possibly clot if present
- Transplanted ureteral stenosis
  - Hydronephrosis seen on renal ultrasound, CT or MRI
  - Obstruction seen on renogram

Diagnostic Procedures/Surgery

- Hemorrhagic cystitis
  - Cystoscopy can show evidence of clots/active bleeding
- BK virus Nephropathy
  - Renal Biopsy
    - Most often percutaneous approach
    - Histopathology results listed below
    - Can also use Immunohistologic or in situ hybridization evidence of virally infected cells to make diagnosis
    - Strongly positive using an SV40 immunohistochemical stain

Pathologic Findings

- BK Virus nephropathy
  - Usually infects tubular epithelial cells
  - Anisonucleosis, hyperchrmoasia, and chromatin clumping of infected cells
  - Interstitial mononuclear or polymorphonuclear cell infiltrates in the areas of tubular damage
  - Tubular injury with tubular cell apoptosis
  - Intranuclear basophilic viral inclusions with a surrounding halo
  - Not pathognomonic for BK virus
    - CMV has cytoplasmic inclusion
    - HHSV has both intranuclear and cytoplasmic inclusions

DIFFERENTIAL DIAGNOSIS

- Hemorrhagic cystitis
  - Medication related (high-dose cyclophosphamide)
    - Often occurs within 72 hr
  - Adenovirus related
  - Radiation induced
  - Infectious source
  - Trauma

    - Possibly from urethral catheter placement
  - BPH related
- BK virus nephropathy
  - Cellular rejection
- Transplanted ureteral stenosis
  - Surgical technique; ischemia of distal ureter
  - Typically occurs in 7–10 days

TREATMENT

GENERAL MEASURES

- Reduction of immunosuppression if possible (4)
  - Often most effective strategy

MEDICATION

First Line

- Quinolone antibiotic (ciprofloxacin, etc.)
  - Suggested for prophylactic role
- Intravenous immunoglobulin
  - Can be used in hypogammaglobulinemic patients
  - Leflunomide: Antiviral activity
- Hemorrhagic cystitis
  - Increased hydration
  - Catheter placement with clot evacuation
  - Continuous bladder irrigation (CBI)

Second Line

- Intravesical vs. intravenous cidofovir
  - Nucleotide analog of cytosine
  - Active against DNA viruses
  - Anecdotal evidence for use against polyoma viruses
  - Highly nephrotoxic
- Hemorrhagic cystitis
  - Cystoscopic fulguration (electro cautery or laser)
  - Conjugated estrogens: Act by stabilization of microvasculature
  - Intravesical instillation of alum
    - An astringent precipitates protein over bleeding surface
    - 1% Alum solution in CBI
    - Can be used in presence of VUR
  - Intravesical instillation of silver nitrate
    - Chemical coagulation and eschar at bleeding sites
    - 0.5–1% instilled for 10–20 min
    - VUR may lead to renal failure due to precipitation and obstruction of upper tracts
  - E-aminocaproic acid
    - Inhibits fibrinolysis preventing activation of plasminogen to plasmin
    - Given orally, parenterally, or intravesically

- Patients can form hard clots that are difficult to flush from the bladder
- Intravesical instillation of prostaglandin
  - PGE2: May encourage platelet aggregation and induce vasoconstriction
  - PGE2: 0.75 mg in 200 mL of normal saline and left indwelling
  - May cause bladder spasms
- Intravesical instillation of formalin (40% formaldehyde)
  - Hydrolyzes proteins and coagulates tissue on superficial level
  - Painful and needs to be done with general anesthesia
  - Should not be done with VUR. Can fibrose the ureters, cause obstruction, hydronephrosis and also papillary necrosis
  - Can result in small contracted bladder

SURGERY/OTHER PROCEDURES

- Hemorrhagic cystitis (5)
  - Cystectomy if refractory life-threatening cases
  - Selective embolization
    - Vesical or internal iliac artery
- BK virus Nephropathy
  - Kidney re-transplant
    - Limited information for outcomes
    - Recommend patients have absence of BK replication prior to re-transplantation
- Transplant ureteral stenosis
  - Decompression of the transplanted kidney
    - Percutaneous nephrostomy tube
    - Ureteral stent placement
  - Surgical excision of stenotic segment

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Hemorrhagic cystitis
  - Hyperbaric oxygen: Promotes healing of hypoxic tissues and aid in angiogenesis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Hemorrhagic cystitis: Dramatic in presentation but usually resolves spontaneously within 2 wk with supportive care
- BK virus nephropathy: Graft failure in 15–50%

FOLLOW-UP

Patient Monitoring

BK virus nephropathy: After transplant some recommend periodic monitoring for viremia

Patient Resources
N/A

REFERENCES

1. Dalianis T, Hirsch HH. Human polyomaviruses in disease and cancer. *Virology.* 2013;437(2):63–72.
2. Hirsch HH, Randhawa P. BK polyomavirus in solid organ transplantation. *Am J Transplant.* 2013;13 suppl 4:179–188.
3. Thomas A, Dropulic LK, Rahman MH, et al. Ureteral stents: A novel risk factor for polyomavirus nephropathy. *Transplantation.* 2007;84(3):433–436.
4. van Aalderen MC, Heutinck KM, Huisman C, et al. BK virus infection in transplant recipients: Clinical manifestations, treatment options and the immune response. *Neth J Med.* 2012;70(4):172–183.
5. Manikandan R, Kumar S, Dorairajan LN. Hemorrhagic cystitis: A challenge to the urologist. *Indian J Urol.* 2010;26:159–166.

ADDITIONAL READING

Kazory A, Ducloux D. BK virus-associated urologic complications. *Pediatr Transplant.* 2007;11(7):821–822.

See Also (Topic, Algorithm, Media)

- Cystitis, Hemorrhagic (Infectious, Noninfectious, Radiation)
- Immunocompromised Patients, Urologic Considerations
- Polyoma Virus (BK, JC), Urologic Considerations Image

CODES

ICD9

- 079.89 Other specified viral infection
- 593.3 Stricture or kinking of ureter
- 595.9 Cystitis, unspecified

ICD10

- B33.8 Other specified viral diseases
- N13.5 Crossing vessel and stricture of ureter w/o hydronephrosis
- N30.90 Cystitis, unspecified without hematuria

CLINICAL/SURGICAL PEARLS

Polyoma virus will only have clinical sequelae in immunocompromised patients.

POSTERIOR URETHRAL VALVES

Steve J. Hodges, MD
Anthony Atala, MD

BASICS

DESCRIPTION

- Congenital obstruction of the posterior urethra that can cause variable degrees of dysfunction of all segments of the urinary tract, including the bladder, ureters, and kidneys
- Urinary tract dysfunction can include
  - Functional bladder disorders including increased bladder wall thickness, fibrosis, and hyperactivity that may progress to myopathy and poor function
  - The bladder changes may affect the upper tracts by transmitting high pressure to the renal parenchyma, causing deterioration of renal function
  - Patients may have congenital renal dysplasia

EPIDEMIOLOGY

Incidence/Prevalence

- Congenital disorder
- 1 in 4,000–7,500 live male births
- No racial predilection
- Most common cause of lower urinary tract obstruction in males
- Accounts for 16.8% of children with ESRD
- The prevalence is 1:2,400–1:8,000

RISK FACTORS

- No racial predilection
- Only affects males

Genetics

- This disorder is usually sporadic.
- Cases have been seen in twins and siblings suggesting a poorly understood genetic component.

PATHOPHYSIOLOGY

- Congenital mucosal membrane (fold/valve) in the posterior urethra
- Hugh H. Young Classification (1919)
  - Type I: Folds that extend distally from the verumontanum to divide into 2 membranes that attach to the anterolateral wall, most common variant (95%)
  - Type II: Folds extending from the verumontanum to the bladder neck superiorly, not clinically obstructing, only of historical significance
  - Type III: Transverse membrane in the posterior urethra, has a central aperture, located distal to verumontanum, rare (5%)

ASSOCIATED CONDITIONS

- Renal dysplasia

- Bladder diverticula
- Ascites
- Urine extravasation
- Vesicoureteral reflux
- Azotemia
- Hydroureteronephrosis
- VURD

GENERAL PREVENTION

No known methods of prevention

ALERT

High risk of end-stage renal disease in urethral valve patients.

DIAGNOSIS

HISTORY

- Antenatally
  - No specific questions in the maternal or family history aid in diagnosis
  - Prenatal US usually demonstrates bilateral hydroureteronephrosis and thick walled bladder in males (+/– oligohydramnios)
- Postnatally
  - Nature or strength of urinary stream is a poor predictor of valves, or severity of obstruction
  - Failure to thrive may be seen
  - Straining or grunting while voiding
  - May present with symptoms indicative of sepsis in a neonate due to UTI
  - Delayed presentation considered in any male with a chronic history of day and night urinary incontinence, UTI, and/or chronic polydipsia/polyuria

PHYSICAL EXAM

- Common neonatal presentation
  - General: Palpably enlarged bladder, possible abdominal distention due to ascites
  - Pulmonary: Pulmonary distress syndrome, pulmonary hypoplasia
  - Musculoskelet al: Potter's facies, limb deformities (in patients with severe oligohydramnios)
  - Genitalia: Bulge in the penoscrotal junction during urination is a sign of anterior urethral valves

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis and urine culture
- Serum electrolytes, BUN, and Cr
- Cr has early prognostic value
- Elevated Cr in 1st few days of life (after the 1st 5 days) indicates renal dysfunction and poor prognosis
- Cr >1 at the end of the 1st yr of life predictive of eventual ESRD

Imaging

- Renal/Bladder US
  - Assesses for hydroureteronephrosis, corticomedullary differentiation, echogenicity, signs of renal dysplasia, thickness of renal parenchyma and bladder wall
- VCUG
  - Diagnoses urethral valves, detects vesicoureteral reflux and bladder trabeculation diverticula
  - Shows dilated posterior urethra, trabeculated bladder, vesicoureteral reflux, perhaps ascites
  - Hydroureteronephrosis
- DMSA Renogram
  - After 6 wk of life may be used to evaluate renal function, dysplasia

Diagnostic Procedures/Surgery

- Prenatal
  - Antenatal US: Bilateral hydroureteronephrosis (+/– oligohydramnios, the earlier the diagnosis the worse the prognosis)
- Postnatal
  - US, VCUG, laboratory evaluation
  - Cystoscopy: Confirms the diagnosis of PUV by direct visualization of the obstructing valves

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Anterior urethral valves
- Bilateral UPJ obstruction
- Congenital urethral polyp
- Congenital urethral stricture (Cobb collar)
- Megacystis-megaureter
- Megalourethra
- Multicystic dysplastic kidney
- Neuropathic bladder
- Nonneurogenic neurogenic bladder (Hinman syndrome)
- Plicae colliculi
  - Normal anatomic finding
  - Represents this folds of mucosa that extend from the verumontanum in the prostatic urethra to the membranous urethra
- Prune belly syndrome
- Urethral atresia

TREATMENT

GENERAL MEASURES

- Place urethral catheter immediately after birth to drain the bladder (1)

- Measure daily weights, I/O's (fluid balance), routine vital signs
- Fluid and electrolytes as needed

MEDICATION

First Line

- Prophylactic antibiotics
  - < 2 mo age: Amoxicillin 20 mg/kg/d
  - ≥ 2 mo of age: Trimethoprim-sulfamethoxazole 2 mg/kg/d (concentrates in urine); nitrofurantoin is an alternative
- Anticholinergics for bladder dysfunction

SURGERY/OTHER PROCEDURES

- Transurethral ablation of urethral valves is possible in 80% of neonates
- Cutaneous vesicostomy in children too small for endoscopy (usually < 2,000 g)
- Bilateral cutaneous pyelostomies of mostly historical significance, but may be used in extreme cases

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Prenatal surgical intervention remains investigational
  - Associated with risk of fet al and maternal morbidity; long-term renal benefit proven
- In children with persistent worsening renal function and hydroureteronephrosis following valve ablation may require upper tract diversion if possible to salvage renal function
- Persistent vesicoureteral reflux following valve ablation may require vesicoureteral reflux
- Low compliance fibrotic bladder or myogenic failure (valve bladder) may require enterocystoplasty and/or clean intermittent catheterization (CIC)

Complementary & Alternative Therapies

- Behavioral measures
  - Timed voiding, constipation therapy
- Biofeedback
  - Physical therapy to relax external sphincter
- Diet
  - Avoid bladder irritant, caffeine
- Perineal hygiene
  - Voiding positioning

ONGOING CARE

PROGNOSIS

- Depends on the amount of congenital renal dysplasia, vesicoureteral reflux, bladder function
- Incontinence and later ESRD correlated
- Cr > 1 mg/dL at the end of the 1st yr of life correlated with ESRD
- Long-term bladder dysfunction may progress to overactive/fibrotic bladder or possibly eventual myogenic failure

• Sexual function and fertility seems to be normal in most patients

COMPLICATIONS
• End-stage renal disease
• Voiding dysfunction
• Incontinence

FOLLOW-UP
Patient Monitoring
• Follow-up for observation of progress of renal function, as high risk of ESRD
  – Usual late or difficulty toilet training; treat voiding dysfunction, incontinence
  – Patients need serial electrolyte and Cr measurements, US evaluations, VCUG following ablation to monitor success of surgery, resolution of reflux
  – UDS for bladder function
  – Prophylactic antibiotics as needed

Patient Resources
http://www.chop.edu/healthinfo/posterior-urethral-valves-puv.html

REFERENCE
1. Hodges SJ, Patel B, McLorie G, et al. Posterior urethral valves. *Scientific World Journal.* 2009;9:1119–1126.

ADDITIONAL READING
• Heikkilä J, Holmberg C, Kyllönen L, et al. Long-term risk of end stage renal disease in patients with posterior urethral valves. *J Urol.* 2011;186(6):2392–2396.
• Taskinen S, Heikkilä J, Rintala R. Effects of posterior urethral valves on long-term bladder and sexual function. *Nat Rev Urol.* 2012;9(12):699–706.

See Also (Topic, Algorithm, Media)
• Anterior Urethral Valves
• Bladder Outlet Obstruction
• Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric
  Incontinence, Pediatric
• Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Prenatal
• Posterior Urethral Valves Image
• Urethra, Obstruction
• VURD Syndrome

CODES

ICD9
• 599.69 Urinary obstruction, not elsewhere classified
• 753.8 Other specified anomalies of bladder and urethra
• 753.15 Renal dysplasia

ICD10
• N13.8 Other obstructive and reflux uropathy

- Q61.4 Renal dysplasia
- Q64.79 Other congenital malformations of bladder and urethra

CLINICAL/SURGICAL PEARLS

- No benefit to early delivery as children with pulmonary hypoplasia also have severe renal dysplasia.
- Select centers offer prenatal interventions with dubious efficacy.
- Poor kidney function at presentation is associated with worse renal prognosis.

POSTOBSTRUCTIVE DIURESIS

John J. Pahira, MD

BASICS

DESCRIPTION

- Postobstructive diuresis is excessive polyuria resulting from the relief of bilateral ureteral obstruction or obstruction of a solitary kidney, bladder outlet obstruction
- More likely with chronic rather than acute obstruction
- After relief of obstruction, >3 L over 24 hr or >200 mL/hr over each of 2 consecutive hr is diagnostic of polyuria found with POD

EPIDEMIOLOGY

Incidence

- Peak incidence in men 70–90, due to increased obstruction from BPH and prostatic cancer
- Peak incidence in women 40–60, due to obstruction from pregnancy and carcinoma of the cervix and uterus

Prevalence

N/A

RISK FACTORS

- Urinary tract obstruction is caused by a number of processes, grouped into extrinsic and intrinsic causes:
  - Intrinsic: Nephrolithiasis, blood clot, ureteral strictures, urethral strictures, neurogenic bladder, anticholinergic agents, levodopa
  - Extrinsic: BPH, prostate cancer, tubo-ovarian abscess, ovarian tumor or cyst, endometriosis, arterial aneurysms, tumors of the kidney, ureter, bladder, and urethra and their corresponding lymphatic and metastatic spread
- Obstructed patients most likely to have POD
  - Chronic obstruction
  - Edema
  - Congestive heart failure
  - HTN
  - Weight gain
  - Azotemia
  - Uremic encephalopathy

Genetics

N/A

PATHOPHYSIOLOGY

- Retained urea, sodium, and water; impaired sodium reabsorption and concentrating ability of the renal tubule; and circulating hormones all contribute:
  - Increased sodium, potassium, and magnesium losses result in increased water excretion
  - Accumulated urea acts as an osmotic agent, bringing fluid with it as it is cleared, thereby

increasing diuresis
  – Impaired concentrating ability of the renal tubule leads to continuing fluid losses and hypovolemia
- ANP, which causes vasodilation, natriuresis, and diuresis, has been found to be elevated in patients with ureteral obstruction (1)[B]

ASSOCIATED CONDITIONS
- BPH
- Malignancies (bladder or prostate cancer)
- Urolithiasis
- Any cause of chronic obstruction with hydronephrosis

GENERAL PREVENTION
Treat and repair the cause of obstruction to prevent recurrence

DIAGNOSIS
HISTORY
- Obstruction:
  – Asymptomatic but often associated with flank pain radiating to groin and/or ipsilateral thigh, nausea, vomiting, fevers, chills
  – Resulting uremia may cause mental status changes, tremors, and GI bleeding (2)[A]
- Diuresis:
  – Increase in urine output out of proportion to fluid intake, usually >200 mL/hr
- Chronic obstruction:
  – Weight gain, malaise, fatigue, shortness of breath
- Acute obstruction
  – Flank pain associated with forced diuresis (consumption of coffee, tea, or alcohol), nausea, vomiting, hematuria, anuria

PHYSICAL EXAM
- Chronic obstruction:
  – Pulmonary congestion, pitting edema of lower extremities, HTN
- Acute obstruction:
  – Abdominal mass, suprapubic tenderness, flank tenderness

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC, urine culture and sensitivity:
  – Infection in the setting of obstruction requires emergent evaluation and treatment
- SMA-7
  – BUN and creatinine are typically elevated and are monitored after relief of obstruction
  – POD may cause profound hypokalemia
- Magnesium and calcium may need preplacement
- Urine osmolality:
  – Evaluate the kidney's ability to concentrate urine; typically impaired concentrating ability

Imaging

- US is the screening test of choice to evaluate obstruction:
  - Avoid risk of contrast agents
  - Without hydronephrosis, diagnosis of POD should be questioned

Diagnostic Procedures/Surgery

Monitor urine output

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Causes of polyuria:
  - Medications:
    - Lithium carbonate, methoxyflurane, demethylchlortetracycline, amphotericin B, mannitol, glycerol, diuretics, ethanol, opiate antagonist, phenytoin
  - Diabetes insipidus, diabetes mellitus
  - Renal disease: Diuretic phase of ATN
  - Physiologic diuresis from fluid excess

TREATMENT

GENERAL MEASURES

- After the obstruction is relieved, admit the patient to the hospital to closely monitor hemodynamic status and electrolytes, I/O's and daily weights
- Monitor urine output q2h and replace with oral fluids or if oral intake is not keeping up then with IV fluids (0.5–1.0 mL of 1/2 NS/mL of urine output) in addition to PO fluids
  - If urine output decreases to <250 mL/hr replace fluids volume <50 mL of the urine output per hour. Adjust accordingly as the diuresis resolves
- If patient at risk of congestive heart failure or has pulmonary edema, replace at a slower rate
- Check serum sodium and potassium q6–12h and replace as needed
- Follow BUN and creatinine values until normal:
- Replace sodium, potassium, magnesium, and bicarbonate as needed
- Diuresis is usually self-limiting and typically lasts <48 hr
- If diuresis lasts >48 hr, usually due to impaired proximal tubular reabsorption of sodium causing a salt diuresis
  - If outputs remain elevated, obtain a follow-up renal US to rule out hydronephrosis

ALERT

If there is persistent hydronephrosis, consider persistent obstruction of ureter(s) above the level of the bladder or a nonfunctioning stent/percutaneous tube (3)[A].

MEDICATION

First Line

None needed beyond replacement of fluid and electrolyte losses as noted above

Second Line

N/A

SURGERY/OTHER PROCEDURES
N/A

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
Management of any renal insufficiency

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- The rate of recovery is largely determined by the duration and severity of obstructive disease.
- Extent of recovery can be estimated by the improvement in renal function within 7–14 days after the obstruction has been relieved:
  – Some patients may require short-term treatment with dialysis, until their renal function recovers.

COMPLICATIONS
- Uremic death
- Hypovolemic circulatory collapse
- Bladder mucosal bleeding secondary to vein rupture resulting from rapid bladder decompression
- Arrhythmia secondary to electrolyte abnormalities

FOLLOW-UP
Patient Monitoring
Serial (weekly to monthly) renal function testing (creatinine, BUN), renal US imaging if lab values do not return to normal range

Patient Resources
N/A

REFERENCES

1. Li C, Wang W, Kwon TH, et al. Downregulation of AQP1, -2, and -3 after ureteral obstruction is associated with a long term urine concentrating defect. *Am J Physiol Renal Physiol*. 2001;281:F163–F171.
2. Pais VM, Strandhoy JW, Assimos DG. Pathophysiology of urinary tract obstruction. In: Wein AJ, ed. *Campbell-Walsh Urology*. 9th ed. St. Louis, MO: WB Saunders; 2007.
3. Gulmi FA, Felson D, Vaughan ED. Management of post-obstructive diuresis. *AUA Update Series*. Lesson 23. 1998;27:177–183.

ADDITIONAL READING

Nyman MA, Schwenk NM, Silverstein MD. Management of urinary retention: Rapid versus

gradual decompression and risk of complications. *Mayo Clin Proc*. 1997;72(10):951–956.

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Polyuria
- Urinary Retention, General

CODES

ICD9

- 592.0 Calculus of kidney
- 599.60 Urinary obstruction, unspecified
- 788.42 Polyuria

ICD10

- N13.9 Obstructive and reflux uropathy, unspecified
- N20.0 Calculus of kidney
- R35.8 Other polyuria

CLINICAL/SURGICAL PEARLS

- Maintain a high degree of suspicion for the potential for postobstructive diuresis when relieving chronic obstruction of the urinary tract.
- Diuresis is usually self-limiting and typically lasts <48 hr.

PREGNANCY, UROLITHIASIS

Demetrius H. Bagley, MD, FACS
Kelly A. Healy, MD

BASICS

DESCRIPTION

- The presence of calculi in the urinary tract during pregnancy can lead to severe risks and problems in management
- Urolithiasis is the most common cause of nonobstetric abdominal pain that requires hospitalization among pregnant patients
- Symptoms in urolithiasis can result in premature labor and fet al loss
- Stones with obstruction may lead to urosepsis requiring appropriate treatment
- Calcium phosphate most common followed by calcium oxylate

EPIDEMIOLOGY

Incidence

- Calculi in pregnant women occur at a rate of 1/1,500 pregnant patients; a rate similar to that of nonpregnant females (0.03–0.53%)
- Ureteral stones occur twice as often as kidney stones in pregnant patients
- Usually present in the 2nd or 3rd trimester
- Incidence—right vs. left side is similar
- Hispanics and whites more likely than blacks to develop stones during pregnancy
- Multiparous women are more commonly affected than are primiparous women

Prevalence

N/A

RISK FACTORS

- Dehydration
- Relative immobility
- Voluntary dietary modification (increased calcium)

Genetics

- Increased stone formation is likely with a positive family history
- Factors related to stone formation tend to group in families
- Women with known cystinuria should obtain genetic counseling and management of the stone disease before becoming pregnant

PATHOPHYSIOLOGY

- Several factors occur in pregnancy may enhance formation of stones:
  - Pregnancy-induced urinary stasis
  - Hypercalcemia and hypercalciuria
  - Decreased ureteral peristalsis
  - Physiologic hydronephrosis
    - Starts 6–20 wk, in 90% by 3rd trimester

- Right side > left; may persist postdelivery

– Infection

- Associated higher incidence of maternal UTI (10–20%)
- Stone passage can precipitate premature labor and/or interfere with normal labor
- Controversial considerations may cause a higher rate of spontaneous abortions
- Physiologic dilation of calyces, ureters, and renal pelves begins in the 1st trimester and continues into the postpartum period
- Dilation is greater on the right than the left
- Decreased ureteral peristaltic activity because of hormonal and mechanical factors
- Dilation and decreased peristalsis allowed relative urinary stasis
- Increased urinary calcium excretion in pregnancy (↑2–3 times)

– Increased levels of 1, 25-dihydroxy vitamin D

– GFR increases 25–50% in pregnancy

- Urine is more alkaline in pregnancy and thus protective against uric acid stones
- Increase in excretion of stone inhibitors including citrate and magnesium

ASSOCIATED CONDITIONS

- Hydroureteronephrosis is the most significant renal alteration during pregnancy
- Physiologic dilatation of the collecting system begins in the 1st trimester and persists until 4–6 wk following delivery. This factor may also allow the passage of relatively larger calculi
- Increased urinary calcium excretion during pregnancy may present the major problem with indwelling stents and catheters

GENERAL PREVENTION

- Prophylactic measures to prevent the difficulties of treating urolithiasis during pregnancy should be considered
- Metabolic evaluation should be performed for known stone formers at a time when they are not pregnant and not lactating
- There should be consideration of treatment of asymptomatic stones prior to pregnancy
- As noted above, cystinurics have good management of the disease before becoming pregnant

DIAGNOSIS

HISTORY

- Pregnancy history
- History of previous calculi
- Flank and back pain and changes in symptoms
- Dietary modifications
- Medications
- Voiding symptoms—urgency and frequency with urination

PHYSICAL EXAM

- Abdominal tenderness
- Tenderness at costovertebral angle
- Fever/chills
- Nausea/vomiting

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis:
  - Hematuria/pyuria
- Urine culture:
  - UTIs are more common in pregnancy associated with stone disease (10–20%)
  - A UTI can induce premature labor
- Serum creatinine:
  - May be lower if the increased GFR (25–50%) in pregnancy
- CBC

Imaging

- Renal ultrasound (Standard initial imaging study in evaluation of pregnant patients) (1)
  - Hydronephrosis
  - Renal stones/proximal ureteral stones
  - Extravasation/perirenal urinoma
  - Abscess
  - Resistive index (RI) >0.70 in intrarenal arteries supportive of acute obstruction
  - No radiation exposure to fetus
- Transvaginal ultrasound
  - Can demonstrate distal ureteral stones
  - Can demonstrate ureteral jets, confirming urinary flow
  - Document the diameters of distal ureter
- Noncontrast helical/spiral CT
  - Although utilized increasingly in nonpregnant patients, delivers a relatively high radiation exposure
  - Recent techniques have been decreased the radiation exposure
- Other imaging including standard excretory urogram and computerized tomographic scan are discouraged during the 1st and 2nd trimesters
  - Abdominal radiographic and one excretory urogram has been widely used in pregnancy
  - There has been no adverse effect of contrast material reported on the fetus
  - Radiation exposure is the major concern
    - Typical urogram gives <1.5 rads of exposure
    - 5–15 rads to the maternal pelvis in the 1st trimester increases the risk of congenital anomalies by 1–3%
    - As little as 0.4–1.0 rads of fet al exposure can increase the risk of childhood malignancy 2.4 times
- MRI urography:
  - Effect on fet al development poorly defined
  - May be able to distinguish acute obstruction from the dilation of pregnancy

Diagnostic Procedures/Surgery

- The presence of ureteral calculi with obstruction is generally defined before interventional procedures
  - Occasionally, the diagnosis is not certain and the presence of an obstructing calculus is defined only at the time of ureteroscopy

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Acute pyelonephritis
- Appendicitis
- Cholecystitis
- Gastroenteritis
- Hydronephrosis of pregnancy
- Neurologic/musculoskelet al pathology
- Obstetric etiology of pain
- Other intra-abdominal conditions
- Renal vein thrombosis

TREATMENT

GENERAL MEASURES
- Often misdiagnosed initially (appendicitis/diverticulitis/placental abruption)
- Conservative measures are taken initially to manage pain and infection so that the stone may pass (2)
- Hydration and analgesia, antiemetics and antibiotics are used
- Approximately 60–80% of renal calculi pass spontaneously. Among pregnant patients with dilated ureter, the passage rate is not defined
- Ureteral calculi associated with obstruction and upper tract infection demand immediate treatment with drainage and antibiotics

MEDICATION
First Line
- Narcotics including morphine, hydromorphone, butorphanol, meperidine, and acetaminophen can provide short-term pain relief without fet al harm
- Avoid codeine during pregnancy because of its association with fet al defects
- Nonsteroidal anti-inflammatory drugs are contraindicated because of the increased risk of miscarriage in the 1st trimester and other risks including fet al renal anomalies, fet al pulmonary hypertension and premature closure of the ductus arteriosus when used near term
- Medical management for the prevention of calcium stones should be delayed until after delivery

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Intervention may be required in 20–30% of cases (3)
- Drainage may be necessary
- Cystoscopy/stent placement can be done with or without ultrasound guidance (4)
  - Stents must be changed every 6 to 8 wk because of rapid encrustation in the pregnant women's urine

- Percutaneous nephrostomy placement can be done under ultrasound:
  - To minimize radiation exposure
  - The stone or obstruction can be addressed postpartum
  - The tube should be changed every 6–8 wk
  - Clearly tube drainage alone must consider the duration of pregnancy
- Ureteroscopy with laser lithotripsy or impact lithotripsy has been very successful in treating stones in the upper urinary tract in the pregnant patient
- Shock wave lithotripsy has generally not been employed because of concerns of safety and the readily available alternatives

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Dietary changes including:
  - Limiting high oxalate foods and purines
  - Increase in fluid intake
  - Limiting salt and sodium intake
  - May be best preserved until metabolic evaluation postpartum

ONGOING CARE

PROGNOSIS

Pregnancy outcome is not appreciably worsened because of symptomatic urolithiasis with appropriate management (5)

COMPLICATIONS

- Premature labor, fet al loss
- Urosepsis, renal insufficiency

FOLLOW-UP

Patient Monitoring

- During gestation:
  - Conservative management with hydration
  - Indications for intervention:
    - Worsening renal function associated with persistent obstruction
    - Intractable pain
    - Obstruction of a solitary kidney
    - Persistent infection associated with an obstruction
    - Renal colic, precipitation premature labor that is refractory to treatment
  - Preventive medications for stone disease have unacceptable side effects during pregnancy
    - Thiazides: Can cause fet al thrombocytopenia, hypoglycemia, and hyponatremia
    - Xanthanine oxidase inhibitors: No adverse effects on fet al animals but effects on human fetus known

- Penicillamine: Teratogenic in rats; fet al defects have been found in infants of mothers who took this during gestation

- Postpartum:
  - Metabolic screening should be undertaken postpartum and should be delayed until completion of lactation period

Patient Resources

N/A

REFERENCES

1. Masselli G, Derme M, Laghi F, et al. Imaging of stone disease in pregnancy. *Abdom Imaging*. 2013;38(6):1409–1414.
2. Hoscan MB, Ekinci M, Tunç ran A, et al. Management of symptomatic calculi complicating pregnancy. *Urology*. 2012;80:1011–1014.
3. Bozkurt Y, Soylemez H, Atar M, et al. Effectiveness and safety of ureteroscopy in pregnant women: A comparative study. *Urolithiasis*. 2013;41:37–42.
4. Deters LA, Belanger G, Shah O, et al. Ultrasound guided ureteroscopy in pregnancy. *Clin Nephrol*. 2013;79(2):118–123.
5. Laing KA, Lam TB, McClinton S, et al. Outcomes of ureteroscopy for stone disease in pregnancy: Results from a symptomatic review of the literature. *Urolo Int*. 2012;89:380–386.

ADDITIONAL READING

Evan AP, Lingeman JE, Matlaga BR. Surgical management of upper urinary tract calculi. *Urology*. 2007;2:1456–1458.

See Also (Topic, Algorithm, Media)

- Pregnancy, Bacteruria, Pyuria, and UTI
- Pregnancy, Hematuria
- Pregnancy, Radiologic Considerations
- Pregnancy, Urinary Tract Obstruction
- Pregnancy, Urologic Considerations
- Pregnancy, Urologic Medications
- Urolithiasis, Adult General
- Urolithiasis, Ureteral Calculi Algorithm

CODES

ICD9

- 592.1 Calculus of ureter
- 592.9 Urinary calculus, unspecified
- 646.80 Other specified complications of pregnancy, unspecified as to episode of care or not applicable

ICD10

- N20.1 Calculus of ureter

- N20.9 Urinary calculus, unspecified
- O99.89 Oth diseases and conditions compl preg/chldbrth

CLINICAL/SURGICAL PEARLS

- Most urinary stones pass.
- Intractable pain or infection with obstruction may necessitate drainage.
- Catheters, ureteral stent, or percutaneous nephrostomy (must be changed frequently at 4 to 6 wk because of the risks of encrustation).
- Ureteroscopic treatment with endoscopic lithotripsy appears to be the most efficacious and possibly safest treatment.

PRIAPISM

Hunter Wessells, MD, FACS
Brad Figler, MD

BASICS

DESCRIPTION

- Prolonged, usually painful erection, occurring in the absence of sexual stimulation
  - Named for Priapus, the Greek god of fertility who had an oversized, eternally erect penis
- Ischemic priapism (low-flow, veno-occlusive) is most common: Compartment syndrome of the erectile bodies causing ischemia, and ultimate necrosis of the cavernosal smooth muscle
- Nonischemic priapism (high flow, arterial) is less common: Uncontrolled arterial inflow into the cavernosal sinusoids without ischemia or necrosis of cavernosal smooth muscle
- Recurrent (Stuttering) priapism: Episodes are recurrent but of limited duration
- Refractory priapism: Persistent after surgical therapy
- Clitoral priapism (Clitorism): Described in case reports and usually presents as severe vulvar pain; associated with the use of antipsychotics:
  - Management is conservative with removal of the inciting agent
- Priapism in children usually associated with leukemia or sickle cell disease

ALERT
A low-flow ischemic priapism is considered an emergency since early intervention improves the chances for proper erectile function after.

EPIDEMIOLOGY

Incidence

- It is suggested that 10% of patients with sickle cell disease experience priapism, either recurrent short episodes (stuttering priapism) or single prolonged episodes. A higher percentage of men with sickle cell disease may report past attacks, although not all of them requiring medical care
- Priapism is most common between ages 5 and 10 in boys and ages 20 and 50 in men
- Alprostadil intracavernosal injection for the treatment of erectile dysfunction associated with a 1% rate of priapism in clinical trials
- FDA data (2007): 93 cases due to PDE5 inhibitors (likely higher due to unreported cases)

Prevalence

N/A

RISK FACTORS

- Ischemic priapism
  - Sickle cell, other hematologic disorders
    - Neonatal polycythemia, thalassemia
  - Intracavernosal injection therapy (papaverine, phentolamine, prostaglandin E1)
  - Prescription drugs
    - PDE5 inhibitors (sildenafil, others in class)

    - Hydralazine, guanethidine, α-adrenergics [eg, tamsulosin], psychotropics (risperidone, olanzapine, trazodone, SSRIs (fluoxetine bupropion), heparin, coumadin, erythropoietin, methylphenidate
  - Illegal drugs: Cocaine, marijuana
  - Poisonous venom, spinal cord injury
  - Malignancy: Metastatic cancers (GU tumors most common), melanoma, leukemia
  - Dialysis, TPN
- Nonischemic priapism: Straddle injury to the perineum or direct blow to the cavernosal bodies anywhere along the length

Genetics

Associated with genetic blood dyscrasias (sickle cell anemia, sickle cell trait, thalassemia) and Fabry disease

PATHOPHYSIOLOGY

- Ischemic priapism comprises the great majority of cases of prolonged erection
  - Ischemic priapism is caused by a veno-occlusive phenomenon in which a variety of environmental factors lead to hypoxia, acidosis, and dysregulation of cavernosal smooth muscle relaxation leading to persistent veno-occlusion, a compartment syndrome, with absent further arterial inflow
  - A feature of ischemic priapism is the ischemia reperfusion injury and oxidative stress that occurs after release of the ischemic insult
  - Hematologic abnormalities generally cause a low-flow state with red blood cells sludging and veno-occlusion (sickle cell disease, thrombophilia, thalassemia, leukemic infiltration, splenism, erythropoietin, hemodialysis with heparin, total parental nutrition)
  - Pharmacologic (α-adrenergic antagonist, intracavernosal injection, intraurethral alprostadil, antihypertensive medications, psychotropic medications)
  - Neurologic (spinal cord injury, brain tumor, neurosyphilis)
  - Neoplastic (local vs. metastatic, infiltration)
  - Idiopathic
- Nonischemic priapism
  - Unregulated arterial inflow due to traumatic injury to cavernosal artery or one of its branches with unimpeded arterial inflow to the corporal sinusoids
  - Persisting fluid shear stress due to increased inflow leads to further vasorelaxation due to endothelial NO synthase activation

ASSOCIATED CONDITIONS

- Alcohol abuse, psychiatric disorders
- Attention deficit hyperactivity disorder (ADHD): Methylphenidate use
- Blood dyscrasias
- Cocaine abuse
- Epidural anesthesia and analgesia
- Hemoglobinopathies
- Hypercoagulable states
- Intracavernous or intraurethral ED therapy
- Oral PDE5 inhibitors (sildenafil, etc.)

- Pelvic/perineal trauma
- Prostate or bladder cancer
- Renal failure and dialysis

GENERAL PREVENTION

Oral pseudoephedrine (60 mg) if high-risk for recurrence has been suggested

DIAGNOSIS

HISTORY

- Pain, duration of priapism, precipitating factors, and prior episodes
- Medical, drug, and social history. Include intracorporal injection of PDE5 inhibitors
- Determine current level of sexual function
- Prior episodes; successful treatments
- History of perineal straddle injury, malignancy

PHYSICAL EXAM

- Palpation of penis will demonstrate nontender tumescence (nonischemic priapism) or tender rigidity (ischemic priapism).
- The hallmark of a priapism is that the corpora are involved but the glans penis and corpora spongiosum are flaccid and soft
- Abdominal, perineal, and digital rectal exam to search for traumatic or malignant etiology

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC with differential and platelet count
  - Reticulocyte count (may be increased in sickle cell disease)
- Sickle cell prep for "S" hemoglobin
- Hemoglobin electrophoresis
- Urine toxicology for prohibited drugs
- Psychoactive drug screen
- "Penile blood gas" (see below)

Imaging

- Color Doppler US imaging of the cavernous arteries can distinguish ischemic priapism (minimal arterial flow) from nonischemic priapism (high peak systolic arterial flow velocity)
  - Color Doppler imaging may reveal cavernous arterial fistula or perineal arterial extravasation
- Pudendal arteriography (with the potential for therapeutic super-selective embolization) if nonischemic priapism is suspected

Diagnostic Procedures/Surgery

- Aspiration of cavernosal blood with a "butterfly needle" and blood gas syringe for "penile blood gas" allows differentiation between ischemic priapism (low pH, low PO_2, high PCO_2, blood is very dark) vs. nonischemic priapism (normal penile blood gas, blood bright red). Typical values:
  - Ischemic priapism (pO_2 <30 mm Hg, pCO_2 >60 mm Hg, pH <7.25)

– Nonischemic priapism (pO_2 >90 mm Hg, pCO_2 <40 mm Hg, pH >7.4)

Pathologic Findings

Initially liquefactive necrosis of the corporal tissue; later corporal smooth muscle fibrosis

DIFFERENTIAL DIAGNOSIS

- Ischemic vs. nonischemic priapism
- "Pseudo priapism" in men with penile prosthesis, vacuum constriction device with band, intraurethral foreign body causing penile rigidity

TREATMENT

GENERAL MEASURES

- Appropriate differentiation between ischemic and nonischemic priapism is critical (1)
- Ischemic priapism of longer than 4-hr duration is a urologic emergency that requires prompt penile decompression. This is usually a bedside corporal aspiration with or without irrigation
- Aspirate cavernosal blood for "penile blood gas"
  - Duplex color ultrasound has been suggested in lieu of penile blood gas to differentiate ischemic and nonischemic priapism
- All patients should undergo monitoring of blood pressure and pulse, peripheral IV placement, appropriate use of pain medication and sedation

MEDICATION

First Line (3)

- Ischemic priapism
  - Use local anesthesia (lidocaine without epinephrine) and choose technique (local injection site, dorsal nerve block, etc.)
  - Corporal body aspiration +/− irrigation with dilute adrenergic agent
    - Phenylephrine 100–500 mcg/mL (1 mL/1 mg) in 9 mL of injectable normal saline
    - A 27–29G needle is used to inject about 0.5 mL directly into the corpora every 3–5 min until a response. Can be repeated to a max of 1.5 mg phenylephrine has been administered or a total of 1 hr (if no response after 1 hr should be considered initial treatment failure)
    - Use lower volumes in children or with significant cardio vascular disease
    - Corporal compression helps facilitate the process
  - This technique has best results for priapism <24 hr in duration:
    - Aspirate with a large needle (16–18G) connected to a 50-mL syringe and a 3-way stopcock. Insert the needle perpendicular into the skin into the lateral aspect of the corpora and aspirate 20–30 mL at a time (the glans is a less desirable site). Continue until the dark ischemic blood turns bright red
    - If not successful, aspirate and irrigate the corpora with dilute solution of phenylephrine (10 mg in 500 mL saline) using 10–20 mL each time
    - When aspirations and irrigations are completed, apply pressure for 5–10 min to limit hematoma and refilling of corpora
- Ischemic priapism in sickle cell disease:

  - Opioid, analgesics, aggressive hydration, and supplemental oxygen if <4 hr duration
  - Standard treatment if >4 hr, as for ischemic priapism above
  - Terbutaline or other oral agents not recommended per AUA guidelines
- Nonischemic priapism
  - No role for pharmacologic therapy
- Stuttering priapism
  - Treat as for ischemic priapism
  - LHRH agonists/antiandrogens may be considered (but not for children/adolescents)
  - Intracavernous self-injection who fail or reject systemic treatment

Second Line

Injection of epinephrine (1 mg in 1,000 mL saline) has been used in place of phenylephrine; however, phenylephrine is more of a pure α-agonist with a lower systemic side-effect profile

SURGERY/OTHER PROCEDURES

- Surgical intervention is considered 2nd line after corporal injection/aspiration attempts fail
- Ischemic priapism
  - If aspiration/irrigation fails, cavernosal glanular shunting is recommended; creating a fistula between the corpora cavernosa and the glans. Unilateral usually sufficient; if not successful perform bilateral procedure
  - Distal cavernosal glanular shunt is 1st line
    - Winter shunt: 16G core biopsy needle passed from glans into 1 or both of the corporal bodies. Biopsy needle removes tissue core
    - Ebbehoj shunt using a pointed scalpel blade
    - Al-Ghorab shunt is an open excision of tunical tip and usually next if Winter shunt fails
    - T-shunt #11 scalpel blade inserted dorsolaterally to the meatus on both sides, and rotated (blade-edge) 90 degrees laterally
  - Consider proximal shunting if distal shunting fails (cavernosal–spongiosal shunt [Quackles])
- Nonischemic priapism
  - No role for shunting in nonischemic priapism
  - Conservative measures are appropriate in the short term as nonischemic cases of priapism do not lead to underlying cavernosal tissue damage
  - Duplex Doppler Ultrasonography with color flow to localize potential abnormal vascular accumulation (arteriovenous fistula, see image)
  - Internal pudendal arteriography with selective embolization (clot or gel foam)
  - Surgical exploration of the cavernosal body and ligation in cases refractory to embolization

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Immediate placement of penile prosthesis if priapism is of significantly prolonged duration and ED is highly likely is advocated by some

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Based on duration/severity of ischemia. Priapism associated with sickle cell disease may resolve in 35% of patients treated systemically.
- Risk of permanent erectile dysfunction increases substantially after 24 hr of ischemic priapism (92% potency preserved with <1 day of priapism vs. 69% or less if more prolonged) (2).
- Monitoring of ischemic priapism may be clinical (complete flaccidity of the penis) or radiologic (color duplex Doppler ultrasonography showing persistent flow in cavernosal artery)

COMPLICATIONS
- Erectile dysfunction, particularly with cases of prolonged ischemic priapism
- Cavernosal urethral fistula (after cavernosal spongiosal shunt)
- Cavernositis and corporal fibrosis
- Penile deformity

FOLLOW-UP
Patient Monitoring
- Patient should be monitored for development of erectile dysfunction
- Patient should undergo appropriate testing to complete workup for any hematologic abnormalities or other potential underlying causes

Patient Resources
AUA Foundation. www.auanet.org/education/guidelines/priapism.cfm

REFERENCES

1. AUA Guidelines on the Management of Priapism – www.auanet.org/education/guidelines/priapism.cfm
2. Kulmala RV, Lehtonen TA, Tammela TL, et al. Preservation of potency after treatment after priapism. *Scand J Urol Nephrol.* 1996;30:313–316.
3. Salonia A, Eardley I2, Giuliano F3, et al. European Association of Urology guidelines on priapism. *Eur Urol.* 2014;65(2):480–489.

ADDITIONAL READING
N/A

See Also (Topic, Algorithm, Media)
- Priapism Algorithm
- Sickle Cell Disease, Urologic Considerations

CODES

ICD9
607.3 Priapism

ICD10
- N48.30 Priapism, unspecified
- N48.33 Priapism, drug-induced
- N48.39 Other priapism

CLINICAL/SURGICAL PEARLS
- The hallmark of a priapism: Corpora are involved but the glans is flaccid and soft.
- Penile blood gas allows appropriate diagnosis.
- Ischemic priapism is an emergency and intervention should start within 4–6 hr, including decompression of the corpora cavernosa by aspiration and intracavernous injection of sympathomimetic drugs (eg, phenylephrine).
- Nonischemic priapism can be managed in a semielective manner once diagnosis confirmed.

PROSTATE BIOPSY, INFECTIONS AND COMPLICATIONS

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BASICS

DESCRIPTION

- The current standard for the diagnosis of prostate cancer is transrectal ultrasound (TRUS) guided biopsy of the prostate
- A 12-core biopsy scheme is optimal for 1st time prostate biopsy strategy using local anesthesia
- Active surveillance programs incorporate serial prostate biopsy and may result in a potential for increased risk for biopsy-related complications
- Bleeding is the most common complication observed after prostate biopsy. However, the use of aspirin or nonsteroidal anti-inflammatory drugs is not an absolute contraindication to prostate biopsy

EPIDEMIOLOGY

Incidence

- Prostate biopsy is integral to the workup of elevated prostate-specific antigen (PSA) as well as abnormal prostate exams
- An estimated 800,000–1 million prostate biopsies are performed each year in the United States
- In 1 recent series of repeat biopsies in men on active surveillance 3.5% experienced infectious complications with most requiring hospitalization (1)
- The Rotterdam center of the ERSPC trial noted (0.5%) men required hospitalization for signs of prostatitis or urosepsis (2)

Prevalence

Due to a variety of factors including an aging population widespread use of PSA testing, the number of TRUS and prostate biopsies has increased significantly over the last decade

RISK FACTORS

- For the diagnosis of prostate cancer:
  - 1st-degree relatives with prostate cancer
  - Older age
  - African American race
  - Family history of breast cancer
- For infectious complications the following have been suggested as risk factors:
  - Number of previous prostate biopsies was significantly associated with an increased risk of infectious complications
  - Long-term fluoroquinolone use (3)
  - Healthcare workers

Genetics

- HPC-1 gene on chromosome 1 associated with familial CaP
- Many polymorphisms in genes, such as ELAC2 (locus HPC2), RNase L (locus hereditary prostate cancer 1 gene [HPC1]), and MSR1 may confer an increased risk of developing prostate cancer in many populations (4)

PATHOPHYSIOLOGY
- Normal adult prostate is approximately 20 g
- The majority of prostate cancer is adenocarcinoma and located in the peripheral zone of the prostate
- In the absence of antibiotic prophylaxis, bacteremia and bacteruria occur in 16% and 44% respectively of transrectal ultrasound-guided prostate biopsy

ASSOCIATED CONDITIONS
Benign prostate hypertrophy

GENERAL PREVENTION
- Consider urine culture before prostate biopsy if there is any concern over subclinical UTI
- Preprocedure enema does not appear to have any impact on complication rates
- Rectal swab with culture and sensitivity has been suggested as a method to identify potentially resistant pathogens and is not considered standard of care
- Transperineal biopsy may have a lower rate of infection than the transrectal approach
- Continuing or cessation of antiplatelet or anticoagulant medications prior to biopsy is based upon risk/benefit for each patient. Consider discussion with the patient's cardiologist or primary care physician as needed

DIAGNOSIS
HISTORY
- Prostate cancer most commonly presents without any symptoms
- Family history of prostate cancer
- Specific review of any recent urinary tract infections, catheterization, or acute prostatitis
- Further review of the patient's medication list, with special attention to anticoagulation or antiplatelet medication (ie, aspirin)
- Determine any symptoms of urinary tract infection
- History of anorectal surgery

PHYSICAL EXAM
- Digital rectal exam may reveal nodularity, induration, or an asymmetric gland
- Other anorectal pathology (anal stenosis, significant hemorrhoids) may be detected that might impact on the prostate biopsy procedure

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- PSA
- Screening UA with culture if indicated

Imaging
- TRUS provides images of the prostate
  – Nodules may be hypoechoic on ultrasound

Diagnostic Procedures/Surgery

- A rectal probe should be gently placed with the patient in a lateral decubitus position (5)
- A periprostatic nerve block injecting approximately 5 cc of local anesthetic via a spinal needle can decrease discomfort and pain
- Full visualization of the prostate in transverse and sagittal views should be performed for an overview of the prostate and any abnormalities identified
- The prostate volume should be calculated
- Using a spring-loaded biopsy needle, a minimum of 12 cores, and additional biopsies as needed to obtain representative samples
- The peripheral zone in the posterolateral aspect of the prostate account for the majority of prostate cancers
- Additional biopsy of palpable nodule or hypoechoic areas may be performed at the discretion of provider

Pathologic Findings

- Prostate adenocarcinoma
- Prostatic intraepithelial neoplasia (PIN)
- Atypical small acinar proliferation (ASAP)
- Benign prostate tissue

DIFFERENTIAL DIAGNOSIS

- ASAP
- Benign prostatic hypertrophy
- No evidence of malignancy
- PIN

TREATMENT

GENERAL MEASURES

Although many clinicians have patients perform a self-administered enema, this is not needed. There is little evidence to support their use.

MEDICATION

First Line

- At our institution (Cleveland Clinic), patients receive an oral single dose of fluoroquinolone as well as a single dose of intramuscular aminoglycoside (80 mg gentamicin)
- AUA guidelines (see “Complications” below)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- For patients with anorectal malformations or previous colorectal operations preventing TRUS, a transperineal biopsy can be performed.
- The increasing incidence of antimicrobial resistance with increasing concerns of the risk of sepsis is favoring renewed interest in transperineal biopsy as a relatively sterile alternative to standard TRUS-guided biopsy.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- A retrospective analysis from Israel suggests that a single injection of 240 mg gentamicin along with a quinolone for 3 days significantly reduces infectious complications (6)
- Another case series demonstrated that 500 mg intravenous amikacin 30 min before the biopsy along with several days of ciprofloxacin reduced the incidence of urosepsis/septicemia following prostate biopsy (7)

Complementary & Alternative Therapies

Topical rectal cleansing with povidone-iodine resulted in a 42% reduction in infectious complications in 1 prospective clinical trial but was not statistically significant

ONGOING CARE

PROGNOSIS

Although prostate biopsy is usually generally safe and well tolerated, it is an invasive procedure that is not without risk and required a clear understanding through informed consent of the patient.

COMPLICATIONS

- Bleeding is the most common complication and includes hematuria, hematospermia, and rectal bleeding
  - Bleeding is usually minor, self-limiting, and resolves with conservative measures. More significant bleeding has been reported and may require transfusion or colorectal intervention
- The 2nd most common complication is infection
  - The incidence of infectious complications, including sepsis, is increasing
  - Compared to controls, men undergoing biopsy have a significant risk for serious infection as requiring hospitalization (approximately 2.26 risk increase and 2.65 risk increase, respectively)
  - Updated AUA Best Practice Policy Panel (8): Antibiotic prophylaxis should be given for all prostate biopsy procedures, duration of therapy is <24 hr. Recommended 1/1/2014 drug of choice regimens and are:
    - Fluoroquinolones or
    - 1st/2nd/3rd-generation cephalosporin
    - Alternative regiments: Trimethoprim Sulfamethoxazole (TMP-SMX) or Aminoglycoside (Aztreonam can be substituted for aminoglycosides in patients with renal insufficiency)
    - Familiarity with local resistance patterns including fluoroquinolone-resistant bacteria is important

FOLLOW-UP

Patient Monitoring

- Prompt medical evaluation for patient with signs and symptoms of infection or significant bleeding

- Counseling regarding transient hematuria and the potential for hematospermia that may last for several weeks
- Follow-up of prostate biopsy results

Patient Resources

http://men.webmd.com/prostate-biopsy

REFERENCES

1. Ehdaie B, Vertosick E2, Spaliviero M3, et al. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. *J Urol*. 2014;191(3):660–664.
2. Raaijmakers R, Kirkels WJ, Roobol MJ, et al. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology*. 2002;60:826–830.
3. Akduman B, Akduman D, Tokgöz H, et al. Long-term fluoroquinolone use before the prostate biopsy may increase the risk of sepsis caused by resistant microorganisms. *Urology*. 2011;78(2):250–255.
4. Alvarez-Cubero MJ, Saiz M, Martinez-Gonzalez LJ, et al. Genetic analysis of the principal genes related to prostate cancer: A review. *Urol Oncol*. 2013;31(8):1419–1429.
5. Patel AR, Jones JS. Optimal biopsy strategies for the diagnosis and staging of prostate cancer. *Curr Opin Urol*. 2009;19:232–237. (1)[B]
6. Lorber G, Benenson S, Rosenberg S, et al. A single dose of 240 mg gentamicin during transrectal prostate biopsy significantly reduces septic complications. *Urology*. 2013;82(5):998–1002.
7. Kehinde EO, Al-Maghrebi M, Sheikh M, et al. Combined ciprofloxacin and amikacin prophylaxis in the prevention of septicemia after transrectal ultrasound guided biopsy of the prostate. *J Urol*. 2013;189(3):911–915.
8. American Urological Association. Best practice policy statement on urologic surgery antimicrobial prophylaxis. 2008(updated January 1, 2014). [A]

ADDITIONAL READING

- Chang DT, Challacombe B, Lawrentschuk N, et al. Transperineal biopsy of the prostate-is this the future? *Nat Rev Urol*. 2013;10(12):690–702.
- Ismail MT, Gomella LG. Transrectal prostate biopsy. *Urol Clin North Am*. 2013;40(4):457–472.
- Loeb S. Antimicrobial prophylaxis for transrectal ultrasound biopsy. *AUA Update Series*. 2013;32, lesson 1. [A]
- Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. *Eur Urol*. 2013;64(6):876–892.
- Raman JD. Infectious complications following prostate biopsy: A problem with need for solution. *Can J Urol*. 2013;20(3):6815.
- Satyanarayana R, Parekh D. Prevention and treatment of biopsy-related complications. *Curr Urol Rep*. 2014;15(2):381.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General

- PSA Elevation
- Urosepsis

CODES

ICD9

- 602.9 Unspecified disorder of prostate
- 998.59 Other postoperative infection
- 998.9 Unspecified complication of procedure, not elsewhere classified

ICD10

- N42.9 Disorder of prostate, unspecified
- T81.4XXA Infection following a procedure, initial encounter
- T81.9XXA Unspecified complication of procedure, initial encounter

CLINICAL/SURGICAL PEARLS

- A minimum of 12 cores is considered standard of care in the United States.
- Additional biopsy of nodules and hypoechoic areas may be needed.
- Be familiar with local resistance patterns when selecting antibiotic prophylaxis.
- In men with prostate cancer on active surveillance the number of previous prostate biopsies may be associated with a significant risk of infectious complications and every previous biopsy increases the risk of infectious complication.

PROSTATE CANCER, BIOCHEMICAL RECURRENCE (ELEVATED PSA) FOLLOWING CRYOTHERAPY

Michael C. Large, MD

BASICS

DESCRIPTION

- Primary cryotherapy is an option for patients with clinically localized prostate cancer of low-, intermediate- or high-grade (1)[B]
- Especially suited for comorbid patients who cannot tolerate alternative therapy (extensive previous surgery, inflammatory bowel disease) (1)[B]

EPIDEMIOLOGY

Incidence

- Nearly 7,000 cryoablations for prostate cancer were performed in US in 2005 (2)[C]
  - Usage projected to increase

RISK FACTORS

- For recurrence after primary cryotherapy:
  - Larger glands make uniform freezing more difficult
  - PSA >10 ng/mL
- For complications after primary cryotherapy:
  - Prior TURP increases risk of urethral necrosis

PATHOPHYSIOLOGY

- Tissue destruction from cryotherapy multifactorial
  - Induces apoptosis
  - Intracellular ice formation and local hypoxia cause necrosis
  - Maximum cell death with: Nadir temperature $< -20^{\circ}C$, rapid freezing rate, slow thawing rate, multiple freeze/thaw cycles
  - Urethral warming catheter protects urothelium but increases potential for preserving PSA-producing tissue

DIAGNOSIS

HISTORY

- History of prostate cancer treated by primary cryotherapy
  - Recommend ≥3 mo elapse from primary treatment before testing for recurrence

PHYSICAL EXAM

- Digital rectal exam
  - Findings may be difficult to interpret given previous therapy

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA spikes initially from necrosis of the prostate tissue

- Following cryotherapy PSA rechecked every 3 mo × 1 yr, then every 6 mo thereafter
- PSA may not decrease to undetectable
- PSA-based definition for biochemical recurrence is not standardized. Various parameters used:
  - PSA >0.4 ng/mL, >0.5 ng/mL, >1.0 ng/mL,
  - 3 consecutive increases ("ASTRO" definition)
  - Nadir + 2 ng/mL ("Phoenix" definition)

Imaging

- Complete metastatic workup may include:
  - CXR
  - CT abdomen/pelvis
  - Bone scan
  - Endorectal MRI

Diagnostic Procedures/Surgery

- Transrectal biopsy
  - Commonly performed post-cryotherapy
  - Recommend waiting 6 mo for inflammation to resolve
  - Negative biopsy reported in 75–95% (1)[B],(2)[C]
  - Lower PSA nadir and lower clinical stage predict negative re-biopsy

DIFFERENTIAL DIAGNOSIS

- Necrosis, especially if within 3 mo of procedure
- Residual benign prostatic tissue
- Treatment failure
- Recurrent disease (local or metastatic)

TREATMENT

GENERAL MEASURES

Confirmation of recurrence via transrectal biopsy

MEDICATION

First Line

- No first-line medication therapy
  - Consider androgen-deprivation therapy or clinical trial if metastatic disease
  - No significant data on the use of androgen-deprivation after local cryotherapy failure

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Salvage prostatectomy feasible but large series are lacking
- Reported techniques include:
  - Open retropubic or perineal
  - Laparoscopic or robotically assisted
- Salvage cystoprostatectomy with urinary diversion

- Option for extensive local recurrence with severe, treatment-refractory lower urinary tract symptoms

ADDITIONAL TREATMENT

Radiation Therapy

- Conformal or Intensity-modulated radiotherapy
  - Largest series 49 patients, received conformal RT (3)[C]
  - Mean preradiation PSA 2.4 ng/mL
  - Mean RT dose 62.9 Gy
  - At median follow-up 32 mo, biochemical-free survival rate 61%

Additional Therapies

- Repeat cryotherapy
  - Largest series 32 patients (4)[C]
  - Median follow-up 63 mo
    - 22, 23, and 29 were biochemical disease free by definitions of 0.5 ng/mL, 1.0 ng/mL, and ASTRO definition

Complementary & Alternative Therapies

None widely studied

ONGOING CARE

PROGNOSIS

- Biochemical recurrence-free survival after primary cryotherapy (Phoenix definition)
  - 5-yr estimates based on D'Amico risk category: (1)[B],(2)[C]
    - Low risk: 85–90%
    - Intermediate risk: 80%
    - High risk: 60–70%
  - 10-yr estimates based on D'Amico risk category:
    - Low risk: 80%
    - Intermediate risk: 75%
    - High risk: 45%

COMPLICATIONS

- No large series following postcryotherapy salvage treatment
- Surgery:
  - Intraoperative rectal injury
    - Small injury: 2-layer primary repair and omental interposition
    - Large injury, gross spillage, poor tissue viability: Primary repair and diverting colostomy
  - Urinary incontinence, impotency
- Radiation
  - Rectourethral fistula, urethral stricture, urinary incontinence, impotency, and bladder and rectal toxicities
- Repeat cryotherapy
  - Rectourethral fistula, urethro-cutaneous fistula, urethral stricture, urinary incontinence, impotency, and bladder and rectal toxicities

FOLLOW-UP

Patient Monitoring

- No standards exist for postcryotherapy recurrence follow-up
- If biochemical disease untreated, may treat patient according to algorithms for (1) localized or (2) advanced prostate cancer outlined in prior chapters
- If patient has undergone salvage treatment after cryotherapy, no standards exist
  - PSA often performed every 3 mo after salvage therapy
  - Re-biopsy may be offered 6 mo after treatment, or if clinically indicated

Patient Resources

American Cancer Society
http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-cryosurgery

REFERENCES

1. Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. *J Urol*. 2008;180:1993–2004.
2. Finley DS, Pouliot F, Miller DC, et al. Primary and salvage cryotherapy for prostate cancer. *Urol Clin North Am*. 2010;37:67–82.
3. Burton S, Brown DM, Colonias A, et al. Salvage radiotherapy for prostate cancer recurrence after cryosurgical ablation. *Urology*. 2000;56:833–838.
4. Bahn DK, Lee F, Badalament R, et al. Targeted cryoablation of the prostate: 7-yr outcomes in the primary treatment of prostate cancer. *Urology*. 2002;60(2A):3–11.

ADDITIONAL READING

AUA best practice policy statement on cryosurgery for the treatment of localized prostate cancer: http://www.auanet.org/content/media/cryosurgery08.pdf (Accessed July 22, 2014)

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Biochemical Recurrence (elevated PSA) Following Radiation Therapy
- Prostate Cancer, Biochemical Recurrence (elevated PSA) Following Radical Prostatectomy
- Prostate Cancer, General
- PSA Elevation, General Considerations
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 790.93 Elevated prostate specific antigen [PSA]
- V10.46 Personal history of malignant neoplasm of prostate

ICD10

- C61 Malignant neoplasm of prostate
- R97.2 Elevated prostate specific antigen [PSA]
- Z85.46 Personal history of malignant neoplasm of prostate

CLINICAL/SURGICAL PEARLS

- An early rise in PSA after cryotherapy is normal, and further testing should be deferred until at least 3 mo following treatment.
- Various definitions of PSA failure after cryotherapy exist: >0.4 ng/mL, >0.5 ng/mL, >1.0 ng/mL, 3 consecutive rises, and nadir $+$ 2 ng/mL.
- Prostate biopsy is useful in the workup of postcryotherapy biochemical recurrence.
- Postcryotherapy treatment of recurrent disease should be reserved for highly experienced surgeons and radiation oncologists.

PROSTATE CANCER, BIOCHEMICAL RECURRENCE (ELEVATED PSA) FOLLOWING RADIATION THERAPY

Robert B. Den, MD
Mark Hurwitz, MD

BASICS

DESCRIPTION

- Rising PSA after treatment, referred to as biochemical recurrence, is nearly always the first indication of recurrent prostate cancer. The site of recurrence—local, regional, distant, or a combination of sites, however, cannot be discerned by PSA level alone
- Definitions of biochemical recurrence following radiation:
  – ASTRO definition: 3 consecutive rises in PSA (backdating)
  – Phoenix definition: PSA nadir + 2 ng/mL

EPIDEMIOLOGY

Incidence

- Most men with clinically localized disease will not experience recurrence. However, given the widespread use of radiation therapy for treatment of prostate cancer, biochemical recurrence is not an uncommon problem in routine clinical practice.
- 5-yr rates of biochemical recurrence ~5–40% depending on risk stratification criteria

Prevalence

The time from biochemical recurrence to clinical recurrence is typically measured in years. Therefore prevalence is relatively high as compared to incidence.

RISK FACTORS

- Risk of recurrence is associated with original risk stratification including clinical stage, PSA, and Gleason score.
- A rise in PSA of >2 points in the year preceding diagnosis is associated with increased risk for both recurrence and prostate cancer–specific mortality
- Gleason score 4 + 3 = 7 vs. 3 + 4 = 7 and/or ≥50% positive biopsies in intermediate-risk patients
- Lower doses of radiation
- Lack of use of androgen deprivation therapy in high-risk patients

Genetics

New tests linking tumor-specific genetic profiles to adverse risk in prostate cancer including risk of recurrence after prostatectomy have recently become clinically available. Their ultimate clinical value remains to be fully defined. In regard to biochemical recurrence following radiation therapy, the utility of such tests to guide further therapy is not yet known.

PATHOPHYSIOLOGY

- >95% of prostate cancers are adenocarcinoma
- Rare variants such as TCC, small cell carcinoma, and sarcomas are not associated with

elevation of PSA

ASSOCIATED CONDITIONS

Symptoms of urinary outlet obstruction can occur but are uncommon during the initial period of biochemical recurrence.

GENERAL PREVENTION

- Optimized radiation therapy including dose escalation with daily image guidance to ensure proper targeting with external beam radiation and use of proper brachytherapy techniques
- Use of androgen deprivation in combination with radiation for high risk and selected intermediate risk patients

DIAGNOSIS

HISTORY

- Prior radiation treatment information should be obtained including type of radiation, technique, and dose prescribed. For prostate brachytherapy postimplant dosimetry analysis should be reviewed to determine if there were underdosed regions.
- Thorough assessment of general health with emphasis on urinary and bowel function is important in guiding the advisability of potential salvage therapies.

PHYSICAL EXAM

General physical exam including rectal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA.
  - In addition to total PSA, PSA kinetics may be helpful in identifying patients at greater risk of development of distant vs. local recurrence.
  - Patients with short time to PSA nadir after treatment and short doubling times (PSADT) are at greater risk of subsequent diagnosis of metastatic disease (PSDAT < 3–6 mo)
- Testosterone establishes baseline for future hormonal intervention
- Basic metabolic panel
- CBC

Imaging

- Bone scan
- CT of abdomen and pelvis
- Pelvic/prostatic MR. Magnetic resonance spectroscopic imaging may improve results over MR alone
- New techniques for PET/CT including use of ^{18}F-NaF may be useful in select cases
- Other imaging as clinically indicated

Diagnostic Procedures/Surgery

- Prostate biopsy should be considered if more than 2 yr have elapsed since completion of radiation therapy and additional local therapy is being contemplated.
  - As the full effects of radiation are not manifested for 24–30 mo, biopsy before this time is not indicated.

- Approximately 20% of patients who have postradiation biopsies will have no clinical evidence of disease with additional long-term follow-up. Conversely, given the limitations of sampling, local recurrence may be present despite negative biopsy.
- Biopsy to assess findings concerning for distant metastases as clinically indicated.

Pathologic Findings

- Discerning posttreatment change from residual disease in irradiated prostate tissue can be difficult.
  - Immunohistochemical analysis with basal cell-specific keratin monoclonal antibodies can aid in differentiating benign and malignant glands since only benign glands display basal cell immunoreactivity.

DIFFERENTIAL DIAGNOSIS

- PSA bounce phenomenon
  - 35% incidence after brachytherapy
  - Less common with external beam radiation
- Testosterone rebound after completion of androgen deprivation with associated rise in PSA

TREATMENT

GENERAL MEASURES

- Efforts should be made to discern if biochemical recurrence is due to presence of local vs. distant disease or a combination of both.
- In the presence of metastatic disease androgen ablation is the standard choice.
- In cases of only localized disease there are many more options including observation, androgen ablation or salvage therapies including radical prostatectomy or cryotherapy.
  - In general candidates for local salvage therapy should have original clinical stage tumor T-1, T2 NX/N), life expectancy of >10 yr, and a PSA <10 ng/mL (1)
  - Patient who are not ideal candidates for salvage therapy should be treated by androgen deprivation or observation

MEDICATION

First Line

- Hormonal therapy (androgen deprivation):
  - LHRH agonists: Leuprolide, goserelin, triptorelin
    - Suppress LH and FSH release by the pituitary
  - LHRH antagonists: Degarelix (only 1 FDA approved in US;
    - Suppress LH and FSH release by the pituitary
  - Antiandrogens: Flutamide, bicalutamide, nilutamide, directly block the activity of androgens on the androgen receptor
  - LHRH agonists can be used alone or in combination with oral antiandrogens
  - When LHRH agonist therapy is initiated, a release of testosterone is induced (androgen flare) that may exacerbate symptoms from metastatic lesions. In particular, patients with spinal metastasis may be in jeopardy of cord compression
    - Flare avoided by initiating antiandrogen therapy 2 wk prior to 1st LHRH agonist injection

– Orchiectomy remains an infrequently utilized option for androgen ablation

Second Line

Alternate androgen deprivation therapy or clinical trial

SURGERY/OTHER PROCEDURES

- Radical prostatectomy is rarely performed following prostate radiation due to high rates of morbidity (2)
  – However, surgery can be considered in carefully selected cases for relatively young healthy patients with established local recurrence
  – 5- and 10-yr rates of freedom from biochemical recurrence with salvage radical prostatectomy range up to 59% and 37% respectively with disease-specific survival as high as 83% at 10 yr
  – Common toxicities include bladder neck contracture (17–47%), rectal fistula (7–20%), and erectile dysfunction in nearly all patients

ADDITIONAL TREATMENT

Radiation Therapy

- Administration of additional radiation therapy in most instances should be limited to research protocols.
  – The most commonly investigated approach is salvage brachytherapy following external beam radiation failures.
  – 5-yr freedom from biochemical recurrence has been reported between 25–75% and disease-specific survival between 74–100%. Wide variation in reported outcomes is likely due to variation in risk criteria across studies.
  – Crude rates of grade ≥3 GU and GI complications average 13% and 5%, respectively. Rates may be higher in elderly patients.

Additional Therapies

- Thermal ablative therapies including cryoablation and high-intensity focused ultrasound remain investigational.
- Cryotherapy in particular has shown promise in selected series.
  – 5–10-yr freedom from biochemical recurrence with cryotherapy ranges between 34–59%.
  – Rates of ≥3 GU and GI complications average approximately 10% and 3% across reported series.
- Focal ablative therapies that attempt to identify the site of recurrence and ablate the site are investigational (3).

Complementary & Alternative Therapies

Low-fat diets and diets high in polyphenols as found in broccoli, turmeric, pomegranate, and green tea may be beneficial

ONGOING CARE

PROGNOSIS

PSA doubling time of less than approximately 6 mo and in particular 3 mo has been linked to increased risk of prostate cancer–specific mortality

COMPLICATIONS

- Urinary outlet obstructive symptoms
- Proctalgia due to rectal invasion is typically seen only with advanced stages of recurrence

FOLLOW-UP

Patient Monitoring

- Dependent in part on subsequent treatment
- Every 3–6 mo including general and prostate exam and PSA

Patient Resources

American Cancer Society.
http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-recurrence

REFERENCES

1. NCCN Practice Guidelines Version 1. 2014 http://www.nccn.org/. Accessed January 6, 2014
2. Punnen S, Cooperberg MR, D'Amico AV, et al. Management of biochemical recurrence after primary treatment of prostate cancer: A systemic review of the literature. *Eur Urol*. 2013;64(6):905–915.
3. Valerio M, Ahmed HU2, Emberton M2, et al. The role of focal therapy in the management of localised prostate cancer: A systematic review. *Eur Urol*. 2013. pii: S0302–2838(13)00557–5. doi: 10.1016/j.eururo.2013.05.048.

ADDITIONAL READING

Kanthabalan A, Arya M, Punwani S, et al. Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer. *World J Urol*. 2013;31(6):1361–1368.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Cryotherapy
- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Radical Prostatectomy
- Prostate Cancer, Metastatic (Clinical and Pathologic N+, M+)
- PSA Elevation, General Considerations
- PSA, Bounce
- PSA, General Considerations
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 790.93 Elevated prostate specific antigen [PSA]
- V15.3 Personal history of irradiation, presenting hazards to health

ICD10

- C61 Malignant neoplasm of prostate
- R97.2 Elevated prostate specific antigen [PSA]

- Z92.3 Personal history of irradiation

CLINICAL/SURGICAL PEARLS

- Risk stratification, morbidities associated with the primary course of radiation, and PSA kinetics posttreatment are important to consider in selecting the best management option.
- Participation in clinical trials should be encouraged in areas such as this where no consensus exists.

PROSTATE CANCER, BIOCHEMICAL RECURRENCE (ELEVATED PSA) FOLLOWING RADICAL PROSTATECTOMY

Gurdarshan S. Sandhu, MD
Gerald L. Andriole, MD, FACS

BASICS

DESCRIPTION

- Biochemical recurrence following radical prostatectomy is a clinical state characterized by a detectable and increasing serum prostate specific antigen (PSA) after radical prostatectomy in the absence of detectable disease based on current imaging modalities
- Men with a biochemical recurrence fall into 3 groups
  - Those with a PSA that fails to fall to undetectable after surgery (persistent disease)
  - Those with an initially undetectable PSA after surgery that subsequently increases on 2 or more tests (recurrent disease)
  - Those with stable but low PSA levels (rare)
    - Attributed generally to residual benign disease
- Generally defined as detectable or rising PSA value after surgery that is ≥ 0.2 ng/mL with a 2nd confirmatory level ≥ 0.2 ng/mL

EPIDEMIOLOGY

Incidence

Up to 30% of men will develop a biochemical recurrence after radical prostatectomy in large, institutional, long-term follow-up series (1)

Prevalence

Based on the estimated probability of relapse after surgery OR radiation therapy, more than 50,000 American men have biochemical recurrence without other detectable disease (2)

RISK FACTORS

- Biochemical recurrence is predicted by several factors:
  - Advanced pathologic tumor stage (3)
    - Adverse features include positive surgical margins, non-organ confined disease, seminal vesicle invasion, and lymph node metastases
  - High Gleason score
  - High preoperative PSA
- In addition to the risk factors above, risk factors for the development of clinical metastases and prostate cancer related mortality include:
  - Time to biochemical recurrence
  - PSA doubling time (PSADT) after recurrence

Genetics

See “Prostate cancer, general considerations”

PATHOPHYSIOLOGY

- In a patient with biochemical recurrence, it is important to try to distinguish local from systemic
  - In general, low preoperative PSA, lower Gleason grade, lower tumor stage, prolonged time from surgery to biochemical recurrence and long PSADT are more suggestive of local recurrence
  - Conversely, higher stage, higher Gleason score, shorter (< 2 yr) time to biochemical recurrence and shorter (< 3–6 mo) doubling time suggest distant disease

ASSOCIATED CONDITIONS

- Biochemical recurrence of PSA after surgery when the PSA after surgery was initially undetectable generally precedes metastatic progression and prostate cancer specific mortality by a median of 8 and 13 yr, respectively (4)
  - Importantly, not **all** men with biochemical recurrence will develop metastases or die of prostate cancer (1)
  - PSADT after recurrence is an important factor in assessing the risk of subsequent metastases and prostate cancer mortality

GENERAL PREVENTION

Although proper surgical technique can limit the risk of PSA recurrence it cannot be guaranteed to do so due to varying tumor biology

DIAGNOSIS

HISTORY

- Preoperative PSA
- Time since surgery
- Pathologic information from the radical prostatectomy
- Postoperative continence and erectile function
  - Timing of adjuvant/salvage therapy after surgery may be affected by the patient's functional recovery

PHYSICAL EXAM

Digital rectal exam to palpate for local recurrence in the prostate bed

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serial surveillance of PSA after biochemical recurrence is necessary to monitor disease progression and response to additional treatment if offered
  - PSADT assessment (can be calculated using widely available online calculators)
  - PSA level can vary depending on the lab assay used so use of the same laboratory recommended for serial follow-up
- Baseline testosterone to guide future therapy

Imaging

- Imaging evaluation is necessary to determine if distant metastases are present under some circumstances (eg, short time to recurrence, short PSADT, rapid rise in PSA)
  - Computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen/pelvis
    - Identify local recurrence or lymphadenopathy

- Multiparametric MRI has an emerging role in this setting and appears to be more sensitive than CT in detecting local recurrence
- Bone scintigraphy to evaluate for bony metastases
  - Unlikely to be positive unless the PSA is generally >20 ng/mL
- ProstaScint is approved by the US Food and Drug Administration (FDA) to detect occult metastatic disease in patients with early prostate cancer
  - Is associated with a significant number of false positive and false-negative results
- Positron emission tomography/computed tomography (PET-CT), with choline
  - Approved by the FDA in September 2012
  - Falsely positive PET scans can be observed in 15–47% so confirmatory tissue sampling of abnormalities detected with PET-CT is required

Diagnostic Procedures/Surgery

Transrectal ultrasound guided biopsy of the prostate bed may be helpful only if imaging or digital rectal exam suggest local recurrence

ALERT

"Blind biopsies" of the prostate bed in the absence of evidence to suggest locally recurrent disease have a low yield, often do not affect decision making, poorly predict the efficacy of salvage radiation and should not be a standard of care.

Pathologic Findings

Dictated by pathology from the radical prostatectomy. Often positive surgical margins or seminal vesicle invasion is noted

DIFFERENTIAL DIAGNOSIS

- PSA elevation due to residual benign epithelium after prostatectomy
- Local recurrence of adenocarcinoma
- Systemic recurrence of adenocarcinoma
- Local and systemic recurrence of adenocarcinoma

TREATMENT

GENERAL MEASURES

- Close monitoring of the serum PSA postoperatively. NCCN Guidelines recommend PSA every 3 mo if high risk or 6–12 mo up to 5 yr, then annually thereafter; annual DRE
- Follow up treatment decision primarily based on pathology, imaging, and PSA dynamics
- Can include observation, androgen ablation, or pelvic radiation
- Careful observation can be considered with slow PSADT, in older patients with other comorbidities

MEDICATION

First Line

- Androgen deprivation therapy (ADT)
  - ADT drug classes include Gonadotropin-Releasing Hormone(GnRH) agonists (eg, goserelin, histrelin, leuprolide, and triptorelin) and antagonists (Degarelix)
  - Depot injections of the GnRH agonists allow dosing to extend from 28 days up to 1 yr

- GnRH antagonist dosing is every 28 days
- See “Prostate Cancer, metastatic” for more information on drug classes

• No data are available on the optimal PSA value at which to initiate treatment
- ADT is potentially detrimental to cognitive function, quality of life, sexual health, cardiovascular risk, and bone integrity
- Timing of initiation of ADT should be based on a patient’s risk of metastatic progression and risk of death from disease as opposed to absolute PSA levels
- When ADT is initiated, in the absence of metastases, intermittent ADT is preferred to continuous ADT given the side effects of this treatment and the non-inferior overall survival of intermittent ADT (6)
- With the benefits that have been observed with adjuvant/salvage radiation, the role of ADT as monotherapy may be somewhat limited

Second Line

See “Prostate Cancer, metastatic” and “Prostate Cancer, rising PSA following androgen ablation” for more information on additional drug classes

SURGERY/OTHER PROCEDURES

• Scrotal orchiectomy
- Can be used instead of ADT
  - Is more cost effective than ADT
  - Does not allow for intermittent androgen deprivation
- Quickly achieves castrate levels of testosterone (< 50 ng/mL) within 24 hr
- Subcapsular scrotal orchiectomy can also be offered in lieu of ADT
  - May help avoid the psychological consequences of an empty scrotum

ADDITIONAL TREATMENT

Radiation Therapy

• Patients with demonstrable disease in the prostate bed or those with suspected local recurrence may be considered for adjuvant/salvage radiation
- Favorable responses to adjuvant/salvage radiation are associated with low PSA levels prior to radiation(< 1 ng/mL), long PSADTs, lower Gleason scores, longer time to biochemical recurrence and positive surgical margins
- Adjuvant or early salvage radiation (based on a lower PSA trigger value) should be considered for patients with positive margins, extraprostatic extension, and seminal vesicle invasion (3)
  - Such therapy, compared to radical prostatectomy only, reduces the risk of biochemical recurrence, local recurrence, and clinical progression of cancer (3,7)
  - The impact on subsequent metastases, prostate-cancer specific mortality, and overall survival is less clear (3,7). The survival benefit was established in one randomized trial but was refuted in another randomized trial, which was not powered to look at this outcome (3,7)
  - Adjuvant/early salvage radiation is well supported by randomized trials for patients with adverse pathology at the time of prostatectomy and is endorsed by AUA/ASTRO Guidelines

Additional Therapies

Clinical trials should be available and offered

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prognosis is dictated by several variables including:
  - Preoperative PSA
  - Pathologic Gleason score
  - Pathologic tumor stage
  - Time to biochemical recurrence
  - PSADT: <3–6 mo associated with the development of metastatic disease
- For those patients that progress after biochemical recurrence, in general, metastatic progression and prostate cancer specific mortality occur at a median of 8 and 13 yr after biochemical recurrence (4)

COMPLICATIONS

- Patient anxiety
- Complications are dictated by adjuvant and salvage therapy offered
  - Either radiation or ADT

FOLLOW-UP

Patient Monitoring

- Monitoring of serum PSA is necessary to diagnose biochemical recurrence and the response to treatment when/if it is offered
- For patients on ADT, baseline and periodic assessment of bone density is recommended
  - If PSA begins to rise on ADT, serum testosterone should be assessed to ensure a castrate level

Patient Resources

- NCCN. http://www.nccn.org/patients/patient_guidelines/prostate/index.html
- American Cancer Society. http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-recurrence

REFERENCES

1. Roberts WB, Han M. Clinical significance and treatment of biochemical recurrence after definitive therapy for localized prostate cancer. *Surg Oncol.* 2009;18(3):268–274.
2. Moul JW. Prostate specific antigen only progression of prostate cancer. *J Urol.* 2000;163(6):1632–1642.
3. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline. *J Urol.* 2013;190(2):441–449.
4. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999;281(17):1591–1597.
5. Alfarone A, Panebianco V, Schillaci O, et al. Comparative analysis of multiparametric

magnetic resonance and PET-CT in the management of local recurrence after radical prostatectomy for prostate cancer. *Crit Rev Oncol Hematol.* 2012;84(1):109–121.
6. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med.* 2012;367(10):895–903.
7. Stephenson AJ, Bolla M, Briganti A, et al. Postoperative radiation therapy for pathologically advanced prostate cancer after radical prostatectomy. *Eur Urol.* 2012;61(3):443–451.

ADDITIONAL READING

- NCCN Practice Guidelines Version 1.2014 http://www.nccn.org./ (Accessed January 6, 2014).
- Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol.* 2013;190(2):441–449.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General
- Prostate Cancer, Locally Advanced (Pathologic T3, T4)
- Prostate Cancer, Metastatic (Clinical and Pathologic N+, M+)
- PSA elevation, General Considerations
- PSA, General Considerations
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 790.93 Elevated prostate specific antigen [PSA]
- V45.77 Acquired absence of organ, genital organs

ICD10

- C61 Malignant neoplasm of prostate
- R97.2 Elevated prostate specific antigen [PSA]
- Z90.79 Acquired absence of other genital organ(s)

CLINICAL/SURGICAL PEARLS

- Distinguishing local from systemic disease recurrence dictates adjuvant/salvage therapy options.
- Adjuvant/early salvage radiation is supported by randomized trials for patients with adverse pathology at the time of prostatectomy and is endorsed by AUA/ASTRO Guidelines.

PROSTATE CANCER, GENERAL

Robert B. Den, MD
Mark Hurwitz, MD

BASICS

DESCRIPTION

Prostate cancer (CaP) usually refers to adenocarcinoma as other types are rare

EPIDEMIOLOGY

Incidence/Prevalence

- Most common solid tumor in US males
- 2014: 233,000 new cases; 29,480 deaths
- Advent of PSA blood test led to a sharp increase of CaP incidence from 1989 to 1992
- Highest worldwide incidence is in African Americans, with a relative incidence of ~2 compared to US whites
- Lowest worldwide incidence is in Asian men (1.9/100,000/yr in China); however, Asians who immigrate to US increase risk to that of US men
- Mortality rate decreased sharply since 1991; now lower than before PSA era
- 5-yr relative survival rates ~100%
- Lifetime CaP risk is 16.15%

RISK FACTORS

- Genetic and environmental factors are important in CaP development
- Family history: Risk is increased by number of affected family members, degree of relation, and age at diagnosis.
- Infection/inflammation: Prostatitis and STD
- Oxidant stress: Several genetic determinant of CaP code for proteins that repair oxidant stress
- Western diet (high levels of meat, dairy, and saturated fat); folate supplements
- Androgens: Essential for development and maturation of prostate gland
  - Lack of androgen associated with decreased risk of CaP, although no dose-dependent relationship has been established
  - Shortened CAG repeat length in the AR gene associated with increased risk
  - Estrogen: Mixed effects on CaP
  - IGF-1
  - Vitamin D may protect against CaP

Genetics

- HPC-1 gene on chromosome 1 associated with familial CaP; HPC-1 mutation leads to defective RNase L, accumulation of genetic defects, and eventually cancer
- CaP susceptibility genes: P53 tumor suppressor, ELAC2/HPC2, SR-A/MSR1, CHEK2, BRCA2, PON1, OGG1, and MIC1.
  - Multifocal and heterogeneous nature of CaP makes clinical genetic studies difficult
- Familial CaP tends to follow a similar clinical course to sporadic CaP

PATHOPHYSIOLOGY
- Normal adult prostate 20–25 g; secretes fluid comprising about 30% of ejaculate
- Most CaP arise in peripheral zone of gland
- High-grade prostatic intraepithelial neoplasia (HGPIN) may be a premalignant lesion:
  - Risk of CaP on subsequent biopsy 16–44%; repeat biopsy within a year not necessary unless other signs of cancer
- Atypical small acinar proliferation (ASAP) considered premalignant; 42–49% risk of cancer, biopsy should be repeated

ASSOCIATED CONDITIONS
ED and urinary incontinence are associated with all local CaP therapies.

GENERAL PREVENTION
- Randomized trials have been conducted
  - Prostate Cancer Prevention Trial (PCPT) finasteride vs. placebo; REDUCE (dutasteride vs. placebo); while there was 23–25% reduction in CaP risk, concern over slight increase in diagnosis of high-grade cancers prevented these from being FDA-approved agents
  - SELECT: Examined antioxidants Vit E and selenium terminated in 2008 due to lack of benefit; increased risk of CaP and diabetes

DIAGNOSIS
HISTORY
- Rarely presents with symptoms; most cases are detected by PSA screening and/or DRE
- Occasionally local tumor symptoms: Urinary obstruction, irritative voiding symptoms, rarely impotence, hematuria, hematospermia
- Metastatic symptoms: Bone pain, weight loss, malaise; spinal cord compression with paralysis

PHYSICAL EXAM
DRE may reveal induration, nodularity, or asymmetry in the gland (uncommon in most men)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- PSA, is typically elevated in serum of patients with CaP (See Section I: PSA Elevation, General)
- PSA is the most widely used and controversial screening test (sensitivity/specificity suboptimal)
- Recent guidelines have called PSA screening into question
- PSA velocity of >2.0 ng/mL/yr: Poorer prognosis after prostatectomy or radiation therapy
- Free PSA: Lower % free PSA indicates higher risk of CaP
- Prostatic acid phosphatase: Limited utility
- Alkaline phosphatase: Elevated in bone mets

Imaging
- Transrectal ultrasound (TRUS) primarily used to guide biopsy; CaP classically a hypoechoic nodule on TRUS, but can be iso- and hyperechoic
- Multiparametric MRI w/ or w/o endorectal coil may identify some cancers, used to assess

local extent of disease; utility of multiparametric MRI growing
- Bone scan: Usually ordered in intermediate- and high-risk patients; blastic bone lesions w/mets
- CT abdomen/pelvis: Used to assess for visceral or lymph node metastasis; indicated for intermediate- and high-risk patients
- ProstaScint: Nuclear scan using a PSMA monoclonal antibody to detect occult metastases. FDA-approved post prostatectomy; limited use

Diagnostic Procedures/Surgery
- TRUS-guided needle biopsy extended template now standard (10–12 cores)
- Effort should be made to sample all hypoechoic lesions and palpable nodules
- Transperineal w/ or w/o MRI image fusion increasing

Pathologic Findings
- >95% CaP adenocarcinoma, with <5% transitional cell (next most common), small cell carcinoma, and sarcoma
- Gleason Grade (1–5) determined by architectural features observed at low magnification. The 2 most prominent grades are added together for Gleason score (2–10):
  - Main criterion of CaP: Loss of basal cell layer
  - Small, crowded acini with irregular contours, nuclear, and nucleolar enlargement
  - Hormonal Rx artifactual grade increase
  - Score <6 rare today; 6, 7, 8–10 are low-, intermediate-, and high-grade disease, respectively
- Staging:
  - TNM staging, see Section VII
  - 75% of newly diagnosed cases are T1c
  - PSA >10, Gleason score ≥7, or T2b or higher should undergo imaging (CT/bone scan)
  - CaP spreads from the prostate directly to adjacent tissues, usually via the perineural and lymphovascular spaces
  - Can also directly invade the seminal vesicle
  - Early metastasis to the pelvic lymph nodes
  - Distant metastasis: To bone, less common lung, and in advanced stages, the liver and CNS

DIFFERENTIAL DIAGNOSIS
- Localized: BPH, prostatitis (granulomatous, acute, chronic), recent instrumentation, nonadenocarcinoma prostate malignancy (sarcoma, urothelial carcinoma)
- Metastatic: Paget disease, other causes of pelvic/retroperitoneal lymphadenopathy (lymphoma, TB, etc.)

TREATMENT

GENERAL MEASURES
- Localized disease, best treatment controversial and must be individualized; includes active surveillance, radical prostatectomy, radiation therapy, cryotherapy
- Consider age, overall health, life expectancy, patient and physician preferences
- Metastatic disease less controversial and relies primarily on reduction of testosterone

- Risk groups (localized disease, per NCCN)
  - Low risk: T1-2a/Gleason 2–6/PSA <10 ng/mL
  - Intermediate: T2b–T2c/Gleason 7/PSA 10–20 ng/mL
  - High:T3a or greater or Gleason score 8–10 or PSA >20 ng/mL

MEDICATION

First Line

- Metastatic disease: Androgen deprivation
  - LHRH agonists: Leuprolide, goserelin, triptorelin; histrelin; transient flare then suppression of pituitary LH and FSH
  - LHRH antagonists: Degarelix; suppress LH and FSH release by the pituitary
  - Antiandrogens: Flutamide, bicalutamide, nilutamide, directly block the activity of androgens on the androgen receptor
  - LHRH agonists can be used alone or in combination with oral antiandrogens
  - LHRH agonist 1st dose, a release of testosterone is induced (androgen flare) that may exacerbate symptoms from metastatic lesions. In particular, patients with spinal metastasis may be in jeopardy of cord compression. Minimize flare by antiandrogen therapy 2 wk prior to 1st LHRH agonist injection

Second Line

- Metastatic castrate–resistant CaP: W/rising PSA and "castrate" testosterone (<50 ng/dL)
  - Secondary hormonal manipulations
    - Ketoconazole: Inhibits adrenal and gonadal androgen synthesis; castration hormone levels in <8 hr, historically used w/ spinal compression
    - Add/stop nonsteroidal antiandrogens
  - Sipuleucel-T: Autologous immunotherapy; minimally symptomatic or asymptomatic disease
  - Abiraterone: Androgen biosynthesis inhibitor; approved in men with metastatic castrate–resistant prostate cancer previously treated with docetaxel and pre-docetaxel
  - Enzalutamide: 2nd gen oral antiandrogen, previously treated with docetaxel and pre-docetaxel
  - Radium 223 chloride; systemic α-emitter for symptomatic bone mets, no visceral disease
  - Cabazitaxel and prednisone: Systemic microtubule inhibitor failing docetaxel
  - Docetaxel and prednisone: Systemic microtubule inhibitor

SURGERY/OTHER PROCEDURES

- For low-risk (T1 and T2a) cancer, 5-yr biochemical disease-free rates are equivalent for prostatectomy, radiation therapy, and brachytherapy. Thus, therapy should be driven by the preferences of the well-informed patient
- Radical prostatectomy:
  - Resection of prostate and seminal vesicles and reanastomosis of bladder to urethra
  - Nerve-sparing technique if possible
  - Open (retropubic, perineal), laparoscopic, or robot-assisted laparoscopic; Laparoscopic approaches may offer quicker discharge, lower blood loss; equivalent functional/oncologic results between techniques; robot higher cost
- Bilateral orchiectomy provides permanent androgen ablation in men with advanced disease

- Cryotherapy uses multiple probes to ablate prostate tissue by freezing and thawing, using TRUS to monitor the extent of the ice ball

ADDITIONAL TREATMENT

Radiation Therapy

- External beam RT:
  - IMRT with IGRT: Provides high doses of radiation to prostate, minimal dose to surrounding tissues
  - Wide-field pelvic XRT with neoadjuvant androgen deprivation may be considered in men at high risk for nodal metastases
  - Proton beam gaining support
  - Hypofractionation approaches in clinical trials
- Brachytherapy:
  - RT is delivered locally by permanent radioactive (low dose rate I125 or Pd103) seeds or temporary (high dose rate with Ir192) placed percutaneously through the perineum:
  - Low-dose monotherapy appropriate for low-risk disease and gland <60 g
  - Gleason ≥ 7, PSA ≥ 10, and $\geq$T2b use EBRT in lieu of or in addition to brachytherapy
- Neoadjuvant/concurrent androgen deprivation for 6 mo–3 yr with XRT increases survival vs. XRT alone or hormonal therapy alone (select intermediate and all high-risk patients)

Additional Therapies

- Active surveillance: Option for many patients due to the slow progression of CaP, especially in men >70 who may be likely to die of other causes
  - Ideal patient: PSA <10 ng/mL, T1c, Gleason ≤ 6; <3 biopsy cores positive ($<50\%$ cancer in any core); PSA density <0.15 ng/mL/g
- HIFU: Investigational focal ablative therapy in use outside of US

Complementary & Alternative Therapies

Consider dietary changes: Reduced meat and saturated fat; increased vitamin D (see "Risk Factors"); increased lycopenes (cooked tomato products, red fruits; increased fiber and exercise

ONGOING CARE

PROGNOSIS

- Determining prognosis is multimodal
- Increased recurrence risk with:
  - High PSA (≥ 10), high Gleason score (≥ 7), advanced clinical stage ($\geq$T3)
  - Pathologic features: Positive surgical margins, seminal vesicle invasion, capsular penetration, lymph node involvement
  - New genomic markers available for prognosis (See Section II: "Prostate Cancer, Genomic markers.")

COMPLICATIONS

- Disease related:
  - Bladder outlet obstruction, bone pain, pathologic fractures, spinal cord compression, ureteral obstruction usually due to metastasis

- Treatment related:
  - Local therapy (surgery, radiation): Impotence, incontinence, rectal injury
  - Androgen deprivation: Hot flashes, loss of libido, impotence, fatigue, osteoporosis
  - Chemotherapy: Neutropenia, sepsis

FOLLOW-UP

Patient Monitoring

- PSA every 6–12 mo × 5 yr; yearly after:
  - Should be undetectable (< 0.1 ng/mL) after prostatectomy
  - Should drop to < 0.5 ng/mL after radiation for best prognosis
- DRE every other year
- CT of abdomen/pelvis and/or bone scan if patient has new bone pain, rapid PSA rise, short doubling time

Patient Resources

American Cancer Society. http://www.cancer.org/cancer/prostatecancer/index?sitearea=%26dt=10

REFERENCES

1. NCCN Practice Guidelines Version 1.2014 http://www.nccn.org./ Accessed January 6, 2014
2. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215–224.
3. D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med*. 2004;351:125–135.
4. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502–1512.
5. Pilepich MV, Winter K, John MJ, et al. Phase III Radiation Therapy Oncology Group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 2001;50:1243–1252.

ADDITIONAL READING

Thompson IM, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007;177:2106–2131.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Castration Resistant
- Prostate Cancer, General Images
- Prostate Cancer, Genomic Markers
- Prostate Cancer, Localized (T1, T2)
- Prostate Cancer, Locally Advanced (T3, T4)
- Prostate Cancer, Metastatic (N+, M+)
- Prostate Cancer, Very Low Risk and Active Surveillance
- PSA Elevation, General
- PSA, General Considerations
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 601.9 Prostatitis, unspecified
- V16.42 Family history of malignant neoplasm of prostate

ICD10

- C61 Malignant neoplasm of prostate
- N41.9 Inflammatory disease of prostate, unspecified
- Z80.42 Family history of malignant neoplasm of prostate

CLINICAL/SURGICAL PEARLS

Prostate cancer requires informed decision making and a risk based approach; consider active surveillance if low risk and $<$10-yr life expectancy.

PROSTATE CANCER, LOCALIZED (T1, T2)

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Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Biopsy-proven adenocarcinoma of the prostate, clinically confined to the prostate gland
- Clinical T1 or T2, N0, M0

EPIDEMIOLOGY

Incidence

- Prostate cancer (CaP) (American Cancer Society Data)
  - Estimated 233,000 new cases and 29,480 deaths in 2014 in US
- Localized prostate cancer (LCaP)
  - 81% of newly diagnosed CaP

Prevalence

- Age dependent
  - CaP cumulative prevalence in US men
    - Age 50–60: 44%; Age 70–80: 83%
- 20–35% worldwide

RISK FACTORS

- Age
- Family history of CaP with highest risk in 1st-degree relative
  - Suggestion that familial breast cancer increasies prostate cancer risk
- African American race
  - 40% increased risk of disease
  - 2.4 times risk of mortality

Genetics

See “Prostate cancer, general considerations”

PATHOPHYSIOLOGY

- Genetic predisposition
- Chronic inflammatory states
- Oxidative stress

ASSOCIATED CONDITIONS

- Benign prostatic hypertrophy (BPH)
- Lower urinary tract symptoms (LUTS) (unrelated to cancer)
- Obesity

GENERAL PREVENTION

- See also “Prostate Cancer, prevention”
- There are unfortunately no approved agents for the chemoprevention of CaP. Major clinical

trials include:
- 5α-reductase inhibitors
  - Finasteride (PCPT trial, 2003)
    - 25% CaP risk reduction
  - Dutasteride (REDUCE trial, 2009)
    - 27% CaP risk reduction
- Vitamin E and selenium (SELECT trial, 2011)
  - Increases the risk of CaP by 17%

DIAGNOSIS

HISTORY
- LCaP is rarely symptomatic
- Unintentional weight loss or new-onset skelet al pain suggests nonlocalized disease
- LUTS
  - More commonly attributed to BPH

PHYSICAL EXAM
- Digital rectal exam (DRE)
  - No palpable nodule (cT1)
  - Nodule confined to prostate gland (cT2)
  - Ablation of lateral sulcus or palpable seminal vesicles suggests more advanced disease than T2

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Prostate-specific antigen (PSA)
  - Produced by prostatic epithelium
  - Half-life of 2–3 days; Not specific to CaP
  - A continuous parameter
    - The higher the value, the more likely the existence of CaP (1)[A]
- Routine PSA screening is controversial
  - 2013 AUA Guidelines (2):
    - Under age 40 yr: Do not screen [C]
    - 40–54 yr, average risk: Do not screen [C]
    - <55 yr at higher risk: Individualized decision [C]
    - 55–69 yr: Shared decision-making if considering PSA screening [B]
    - Greatest benefit of screening in men ages 55–69 yr
    - Routine screening interval: 2 yr [C]
    - >70 yr and <10–15-yr life expectancy: Do not screen [C]
- Other PSA parameters
  - PSA velocity/doubling time
    - Limited use in diagnosis (1)[A]
    - Velocity >2 ng/mL: Increased risk for death from CaP
  - % free PSA <10

- Increased (56%) risk of cancer (1)[A]
  - PSA density
    - ≥0.15 mg/mL/g suggests CaP
- CaP antigen 3 (PCA3) (see "PCA3 Prostate Cancer Gene 3 urine assay")
  - Limited clinical use in diagnosis
  - May help in decision to a repeat biopsy in men with a negative 1st biopsy (1)[A]

Imaging

- 2014 NCCN Guidelines for LCaP:
  - No imaging if low risk
  - Bone scan: PSA >10 ng/mL or Gleason ≥8
  - Pelvic CT or MRI
    - Lymph node involvement risk >10%
- ProstaScint imaging: Not indicated for LCaP
- No imaging modality can accurately estimate the extent of tumor and location within or surrounding the prostate

Diagnostic Procedures/Surgery

- Prostate biopsy (3)[C]
  - Diagnosis is based on histologic exam
  - Transrectal ultrasound guided (TRUS) transrectal or transperineal needle biopsy
    - Laterally directed, 18G, 10–12 cores
    - Increases detection rate
  - Periprostatic local anesthetic injection
  - Antibiotic prophylaxis is always recommended
  - Infection rate: 0.5–1% (see "Prostate biopsy, Infections and Complications")

Pathologic Findings

- Gleason score (See "Gleason Grading/Scoring System")
- Proportion of biopsies positive for carcinoma
- Presence of extraprostatic extension
- High-grade PIN and perineural invasion is usually reported

DIFFERENTIAL DIAGNOSIS

- Abnormal DRE: Granulomatous prostatitis prostatic cyst, calcifications, cancer
- Elevated PSA: UTI, BPH, acute or chronic prostatitis, recent prostatic instrumentation

TREATMENT

GENERAL MEASURES

- Assess life expectancy, overall health status, and tumor characteristics prior to treatment decisions (4)[A]
- Review risk and benefits of all treatments and engage patient in informed decision making process.
- Treatment recommendations based on cancer biology, patient overall health, life expectancy, and preferences

- Gleason score and tumor stage are predictive of cancer outcomes
- Risk strata are used to develop treatment recommendations (4)[A]
  - Low risk: PSA 10 and a Gleason score of 6 or less and clinical stage T1c or T2a
  - Intermediate risk: PSA >10–20 or a Gleason score of 7 or clinical stage T2b
  - High risk: PSA >20 or a Gleason score of 8 to 10 or clinical stage T2c

MEDICATION

First Line

- Primary androgen deprivation therapy (ADT)
  - Rarely indicated for LCaP (4)[C]
    - Palliation of symptomatic patients
    - Extensive or poorly differentiated tumors
    - Short life expectancy
  - Not recommended by 2014 NCCN Guidelines
- Neoadjuvant ADT for surgical treatment
  - Not recommended (1)[A]
- Neoadjuvant/concurrent androgen deprivation for 6 mo–3 yr with XRT increases survival vs. XRT alone or hormonal therapy alone (select intermediate and all high-risk patients)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical prostatectomy (RP)
  - Removal of prostate gland, seminal vesicles, and ampulla of the vas; pelvic lymph node dissection for elevated risk of positive nodes
  - Cancer "cure" in truly localized disease
  - Option for low, intermediate risk with ≥10-yr life expectancy and selected high-risk patients (1)[B]
  - Similar survival between RP and watchful waiting in low-risk CaP, <65 yr (4)[B]
  - Technique:
    - Open (perineal or retropubic)
    - Laparoscopic (LRP), Robotic assisted laparoscopic prostatectomy (RALP): Lower blood loss and transfusion rates; oncologic and long-term outcome similar
    - Pelvic lymphadenotomy (PLND) if predicted nodal mets is ≥2%
    - Nerve-sparing surgery: Preoperatively potent patients, T1c, Gleason <7, and PSA <10 (1)[B]
    - Non–nerve-sparing for high risk (high erectile dysfunction rates)
- Salvage RP
  - Highly selected patients with local recurrence
  - Absence of metastatic disease
  - High morbidity

ADDITIONAL TREATMENT

Radiation Therapy

- External beam RT (EBRT)

- Intensity-modulated RT (IMRT) is preferred
- Image-guided RT (IGRT) if dose >78 Gy
- Dose: Low risk: 75–79 Gy, 8–9-wk fractionation; intermediate/high risk: Up to 81 Gy
- Combined with ADT
  - Neoadjuvant, concomitant, or adjuvant ADT
  - Increased survival in high-risk patients if given before and during EBRT (1)[B]
  - 4–6 mo or 2–3 yr for high risk (high Gleason or high volume based on biopsy)
- Irradiation to the pelvic lymph nodes; no general indication; ongoing trials (1)[B]

• Brachytherapy
- Delivered via interstitial seeds
  - Temporary: High-dose rate (HDR): Ir^{192}
  - Permanent: Low-dose rate (LDR): I^{125} or Pd^{103}
- Monotherapy: Low-risk disease
  - Dose: I^{125} 145 Gy and Pd^{103} 125 Gy
- Combined with EBRT: Intermediate/high risk
  - 40–50 Gy of EBRT
  - ± 4–6 mo of ADT
- Higher risk of side effects:
  - Previous TURP
  - Large (60–80 g) or small (<20 g) gland
  - Bladder outlet obstruction

• Stereotactic body RT (SBRT), ie, CyberKnife
- Highly conformal, high dose
- Hypofractionation (as little as 5 fractions)
- May be equivalent to EBRT; under trial

• Proton therapy
- Not recommended for routine use currently

Additional Therapies

• Active Surveillance
- See “Prostate Cancer, Very Low Risk and Active Surveillance”

• Cryosurgical ablation of the prostate (CSAP)
- Patients not suitable for RP or life expectancy <10 yr, gland <40 mL
- Freezing techniques to induce cell death
  - Placement of 12–15 17G cryoneedles under TRUS guidance
  - Thermosensors at external sphincter and bladder neck
  - Insertion of urethral warmer
  - 2 freeze–thaw cycles: –40°C at midgland and at the neurovascular bundle
- NCCN: Currently not recommended as routine primary therapy for LCaP

• High-intensity focused ultrasound (HIFU) and vascular-targeted photodynamic (VTP) therapies
- Currently not considered valid treatment options

Complementary & Alternative Therapies

Not applicable

ONGOING CARE

PROGNOSIS

- Dependent on risk strata
  - Low, intermediate, and high risk
  - Indicate probability of biochemical failure after definitive local therapy
- See on line prediction tools such as http://www.mskcc.org/cancer-care/adult/prostate/prediction-tools orPartin tables: http://urology.jhu.edu/prostate/partintables.php (Accessed August 23, 2014)

COMPLICATIONS

- RP
  - Significantly reduced if performed in a high-volume hospital and experienced surgeon
  - Intraoperative: Rectal injury (0–5%), major bleeding (1–12%), death (0–2%)
  - Postoperative: Deep vein thrombosis (0–8%), pulmonary embolus (1–8%), lymphocele (1–3%)
  - Long term: Incontinence (0–50%), stricture (2–9%), impotence (30–100%)
- RT
  - Short term: Bowel symptoms (bleeding, diarrhea, fecal incontinence), irritative voiding symptoms
  - Long term:
    - Genitourinary (16%): Strictures, hematuria, cystitis, incontinence
    - Gastrointestinal (10%) Proctitis, chronic diarrhea, small bowel obstruction
    - Increased risk of secondary cancers

FOLLOW-UP

Patient Monitoring

- No consensus for follow-up after definitive treatment of LCaP
- Usually followed for at least 10 yr
- NCCN: PSA every 6–12 for 5 yr, then every year, DRE every year (omitted if PSA undetectable)
- Palpable nodule on DRE and rising PSA can indicate local disease recurrence (1)[B]
- See “Prostate cancer, biochemical recurrence (elevated PSA)”

Patient Resources

- National Cancer Institute. www.cancer.gov/cancertopics/types/prostate
- AUA patient guide. www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-PatientGuide.pdf

REFERENCES

1. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. *Euro Urol.* 2011;59(1):61–71.
2. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol.* 2013;190(2):419–426.
3. Damber JE, Aus G. Prostate cancer. *Lancet.* 2008;17:371(9625):1710–1721.
4. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized

prostate cancer: 2007 update. *J Urol.* 2007;177(6):2106–2131.

ADDITIONAL READING

- Healy KA, Gomella LG. Retropubic, laparoscopic, or robotic radical prostatectomy: Is there any real difference? *Semin Oncol.* 2013;40(3):286–296.
- NCCN Practice Guidelines Version 1.2014. http://www.nccn.org./ Accessed January 6, 2014
- Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* 2012;367(3):203–213.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Castration resistant
- Prostate Cancer, Genomic markers
- Prostate Cancer, Locally Advanced (T3, T4)
- Prostate Cancer, Metastatic (N+, M+)
- Prostate cancer, Very Low Risk and Active Surveillance
- PSA Elevation, General
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- V16.42 Family history of malignant neoplasm of prostate

ICD10

- C61 Malignant neoplasm of prostate
- Z80.42 Family history of malignant neoplasm of prostate

CLINICAL/SURGICAL PEARLS

- Represents majority of newly diagnosed men with CaP; minority of men will die from their disease.
- Nerve-sparing RP technique is standard of care.
- Surgical outcomes are highly dependent on surgeon experience.
- Radiation techniques, improving disease control, and reducing side effects.
- Consider active surveillance if low risk and <10-yr life expectancy.

PROSTATE CANCER, LOCALLY ADVANCED (CLINICAL T3, T4)

Erin M. Burns, MD
James S. Rosoff, MD

BASICS

DESCRIPTION

- Clinical stage T3 prostate cancer (CaP) refers to disease that is thought to extend outside the prostate and may be palpable or seen on imaging
- Pathologic stage T3 CaP refers to extracapsular extension (T3a), or tumor invading seminal vesicles (SVs) (T3b) based on final surgical pathology
- Clinical stage T4 CaP refers to palpable tumor that is fixed and/or invading adjacent structures
- Pathologic stage T4 CaP refers to tumor that is invading the bladder neck, external sphincter, rectum, or levator muscle, and/or is fixed to the pelvic sidewall based on final surgical pathology
- Transrectal ultrasound (TRUS) of the prostate, magnetic resonance imaging (MRI), and computed tomography (CT) can supplement physical exam findings to assist with diagnosing clinical stage T3 and T4 disease

EPIDEMIOLOGY

Incidence

Declining incidence of locally advanced CaP: 10–15% in 1989–1990, 1–5% in 2001–2003 (1,2)

Prevalence

N/A

RISK FACTORS

- Higher Gleason score, elevated prostate-specific antigen (PSA), and increased tumor volume on biopsy predict increased likelihood of locally advanced disease
- Older males (≥75) are more likely to present with high-risk prostate cancer (3)
- African Americans and men with diabetes tend to have more aggressive disease and higher stage at presentation (4)

Genetics

Research is ongoing to determine genetic markers that differentiate organ confined from locally advanced CaP

PATHOPHYSIOLOGY

- Extension beyond prostatic capsule occurs when tumor develops biologic ability to degrade physical barriers to cancer cell movement, such as the prostatic capsule and/or fascial investments of the prostate and SVs
  - Intermediate-grade (Gleason 7) and high-grade (Gleason 8–10) CaPs more commonly extend outside the prostate than low-grade (Gleason 6) CaP.

ASSOCIATED CONDITIONS
Locally invasive prostate cancer can present with resulting symptoms such as hematuria, obstructive voiding symptoms and changes in bowel habits

GENERAL PREVENTION
- 5α-Reductase inhibitors (5-ARIs): Finasteride and dutasteride
  - Discuss with patient risks/benefits of 5-ARI use for CaP prevention (5)[A]
- Vitamin E, selenium, vitamin C:
  - No beneficial effect; should not be used
- Statins, green tea, lycopene
  - Insufficient evidence to advocate these supplements for CaP prevention (6)

DIAGNOSIS
HISTORY
- Family history of CaP
- Voiding symptoms: Obstructive/irritative, hematuria

PHYSICAL EXAM
Digital rectal exam (DRE): Note palpable abnormalities, unilateral vs. bilateral, whether prostate is fixed, any extension of mass into adjacent structures

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- PSA
  - Positive predictive value (PPV): 12–32% for PSA levels 4–10, 60–80% for PSA levels >10, higher PSA increases risk for capsular penetration and SV invasion
  - Value is decreased by 5-ARIs, elevated with instrumentation, infection, larger prostate volume
  - Lab variability: 20–25% (7)[A]
- PSA density: Serum PSA/prostate volume
  - >0.15 is associated with CaP, >0.35 is associated with 66% risk of extraprostatic extension
- PSA velocity
  - Rate of rise of >0.75/yr is a specific marker for CaP
  - Should be calculated over 18 mo with 3 PSA measurements
- Free PSA (fPSA)
  - Lower fPSA is found in CaP; <10% free correlates with 56% probability of CaP
    - PSA velocity, density, and fPSA do not correlate with Gleason score or CaP stage
- PCA3
  - RNA overexpressed in CaP, higher values indicate higher risk of CaP
  - Collected via post-DRE urine sample
  - Sensitivity 48%, specificity 79%, not currently used for routine screening
  - May correlate with Gleason score (8)

Imaging
- TRUS

  - Low sensitivity (23–66%), specificity (46–86%), and PPV (50–62%) for predicting extracapsular extension (9)[A]
  - Useful in guiding widespread sampling of prostate tissue during biopsy
- MRI
  - May delineate T2 from T3 disease
  - Specificity for T3 disease is 95% when PSA >10, abnormal DRE and >3 cores positive on TRUS biopsy (10)[A]
- CT
  - Consider for staging when PSA >20 or Gleason score ≥8
- Bone scan
  - Indicated when PSA ≥20 to evaluate for skelet al metastases
- ProstaScint
  - May be useful in ruling out metastatic disease in patients with locally advanced CaP

Diagnostic Procedures/Surgery
- TRUS-guided prostate biopsy
  - Should be performed for abnormal DRE or PSA elevation

Pathologic Findings
TRUS biopsy can confirm T3 disease with biopsy of the capsule or SVs

DIFFERENTIAL DIAGNOSIS
- PSA can be elevated in the setting of prostatic and/or urethral instrumentation, infection, or benign prostatic hypertrophy (BPH)
- Lesions of the prostate seen on imaging can be areas of infarct, prostatitis, or tumor
- No single diagnostic modality can accurately predict pathologic stage of CaP; incorporating multiple clinical parameters helps to best determine disease extent

TREATMENT

GENERAL MEASURES
- Currently no consensus regarding optimal management of locally advanced CaP
- Compared to clinically localized, low-grade CaP, locally advanced CaP has a higher risk of recurrence after any single treatment modality (up to 30%), and should be treated unless life expectancy is ≤5 yr

MEDICATION
First Line
- Androgen deprivation therapy (ADT): Option for patients unable or unwilling to undergo surgery or radiation therapy (RT)
  - Orchiectomy, luteinizing hormone-releasing hormone (LHRH) agonist or antagonist
  - Can be administered continuously or intermittently; optimal timing of administration with respect to quality of life and survival benefit is debated
  - More effective when combined in neoadjuvant or adjuvant fashion with RT

Second Line
Antiandrogen monotherapy is less effective and not usually recommended; however, side

effects are more tolerable overall

SURGERY/OTHER PROCEDURES

- Radical prostatectomy (RP) with pelvic lymph node dissection (PLND)
  - Select patients can benefit from local control
  - Complete excision/cure is possible
  - Clinical overstaging of T3 disease can occur in up to 7–27% of patients, thus exclusion from surgery on the basis of clinical staging may be inappropriate
- Neoadjuvant ADT does not confer cancer specific or overall survival (OS) benefit
- Adjuvant RT 55–70 Gy improves local control and reduces the risk of biochemical recurrence for T3 disease; it may also confer OS benefit (11)[A]
  - Indications include T3 disease, positive surgical margins, Gleason score of 8–10
  - Should be administered within 1 yr of surgery and after operative side effects (eg, urinary continence) have improved/stabilized

ADDITIONAL TREATMENT

Radiation Therapy

- 75–80 Gy to prostate, SVs, and pelvic lymph nodes, or 40–50 Gy and brachytherapy for cT3/T4 disease
  - NCCN guidelines recommend 2–3 yr neoadjuvant/concomitant/adjuvant ADT for higher disease free and OS in men with T3 and T4 disease (12)[A]
- Advances in 3D conformal, intensity-modulated and image-guided RT are designed to deliver higher doses directly to prostate, avoiding adjacent structures and thus limiting side effects

Additional Therapies

- Cryoablation of the prostate
  - Higher rates of biochemical failure than RT (87% vs. 53%) for T2c–T3 CaP (13)[A]
- High-intensity focused ultrasound (HIFU)
  - Currently investigational, may prove to be an option in combination with ADT for intermediate- and high-risk CaP

Complementary & Alternative Therapies

Clinical trials should be considered

ONGOING CARE

PROGNOSIS

- Significant risk of progression and disease-specific death if locally advanced prostate cancer is left untreated
  - OS without intervention ranges from 10 to 92% at 5 yr and 14–78% at 10 yr for high-grade/stage CaP
- RP for T3 CaP: OS 64–96% at 5 yr, 13–72% at 10 yr
  - Cancer-specific survival (CSS): 85–92% at 5 yr, 79–82% at 10 yr
- RT monotherapy: OS 60–70% at 5 yr and $<50\%$ at 10 yr
  - RT with ADT: OS 72–87% at 5 yr

COMPLICATIONS

- Therapy complications are similar to those for localized CaP
- Untreated T3–T4 CaP may lead to hematuria, obstruction at the level of the prostate requiring indwelling catheter or transurethral resection of the prostate, or ureterovesical junction obstruction requiring ureteral stents or percutaneous nephrostomy

FOLLOW-UP

Patient Monitoring

- Periodic PSA measurements, initially at 3-mo intervals posttherapy and then gradually increasing to annually
- Failure of PSA to nadir or consecutive rises in PSA should prompt further evaluation with bone scan and/or CT
  - Risk of biochemical recurrence increased in: Gleason score 8–10, PSA doubling time <10 mo (14)
  - ProstaScint scan may be helpful in identifying local recurrence if bone scan and CT scan are negative
  - Consider additional treatment options such as ADT, adjuvant RT, and/or chemotherapy and participation in clinical trials

Patient Resources

- AUA Prostate Cancer Guide: http://www.auanet.org/content/media/pc08.pdf
- NCCN Patient Guidelines for Prostate Cancer: http://www.nccn.org/patients/patient_guidelines/prostate/index.html

REFERENCES

1. Greene KL, Cowan JE, Cooperberg MR, et al. ; Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators. Who is the average patient presenting with prostate cancer? *Urology*. 2005;66(5 suppl):76–82.
2. Cooperberg MR, Lubeck DP, Mehta SS, et al. Time trends in clinical risk stratification for prostate cancer: Implications for outcomes (data from CaPSURE). *J Urol*. 2003;170(6):21–27.
3. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J Clin Oncol*. 2011;29(2):235–241.
4. Mitin T, Chen MH, Zhang Y, et al. Diabetes mellitus, race, and odds of high grade prostate cancer in men treated with radiation therapy. *J Urol*. 2011;186(6):2233–2237.
5. Kramer BS, Hagerty KL, Justman S, et al. Use of 5-α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol*. 2009;27(9):1502–1516.
6. Stephenson AJ, Abouassaly R, Klein EA. Chemoprevention of prostate cancer. *Urol Clin North Am*. 2010;37(1):11–21.
7. AUA PSA Best Practice Statement. Available at http://www.auanet.org/content/media/psa09.pdf. (Accessed May 21, 2014)
8. Artibani W. Landmarks in prostate cancer diagnosis: The biomarkers. *BJU Int*. 2012;110:8–13.
9. Hsu CY, Joniau S, Oyen R, et al. Detection of clinical unilateral T3a prostate cancer-by digital rectal exam or transrectal ultrasonography. *BJU Int*. 2006;98(5):982–985.

10. Cornud F, Flam T, Chauveinc L, et al. Extraprostatic spread of clinically localized prostate cancer: Factors predictive of pT3 tumor and of positive endorectal MR imaging examination results. *Radiology*. 2002;224(1):203–210.
11. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologic T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. *J Urol*. 2009;181:956–962.
12. NCCN Prostate Cancer Guidelines. Available at http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (Accessed May 21, 2014)
13. Chin JL, Ng CK, Touma NJ, et al. Randomized trial comparing cryoablation and external beam radiotherapy for T2c-T3b prostate cancer. *Prostate Cancer Prostatic Dis*. 2008;11:40–45.
14. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA*. 2004;291:1325–1332.

ADDITIONAL READING

Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol*. 2013;190(2):441–449.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General
- Prostate Cancer, Locally Advanced (Clinical T3, T4) Images
- Prostate Cancer, Locally Advanced (Pathologic T3, T4)
- Prostate Cancer, Positive Margin Following Radical Prostatectomy
- PSA Elevation, General Considerations
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 198.1 Secondary malignant neoplasm of other urinary organs
- 198.82 Secondary malignant neoplasm of genital organs

ICD10

- C61 Malignant neoplasm of prostate
- C79.11 Secondary malignant neoplasm of bladder
- C79.82 Secondary malignant neoplasm of genital organs

CLINICAL/SURGICAL PEARLS

- Risk assessment requires incorporating serum PSA, clinical stage, Gleason score, tumor volume, and patient age and comorbidities to best provide counseling and treatment recommendations.
- RP should include PLND for locally advanced CaP, and adjuvant RT should be offered for T3–T4 disease, particularly if surgical pathology demonstrates positive margins.

- RT should be administered in conjunction with ADT for locally advanced CaP to maximize survival benefit with support from randomized clinical trials.

PROSTATE CANCER, LOCALLY ADVANCED (PATHOLOGIC T3, T4)

Divya Ajay, MD
Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Pathologic T3/T4 (pT3/T4) is prostate cancer that extends beyond the confines of the prostatic gland without evidence of lymph node or distant metastases after radical prostatectomy (RP) based on pathology
- Pathologic stage is determined by histologic analysis of the prostate, SVs, and lymph nodes
- Per the TNM system, this is considered locally advanced prostate cancer defined by the categories T3a, T3b, T4, if combined with an absence of regional lymph node metastasis (N0) and distant metastasis (M0). Where:
  - T3a: Extracapsular extension
  - T3b: Tumor invades seminal vesicle(s)
  - T4: Tumor is fixed or invades adjacent structures other than seminal vesicles (bladder neck, external sphincter, rectum, levator muscles, or pelvic wall)
- Tumor volume, grade, pelvic lymph node involvement, extracapsular and SV extension, and surgical margin status predict biochemical recurrence-free survival and cancer-specific survival

EPIDEMIOLOGY

Incidence

PSA screening has led to downward pathologic stage migration. Since 2001, rates of extracapsular extension had remained stable at 25%. In 2012 and 2013, USPSTF and AUA revised guidelines against PSA screening; this may increase rates of T3–T4 disease.

RISK FACTORS

- Poor health literacy, use of multivitamins more than 7 times a week, obesity, and lack of screening increase the risk of locally advanced disease at presentation
- Partin tables use DRE-based primary T stage, serum PSA, and Gleason grade to predict cancer extent and long-term outcomes
- D'Amico has also suggested a risk stratification into low, intermediate, and high risk based on DRE, PSA, and Gleason grade
- While these predictive models are helpful in counseling patients, studies show that status post prostatectomy up to 3% of men were down-T-staged and 35% of men were up-T-staged (1)

Genetics

- Abnormal p53 expression, low levels of p16 and deregulation of the RB pathway and aneuploidy of Chr 9 have been associated with locally advanced prostate cancer
- In 2013, 2 commercial genetic biomarker assays (Prolaris, Oncotype Dx-prostate) became

available. Based on RNA expression profiles, these assays may help to predict more advanced stage/grade

PATHOPHYSIOLOGY

- Peripheral zone tumors tend to invade the capsule more often than transition zone tumors
- Tumor spread:
  - T3a (extracapsular invasion) occurs posteriorly and posterolaterally by vascular invasion and increases risk of recurrence after RP
- Tumor volume:
  - Extraprostatic invasion is more common in tumors >0.5 cm^3 and seminal vesicle invasion is more common in tumors >4 cm^3
  - Tumor volume does not independently predict postsurgical progression once grade, pathologic stage, and margins are accounted for

ASSOCIATED CONDITIONS

Locally invasive prostate cancer can present with resulting symptoms such as hematuria, obstructive voiding symptoms, and changes in bowel habits

GENERAL PREVENTION

- 5-Alpha Reductase Inhibitors (5-ARIs): Finasteride and dutasteride; discuss with patient risks/benefits of 5-ARI use for CaP prevention; not FDA approved
- Vitamin E, Selenium, Vitamin C: No beneficial effect; should not be used
- Statins, Green Tea, Lycopene: Insufficient evidence to advocate these supplements for CaP prevention

DIAGNOSIS

HISTORY

- Family history of CaP; race
- Voiding symptoms: Obstructive/irritative, hematuria
- Any bone/back/hip pain or hematuria?

PHYSICAL EXAM

Digital rectal exam (DRE): Note palpable abnormalities, unilateral vs. bilateral, whether prostate is fixed, any extension of mass into adjacent structures

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA
  - Positive predictive value (PPV): 12–32% for PSA levels 4–10, 60–80% for PSA levels >10, higher PSA increases risk for capsular penetration and SV invasion
  - Value is decreased by 5-ARIs, elevated with instrumentation, infection, larger prostate volume
  - Laboratory variability: 20–25%
- PSA density: Serum PSA/Prostate volume
  - >0.15 is associated with CaP, >0.35 is associated with 66% risk extra-prostatic extension
- PSA velocity
  - Rate of rise of >0.75/yr is a specific marker for CaP

  – Should be calculated over 18 mo with 3 PSA measurements
- Free PSA (fPSA)
  – Lower fPSA is found in CaP; <10% free correlates with 56% probability of CaP
- PSA velocity, density, and fPSA do not correlate with Gleason score or CaP stage
- PCA3
  – RNA overexpressed in CaP, higher values indicate higher risk of CaP
  – Collected via post-DRE urine sample
  – Sensitivity 48%, Specificity 79%, not currently used for routine screening
  – May correlate with Gleason score

Imaging
- Preoperative imaging for locally advanced cancer:
  – Pelvic CT or MRI is indicated for locally advanced disease (PSA >20 ng/mL, Gleason score 8 or greater, or a T3/T4 tumor) to evaluate for pelvic lymph node involvement
  – Distal metastasis may be ruled out using Technetium 99 bone scan, axial MRI, PET, and immunoscintigraphy
  – Multiparametric prostate MRI using a 3T magnet and/or an endorectal coil is being touted to improve accuracy
  – Repeat or 1st time staging with bone scan and/or CT may be needed in selected patients who are significantly upstaged and/or upgraded after RP

Diagnostic Procedures/Surgery
Prostate biopsy rarely indicates the presence of pathologic T3 disease; seminal vesical biopsy may confirm T3

Pathologic Findings
- Clinically localized disease is upstaged if pathologic tissue from a prostatectomy indicate T3 or T4 disease
- The risk of cancer recurrence after prostatectomy is based on extracapsular extension, seminal vesicle involvement, lymph node involvement, and corresponds most strongly with a positive surgical margin
- A gross PSMs carry worse 5-r progression survivals vs. microscopic margins 65% vs. 40%
- PSM at the bladder neck, vas deferens, and posterolateral surface of the prostate have been shown to have a particularly poor progression-free outcomes in comparison to PSM at the apex, posterior, anterior, or lateral prostate
- With respect to the nerve-sparing technique, when patients are selected appropriately, no statistical difference has been shown in PSM in comparison to the nonnerve sparing technique

TREATMENT

GENERAL MEASURES
- The American Society of Therapeutic Radiation Oncology (ASTRO) and the American Urologic Association (AUA) have a joint guideline on the use of adjuvant and salvage radiotherapy after prostatectomy
  – They note clinical benefit of adjuvant radiotherapy in reducing clinical progression in

high-risk patients (seminal vesicle involvement, positive surgical margins, extra prostatic extension) while the impact on future development of metastasis and survival remains less clear
  - It also emphasizes the value of early intervention with a threshold PSA $\geq$ 0.2 ng/mL with a 2nd confirmatory after surgery to confirm relapse (2)
- Therapy is considered adjuvant if the postoperative PSA level is undetectable ($<$0.2 ng/mL)
- Therapy is considered salvage if there is a biochemical/PSA recurrence
- Lymph node metastasis is an indication for ADT, pelvic RT, or observation

MEDICATION

First Line

- Androgen deprivation therapy (ADT) using an LHRH agonist or GNRH antagonist with or without an oral antiandrogen is sometimes added to adjuvant or salvage EBRT although there is not yet level I evidence from RCTs in the adjuvant/salvage setting for pathologic T3/T4 disease
- Potential benefits of ADT must be balanced against the side-effect profile

Second Line

Newer generation oral hormonal therapies (abiraterone acetate, enzalutamide) may have future role in adjuvant and salvage therapy

SURGERY/OTHER PROCEDURES

- In the setting of clinical T3/T4 disease, extended lymph node dissection is gaining support in these patients (obturator, external iliac, internal iliac, and presacral nodes)
- Neoadjuvant ADT with leuprolide and flutamide for 3 mo prior to RP has shown to reduce positive margins, but has no impact on lymph node metastasis or 5-yr biochemical recurrence rate. It may be used in selected cases for technical downsizing
- Chemo hormonal downstaging trials are ongoing before RP for clinical T3/T4 disease

ADDITIONAL TREATMENT

Radiation Therapy

- 3 randomized trials have been completed demons-trating a benefit to early adjuvant radiation therapy
- Treatment is optimally offered after continence is restored, to allow healing to take place after surgery
- With a median follow-up of 12 yr, (Southwest Oncology Group [SWOG] 8794), confirmed a significant improvement in the risk of metastasis (43% vs. 54%) and overall survival (41% vs. 52%) among patients randomized to adjuvant radiation (3)
- The largest trial included 1,000 patients with T3 disease randomly assigned to 60 Gy of radiation vs. observation. At 5-yr, progression-free survival was significantly improved (74% vs. 53%), with no demonstration of an overall survival benefit (4)
  - A subsequent update suggested that the benefit might be limited to patients with positive surgical margins
- A German trial of 395 patients demonstrated a biochemical progression-free survival benefit (72% vs. 54%) to early radiation therapy in this pT3 group. The benefit of therapy was observed with or without positive margins (5)
- Genomic assays may allow more rationale decision making for post operative radiation

following radical prostatectomy (7)

Additional Therapies

Proton beam external radiotherapy is offered at selected major US centers. However, there is no Level I evidence that it is superior to photon-based radiotherapy using an intensity modulated method.

Complementary & Alternative Therapies

No level I evidence of benefit

ONGOING CARE

PROGNOSIS

- With salvage EBRT and persistent or increasing PSA levels after surgery 45% of patients were free of disease at 4 yr after salvage EBRT
  - Patients with no adverse risk features achieved a 4-yr progression-free probability of 77%. A nomogram based on established risk factors to more accurately identify patient-specific risks to assist in clinical decision-making is available (6)

COMPLICATIONS

- Morbidity from pelvic RT include radiation proctitis, cystitis, incontinence, ED, lymphedema, and stricture disease
- Morbidity from hormone therapy include hot flushes, breast tenderness, osteoporosis, diabetes mellitus, depression, and cardiac disease

FOLLOW-UP

Patient Monitoring

For pT3/T4 after RP; patients are generally followed every 3 mo for the 1st yr, every 6 mo for the next 2–5 yr and yearly thereafter depending on risk.

Patient Resources

- AUA Prostate Cancer Guide: http://www.auanet.org/content/media/pc08.pdf
- NCCN Patient Guidelines for Prostate Cancer: http://www.nccn.org/patients/patient_guidelines/prostate/index.html

REFERENCES

1. Cooke EW, Shrieve DC, Tward JD, et al. Clinical versus pathologic staging for prostate adenocarcinoma: How do they correlate? *Am J Clin Oncol.* 2012;35(4):364–368.
2. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. *J Urol.* 2013;190(2):144–149.
3. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term follow-up of a randomized clinical trial. *J Urol.* 2009;181:956–962.
4. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomized trial. *Lancet.* 2002;360:103–106.
5. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer

with postoperative undetectable prostate-specific antigen: ARO96-02/AUO AP 09/95. *J Clin Onc*. 2009;27(28):2924–2930.
6. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA*. 2004;291:1325–1332.
7. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;89(5):1038–1046.

ADDITIONAL READING

NCCN Prostate Cancer Guidelines:
http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (Accessed May 21, 2014)

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General
- Prostate Cancer, Locally Advanced (Clinical T3, T4)
- Prostate Cancer, Locally Advanced (Pathlogic T3, T4) Images
- PSA Elevation, General Considerations
  – PSA, General Considerations
- Reference Tables: TNM: Prostate Cancer
- Prostate Cancer, Positive Margin Following RP

CODES

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ICD10

- C61 Malignant neoplasm of prostate
- C79.11 Secondary malignant neoplasm of bladder
- C79.82 Secondary malignant neoplasm of genital organs

CLINICAL/SURGICAL PEARLS

- Pathologic T3/T4 prostate cancer includes extracapsular cancer than extends beyond the gland, without distant metastasis.
- High clinical stage, PSA levels, and Gleason score (from biopsy cores) predict more advanced pathologic staging.
- Level I evidence from 3 RCTs support adjuvant EBRT for high-risk pT3/T4 prostate cancer after RP.
- For patients who do not receive adjuvant EBRT, close follow-up with early salvage EBRT is very commonly practiced.
- There is no level I evidence for adding ADT to EBRT as part of adjuvant or salvage EBRT, but selected high-risk patients may benefit.

PROSTATE CANCER, METASTATIC (CLINICAL AND PATHOLOGIC N+, M+)

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BASICS

DESCRIPTION

- Metastatic prostate cancer (CaP) can be nodal disease discovered at prostatectomy or on imaging (N+), or can be distant spread (M+). Most commonly, it affects distant lymph nodes and bone.
- Can be the initial presentation or develop after previous local therapy for CaP, such as radiation therapy or RP.

EPIDEMIOLOGY

Incidence

With PSA screening, the number of men with metastatic disease at 1st presentation has declined over the last 20 yr (~4%, 2003–2009, SEER data).

Prevalence

Nearly 28,800 men die annually (US) from metastatic disease.

RISK FACTORS

- African American ancestry
- High-fat diet
- Family history

Genetics

None

PATHOPHYSIOLOGY

- CaP arises in prostate glandular epithelium and can spread through the lymphatics or hematogenously.
- Batson plexus are paravertebral veins that extend up from the pelvis to the dural sinuses. This plexus is likely responsible for the high rate of spread of CaP to the vertebral column.
- Testosterone and dihydrotestosterone are the primary regulators of prostate growth.
- 2 sources of androgens in men; testes (95% of total androgens); adrenal glands (remaining 5%).

ASSOCIATED CONDITIONS

Osteoporosis secondary to hormonal therapy

GENERAL PREVENTION

Early androgen blockade for high-risk patients with localized cancer may delay the development of detectable metastatic disease.

DIAGNOSIS

HISTORY

- Urinary symptoms can be indistinguishable from those of BPH and include increased urinary frequency, nocturia, difficulty initiating and maintaining a steady stream of urine, dysuria, and hematuria, and sexual dysfunction.
- The most common symptom of metastatic disease is bone pain, often in vertebrae, pelvis, or ribs.

PHYSICAL EXAM

- DRE may reveal a nodular or enlarged prostate, but the exam may be unremarkable.
- After RP the fossa may be empty or contain palpable recurrent cancer.
- Adenopathy may be detected in the supraclavicular and inguinal lymph nodes.
- Point tenderness elicited on vertebral bodies or rib cage may be indicative of spinal or epidural metastasis.
- CaP metastatic to the spine may result in neurologic symptoms, either from vertebral instability or epidural extension of tumor. Note any leg weakness or urinary and fecal incontinence.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum PSA should be obtained on all patients prior to the start of therapy and is a useful marker of response to therapy.
- Prostatic acid phosphatase is elevated in up to 67% of men with metastatic disease
- Monitor serum testosterone to verify that androgen ablation has testosterone <50 ng/dL

Imaging

- CT of the abdomen and pelvis and bone scan should be performed after initial diagnosis. Bone metastases are typically osteoblastic.
- Evaluate for hydronephrosis secondary to ureteral obstruction.

Diagnostic Procedures/Surgery

Biopsy of prostate or metastatic lesions is required to establish a diagnosis. Identification of visceral metastasis with neuroendocrine features may alter initial management to include initial chemotherapy.

Pathologic Findings

- Adenocarcinoma most common.
- Neuroendocrine carcinoma of the prostate is associated with high Gleason score (9–10), low or undetectable PSA levels, and visceral and lytic bone metastases.

DIFFERENTIAL DIAGNOSIS

- Paget disease; bone metastases from other malignancies
- Adenopathy can be due to lymphoma or other advanced malignancy.

TREATMENT

GENERAL MEASURES

- Androgen blockade for metastatic disease, which is usually considered noncurative.

- Androgen deprivation therapy (ADT) can be administered continuously as well as intermittently (intermittent hormonal therapy or IHT); studies suggest similar survivals when continuous combined androgen blockade (CAB) is compared to intermittent CAB, especially with lower disease burdens.

MEDICATION

First Line

- ADT (1)[B]
  - ADT to achieve castrate levels of testosterone, generally considered <50 ng/mL, with some advocating <20 ng/mL (similar to orchiectomy levels)
  - Testicular androgen secretion is regulated by the hypothalamus, and the pulsatile secretion of luteinizing hormone releasing hormone (LHRH)
  - LHRH agonists (leuprolide, goserelin, triptorelin) interfere with this pulsatile secretion, and after initial flare (testosterone increase) at 7–10 days, achieve medical castration at about 30 days.
  - LHRH antagonists (degarelix) rapidly decrease testosterone levels with 44% testosterone castration (<50 ng/dL) at day 1, 96% by day 3. No flare, so useful in situations such as spinal cord compression.
  - Antiandrogens (bicalutamide, flutamide, nilutamide) block the LHRH flare reaction initially caused by LHRH agonists and should be used for 7–10 days. Long-term use of antiandrogens + LHRH agonists past the flare period, or CAB is controversial.
  - ADT using high-dose bicalutamide (150 mg/d), called antiandrogen monotherapy, is associated with less side effects but may also be a less effective form of ADT and should not be routinely used (not FDA approved in US).
  - Initial chemohormonal therapy has recently been reported to extend survival in men presenting with newly diagnosed metastatic prostate cancer (4)
    - ECOG3805 clinical trial demonstrated a 12 month survival advantage when docetaxel was initially combined with androgen deptivation therapy

Second Line

- Most patients initially benefit from ADT, but the disease usually progresses after 1–4 yr
  - Castration-resistant CaP (CRPC): Progression on primary hormonal with a testosterone level of <50 ng/mL, and a rising PSA
  - With measurable disease on bone or CT scan of the abdomen and pelvis, the disease is classified as metastatic castration-resistant prostate cancer (mCRPC)
- Secondary hormonal therapy is often utilized for CRPC without metastasis
  - If on antiandrogen, the antiandrogen should be discontinued; this will result in a PSA decline in 5–20% of patients
  - Addition of an antiandrogen will result in PSA declines of 50% in 15–54% of patients, with median duration of response 4–6 mo
  - Ketoconazole blocks testicular and adrenal androgen synthesis; associated with $>50\%$ PSA decline in over 50% of patients
  - LHRH agonists are continued during therapy to prevent escape from androgen blockade
- Several systemic therapies have demonstrated improved overall survival for metastatic castrate-resistant disease and are discussed in detail in the section on Prostate cancer, rising

PSA following androgen ablation (Castratration Resistant Prostate Cancer (CRPC, and mCRPC), Section I.
  - Docetaxel, sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium 223
  - Mitoxantrone is also an FDA-approved agent for palliation of symptomatic CRPC
  - For asymptomatic or minimally symptomatic patients, sipuleucel-T immunotherapy can be used; other agents can be used with more significant symptoms
  - In patients with neuroendocrine features, androgen blockade should be initiated along with an immediate chemotherapy regimen incorporating cisplatin/etoposide, carboplatin/etoposide, or a docetaxel-based regimen

SURGERY/OTHER PROCEDURES

- Resection of solitary metastases is not generally performed with curative intent.
- Decompression of epidural metastatic CaP can result in stabilization of the spinal cord and neurologic symptoms. Best results are obtained if the procedure is performed within 24 hr of the onset of symptoms.
- Stabilization of weight-bearing bones (femur and hip) by internal fixation or replacement of the joint prophylactically may prevent fracture.
- In one randomized trial, immediate ADT was associated with improved overall and disease-specific survival among men who had pathologically positive lymph nodes after RP (2)[A]. However, this study was limited by sample size and lack of central pathologic review. In a randomized EORTC study with clinically node-positive disease, early ADT did not have any survival benefit. Because of the gradual natural history of CaP (median survival after development of metastasis after RP = 5 yr (3)[C]) and because the oncologic benefit of early ADT is uncertain, many consider it reasonable to delay ADT until symptoms or measurable disease on imaging are present, to minimize systemic adverse effects of ADT.

ADDITIONAL TREATMENT

Radiation Therapy

- Radiation can be used to palliate solitary painful bony metastases.
- Strontium^{89} and samarium^{153} (β-emitters) can palliate bone pain and are most useful for diffuse metastasis.
- Radium-223 (α-emitter) can also be used in the setting of symptomatic bone metastasis

Additional Therapies

- Bone health
  - Patients should receive calcium (1,200 mg/d) and vitamin D (800–1,000 IU/d) supplements.
  - With ADT, consider zoledronate 4 mg IV yearly, alendronate 70 mg PO weekly, denosumab (RANK ligand inhibitors Prolia 60 mg q6mo SQ for men on ADT or Xgeva with bone mets 120 mg SQ q4wk).
- Metastatic CRPC: Zoledronate 4 mg adjusted to renal function every 3–4 wk IV or denosumab (Xgeva) 120 mg SQ q4wk to prevent skelet al-related events.

Complementary & Alternative Therapies

Weight-bearing exercise and stopping smoking benefits osteoporosis.

ONGOING CARE

PROGNOSIS

- The estimated 5-yr survival of metastatic CaP is 28% (3)[C].
- For patients with lymph node–positive disease post-RP, adjuvant hormone ablation following RP increases overall survival by 2.6 yr vs. RP alone (13.9 vs. 11.3 yr) and reduces mortality risk by ~46%.
- With metastatic CaP starting androgen blockade, the median time to progression is 18–24 mo. The median survival once patients progress on androgen blockade is 12–19 mo.

COMPLICATIONS

- ADT: Hot flashes, loss of sexual function and libido, loss of muscle mass, decreased in bone mineral density, weight gain, diabetes, lipid profile changes, and neurocognitive dysfunction.
- In a metaanalysis of 8 randomized controlled trials, long-term ADT was not associated with an increased risk of death from cardiovascular causes, however.
- Antiandrogens: Increased liver function test.
- Skelet al-related events: Defined by pathologic fracture, spinal compression/vertebral body collapse, osteonecrosis of the jaw, radiation or surgery to bone, or change in antineoplastic therapy. Androgen blockade can cause osteopenia/osteoporosis; bisphosphonate/RANK ligand therapy can limit reductions in bone mineral density.
  - Zoledronic acid: Renal insufficiency, adjust based on creatinine.
  - Osteonecrosis of the jaw can result from bisphosphonates and RANK ligand inhibitors; avoid major dental work (extractions) on therapy; perform oral exam before starting.

FOLLOW-UP

Patient Monitoring

- Monitoring patients is controversial. With start of androgen blockade: Check PSA every 3 mo. Confirm castrate testosterone (<50 ng/dL) periodically and upon demonstration of rising PSA while on LHRH therapy.
- At PSA progression, antiandrogen should be withdrawn, and if the patient continues to progress, a CT scan of the abdomen and pelvis should be obtained.
- Timing of PSA testing during chemotherapy is controversial; usually every 3 wk.
- Serum creatinine should be monitored for patients on bisphosphonates. Zoledronic acid should not be given with a Cr >2 mg/dL.
- Monitoring for osteoporosis, obesity, insulin resistance, lipid alteration, and the concern of increased risk of diabetes and cardiovascular diseases in men on ADT should be considered.

Patient Resources

American Cancer Society. http://www.cancer.org/cancer/prostatecancer/index?sitearea=%26dt=10

REFERENCES

1. NCCN Practice Guidelines Version 1.2014. http://www.nccn.org./ Accessed January 6, 2014.
2. Messing, EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-

positive prostate cancer. *N Engl J Med.* 1999;341:1781–1788.
3. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281(17):1591–1597.
4. NIH-funded study shows increased survival in men with metastatic prostate cancer who receive chemotherapy when starting hormone therapy http://www.cancer.gov/newscenter/newsfromnci/2013/E3805 (Posted December 5, 2013).

ADDITIONAL READING

- Antonarakis ES, Eisenberger MA. Expanding treatment options for metastatic prostate cancer. *N Engl J Med*. 2011;364:2055–2058.
- Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med.* 2012;368(14):1314–1325.
- Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007;25(12):1596–1605.
- Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: A meta-analysis of randomized trials. *JAMA*. 2011;306(21):2359–2366.

See Also (Topic, Algorithm, Media)

- Antiandrogen Withdrawal Syndrome (Flutamide Withdrawal Syndrome)
- Prostate Cancer, General
- Prostate Cancer, Metastatic (Clinical and Pathologic N+, M+) Images ☼
- Prostate Cancer, Rising PSA Following Androgen Ablation (Castration-resistant Prostate Cancer,)
- PSA Elevation, General
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 196.5 Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
- 198.5 Secondary malignant neoplasm of bone and bone marrow

ICD10

- C61 Malignant neoplasm of prostate
- C77.4 Sec and unsp malig neoplasm of inguinal and lower limb nodes
- C79.51 Secondary malignant neoplasm of bone

CLINICAL/SURGICAL PEARLS

- ADT is the 1st-line treatment for metastatic CaP.
- There are several antiandrogen and chemo-immunotherapeutic options for men with ADT-refractory metastatic CaP.

- Bone-related issues should be considered in this population.

PROSTATE CANCER, POSITIVE MARGIN FOLLOWING RADICAL PROSTATECTOMY

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BASICS

DESCRIPTION

- Prostate cancer that extends to the margin of resection upon pathologic analysis of radical prostatectomy specimen
- May be reported as: Focal or extensive, solitary or multiple

EPIDEMIOLOGY

Incidence

- 5–27% for organ-confined prostate cancer (1)
- 17–65% for nonorgan-confined prostate cancer (1)

Prevalence

N/A

RISK FACTORS

- Higher preoperative prostate-specific antigen (PSA)
- Higher clinical stage
- Higher Gleason score
- Higher pathologic stage
- Surgeon experience

Genetics

None directly correlate with positive surgical margin (PSM)

PATHOPHYSIOLOGY

- 3 causes of PSM:
  - Tumor extends beyond prostate to margin of resection
  - Disruption of prostate capsule exposed cancerous glands
  - Artifact from intraoperative manipulation of prostate or pathologic processing

ASSOCIATED CONDITIONS

Nonorgan-confined prostate cancer: Higher likelihood of PSM compared to organ confined

GENERAL PREVENTION

- Do not dissect too closely at prostatic apex or posterolaterally since PSM frequently seen there
- For radical prostatectomy, choose surgical approach with most familiarity to surgeon

DIAGNOSIS

HISTORY

History of risk factors (higher PSA, clinical stage, and Gleason grade) may increase chance of PSM

PHYSICAL EXAM

Digital rectal exam has been shown to be unnecessary if PSA is undetectable

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Monitor PSA at follow-up visits
- In patients with PSM, there is 25–40% chance of subsequent biochemical recurrence (1)[B]

Imaging

- No additional imaging needed after radical prostatectomy for PSM unless there is suspicion of locoregional recurrence or metastatic disease
- Bone scan, pelvic MRI, and/or computer tomography scan may be considered if above suspected (2)[C]
- Indium In 111 ProstaScint is also indicated as a diagnostic imaging agent in postprostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease. Limited utility for use in this setting

Diagnostic Procedures/Surgery

None indicated

Pathologic Findings

- PSM is a pathologic diagnosis
  - Most common site is prostatic apex
  - Posterolateral margin and bladder neck also commonly involved
  - Note that capsule is missing at the apex, so PSM at the apex may be artifactual
- Often classified as: Focal or extensive, solitary or multiple
  - Extensive and/or multiple PSM increase chance of biochemical recurrence, but these subclassifications of PSM do not have greater predictive usefulness than comparing positive vs. negative surgical margin alone (1)[B]

DIFFERENTIAL DIAGNOSIS

- Nonorgan-confined disease with extraprostatic extension or locally advanced disease
- Iatrogenic capsular incision

TREATMENT

GENERAL MEASURES

- Surgical approach (open, laparoscopic, robotic) does not appear to influence rate of PSM (3)[B]
  - Use good surgical principles to avoid PSM
  - PSM vary by different pathologic sectioning
  - Surgical experience decreases rate of PSM

MEDICATION

First Line
N/A

Second Line
N/A

SURGERY/OTHER PROCEDURES
N/A

ADDITIONAL TREATMENT
Radiation Therapy
- External beam, delivered as 3D-conformal or intensity modulated
  – 64–65 Gy usual dose
- Adjuvant radiotherapy shown to decrease biochemical and local recurrence, and clinical progression (2)[A]
- Effect on subsequent metastasis and overall survival not as clear
- Treatment with adjuvant radiotherapy results in lower use of salvage treatment
- Since majority of patients with PSM do not develop clinical recurrence, immediate adjuvant radiotherapy may lead to overtreatment
- However, salvage radiotherapy may not be as effective for high-risk disease
- Controversy over use of immediate vs. salvage adjuvant therapy

Additional Therapies
- ·Radiation Therapy Oncology Group trial 9601 is investigating radiotherapy with or without long-term androgen deprivation in postprostatectomy men with pT3N0 disease or pT2N0 disease with a positive margin with PSA $\geq$0.2–4 ng/mL
  – Preliminary results show that 24 mo of antiandrogen therapy (bicalutamide) and radiotherapy improve biochemical-free survival and incidence of metastatic disease
  – Full results awaited
- Radiotherapy and androgen deprivation in combination after local surgery (RADICALS) trial is evaluating immediate adjuvant radiotherapy vs. salvage radiotherapy
  – Also addresses role of androgen deprivation
  – Results awaited

Complementary & Alternative Therapies
See “Additional Therapies” above

ONGOING CARE

PROGNOSIS
- Not all PSM result in biochemical recurrence, nor higher risk of metastatic disease and death, but those with PSM are at higher risk of both than those with negative margins; these risks are associated with other pathologic features as well
- Prediction tools such as http://nomograms.mskcc.org/Prostate/PostRadicalProstatectomy.aspx are used at some centers for decision making concerning postradical prostatectomy management
- Preliminary results with new genomic classifers may indicate which patients might benefit form adjuvant radiaion therap (4)

COMPLICATIONS

- Complications related to radiotherapy (2):
  - Grade 1 or 2 acute toxicities: Common, up to 45%
  - Grade 3 or 4 acute toxicities: Up to 20%
  - Up to 28% may develop late toxicities
    - Urinary incontinence, stricture more common than gastrointestinal toxicities (proctitis)

FOLLOW-UP

Patient Monitoring

- PSA every 3–6 mo for 1st 3–5 yr, then annually thereafter
  - Value $\geq$0.2 ng/dL after surgery with confirmatory value of $\geq$0.2 ng/dL defines biochemical recurrence

Patient Resources

American Cancer Society.
http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-recurrence

REFERENCES

1. Stephenson AJ, Wood DP, Kattan MW, et al. Location, extent, and number of positive surgical margins do not improve accuracy of predicting prostate cancer recurrence after radical prostatectomy. *Journal of Urology*. 2009;182:1357–1363.
2. Thompson IM, Valicenti R, Albertsen PC, et al. Adjuvant and salvage radiotherapy after prostatectomy: *ASTRO/AUA Guideline*. 2013. Available online at https://www.auanet.org/common/pdf/education/clinical-guidance/Radiation-After-Prostatectomy.pdf.
3. Eastham JA, Kattan MW, Riedel E, et al. Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol*. 2003;170:2292–2295.
4. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;89(5):1038–1046.

ADDITIONAL READING

Touijer K, Kuroiwa K, Eastham JA, et al. Risk-adjusted analysis of positive surgical margins following laparoscopic and retropubic radical prostatectomy. *Eur Urol*. 2007;52:1090–1096.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Radical Prostatectomy
- Prostate Cancer, Locally Advanced (Pathologic T3, T4)
- Prostate Cancer, Positive Margin Following Radical Prostatectomy Image ☼
- PSA Elevation, General
- Reference Tables: TNM: Prostate Cancer

CODES

ICD9

- 185 Malignant neoplasm of prostate
- V45.77 Acquired absence of organ, genital organs

ICD10

- C61 Malignant neoplasm of prostate
- Z90.79 Acquired absence of other genital organ(s)

CLINICAL/SURGICAL PEARLS

- PSM most commonly found at prostatic apex, posterolaterally, and bladder neck.
- Avoid overzealous dissection at these locations during radical prostatectomy in patients suspected of being high-risk for PSM.
- PSM are diagnosed pathologically and may be real or artifactual.
- Subset of men with PSM develop biochemical recurrence.
- Adjuvant radiotherapy decreases chance of biochemical and local recurrence but effect on metastatic disease and overall survival not clear.

PROSTATE CANCER, RISING PSA FOLLOWING ANDROGEN ABLATION (CASTRATION-RESISTANT PROSTATE CANCER, CRPC AND mCRPC)

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BASICS

DESCRIPTION

- Castration-resistant prostate cancer (CRPC) is defined as prostate cancer with disease progression despite effective androgen deprivation (serum total testosterone <50 ng/dL)
- CRPC patients are classified as having metastatic disease (bone or soft tissue visible on imaging) (mCRPC) or nonmetastatic disease (CRPC rising PSA without any radiographic evidence of metastasis)
- CRPC survival is improved significantly with more effective treatment options
- Synonym(s): The preferred term is castrate-resistant prostate cancer but sometimes called castrate refractory prostate cancer. Older terms such as hormone refractory or androgen-independent prostate cancer are not considered accurate
  - Latest data shows that in CRPC prostate cells are still sensitive to low levels of androgens

EPIDEMIOLOGY

Incidence

- 233,000 cases of prostate cancer will be diagnosed in the United States in 2014
- There will be 29,480 deaths due to prostate cancer in 2014
- The vast majority of patients who die with prostate cancer will die from progressive metastatic CRPC
- Historically the median survival with mCRPC is <2 yr; newer agents, most introduced since 2010, have improved overall survival by several months

Prevalence

N/A

RISK FACTORS

- No definitive tool is available to determine the risk of developing CRPC
  - Molecular biomarkers and genomic profiles are being explored for prognosis and treatment
- CRPC risk features for poor survival
  - Low hemoglobin
  - Elevated lactate dehydrogenase
  - Elevated alkaline phosphatase
  - Poor performance status
  - Visceral metastasis particularly liver metastasis
  - Narcotic use for pain
  - Nomogram based on these clinical features can predict overall prognosis for CRPC (1)

Genetics
Common chromosomal translocations found in CRPC include the TMPRSS2-ERG fusions. Epigenetic abnormalities are common in CRPC

PATHOPHYSIOLOGY
Restored androgen receptor (AR) activity is a major driver of therapeutic failure and CRPC development. This may occur through intracrine (intracellular) androgen synthesis, AR deregulation; AR mutation and alternative splicing; and posttranslational modifications and cofactor alterations.

ASSOCIATED CONDITIONS
- Fatigue, muscle wasting, metabolic syndrome
- Bone pain/fracture
- Hematuria, urinary retention
- Edema
- Spinal cord compression
- Anemia
- Renal failure, usually due to hydronephrosis
- Cognitive dysfunction

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY
- Prostate cancer history including Gleason score, disease stage at diagnosis, initial treatment for localized prostate cancer
- Time of 1st diagnosis of metastatic disease
- Past hormonal treatments including time when treatments were started
- PSA history
- Extent of disease at the time of diagnosis and also current extent of disease on the bone and CT/MRI scan
- Recent changes in bowel and urinary habits
- Potency
- New neurologic symptoms
- Past medical history including any specific cardiac, renal, or gastrointestinal disease
- Performance status
- Mental status evaluation
- Current medications and allergies
- Caregiver
- Family history of prostate cancer or other cancers
- Smoking, alcohol, and drug history

PHYSICAL EXAM
- Examine for adenopathy
- Gynecomastia

- GU and rectal exam
- Extremity edema and swelling
- Neurologic exam with focus on lower extremity weakness and sensation

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Complete blood count
- Renal, electrolyte, and liver function panel
- Testosterone: Confirm <50 ng/dL
- Prostate-specific antigen (PSA)

Imaging

- Determine presence of radiographic metastasis as a guide to treatment
- Bone scan, CT, or MRI of the abdomen and pelvis at baseline and then every 6–12 mo or based on clinical setting
- Bone density as needed

Diagnostic Procedures/Surgery

- Postvoid residue (PVR) to evaluate for urinary retention
- Cystoscopy and other tests as needed

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Bone pain may also be due to degenerative joint disease, osteoarthritis, Paget disease, or secondary malignancy
- Weight loss due to depression, other malignancies, or failure to thrive
- Anemia related to iron and vitamin deficiency, second malignancy (ie, multiple myeloma), or prior therapies

TREATMENT

GENERAL MEASURES

- Initial strategies for nonmetastatic CRPC are unclear as no randomized clinical trial has shown survival advantage in the setting of no radiographically measurable metastatic disease
- Continuing medical castration recommended
- Verify castrate levels of testosterone. If not <50 ng/dL, consider alternative LHRH agonist/antagonist administration or orchiectomy if not castrate
- Define the treatment objectives for patients: Palliative vs. prolonging survival
- Disease progression based on a rapidly rising PSA, objective changes on bone scan or CT/MRI scan or symptoms from the metastatic CRPC
- Sequencing of newer agents in the setting of disease progression remains under study
- AUA, ASCO, NCCN, and other groups have issued guidelines for the management of CRPC

MEDICATION

First Line

- There are multiple treatment options based on disease acuity and prior treatment history such as before or after docetaxel-based chemotherapy; clinical trials always need to be considered.
- Often secondary or tertiary hormonal manipulation is the initial therapy in asymptomatic mCRPC. These include
  - Antiandrogen withdrawal (ie, stopping bicalutamide, etc.)
    - Paradoxical decrease in PSA after stopping
  - 2nd-line hormonal therapy with nonsteroidal antiandrogen: bicalutamide, flutamide, nilutamide
    - Rarely results in a durable response
- Immunotherapy with sipuleucel-T: Autologous immunotherapy for minimally symptomatic or asymptomatic mCRPC; improved survival (2)
- Androgen biosynthesis inhibitors:
  - Ketoconazole/hydrocortisone (not FDA approved for CRPC); a high-dose ketoconazole with steroid supplementation
  - Abiraterone acetate/prednisone
    - 1,000 mg (four 250 mg tabs) with 5-mg prednisone BID
    - Specific CYP17 inhibitor; approved both pre- and postchemotherapy
    - Improved overall survival (3,4)
- Pure AR antagonist:
  - Enzalutamide (160 mg PO daily)
  - Blocks AR translocation to nucleus; approved for both pre and post docetaxel chemotherapy in mCRPC (5,6)
- First-line chemotherapy: Docetaxel 75 mg/m^2 IV every 3 wks w/prednisone (5 mg PO twice daily) (7)
- Radium 223 (Alpharadin)
  - mCRPC with symptomatic bone metastases (not for visceral disease as only site)
  - 6 injections at 4-wk intervals
  - Delays time to disease progression and improves survival; low rate of adverse events (8)

Second Line

- Consider abiraterone or enzalutamide with mCRPC progression if either was not used previously
- Chemotherapy: Cabazitaxel (20–25 mg/m^2 IV every 3 wk) with 10-mg prednisone daily (9)
  - Approved postdocetaxel
- Mitoxantrone; chemotherapy FDA approved for palliation; limited utility
- Consider clinical trials

SURGERY/OTHER PROCEDURES

- Urinary diversion (stents or percutaneous nephrostomy) in cases of hydronephrosis and renal insufficiency
- Bladder outlet procedures such as TURP for obstruction
- Decompressive laminectomy for spinal cord compromise

ADDITIONAL TREATMENT

Radiation Therapy

- Samarium-153 or Strontium-89
  – For palliation painful bony mets; no survival benefit; cause bone marrow suppression
- Palliative radiotherapy
  – Focal painful bone lesion
  – Epidural disease associated with neurologic symptoms or pain, or spinal cord compression
- Radium 223 (alpharadin) see “First Line" above

Additional Therapies
- Daily calcium (≥1,200 mg daily)/vitamin D (800–1,000 IU daily)
- Bisphosphonate (zoledronic acid) or denosumab for bone health for mCRPC to reduce skeletal-related events (fractures, etc.)
- High dose of steroids (dexamethasone 2–10 mg) useful in acute pain syndromes or neurologic compromise
- Adding nonsteroidal anti-inflammatory drugs or narcotics for pain
- Palliative care or pain specialist referral for refractory pain

Complementary & Alternative Therapies
May be helpful but randomized clinical trials needed to establish clinical benefit

ONGOING CARE

PROGNOSIS
Median survival of patients with CRPC range from 18 to 27 mo depending on the extent of disease

COMPLICATIONS
- Altered mental status
- Anemia
- Bone marrow failure
- Cord compression with loss of motor or sensory function
- Cranial nerve deficits from prostate cancer in the base of the skull
- Depression
- Disseminated intravascular coagulation (DIC)
- Fatigue
- Hematuria
- Muscle wasting/weakness
- Pain
- Pathologic fractures (vertebral, hip, and long bone)
- Rectal bleeding
- Renal failure (acute and chronic)
- Urinary retention

FOLLOW-UP
Patient Monitoring
Frequency of visits, exams, blood work, and radiographs will be dependent upon the patient’s acuity and prostate cancer symptoms

Patient Resources

- American Cancer Society
  http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-references
- National Cancer Institute (NCI) http://www.cancer.gov/cancertopics/treatment/prostate

REFERENCES

1. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol*. 2003;21(7):1232–1237.
2. Kantoff PW, Higano CS, Shore ND, et al. ; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411–422.
3. de Bono JS, Logothetis CJ, Molina A, et al. ; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995–2005.
4. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148.
8. Scher HI, Fizazi K, Saad F, et al. ; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197.
9. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–433.
5. Tannock IF, de Wit R, Berry WR, et al. ; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–1512.
6. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213–223.
7. de Bono JS, Oudard S, Ozguroglu M, et al. ; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376(9747):1147–1154.

ADDITIONAL READING

- Basch E, Loblaw DA, Oliver TK, et al. Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline; JCO, Online before print September 8, 2014, doi: 10.1200/JCO.2013.54.8404.
- Cookson MS, Roth BJ, Dahm P, et al. Castration-Resistant Prostate Cancer: AUA Guideline. *J Urol*. 2013;190(2):429–438.
- Gomella LG, Petrylak DP, Shayegan B. Current management of advanced and castration resistant prostate cancer. *Can J Urol*. 2014;21(2 suppl 1):1–6.
- Knudsen KE, Kelly WK. Outsmarting androgen receptor: Creative approaches for targeting aberrant androgen signaling in advanced prostate cancer. *Expert Rev Endocrinol Metab*. 2011;6(3):483–493.
- Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009;361(8):745–755.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General
- Prostate Cancer, Metastatic (N+, M+)
- Prostate Cancer, Rising PSA Following Androgen Ablation (Castration-resistant Prostate Cancer) Algorithm

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 790.93 Elevated prostate specific antigen [PSA]
- V45.77 Acquired absence of organ, genital organs

ICD10

- C61 Malignant neoplasm of prostate
- R97.2 Elevated prostate specific antigen [PSA]
- Z90.79 Acquired absence of other genital organ(s)

CLINICAL/SURGICAL PEARLS

- Castration resistant prostate cancer must be classified as with (mCRPC) or without (CRPC) radiographic metastasis.
- Bone or visceral metastasis will evolve if not initially present.
- Androgen–androgen receptor axis remains the key survival factor and treatment target for CRPC.
- Androgen receptor targeted therapy, immunotherapy, chemotherapy, and bone-targeted therapy are all effective to improve survival.

PROSTATE CANCER, UROTHELIAL

Eric A. Klein, MD, FACS
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BASICS

DESCRIPTION

- 1st described in 1952 by Melicow and Hollowell—originally noted as Bowen's disease of the prostatic urethra (1)
- Can occur in 1 of the 3 forms
  - Primary urothelial carcinoma (UC) of the prostate
  - Direct extension of bladder UC
  - Nondirect extension of bladder UC
- Multiple prior staging systems
- Primary UC of the prostate—TNM staging 2001
  - Tis pu—carcinoma in situ (CIS) affecting prostatic urethra
  - Tis pd—CIS affecting prostatic ducts
  - T1—tumor invading subepithelial connective tissue
  - T2—tumor invading prostatic stroma, spongiosum body, periurethral muscle
  - T3—tumor invading cavernous body prostatic capsule or bladder neck (extraprostatic extension)
  - T4—tumor that invades surrounding organs
- Prostatic UC concurrent with bladder UC
  - Prior TNM staging defined prostatic invasion of bladder UC as T4a disease
  - However, given the heterogeneity of this classification, did not accurately predict survival
  - Most recent TNM classification (2010) clarifies T4a as prostatic invasion from direct transmural or extravesical spread
  - Stromal invasion from subepithelial invasion of prostatic urethra classified as organ confined disease
- Synonyms: Transitional cell carcinoma (TCC)

EPIDEMIOLOGY

Incidence

- Of all patients with bladder UC undergoing cystoprostatectomy, 12–48% will have prostatic involvement (1).
- However, underreporting of prostatic involvement likely present in radical cystectomy specimens.
- Prostatic involvement of UC is a predictor of understaging in recurrent nonmuscle invasive bladder UC (2).
- Stromal invasion of the prostate is present in 7–17% of cystectomy specimens (1).
- Primary UC of the prostate is rare malignancy—~1–4% of all primary prostatic tumors (1).

Prevalence

N/A

RISK FACTORS

- Risk factors for prostatic involvement
  - CIS of the bladder
  - Multifocal disease in bladder
  - High-stage bladder UC
  - Previous involvement of prostate
  - Tumors involving trigone or bladder neck
- Risk factors for stromal invasion—presence of CIS (odds ratio 3.2) and location of tumor at or below trigone (odds ratio 3.3) (2)

Genetics

- Genetics:
  - No specific genes associated with prostatic UC

PATHOPHYSIOLOGY

- May involve any part of the prostatic urethra, prostatic duct system, or prostate stroma
- Arises from extension of bladder primary tumor, implantation of malignant cells, or transformation secondary to carcinogenic field effect
- Metastases commonly to bone, lung, liver

ASSOCIATED CONDITIONS

Almost all cases (>95%) associated with bladder UC

GENERAL PREVENTION

General Prevention: Prevention strategies similar as to bladder UC

DIAGNOSIS

HISTORY

- Risk factors similar to bladder UC—tobacco exposure, chemical/workplace exposures
- Hematuria is the most common complaint
- Other symptoms include obstructive voiding symptoms, hematospermia, or systemic symptoms (bone pain, fatigue, weight loss)

PHYSICAL EXAM

- Hematuria or bloody urethral discharge
- Lymphadenopathy
- Abnormal digital rectal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA: Elevations rare in UC
- Urine studies: Urinalysis, urine cytology

Imaging

- Staging workup involves abdominal and chest imaging (CT vs. MRI) to identify local, regional, and distant spread
- Bone scan: UC lesions osteolytic vs. adenocarcinoma (ADC) lesions osteoblastic

Diagnostic Procedures/Surgery

- Cystoscopy—sensitivity 83.3%, specificity 95.1% (2)[C]
  - Focus on macroscopic disease and concurrent bladder lesions
  - Unlikely to find microscopic disease or CIS
- Transurethral biopsy (3)[C]
  - No clear consensus on timing or methods
  - Spectrum of sampling recommended in literature from few resectoscope swipes to complete TURP
  - Pathologic analysis shows involvement most frequently observed around verumontanum
  - Biopsies recommended if positive cytology and/or macroscopic lesions
- Methods of biopsy have varying accuracy (1)[C]
  - Transurethral resection (TUR) biopsy is most accurate: 90% accuracy
  - Fine needle aspirate (FNA) biopsies: 40% accuracy
  - Transrectal needle biopsy: 20% accuracy
- Biopsies poor at accurately detecting stromal invasion—sensitivity 53%, specificity 77%, positive predictive value (PPV) 45%
- Diagnosis of primary UC of prostate requires both transrectal prostate biopsy and random biopsies of bladder to exclude concurrent UC in the bladder (4)[C].

Pathologic Findings

- Urothelial cancer in situ (CIS) of the prostate:
  - Can involve the prostatic urethra, the prostatic ducts, and the prostatic acini.
  - Most prostate urothelial CIS arises along with bladder urothelial neoplasia or from pagetoid spread from the bladder into the prostate.
  - Partial or complete replacement of urethra or duct by atypical urothelial cells with pleomorphic nuclei, coarse chromatin, and frequent mitoses. Fibrosis and chronic inflammation may be seen.
- Invasive UC into prostatic stroma consists of irregular nests, clusters, or single atypical cells that infiltrate prostatic tissue. There are 2 distinct pathways that invade the prostate:
  - Invasive carcinoma arising from the prostatic urethra and duct, which is often associated with CIS within the prostatic duct or acini.
  - Prostatic stroma invasion, in which bladder cancer penetrates from posterior periprostatic soft tissue or the bladder neck.
- Immunohistochemistry (IHC) of prostatic urethral carcinoma is identical to bladder UC: Positive for cytokeratin (CK) 7 (90%), and high–molecular-weight CK (HMWCK) 34βE12 (59%), and do not stain positive for PSA or PAP.

DIFFERENTIAL DIAGNOSIS

- High-grade prostatic intraepithelial neoplasia (HGPIN)
- Prostatic adenocarcinoma
- Other uncommon prostatic tumors

TREATMENT

GENERAL MEASURES

- Risk reduction
- Assessment of the degree of invasion is imperative—management decision strongly

dependent on this

MEDICATION

First Line

- Bacille Calmette–Guerin (BCG)
  - – As with primary bladder UC, BCG efficacious for prostatic urethra CIS
  - – Evidence regarding depth of penetration of BCG into prostatic stroma is unclear
  - – CIS of prostatic urethra has response rates to BCG of ~70–100%. Response rate when combined with bladder primary decreases to 47–72% (1)[C].
  - – Response rate of bladder CIS of prostatic urethra to BCG immunotherapy is ~70–100%.
  - – Some propose TUR prior to BCG therapy to increase exposure—improved prevention of recurrence compared to TUR alone (5)[C].
  - – Absolute contraindications to BCG: Active urinary infection, gross hematuria, traumatic catheterization.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Options include TUR alone, TUR with BCG (as in “First line" above), and radical cystoprostatectomy
- Radical cystoprostatectomy is the treatment of choice for stromal-invasive prostatic UC. It should also be recommended for patients with progression or recurrence after nonsurgical therapies. (1,2,5)[C]
- Cystoprostatectomy may also be considered as treatment for prostatic UC involving the prostatic ducts.
- Pelvic lymphadenectomy should be performed as with primary bladder UC.
- Options for diversion similar to bladder UC. While debated, prostatic urethral involvement of UC is not an absolute contraindication to orthotopic diversion (1).

ADDITIONAL TREATMENT

Radiation Therapy

Radiotherapy has insufficient data to make recommendations (1)[C]

Additional Therapies

- Chemotherapy
- Data not sufficient to evaluate use of neoadjuvant/adjuvant chemotherapy with respect to prostatic UC (1)[C]. Data from bladder UC shows ~5% survival advantage with neoadjuvant chemotherapy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Degree of prostatic invasion has prognostic implications with respect to 5-yr survival rates (1)

  – Involvement of the urethral mucosa: 100%
  – Ductal/acinar involvement: 50%
  – Stromal invasion: 40%
- In addition, the path of invasion from concurrent bladder UC also has significant prognostic role on 5-yr survival rate (1)
  – Contiguous from bladder: 7% survival
  – Noncontiguous from bladder: 46%
- Prostatic stromal invasion is associated with higher rates of node-positive disease as well as decreased survival (3)[C]
- Decreased survival associated with prostatic stromal invasion persists regardless of concurrent bladder UC stage (4) or surgical resection (3)[C]

COMPLICATIONS

- Adverse reactions to BCG therapy
  – Local reactions include hematuria, fever, dysuria
  – BCG infectious complications include fevers and/or sepsis, and are managed with hospitalization and antibiotics (eg, isoniazid, rifampin, ethambutol, and fluoroquinolones)
- Erectile dysfunction may occur after cystoprostatectomy
- Bowel diversion risks include electrolyte abnormalities, nutritional deficiencies, bowel obstruction, and ureteral strictures

FOLLOW-UP

Patient Monitoring

- Detection of prostatic relapse can be difficult, requiring frequent and/or lifelong biopsies of bladder, neck, and prostate.
- Surveillance of prostatic urethra recommended with high-risk bladder UC or prior prostatic involvement.
- Monitor with urine cytology, cystoscopy, and transurethral prostate biopsies.
- Biopsy is surveillance of choice with positive cytology and no identifiable bladder lesion. (1)
- Random biopsies occasionally recommended given frequent microscopic disease.

Patient Resources

N/A

REFERENCES

1. Walsh DL, Chang SS. Dilemmas in the treatment of urothelial cancers of the prostate. *Urol Oncol*. 2009;27(4):352–357.
2. Roupret M, Wood D, Bochner BH, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Urothelial carcinoma of the prostate. *Eur Urol*. 2013;63(1):81–87.
3. Liedberg F, Chebil G, Månsson W. Urothelial carcinoma in the prostatic urethra and prostate: Current controversies. *Expert Rev Anticancer Ther*. 2007;7(3):383–390.
4. Esrig D, Freeman JA, Elmajian DA, et al. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. *J Urol*. 1996;156(3):1071–1076.
5. Palou J, Baniel J, Klotz L, et al. Urothelial carcinoma of the prostate. *Urology*. 2007;69(1 suppl):50–61.

ADDITIONAL READING

Patel AR, Cohn JA, Abd El Latif A, et al. Validation of new AJCC exclusion criteria for subepithelial prostatic stromal invasion from pT4a bladder urothelial carcinoma. *J Urol*. 2013;189(1):53–58.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, Urothelial, Invasive (T2/3/4)
- Bladder Cancer, Urothelial, Superficial (CIS, Ta, T1)
- Prostate Cancer, General
- Prostate Cancer, Urothelial Images

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 198.1 Secondary malignant neoplasm of other urinary organs
- 233.6 Carcinoma in situ of other and unspecified male genital organs

ICD10

- C61 Malignant neoplasm of prostate
- C79.11 Secondary malignant neoplasm of bladder
- D09.19 Carcinoma in situ of other urinary organs

CLINICAL/SURGICAL PEARLS

- Incidental prostatic involvement frequently found at cystoprostatectomy.
- Detecting stromal invasion important for determination of appropriate therapy.
- Involvement of prostatic urethra only may be treated with BCG therapy.
- Stromal invasion of prostate necessitates radical cystoprostatectomy.
- Prognosis highly dependent on degree of prostatic invasion.

PROSTATE CANCER, VERY LOW RISK AND ACTIVE SURVEILLANCE

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BASICS

DESCRIPTION

- The National Comprehensive Cancer Network (NCCN) (1) defines very–low-risk prostate cancer (PCa) with the following criteria: Clinical stage T1c, prostate-specific antigen (PSA) <10 ng/mL, PSA density <0.15 ng/mL/g, biopsy Gleason score ≤6, ≤2 positive biopsy cores, and ≤50% cancer in any 1 core.
  - This definition is based on the work of Epstein et al. (2) which identified parameters associated with low-volume organ-confined (ie, insignificant) PCa at the time of radical prostatectomy.
- Active surveillance (AS) aims to spare men with insignificant tumors the side effects of treatment while maintaining the ability to intervene with curative intent upon the detection of disease progression.
  - The goals of AS are accomplished by carefully following men with serial PSA measurements, digital rectal exams (DREs), and prostate biopsies.
- AS is most appropriate for men with very–low-risk PCa and a life expectancy of <20 yr, or for those with low-risk PCa (defined by the NCCN as clinical stage T1 to T2a, biopsy Gleason score ≤6, and PSA <10 ng/mL) and a life expectancy of <10 yr (1).
- The exact criteria for AS enrollment vary by institution.
  - Triggers for intervention while on AS also vary by center, but typically include violation of the enrollment criteria or a rapid rise in PSA.
    - Dahabreh et al. (3) have reviewed the enrollment and progression criteria used at number of different institutions.

EPIDEMIOLOGY

Incidence

- ~240,000 new cases of PCa are diagnosed annually in the United States.
- >90% of new cases will be clinically localized.
- Up to 40% cases would have remained clinically insignificant had they not been detected on routine screening.

Prevalence

An estimated 2.6 million men in the United States carry a diagnosis of PCa.

RISK FACTORS

- Age
- Family history/genetics
- African American race
- Possibly obesity and a Western diet

Genetics

Mutations in a number of genes have been linked to PCa including BRCA1, BRCA2, HOXB13, and HPC1.

PATHOPHYSIOLOGY

- A combination of genetic, hormonal, and environmental factors underlies the development of PCa.
- >95% of all tumors are adenocarcinoma.
  - Other histologic types include transitional cell, small cell, and sarcoma.
    - NCCN risk categories and AS only pertain to adenocarcinoma.
- High-grade prostate intraepithelial neoplasia is felt to be a precursor to adenocarcinoma.
- Early-stage adenocarcinoma is androgen dependent. As PCa becomes more advanced, tumors dedifferentiate and lose this dependency.
- ~70% of PCa arise from the peripheral zone of the prostate.
- Tumors are often multifocal.

ASSOCIATED CONDITIONS

- Many men with PCa also have benign prostatic hyperplasia (BPH)/lower urinary tract symptoms.
  - BPH is not a precursor to PCa.

GENERAL PREVENTION

- The 5α-reductase inhibitors (5-ARIs) finasteride and dutasteride have been shown in 2 randomized clinical trials (PCPT and REDUCE) to decrease the incidence of PCa.
  - These medications, however, failed to receive FDA approval for PCa prevention due to their suggested association with increased risk of high-grade tumors (controversial).
- The SELECT trial showed that daily selenium and/or vitamin in E do not prevent PCa and should not be recommended to patients.

DIAGNOSIS

HISTORY

- Uniformly asymptomatic.
  - Typically detected on prostate biopsy performed for an elevated PSA and/or finding of a prostate nodule on DRE.
  - Occasionally detected at the time of transurethral resection of the prostate for BPH.

PHYSICAL EXAM

Very–low-risk PCa has no findings on DRE (clinical stage T1c).

DIAGNOSTIC TESTS & INTERPRETATION

Lab

PSA <10 ng/mL and PSA density <0.15 ng/mL/g are required for the definition of very–low-risk PCa.

Imaging

- Transrectal ultrasound is used to guide template-based prostate biopsies.
- A bone scan and/or cross-sectional imaging are unnecessary due to the exceedingly low risk of metastatic disease.

- Magnetic resonance imaging (MRI) of the prostate is currently under investigation for its utility in evaluating tumor extent and the presence of high-grade disease.

Diagnostic Procedures/Surgery

- PCa is definitively diagnosed with prostate biopsy.
  - Most commonly performed in the office setting using transrectal ultrasound.
    - A 10–12-core biopsy should be performed to ensure adequate sampling of the prostate.
    - Requires only local lidocaine for analgesia.
    - A hypoechoic lesion may represent an area of cancer but is not a sensitive finding.
  - Transperineal biopsy is typically reserved for men with several negative biopsies in whom PCa is still suspected.
    - Allows for systematic saturation biopsies using a grid-based approach.
    - Requires general anesthesia.
  - Image fusion biopsy combining ultrasound/MRI images are being explored.

Pathologic Findings

- Biopsy Gleason score ≤ 6 and ≤ 2 positive cores with $\leq 50\%$ cancer in each core are required for the definition of very–low-risk PCa.
- Evolving use of genomic assays based on the prostate biopsy to determine risk of progression on AS (Oncotype DX and Prolaris).

DIFFERENTIAL DIAGNOSIS

- Localized PCa:
  - BPH, prostatitis (granulomatous, acute, or chronic), recent instrumentation, nonadenocarcinoma prostate malignancy (sarcoma, urothelial carcinoma)

TREATMENT

GENERAL MEASURES

- Adequate patient evaluation and review of all treatment options is essential
- Identification of patients who may be an appropriate candidate for AS

MEDICATION

First Line

- No role for chemotherapy or androgen deprivation for men who are candidates for AS.
- 5-ARIs do not appear to prevent disease progression of men on AS.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical prostatectomy may be offered to men who desire treatment.
  - A pelvic lymph node dissection may be omitted given the low risk of lymph node metastases in this population.
  - Comparing open to robotic or laparoscopic surgery, outcomes appear to be equivalent between surgical approaches (4).
  - Major side effects of surgery include urinary incontinence and erectile dysfunction.

ADDITIONAL TREATMENT

Radiation Therapy

- External beam radiation therapy or brachytherapy are acceptable alternatives to AS and surgery.
  - Adjuvant hormonal therapy is not indicated with either approach in this group of men.
  - When external beam radiation therapy is performed, treatment with either intensity-modulated or 3-dimensional conformal radiation therapy should be utilized to limit toxicity to surrounding organs.
  - Brachytherapy should be avoided in men with symptoms of bladder outlet obstruction (high International Prostate Symptom Score) due to the risk of worsening lower urinary tract symptoms.
  - Major side effects of radiation include urinary incontinence, irritative voiding symptoms, erectile dysfunction, radiation induced proctitis, hemorrhagic cystits and secondary malignancies most commonly of the bladder and rectum.

Additional Therapies

- Technologies for focal and hemi- ablation are currently in the early phases of investigation.
  - Modalities include cryotherapy, high intensity focused ultrasound, interstitial laser and electroporation.

Complementary & Alternative Therapies

Low fat diet appropriate recommendation

ONGOING CARE

PROGNOSIS

- Up to 30% of men enrolled in AS will be reclassified and go onto require some form of treatment.
  - It remains unknown if these men would have had a superior oncologic outcome had they undergone immediate treatment.

COMPLICATIONS

- AS spares men with insignificant tumors the side effects of unnecessary treatment.
- The major risk of AS is missing the opportunity to intervene when cure is still possible.
- A small percentage of men will experience an infectious or bleeding complication related to a prostate biopsy.

FOLLOW-UP

Patient Monitoring

- The optimal protocol for monitoring men on AS is unknown.
  - Most advocate for biannual PSA measurements with DRE and annual 12–14-core prostate biopsy.
    - PSA kinetics do not appear to be helpful in predicting disease progression (5).
- Monitoring for disease progression is not indicated after age 75 of when life expectancy is <10 yr.

Patient Resources

- The NCCN Guidelines for Patients: Prostate Cancer. (http://www.nccn.org/patients/guidelines/prostate/)

- What You Need to Know About Prostate Cancer from the National Cancer Institute. (http://www.cancer.gov/cancertopics/wyntk/prostate/prostate.pdf).

REFERENCES

1. NCCN Practice Guidelines Version 1. 2014. http://www.nccn.org./ Accessed January 6, 2014.
2. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271:368–374.
3. Dahabreh IJ, Chung M, Balk EM, et al. Active surveillance in men with localized prostate cancer: A systematic review. *Ann Intern Med*. 2012;156:582–590.
4. Magheli A, Gonzalgo ML, Su LM, et al. Impact of surgical technique (open vs laparoscopic vs robotic-assisted) on pathological and biochemical outcomes following radical prostatectomy: An analysis using propensity score matching. *BJU Int*. 2011;107:1956–1962.
5. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol*. 2010;28:2810–2816.

ADDITIONAL READING

- Heidenreicha A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*. 2011;59:61–71.
- Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007;177:2106–2131.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, General Considerations
- Prostate Cancer, Genomic Markers
- Prostate Cancer, Localized (T1, T2)
- PSA Elevation, General Considerations

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 790.93 Elevated prostate specific antigen [PSA]
- V76.44 Screening for malignant neoplasms of prostate

ICD10

- C61 Malignant neoplasm of prostate
- R97.2 Elevated prostate specific antigen [PSA]
- Z12.5 Encounter for screening for malignant neoplasm of prostate

CLINICAL/SURGICAL PEARLS

- A large percentage of older men with screen-detected PCa will have insignificant tumors and, therefore, not benefit from intervention.
- To avoid the potential morbidity associated with treatment, AS should be offered to men

with very–low-risk PCa and a life expectancy of <20 yr.

- The optimal follow-up protocol is not well defined but typically includes biannual PSA measurements with DRE and annual 12–14-core prostate biopsy.
- PSA kinetics are less useful than biopsy findings for accurately reclassifying men while on AS.
- It is unknown if men reclassified on AS would have been better served with immediate treatment; however, long-term data from a number of centers suggest good oncologic outcomes with this management strategy.

PROSTATE, ABSCESS

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BASICS

DESCRIPTION

- Prostate abscess is an infection of the prostate with focal accumulation of pus within the prostate gland
- Difficult to initially clinically distinguish from acute bacterial prostatitis
- Usually as a result of ineffective antibiotic therapy for acute prostatitis
  – Rare in nonhospitalized patients

EPIDEMIOLOGY

Incidence

Decreasing with widespread use of antibiotics

Prevalence

Diagnosed in 0.2% of patients with urologic symptoms, 0.5–2.5% of patients hospitalized for prostatic symptoms (1)

RISK FACTORS

- Bladder outlet obstruction, history of bacterial prostatitis
- Chronic hemodialysis
- Compromised immune system (eg, HIV/AIDS, diabetes, etc.)
- Indwelling catheters
- Lower urinary tract instrumentation
- Sexually transmitted infections

Genetics

N/A

PATHOPHYSIOLOGY

- Usually an ascending infection in association with poor bladder emptying.
- Urethral infection combined with intraprostatic reflux of infected urine causes acute prostatitis.
- Acute prostatitis can, in patients with immunosuppression or other risk factors, progress to abscess.
- Hematogenous dissemination, especially with *Staphylococcus* sp. seen in immunocompromised patients/IV drug users.
- Most common etiologic agent is *Escherichia coli* (2)[B].
- With the advent of antibiotics, the incidence of *Neisseria gonorrhea* as causative agent has decreased significantly.
- Most common etiologic agent seen in emphysematous prostate abscess (EPA) is *Klebsiella pneumoniae* (3)[B].

- With severe immunocompromise, such as HIV; more unusual organisms such as TB, *Cryptococcus*, histoplasmosis, and *Candida* should be considered.
- Melioidosis is an infection (usually abscesses in many sites including the prostate).
  - Caused by the gram-negative *Burkholderia pseudomallei.*
  - Usually associated with diabetes.
  - Very high prevalence in East Asia and Northern Australia.

ASSOCIATED CONDITIONS

- Any disease process that causes immunocompromise:
  - Cancer
  - Chronic renal failure, hemodialysis
  - Cirrhosis
  - Diabetes
  - HIV/AIDS

GENERAL PREVENTION

- Aimed at preventing and treating sexually transmitted infections
- Relieving/improving signs/symptoms of bladder outlet obstruction
- Diabetic glycemic control
- Appropriate treatment of patients with acute prostatitis

DIAGNOSIS

HISTORY

- Fevers, chills
- Urinary symptoms with attention paid to voiding patterns prior to acute presentation
  - Dysuria, urinary urgency and frequency are almost universal symptoms
  - Suprapubic or subpubic pain,
  - Severe perineal pain
  - Rectal tenesmus
- Acute urinary retention
- Sexual history/social history (IV drug use, etc.)
- Associated medical comorbidities

ALERT
Where prostate abscess or acute prostatitis is suspected, rectal exam may be contraindicated.

PHYSICAL EXAM

- Perineal pain, tenderness
- Urethral discharge
- Digital rectal exam can reveal exquisitely tender and warm prostate with fluctuance or simply an enlarged prostate
- Signs of other medical comorbidities (ie, new cardiac murmur, ascites, cough, track marks, etc.)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Complete blood count with differential

- Urinalysis, urine/blood cultures
- Gram stain/culture of prostatic fluid once drained
- AFB or mycobacterium-specific PCR if TB suspected
- Prostate-specific antigen should not be obtained in this setting as it will usually be elevated due to the inflammatory process

Imaging

- Transrectal ultrasound (TRUS)
  - Will reveal hypoechoic zones with irregular internal echoes, septations, and indirect borders with the surrounding prostate;
  - Must be performed cautiously.
  - May guide drainage and aspiration
  - The presence of gas suggests EPA
- Color Doppler sonography
  - Will show an increase in vascularity around the abscess, due to hyperemia stemming from the surrounding inflammation
- Computed tomography (CT)
  - Can determine penetration of the abscess into the periprostatic tissues and identify gas within the prostate
  - CT findings include nonenhancing fluid-density collections that can be multiseptated or rim-enhancing lesions.
- MRI
  - MRI may not be feasible in patients who are critically ill and require acute management

Diagnostic Procedures/Surgery

- TRUS with aspiration
- Transperineal ultrasound with aspiration
- Transurethral unroofing of prostate abscess

Pathologic Findings

- Purulent material will be expressed from prostate during surgical drainage procedure:
  - Gram stain and culture of material will give causative agent, most commonly bacterial

DIFFERENTIAL DIAGNOSIS

- Clinically can be hard to distinguish from urinary tract infection (UTI), acute prostatitis, or any other lower UTI.
- Should have clinical suspicion, which can be confirmed with imaging.

TREATMENT

GENERAL MEASURES

- Initial treatment should focus on broad-spectrum antibiotics, IV hydration, and pain control.
- In the setting of acute urinary retention, a Foley catheter placement can be attempted.
  - Occasionally the transurethral catheter may block drainage of an acutely inflamed prostate or cause bacteremia.
  - In the setting of extreme discomfort or if the catheter is difficult to pass, a suprapubic punch cystostomy is preferred.

MEDICATION

First Line

- Broad-spectrum IV antibiotic therapy followed by directed therapy after causative organism determined by urine culture or Gram stain/culture of abscess fluid:
  - 2nd-generation cephalosporins (cefoxitin, zinacef) or 3rd-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime)
  - IV fluoroquinolones
  - Clindamycin for additional anaerobic coverage is recommended initially
    - 600–900 mg IV every 8 hr (q8h)
  - After acute phase, continue oral antibiotic regimen based on cultures for up to 4 wk

Second Line

- Vancomycin for coverage of MRSA is suspected.
  - Dose based on renal function
- Fungal infections may require 4–6 wk of systemic therapy in addition to drainage.

SURGERY/OTHER PROCEDURES

- Transurethral unroofing of prostate abscess
- Transperineal or transrectal needle aspiration with US guidance followed by urethral catheter drainage
  - Can be performed using local anesthesia or sedation
  - Higher risk of recurrence of abscess
- Open incision and drainage through a perineal approach
  - Utilized in patients with penetration of the abscess through the capsule of the prostate or through the levator ani
  - Allows placement of a drain
  - Increased morbidity compared to open percutaneous or transurethral approaches
- Suprapubic cystotomy can be used as an adjunct for urinary diversion in patients with urinary retention

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Relates to predisposing conditions
- For patients with bladder outlet obstruction, therapy should be started to relieve obstruction, (ie, α-blockers or 5α-reductase inhibitors)

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Should recover fully once definitive therapy undertaken
- Although EPA is rare, a 25% mortality rate has been reported

COMPLICATIONS

- May progress to spontaneous fistulization into the urinary bladder, prostatic urethra, rectum, or perineum.
- Urosepsis, and possibly death if diagnosis not made in timely manner.

FOLLOW-UP

Patient Monitoring

- Supportive once definitive therapy performed
- Once acute events resolves, monitoring focuses on optimizing medical comorbidities and improving voiding symptoms.
- Author recommendation: CT or TRUS 4–6 wk after definitive therapy to confirm that no residual abscess remains
- Follow-up urine culture recommended

Patient Resources

N/A

REFERENCES

1. Granados EA, Riley G, Salvador J, et al. Prostatic abscess: Diagnosis and treatment. *J Urol*. 1992;148:80–82.
2. Ludwig M, Schroeder-Printzen I, Schiefer HG, et al. Diagnosis and therapeutic management of 18 patients with prostatic abscess. *Urology*. 1999;53(2):340–345.
3. Tai H. Emphysematous prostatic abscess: A case report and review of literature. *J Infect*. 2007;54:e51–e54.

ADDITIONAL READING

- Baker SD, Horger DC, Keane TE. Community-acquired methicillin-resistant Staphylococcus aureus prostatic abscess. *Urology*. 2004;64(4):808–810.
- Jang K, Lee DH, Lee SH, et al. Treatment of prostatic abscess: Case collection and comparison of treatment methods. *Korean J Urol*. 2012:53(12):860–864.

See Also (Topic, Algorithm, Media)

- Prostate, Abscess Image
- Prostatitis, Acute, Bacterial (NIH I)
- Urinary Tract Infection (UTI), Adult Male
- Urosepsis

CODES

ICD9

- 596.0 Bladder neck obstruction
- 601.0 Acute prostatitis
- 601.2 Abscess of prostate

ICD10

- N32.0 Bladder-neck obstruction
- N41.0 Acute prostatitis

- N41.2 Abscess of prostate

CLINICAL/SURGICAL PEARLS

- Prostate abscess is uncommon and thus often overlooked in the differential diagnosis.
- Suspect prostatic abscess in patients presenting with fever and persistent lower urinary tract symptoms that do not respond to antibiotics.
- A pelvic CT scan is generally the best test to evaluate for the possibility of a prostate abscess.
- A delay of antimicrobial therapy in the management of acute bacterial prostatitis can increase the risk of prostatic abscess.

PROSTATE, BENIGN HYPERPLASIA/HYPERTROPHY (BPH)

Shaun G.S. Grewal, MD
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BASICS

DESCRIPTION

- Benign prostatic hypertrophy (BPH) refers to histologic changes within the prostate gland.
  - May not imply the presence of an enlarged prostate or symptoms.
  - LUTS are 1 manifestation of BPH.
  - Synonym(s): Nodular hyperplasia
- Definitions from the International Continence Society (ICS):
  - Benign prostatic hyperplasia is a term used (and reserved for) the typical histologic pattern which defines the disease.
  - Benign prostatic obstruction is a form of bladder outlet obstruction (BOO) and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic enlargement, due to histologic benign prostatic hyperplasia.
  - Benign prostatic enlargement (BPE) is defined as prostatic enlargement due to histologic benign prostatic hyperplasia. The term "prostatic enlargement" should be used in the absence of prostatic histology.

EPIDEMIOLOGY

Incidence

- 50% of men >40 yr will develop histologic evidence of BPH
  - 30–50% of these men will develop bothersome LUTS (1)

Prevalence

- Histologic prevalence of BPH increases with age:
  - 10% for men in their 30s
  - 20% for men in their 40s
  - 50–60% for men in their 60s
  - 80–90% for men in their 70s and 80s
- Men with significant prostate enlargement (>50 cc) 3.5 times more likely to have moderate-to-severe LUTS (2)
  - BPH is a histologic diagnosis that does not always result in clinical LUTS

RISK FACTORS

- Although family history and advancing age are risk factors for BPH, evidence for comorbidity, environmental, dietary, or lifestyle-related risk factors are generally weak.
- Massachusetts Male Aging Study: Cigarette smoking and increased physical activity protective against BPH, heart disease correlated with development of BPH. Possible association between obesity and prostate volume/LUTS.

Genetics

Some men with younger age of onset and larger glands have a family history of BPH.

PATHOPHYSIOLOGY

- BPH/LUTS begins with abnormal microscopic hyperplasia and macroscopic growth. Causes outflow obstruction and obstructive voiding symptoms (decreased force of stream, intermittent stream, and hesitancy).
- Detrusor response to increased resistance is to generate higher pressures to overcome the outlet resistance. Leads to a variety of cellular and morphologic changes in the bladder. Causes the common storage symptoms of frequency, urgency, and nocturia.
- May lead to bladder decompensation, in which the bladder is no longer able to generate sufficient pressures to empty.
- Primary androgen-dependent growth process involves periurethral and transition zones of the prostate.

ASSOCIATED CONDITIONS

- OAB (overactive bladder defined as urinary frequency, urgency, nocturia, urge incontinence)
- Sexual dysfunction (erectile and/or ejaculatory dysfunction)

GENERAL PREVENTION

- Randomized clinical trials (MTOPS) suggested that the combination of an α-blocker with a 5α-reductase inhibitor (5-ARI) can reduce the lifetime risk of acute urinary retention and may prevent symptomatic disease progression in men with enlarged prostate volume (>25 cc) (3).
- Bladder decompensation may be prevented by treatment of BOO.

DIAGNOSIS

HISTORY

- Focus on identifying the presence of LUTS
  - Voiding symptoms (previously called obstructive symptoms): Hesitancy, intermittency, weak stream, abdominal straining to void, postvoid dribbling, incomplete emptying, double voiding)
  - Storage symptoms (previously called irritative symptoms): Daytime frequency, nocturia, urgency, urge incontinence, enuresis, dysuria)
- Identify other contributing factors to LUTS
  - Medications (ie, diuretics, cold medications)
  - Comorbidities (ie, diabetes, multiple sclerosis, Parkinson)
- Previous interventions/therapies
- Family history
- IPSS is a reproducible, validated index designed to determine disease severity and response to therapy:
  - Scores of 0–7, 8–19, and 20–35 signify mild, moderate, and severe symptoms, respectively.
  - Equivalent to AUASS with the addition of a quality of life (QOL) score

PHYSICAL EXAM

- Evaluation of the abdomen, pelvis, perineum
- Examine external genitalia
- DRE to estimate prostate size and detect any nodularity suggestive of prostate cancer:

  – Anal sphincter tone and sensation should be noted
- Focused neurologic exam on the anus and lower extremity motor and sensory function. A more extensive neurologic exam is indicated for patients with possible neurogenic lower urinary tract dysfunction

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis to exclude hematuria or evidence of infection
- PSA:
  – May be a proxy for prostate size
    ◦ PSA of 1.5 ng/dL correlates with prostate volume >30 mL in most men (4)
  – Informed discussion of risks/benefits of PSA screening warranted
- Urine cytology: Not considered standard; only if there is a predominance of irritative symptoms, hematuria, and/or risk factors for bladder cancer such as smoking

Imaging

- Not indicated unless there is evidence of upper tract deterioration or a need to further evaluate hematuria
- TRUS may be beneficial in determining accurate size prior to surgical intervention

Diagnostic Procedures/Surgery

- Uroflowmetry is a simple noninvasive urodynamic measurement in which a patient voids into a device that measures the volume/time of urine accumulation:
  – Combined with a measurement of PVR (post void residual) volume (see next heading below), it is an excellent screening tool for BOO in men with LUTS.
  – Uroflowmetry measures voided volume, voiding time, average flow rate, and maximum flow rate (Qmax), also called the PFR.
  – Qmax: The single best measurement obtained by this study to assess voiding dysfunction. While formal definitions vary, in general with a voided volume of >125–150 mL, a Qmax of >15 mL/s is often considered normal, whereas a value of <7 mL/s is suggestive of significant obstruction.
  – May need urodynamics to differentiate BOO from hypocontractile bladder (pressure flow study).
    ◦ Obstruction confirmed with low flow (Qmax <15 mL/s) and high voiding pressure >60 cm water.
- PVR: Although generally used, PVR does not convincingly correlate with the severity of LUTS, the presence of BOO, or treatment outcomes:
- Voiding diary to evaluate for occult polyuria or polydipsia.
- Cystoscopy not essential unless there is concern for malignancy, obstruction due to foreign body, or stricture. May be useful to evaluate for most appropriate surgical or minimally invasive treatments.

Pathologic Findings

- Varying degrees of glandular and stromal nodular hyperplasia (as such, hypertrophy is a misnomer). The glandular component is made up of small and large acini lined by basal and secretory cells. The stromal component is rich in smooth muscles. Nodular growth is a major histologic component of BPH.

- Diffuse stromal infiltration of plasma cells and lymphocytes can be seen, but no infectious agent nor clinical diagnosis of prostatitis is typically present.

DIFFERENTIAL DIAGNOSIS

- Obstructive symptoms: Detrusor sphincter dyssynergia, foreign body, meatal stenosis, neurogenic bladder, pelvic floor dysfunction, prostate cancer, prostatic abscess, prostatitis syndrome, urethral obstruction (stricture, condyloma)
- Irritative/storage symptoms: Bladder cancer, detrusor hyperreflexia/OAB, interstitial cystitis, polyuria/polydipsia, prostatitis syndromes

TREATMENT

GENERAL MEASURES

- Directed at QOL unless evidence of significant damage to urinary tract from obstruction (hydronephrosis, bladder calculi, recurrent infections)
- Guidelines suggest watchful waiting for men with mild symptoms IPSS ≤ 7 or for more severe symptoms if they are not bothersome to the patient. Simple behavior modification (fluid restriction, decreased alcohol/caffeine) may help
- Medical therapy considered 1st-line by most, but usually requires continuous therapy to maintain benefit
- α-Blocker and 5-ARIs often prescribed together

MEDICATION

First Line

- α-Blockers (reduce muscle tone in prostate/bladder neck):
  - Terazosin (start 1 mg/d to max 20 mg)
  - Doxazosin (start 1 mg/d to max 8 mg; XL form 2–8 g/d)
  - Tamsulosin (start 0.4 mg to max 0.8 mg)
  - Alfuzosin (10 mg/d)
  - Silodosin (8 mg/d)
    - Dizziness, orthostatic hypotension, and ejaculatory dysfunction are most common side effects
- 5-ARIs (block intracellular DHT conversion; generally best for larger glands, may take 6–12 mo for improvement):
  - Finasteride (5 mg/d)
  - Dutasteride (0.5 mg/d)
- α-Blocker (tamsulosin 0.4 mg) combined with 5-ARI (dutasteride 0.5 mg)

Second Line

- Antimuscarinic agents may help with bladder overactivity:
  - Various agents including oxybutynin (5 mg TID), tolterodine (2–4 mg/d), solifenacin (5–10 mg/d), others
- Phosphodiesterase-5 inhibitor
  - Tadalafil (2.5–5 mg/d)
    - FDA approved for LUTS secondary to BPH
    - Contraindicated in patients on nitrates, nonselective α-blockers, and CYP 450 inhibitors

- Side effects include back pain, dizziness, headache, and dyspepsia (5)

SURGERY/OTHER PROCEDURES

- Often considered 2nd-line after failure of medical therapy; may be 1st-line in retention or if very large prostate.
- TURP represents gold standard against which all other therapies are compared.
- Open simple prostatectomy usually for glands >100 g:
  - Suprapubic prostatectomy: Enucleation of adenoma through bladder; useful with coexisting problems such as very large bladder calculi or to repair diverticulum
  - Retropubic simple prostatectomy: Enucleation of adenoma through incision in anterior prostate commissure
- Many minimally invasive alternative surgical procedures: Microwave- and water-induced hyper thermia, transurethral needle ablation, laser vaporization (contact, noncontact, interstitial, diode), laser prostatectomy (holmium, KTP)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Prostatic stents; best if need TURP but poor surgical risk
- Prostatic urethral lift (UroLift TM) mechanically opens the prostatic urethra with UroLift implants that are placed transurethrally under cystoscopic visualization, thereby separating the encroaching prostatic lobes (6)

Complementary & Alternative Therapies

Phytotherapy (plant extracts) includes saw palmetto, *Pygeum africanum*; β-sitosterols have limited support in the literature

ONGOING CARE

PROGNOSIS

- Symptoms usually well managed by medications
- Progression of disease, when risk factors identified, can be well managed

COMPLICATIONS

- Generally accepted sequelae of untreated, undertreated, or progressive BPH
- Historically, many men typically had complications of BPH including UTIs, hematuria, bladder calculi, bladder decompensation, incontinence, and upper tract deterioration. With modern awareness and management techniques, this is less common.
- The most commonly used endpoints in medical trials are symptom deterioration, BPH-related surgery, and AUR. AUR continues to be the most widely accepted and most scientific endpoint, although the exact pathophysiologic mechanism is not completely understood.

FOLLOW-UP

Patient Monitoring

- Periodic monitoring depending on severity of symptoms
  - Monitor response to therapy with history, AUA SS, PVR, flow rate

– Upper tract imaging and measure of renal function if elevated PVR (>300 cc)

Patient Resources

Urology Care Foundation. www.urologyhealth.org

REFERENCES

1. Roehrborn C. Male lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia. *Med Clin North Am*. 2011;95:87–100.
2. Bushman W. Etiology, epidemiology and natural history of benign prostatic hyperplasia. *Urol Clin North Am*. 2009;36:403–415.
3. McConnel JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*. 2003;349:2387–2398.
4. Roehrborn CG, Boyle P, Gould AL. Waldstreicher J Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999;53(3):581–589.
5. Cantrell MA, Baye J, Vouri SM. Tadalafil: A phosphodiesterase-5 inhibitor for benign prostatic hyperplasia. *Pharmacotherapy*. 2013;33(6):639–649.
6. McNicholas TA, Woo HH, Chin PT, et al. Minimally invasive prostatic urethral lift: surgical technique and multinational experience. *Eur Urol*. 2013;64(2):292–299.

ADDITIONAL READING

- AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol*. 2003;170:530–547.
- McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185:1793–1803.

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Lower Urinary Tract Symptoms (LUTS)
- Prostate, Benign Hyperplasia/Hypertrophy (BPH) Image
- Prostate, Stents (UroLume and Spanner)
- Reference Tables: AUA Symptom Index/International Prostate Symptom Score (I-PSS)

CODES

ICD9

- 600.00 Hypertrophy (benign) of prostate without urinary obstruction and other lower urinary tract symptom (LUTS)
- 600.01 Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)
- 600.10 Nodular prostate without urinary obstruction

ICD10

- N40.0 Enlarged prostate without lower urinary tract symptoms

- N40.1 Enlarged prostate with lower urinary tract symptoms
- N40.2 Nodular prostate without lower urinary tract symptoms

CLINICAL/SURGICAL PEARLS

- 5-ARIs (such as finasteride and dutasteride) contraindicated if prostate enlargement absent (< 25 g).
- Goal of treatment is improving symptoms/QOL.

PROSTATE, CALCULI

Christopher Amling, MD, FACS
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BASICS

DESCRIPTION
- Prostatic calculi are extremely common and rarely symptomatic
- Most stones are discovered incidentally
- Treatment typically reserved for severely symptomatic men
- Stones within the prostatic urethra rare and likely due to bladder or upper tract stones that become trapped in the prostatic urethra
- Reports of calculi in the prostatic urethra following transurethral resection of the prostate

EPIDEMIOLOGY
Incidence
- 7% in pathologic specimens
- 20% in autopsies
- 30% in radiologic studies, with higher percentages in ultrasound scan exams

Prevalence
- Small areas of microcalcification can be seen in 2nd and 3rd decades of life
- Almost all men (99%) have some degree of prostatic calcification noted at autopsy
  - Stone burden and size typically increase as a man ages

RISK FACTORS (1)
- Intraprostatic calculi:
  - Recurrent urinary tract infections (UTIs)
  - Pelvic radiation (for prostate cancer)
  - Studies are mixed on role of inflammation in stone development
- Prostatic urethral calculi
  - Urolithiasis
  - Enlarged prostatic utricle
  - History of transurethral resection of the prostate

Genetics
N/A

PATHOPHYSIOLOGY
- Urinary intraprostatic reflux implicated in stone formation
- Intraprostatic calculi presumed to form by the precipitation of prostatic secretions and calcification of the corpora amylacea under inflammatory conditions
  - Inspissation of prostatic secretions within the prostatic ducts
  - Concentric layering of calcium phosphate and calcium carbonate on inspissated core result in growth
  - Stone elements may contain constituents found only in urine and not in prostatic

secretions
- Stones may harbor bacteria and serve as source for relapsing UTI
- For prostatic utricle stones, prostatic utricle distends during voiding and then passively drains.
  - Impaired emptying results in urinary stasis stone formation. Patients present clinically with chronic UTI, hematuria, urethral discharge, epididymitis, and voiding dysfunction.

ASSOCIATED CONDITIONS
- Chronic pelvic pain syndrome
- Prostatitis
- No association between prostate calculi and risk of prostate cancer
- Hypospadias (enlargement of the prostatic utricle, a Müllerian duct remnant)

GENERAL PREVENTION
No known preventative strategies

DIAGNOSIS
HISTORY
- Typically stones are asymptomatic
- Evaluate for history of lower urinary tract symptoms (LUTS) (2)
  - Patients should complete the international prostate symptom score (IPSS)
  - Presence of large calculi associated with moderate LUTS
- 25–47% of men with chronic pelvic pain have significant prostatic calcifications
  - Correlation seen with stone size, not number
- Prostatitis history
- With prostatic utricle stones patients typically present with chronic UTI, hematuria, urethral discharge, epididymitis, and voiding dysfunction. Often a history of hypospadias is present

PHYSICAL EXAM
- Genitourinary exam including DRE
  - DRE unlikely to localize stones
- Presence of hypospadias

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urine culture
  - *Escherichia Coli,* enterococci, and *Klebsiella* spp. more common
- Expressed prostatic secretions
  - May see increased leukocytes
- PSA optional
  - PSA levels not influenced by presence or volume of prostatic calculi, but infection related to chronic nidus may falsely elevate PSA (3)

Imaging
- Stones often identified incidentally
- Transrectal ultrasound (TRUS)
  - Highly sensitive for large calculi

• Sometimes seen on plain film

Diagnostic Procedures/Surgery
• Postvoid residual (PVR)
• Uroflow if significant obstructive voiding symptoms present
• If intraurethral stones are suspected, cystoscopy is diagnostic

Pathologic Findings
• Majority of calculi are found in the posterior and posterolateral zones of the prostate
  – Rare to find large stones obstructing the urethra

DIFFERENTIAL DIAGNOSIS
• Benign prostatic enlargement (BPE)
• Calcified prostatic utricle cyst or utricle stone
• False prostatic calculi: Calculi trapped in dilated prostatic urethra or in dilated prostatic utricle
• Prostate cancer
• Prostatitis
• Seminal vesical calculi
• UTI

TREATMENT

GENERAL MEASURES
Evaluate and treat coexisting conditions such as UTI, prostatitis, and BPO

MEDICATION
First Line
Culture-directed antibiotic therapy if urine culture positive

Second Line
N/A

SURGERY/OTHER PROCEDURES
• Surgery rarely indicated and is typically for severely symptomatic patients
• Transurethral resection of the prostate
  – Unroof stone containing cavities where nidus of infection is thought to exist
  – Stone burned usually visible on TRUS
• Open prostatolithotomy for large stones
• Cystoscopy with lithotripsy for stones within the prostatic urethra or prostatic utricle

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

Excellent, as majority of stones are asymptomatic

COMPLICATIONS

- Rarely results in urinary obstruction
- May predispose to chronic UTI.

FOLLOW-UP

Patient Monitoring

- No follow-up necessary for asymptomatic incidentally identified stones
- Consider postoperative PVR or uroflow if surgical intervention undertaken

Patient Resources

N/A

REFERENCES

1. Klimas R, Bennett B, Gardner WA Jr. Prostatic calculi: A review. *Prostate*. 1985;7(1):91–96.
2. Kim WB, Doo SW, Yang WJ, et al. Influence of prostatic calculi on lower urinary tract symptoms in middle-aged men. *Urology*. 2011;78(2):447–449.
3. Lee SE, Ku JH, Park HK, et al. Prostatic calculi do not influence the level of serum prostate specific antigen in men without clinically detectable prostate cancer or prostatitis. *J Urol*. 2003;170:745–748.

ADDITIONAL READING

- Geramoutsos I, Gyftopoulos K, Perimenis P, et al. Clinical correlation of prostatic lithiasis with chronic pelvic pain syndromes in young adults. *Euro Urol*. 2004;45:333–337.
- Kirby RS, Lowe D, Bultitude MI, et al. Intraprostatic urinary reflux: An aetiological factor in abacterial prostatitis. *Br J Urol*. 1982;54:729–731.

See Also (Topic, Algorithm, Media)

- Corpora Amylacea
- Prostate, Benign Hyperplasia/Hypertrophy
- Prostate, Nodule
- Prostatic Utricle Anomalies
- Prostatitis, Acute, Bacterial (NIH I)
- Prostatitis, Chronic, Bacterial (NIH II)
- Prostatitis, General
- Urinary Tract Infection, Adult Male

CODES

ICD9

- 599.0 Urinary tract infection, site not specified
- 599.70 Hematuria, unspecified
- 602.0 Calculus of prostate

ICD10

- N39.0 Urinary tract infection, site not specified
- N42.0 Calculus of prostate
- R31.9 Hematuria, unspecified

CLINICAL/SURGICAL PEARLS

Prostate calculi are very common and rarely require treatment.

PROSTATE, NODULE

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BASICS

DESCRIPTION

- A prostatenadule is usually described as a palpable lesion detected on digital rectal exam (DRE) raise concern for prostate cancer (CaP)
- Nodules can be described as soft, rubbery, firm, hard, or rock hard
- Nodules can be well circumscribed or irregular and diffuse
- A normal prostate is about the size of a chestnut and has a consistency similar to that of the contracted thenar eminence of the thumb.
  - This can be simulated by opposing the thumb to the little finger and palpating the contracted muscle
- Consistency of nodule can denote underlying pathology.
- Rapidity of appearance and changes in size and consistency can infer malignant potential.
- Nodule detection by DRE is recommended as part of prostate cancer detection programs.
  - Current recommendations from the American Cancer Society are, if men decides to be tested for prostate cancer, they should have the PSA blood test with or without a rectal exam.

EPIDEMIOLOGY

Incidence

- Prostate nodule as an isolated finding with normal PSA is found in $<10\%$ of cases of prostate cancer in the US
- Increasingly men are being diagnosed with prostate cancer based on an elevated serum prostate-specific antigen (PSA) and not an abnormal DRE (50% of diagnoses in 2002) (1)
- 94% of men diagnosed with prostate cancer in 2004–2005 have localized disease (cT1 or cT2) (2)

Prevalence

5–10% of men in screening programs have abnormal/suspicious DRE

RISK FACTORS

- Prostate cancer
  - Nodule that changes in consistency and size over time
  - Elevated serum PSA (>2.5–4 ng/mL)
  - Positive family history
- Benign nodule
  - No significant change over time
  - Nodule may be softer
  - Prior episodes of prostatitis, biopsy, or prostate surgery (transurethral resection)
  - Prior therapy with intravesical Bacillus Calmette–Guérin (BCG)
  - Granulomatous nodules can be due to infectious causes (eg, tuberculosis [TB]) or systemic

granulomatous diseases

Genetics

See “Prostate Cancer, General Considerations”

PATHOPHYSIOLOGY

- Normal prostate has a soft, uniform consistency.
- Prostate enlarges with age.
- Microscopically, nodular prostatic hyperplasia consists of nodules of glands and intervening stroma. May occasionally form benign palpable nodules.
- Nodule can be subjectively graded by degree of firmness/hardness (grades 1–3)
- CaP has to have a volume of 0.2 mL or larger to be detected by DRE.

ASSOCIATED CONDITIONS

- Prostate adenocarcinoma
- Benign prostatic hyperplasia (BPH)
- History of intravesical BCG for bladder cancer

GENERAL PREVENTION

None

DIAGNOSIS

HISTORY

- History of lower urinary tract symptoms
  - Irritative voiding symptoms
  - Obstructive voiding symptoms
  - Fever
  - Previous prostate biopsy or surgery such as TURP
  - Previous pelvic external beam radiation or prostate brachytherapy
  - History of prostatitis, abscess, or exposure to TB
  - Systemic granulomatous disease (Wegner’s, etc.)
  - Family history of genitourinary malignancies

ALERT

Where prostate abscess or acute prostatitis is suspected, rectal exam may be contraindicated.

PHYSICAL EXAM

- DRE
  - Carcinoma (prostatic or urothelial cell carcinoma)
    - Firm, indurated nodules within the prostate gland
    - Prostate cancer most often arises in the posterior peripheral region of the prostate
    - Advanced prostate cancer can make the entire gland firm and cause obliteration of the medial and lateral sulci
    - Advanced cancer can also extend into the seminal vesicles or toward the side wall laterally
- BPH
  - Prostate gland can be variably enlarged (size does not correlate with extent of voiding

symptoms)
  – Rubbery consistency
- Infectious lesions
  – Prostatitis
    - Warm, tender prostate
    - Can be fluctuant or feel “boggy”
  – Prostate abscess
    - Localized, fluctuant tender region in prostate
- Calculus can present as hard, small nodule

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA
  – Serum levels vary with age, race, and prostate volume
  – Improves the positive predictive value of DRE for cancer
  – No cut-off value below which the absence of prostate cancer can be guaranteed
    - Risk of prostate cancer is continuous as PSA increases (3)
  – See “PSA Elevation, General Considerations” for further specifics on PSA
- Urinalysis
  – Variable findings in men with abnormal DRE; sterile pyuria in granulomatous prostatitis
  – Generally normal in men with prostate cancer without urinary tract infection
  – Urine culture can be positive for gram-negative bacteria in acute and chronic bacterial prostatitis
  – Urine cytology can be positive in urothelial cancer

Imaging

- Transrectal ultrasound (TRUS)
  – Classic appearance of prostate adenocarcinoma is a round or oval hypoechoic lesion located in the peripheral zone
    - Not very sensitive as 39% of tumors can be isoechoic
    - Also nonspecific as granulomatous lesions can be hypoechoic
  – BPH can have variable appearance
    - Distinguishable from prostate cancer only by biopsy
- Abdominal computed tomography (CT) or magnetic resonance imaging (MRI)
  – Primarily used for staging purposes in patients with high-risk prostate cancer
- Bone scan to detect bone metastases
  – Also primarily used for staging purposes in patients with high-risk prostate cancer

Diagnostic Procedures/Surgery

- TRUS-guided biopsy (4)
  – Used to widely sample the prostate during biopsy in men with an elevated PSA and/or abnormal DRE
  – Modern biopsy schemes have modified the standard sextant biopsy scheme to focus on laterally directed cores
    - Generally 12 cores
- Cystoscopy

– Used to evaluate bladder outlet obstruction and hematuria when present

Pathologic Findings

See “Prostate Cancer, General Considerations”

DIFFERENTIAL DIAGNOSIS

- Neoplasm, malignant
  - Lymphoma, primary and secondary
  - Prostate adenocarcinoma
  - Other prostate malignancies
    - Sarcoma
    - Small cell carcinoma
    - Other more rare tumors and metastasis
  - Urothelial carcinoma
- Benign
  - BPH
  - Calculus
  - Ejaculatory duct cyst
  - Granulomatous prostatitis
    - BCG related or other cause
  - Scarring from prior radiation, surgery, or infection (TURP, etc.)
  - Rectal wall lesions (thrombosed hemorrhoid, carcinoma, etc.)

TREATMENT

GENERAL MEASURES

- Abnormal DRE is an indication for TRUS-guided biopsy of the prostate
  - Workup includes assessment of PSA
  - Staging investigations including bone scan, CT, and/or MRI are reserved for high-risk cases as dictated by PSA, Gleason score, and DRE

MEDICATION

First Line

Antibiotics may be required for infectious causes of nodules such as bacterial prostatitis or TB

Second Line

N/A

SURGERY/OTHER PROCEDURES

See “Diagnostic Procedures/Surgery" above

ADDITIONAL TREATMENT

This is dictated by the results of the TRUS biopsy and presence/extent of prostate cancer

Radiation Therapy

While not a specific treatment of the nodule, it can be used as primary therapy or as additional adjuvant/salvage therapy after prostatectomy in patients with prostate cancer

Additional Therapies

May be required in cases with metastatic disease or disease that recurs after definitive local therapy

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Depends on diagnosis after TRUS-guided biopsy

COMPLICATIONS
- TRUS-guided biopsy
  - Hematuria
  - Hematochezia
  - Hematospermia
  - Urinary tract infection or sepsis
  - Urinary retention

Other complications are dictated by the treatment received for prostate cancer

FOLLOW-UP
Patient Monitoring
Negative biopsy in a patient with an abnormal DRE or elevated PSA requires follow-up with serial PSA and DRE

Patient Resources
- NCCN. http://www.nccn.org/patients/patientguidelines/prostate/
- American Cancer Society. http://www.cancer.org/cancer/prostatecancer/index?sitearea=%26dt=10

REFERENCES

1. Cooperberg MR, Lubeck DP, Mehta SS, et al. Time trends in clinical risk stratification for prostate cancer: Implications for outcomes (data from CaPSURE). *J Urol*. 2003;170:S21–S25; discussion S26–S27.
2. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst*. 2009;101:1280–1283.
3. Thompson IM, Bermejo C, Hernandez J, et al. Screening for prostate cancer: Opportunities and challenges. *Surg Oncol Clin N Am*. 2005;14(4):747–760.
4. Trabulsi EJ, Halpern EJ, Gomella L. Ultrasonography and biopsy of the prostate. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:2735–2747.

ADDITIONAL READING
American Urological Association. Prostate-specific antigen (PSA): Best practice statement. http://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm

See Also (Topic, Algorithm, Media)
- BCG Sepsis/BCG Ossis

- Prostate Biopsy, Infections and Complications
- Prostate Cancer, General Considerations
- Prostate Cancer, Localized (T1, T2)
- Prostate Cancer, Urothelial
- Prostate Nodule, Image
- Prostatitis, Granulomatous
- Tuberculosis, Genitourinary, General Considerations

CODES

ICD9

- 600.10 Nodular prostate without urinary obstruction
- 600.11 Nodular prostate with urinary obstruction
- 790.93 Elevated prostate specific antigen [PSA]

ICD10

- N40.2 Nodular prostate without lower urinary tract symptoms
- N40.3 Nodular prostate with lower urinary tract symptoms
- R97.2 Elevated prostate specific antigen [PSA]

CLINICAL/SURGICAL PEARLS

- A firm prostate nodule generally deserves further workup with a serum PSA and prostate biopsy.
- Up to 40% of patients may develop granulomatous prostatitis after intravesical BCG that may present as a prostate nodule.

PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

Joseph C. Klink, MD
Eric A. Klein, MD, FACS

BASICS

DESCRIPTION

- Prostatic intraepithelial neoplasia (PIN) describes cytologically atypical cells confined within architecturally benign prostatic glands and acini
- Historically subclassified
  - Low-grade PIN (LGPIN) and high-grade PIN (HGPIN)
  - PIN 1, 2, or 3
- LGPIN no longer reported because
  - Not reliably distinguished from benign prostate by pathologists
  - LGPIN carries no increased risk of prostate cancer (PCa) on future biopsies
- HGPIN, and atypical small acinar proliferation (ASAP) are both considered by most to be premalignant and the terms should not be used interchangeably.
- Antiquated names for PIN include intraductal hyperplasia, hyperplasia with malignant change, large acinar atypical hyperplasia, marked atypia, ductal-acinar dysplasia
- Remainder of this chapter will focus on HGPIN

EPIDEMIOLOGY

Incidence

- Parallels PCa incidence
- Increases with age
- In PSA screened men, incidence ranges 0–25%
  - Mean incidence 7.7%

Prevalence

- Parallels PCa prevalence
- 7% of men in their 30s
- 91% of elderly African American men
- 67% of elderly Caucasian men
- 21% of Korean men undergoing cystoprostatectomy

RISK FACTORS

- Age
- PCa
  - HGPIN often found close to PCa, but does not carry independent prognostic significance once PCa is diagnosed

Genetics

- Many genetic abnormalities shared by HGPIN and PCa
  - Leads to conclusion that HGPIN is a precursor of PCa
- TMPRSS2-ERG gene fusion in 16–19% of HGPIN lesions in patients with PCa

- Overexpression of PTOV1 in HGPIN is an independent predictor of PCa on repeat biopsy
- mTOR pathway upregulation
- Chromosomal anomalies in >50% of HGPIN
- Gains of chromosomes (decreasing order of frequency) 8, 10, 7, 12, and Y
- Loss of heterozygosity on 8p12–21
- Telomerase activation
- Epigenetic changes including hypermethylation

PATHOPHYSIOLOGY

- HGPIN may be precursor of PCa (1)
  - PCa can develop without HGPIN
- HGPIN extent and frequency greater when PCa present
- Usually in peripheral zone
- Often multifocal

ASSOCIATED CONDITIONS

ALERT
Multifocal HGPIN Predicts Increased Risk of PCa on subsequent biopsy.

- Historically, HGPIN on prostate biopsy often represented failure to sample a nearby PCa (2)
  - As the number of cores routinely sampled at prostate biopsy increased, the predictive value of HGPIN for PCa decreased
- With modern 12-core biopsies, a single focus of HGPIN does NOT increase the risk of PCa diagnosis on subsequent biopsies
  - Decision for repeat prostate biopsy should be made on other clinical factors (elevated PSA, high PSA velocity, new nodule on DRE), not influenced by the presence of 1 focus of HGPIN
- Multifocal HGPIN indicates higher risk of PCa on repeat biopsy (3)
  - Multivariate odds ratio 3.2 for increased cancer detection with multifocal HGPIN
  - 16–75% (usually around 30%) PCa rate on repeat biopsy for multifocal HGPIN
- Repeat biopsy usually done 1 yr after initial biopsy

GENERAL PREVENTION

- 5α-reductase inhibitors can reduce the incidence of PIN but are not FDA approved for this use
  - Finasteride daily for 7 yr decreased the incidence of HGPIN from 7.1–6% in the Prostate Cancer Prevention Trial
  - Dutasteride reduced the incidence of HGPIN from 6–3.7% in the REDUCE trial
- The risk posed by unifocal HGPIN to a patient's health and life in the absence of PCa is so low that prevention is not indicated

DIAGNOSIS

HISTORY

HGPIN produces no symptoms

PHYSICAL EXAM

- Digital rectal exam (DRE) is usually normal, but may reveal a prostate nodule or induration

• No other physical exam findings

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Elevated PSA may be present but not caused by the HGPIN

Imaging

Not reliably seen on any imaging

Diagnostic Procedures/Surgery

• Transrectal ultrasound-guided biopsy of the prostate taking at least 12 cores
  – Indicated to look for PCa. HGPIN is an incidental finding

Pathologic Findings

• Characterized by proliferation of secretory cells with significant cytologic atypia within prostate glands and acini
• Secretory cells are enlarged with increased nuclear/cytoplasmic ratio and prominent nucleoli
• Cytoplasm of the HGPIN cells tends to stain positively for α-methylacyl-CoA
• Most of these features are shared by PCa
• In PCa, basal cells are absent. In HGPIN the basal cell layer is retained although is often discontinuous on H&E stain (Figure 2)
  – Basal cells can be demonstrated by immunohistochemical staining with antibodies to high–molecular-weight cytokeratins or nuclear p63
• 4 main architectural patterns of HGPIN have been described (tufting, micropapillary, cribriform, and flat), but these do not make a difference clinically
• HGPIN usually found in the peripheral zone

DIFFERENTIAL DIAGNOSIS

• Prostate Cancer (PCa)
• ASAP
  – Confers an increased risk of subsequent PCa diagnosis
  – Requires repeat prostate biopsy in a few months to rule out PCa
• Normal anatomic structures and embryonic rests
• Atypia induced by inflammation, infarction, or radiation
• Lobular atrophy and postatrophic hyperplasia
• Transitional cell metaplasia
• Typical and atypical basal cell metaplasia
• Cribriform hyperplasia
• Cribriform, ductal endometrioid, and urothelial carcinoma

TREATMENT

GENERAL MEASURES

• If HGPIN was found on initial prostate biopsy of <10 cores, the biopsy should be repeated with an extended scheme
• If multifocal HGPIN is found on initial prostate biopsy, the biopsy should be repeated within 1 yr

- Repeat biopsy should sample the entire prostate, not just the HGPIN area

MEDICATION

First Line

- Not necessary to treat HGPIN
- HGPIN often used to identify patients at "high risk" of developing PCa to enroll them in clinical trials of medications to prevent PCa

Second Line

N/A

SURGERY/OTHER PROCEDURES

Radical prostatectomy not indicated for HGPIN in the absence of PCa

ADDITIONAL TREATMENT

Radiation Therapy

Not indicated for HGPIN in the absence of PCa

Additional Therapies

N/A

Complementary & Alternative Therapies

- Green tea catechins for 1 yr in men with HGPIN reduced the incidence of PCa from 30 to 3%
- Soy, vitamin E, and selenium did not slow the rate of progression of HGPIN to PCa in a randomized double-blind trial (SELECT Trial)
- None of these therapies routinely recommend to men with HGPIN

ONGOING CARE

PROGNOSIS

- Excellent prognosis in the absence of PCa
- Must monitor for the development of PCa as outlined above

COMPLICATIONS

None other than the risks of biopsy

FOLLOW-UP

Patient Monitoring

- In certain situations as noted, HGPIN may indicate an increased risk of PCa and, therefore, may require repeat biopsy at 1 yr
- LGPIN should not be diagnosed on pathology and, therefore, does not require any follow-up

Patient Resources

- American Cancer Society
  http://www.cancer.org/treatment/understandingyourdiagnosis/understandingyourpathology
  grade-prostatic-intraepithelial-neoplasia
- http://prostatecancerinfolink.net/diagnosis/pin/

REFERENCES

1. Klink JC, Miocinovic R, Magi Galluzzi C, et al. High-grade prostatic intraepithelial neoplasia. *Korean J Urol*. 2012;53(5):297–303.
2. Bostwick DG, Cheng L. Precursors of prostate cancer. *Histopathology*. 2012;60:4–27.
3. Epstein JI, Grignon DJ, Humphrey PA, et al. Interobserver reproducibility in the diagnosis of prostatic intraepithelial neoplasia. *Am J Surg Pathol*. 1995;19:873–886.

ADDITIONAL READING

- Antonelli A, Tardanico R, Giovanessi L, et al. Predicting prostate cancer at rebiopsies in patients with high-grade prostatic intraepithelial neoplasia: A study on 546 patients. *Prostate Cancer Prostatic Dis*. 2011;14:173–176.
- Bostwick DG, Qian J. High-grade prostatic intraepithelial neoplasia. *Mod Pathol*. 2004;17:360–379.
- Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localized disease. *Eur Urol*. 2011;59:61–71.
- Kawachi MH, Bahnson RR, Barry M, et al. NCCN clinical practice guidelines in oncology: Prostate cancer early detection. *J Natl Compr Canc Netw*. 2010;8:240–262.

See Also (Topic, Algorithm, Media)

- Atypical Small Acinar Proliferation, Prostate (ASAP)
- Prostate Cancer, General
- Prostate Nodule
- Prostatic Intraepithelial Neoplasia (PIN) Images
- PSA Elevation, General Considerations

CODES

ICD9

- 233.4 Carcinoma in situ of prostate
- 602.3 Dysplasia of prostate

ICD10

- D07.5 Carcinoma in situ of prostate
- N42.3 Dysplasia of prostate

CLINICAL/SURGICAL PEARLS

- If HGPIN was found on initial prostate biopsy of <10 cores, the biopsy should be repeated with an extended scheme.
- If multifocal HGPIN is found on initial prostate biopsy, the biopsy should be repeated within 1 yr.
- With modern 12-core biopsies, a single focus of HGPIN does NOT increase the risk of PCa diagnosis on subsequent biopsies.
- Decision for repeat prostate biopsy should be made on other clinical factors (elevated PSA, high PSA velocity, new nodule on DRE), not influenced by the presence of 1 focus of HGPIN.

PROSTATITIS, ACUTE, BACTERIAL (NIH I)

Nicholas J. Kuntz, MD
Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Acute bacterial prostatitis is cute, potentially life-threatening bacterial infection of the prostate
- The symptoms are typically severe and sudden and usually cause the patient to seek emergency care
- The NIH prostatitis classification system it is referred to as NIH:I

EPIDEMIOLOGY

Incidence

- Least common form of prostatitis
  - 1–5%
- Incidence peaks at 20–40 yr (1)[B]
- Not affected by race and ethnicity (1)[B]

Prevalence

Estimated to be ~10% for all types of prostatitis worldwide (1)[B]

RISK FACTORS

- Bladder outlet obstruction
  - Benign prostatic hyperplasia (BPH)
  - Stricture disease
- Previous episodes of prostatitis
- Lower urinary tract procedures
  - Prostate biopsy or urethral catheterization
- Phimosis
- Immunocompromised
  - Human immunodeficiency virus (HIV)
- Immunosuppression
  - Diabetes
- Indwelling urethral catheter
- Urinary tract infection (UTI)
- History of sexually transmitted disease

Genetics

Not applicable

PATHOPHYSIOLOGY

- Intraprostatic reflux of infected urine
- Ascending urethral infection:

- Unprotected sexual intercourse
- Urologic instrumentation
- Prolonged catheterization

• Direct invasion or lymphogenous spread from the rectum
- Following biopsy, BPH procedures

• Hematogenous seeding
- *Staphylococcus aureus* most common, including methicillin-resistant strands (MRSA)

• Usually a single bacterial uropathogen
- *Escherichia coli* 87% (2)[B]
- Pseudomonas, Proteus, Klebsiella
- Enterococci 5–10%

• Sexually active and < 35 yr
- *Neisseria gonorrhoeae*

• Severe immunocompromise (HIV/AIDS)
- Mycobacterium tuberculosis, Serratia, Salmonella, and fungi (Candida, Histoplasma, Aspergillus, Cryptococcus) (1)[B]

• NIH classification: (3)[A]
- I: Acute bacterial prostatitis
- II: Chronic bacterial prostatitis: Recurrent infection
- III: Chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS): No demonstrable infection:
  - IIIA: Inflammatory CPPS: White blood cells (WBCs) present in semen/expressed prostatic secretions or voided bladder urine (VB3)
  - IIIB: Noninflammatory CPPS: WBCs not present in semen/expressed prostatic secretions or voided bladder urine (VB3)
- IV: Asymptomatic inflammatory prostatitis: Detected by prostate biopsy or presence of WBCs in prostatic secretions during evaluation for other disorders

ASSOCIATED CONDITIONS
• BPH
• Urethral stricture disease
• Diabetes
• HIV
• UTI

GENERAL PREVENTION
• Safe sex practices may prevent some cases.
• Management of underlying BPH, DM, etc.

DIAGNOSIS
HISTORY
• Systemic symptoms
- Fever, chills, malaise, arthralgia, myalgia

• Irritative or obstructive voiding symptoms
- Dysuria, urgency, frequency

- Acute urinary retention (20%)
  - Due to bladder neck spasm
- Perineal/rectal pain, lower back pain

PHYSICAL EXAM

ALERT
Avoid vigorous prostatic exam or massage in a patient with suspected acute bacterial prostatitis. This may cause bacteremia and sepsis. Likewise urethral instrumentation should be avoided if possible (4)[C].

- Vital signs:
  - Signs of sepsis including fever, tachycardia, and hypotension
- Abdominal exam:
  - Palpable bladder or abdominal fullness suggesting acute urinary retention
- Digital rectal exam (DRE):
  - Perform cautiously
  - Exquisitely tender, warm, boggy, swollen prostate gland

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Complete blood count
  - Leukocytosis with left shift
- Urinalysis
  - Proteinuria, pyuria, and hematuria
  - Positive leukocyte esterase and nitrite has a sensitivity of 68–88% (1)[B]
- Urine culture
- Blood cultures
  - Particularly for immunosuppressed patients
- Prostate-specific antigen (PSA)
  - Little clinical value in the acute setting
  - Will be elevated in the majority of cases
  - Should be repeated 1–2 mo following treatment

Imaging

- Not routinely required
- Indicated if fever persists despite appropriate treatment to evaluate for prostatic abscess
  - CT scan
    - Area of low attenuation
    - Rim enhancing with IV contrast
  - Ultrasound
    - Hypoechoic lesion
  - MRI
    - High intensity on T2-weighted images
    - Rim enhancing with gadolinium

Diagnostic Procedures/Surgery

None: Clinical diagnosis

Pathologic Findings

Prostate biopsy is contraindicated in the presence of acute bacterial prostatitis

DIFFERENTIAL DIAGNOSIS

- UTI
- Pyelonephritis
- Chronic bacterial prostatitis
- Granulomatous prostatitis
- Perirectal abscess
- Prostate cancer
- Prostatic abscess
- Prostatodynia

TREATMENT

GENERAL MEASURES

- Indications for admission and IV antibiotics:
  - High fever
  - Significant leukocytosis
  - Sepsis
- Analgesics/antipyretics
- Stool softeners
- Bladder drainage if there is evidence of urinary retention:
  - A urethral catheter should be placed cautiously
  - With any difficulty or if the patient is too uncomfortable, percutaneous suprapubic tube should be placed
- If no clinical response in 48 hr despite appropriate treatment consider prostatic abscess
- Postprostate biopsy prostatitis suspect resistance to fluoroquinolones

MEDICATION

First Line (4)[C]

- Antibiotics with high lipid solubility and concentrated in prostatic tissue
  - Fluoroquinolones
    - Levofloxacin, 250–750 mg daily IV or by mouth (PO)
    - Ciprofloxacin, 250–750 mg PO twice daily (BID), 400 mg IV BID
    - Ampicillin with gentamicin (ampicillin 1–2 g IV every 4–6 hr, 500 mg PO every 6 hr; gentamicin 1–2 mg/kg IV every 8–12 hr or daily dosing 4–7 mg/kg every 24 hr IV)
    - Ceftriaxone 1–2 g IV or IM daily
  - Afebrile 24–48 hr may change to oral antibiotics
- Adjust antibiotic regimen based on urine and/or blood culture results
- Transition to oral antibiotic following resolution of acute toxicity
- Total antibiotic duration: 2–4 wk

Second Line

- Oral antibiotics are a reasonable 1st option in nontoxic patients.
  - Fluoroquinolones (see above oral dose) for 10 days (4)[C]

– Trimethoprim–sulfamethoxazole 160/800 mg PO every 12 hr
- If STD is suspected (sexually active male younger than 35 yr) empiric treatment with ceftriaxone 250 mg IM and doxycycline 100 mg BID for 7 days may be warranted, but this is controversial (5)[C]

SURGERY/OTHER PROCEDURES
- Suprapubic tube placement
  – If Foley catheter cannot be passed easily in setting of acute urinary retention
- If prostatic abscess develops, surgical drainage of prostatic abscess is usually required (4)[B]
  – Transrectal or perineal needle aspiration
    - Ultrasound guided
    - Local anesthetic
  – Transurethral drainage
    - Incision or unroofing
    - Resection may be associated with higher rates of sepsis
  – Open drainage
    - If less invasive methods fail
    - Abscess extends beyond prostate

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Limited, if any role in the acute setting

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS
- If initial response to therapy is favorable then patient prognosis is excellent.
- Studies using quinolone antibiotics suggest that a negative culture after 7 days of therapy is predictive of a long-term response.
- If the patient with suspected bacterial prostatitis is not responding to initial empiric therapy, consider prostatic abscess.

COMPLICATIONS
- Prostatic abscess
- Decreased fertility
- Epididymitis
- Chronic prostatitis
- Emphysematous prostatitis
- Pyelonephritis
- Sepsis
- Urinary retention

FOLLOW-UP

Patient Monitoring

- Follow-up urine cultures to verify that the infection has cleared and that chronic bacterial prostatitis is not present.
- If PSA was obtained during the acute episode, and was elevated, repeat in 1–2 mo to resolution.

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=15

REFERENCES

1. Ramakrishnan K, Salinas RC. Prostatitis: Acute and chronic. *Prim Care*. 2010;37(3):547–563, viii–ix.
2. Millan-Rodriguez F, Palou J, Bujons-Tur A, et al. Acute bacterial prostatitis: Two different sub-categories according to a previous manipulation of the lower urinary tract. *World J Urol*. 2006;24(1):45–50.
3. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236–237.
4. National Guideline C. Prostatitis and chronic pelvic pain syndrome. In: Guidelines On Urological Infections Rockville MD: Agency for Healthcare Research and Quality. [5/15/2013]. Available from www.guideline.gov/content.aspx?id=14811&search=prostatitis.
5. Etienne M, Chavanet P, Sibert L, et al. Acute bacterial prostatitis: Heterogeneity in diagnostic criteria and management. Retrospective multicentric analysis of 371 patients diagnosed with acute prostatitis. *BMC Infect Dis*. 2008;8:12.

ADDITIONAL READING

- Barozzi L, Pavlica P. Prostatic abscess: Diagnosis and treatment. *AJR Am J Roentgenol*. 1998;(3):753–757.
- Lipsky BA. Prostatitis and urinary tract infection in men: What's new; what's true? *Am J Med*. 1999;(3):327–334.
- Nickel JC. Prostatitis: Myths and realities. *Urology*. 1998;51(3):362–366.
- Pewitt ED, Schaeffer AJ. Urinary tract infection urology, including acute and chronic prostatitis. *Infect Dis Clin North Am*. 1997;11(3):623–646.
- Schaeffer AJ. Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med*. 2006;355:1690–1698.

See Also (Topic, Algorithm, Media)

- Prostate Biopsy, Infections and Complications
- Prostate, Abscess
- Prostatitis, Acute, Bacterial (NIH I) Image
- Prostatitis, Chronic Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B)
- Prostatitis, Chronic, Bacterial (NIH II)
- Prostatitis, General Considerations
- Prostatitis, Granulomatous

• Urinary Tract Infection (UTI), Adult Male

CODES

ICD9

• 041.49 Other and unspecified *Escherichia coli* [*E. coli*]
• 098.12 Gonococcal prostatitis (acute)
• 601.0 Acute prostatitis

ICD10

• A54.22 Gonococcal prostatitis
• B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
• N41.0 Acute prostatitis

CLINICAL/SURGICAL PEARLS

• *E. coli* is most common organism in acute bacterial prostatitis.
• Avoid vigorous prostatic exam or massage during an episode of acute bacterial prostatitis.
• It is not advisable to measure serum PSA during an episode of acute bacterial prostatitis as it will most likely be falsely elevated.
• Urinary retention requires bladder drainage.
• May require hospital admission and IV antibiotics.
• Consider prostatic abscess if no clinical response in 48 hr.

PROSTATITIS, CHRONIC NONBACTERIAL, INFLAMMATORY AND NONINFLAMMATORY (NIH CP/CPPS III A AND B)

Amin S. Herati, MD
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BASICS

DESCRIPTION

- Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), NIH categories IIIA and IIIB are characterized by pelvic, perineal, and/or testicular pain ± LUTS in the absence of other well-defined pathology.
  - IIIA: Inflammatory CPPS: WBCs present in prostatic secretions
  - IIIB: Noninflammatory CPPS: WBCs not present in prostatic secretions

EPIDEMIOLOGY

Incidence

N/A

Prevalence

Estimated prevalence of CP/CPPS is 1.8%, equating to approximately 2,000,000 US men (1).

RISK FACTORS

- Urethral catheterization or instrumentation
- Inadequately treated urinary tract infections
- Pelvic trauma
- Urethral strictures
- Psychological stress or depression

Genetics

- A large proportion of patients with CP/CPPS express the IL-10 AA genotype with low IL-10 expression
- Category IIIA patients are more likely to have a low TNFα genotype

PATHOPHYSIOLOGY

- 90% of cases of CP/CPPS have an unclear etiology, the remainder of cases can be attributed to bacterial in origin (Category II)
- Although the exact cause is not known, it is thought to be multifactorial with a combination of factors contributing to the pathophysiology (image)
- Current theories include:
  - Nanobacterial colonization
  - Atypical bacterial infection
  - Voiding dysfunction causing intraprostatic urinary reflux and elevated intraprostatic pressure
  - Pelvic floor muscle dysfunction
  - Endocrine

  - Neuropathic
  - Autoimmune
- Stratification of each patient into a 6-point clinical phenotyping system, termed UPOINT, based on likely etiologic mechanisms has been proposed to improve outcomes by tailoring therapies to target the involved mechanisms (2).

ASSOCIATED CONDITIONS
- Allergies
- Sinusitis
- Erectile dysfunction
- Irritable bowel syndrome
- Depression
- Fibromyalgia
- Fatigue
- Neurologic disorders

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Determine duration of symptoms (of at least >3-mo duration)
- Pain in the suprapubic region, lower back, penis, testes, and/or scrotum
- Painful ejaculation: One of the most discriminatory symptoms associated with CP/CPPS III and a strong predictor of QOL and severity of pain (3)
- Sexual dysfunction
- Pelvic floor muscle spasms
- Irritative and obstructive voiding symptoms
  - Urgency
  - Frequency
  - Hesitancy
  - Poor interrupted flow
- History should also cover neurologic disease, hematologic, cardiovascular, and infectious diseases
- NIH-CPSI is a validated questionnaire assessing pain, urinary function, and QOL. Can be used to measure symptoms upon initial presentation and follow-up

PHYSICAL EXAM
- Careful exam of the genitalia, groin, perineum, coccyx, external anal sphincter, and internal pelvic floor and side walls
- Exam is usually unremarkable except for pain: Degree of pain not helpful in differentiating between various categories of CP/CPPS
- Digital rectal exam should not be performed until urine from preprostatic massage has been collected

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis and urine culture
- Stamey test (Meares–Stamey 4-glass test)—considered to be "gold standard" in diagnosis
- Limitations: EPS cannot be obtained in all patients, variable interpretation of WBC counts, difficult-to-culture organisms not routinely identified
- 2-glass test (premassage and postmassage test)
  - Difficulties encountered with interpretation of bacterial localization studies as asymptomatic individuals often harbor uropathogens

Imaging
- Pelvic imaging with ultrasonography, CT, or MRI is considered optional and can be obtained if clinically indicated to rule out other causes of pelvic pain
- TRUS has poor specificity in differentiating among the subtypes of CP/CPPS

Diagnostic Procedures/Surgery
- Stamey test (Meares–Stamey 4-glass test)
- Video-urodynamics: Should be considered in patients with significant lower urinary tract symptoms in addition to pain. Findings often include decreased peak and mean urinary flow rates, elevated maximal urethral closing pressure, incomplete funneling of the bladder neck, and urethral narrowing at the level of the external urethral sphincter (4)
- Cystoscopy is not indicated in the majority of cases: Can be performed if history indicates other etiology
- Prostate biopsy: Tissue for culture not helpful in diagnosis and not recommended

Pathologic Findings
Not formally reported for Category III, therefore N/A

DIFFERENTIAL DIAGNOSIS
- Acute or chronic bacterial prostatitis
- Benign prostatic hyperplasia
- Bladder calculus
- Bladder cancer
- Bladder neck contracture
- Interstitial cystitis
- Primary voiding dysfunction
- Prostate abscess
- Prostate cancer
- Prostate cyst
- Radiation cystitis
- Tuberculosis of the prostate
- Urethral stricture
- Urethritis

TREATMENT

GENERAL MEASURES
- As the pathogenesis of CP/CPPS category III is considered multifactorial, effective treatment

for CP/CPPS III often requires multimodal therapy
- A meta-analysis comparing α-Blockers, antibiotics and anti-inflammatory/immune modulating therapies found a combination of α-blockers and antibiotics to be superior to α-blockers, antibiotics, or anti-inflammatory/immune modulating therapies alone in the reduction of NIH-CPSI scores (5)
- Treatment should also be targeted to the etiologic mechanisms using the UPOINT system
- Focus of therapy should be on symptom relief
- Conservative measures such as diet modification, myofascial physical therapy, phytotherapies, acupuncture should be considered as part of the 1st-line therapy
- Symptoms should be followed with NIH-CPSI questionnaires and voiding diaries

MEDICATION

First Line

- The choice of agents in the 1st- or 2nd-line setting is practitioner dependent with no specific agent approved specifically for this condition
- α-Blockers: Multiple randomized, placebo-controlled trials have demonstrated a duration of at least 3 mo or longer may be needed before assessment can be made of treatment failure or success.
  - Side effects of α-blockers include hypotension, dizziness, fatigue, and retrograde ejaculation
    - Alfuzosin 10 mg BID for 12 wk; contraindicated with moderate hepatic insufficiency or with cytochrome P450 3A4 inhibitors
    - Doxazosin 1–4 mg daily for 12 wk; escalate dose until symptom relief obtained
    - Tamsulosin 0.4 mg daily for 12 wk
    - Terazosin 1–5 mg daily; escalate dose until symptom relief obtained
    - Silodosin (8 mg/d)
- Antibiotic therapy: Data conflicting on the benefit and therapeutic benefit should be reassessed after 2 to 4 wk of initiating therapy
  - Can be considered in antibiotic-naïve patients
  - Fluoroquinolones: Side effects include dizziness, restlessness, headache, nausea, rash
    - Ciprofloxacin, levofloxacin 500 mg daily for 4 wk (some concern over growing resistance to this class of drugs)
    - Trimethoprim–sulfamethoxazole 160/80 mg BID for 4 wk: Side effects include anorexia, nausea, vomiting, rash, urticaria
- 5α-Reductase inhibitor:
  - Finasteride 5 mg daily or
  - Dutasteride 0.5 mg daily
- Anti-inflammatory agents
  - Rofecoxib 25–50 mg daily: Symptom relief at higher doses, but not recommended because of cardiovascular risk
  - Oral prednisolone
- Pentosan polysulfate 100 mg TID
- Gabapentanoids
  - Pregabalin 150–600 mg daily
- Muscle relaxants

– Baclofen
– Diazepam

Second Line
See above

SURGERY/OTHER PROCEDURES
• Not recommended. Last resort unless other indications are discovered during the workup
– Transurethral microwave thermotherapy

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
See below

Complementary & Alternative Therapies
• Dietary and lifestyle modification
• Phytotherapy
– Pollen extract
– Quercetin
– Saw palmetto
• Acupuncture
• Myofascial physical therapy
• Stress management/cognitive-behavioral therapy
• Frequent ejaculation

ONGOING CARE

PROGNOSIS
Remissions and flare-ups common over the long term

COMPLICATIONS
None known

FOLLOW-UP
Patient Monitoring
Long-term supportive care

Patient Resources
• Urology Care. Foundation. http://www.urologyhealth.org/urology/index.cfm?article=15
• http://www.prostatitis.org

REFERENCES
1. Suskind AM, Berry SH, Ewing BA, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial Cystitis Epidemiology Male Study. *J Urol.* 2013;189:141–145.
2. Shoskes DA, Nickel JC, Kattan MW. Phenotypically directed multimodal therapy for

chronic prostatitis/chronic pelvic pain syndrome: A prospective study using UPOINT. *Urology*. 2010;75:1249–1253.
3. Shoskes DA, Landis JR, Wang Y, et al; Chronic Prostatitis Collaborative Research Network Study Group. Impact of post-ejaculatory pain in men with category III chronic prostatitis/chronic pelvic pain syndrome (CPPS). *J Urol.* 2004;172:542–547.
4. Barbalias GA, Meares EM Jr, Sant GR. Prostatodynia: Clinical and urodynamic characteristics. *J Urol.* 1983;130:514–517.
5. Thakkinstian A, Attia J, Anothaisintawee T, et al. α-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. *BJU Int.* 2012;110:1014–1022.

ADDITIONAL READING

- Nickel JC. Prostatitis and related conditions, orchitis, and epididymitis. In: Wein AJ, Kavoussi LR, Novick AC, et al. eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier; 2011.
- Schaeffer AJ. Chronic Prostatitis and the chronic pelvic pain syndrome. *N Eng J Med.* 2005;355:1690–1698.

See Also (Topic, Algorithm, Media)

- NIH-CPSI Questionnaires
- Prostatitis, Acute Bacterial (NIH I)
- Prostatitis, Asymptomatic Inflammatory (NIH IV)
- Prostatitis, Chronic Bacterial (NIH II)
- Prostatitis, Chronic Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B) Image ☼
- Prostatitis, General
- Stamey Test (3-glass test, 4-glass tests, Meares–Stamey Test)

CODES

ICD9

- 338.4 Chronic pain syndrome
- 601.1 Chronic prostatitis
- 789.09 Abdominal pain, other specified site

ICD10

- G89.29 Other chronic pain
- N41.1 Chronic prostatitis
- R10.2 Pelvic and perineal pain

CLINICAL/SURGICAL PEARLS

Multimodal therapy is oftentimes required because of the varied pathologies associated with this condition.

PROSTATITIS, CHRONIC, BACTERIAL (NIH II)

John J. Pahira, MD

BASICS

DESCRIPTION

- Chronic bacterial prostatitis (NIH II) includes symptoms of prostatitis with positive urine culture and no signs of systemic infection
- Occasionally, without local symptoms
- Recurrent UTI with a single organism that persists is the classic hallmark
- Overlap of symptoms makes it difficult to distinguish clinically from chronic nonbacterial prostatitis (NIH Type III, CP/CPPS); about 10% of these patients with type III prostatitis will have positive cultures
- NIH classification and current definitions of prostatitis (1):
  - Type I: Acute bacterial prostatitis
  - Type II: Chronic bacterial prostatitis; recurrent infection
  - Type III: Chronic abacterial prostatitis/CPPS; no demonstrable infection:
    - IIIA: Inflammatory CPPS: WBCs present in semen/expressed prostatic secretions or voided bladder urine (VB3)
    - IIIB: Noninflammatory CPPS: WBCs not present in semen/expressed prostatic secretions or voided bladder urine (VB3)
  - Type IV: Asymptomatic inflammatory prostatitis: Detected by prostate exam or presence of WBCs in prostatic secretions during evaluation for other disorders

EPIDEMIOLOGY

- Prostatitis in general is the most common urologic diagnosis in men <50 yr old, and the 3rd most common diagnosis in men >50 yr old.
- Affects 10–14% of men of all ages and accounts for 2 million office visits annually.
- Chronic bacterial prostatitis is the most common cause of recurrent UTI in the adult male population.

RISK FACTORS

- Inadequately treated episodes of acute bacterial prostatitis may increase risk for developing chronic prostatitis syndromes
- Older men with BPH/bladder outlet obstruction
- Urethral strictures
- Urethral catheterization
- Possibly reduced sexual activity with resulting prostatic congestion

Genetics

N/A

PATHOPHYSIOLOGY

- With progressive benign prostatic enlargement, obstruction causes reflux into prostatic ducts (2).

- Obstructive, turbulent, and/or high-pressure voiding combined with intraprostatic ductal reflux, leads to acute intraductal inflammation.
- Progresses to chronic intraductal inflammation.
- Bacteria are present in inflamed ducts in protected bacterial aggregates or bacterial biofilms.
- Increased incidence of prostatic calculi may serve as a nidus of infection.
- Prostatic zinc levels (zinc is thought to be antibacterial) are lower in patients with chronic bacterial prostatitis; however, it is not clear if this is a cause of or due to the infection.
- pH of prostatic fluid may increase from a normal of ~6.5 to >8.0 with infection.
- Common pathogens: *Escherichia coli* (most common), *Enterococcus faecalis*, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus spp.*
- Others: *Staphylococcus epidermatitis, S. saprophyticus, Corynebacterium,* and *Ureaplasma urealyticum*, *Chlamydia trachomatis, Candida*, *trichomonas*, *Mycobacterium hominis*, and *Tuberculosis*:
  - *Chlamydia, Ureaplasma, Mycoplasma spp.* can cause prostatitis but do not grow in routine culture.

ASSOCIATED CONDITIONS
- BPH
- Detrusor/sphincter dyssynergia
- Sexual dysfunction
- STDs
- Subfertility/infertility
- Urethral stricture

GENERAL PREVENTION
- Adequate treatment of acute bacterial prostatitis
- Protected intercourse
- Voiding after all sexual experiences may help

DIAGNOSIS

HISTORY
- Fever and chills are not usual and suggest acute bacterial prostatitis.
- Dysuria, urgency, nocturia, weak stream
- Perineal, penile, scrotal, suprapubic, or groin pain; pain with or after ejaculation
- ED, decreased libido
- Prior UTIs, STDs
- Unprotected intercourse, new partners, sexual orientation
- Urethral catheterization or other lower genitourinary surgery
- NIH-CPSI, a self-administered validated symptom index, may be useful.

PHYSICAL EXAM
- Exam of the genitalia may reveal vague widespread pelvic discomfort.
- Perineal tenderness may be present.
- DRE may reveal a minimally tender or boggy prostate.
- Prostatic calculi may be palpable.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis and culture (2):
  - Routine urine culture may be negative. A positive culture may be obtained as part of the Meares–Stamey 4-glass test (see below):
  - Pyuria and bacteruria may be present.
  - Hematuria should prompt workup for other causes.
- PSA may be elevated in the setting of prostate infection and should not be obtained until the infection clears.

Imaging

Imaging has low yield and is performed only to exclude the presence of other more definable and treatable causes of the patient's symptoms.

- Transrectal US performed in patients with pain on ejaculation may reveal enlargement of the prostate or seminal vesicle. Prostatic calculi may be visualized.

ALERT
In the setting of possible acute bacterial prostatitis or prostatic abscess, prostatic massage should not be performed.

Diagnostic Procedures/Surgery

- Meares–Stamey 4-glass test considered gold standard for the diagnosis of chronic bacterial prostatitis and involves isolated cultures of different portions of the lower urinary tract:
  - Make sure that the patient has a full bladder
  - Clean the glans thoroughly with antimicrobial solution. Retract foreskin as necessary
  - Void 10 mL into sterile container (VB1). Represents urethral flora sample
  - After voiding 100 mL, collect 10 mL midstream urine in another sterile container (VB2). Represents bladder flora sample
  - Perform prostatic massage to collect EPS from the urethra; submit for culture and examine on a glass slide under 40×. Represents prostate flora
  - Collect the next voided 10 mL in a sterile container. Represents a combination of prostate and bladder flora
- Normal:
  - Negative urethral, prostatic, and bladder cultures (VB1, VP2, EPS, and VB3 negative)
  - Normal prostatic secretions show no evidence of excess WBCs (<10 WBC cells per high-power field)
- Positive:
  - If EPS or VB3 colony counts are 10× higher than VB1 or VB2, bacterial prostatitis is present
  - If all cultures are positive, then bacterial cystitis is likely present and the test should be repeated after 5 days of antibiotics (prostatitis and cystitis can coexist, and cystitis in men is often secondary to prostatitis)
  - EPS result is >10–20 WBC per high-power field or clumping of WBC. It is not diagnostic for bacterial infection as it can also be seen with NIH Class IIIA prostatitis
- A modified Meares–Stamey test (2-glass test) can also be performed that is considered more convenient and practical

  - After cleansing the glans, obtain 10 mL of a midstream urine for culture (preprostate massage). Represents bladder flora. Should also be dipped for white cells
  - Perform prostate massage and obtain 10 mL of urine (postprostate massage) for culture and microscopic exam. Represents prostate and bladder flora. If white cells are present, they may represent bacterial prostatitis or NIH type IIIA
  - If postmassage colony counts are 10× higher than premassage sample, bacterial prostatitis is present. If both cultures have similar counts, cystitis is present
- Semen culture is of limited use, demonstrating low sensitivity but high specificity compared to Stamey test
- Uroflowmetry may demonstrate diminished flow with intermittency
- Elevated PVR may be present

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Acute bacterial prostatitis/prostatic abscess
- Bladder outlet obstruction/BPH
- Chronic nonbacterial prostatitis (NIH IIIA/B)
- Cystitis
- Interstitial cystitis
- Prostatic cyst
- Seminal vesiculitis
- STDs
- Tuberculous/granulomatous prostatitis
- Urethritis or urethral pathology (stricture)

TREATMENT

GENERAL MEASURES

- Antibiotic course normally extends for 6–8 wk and sometimes longer with refractory infections. Goal is to eradicate the nidus of infection in the prostate. Follow culture results (3,4).
- Avoid alcohol, spicy foods, perineal pressure for extended times (sitting or bicycle riding), acidic beverages.
- Continue to engage in safe protected sexual activity, as this is thought to reduce prostatic congestion.

MEDICATION

First Line

- Current sensitivity patterns are showing increased resistance to quinolones, TMX/SULFA, ampicillin. In choosing antibiotic coverage prior to culture sensitivity reports, know local resistance patterns based on your hospital antibiogram
- Fluoroquinolones still preferred
  - No difference in bacterial eradication between levofloxacin and ciprofloxacin, although prostatic fluid concentration of levofloxacin is higher than ciprofloxacin. Levofloxacin has

daily dosing and may have better prostatic penetration
  - Ciprofloxacin 500 mg PO BID for 4–6 w;
  - Levofloxacin 500 mg/d for at least 6–8 wk
- Trimethoprim 60 mg–sulfamethoxazole 80 mg BID for at least 6–8 wk
- Tetracycline derivatives (eg, doxycycline) only if *Chlamydia* or *Mycoplasma* suspected

Second Line
- Anti-inflammatories (ibuprofen) for symptoms
- α-Blockers (doxazosin, tamsulosin, alfuzosin, silodosin) may help with LUTS

SURGERY/OTHER PROCEDURES
- Not generally recommended
- TURP
  - Can be considered in select cases of refractory prostatitis with infected calculi and/or obstruction

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Frequent ejaculation (in patients with enlarged, symptomatically congested glands)
- Dietary modifications of common comestibles found to irritate the lower urinary tract
- Moist heat with Sitz baths or heating pad for symptomatic relief

Complementary & Alternative Therapies
- Prostate massage (very controversial):
  - May work by stimulating hibernating bacterial biofilms (making them more susceptible to antimicrobials), draining the obstructed inflamed ducts (allowing for better antimicrobial penetration), and stimulating blood supply to the area.
- Avoid bicycling or other activities that cause perineal pressure
- Zinc supplements: Unproven benefit
- Phytotherapy: Plant extracts and herbal medications (ie, saw palmetto) popular but may only be as effective as placebo (5)

ONGOING CARE

PROGNOSIS
- Fluoroquinolones have improved the ability to clear the infection (60–90% cure reported).
- Variable course with flare-ups possible. If culture-positive infection persists, consider longer course of therapy (3–6 mo) with a lower daily dose.
- Treating underlying obstruction or prostatic calculi if necessary may prevent further infections.

COMPLICATIONS
- Recurrent cystitis, epididymitis, urethritis
- CPPS
- Infertility (effect on semen quality debatable)

- Primarily affects QOL
- Unknown if predisposes to prostate cancer

FOLLOW-UP

Patient Monitoring

- Document clearing of positive culture
- Following prostate cancer screening guidelines is recommended. Do not obtain PSA for at least 6 wk after culture clears.

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=15

REFERENCES

1. Schaeffer AJ. Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med*. 2006;355:1690–1698.
2. Schaeffer AJ, Knauss JS, Landis JR, et al. Leukocyte and bacterial counts do not correlate with severity of symptoms in men with chronic prostatitis: The National Institutes of Health Chronic Prostatitis Cohort Study. *J Urol*. 2002;168:1048–1053.
3. Naber KJ. Management of chronic bacterial prostatitis: What's New? *BJU Intern*. 2008;101(S3):7–10.
4. Wagenlehner FM, Weidner W, Sörgel F, et al. The role of antibiotics in chronic bacterial prostatitis. *Int J Antimicrob Agents*. 2005;26:1–7.
5. Shoskes DA. Phytotherapy in chronic prostatitis. *Urology*. 2002;60:35–37.

ADDITIONAL READING

Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236–237.

See Also (Topic, Algorithm, Media)

- Prostatitis, Acute, Bacterial (NIH I)
- Prostatitis, Asymptomatic Inflammatory (NIH IV)
- Prostatitis, Chronic, Bacterial (NIH II)
- Prostatitis, Chronic, Nonbacterial, Inflammatory (NIH CP/CPPS IIIA)
- Prostatitis, Chronic, Nonbacterial, Noninflammatory (NIH CP/CPPS IIIB)
- Prostatitis, General
- Prostatitis, Granulomatous
- Stamey Test (3-Glass Test, 4-Glass Tests, Meares–Stamey Test)

CODES

ICD9

- 041.49 Other and unspecified Escherichia coli [E. coli]
- 131.03 Trichomonal prostatitis
- 601.1 Chronic prostatitis

ICD10

- A59.02 Trichomonal prostatitis

- B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
- N41.1 Chronic prostatitis

CLINICAL/SURGICAL PEARLS

Inadequately treated acute bacterial prostatitis may increase risk for developing chronic prostatitis syndromes including chronic bacterial prostatitis.

PROSTATITIS, GENERAL

Ryan S. Levey, MD
Justin D. Ellett, MD, PhD

BASICS

DESCRIPTION

- Prostatitis is a general term that refers to inflammation of the prostate.
- Traditionally classified as acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostatodynia today the definitions used are much more precise and based on the NIH system (1).
- Revised 1995 NIH classification of prostatitis is standard nomenclature:
  - NIH Class I: Acute bacterial prostatitis; infection of prostate, sudden onset, often associated with UTI
    - >10 WBC/HPF in 1st 10 mL voided urine and midstream catch
    - Positive culture in 1st 10 mL voided urine and midstream catch
  - NIH Class II: Chronic bacterial prostatitis; insidious onset, relapsing, recurrent UTI
    - >10 WBC/HPF
    - Positive culture in expressed prostatic secretions (EPS) and 1st 10 mL of voided urine after EPS
  - NIH Class III: Chronic prostatitis (CP)/Chronic pelvic pain syndrome (CPPS):
  - NIH Class IIIA: Inflammatory: Inflammatory cells in prostatic secretion, seminal fluid, postprostatic massage urine
    - >10 WBC/HPF in EPS, 1st 10 mL of voided urine after EPS, or semen
  - NIH Class IIIB: Noninflammatory: Insignificant inflammatory cells
    - <10 WBC/HPF in EPS, 1st 10 mL voided urine after EPS, or semen
  - NIH Class IV: Asymptomatic inflammatory prostatitis, incidental biopsy finding
    - >10 WBC/HPF and/or bacteria in EPS, 1st 10 mL voided urine after EPS, semen, or histologic specimens in asymptomatic patients

EPIDEMIOLOGY

Incidence

- 2 million cases annually
- 9–16% men have had diagnosis of prostatitis
- 3–12% male outpatient urology visits
- Most common urologic diagnosis in men <50 yr, 3rd most common >50 yr (2)
  - Overall incidence of acute prostatitis or prostatitis NOS 2.8/1,000 person-years (PY) over 70,166 PY of follow-up (3)
    - 3.2/1,000 PY in patients aged 20–29 yr
    - 3.6/1,000 PY in patients aged 30–39 yr
    - 5.4/1,000 PY in patients aged 70–79 yr

Prevalence

N/A

RISK FACTORS

- Acute epididymitis
- Chronic catheterization (indwelling or condom)
- Dysfunctional voiding
- Immunocompromised states
- Intraprostatic ductal reflux
- Phimosis
- Urethral stricture, distal
- BPH
- Prostatic calculi
- Transurethral surgery/instrumentation
- Transrectal prostate biopsy
- Unprotected anal sex
- UTI

Genetics

N/A

PATHOPHYSIOLOGY

- Extension of UTI
- Manipulation of urinary tract or prostate
- Bacterial:
  - Ascending infection through urethra
  - Refluxing urine into prostate ducts
  - Direct extension or lymphatic spread from rectum
  - Hematogenous spread
  - Calculi serve as a nidus for infection
  - Aerobic gram-negative bacteria (Enterobacteriaceae [most common cause], *Escherichia coli* [most common organism], Pseudomonas, Klebsiella, Proteus, Serratia), *Neisseria gonorrhoeae*, *Burkholderia pseudomallei*
  - Miscellaneous: *Chlamydia trachomatis*
  - Gram-positive bacteria (Enterococcus, *Streptococcus faecalis*, *Staphylococcus aureus*)
- Organisms suspected, but unproven: *Staphylococcus epidermidis*, micrococci, nongroup D Streptococcus, diphtheroids, *Ureaplasma urealyticum*, *Trichomonas vaginalis*
- Nonbacterial:
  - Leading theory: Nonrelaxation of internal urinary sphincter and pelvic floor muscles leading to increased prostatic urethral pressure and intraprostatic urinary reflux
- Uncommon: *Mycobacterium tuberculosis*, parasitic, mycoses (blastomycosis, coccidioidomycosis, Cryptococcus, histoplasmosis, candidiasis paracoccidiomycosis)

ASSOCIATED CONDITIONS

- Cystitis (secondary to bacterial prostatitis)
- Epididymitis
- Prostatic hypertrophy
- STD
- Urethritis/urethral stricture

- UTI

GENERAL PREVENTION

- Proper treatment of acute bacterial prostatitis may reduce chronic bacterial prostatitis (NIH II)
- Safe sex practices

DIAGNOSIS

HISTORY

- Acute bacterial prostatitis (NIH I)
  - Fever, chills, malaise
  - Perineal, suprapubic pain
  - Irritative voiding symptoms: Urgency, frequency, dysuria
  - Obstructive voiding symptoms: Hesitancy, intermittent stream, acute urinary retention
  - Rare sepsis
  - 5% will develop CP
- Chronic bacterial prostatitis (NIH II)
  - Recurrent UTIs
  - Asymptomatic or CPPS (see below)
- CP/CPPS (NIH IIIA/B)
  - Pain in perineum, suprapubic region, penis, testicles, groin, low back
  - Pain especially after or during ejaculation
  - Irritative/obstructive voiding symptoms lasting >3 mo
  - ED, sexual disturbances, severe effect on quality of life
- NIH Class IV: None; usually only elevated PSA or nodule that prompts biopsy

PHYSICAL EXAM

- Acute bacterial prostatitis (NIH I):
  - Suprapubic tenderness
  - Assess for acute urinary retention
  - DRE: Hot, boggy, exquisite tenderness
  - Sepsis: Febrile, tachycardia
- Chronic bacterial prostatitis/CPPS (NIH II/IIIA/IIIB)
  - Suprapubic tenderness
  - DRE: May be normal or soft/boggy, variable amounts of pain, prostatic calculi

ALERT
Do not perform massage or aggressive rectal exam in the face of acute prostatitis or prostatic abscess.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- PSA may be elevated with prostatitis PSA should not be checked in cases of acute bacterial prostatitis.
- Suspected acute bacterial prostatitis:
  - Urinalysis, urine culture, CBC, blood culture

- Suspected CPB/CP/CPPS (NIH II/III)
  - Urinalysis, urine culture
  - Meares–Stamey 4-glass test (gold standard)
  - 2-glass test more convenient: Pre/postprostatic massage:
    - Urine microscopy and culture of midstream urine specimen prior to prostate massage (Pre-M)
    - Urine microscopy and culture of 10-mL urine postprostate massage (Post-M)
    - With NIH II (chronic bacterial):
  - Pre-M: ± Urine WBC, ± culture
  - Post-M: + Urine WBC, + culture
    - NIH IIIA inflammatory CP/CPPS:
  - Pre-M: − Urine WBC, − culture
  - Post-M: + Urine WBC, − culture
    - NIH IIIB noninflammatory CP/CPPS
  - Pre-M: − Urine WBC, − culture
  - Post-M: − urine WBC, − culture

Imaging
- CT: If suspicion of abscess/malignancy or failure appropriate antimicrobial treatment
- Transrectal US: If suspicion of abscess or fail antibiotic therapy (rule out abscess, calculi)

Diagnostic Procedures/Surgery
- PVR if sensation of incomplete emptying
- Urodynamics: CPPS patients; debatable utility
- Cystoscopy: CPPS patients with hematuria; rules out bladder neck pathology, lower tract malignancy

Pathologic Findings
- Sheets, clusters, nodules of lymphocytes, plasma cells in fibromuscular stroma
- No relationship to the ducts and acini
- Infiltrates of inflammatory cells restricted to the glandular epithelium and lumen found in prostate and BPH
- Inflammatory changes noted in up to 44% of asymptomatic males at autopsy

DIFFERENTIAL DIAGNOSIS
- Acute urinary retention
- Cystitis (bacteria, interstitial)/urethritis
- Obstructive bladder calculus
- Prostate cancer
- Prostatic abscess
- Pyelonephritis

TREATMENT

GENERAL MEASURES
- NIH I acute prostatitis:
  - IV antibiotics, then switch to oral agents

- Acute retention may be treated with in-and-out catheter or small-caliber Foley for <12 hr or suprapubic drainage with acute prostatitis
- Acute bacterial prostatitis that does not resolve with conventional measures; must rule out prostate abscess

- NIH II: Long-term antibiotic therapy
- NIH IIIA/B: Similar management; empiric antibiotics often used with variable success, focus on symptomatic and supportive therapy; α-adrenergic blockers and NSAIDs may be useful adjuncts in this population
- NIH IV is only a histologic diagnosis and no specific therapy necessary

MEDICATION

First Line

- Antibiotics: For acute bacterial prostatitis (inpatient)
  - Ampicillin with gentamicin (ampicillin 1–2 g IV every 4–6 hr, 500 mg PO every 6 hr; gentamicin 1–2 mg/kg IV every 8–12 hr or daily dosing 4–7 mg/kg every 24 hr IV)
  - Fluoroquinolones
    - Levofloxacin, 250–750 mg daily IV or by mouth (PO)
    - Ciprofloxacin, 250–750 mg PO twice daily (BID), 400 mg IV BID
  - Ceftriaxone 1–2 g IV or IM daily
  - Afebrile 24–48 hr may change to oral antibiotics
- Acute bacterial prostatitis (outpatient)
  - Trimethoprim–sulfamethoxazole DS PO BID for 2–4 wk
  - Ciprofloxacin 500 mg PO BID for 2–4 wk
- Chronic bacterial prostatitis:
  - Ciprofloxacin 500 mg PO BID for 4–6 wk; levofloxacin has daily dosing and may have better prostatic penetration
  - Fluoroquinolones more cost effective and may be superior to TMP/SMX
- CP/CPPS:
  - NIH IIIA: Antibiotics may reduce symptoms but should work within 4–6 wk
  - Previously treated men do not benefit from further antibiotics
- α-Adrenergic blockers:
  - Chronic bacterial prostatitis (NIH II): In combination with antibiotics, will reduce symptoms
  - CP/CPPS (NIH III): Benefit men with recent onset of symptoms, not heavily treated, and on medication for >6 mo
- Anti-inflammatory agents:
  - NSAIDs/analgesics/antipyretics
- Stool softeners

Second Line

- Antibiotics: Erythromycin, azithromycin, clarithromycin if *Chlamydia trachomatis* implicated
- Finasteride or dutasteride: Only if associated BPH in patients with CP/CPPS

SURGERY/OTHER PROCEDURES

- Transurethral resection: If concern for prostatic abscess or in the setting of intractable chronic bacterial disease

- Transurethral microwave therapy: Refractory CP

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Numerous unproven therapies have been suggested with little to no evidence for treatment of CP or CPPS, including: Allopurinol, balloon dilation, TUNA, acupuncture, neuromodulation
- Frequent ejaculation (in patients with enlarged, symptomatically congested glands), prostatic massage (not in acute prostatitis)
- Dietary modification
- Sitz baths for symptomatic relief

Complementary & Alternative Therapies

- Phytotherapy provides modest benefit in CP/CPPS
- Neuromodulation (CP/CPPS): Amitriptyline, gabapentin, acupuncture, biofeedback, massage, neurostimulation

ONGOING CARE

PROGNOSIS

- Prolonged course, often difficult to cure
- 50–97% cure rate, depending on category
- 20% with recurrent or persistent infection

COMPLICATIONS

- Acute urinary retention
- Chronic bacterial prostatitis with incomplete treatment of acute bacterial prostatitis
- Epididymitis, orchitis, seminal vesiculitis (rare)
- Gram-negative sepsis, bacteremia
- Prostatic abscess

FOLLOW-UP

Patient Monitoring

- Most improve with antibiotics in 3–4 wk
- Long-term management of CP/CPPS requires multimodal therapy and supportive care

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=15

REFERENCES

1. Sharp VJ, Takacs EB, Powerll CR. Prostatitis: Diagnosis and treatment. *Am Fam Physician*. 2010;82(4):397–406.
2. Roberts RO, Lieber MM, Rhodes T, et al. Prevalence of a physician-assigned diagnosis of prostatitis: The Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology*. 1998;51(4):578–584.

ADDITIONAL READING

Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236–237.

See Also (Topic, Algorithm, Media)

- Prostate, Abscess
- Prostatitis, Acute, Bacterial (NIH I)
- Prostatitis, Asymptomatic Inflammatory (NIH IV)
- Prostatitis, Chronic, Bacterial (NIH II)
- Prostatitis, Chronic Nonbacterial, Inflammatory and Noninflammatory (NIH CP/CPPS III A and B)
- Prostatitis, Granulomatous
- Stamey Test (3-Glass Test, 4-Glass Tests, Meares–Stamey Test)

CODES

ICD9

- 601.0 Acute prostatitis
- 601.1 Chronic prostatitis
- 601.9 Prostatitis, unspecified

ICD10

- N41.0 Acute prostatitis
- N41.1 Chronic prostatitis
- N41.9 Inflammatory disease of prostate, unspecified

CLINICAL/SURGICAL PEARLS

- Prostatitis is considered the most common urologic diagnosis in men <50.
- If suspected CBP/CP/CPPS, perform 2-glass test to help establish the diagnosis.
- Most chronic bacterial prostatitis cases improve after 3–4 wk of antibiotics.

PROSTATITIS, GRANULOMATOUS

Brian Cox, MD
Christopher Amling, MD, FACS

BASICS

DESCRIPTION

- Granulomatous prostatitis is inflammation of the prostate associated with granuloma formation
- Often confused with carcinoma of the prostate
  - Similar findings on digital rectal exam (DRE); has the findings of a “prostate nodule"
  - Similar elevations in prostate-specific antigen (PSA)
  - Similar findings on transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) images
  - Can be due to infectious and noninfectious etiologies

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- 0.8–1% of benign inflammatory prostatic specimens
- Reported up to 4–10% of prostatitis cases
- Reported in 1.3–40% of post-Bacillus Calmette–Guérin (post-BCG) patients

RISK FACTORS

- Age: Mean age 62 yr (range 18–86 yr) (1)
  - Typically 50–70 yr of age
- Infections:
  - Bacterial, viral, fungal, parasitic, Mycobacterium, and sexually transmitted diseases (STDs)
  - Human immunodeficiency virus (HIV) infection may increase risk for tuberculosis (TB) prostatitis
  - Infectious etiologies make up ~15–20% of granulomatous prostatitis cases
- Iatrogenic causes:
  - Transurethral resection of prostate (TURP)
  - BCG instillation for bladder cancer—up to 40% may develop granulomatous prostatitis after BCG.
  - Iatrogenic etiologies make up ~75% of granulomatous prostatitis cases
- Systemic granulomatous diseases:
  - Wegener granulomatosis, Churg–Strauss syndrome, sarcoidosis, rheumatoid arthritis, polyarteritis nodosa, malakoplakia
  - These make up a minority of granulomatous prostatitis cases
- Idiopathic: No specific cause identified
  - Theory: Ductal/acinar obstruction causes prostatic secretions to leak into the stroma and cause granulomatous reaction

– Idiopathic etiologies make up a significant proportion of granulomatous prostatitis cases

Genetics
N/A

PATHOPHYSIOLOGY
- Specific subtype:
  – Caused by identifiable infectious agent (mycobacterium, fungi, syphilis, brucellosis, virus, parasites)
    - It is often associated with systemic TB
    - With HIV, TB may cause prostatic abscess
- Nonspecific subtype:
  – Usually an incidental finding on biopsy
    - Reported 0.3–3.0%
- Iatrogenic:
  – After TURP- or TRUS-guided biopsy, necrotizing lesions may resemble lesions associated with rheumatoid diseases
- Eosinophilic subtype:
  – Very rare, may suggest allergic etiology
  – Associated with systemic condition (asthma, Wegener granulomatosis, Churg–Strauss syndrome
- Autoimmune based:
  – HLA-DR15–linked T-cell–mediated response against PSA

ASSOCIATED CONDITIONS
- Prostate cancer can be coincident with granulomatous prostatitis in 10–14% of biopsy specimens (2)
- May be associated with systemic conditions
  – Asthma, Wegener granulomatosis, Churg–Strauss syndrome, sarcoidosis, rheumatoid arthritis, polyarteritis nodosa, malakoplakia

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY
- Often asymptomatic
- Previous urinary tract infection (UTI) or STD:
  – Syphilis, TB, or other infectious etiology
  – Often associated with UTI 2–3 m prior to onset of symptoms
- History of lower urinary tract symptoms (LUTS)
  – Voiding symptoms including urgency, frequency, dysuria
  – Obstructive voiding symptoms, including acute urinary retention
- Systemic granulomatous disease:
  – If associated with systemic vasculitis or granulomatous disease, may have constitutional signs/symptoms

- History of prostate surgery or bladder cancer:
  - BCG or TURP can cause granulomatous prostatitis
- Fever, chills, or other constitutional signs:
  - Suggest infectious, systemic etiology

PHYSICAL EXAM

- DRE may be normal or abnormal
- Abnormal DRE:
  - Indurated gland with/without nodule
  - Tender or nontender
- TB prostatitis should be suspected if a draining perineal fistula is present

ALERT

- Digital Rectal Exam (DRE) cannot differentiate between prostate nodules due to granulomatous prostatitis and prostate cancer.
- Biopsy is required to differentiate these 2 etiologies.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis may be unremarkable
- Urine cultures
  - Are often sterile
- Elevated erythrocyte sedimentation rate (ESR), acid phosphatase, serum eosinophils may be present
- PSA may rise transiently
- If evidence of TB/mycotic disease, appropriate testing includes:
  - AFB stain of urine and semen
  - TB cultures (may take up to 10 wk)
  - Polymerase chain reaction (PCR): Genomic amplification of *Mycobacterium Tuberculosis* DNA
    - High sensitivity/specificity
    - Rapid: Takes 48 hr

Imaging

- TRUS
  - Limited utility except to direct biopsy
  - Appears as focal hypoechoic area
  - Difficult to discern granulomatous prostatitis and prostate cancer
- MRI
  - Limited utility
  - Difficult to discern granulomatous prostatitis from prostate cancer on MRI

Diagnostic Procedures/Surgery

TRUS-guided prostate biopsy is needed for pathologic diagnosis

Pathologic Findings

- Histologically granulomatous prostatitis appears as noncaseating granulomas, prominent macrophage infiltrates with occasional multinucleated giant cells (Langerhan cells) which

are characteristic of granulomas
  – Immunohistochemistry for cytokeratin (CAM 5.2) may stain glands positive but not the macrophage infiltrate
  – Macrophage infiltrate stains for macrophage marker CD68
- Fibrosis replaces parenchyma
- BCG therapy related
  – Caseating or noncaseating granulomas located next to benign prostatic glands (not engulfing them)
  – Usually AFB negative

DIFFERENTIAL DIAGNOSIS
- Nodular DRE (neoplasm/malignant):
  – Lymphoma, primary, and secondary
  – Prostatic adenocarcinoma
  – Sarcoma, small-cell carcinoma, and other rare tumors and metastases
  – Urothelial carcinoma
  – Granulomatous prostatitis
    - Infectious, iatrogenic, etc. (See Risk Factors)
- Nodular DRE (benign):
  – Prostatic calculus/calcification
  – Ejaculatory duct cyst
  – Scarring/fibrosis from prior surgery or infection
    - TURP, prostate biopsy
  – Granulomatous prostatitis
- Rectal wall lesions (thrombosed hemorrhoid, carcinoma, etc.)

TREATMENT

GENERAL MEASURES
- Majority of granulomatous prostatitis symptoms resolve spontaneously including those that are BCG related (3 – 5)
- DRE changes and PSA elevation may persist
- Use antibiotics as indicated for UTI
- Symptom control:
  – Sitz baths, fluids, anti-inflammatory α-blockers, and other symptomatic medications
- Temporary transurethral urinary catheterization if acute urinary retention or severe symptoms are present
- TRUS biopsy is indicated for:
  – Differentiating granulomatous prostatitis from prostate carcinoma
  – Consider rebiopsy if PSA remains elevated or DRE remains abnormal several months after treating symptomatic granulomatous prostatitis

MEDICATION
First Line
- Antibiotics as indicated for documented UTI
- Anti-TB medications for TB prostatitis:

– Use only if documented TB cause
– Isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin for initial regimen, then change based on TB isolate sensitivities
– Pyridoxine (Vitamin B6) 25–50 mg/d to prevent isoniazid neuropathy

Second Line
N/A

SURGERY/OTHER PROCEDURES
• Majority of symptomatic cases of granulomatous prostatitis resolve spontaneously
• Reserve TURP or prostatectomy for refractory cases
– Reported in up to 10% of cases in some series

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
Corticosteroids and antihistamines have been recommended in idiopathic cases

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
• Majority of symptomatic cases of granulomatous prostatitis resolve spontaneously
• DRE findings may persist for months/years
• PSA elevation may last up to 3 mo

COMPLICATIONS
• Acute urinary retention
• Possible transmission of infectious etiology to sexual partner
• Possible infertility
• Possible undetected prostate cancer

FOLLOW-UP
Patient Monitoring
Rebiopsy may be indicated if DRE remains abnormal or PSA remains elevated after treatment to avoid missing coincident prostate cancer (reported in 10–14% of cases)

Patient Resources
Prostatitis Foundation. http://www.prostatitis.org/

REFERENCES
1. Stillwell T, Engen DE, Farrow GM. The clinical spectrum of granulomatous prostatitis: A report of 200 cases. *J Urol.* 1987;138:320–323.
2. Oppenheimer J, Kahane H, Epstein JI. Granulomatous prostatitis on needle biopsy. *Arch Pathol Lab Med.* 1997;121:724–729.
3. Uzoh CC, Uff JS, Okeke AA. Granulomatous Prostatitis. *BJU Int.* 2007;99(3):510–512.

4. Eyre RC, Aaronson AG, Weinstein BJ. Palisading granulomas of the prostate associated with prior prostatic surgery. *J Urol.* 1986;136:121–122
5. Lafontaine PD, Middleman BR, Graham SD Jr, et al. Incidence of granulomatous prostatitis and acid-fast bacilli after intravesicular BCG therapy. *Urology*. 1997;49:363–366.

ADDITIONAL READING

• Humphrey PA. *Prostate Pathology*, ASCP Press: Chicago. 2003;87–95.
• Warrick J, Humphrey PA. Nonspecific granulomatous prostatitis. *J Urol.* 2012;187:2209–2210.

See Also (Topic, Algorithm, Media)

• BCG Sepsis/BCGosis
• Prostate, Nodule
• Prostatitis, General
• Prostatitis, Granulomatous Image
• Prostatitis, Tuberculosis
• Tuberculosis, Genitourinary, General Considerations

CODES

ICD9

• 135 Sarcoidosis
• 446.4 Wegener's granulomatosis
• 601.8 Other specified inflammatory diseases of prostate

ICD10

• D86.9 Sarcoidosis, unspecified
• M31.30 Wegener's granulomatosis without renal involvement
• N41.4 Granulomatous prostatitis

CLINICAL/SURGICAL PEARLS

• Majority of symptomatic cases of granulomatous prostatitis resolve spontaneously.
• Up to 40% of patients may develop granulomatous prostatitis after intravesical BCG.
• DRE changes and PSA elevation may persist for months.
• TRUS-guided prostate biopsy is needed for pathologic diagnosis.
• Rebiopsy may be indicated if DRE remains abnormal or PSA remains elevated after treatment to avoid missing coincident prostate cancer (reported in 10–14% of cases).

PROTEINURIA

Anthony J. Tracey, MD, MPH
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BASICS

DESCRIPTION

- Persistent abnormal amounts or types of protein in the urine:
  - May be 1st indication of renal disorders either primary (eg, proliferative glomerulonephritis) or secondary (eg, hypertension [HTN], lupus nephritis, diabetes [DM])
  - Marker of overall cardiovascular health
- Healthy adult excretes 80–150 mg of protein per day in urine, consisting of 30% albumin, 30% serum globulins, and 40% tissue proteins.
- Dipstick urinalysis detects proteinuria only when protein excretion >300 mg/d:
  - Microalbuminuria: 30 and 300 mg/d:
    - Earliest sign of diabetic nephropathy
    - Identifies those at risk of cardiovascular disease in both diabetic and nondiabetic populations (1)[2]
- Important to distinguish between benign (no long-term renal significance) and pathologic causes of proteinuria. Can often differentiate based on:
  - Associated clinical findings (eg, known diabetes or HTN; edema and lipiduria in nephrotic syndromes)
  - *Persistency* of proteinuria:
    - Transient or intermittent proteinuria is unlikely to be associated with significant renal pathology
    - Example etiologies: Exercise, emotional stress, fever, orthostatic proteinuria
    - Document proteinuria on >1 visit
  - Degree of proteinuria:
    - 500 mg/24 hr usually heralds significant glomerular disease
    - Proceed to quantitative measurement when dipstick is persistently positive

EPIDEMIOLOGY

Incidence

- In diabetic patients, progression to microalbuminuria 2% per year; from microalbuminuria to proteinuria 2.8% per year
- 1.7% of males and 0.9% of females
- Increases with age
- Higher in patients with DM:
  - Microalbuminuria 24.9%; proteinuria 5.3%

Prevalence

- African Americans afflicted with higher levels of proteinuria due to increased risk of associated diseases

- Orthostatic proteinuria in 2–5% of adolescents:
  - Uncommon in age >30 yr:
    - Increased protein excretion in the upright position. Resolves in supine position (2)[2]
    - No therapy required, often resolves with time

RISK FACTORS
- DM
- HTN
- Obesity (BMI >35 kg/m^2), but progression to renal disease not proven

Genetics
Disease specific

PATHOPHYSIOLOGY
- Glomerular proteinuria:
  - Results from increased glomerular capillary permeability to albumin
  - Usually >1 g/24 hr
  - When total protein >3 g/24 hr: Nephrotic syndrome (look for hypoalbuminemia, lipiduria, edema, ascites)
- Tubular proteinuria:
  - Inability of proximal convoluted tubule to absorb low–molecular-weight proteins such as immunoglobulin light chains, β2-microglobulin, amino acids, and retinol-binding protein
  - Proteinuria usually 2–3 g/24 hr
- Overflow proteinuria:
  - No underlying renal disease
  - Absorptive capacity of PCT is overwhelmed by overproduction and accumulation of immunoglobulins and low–molecular-weight proteins.
- Tissue proteinuria:
  - Associated with acute inflammation of urinary tract due to cystitis, acute prostatitis, and urinary tract tumors
- Transient proteinuria:
  - Glomerular permeability and decreased tubular reabsorption have both been proposed as possible mechanisms (2)

ASSOCIATED CONDITIONS
- See “Differential Diagnosis”
- Hypercoagulability, lipiduria, edema, and hypoalbuminemia (nephrotic syndrome)

DIAGNOSIS

HISTORY
- Presence of underlying systemic disease:
  - DM, HTN, autoimmune disorders, cardiac disease, multiple myeloma
- Transient proteinuria triggered by:
  - Exercise, emotional stress, fever, recent illness
- Medication-induced glomerular injury
- Associated symptoms that would suggest clinically significant proteinuria:

  - Hematuria, bone pain (myeloma)
- Age <30 and healthy (orthostatic proteinuria) (1,2)

PHYSICAL EXAM
- BP measurement to rule out HTN
- Edema with nephrotic syndrome, heart failure
- Papilledema: Uncontrolled HTN
- Jugular venous pressure elevation, heart sounds (heart failure, HTN)
- Abdominal bruits: Renal artery stenosis

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urine dipstick:
  - Qualitative test only (1+ to 4+); detects protein concentration >20–30 mg/dL
  - Cannot detect microalbuminuria; if persistently positive proceed to quantitative test (spot or 24-hr protein)
  - False positive: Alkaline urine; concentrated urine; contamination with blood; recent IV contrast dye
  - False negative: Dilute urine; dipstick only detects albumin and will miss other plasma proteins (eg, Bence Jones proteinuria in multiple myeloma)
- Urinalysis for associated hematuria, casts (glomerulonephritis)
- Serum creatinine to rule out renal insufficiency
- Blood glucose: DM
- Albumin-to-creatinine ratio or total protein-to-creatinine ratio in a random urinary sample:
  - Quantitative test that is reliable and not dependent on concentration. Less cumbersome than 24-hr collection
  - Corresponds to 24-hr albumin excretion in a linear manner (eg, ratio of 3 = 3 g/24 hr)
  - Serial measurements monitor therapeutic response
  - Preferred screening strategy for diabetic patients
  - 2 out of 3 positive tests separated by 3–6 mo considered persistent proteinuria
- Albumin, cholesterol: Nephrotic syndrome
- 3% sulfosalicylic acid test:
  - Detects all types of proteinuria
  - Strongly consider in patients with acute renal failure and negative or trace protein on dipstick to rule out myeloma
- Split urine collection: Daytime (7 AM to 11 PM) and overnight (11 PM to 7 AM) to rule out orthostatic proteinuria
- Urine protein electrophoresis: To assess for light chain immunoglobulins/Bence Jones proteins associated with multiple myeloma
- Others as indicated: Hepatitis and/or HIV testing, autoantibodies (ANA, etc.) (2)

Imaging
- Renal US in cases of persistent proteinuria to rule out anatomic abnormality
- 3-phase CT if renal function sufficient and associated hematuria
- MRI urogram

Diagnostic Procedures/Surgery

- Tissue analysis:
  - Renal biopsy strongly considered for:
    - Proteinuria with hematuria
    - Prolonged ARF of unknown etiology
    - Nephrotic proteinuria
    - Transplanted kidney (3)
- Cystoscopy if concurrent hematuria
- Cystoscopy with retrograde pyelogram if upper tract imaging indicated (hematuria, hydronephrosis) and unable to evaluate upper tracts with excretory phase imaging

Pathologic Findings

Depends on underlying etiology

DIFFERENTIAL DIAGNOSIS

- Glomerular proteinuria:
  - IgA nephropathy
  - Diabetic nephropathy
  - Medications (eg, NSAIDs, captopril, lithium)
  - Minimal change
  - Primary glomerulonephritides
  - Autoimmune (eg, SLE, amyloidosis)
- Tubular proteinuria:
  - Obstructive uropathy
  - Toxins and drugs
  - Fanconi syndrome
- Overflow proteinuria:
  - Multiple myeloma
  - Monoclonal gammopathy of unknown significance
  - Rhabdomyolysis causing myoglobinuria
  - Any hemolytic state causing hemoglobinuria
- Transient proteinuria:
  - Fever
  - Strenuous exercise
  - Emotional stress
  - Pregnancy
  - Cold exposure
  - Orthostatic proteinuria

TREATMENT

GENERAL MEASURES

- Treat specific underlying etiology.
- All patients with persistent proteinuria should be referred to a nephrologist.
- Hematology–oncology evaluation for patients with Bence Jones protein for treatment of multiple myeloma
- Mild dietary protein restriction may prevent progression of chronic kidney disease.

- Strict glycemic and BP control in diabetics
- Salt/fluid restriction for edema associated with nephrotic syndrome

MEDICATION

First Line

- ACE inhibitors reduce proteinuria and can both prevent and slow deterioration of renal function in patients with diabetes or nondiabetic renal disease, independent of their antihypertensive effects (3)[A]:
  - Can reduce protein excretion by 35–45%
  - Lisinopril 2.5 mg/d PO; increase as tolerated
  - Ramipril 2.5–5 mg/d PO, 20 mg/d max
  - Captopril 12.5–25 mg PO BID/TID, 50 mg TID max

Second Line

- Angiotensin II receptor antagonists:
  - Use if side effects such as cough and angioedema develop from ACE inhibitors
  - Candesartan, eprosartan, irbesartan, losartan, valsartan
  - Calcium channel blockers: May be better for HTN with less renal effect in the relatively ischemic kidney

SURGERY/OTHER PROCEDURES

N/A

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Isolated proteinuria; degree dependent:
  - Nonnephrotic proteinuria has low risk of progressive kidney disease (3)[2]
  - Nephrotic proteinuria (>3 g/d) associated with glomerular disease and high risk of progression to chronic kidney disease
  - Japanese study of screened healthy patients; cumulative incidence of ESRD over 17 yr:
    - 1.4% with 1+ proteinuria
    - 7.1% with 2+ proteinuria

COMPLICATIONS

- Progression to renal failure
- Proteinuria is a marker for overall cardiovascular health (3)[2]

FOLLOW-UP

Patient Monitoring

- Transient proteinuria: Active monitoring unnecessary
- Nephrologist for any patient with large quantity of proteinuria and high-risk patients with microalbuminuria:
  - Monitor urine albumin-to-creatinine ratio
  - Monitor serum creatinine

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
http://kidney.niddk.nih.gov/kudiseases/pubs/proteinuria/

REFERENCES

1. Ruiz J, Sánchez-Fructuoso A, Zárraga S. Management of proteinuria in clinical practice after kidney transplantation. *Transplant Rev (Orlando)*. 2012;26:36–43.
2. Bello A, Thompson S, Lloyd A, et al; Alberta Kidney Disease Network. Multiple versus single and other estimates of baseline proteinuria status as predictors of adverse outcomes in the general population. *Am J Kidney Dis*. 2012;59:364–371.
3. Turin TC, Tonelli M, Manns BJ, et al. Proteinuria and life expectancy. *Am J Kidney Dis*. 2013;61:646–648.

ADDITIONAL READING

- American Diabetes Association. Standards of medical care in diabetes–2007. *Diabetes Care*. 2007;30:S4–S41.
- www.kidney.org/professionals/kdoqi/guidelines.cfm.

See Also (Topic, Algorithm, Media)

- Glomerulonephritis, Acute
- Glomerulonephritis, Chronic
- Proteinuria Algorithm
- Renal Failure, Acute
- Renal Failure, Chronic
- Urinalysis and Urine Studies

CODES

ICD9

791.0 Proteinuria

ICD10

- R80.0 Isolated proteinuria
- R80.2 Orthostatic proteinuria, unspecified
- R80.9 Proteinuria, unspecified

CLINICAL/SURGICAL PEARLS

Proteinuria in excess of 500 mg/d likely represents significant glomerular disease.

PRUNE BELLY (EAGLE–BARRETT OR TRIAD) SYNDROME

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BASICS

DESCRIPTION

- Prune belly refers to the classic appearance of abdominal wall wrinkling and budging flanks caused by varying degrees of abdominal wall deficiency, found almost exclusively in males (image) (1)
- Prune belly syndrome (PBS) triad:
  - Deficient abdominal musculature
  - Bilateral cryptorchidism
  - Urinary tract anomalies (eg, dilated prostatic urethra, renal dysplasia, hydroureteronephrosis)
- Incomplete variants lack abdominal wall features; females lack gonadal anomalies
- Woodard classification:
  - Type I: Usually fatal; marked oligohydramnios due to severe renal dysplasia or bladder outlet obstruction with pulmonary hypoplasia and skelet al anomalies (Potter sequence)
  - Type II: Full spectrum of disease with no immediate threat to life; renal dysplasia; hydroureteronephrosis; possible mild pulmonary hypoplasia
  - Type III: Mild external features of triad or incomplete variant; no evidence of pulmonary hypoplasia, mild uropathy
- Synonyms: Eagle–Barrett or Triad syndrome

EPIDEMIOLOGY

Incidence

- 3.8/100,000 live births
- 95% males
- Higher incidence in African Americans
- Lower incidence in Hispanic population
- Increased incidence in younger mothers

Prevalence

N/A

RISK FACTORS

Slightly increased risk in African Americans and younger mothers

Genetics

- Most cases are sporadic, with normal karyotype.
- Potential inheritance patterns in rare familial cases (influenced autosomal recessive; X-linked)
- Monozygotic twins reported concordant and discordant for PBR suggests some nongenetic basis

PATHOPHYSIOLOGY

- Exact mechanism unknown:
  - Early in utero transient urethral obstruction
  - Mesodermal developmental defect
- Abdominal defects due to deficient musculature medially and inferiorly:
  May be partial hypoplasia of the abdominal wall to complete absence of musculature
- Testes:
  - Usually intra-abdominal (over iliac vessels)
  - Epididymis poorly attached
  - Descent in part affected by mechanical forces (eg, large bladder, low intra-abdominal pressures)
- Kidneys:
  - Dysplasia in 50%, to varying degrees
  - Nonobstructive hydronephrosis is common; does not correlate to degree of dysplasia
- Ureters:
  - Dilated, tortuous, and redundant; distal >proximal
  - Increased ratio of collagen to smooth muscle
  - Poor peristalsis and ureteral coaptation lead to stasis and reflux
  - ~75% with reflux
- Bladder:
  - Enlarged with no significant hypertrophy
  - May have urachal pseudodiverticulum
  - Urachus patent in up to 30%
  - Increased ratio of collagen to smooth muscle
  - Urodynamics commonly show normal compliance, delayed sensation, large capacity; 50% void with normal pressures and flow, and have low postvoid residual
- Prostatic urethra:
  - Dilated due to prostatic hypoplasia
  - 20% can have distal obstructive lesions (eg, valves, atresia, stenosis)
- Anterior urethra:
  - Usually normal
  - Most common abnormalities: Megalourethra and urethral atresia (latter can be fatal unless patent urachus)
  - Megalourethra can be caused by transient obstruction
  - Fusiform: Defect in corpus cavernosum and spongiosum; entire phallus dilates on voiding
  - Scaphoid: Defect in corpus spongiosum; only ventral urethra dilates
- Fertility:
  - Usually infertile (rare cases of paternity with sperm retrieval) due to azoospermia
  - Histologic defect in testes
  - Atretic vas deferens and seminal vesicles
  - Retrograde ejaculation from incompetent bladder neck

ASSOCIATED CONDITIONS

- Genetic:
  - Turner syndrome; trisomy 13, 18, and 21; Beckwith–Wiedemann syndrome

- Gastrointestinal:
  - Malrotation of gut (~40%); bowel atresia, gastroschisis, omphalocele, imperforate anus (rare)
- Pulmonary:
  - >50% with pulmonary hypoplasia
- Cardiac:
  - Atrial and ventricular septal defects, tetralogy of Fallot, valvular anomalies, patent ductus arteriosus
- Musculoskelet al:
  - Scoliosis; vertebral anomalies, congenital hip dislocation, club feet

GENERAL PREVENTION
None known

DIAGNOSIS
HISTORY
- Gestational history (eg, oligohydramnios, prenatal hydronephrosis)
- Rarely positive family history

PHYSICAL EXAM
- 75% will have nonurologic manifestations
- General: Observe for Potter facies (eg, wide set eyes, flattened nasal bridge)
- Heart: Auscultate for murmurs due to atrial or ventricular septal defects, patent ductus arteriosus
- Lungs/chest: Auscultate for pneumothorax; evaluate for pectus excavatum/carinatum
- GI: Associated with gastroschisis or omphalocele; imperforate anus; intestinal malrotation, atresia, or stenosis
- Urologic: Evaluate meatus, observe urinary stream, attempt to palpate testes
- Abdomen: Wrinkled, redundant skin over lower abdomen with bulging flanks
- Extremities: Observe for dimpling on lateral aspect of knees, knock knees, clubfoot, hip dislocation, scoliosis

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum electrolytes, urea nitrogen, and creatinine:
- Nadir creatinine <0.7 ng/dL is predictive of adequate renal function through childhood.
- Urinalysis and urine culture as indicated

Imaging
- Prenatal US: Bilateral hydroureteronephrosis, thin-walled distended bladder, possible oligohydramnios
- Chest x-ray (pneumothorax)
- Postnatal renal/bladder US (degree of renal dysplasia and hydroureteronephrosis)
- Radioisotope studies (technetium-99m/99Tc):
  - DMSA at 4–6 wk to assess renal parenchymal function
  - MAG3 scan to assess presence/degree of obstruction

Diagnostic Procedures/Surgery

- VCUG:
  - Perform while on antibiotic prophylaxis
  - Reflux in up to 75% of cases
  - Large bladder and dilated prostatic urethra tapering to membranous urethra

Pathologic Findings

- Renal dysplasia on biopsy
- Ureter and bladder with increased collagen and fibrous tissue

DIFFERENTIAL DIAGNOSIS

- Megacystis microcolon
- Intestinal hypoperistalsis syndrome (marked female predominance
- Posterior urethral valves (prenatal appearance can be similar)

TREATMENT

GENERAL MEASURES

- Primary goal is to preserve renal function and prevent UTI
- Early aggressive surgery for dilated urinary tract without evidence of progressive renal dysfunction or UTIs should be avoided
  - High complication rate
- Demonstrate proper bladder emptying
  - Double voiding
  - Timed voiding
  - Clean intermittent catheterization (CIC)
- UTI prophylaxis
- Avoid instrumentation early to reduce UTI risk

MEDICATION

First Line

- UTI prophylaxis:
  - Ampicillin 25 mg/kg/d as neonates
  - Trimethoprim–sulfamethoxazole 2 mg/kg once daily or nitrofurantoin 1–2 mg/kg once daily beyond 2 mo of age

Second Line

None

SURGERY/OTHER PROCEDURES

- Prenatal: Vesicoamniotic shunting for oligohydramnios in 2nd trimester (controversial)
- Consider circumcision to reduce incidence of UTI
- Urinary tract reconstruction (eg, reimplant) is controversial due to potential for improvement or resolution, stabilization of function, and high complication rates (2)
- Early intervention may be warranted with progressive/severe hydronephrosis, progressive renal failure, or recurrent UTIs (2)
  - Temporary cutaneous vesicostomy or bilateral cutaneous pyelostomies (avoid proximal ureterostomies)

– Ureteral reimplantation with/without tapering
- Reduction cystoplasty reserved for large urachal diverticulum or as part of extensive reconstruction, since large bladder tends to recur
- Orchidopexy:
– Transabdominal, preferably done by 1 yr of age or in combination with other procedures:
- Abdominal wall reconstruction for cosmesis, may enhance Valsalva voiding and improve bladder emptying (3)
- Renal transplantation
– 1/3 will eventually need renal transplant
– Achieve adequate bladder emptying prior to transplant

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Use of corsets for abdominal wall laxity have been reported

ONGOING CARE

PROGNOSIS

- Degree of renal dysplasia most important determinant of long-term survival
- Up to 1/3 develop renal failure and will require dialysis/renal transplantation

COMPLICATIONS

- Renal failure
- Respiratory failure (early)
- Recurrent UTIs
- Urosepsis

FOLLOW-UP

Patient Monitoring

- Serial evaluation of renal function, bladder function and emptying, and for UTIs
- Imaging is individualized

Patient Resources

- http://www.urology.ucsf.edu/patient-care/children/urinary-tract-obstruction/prune-belly-syndrome
- Prune belly syndrome network: www.prunebelly.org

REFERENCES

1. Hassett S, Smith GH, Holland AJ. Prune belly syndrome. *Pediatr Surg Int.* 2012;28:219–228.
2. Denes FT, Arap MA, Giron AM, et al. Comprehensive surgical treatment of prune belly syndrome: 17 years experience with 32 patients. *Urology*. 2004;64:789–793.
3. Lesavory MA, Chang EI, Suliman A, et al. Long-term follow-up of total abdominal wall reconstruction for prune belly syndrome. *Plast Reconstr Surg*. 2012;129:104e–109e.

ADDITIONAL READING

Baskin LS, Kogan BA. *Handbook of Pediatric Urology*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

See Also (Topic, Algorithm, Media)

- Polyhydramnios/Oligohydramnios
- Prune Belly (Eagle–Barrett or Triad) Syndrome Image ☼
- Undescended Testes (Cryptorchidism)

CODES

ICD9

- 257.2 Other testicular hypofunction
- 748.5 Agenesis, hypoplasia, and dysplasia of lung
- 756.71 Prune belly syndrome

ICD10

- E29.1 Testicular hypofunction
- Q33.6 Congenital hypoplasia and dysplasia of lung
- Q79.4 Prune belly syndrome

CLINICAL/SURGICAL PEARLS

- Antireflux surgery with high complication rates; avoid if possible.
- Prenatally can be difficult to distinguish from posterior urethral valves.
- Goal is to avoid renal damage, UTIs.

PSA ELEVATION FOLLOWING NEGATIVE PROSTATE BIOPSY

Michael J. Amirian, MD
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BASICS

DESCRIPTION

- Transrectal ultrasound-guided (TRUS) prostate biopsy (PB) is the gold standard for diagnosis of prostate cancer (CaP)
- While CaP screening is controversial, a subset of men have a negative TRUS PB with persistent or increasing elevation in PSA. This can be a challenge for urologist and the patient
- Repeat PB performed after negative PB suggests up to 30% of patients have cancers not previously identified (1)

EPIDEMIOLOGY

Incidence

800,000–1.2 million prostate biopsies are performed in the United States annually

Prevalence

- 24.1% of men in a screening population undergoing TRUS diagnosed with PCa
- False-negative rate for TRUS PB as high as 35%
  - Cancer detection rate as high as 14% after 3rd repeat biopsy

RISK FACTORS

- Both technical and anatomical considerations contribute to a false-negative PB
- Advances in biopsy techniques have improved positive sampling rates
  - Digital-direct biopsy without ultrasound guidance provides inadequate sampling
  - TRUS guided is gold standard
    - <10 cores are considered inadequate for cancer detection
    - "Double sextant" or 12-core with inclusion of laterally directed cores have lower false-negative rates
- Anatomical
  - Large gland size (>50 cc) may limit detection of CaP on standard core biopsy
  - End-fire ultrasound probe allows better sampling anterior and apical prostate gland
    - These areas likely to harbor unrecognized malignancy in larger glands
- High-grade cancers (Gleason 9–10) may not have PSA elevation

Genetics

- CaP has both familial and genetic component
  - Relative risk increases with number of 1st-degree relatives affected
    - Higher index of suspicion if 1st-degree relatives have diagnosis of prostate malignancy

PATHOPHYSIOLOGY

- 12 biopsy cores from a standard 18G needle enables only 0.04% of prostate gland to be evaluated for pathology (2)

- PSA elevations can be from non-PCa causes
- Series reporting follow-up biopsy results (Mo)
  - In 2012 Ca detection rates on follow-up biopsies 1, 2, 3, and 4 were 22%, 10%, 5%, and 4%, respectively; 58%, 60.9%, 86.3%, and 100% of patients who had RP had organ-confined disease on biopsies 1, 2, 3, and 4.
  - A 2008 series with extended biopsies found CaP 18%, 7%, and 14% of patients had PCa in 2nd, 3rd, and 4th biopsies, respectively; significant CaP in 85% of cases (3).

ASSOCIATED CONDITIONS

The following can cause elevated PSA: infection, recent instrumentation, benign prostatic hypertrophy (BPH)

GENERAL PREVENTION

- Obtain serial PSA at same lab; avoid sexual activity for 24 hr before
- Preventing a false-negative PB is greatly dependent on technique
  - 12-core template is now standard
    - 6 parasagittal plus 6 lateral cores
  - Sextant (6-core) biopsy can miss up to 50% of small tumors
  - No evidence of increased complication rate of 12-core compared to sextant biopsy

DIAGNOSIS

HISTORY

- Prior history of negative prostate biopsies
- Evaluate for nonmalignant causes of elevated PSA
  - Prostatitis
  - Recent instrumentation of genitourinary tract
  - Rarely sexual activity, bicycling can briefly elevate
- Increase risk of PCa
  - 1st-degree relative with PCa and recent data suggestion increased risk with a relative with breast cancer
    - Increase risk by 120–150%
  - Ethnicity: Black race highest risk
  - History of exposure to exogenous androgen or anabolic steroid use
- Percent-free PSA
  - With negative prior biopsy and low percent-free PSA (<12%) have higher risk of malignancy
- PSA velocity
  - Rate of change of PSA over 1-yr period
  - Recommend biopsy if PSA velocity exceeds 0.35 ng/mL/yr
  - PSA velocity independent predictor of overall PCa, intermediate- and high-grade cancer.

PHYSICAL EXAM

- Digital rectal exam (DRE)
  - Induration or nodularity
    - Concerning for malignancy
  - Symmetric and enlarged gland

- BPH more likely with elevated PSA and negative biopsy
  - Tenderness or bogginess on exam
    - Likely acute prostatitis
- Decreased testicular volume
  - Consider exogenous androgen exposure

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Free/total PSA (4)
- Prostate cancer antigen 3 (PCA3)
  - Gene that is overexpressed in PCa; measured in 1st voided urine after attentive digital rectal exam
  - FDA approved for men >50 yr who have had 1 or more previous negative biopsies
  - Cutoff debatable 25–35
  - Compared to PSA
    - Lower sensitivity (67%); higher specificity (83%)
    - Some studies suggest superior to F/T PSA
    - Patient stratified into lower risk or higher risk of having a positive biopsy

Imaging

- MRI may identify anterior tumor not reached by biopsy needle
  - T2-weighted MRI
    - Identify focal lesions within gland
    - Need to wait 6–8 wk after negative biopsy as recent biopsy sites cause distortion
  - Multiparametric (mp) MRI
    - Combination of dynamic contrast-enhanced MRI, MR spectroscopic imaging, and diffusion-weighted imaging; need access to experienced center
  - Contrast-enhanced TRUS
    - Neovascularity of tumor enhances with microbubble contrast agent (not FDA approved)
    - Targeted biopsy show increase sensitivity from 38–65% vs. unenhanced imaging
  - Color Doppler of limited utility w/o contrast
  - Elastography ultrasound: Tumors allow less displacement with compression than normal tissue; color coded map allows targeted biopsy; not widely available
- MRI TRUS fusion biopsy may help identify specific lesions for directed biopsy

Diagnostic Procedures/Surgery

- Mapping/saturation biopsy
  - Obtaining 20 or more cores with standard biopsy technique; can be transrectal but more likely to be done transperineally using a brachytherapy-like template guide
  - Studies vary in yield of detection with increased cores; increased morbidity
  - Usually require additional anesthesia
- Transitional zone targeted biopsy
  - 15% increased detection in gland >50 cc
- Template transperineal PB
  - May allow better sampling of peripheral zone
  - Controversial if better cancer detection

- MRI and ultrasound fusion targeted biopsy
  - Stored MRI is fused with real-time ultrasound using a digital overlay
  - Series report 41% vs. 18% compared to conventional ultrasound in detection of CaP in men with prior negative biopsies
  - Requires specialized training and equipment

Pathologic Findings

- Quality assurance in the initial biopsy is critical. Data suggests a core length of >10 mm and the presence of glandular elements suggest an adequate sample
- High-grade prostatic intraepithelial neoplasia (HGPIN) 0–24.6% on initial biopsy (median 4%)
  - Considered by some to be premalignant lesion: 23–35% risk of diagnosis cancer on subsequent biopsy; however, EAU does not recommend repeat biopsy with HGPIN
- Atypical small acinar proliferation (ASAP)
  - Incidence 0.7–23.4%, median 4.4%
  - Increased CaP risk on subsequent biopsy (up to 40%)

DIFFERENTIAL DIAGNOSIS

- ASAP
- BPH
- HGPIN
- Prostatitis

TREATMENT

GENERAL MEASURES

- Most recommendations are for repeat biopsy for patients with either ASAP or multifocal HGPIN within 3–6 mo regardless of PSA (5)
- For others with negative biopsy and persistently elevated or rising PSA, consider the use of supplementary lab tests such as PCA3, free/total PSA Confirm MDx to guide decision
- Repeat PB appears justified in:
  - An initial negative biopsy and persistent suspicion of PCa based on age, comorbidities, DRE findings, repeated PSA, PSA derivatives, (% free PSA, complexed PSA, PSAD, PSA velocity, or urinary PCA3 score) and patient and physician preferences
- With concerns over the interpretation of the earlier biopsy, consider a 2nd opinion

MEDICATION

First Line

- Limited utility in managing elevated PSA
- Antibiotics if presumed prostatitis cause of elevation
  - 2–3-wk course of oral antibiotics
  - Sulfamethoxazole and trimethoprim (Bactrim DS) BID or ciprofloxacin 500 mg BID
    - Repeat PSA after termination of treatment
  - Studies have not shown routine antibiotics decreased need for future biopsy
- 5-α reductase inhibitors
  - Finasteride 5 mg or dutasteride 0.5 mg PO QD for 6 mo

- Should lower PSA by 50% after 6 mo but not proven useful in determining repeat biopsy, but any PSA rise after 6 mo raises CaP risk

Second Line
N/A

SURGERY/OTHER PROCEDURES
- The number of cores on repeat biopsy is debatable. NCCN guidelines suggest performing a 2nd extended biopsy and consider saturation biopsies only in with high risk of cancer after multiple negative biopsies
- Transurethral resection prostate biopsy
  – Once advocated for diagnosis of transition zone cancers
  – Less than 5% CaP are transitional zone CaP without concomitant peripheral zone tumors
  – Improved TRUS technique in sampling transitional zone; no definite value in performing transurethral resection PB

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- The European Randomized Study of Screening for PCa (ERSPC)-based model has several calculators to determine outcome after negative biopsy (http://www.prostatecancer-riskcalculator.com/)
- Genomic testing may help determine risk after negative biopsy
  – Confirm MDx™: Epigenetic assay to distinguish men who have a true-negative biopsy from those with occult cancer
  – Identifies methylation signature in area near PCa location using recent prostate biopsy material

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- There is no PSA threshold that can rule out PCa in any age range
  – Regardless of initial PSA value, a PSA velocity greater than 0.75 ng/mL/yr warrants repeat biopsy
- Lowering PSA threshold for initial biopsy
  – Many urologists recommend PB to men younger than 60 yr of age once PSA >2.5 ng/mL; enables earlier CaP detection

COMPLICATIONS
See Section I: “Prostate biopsy, Infections and Complications”

FOLLOW-UP
Patient Monitoring
If low risk with negative biopsy can be followed with routine surveillance protocol

Patient Resources

National Cancer Institute Fact Sheet: Prostate-Specific Antigen (PSA) test. www.cancer.gov/cancertopics/factsheet/detection/PSA

REFERENCES

1. Zaytoun O, Moussa AS, Gao T, et al. Office based transrectal saturation biopsy improves prostate cancer detection compared to extended biopsy in repeat biopsy population. *J Urol*. 2011;186:850–854.
2. Resnick MJ, Lee DJ, Magerfleisch L, et al. Repeat prostate biopsy and the incremental risk of clinically insignificant prostate cancer. *J Urol*. 2010;77(3):548–552.
3. Pinsky PF, Crawford ED, Kramer BS, et al. Repeat prostate biopsy in the Prostate, Lung, Colorectal and Ovarian cancer screening trial. *BJU Int*. 2007;99:775–779.
4. Auprich M, Augustin H, Budäus L, et al. A comparative performance analysis of total prostate-specific antigen, percentage free prostate-specific antigen velocity and urinary prostate cancer gene 3 in the first, second, and third repeat biopsy. *BJU Int*. 2011;109:1627–1635.
5. Jones JS. Managing patients following negative prostate biopsy. *Renal & Urology News*. 2011:10:23.

ADDITIONAL READING

- Elshafei A, Li YH, Hatem A, et al. The utility of PSA velocity in prediction of prostate cancer and high grade cancer after initially negative prostate biopsy. *Prostate*. 2013;73(16):1796–1802.
- Levy DA, Jones JS. Management of rising prostate-specific antigen after a negative biopsy. *Curr Urol Rep*. 2011;12(3):197–202.
- Presti JC. Management of patients with persistently elevated PSA level and negative biopsy. AUA Update Series. 2012; Lesson 1, Volume 31.
- Scott JG, John G, Eric K, et al. Emotional consequences of persistently elevated PSA with negative prostate biopsy. *Am J Cancer Prevention*. 2013;1(1);4–8.

See Also (Topic, Algorithm, Media)

- PCA3 (Prostate Cancer Gene 3 Urine Assay)
- Prostate Biopsy, Infections and Complications
- Prostate Cancer, General
- PSA Elevation, General Considerations
- PSA, Free and Total
- PSA, General Considerations

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 601.9 Prostatitis, unspecified
- 790.93 Elevated prostate specific antigen [PSA]

ICD10

- C61 Malignant neoplasm of prostate
- N41.9 Inflammatory disease of prostate, unspecified
- R97.2 Elevated prostate specific antigen [PSA]

CLINICAL/SURGICAL PEARLS

- Threshold for repeat biopsy should be low if atypia seen on initial biopsy.
- PCA3 can elucidate the need for further biopsy in those with prior negative biopsy and persistently elevated PSA.
- Emerging imaging modalities are promising in detecting CaP not found on initial PB.

PSA ELEVATION, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- PSA is used for diagnosis and treatment of prostate cancer (CaP). This section reviews the use of PSA in the diagnosis of CaP recognizing that screening is an area of controversy
- CaP is only diagnosed through tissue biopsy and not by PSA alone
- Normal PSA level is controversial, and can be elevated due to malignant or benign causes.
  - Elevated PSA traditionally >4.0 ng/mL based on the Baltimore Longitudinal Study of Aging
    - Specificity 91%, sensitivity 21% (51% for Gleason ≥8), PPV 30%
  - Elevated PSA >2.5 ng/mL has support
- Age/race-specific proposed, but controversial:

Range (yr)	Asian	Black	White
40–49	0–2.0	0–2.0	0–2.5
50–59	0–3.0	0–4.0	0–3.5
60–69	0–4.0	0–4.5	0–4.5
70–79	0–5.0	0–5.5	0–6.5

- Based on Prostate Cancer Prevention Trial (biopsy regardless of PSA), can have CaP with "low" PSA. No lower cutoff or normal PSA to indicate absence of cancer. PCPT data:

PSA	CaP Rate	PSA	CaP Rate
0–0.5	6.6%	3.1–4.0	26.9
0.6–1.0	10.1%	4.0–10.0	25%
1.1–2.0	17%	>10.0	>50%
2.1–3.0	23.9%		

- The challenge: Lower normal PSA to recommend biopsy where life-threatening cancer is present, but not to point where "overdetection" of incidental (autopsy/insignificant CaP) occurs
- PSA derivatives may overcome problem, but not absolute: Used in PSA range of 4.0–10 ng/mL: PSA density (PSAD), PSA velocity (PSAV), newer PSA assays (free, molecular forms)
- PSA changes over time more useful than a single PSA in screening for CaP
- A single PSA of >1.3 ng/mL before age 50 predicts increased lifetime CaP risk (1)
- PSA >10: More risk of advanced disease.
- PSA proportional to prostate volume; prostate volume/mean PSA were as follows: 14 cm^3/1; 25 cm^3/1.13/52 cm^3 1.45 in 1 study

ALERT
PSA should not be done with acute prostatitis or within 3–4 wk of prostate instrumentation: false-positive risk.

EPIDEMIOLOGY

Incidence

- Across all races, age >50, only 7.9% of men randomly screened have PSA >4.0 ng/mL
- Median PSA: 4th decade, 0.7 ng/mL; 5th decade, 0.9 ng/mL 6th decade, 1.3 ng/mL; 7th decade, 1.7 ng/mL

Prevalence

US CaP approximately 2,106,499 men, or 1.5% all ages and races

RISK FACTORS

- For elevated PSA
  - Advancing age
  - Benign prostatic hypertrophy (BPH)
  - CaP
  - Infection, infarction
  - Recent instrumentation (TURP, cystoscopy, catheterization, prostate biopsy)
- CaP (See chapter "Prostate Cancer, General")

Genetics

- PSA associated with kallikrein genes family (long arm of chromosome 19 region q13.2–q13.4).
- PSA is also called human kallikrein 3 (hKLK3)

PATHOPHYSIOLOGY

- PSA: A serine protease produced by the prostatic epithelium and periurethral glands that liquefies seminal coagulum
- Seminal fluid has high PSA concentrations (mg/mL); PSA is much lower (ng/mL) in serum
- Many forms of serum PSA: Free PSAs (nicked, intact, several forms of proPSA) and complexed PSA (bound to protease inhibitors α1-antichymotrypsin [ACT], α2-macroglobulin [MG], α1-protease inhibitors [API]); bound PSA forms stable complex (no serum enzymatic activity) (2)
  - 60–90% complexed to ACT; free portion is also detected by assay, while that bound to MG is not detected by routine assay
  - Complexed PSA: Hepatic clearance (1/2-life 2.2 days); FPSA cleared by glomerular filtration (1/2-life 2–3 hr)
- CaP PSA elevation is due to disrupted prostatic architecture and compromised integrity of the basal layer or basement membrane
  - CaP makes less PSA/g than benign tissue
- Androgens influence PSA levels
- Sources of fluctuation in PSA:
  - No PSA analytic standard; can vary by lab and use same lab to compare serial values
  - 15% coefficient of variation in PSA assay
  - Physiologic variation in PSA 15–30% in the short term; BPH can vary up to 30%
  - 26–37% with elevated PSA return to normal 1 yr later, and 45–55% normal within 4 yr
  - Seasonal variation: PSA is higher in summer
  - Infection, infarction, trauma, ejaculation within 24 hr, or prostate instrumentation or massage can produce elevations (not routine DRE)

– Finasteride (5 mg BPH; 1 mg alopecia) and dutasteride are 5α-reductase inhibitors; lower PSA by 50% over 6 mo; "correct" PSA by doubling to maintain PSA utility

ASSOCIATED CONDITIONS
- BPH
- Acute and chronic bacterial prostatitis
- Urinary retention

GENERAL PREVENTION
- None for CaP
- Avoid PSA measurement when false-positive elevation likely (See "Risk Factors" above)
- Use same lab/assay for serial measurements

DIAGNOSIS
HISTORY
- Difficulty with urination, such as hesitancy, straining, weak stream, or intermittency
- Dysuria, frequency, or urgency
- Previous PSA levels or prostate biopsies
- Family history of prostate carcinoma
- Medications, including herbals
- Markedly elevated PSA >20 ng/mL with bone, back, or hip pain suggests metastatic CaP

PHYSICAL EXAM
- DRE: Nodules, induration, asymmetry, bogginess, tenderness (Note: American Cancer Society recommends PSA screening with or without DRE)
- Adenopathy, supraclavicular
- Bony pain, point tenderness with metastasis
- Neurologic: Lower extremity strength/sensation

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Routine UA to rule out UTI/prostatitis (1 – 3)
- Consider evaluation for prostatitis by modified Stamey–Meares test or exam of EPS (See Section I: Prostatitis, Chronic, Bacterial [NIH II])
- Consider %FPSA (FPSA/TPSA or F/T PSA)
  – With CaP lower FPSA; postulated that CaP produces more ACT
  – FPSA best with TPSA 4.0–10.0 ng/mL and prostates <50 g; not useful if TPSA >10 ng/mL
  – FPSA stratifies CaP risk on biopsy (table) (3)

PSA ng/mL	CaP Rate	%FPSA	CaP Prob
0–2	1%	0–10	56%
2–4	15%	10–15	28%
4–10	25%	15–20	20%
>10	>50%	20–25	16%
		>25	8%

- Consider PSAD: PSA ÷ TRUS volume:

– Correlates PSA to TRUS prostatic size to distinguish BPH from CaP:

- $\text{PSAD} = \frac{\text{PSA ng/mL}}{\text{Prostate Volume (cc)}}$

– Useful with PSA 4–10 ng/mL and a previous negative biopsy
– Cutoff of 0.15 ng/mL/cm^3 improves specificity by 50%, missed 27–48% CaP
– Cutoff 0.1 avoids 31% of biopsies, misses 10% cancers; cutoff of 0.8 avoids 12% of biopsies, misses 5% of cancers

• Consider PSAV:
– Rate of PSA increase; PSA rises more rapidly if clinically significant CaP present:
– Minimum 18-mo interval with ≥3 repeat PSAs for most accurate PSAV determination.

- $\text{PSAV} = 0.5\left(\frac{\text{PSA}_2 - \text{PSA}_1}{\text{Time}_1} + \frac{\text{PSA}_3 - \text{PSA}_2}{\text{Time}_2}\right)$

  - PSA_1 = 1st PSA (ng/mL)
  - PSA_2 = 2nd PSA (ng/mL)
  - PSA_3 = 3rd PSA (ng/mL)
  - Time_1 = time between PSA_1 & PSA_2 (yr)
  - Time_2 = time between PSA_2 & PSA_3 (yr)

– Baltimore Longitudinal Study: 72% CaP had PSA rise >0.75 ng/mL/yr vs.10% with BPH
– PSAV > 0.35 predicts PCa death w/ PSA <4
– PSAV >0.75 90–100% PCa sensitivity w/ PSA >4
– PSA velocity >02 in year before dx predicts PCa mortality

• "Prostate Health Index" or phi assay
– CaP low FPSA, increased % proPSA
– Calculation ([–2]proPSA/FPSA) × √TPSA
– phi 27–55, CaP 9.8–50%, Gl ≥7 3.9–28.9%; phi 27: 18.8% could be spared biopsy (low risk)

Imaging

• TRUS: Determine prostatic size; PSAD; most useful to guide systematic needle biopsy
• Multiparametric MRI with/without endorectal coil: Useful if CaP suspicion and negative biopsy. Anterior tumors and other sites can be identified
• CT or bone scan: No role in CaP screening

Diagnostic Procedures/Surgery

• TRUS-guided prostate biopsy with 18G biopsy needle and local anesthesia:
– Systematic biopsy (12 cores) with laterally directed samples is now standard for CaP.

Pathologic Findings

See Section I: "Prostate Cancer, General."

DIFFERENTIAL DIAGNOSIS

• Adenocarcinoma of the prostate (CaP)
• BPH
• Prostatitis (usually bacterial infection)

- Prostatic infarction: Idiopathic or after shock
- Iatrogenic: Recent cystourethroscopy, Foley catheter placement, prostate biopsy
- Prostatic massage (but not routine DRE)
- Trauma (cycling, extensive)
- Ejaculation within 24 hr of PSA test (rare)

TREATMENT

GENERAL MEASURES

- Shared decision making before PSA based CaP screening in asymptomatic patients
- Due to PSA fluctuations, confirm an elevated PSA with a 2nd reading before biopsy. Patient should not ejaculate for 48 hr before test.
- Review serial PSA determinations for PSAV
- CaP screening recommendations:
  - See Appendix for ACS, ACP, EAU, NCCN, USPSTF
- AUA 2013 CaP Early Detection Guideline (4):
  - No PSA screening in men under age 40 yr
  - Does not recommend routine screening between ages 40 and 54 yr at average risk
  - Shared decision-making for men 55–69 yr considering PSA screening due to risks/benefits; proceed based on a man's values and preferences
  - To reduce harms, screening intervals of 2 yr preserves the benefits and reduces overdiagnosis and false-positives
  - No routine PSA screening in men age 70+ yr or <10–15-yr life expectancy; but some 70+ yr in excellent health may benefit from screening
- Some published prostate biopsy indications:
  - Prostate nodule, regardless of PSA
  - PSA >10 ng/mL in the absence of prostatitis
  - PSA >4.0 ng/mL and PSAV >0.75 ng/mL/yr
  - PSA <4.0 ng/mL and PSAV >0.3–0.5 ng/mL/yr
  - PSA >2.5 ng/mL and PSAV >0.60 ng/mL/yr
  - PSA 4–10 and F/T PSA<10%
  - F/T PSA <20% and PSAV >0.75 ng/mL/yr
- Numerous assays under study to help differentiate benign form malignant PA elevation (See Section II: "PSA, General Considerations.")

MEDICATION

First Line

- Empiric antibiotics for elevated PSA is no longer recommended by most sources
- With bacterial prostatitis, treat and repeat PSA 4 wk after: Fluoroquinolone (eg, ciprofloxacin 500 mg BID.) or TMP-SMX (180/800 mg BID)

Second Line

N/A

SURGERY/OTHER PROCEDURES

If patient has anorectal pathology, consider transperineal prostate biopsy for CaP diagnosis

ADDITIONAL TREATMENT

- CaP risk calculators are available on the Internet to predict outcome of biopsy.
- PCA3 urine testing after attentive DRE; FDA approved only after initial negative biopsy; PCA3/TMPRSS2-ERG urine test investigational

Additional Therapies

Any PSA rise while on finasteride/dutasteride baseline raises CaP risk

Complementary & Alternative Therapies

No evidence for herbals effect on PSA

ONGOING CARE

PROGNOSIS

- With elevated PSA, positive biopsy rate is about 25–30%; elevated PSA and nodule 18–60%
- Overall, if 2nd biopsy is performed after initial negative, detection rate is 10–35%.

COMPLICATIONS

Failure to diagnose cancer; patient anxiety over repeat testing; risk of biopsy and drugs

FOLLOW-UP

Patient Monitoring

- There is no single threshold PSA which should prompt prostate biopsy. Biopsy decision based on PSA, DRE, and multiple factors (F/T PSA, age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history, comorbidities, patient preferences) (5).
- PSA <2.5 ng/mL, low PSAV: Annual DRE/PSA
- PSA 2.6–10 ng/mL, low PSAV:
  - Consider biopsy or obtain FPSA
  - F/T PSA $>25\%$: Repeat PSA/DRE in 6 mo
- Based on TRUS biopsy results:
  - Negative: Repeat DRE/PSA in 6 mo; consider F/T PSA as guide for another biopsy
  - HGPIN or ASAP:
    - Repeat biopsy (3–6 mo); consider transition zone sampling with any repeat biopsy.
  - Positive biopsy (CaP): Staging studies, discuss treatment options
- Persistent PSA elevation (PSA >10 ng/mL)
  - Repeat biopsy; transition zone sampling; multiparametric MRI of TRUS/MRI fusion biopsy

Patient Resources

AUA Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=68

REFERENCES

1. Lilja H, Cronin AM, Dahlin A, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. *Cancer*. 2011;117(6):1210–1219.
2. Shariat SF, Semjonow A, Lilja H, et al. Tumor markers in prostate cancer I: Blood-based markers. *Acta Oncol*. 2011;50(suppl 1):61–75.
3. Catalona WJ, Beiser JA, Smith DS. Serum free prostate specific antigen and prostate

specific antigen density measurements for predicting cancer in men with prior negative biopsies. *J Urol.* 1997;158:2162–2167.
4. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. *J Urol.* 2013;190(2):419–426.
5. Greene KL, Albertsen PC, Babaian RJ, et al. Prostate specific antigen best practice statement: 2009 update. *J Urol.* 2013;189(1 suppl):S2–S11.

ADDITIONAL READING

Heidenreich A, Abrahamsson PA, Artibani W, et al. Early detection of prostate cancer: European Association of Urology recommendation. *Eur Urol.* 2013;64(3):347–354.

See Also (Topic, Algorithm, Media)

- Prostate Cancer Screening Guidelines
- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Cryotherapy
- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Radiation Therapy
- Prostate Cancer, Biochemical Recurrence (Elevated PSA) Following Radical Prostatectomy
- Prostate Cancer, General
- PSA Elevation Following Negative Prostate Biopsy
- PSA, General Considerations

CODES

ICD9

- 185 Malignant neoplasm of prostate
- 600.00 Hypertrophy (benign) of prostate without urinary obstruction and other lower urinary tract symptom (LUTS)
- 790.93 Elevated prostate specific antigen [PSA]

ICD10

- C61 Malignant neoplasm of prostate
- N40.0 Enlarged prostate without lower urinary tract symptoms
- R97.2 Elevated prostate specific antigen [PSA]

CLINICAL/SURGICAL PEARLS

- Routine DRE will not clinically significantly elevate PSA.
- PSA 1/2-life is 2.2 days; may remain elevated for up to 4 wk after instrumentation.

PSEUDOHERMAPHRODITISM, MALE (XY DSD) AND FEMALE (XX DSD)

Luigi Avolio, MD

BASICS

DESCRIPTION

- Pseudohermaphroditism is an obsolete term that referred to pathologic conditions in which chromosomal sex is inconsistent with phenotypical sex
- Disorders of sexual development (DSDs) is the preferred term which indicates a congenital condition in which development of chromosomal, gonadal or anatomic sex is atypical (1)
- Female pseudohermaphroditism is now defined as XX DSD
  - Karyotype 46XX
  - Gonads: Normal ovaries
  - External genitalia: Varying degree of virilization
- Male pseudohermaphroditism is now defined as XY DSD
  - Karyotype 46XY
  - Gonads: Normal testes
  - External genitalia: Incomplete virilization

EPIDEMIOLOGY

Incidence

- 1 in 5,000 live births
  - 21-hydroxylase deficiency is the most common cause of 46XX DSD; 90% of congenital adrenal hyperplasia (CAH); 1:15,000 live births

Prevalence

N/A

RISK FACTORS

- Family history
- In utero exposure to androgens

Genetics

See “Disorders of Sex Development” chapter

PATHOPHYSIOLOGY

- XX DSD (Female pseudohermaphroditism) Disorders of androgen excess
  - 21-hydroxylase deficiency (21-OHD) is the most common cause for CAH, a family recessive disorders involving impaired synthesis of cortisol from cholesterol by the adrenal cortex
  - Impaired cortisol biosynthesis relieves feedback inhibition and thus increases ACTH secretion, which leads to hyperplasia of the adrenals and to disordered steroidogenesis; as a consequence cortisol precursors are shunted to androgen synthesis

ALERT

Newborns with salt-wasting 21-OHD CAH are at risk for life-threatening salt-wasting crises.

- β-Hydroxysteroid dehydrogenase (HSD3B2) deficiency: Deficiency of this enzyme results in adrenal insufficiency due to lack of conversion of δ5 steroids to δ-4 and consequent accumulation of pregnenolone, dehydroepiandrosterone (DHEA) and androstenediol. Phenotypically girls with mild virilization
- 11b-Hydroxylase (CYP11B1) deficiency: Characterized by accumulation of 11-deoxycorticosterone. This is the 2nd most common causes of virilizing CAH (5% of all cases)
- P450 oxidoreductase (POR) deficiency: Combined deficiencies of 21α-hydroxylase, 17α-hydroxylase and aromatase enzymes.
  - Familial glucocorticoid resistance: Rare condition with mutation in the glucocorticoid receptor determining high ACTH, cortisol, mineralocorticoids and androgens levels.
  - Aromatase (CYP19) deficiency: High serum androgens and low estrogen concentrations with progressive virilization.
- Maternal androgen excess:
  - Ovarian tumors (luteoma, arrhenoblastoma)
  - Ingestion of androgens, progestogens
- XY DSD (male pseudohermaphroditism)
  - Disorders of androgen synthesis
    - Cholesterol synthesis defects: Deficiency of 7-dehydrocholesterol reductase (DHCR7) results in a failure of cholesterol synthesis and elevated levels of its precursor 7-dehydrocholesterol. Causative factor of Smith–Lemli–Opitz syndrome (multiple congenital malformation and mental retardation syndrome)
    - Leydig cell hypoplasia: A defect of LH receptors leads to Leydig cells hypoplasia or agenesia. Genital anomalies range from hypospadias to completely normal female external genitalia
    - Lipoid CAH: Severe disorder of steroid hormone biosynthesis, caused by a defect in the conversion of cholesterol to pregnenolone, the 1st step in adrenal and gonadal steroidogenesis. All affected individuals are phenotypic females with a severe salt-losing syndrome, fatal if not promptly treated in early infancy
    - P450 side-chain cleavage deficiency: Rare disorder with ACTH and plasma renin activity grossly elevated and adrenal steroids inappropriately low or absent; patients have female external genitalia, sometimes with clitoromegaly
    - β-Hydroxysteroid dehydrogenase (HSD3B2) deficiency: (see XX DSD). 46 XY patients phenotype ranges from isolated hypospadias or micropenis to more severe undermasculinization
    - 17α-Hydroxylase/17,20-lyase deficiency: Production of excessive corticosterone and deoxycorticosterone with hypertension and hypokalemic alkalosis; aldosterone synthesis almost totally absent. Variable degree of undermasculinization
    - P450 oxidoreductase (POR) deficiency: (see XX DSD). The genitalia in 46 XY patients range from isolated hypospadias or micropenis to more severe undermasculinization
    - 17β-Hydroxysteroid dehydrogenase (17βHSD) type 3 deficiency: The HSD17B3 isozyme catalyzes the conversion of androstenedione to testosterone in the testis. Deleterious mutations in the HSD17B3 gene cause undermasculinization in genetic males attributable to impaired testosterone biosynthesis

- Steroid 5α-reductase type 2 deficiency: Reduced activity of 5α-RD type 2 with defective conversion of testosterone to DHT. Patients show ambiguous genitalia at birth, including perineal hypospadias

– Disorders of the androgen receptor (AR): Patients with partial or complete androgen insensitivity syndrome (PAIS/CAIS) have normal testosterone level and DHT response to hCG stimulation; usually normal anti-müllerian hormone (AMH) level
  - PAIS: Phenotype ranges from normal male with infertility (mild form) or isolated hypospadias to ambiguous genitalia with blind vaginal pouch
  - CAIS: Patients have female external genitalia, female breast development, blind vagina, absent uterus and female adnexa, and abdominal or inguinal testes

• Persistent müllerian duct syndrome (PMDS): Phenotype produced by a mutation in the gene encoding AMH or by a mutation in the AMH receptor; it results from failure of müllerian duct regression in otherwise normal males. Patients usually present bilateral cryptorchidism and inguinal hernias: A uterus and fallopian tubes are found in the inguinal canal; gonads are testes (2)

ASSOCIATED CONDITIONS

• Hypospadias
• Cryptorchidism
• Inguinal hernia

GENERAL PREVENTION

See “Disorders of Sex Development” chapter

DIAGNOSIS

HISTORY

• Family history:
  – Genital abnormalities
  – Amenorrhea
  – Sterility
  – Hirsutism
  – Early infant deaths (possible unrecognized CAH with salt-wasting crisis)
• Maternal exposure to androgens
• History of maternal virilization (androgen-producing tumor)

PHYSICAL EXAM

• External genitalia
  – Phallic structure (length, breadth, and amount of erectile tissue)
  – Position of urethral meatus
  – Number of orifices in the perineum and their characteristics
  – Labioscrotal folds (separated or fused)
• Gonads
  – Palpable gonads (testis, very rarely ovotestis)
• Abdomen
  – Mass referable to enlarged uterus

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Karyotype
- Serum levels of sodium, potassium, and 17-hydroxyprogesterone
- Androgens (testosterone, dihydrotesterone, androstenedione)
- Cortisol, gonadotrophins, and AMH levels
- Stimulation test with human chorionic gonadotropin (suspected defect of androgen production)

Imaging

- Abdominal/pelvic ultrasound (utero presence)
- Cystogram/genitogram (visualization of vagina, sinus)
- MRI

Diagnostic Procedures/Surgery

- Laparoscopy to define internal anatomy
- Cysto/vaginoscopy to confirm anatomy and level of confluence of urogenital sinus
- Gonadal biopsy to analyze presence of ovarian and/or testicular tissue
- Skin biopsy to obtain cellular lines

Pathologic Findings

See “Disorders of Sex Development” chapter

DIFFERENTIAL DIAGNOSIS

- Cryptorchidism
- Inguinal hernia, hydrocele
- Hypospadias
- Microphallus
- Gonadoblastoma
- Menstruation disorders

TREATMENT

GENERAL MEASURES

- Multidisciplinary team for evaluation of the patient
- Gender assignment early

MEDICATION

First Line

- Salt-wasting CAH
  - Fluid and electrolytes replacement
  - Glucocorticoid and mineralocorticoid replacement
    - Hydrocortisone 10 mg/m^2/d
    - Fludrocortisone 0.1–0.2 mg/d
  - Oral sodium chloride, 1–2 g/d added to formula or breast milk

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Masculinizing genitoplasty (between the ages of 6 and 18 mo) (See "Disorders of Sex Development" chapter)
- Feminizing genitoplasty (during the 1st 6 mo of life) (3)[A] (See "Disorders of Sex Development" chapter)
- Müllerian remnants (See "Disorders of Sex Development" chapter)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Actually some patient groups strongly advocate to delay any surgical procedures until patients are competent to provide informed consent

ONGOING CARE

PROGNOSIS

- Generally good with appropriate care
- Many patients have a good quality of life
- Many patients remain fertile

COMPLICATIONS

See "Disorders of Sex Development" chapter

FOLLOW-UP

Patient Monitoring

- Lifelong psychosocial support mandatory
- Monitoring for increased risk for developing malignancies
- Evaluation of sexual function

Patient Resources

- http://www.congenitaladrenalhyperplasia.org
- http://www.livingwithcah.com
- http://rch.org.au/cah_book/index.cfm?doc_id=1375
- http://www.ahn.org.uk

REFERENCES

1. Hughes IA, Houk C, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Arch Dis Child*. 2006;91:554–563.
2. Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. *Best Pract Res Clin Endocrinol Metab*. 2010;24:197–218.
3. Romao RL, Salle JL, Wherrett DK. Update on the management of disorders of sex development. *Pediatr Clin North Am*. 2012;59:853–869.

ADDITIONAL READING

- Auchus RJ, Chang AY. 46,XX DSD: The masculinized female. *Best Pract Res Clin Endocrinol Metab*. 2010;24:219–242.
- Barbaro M, Wedell A, Nordenström A. Disorders of sex development. *Semin Fet al Neonatal Med*. 2011;16:119–127.
- Barthold JS. Disorders of sex differentiation: A pediatric urologist's perspective of new terminology and recommendations. *J Urol*. 2011;185:393–400
- http://www.ncbi.nlm.nih.gov/omim/ (Online Mendelian Inheritance in Man®)

See Also (Topic, Algorithm, Media)

- Congenital Adrenal Hyperplasia
- Disorders of Sexual Development (DSD)
- Hypospadias
- Micropenis (Microphallus)
- Müllerian Duct Remnants and Persistent Müllerian Duct Syndrome (PMDS)

CODES

ICD9

752.7 Indeterminate sex and pseudohermaphroditism

ICD10

- Q56.1 Male pseudohermaphroditism, not elsewhere classified
- Q56.2 Female pseudohermaphroditism, not elsewhere classified
- Q56.3 Pseudohermaphroditism, unspecified

CLINICAL/SURGICAL PEARLS

- Infants with a DSD presenting with truly ambiguous genitalia are a rare occurrence.
- DSD should be regarded as a heterogeneous group of conditions with substantially different prognoses and treatment prospects.
- DSDs represent a broad complex field that requires the interaction of multiple disciplines with a diverse knowledge base.

PYELONEPHRITIS, ACUTE, ADULT

Sanjay S. Kasturi, MD

BASICS

DESCRIPTION

- An infectious process that involves the renal pelvis and parenchyma.
  - Most often ascending infection from the lower urinary tract.
  - It is most often a result of bacterial infection, but fungi, parasites, and viruses may be involved.
- Classified as uncomplicated or complicated (ie, associated with obstruction, anatomic anomaly, or stones) making treatment more difficult.

EPIDEMIOLOGY

Incidence

- Estimated at 15–17 cases per 10,000 females and 3–4 cases per 10,000 males (1).
- At least 250,000 cases of pyelonephritis are diagnosed annually in the United States.
- Highest among young women, then infants, then the elderly.

RISK FACTORS

- Anatomic or functional abnormalities: Incomplete emptying of the bladder→urine is more prone to infection
  - Vesicoureteral reflux, neurogenic bladder, BOO
- Foreign body: Acts as a nidus for bacterial colonization and infection
  - Calculous disease, medullary sponge kidney
  - Indwelling catheters
- Medical conditions: Diabetes mellitus, immunosuppression, alcohol abuse
- Social: Poor perineal hygiene (soiling)
  - Variables in sexual behavior (new or multiple partners) and use of spermicide
  - Previous episodes of pyelonephritis

Genetics

Related to vesicoureteral reflux

PATHOPHYSIOLOGY

- Women are at increased risk because the female urethra is shorter and in close proximity to the anus, allowing enteric organisms to more easily colonize the urinary tract
- Most common organism are gram-negative rods:
  - *Escherichia coli* accounts for the majority of cases (80% in women, 70% in men)
  - *Klebsiella pneumoniae* is the 2nd most common organism (5–10%)
- Bacteria enter urinary tract:
  - Ascending infection: Urethra and bladder
  - Results from colonization of the vaginal introitus with fecal flora in females
  - Lymphatic and hematogenous dissemination to the kidneys is uncommon
- Bacteria adhere to the urothelium, with subsequent invasion and inflammatory response

- Adhesins and fimbriae: Allow bacteria to adhere to urothelium
- Lipopolysaccharides: Have toxic and inflammatory effects
- Hemolysins: Allow for bacterial invasion by damaging cells
- Aerobacter: Enables bacteria to compete for iron, necessary for aerobic metabolism and reproduction

ASSOCIATED CONDITIONS
See “Risk Factors”

GENERAL PREVENTION
- Eliminate anatomic/functional abnormalities
- Patients with recurrent infections may require low-dose prophylactic antibiotics
- Proper indwelling catheter management

DIAGNOSIS
HISTORY
- Fevers, chills, malaise, nausea, vomiting (2)
- Flank or abdominal pain
- Dysuria, urgency or frequency, gross hematuria
- Prior episodes of UTIs
- History of renal calculi or urinary tract abnormalities
- History of vaginal discharge and irritation makes a urinary source less likely
- History of diabetes, immunosuppression, or alcoholism; recent instrumentation
- Children may present with failure to thrive

PHYSICAL EXAM
- Vital signs for signs of sepsis
- CVA tenderness
- Abdominal distention with decreased bowel sounds may be present
- Pelvic exam in women may help differentiate from gynecologic disease

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC: Leukocytosis with neutrophil predominance (90%)
- Serum chemistry: Renal failure uncommon unless obstruction or sepsis present
- Blood culture: 12% of hospitalized pyelonephritis patients will have bacteremia
- Pregnancy test in women
- Urinalysis: Pyuria >5–10 WBCs/HPF:
  - WBC casts indicate renal source of infection
  - Hematuria and bacteria may be present
  - Leukocyte esterase often positive, but nitrite may not be positive with staph or enterococci
- Gram stain urine may rapidly identify organism
- Urine culture: Positive with >100,000 bacteria/mL and identifies causative organism; 10,000 bacteria/mL suggests acute pyelonephritis in patients with catheterized urine samples
- Newer data suggests that urinary cultures may be negative especially if patients were started

on antibiotics prior to presentation

Imaging

- In uncomplicated acute pyelonephritis, imaging studies are unnecessary; however, the combination of fever and flank pain especially with elevated WBC count requires imaging to rule out ureteral obstruction, which, with fever and infection, is a surgical emergency (3)
- Failure to respond to appropriate therapy within 72 hr requires radiographic evaluation to rule out obstruction, abscess, or other abnormalities
- Pediatric patients are at risk of scarring and should undergo imaging
- Abdominal x-ray (KUB): Evaluate for renal or ureteral calculi
  - Intraparenchymal gas: Emphysematous pyelonephritis
  - Renal shadow may be enlarged and poorly defined secondary to parenchymal edema
- IVP/ExU: 75% of patients with uncomplicated acute pyelonephritis will have a normal ExU
  - ExU shows an enlarged kidney (>15 cm in length or 1.5 cm greater than the unaffected side with decreased nephrogram and delayed excretion)
  - Cortical striations may be seen
  - Focal enlargement of the kidney is consistent with focal bacterial nephritis, or acute lobar nephronia may be confused with tumor or abscess
  - Nonobstructive dilation of the renal pelvis and ureter may be present (endotoxins impair ureteral peristalsis)
- US: Renal enlargement with hypoechoic parenchyma and loss or corticomedullary differentiation
  - Noninvasive; no ionizing radiation
- CT: Noncontrast CT of the abdomen reveals an enlarged kidney with decreased attenuation of parenchyma, and perinephric fat stranding
  - Contrast administration shows delayed enhancement with delayed excretion
- Radionuclide scan: Cortical agents (eg, DMSA) reveal decreased activity in the affected kidney; Useful to identify areas of scarring

Diagnostic Procedures/Surgery

Determine postvoid residual if indicated.

Pathologic Findings

- Gross: Edematous kidney with multiple foci of inflammation
- Microscopic: Focal areas of destruction of renal architecture with lymphocytic infiltrations

DIFFERENTIAL DIAGNOSIS

- Any intra-abdominal inflammatory process
  - Appendicitis, cholecystitis, diverticulitis, pancreatitis, peptic ulcer disease
- Gynecologic conditions:
  - Pelvic inflammatory disease, ectopic pregnancy, ruptured ovarian cysts
- Urologic conditions:
  - Renal colic with fever
  - Renal and perinephric abscesses
- Lower lobe pneumonia
- Musculoskelet al pain

TREATMENT

GENERAL MEASURES

- Supportive care consists of hydration, antipyretics, and analgesics
- Empiric antibiotics that are active against the possible causative organisms and achieve adequate levels in the renal parenchyma and urine are used

MEDICATION

First Line

- Outpatient therapy: In uncomplicated acute pyelonephritis, those who are reliable, tolerate oral intake, and do not have signs of sepsis do not require hospitalization (4,5)
  - Oral fluoroquinolones (ciprofloxacin 500 mg PO BID, or levofloxacin 750 mg/d PO) are adequate for empiric treatment. Levofloxacin is approved for a 5-day regimen
  - An alternative: Trimethoprim–sulfamethoxazole
  - Traditionally, continue therapy for 10–14 days. Recent data shows a 7-day course of ciprofloxacin is not inferior to a 14-day 1 in women with uncomplicated acute pyelonephritis
  - Recent data suggests increased quinolone resistance as well as susceptibility to TMP-SMZ
- Inpatient therapy: If signs of sepsis, bacteremia, or cannot tolerate oral medications
  - Also recommended for children, the elderly, pregnant patients, diabetics, and the immunocompromised and with complicated pyelonephritis
  - Parenteral antibiotic therapy uncomplicated
    - Ampicillin (2 g IV q6h) and gentamicin (1.5 mg/kg IV q8h) is traditional treatment; *OR*
    - Ceftriaxone (1 g/d IV) empirically; *OR*
    - IV fluoroquinolones ciprofloxacin 400 mg q12h or levofloxacin 750 mg q24h; aztreonam is also an acceptable alternative
  - Most patients continue to have fever or flank pain for several days after appropriate therapy has been started.
  - IV therapy continued until the patient is afebrile or cultures indicate another appropriate antibiotic.
  - When able to tolerate oral intake, switch to an oral antibiotic as for oral therapy above.
  - Pregnant patients: Place on suppression therapy (eg, nitrofurantoin 100 mg/d PO, cephalexin 250 mg/d PO) after treatment until delivery, due to a relapse rate of up to 60% in nonsuppressed patients.
  - Patients with a delayed response to therapy should be treated with a longer course of antibiotics (14–21 days), even without evidence of complicated disease.
- Complicated pyelonephritis: Assess for underlying urologic abnormalities (obstruction, stones, etc.) (6)
  - Parenteral antibiotic therapy in complicated cases:
    - Piperacillin–tazobactam 3.375 g q6h, ticarcillin–clavulanate 3.1 g q6h, cefepime 1 g q12h
    - Alternates include meropenem, and imipenem. Dose-adjust with renal failure.
  - After transitioning to species-specific antibiotics, PO continued for 14–21 days
- Pregnancy considerations:
  - Ampicillin, amoxicillin and, PO cephalosporins have proven to be safe;

amoxicillin/clavulanic acid (Augmentin) is recommended for resistant organisms; nitrofurantoin is safe for the fetus but potentially toxic to the mother; fluoroquinolones should be avoided in pregnancy

SURGERY/OTHER PROCEDURES

- Diversion with indwelling stent or percutaneous drain may be necessary in patients with urinary obstruction.
- If a renal abscess forms:
  - 3–5 cm in size then place percutaneous drain
  - >5 cm may require more than 1 percutaneous drain or surgical drainage

ONGOING CARE

PROGNOSIS

With 1st episode of acute pyelonephritis, 1-yr risk of a 2nd episode was 9.2% in females and 5.7% in males. With a 4th episode, the risk of a 5th infection was 50% for females and males.

COMPLICATIONS

- Short term:
  - Septic shock
  - Abscess formation (corticomedullary, perinephric)
  - Papillary necrosis
- Long term: Renal scarring (20%)
- Children with developing kidneys are at significant risk of scarring from even 1 episode of acute pyelonephritis
- Diabetics are at significant risk of developing emphysematous pyelonephritis, a more fulminant process with a high mortality:
  - Characterized by renal intraparenchymal gas and detectable on KUB
- Patients with calculi or urinary tract obstruction who have recurrent episodes of pyelonephritis may develop xanthogranulomatous pyelonephritis:
  - Characterized by large nonfunctioning renal mass
  - Stones are present in 80% of cases
- Pregnant patients are at high risk because of the physiologic changes of pregnancy to the urinary tract:
  - Sepsis
  - Adult respiratory distress syndrome
  - Preterm delivery with low–birth-weight infants

FOLLOW-UP

Patient Monitoring

- Urine cultures 4–6 wk after completion of antibiotics to verify infection cleared
- 10–30% suffer a relapse and may be treated with a 2nd 14-day course of antibiotics
- Occasionally, a 6-wk course needed for cure
- Confirm hematuria clears if initially present

Patient Resources

http://kidney.niddk.nih.gov/kudiseases/pubs/pyelonephritis/

REFERENCES
1. Czaja CA, Scholes D, Hooton TM, et al. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis.* 2007;45:273–280.
2. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am.* 1997;11:551–581.
3. Piccoli GB, Consiglio V, Deagostini MC, et al. The clinical and imaging presentation of acute "non complicated" pyelonephritis: A new profile for an ancient disease. *BMC Nephrol.* 2011;12:68.
4. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in children. *Clin Infect Dis.* 1999;29:745–758.
5. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: A randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *Lancet.* 2012;380(9840):484–490.
6. Siegel J, Smith A, Moldwin R. Minimally invasive treatment of renal abscess. *J Urol.* 1996;155:52–55.

ADDITIONAL READING

Hooton TM. Clinical practice. Uncomplicated urinary tract infection. *N Engl J Med.* 2012;366(11):1028–1037.

See Also (Topic, Algorithm, Media)

- Pyelonephritis, Acute, Adult Image
- Pyelonephritis, Chronic
- Pyelonephritis, Emphysematous
- Pyelonephritis, Xanthogranulomatous
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

- 041.49 Other and unspecified Escherichia coli [E. coli]
- 590.10 Acute pyelonephritis without lesion of renal medullary necrosis
- 593.73 Other vesicoureteral reflux with reflux nephropathy NOS

ICD10

- B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
- N10 Acute tubulo-interstitial nephritis
- N13.729 Vesicoureter-reflux w reflux nephropathy w/o hydrourt, unsp

CLINICAL/SURGICAL PEARLS

- Urine cultures may be negative in patients especially if started on recent antibiotics.
- If fevers last for more than 72 hr after antibiotics, obtain at CT scan to rule obstruction, soft

tissue infection, or abscess formation.

PYELONEPHRITIS, ACUTE, PEDIATRIC

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Paul H. Smith III, MD

BASICS

DESCRIPTION

- Infectious process involving the renal parenchyma and collecting system
- Retrograde ascent of uropathogenic bacteria is most common cause

EPIDEMIOLOGY

Incidence

- 18,000–20,000 children per year hospitalized for diagnosis of pyelonephritis
- Risk of childhood UTI 2% for boys and 8% for girls
- UTI more common in males during 1st yr of life
  - Gender predilection reversed thereafter

Prevalence

Low, given the acuity of illness and prompt treatment

RISK FACTORS

- Circumcision reduces risk of UTI during 1st yr of life
  - 10× greater risk of UTI in uncircumcised boys
- Dysfunctional voiding
- Anatomic urinary tract anomalies
  - Ureteropelvic junction obstruction
  - Vesicoureteral reflux (VUR)
  - Ureterocele/ectopic ureter
- Neurogenic bladder dysfunction

Genetics

P1 blood group antigen associated with recurrent pyelonephritis

PATHOPHYSIOLOGY

- Periurethral and fecal flora are the source of most uropathogens
  - *Escherichia coli* is the most common organism
  - Other common organisms are *Klebsiella, Enterococcus, Pseudomonas, Staphylococcus saprophyticus, Enterobacter*
- Bacterial virulence factors promote upper tract infection
  - P fimbriae: *E. coli* virulence factor promotes adherence and subsequent invasion of bacteria into the urothelium (1)
- Inflammatory response initiated by interaction between bacterial endotoxin and toll-like receptor (TLR) 4 (1)

ASSOCIATED CONDITIONS

- Lobar nephronia: Pyelonephritis affecting only an isolated focus within the kidney

- Pyonephrosis: Purulent material within the collecting system
- Renal abscess

GENERAL PREVENTION
- Prophylactic antibiotics in patients with recurrent episodes of UTI or with VUR
- Surgical correction of anatomic urinary tract anomalies
- Optimization of bladder/bowel management in patients with neurogenic and nonneurogenic bladder dysfunction
- Antibiotic prophylaxis if major GU instrumentation

DIAGNOSIS

HISTORY
- Nonspecific symptoms or failure to thrive in young children
  - High degree of suspicion required in young children
- Fever, nausea, vomiting
- Flank or abdominal pain
- Hematuria, dysuria, foul smelling urine, frequency, urgency
- History of UTIs
- Functional or anatomic urinary tract anomalies

PHYSICAL EXAM
- Fever
- Sepsis
- CVA tenderness
- Exam findings nonspecific in young children

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
  - WBCs: >5 per HPF
  - Presence of any bacteria
  - Positive leukocyte esterase
  - Positive nitrites: ~4 hr of dwell time in the bladder required for nitrites to become positive
- Urine culture: Specimen collected by clean catch, catheterization or suprapubic aspiration (SPA)
  - >50,000 C FU signifies positive culture (2)
- CBC: Leukocytosis with left shift
- Blood cultures
- Elevated CRP, ESR, procalcitonin

Imaging
- Renal and bladder ultrasonography (RBUS)
  - Failure to improve clinically within 1st 2 days of antibiotic treatment should prompt evaluation with RBUS to evaluate for complications
    - Renal abscess

- Pyonephrosis
  - Used to identify structural abnormalities contributing to the development of pyelonephritis
- Voiding cystourethrogram (VCUG)
  - Identifies VUR
  - Requirement for VCUG after 1st febrile UTI controversial
  - Invasive study (requires catheterization)
- Nuclear cystogram
  - More sensitive for low-grade VUR than VCUG but less anatomic detail
- Nuclear renography (DMSA)
  - Gold standard for diagnosis of pyelonephritis
    - Rarely necessary in acute setting
  - Delayed study identifies renal scarring (3)
  - Invasive study (IV injection of radionuclide)
  - Radiation exposure

Diagnostic Procedures/Surgery

SPA for urine culture if clean catch or catheterization not feasible

Pathologic Findings

- Renal scarring
  - Inflammatory reaction to renal parenchymal infection can cause irreversible renal scarring

DIFFERENTIAL DIAGNOSIS

- Renal abscess
- Pyonephrosis
- Other intra-abdominal process

TREATMENT

GENERAL MEASURES

- Prompt initiation of empiric antibiotics after acquisition of urine specimen suitable for culture (clean catch, catheterization, SPA)
- General supportive measures
  - Volume resuscitation, antipyretics, analgesics
- Need for hospitalization based on severity of illness, however admission generally indicated for infants (< 2–3 mo)

MEDICATION

First Line

- Empiric coverage
  - Tailor to local antimicrobial resistance patterns (2)[A]
  - Ampicillin (25–50 mg/kg/d) + gentamicin (2–2.5 mg/kg TID)
    - 3rd-generation cephalosporin an alternative to ampicillin if low risk for *enterococcus* UTI
- Oral culture-directed antibiotics once clinically improving and tolerating oral intake
  - Avoid nitrofurantoin due to minimal tissue penetration
  - Parenteral antibiotics (daily ceftriaxone, IM) also an option for outpatient therapy

- 7–14 days total duration of therapy (2)[B]

Second Line
- Vancomycin if penicillin allergic
- Aztreonam an alternate to aminoglycoside if renal insufficiency

SURGERY/OTHER PROCEDURES
- Urethral catheter if critically ill or poor bladder emptying
- Surgery generally not indicated in acute treatment
- Ureteral stent or nephrostomy tube if obstruction
- Percutaneous aspiration/drainage if progression to renal abscess

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
Probiotics (experimental)

ONGOING CARE

PROGNOSIS
Related to degree of renal injury from pyelonephritic scarring

COMPLICATIONS
- Pyelonephritic scarring, especially with recurrent episodes and delayed treatment
- Pyonephrosis
- Renal abscess
- Xanthogranulomatous pyelonephritis
- Hypertension

FOLLOW-UP
Patient Monitoring
- Current American Academy of Pediatrics guidelines recommends RUS in children with febrile UTI
  - Selective VCUG in patients with abnormal RUS or recurrent episodes (2)[C]
  - Indications for radiographic imaging in children with 1st episode of febrile UTI remain controversial
- Delayed DMSA scan to detect renal scarring

Patient Resources
- National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
  - http://kidney.niddk.nih.gov/kudiseases/pubs/pyelonephritis/index.aspx
  - http://kidney.niddk.nih.gov/kudiseases/pubs/utichildren/

REFERENCES

1. Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. *N Engl J Med*. 2011;365(3):239–250.
2. Roberts KB. Urinary tract infection: Clinical practice guidelines for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595–609.
3. Rushton HG, Majd M. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: A review of experimental and clinical studies. *J Urol*. 1992;148(5 pt 2):1726–1732.

ADDITIONAL READING

- Juliano TM, Stephany HA, Clayton DB, et al. Incidence of abnormal imaging and recurrent pyelonephritis after first febrile urinary tract infection in children 2 to 24 months. *J Urol*. 2013;190(4 suppl):1505–1510. doi: 10.1016/j.juro.2013.01.049.
- Shaikh N, Ewing AL, Bhatnagar S, et al. Risk of renal scarring in children with a first urinary tract infection: A systematic review. *Pediatrics*. 2010;126:1084–1091.
- Shortliffe LD. Infection and inflammation of the pediatric genitourinary tract. In: Wein AJ, Kavoussi LR, Novick AC, et al.*Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2012.

See Also (Topic, Algorithm, Media)

- Pyelonephritis, Acute, Pediatric Image
- Pyonephrosis
- Urinary Tract Infection (UTI), Complicated, Pediatric
- Urinary Tract Infection (UTI), Pediatric
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

- 041.49 Other and unspecified Escherichia coli [E. coli]
- 590.10 Acute pyelonephritis without lesion of renal medullary necrosis
- 593.73 Other vesicoureteral reflux with reflux nephropathy NOS

ICD10

- B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
- N10 Acute tubulo-interstitial nephritis
- N13.729 Vesicoureter-reflux w reflux nephropathy w/o hydrourt, unsp

CLINICAL/SURGICAL PEARLS

- Signs and symptoms are often nonspecific in infants and young children with pyelonephritis.
- Culture of appropriately collected urine specimen mandatory in patients with suspected UTI and in infants with fever and no obvious source.
- Acute imaging (RUS) recommended if critically ill or failure to respond to treatment.

PYELONEPHRITIS, CHRONIC

Debra L. Fromer, MD
Drew A. Freilich, MD

BASICS

DESCRIPTION

- Injury to the kidney with inflammation and fibrosis of the renal parenchyma, pelvis, and calyces. It is most often caused by recurrent or chronic renal infection
- Not usually diagnosed based on clinical presentation, chronic pyelonephritis is usually a radiologic or pathologic diagnosis
- Clinical signs and symptoms are often vague but can be related to the infection and the severity and location of injury within the kidney:
  - Often an incidental finding, it may present as asymptomatic bacteriuria, dysuria and frequency (lower urinary tract symptoms), vague complaints of flank or abdominal discomfort, and intermittent low-grade fevers.
  - Synonym(s): Chronic interstitial nephritis

EPIDEMIOLOGY

Incidence

- Occurs in males and females of all ages:
  - More common in childhood, especially with congenital anomalies such as vesicoureteral reflux (VUR) (1)[B]
- Chronic pyelonephritis accounts for 15–20% of cases of chronic renal failure
- Less common in patients having no underlying functional or structural urinary tract abnormalities

Prevalence

4:1,000 asymptomatic adults

RISK FACTORS

- Female sex
- In 50% of cases, history of a previous episode of acute pyelonephritis
- VUR/reflux nephropathy
- Congenital urinary tract anomalies
- Neurogenic bladder dysfunction
- Pregnancy
- Urinary tract obstruction with complicated UTI can result in renal insufficiency:
  - Mechanical obstruction includes prostatic hyperplasia, calculi, retroperitoneal fibrosis, neoplasms, and congenital anomalies

Genetics

Susceptibility to acute pyelonephritis may have a familial component and may be associated with decreased CXCR1 expression.

PATHOPHYSIOLOGY

- Progressive localized immune response to bacterial infection
- Hyaline casts in tubule may cause resemblance to thyroid colloid known as *renal thyroidization*
- Fibrosis around the glomeruli replaces kidney parenchyma in patches:
  – Calyceal clubbing with nonuniform localized scarring

ASSOCIATED CONDITIONS
- VUR
- Spinal cord injury
- Xanthogranulomatous pyelonephritis (XGP) is a form of chronic pyelonephritis
  – Presents with foamy lipid laden macrophages
  – Often unilateral and associated with longstanding obstructing nephrolithiasis

GENERAL PREVENTION
- Upper urinary tract evaluation in patients with recurrent bacteriuria or recurrent acute pyelonephritis
- Early detection, evaluation, and treatment of childhood UTIs
- Prompt detection and management of VUR
- Detection and treatment of obstructive uropathy

Geriatric Considerations
- Chronic pyelonephritis can present with atypical symptoms and signs (ie, failure to thrive, low-grade fevers). Diagnosis requires a high level of suspicion.

Pregnancy Considerations
- Antibiotic prophylaxis during pregnancy in patients with risk factors including:
  – History of acute pyelonephritis during pregnancy
  – Recurrent bacteriuria after treatment during pregnancy
  – History of recurrent UTIs on previous antibiotic prophylaxis before being pregnant

Pediatric Considerations
- Assess UTI with:
  – Voiding cystourethrogram (VCUG) (to check for VUR or anatomical abnormality)
  – DMSA (to detect scar formation/progression)
  – Renal US (to assess for hydronephrosis)

DIAGNOSIS

HISTORY
- Frequently asymptomatic and discovered incidentally
- UTIs in childhood and during pregnancy
- Presence of HTN, especially in children with known reflux nephropathy
- Proteinuria, polyuria, nocturia, frequency
- Patients with spinal cord injury present with cloudy or malodorous urine, vague abdominal discomfort, malaise, lethargy, leakage between catheterizations, or increased spasticity or autonomic dysreflexia.
- Fever of unknown origin
- Failure to thrive in infant or child

PHYSICAL EXAM

- HTN may be present
- Nonspecific, unless associated with an episode of acute pyelonephritis
- May be mild flank pain or CVA tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis may be normal or indicate pyuria or proteinuria. WBC casts can be seen.
- Urine culture is usually only positive with an active, symptomatic infection. Culture is often negative.
- Microalbuminuria/proteinuria is an adverse prognostic sign.

Imaging

- CT reveals the typical findings of chronic pyelonephritis
  - Small or atrophic kidney, unilaterally or bilaterally
  - Compensatory hypertrophy with unilateral atrophy
  - Blunted and dilated calyces
  - Renal cortical scarring and thinning of the cortex
- Renal US to evaluate for hydronephrosis, renal anatomy, or stones. Not a good test to identify active reflux, but dilated ureters suggest obstruction or reflux
- VCUG for the evaluation of reflux
- CT is more sensitive than US for nephrolithiasis; also to rule out obstruction, hydronephrosis, stone disease, urinary tract abnormality. Pyonephrosis or abscesses are usually identified if present
- Technetium-99m DMSA is the best study to evaluate for renal scarring

Diagnostic Procedures/Surgery

- Cystoscopy in selected cases
- Renal biopsy

Pathologic Findings

- Gross kidney is often diffusely contracted, scarred at periphery with thin cortex
- Microscopically, an interstitial infiltrate of lymphocytes, plasma cells, and occasional neutrophils is present
- Scarring is often polar with underlying calyceal blunting. Histologic changes are patchy:
  - Periglomerular fibrosis is often seen
  - Leukocytes and hyaline casts can be present in tubules, and the hyaline casts may resemble thyroid colloid, hence the description renal thyroidization

DIFFERENTIAL DIAGNOSIS

- Analgesic nephropathy
- Diabetic nephropathy
- Gouty nephritis
- Hypertensive renal disease
- Psoas and subdiaphragmatic abscess
- Renal artery stenosis
- Renal malakoplakia
- Renal tuberculosis

- Urolithiasis
- Xanthogranulomatous pyelonephritis (XGP) (2)[B]

TREATMENT

GENERAL MEASURES

- Chronic pyelonephritis is difficult to manage as it is an irreversible process
- With mild VUR, suppressive antibiotics are used until resolution or puberty in children
- Severe reflux may require reimplantation
- Correct anatomic anomalies or stones if possible

MEDICATION

First Line

- Acute episodes of pyelonephritis should be treated (See Section I: "Pyelonephritis, Acute") (3)[B]
- Suppressive antibiotics VUR in children has become controversial:
  - In children < 3–6 mo, use low-dose amoxicillin or cephalexin, cefazolin, or other 1st-generation cephalosporin can be considered
  - In children > 6 mo, switch to nitrofurantoin, trimethoprim-sulfamethoxazole, or trimethoprim alone can be considered
- Hypertension is best treated by ACE inhibitors (lisinopril, enalapril, ramipril) that may also protect the kidney from progressive renal failure
  - ACE inhibitors are contraindicated in pregnancy

Second Line

Based upon urine culture sensitivities, prior treatment attempts and patient presenting symptoms

SURGERY/OTHER PROCEDURES

- Correction of reflux may be necessary in children with high-grade reflux (Grade 4–5). Low-grade reflux (Grade 1–3) often resolves with time
- Nephrectomy for persistent/recurrent infection unresponsive to systemic treatment, markedly decreased function (ie, 10%), pain, or refractory HTN, XGP

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Little data to support

ONGOING CARE

PROGNOSIS

- 24-hr protein excretion may be an important prognostic indicator of progressive

deterioration of renal function due to focal and segmental glomerulosclerosis superimposed on tubulointerstitial disease
- Radionuclide renal scan can assess renal function and scarring

COMPLICATIONS
- Emphysematous pyelonephritis
- End-stage renal disease (rare)
- Focal segmental glomerulosclerosis
- HTN
- Perinephric abscess: Requires surgical drainage
- Polyuria, nocturia from loss of tubular concentrating ability
- Pregnancy-related miscarriages in women with chronic reflux
- Proteinuria
- Pyonephrosis
- XGP

FOLLOW-UP
Patient Monitoring
- Annual serum creatinine to monitor chronic kidney disease
- Blood pressure monitoring (good control of BP may limit renal damage over time)
  – 15% of patients with reflux nephropathy who reach adulthood have HTN
  – Some advocate screening renal scan or VCUG of siblings who have reflux
- Urine analysis to monitor for proteinuria and bacteruria (4)[A]
- Selective long-term antibiotics to limit infection (5)[A]

Patient Resources
National Kidney and Urologic Diseases Information Clearinghouse (NIH).
http://kidney.niddk.nih.gov/kudiseases/pubs/pyelonephritis/

REFERENCES

1. Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: Congenital reflux nephropathy and acquired renal scarring. *J Urol.* 2010;184(1):265–273.
2. Guzzo TJ, Bivalacqua TJ, Pierorazio PM, et al. Xanthogranulomatous pyelonephritis: Presentation and management in the era of laparoscopy. *BJU Int.* 2009;104(9):1265–1268.
3. Rivera JA, O'Hare AM, Harper GM. Update on the management of chronic kidney disease. *Am Fam Physician.* 2012;86(8):749–754.
4. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005;40(5):643–654.
5. Dai B, Liu Y, Jia J, et al. Long-term antibiotics for the prevention of recurrent urinary tract infection in children: A systematic review and meta-analysis. *Arch Dis Child.* 2010;95(7):499–508.

ADDITIONAL READING
N/A

See Also (Topic, Algorithm, Media)

- Pyelonephritis, Acute
- Pyelonephritis, Chronic Image ☼
- Pyelonephritis, Emphysematous
- Pyelonephritis, Xanthogranulomatous
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

590.00 Chronic pyelonephritis without lesion of renal medullary necrosis

ICD10

- N11.1 Chronic obstructive pyelonephritis
- N11.8 Other chronic tubulo-interstitial nephritis
- N11.9 Chronic tubulo-interstitial nephritis, unspecified

CLINICAL/SURGICAL PEARLS

For best determination of renal function the bladder should be empty and kidneys unobstructed (ie, ureteral stent if large stones).

PYELONEPHRITIS, EMPHYSEMATOUS

Jennifer E. Heckman, MD, MPH
Stephen Y. Nakada, MD, FACS

BASICS

DESCRIPTION

- Acute necrotizing infection of the renal parenchyma and perirenal tissues caused by gas-forming organisms
  - Onset may be acute or insidious
  - Course is potentially life threatening (mortality: 11–42%)
- 1st report in 1898
- >200 reported cases

EPIDEMIOLOGY

Incidence

- All documented cases in adults
  - Most patients >60 yr old
- Female predominance (6:1)
- Bilateral cases, unusual but reported (L > R)

Prevalence

N/A

RISK FACTORS

- Diabetes mellitus (DM) (up to 95%)
  - Especially with poor glycemic control
- Urinary tract obstruction
  - Urinary calculi
  - Papillary necrosis
  - Neoplasm
- Immunosuppression

Genetics

N/A

PATHOPHYSIOLOGY

- Poorly understood
- Impaired host response allows microorganism proliferation
- Hypothesized that elevated tissue glucose levels provide substrate for microorganisms
  - Bacterial fermentation of sugar produces carbon dioxide
  - Low oxygen tension allows urinary tract infection to ascend
- *E. coli* is primary causative organism (70–90%)
  - *Klebsiella*, *Proteus*, *Streptococcus*, and coagulase-negative *Staphylococcus* less common
  - *Candida*, *Entamoeba histolytica*, and *Aspergillus fumigatus* are rare causes

ASSOCIATED CONDITIONS
- Alcohol abuse
- Diabetic ketoacidosis
- Immunocompromised states, including transplant patients
- Impaired renal function
- Malnutrition
- Urinary tract obstruction, including urinary calculi, papillary necrosis, or neoplasm

GENERAL PREVENTION
- Strict glycemic control in diabetes mellitus (DM)
- Adequate treatment of pre-existing pyelonephritis
- Prompt relief of urinary tract obstruction, if present

DIAGNOSIS
HISTORY
- Classic triad:
  - Fever, chills
  - Nausea, vomiting
  - Flank pain and/or abdominal pain
- Urinary frequency/urgency, dysuria
- Malaise
- Altered mental status
- History of DM, urinary calculi, and/or immunocompromise
- Pneumaturia absent unless infection involves collecting system

PHYSICAL EXAM
- Pyrexia
- Abdominal or flank tenderness
- Crepitus over flank (rare)
- Lethargy, confusion, altered mental status
- Sepsis/shock (tachycardia, hypotension)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Complete blood count (CBC)
  - Leukocytosis
  - Thrombocytopenia
- Basic metabolic panel (BMP)
  - Hyperglycemia
  - Elevated serum creatinine
- Urinalysis +/− urine culture
  - Pyuria, bacteriuria, positive urine culture
- Blood cultures
  - Bacteremia (isolated organism same as that in urine)

Imaging

- Abdominal radiograph may show tissue gas in parenchyma (nonspecific, low sensitivity)
- Renal ultrasound may show highly echogenic area with dirty shadowing
- Computed tomography (CT) is imaging modality of choice (most sensitive and specific)
  - May see:
    - Absence of fluid or presence of streaky or mottled gas +/− bubbly and loculated gas in renal parenchyma, collecting system, and/or perirenal tissue
    - Rim-like or crescent-shaped gas distribution surrounding kidney
    - Gas in renal vein, inferior vena cava, or retroperitoneum
    - Urinary tract obstruction (seen in ~25% of cases)
  - Contrast not necessary for diagnosis (and may be contraindicated in renal impairment)
- Classification system (1)[B]:
  - Class 1: Gas confined to collecting system
  - Class 2: Gas confined to renal parenchyma without extension to extrarenal space
  - Class 3A: Perinephric extension of gas or abscess
  - Class 3B: Pararenal extension of gas or abscess (beyond Gerota's fascia and/or extension to adjacent tissues)
  - Class 4: Bilateral emphysematous pyelonephritis or emphysematous pyelonephritis in a solitary kidney
  - Therapeutic and prognostic implications:
    - Class 1 and 2: Percutaneous drainage successful, low mortality
    - Class 3 and 4: Percutaneous drainage less successful, increased mortality

Diagnostic Procedures/Surgery

None, diagnosis is radiographic

Pathologic Findings

- Gross
  - Multiple renal parenchymal abscesses with central, gas-filled region
  - Foci of micro- and macroinfarctions
- Microscopic
  - Glomerulosclerosis, arteriosclerosis, intrarenal vascular thrombi, or papillary necrosis

DIFFERENTIAL DIAGNOSIS

- Acute pyelonephritis
- Emphysematous cystitis
- Fistulous communication with gastrointestinal or respiratory tracts
- Iatrogenic (instrumentation of urinary tract)
- Necrotic renal tumor
- Pyonephrosis with urinary tract obstruction
- Renal abscess
- Xanthogranulomatous pyelonephritis

TREATMENT

ALERT

Emphysematous pyelonephritis is urologic emergency that requires prompt diagnosis and

intervention to prevent morbidity and mortality.

GENERAL MEASURES

- Rapid supportive measures:
  - Fluid resuscitation
  - Correction of electrolyte imbalances
  - Vasopressors as needed
  - Usually requires ICU status
- Indwelling urethral catheter to maximize urinary tract drainage and monitor urine output.

MEDICATION

First Line

- Antimicrobial agents
  - Broad-spectrum parenteral antibiotics initially (dosages assume normal renal function):
    - Ampicillin–sulbactam (1.5 g q6h)
    - Ticarcillin–clavulanate (3.1 g q6h)
    - Piperacillin–tazobactam (3.375 g q6h)
    - Meropenem (500 mg q8h)
    - Imipenem (500 mg q6h)
    - Doripenem (500 mg q8h)
  - Narrow to culture-directed antibiotics
  - At least 14 days of therapy
- Hyperglycemia management
  - Insulin (intravenous or subcutaneous)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Percutaneous drainage
  - Indicated if:
    - Affected kidney is functioning
    - Affected kidney is obstructed
    - Localized area of gas identified
  - $\geq$14Fr catheter (may benefit from more than one catheter)
  - CT guidance preferred
  - In combination with antibiotic therapy reduces mortality rate
  - Helps preserve renal function in affected kidney
- If clinical improvement with medical management and percutaneous drainage, may delay or avoid nephrectomy
- Nephrectomy
  - Requires adequate resuscitation and stabilization preoperatively
  - Immediate vs. delayed (elective) based on clinical course
  - Indicated if:
    - Affected kidney is nonfunctioning and nonobstructed
    - Lack of clinical improvement with medical management and percutaneous drainage
  - Consider if:

- Presence of risk factors, including acute renal failure, thrombocytopenia, altered mental status, or shock
- Gas limited to renal parenchyma (dry-type emphysematous pyelonephritis)

– Flank approach preferred

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Dependent on:
  – Time to diagnosis and treatment
  – Local extent of the infection
- Mortality greatest in those presenting with (2)[B], (3)[B]:
  – Acute renal failure
  – Thrombocytopenia
  – Mental status changes
  – Shock
- Recent meta-analysis demonstrated treatment-based mortality (4)[B]:
  – Medical management alone: 50%
  – Medical management + emergency nephrectomy: 25%
  – Medical management + percutaneous drainage: 13.5%

COMPLICATIONS

- Perinephric abscess
- Renal insufficiency or failure
- Loss of renal unit
- Sepsis/shock
- Death
- Following procedural intervention:
  – Bowel or vascular injury
  – Wound infection

FOLLOW-UP

Patient Monitoring

- Follow urine and blood cultures for growth and sensitivities for directed antibiotic therapy
- Follow-up CT (4–7 days postpercutaneous drainage) (5)[C]
  – Look for other noncommunicating air/fluid collections (insert additional catheters as needed)
  – Maintain all drainage catheters until imaging demonstration of resolution

- Nuclear renal scan to assess degree of renal functional impairment and determine necessity of elective nephrectomy when patient stabilized

Patient Resources

http://www.emedicinehealth.com/urinary_tract_infections/article_em.htm

REFERENCES

1. Huang JJ, Tseng CC. Emphysematous pyelonephritis: Clinicoradiological classification, management, prognosis, and pathogenesis. *Arch Intern Med.* 2000;160(6):797–805.
2. Falagas ME, Alexiou VG, Giannopoulou KP, et al. Risk factors for mortality in patients with emphysematous pyelonephritis: A meta-analysis. *J Urol.* 2007;178:880–885.
3. Lin YC, Lin YC, Lin HD, et al. Risk factors of renal failure and severe complications in patients with emphysematous pyelonephritis—a single-center 15-year experience. *Am J Med Sci.* 2012;343(3):186–191.
4. Somani BK, Nabi G, Thorpe P, et al. Is percutaneous drainage the new gold standard in the management of emphysematous pyelonephritis? Evidence from a systematic review. *J Urol.* 2008;179:1844–1849.
5. Chen MT, Huang CN, Chou YH, et al. Percutaneous drainage in the treatment of emphysematous pyelonephritis: 10-year experience. *J Urol.* 1997;157:1569–1573.

ADDITIONAL READING

- Aswathaman K, Gopalakrishnan G, Gnanaraj L, et al. Emphysematous pyelonephritis: Outcome of conservative management. *Urology.* 2008;71(6):1007–1009.
- Shokeir AA, El-Azab M, Mohsen T, et al. Emphysematous pyelonephritis: A 15-year experience with 20 cases. *Urology.* 1997;49: 343–346.
- Ubee SS, McGlynn L, Fordham M. Emphysematous pyelonephritis. *BJU Int.* 2011;107(9):1474–1478.

See Also (Topic, Algorithm, Media)

- Diabetes Mellitus, Urologic Considerations
- Pyelonephritis, Acute, Adult
- Pyelonephritis, Chronic
- Pyelonephritis, Xanthogranulomatous
- Pyelonephritis, Emphysematous Image ☼
- Urosepsis
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Complex, Adult

CODES

ICD9

- 250.40 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
- 590.10 Acute pyelonephritis without lesion of renal medullary necrosis
- 599.60 Urinary obstruction, unspecified

ICD10

- E11.21 Type 2 diabetes mellitus with diabetic nephropathy
- N10 Acute tubulo-interstitial nephritis
- N13.9 Obstructive and reflux uropathy, unspecified

CLINICAL/SURGICAL PEARLS

- Must have high index of suspicion to diagnose this rare, potentially life-threatening condition promptly.
- Diagnosis made radiographically (CT most sensitive and specific).
- Outcomes most optimal with combination of fluid resuscitation, systemic antibiotics, and percutaneous drainage (with nephrectomy when indicated).

PYELONEPHRITIS, XANTHOGRANULOMATOUS

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BASICS

DESCRIPTION

- Xanthogranulomatous pyelonephritis (XGP) is an uncommon chronic destructive granulomatous process of renal parenchyma in association with long-term urinary tract obstruction and infection
- Associated obstruction, stones
- Diffuse renal destruction with nonfunctioning kidney
- Local mass formation sometimes confused with malignancy

EPIDEMIOLOGY

Incidence

- Rare, occurring in 0.5–1.4% of patients with renal inflammatory disorders (1, 2)
- Female to male (3:1)
- Peak incidence in 5th–7th decade
- Reported in children as young as 6 mo
- Left = right

Prevalence

N/A

RISK FACTORS

- Diabetes
- History of stones
- History of UTIs

Genetics

N/A

PATHOPHYSIOLOGY

- Stones
- Obstruction
- Infection
- Proteus mirabilis is most common organism with *Escherichia coli* secondary.

ASSOCIATED CONDITIONS

- Diabetes (3)
- Renal calculi, including staghorn (35%)
- Immunosuppression

GENERAL PREVENTION

Adequate treatment and follow-up of known UTIs

DIAGNOSIS

HISTORY

- Nonspecific signs
- Fever, chills, flank pain, fatigue, anorexia
- Persistent bacteriuria even after antibiotic therapy
- ~1/3 of XGP patients have a history of stones
- 100% found to have stones at treatment
- Diabetes common

PHYSICAL EXAM

- Fever
- Flank tenderness
- Palpable flank mass
- Rarely elevated BP
- Weight loss
- Less commonly hematuria

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Anemia 71%
- Leukocytosis 62%
- Pyuria 81%
- Urine culture: Proteus and *E. coli* are most common
  - Mixed urine cultures occur in 10% of XGP patients
- Liver enzymes abnormal in as many as ½ of XGP patients

Imaging

- CT is the 1st-choice imaging study (4,5)
  - Demonstrates stones and hydronephrosis
  - Seen multiple renal calculi or staghorn calculi
  - Shows enlarged kidney with mass, usually diffused
  - Renal parenchyma replaced with multiple fluid-filled cavities and extension of inflammatory mass to perinephric spaces
- IV urogram shows nonvisualization in 30–80% of patients
  - Stone visible in 30–80%
  - Cannot distinguish renal mass from neoplasm
- Renal ultrasound demonstrates enlargement of the kidney
  - Hydronephrosis
  - Echogenic focus of the calculus
  - Multiple anechoic areas of parenchyma
- MRI provides little additional information
- Functional renal scans can evaluate differential renal function and may confirm nonfunction of the involved kidney

ALERT

XGP may not be distinguished clinically or radiographically from renal cell carcinoma.

Diagnostic Procedures/Surgery

Diagnosis is made on the basis of clinical suspicion and radiographic imaging studies

Pathologic Findings

- Diffuse involvement of the entire kidney occurs in 80 + % of cases
- Segmental involvement is much less common
- XGP commonly extends beyond the kidney and mass
  - Fistulae, pyelocutaneous and ureterocutaneous have been noted
- Gross findings:
  - Massively enlarged kidney
  - Hydronephrosis
  - Obstructing stones
  - Pus-filled calyces and parenchymal abscesses
  - Yellow nodules surrounding the calyces
- Microscopic findings:
  - Thin cortex with extension of inflammatory response beyond kidney
  - Lipid-laden macrophages (xanthoma cells) mixed with lymphocytes, plasma cells, and giant cells form sheets around the calyces and parenchymal abscesses, show grossly as yellow nodules
  - Mass may resemble a renal cell carcinoma with hemorrhage, necrosis and yellow appearance in gross sectioning
  - Associated rare neoplasms have been reported with XGP

DIFFERENTIAL DIAGNOSIS

- Renal tumor
- Pyelonephrosis
- Renal abscess
- Renal lymphoma
- TB

TREATMENT

GENERAL MEASURES

- Antibiotics, culture specific if possible continued until urine cultures are negative
- Usually managed by nephrectomy
- Partial nephrectomy with rare segmental cases
- Even less, reports of endoscopic treatment with stone removal, drainage continued antibiotics
- In cases of nephrectomy or partial nephrectomy, tissue culture should be used to guide antibiotic therapy

MEDICATION

First Line

- Broad-spectrum antibiotics pending urine culture, such as ampicillin 1 g q8h and an aminoglycoside (ie, gentamicin 5 mg/kg q24h) are usually effective until culture-specific antibiotics can be initiated.

- Negative urine cultures are common, and tissue cultures taken at the time of surgery may be necessary to identify the offending organism.
- Some recommend continuing oral antibiotics for up to 1 wk following nephrectomy.

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Nephrectomy is the most common treatment
  – Diffuse inflammatory process
  – Nonfunctioning kidney
  – Concern for malignancy
  – Inflammatory reaction, nephrectomy can be technically difficult
- Partial nephrectomy in rare cases of segmental XGP
- Mechanical and antibiotic bowel prep is performed since XGP may involve any adjacent organs or tissues
  – Drains should be placed in renal bed
- Laparoscopic nephrectomy has been shown to be safe without increasing complications but, again difficult (6)

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
Percutaneous drainage with antibiotics (7)

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Preservation of renal function related to the function of the contralateral kidney
- Recurrence in the contralateral kidney is very rare
- Chance of recurrent stones is high

COMPLICATIONS
- Postoperative respiratory complications
- Wound infection
- An injury to adjacent organs can occur during nephrectomy
- Major vascular injury related to the inflammatory process
- Fistulas or abscesses postoperatively require drainage and antibiotic therapy
- Renal insufficiency related to the function of the contralateral kidney
- Recurrent stone formation

FOLLOW-UP
Patient Monitoring
- Urinalysis and urine culture

- Serum creatinine, CBC, liver enzymes repeated to follow for normalization
- Further radiographic studies depending upon the histopathology of the kidney specimen

Patient Resources
N/A

REFERENCES

1. Kim SW, Yoon BI, Ha US, et al. Xanthogranulomatous pyelonephritis. Clinical experience with 21 cases. *J Infect Chemother*. 2013;19(6):1221–1224.
2. Korkes F, Favoretto RL, Bróglio M, et al. Xanthogranulomatous pyelonephritis. Clinical experience with 41 cases. *Urology*. 2008;71:178–180.
3. Dwivedi US, Goyal NK, Saxena V, et al. Xanthogranulomatous pyelonephritis: Our experience with review of published reports. *ANZ J Surg*. 2006;76:1007–1009.
4. Loffroy R, Guiu B, Watfa J, et al. Xanthogranulomatous pyelonephritis in adults: Clinical and radiological findings in diffuse and focal forms. *Clin Radiol*. 2007;52:884–890.
5. Zorzos I, Moutzouris V, Korakianitis G, et al. Analysis of 39 cases of xanthogranulomatous pyelonephritis with emphasis on CT findings. *Scand J Urol Nephrol*. 2003;37:342–347.
6. Shah KJ, Ganpule AP, Kurien A, et al. Laparoscopic vs. open nephrectomy for xanthogranulomatous pyelonephritis: An outcome analysis. *Indian J Urol*. 2011;27:470–474.
7. Ergun T, Akin A, Lakadamyali H. Stage III xanthogranulomatous pyelonephritis treated with antibiotic therapy and percutaneous drainage. *JBR-BTR*. 2011;94(4):209–211.

ADDITIONAL READING

Goyal S, Gupta M, Goyal R. Xanthogranulomatous pyelonephritis: A rare entity. *N Am J Med Sci*. 2011;3(5):249–250.

See Also (Topic, Algorithm, Media)
- Pyelonephritis, Acute, Adult
- Pyelonephritis, Acute, Pediatric
- Pyelonephritis, Xanthogranulomatous Image ☼
- Renal Mass
- Urinary Tract Infection (UTI), Complicated, Adult
- Urolithiasis, Renal

CODES

ICD9
- 041.6 Proteus (mirabilis) (morganii) infection in conditions classified elsewhere and of unspecified site
- 590.00 Chronic pyelonephritis without lesion of renal medullary necrosis
- 599.60 Urinary obstruction, unspecified

ICD10
- B96.4 Proteus (mirabilis) (morganii) causing dis classd elswhr
- N11.8 Other chronic tubulo-interstitial nephritis

- N13.9 Obstructive and reflux uropathy, unspecified

CLINICAL/SURGICAL PEARLS

- Be suspicious in patients with fever, flank pain, and weight loss.
- Persistent UTI with adequate treatment is a warning.
- CT scan for diagnosis and extent of disease.
- XGP is primarily a surgically managed disease usually by nephrectomy with antibiotics critical to the management of this condition.
- Usually unilateral and frequently confused clinically and radiographically with renal cell carcinoma.

PYONEPHROSIS

Anthony J. Tracey, MD, MPH
Raju Thomas, MD, MHA, FACS

BASICS

DESCRIPTION

- Pyonephrosis is a collection of purulent material in the renal collection system
- Typically resulting from an underlying obstruction within the upper urinary tract (2)
  - With concomitant urinary tract infection
- Considered a surgical emergency with drainage of obstructed collecting system necessary (1)

EPIDEMIOLOGY

Incidence

- True incidence is unknown
- Increased in patients with upper urinary tract obstruction

Prevalence

See above

RISK FACTORS

- Upper urinary tract obstruction
- History of prior urologic instrumentation
- Immunocompromised patient
- Diabetes mellitus
- Chronic UTIs

Genetics

None

PATHOPHYSIOLOGY

- Etiologies of obstruction (1)
  - Stones and staghorn calculi: In as many as 75% of patients
  - Mucinous adenocarcinoma of the renal pelvis
  - Pregnancy
  - Fungus balls
  - Metastatic retroperitoneal fibrosis—eg, renal tumors, testicular cancer, colon cancer
  - Obstructing transitional cell carcinoma
  - Ureteropelvic junction obstruction (UPJO)
  - Obstructing ureterocele
  - Ureterovesical junction obstruction
  - Chronic stasis of urine and hydronephrosis secondary to neurogenic bladder
  - Ureteral strictures
  - Papillary necrosis
  - Tuberculosis
  - Duplicated kidneys with obstructive components

  – Ectopic ureter with ureterocele
  – Neurogenic bladder
• Infectious agents (in decreasing order of incidence) (1)
  – *Escherichia coli*
  – *Enterococcus* species
  – *Candida* species and other fungal infections
  – *Enterobacter* species
  – *Klebsiella* species
  – *Proteus* species
  – *Pseudomonas* species
  – *Bacteroides* species
  – *Staphylococcus* species
  – Methicillin-resistant *Staphylococcus aureus (MRSA)*
  – *Salmonella* species
  – Tuberculosis (causes both infection and strictures) (2)

ASSOCIATED CONDITIONS
• Nephrolithiasis (most common) (1)
• UPJO
• Urothelial carcinoma (UC) of the upper tracts
• Pyelonephritis
• Emphysematous pyelonephritis/pyelitis
• Xanthogranulomatous pyelonephritis (XGP)
• Ureteral stricture (2)

GENERAL PREVENTION
• Relief of underlying urologic obstruction
• Proper medical management of immunosuppression
• Identification of any anatomic urologic abnormality (ie, horseshoe kidney)

ALERT
Patients may rapidly decline clinically and become septic.

DIAGNOSIS
HISTORY
• Fever
• Flank pain
• Clinical evidence of UTI

PHYSICAL EXAM
CVA tenderness with or without palpable abdominal mass (hydronephrotic kidney)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
• Pyuria
• Elevated white count (less specific)
• Bacteriuria (less specific)

- Urine culture of obstructed system
- Elevated C-reactive protein
  - 1 study showed CRP levels >28 mg/L with flank pain a reliable indication for emergent decompression (1)

Imaging

- CT scan with IV contrast (2)
  - Diagnostic criteria for pyonephrosis
    - Increased wall thickness of the renal pelvis ≥2 mm
    - The presence of renal pelvic contents and debris
    - Parenchymal and perirenal findings, such as perirenal fat stranding (3)
- Ultrasonography (US)
  - Sensitivity of renal US for differentiating hydronephrosis from pyonephrosis is 90%, and the specificity is 97% (1)
    - Debris
    - Low-level echogenic foci
    - Hydronephrosis
- MRI
  - Use increasing for inflammatory disorders of the GU tract
    - Diffusion MRI shows hyperintense collecting system for pyonephrosis and hypointense signal for simple hydronephrosis
    - May be useful for patients with impaired renal function (3)
- Renal nuclear scan
  - Useful in assessing renal function after decompression and to evaluate if involved renal unit is salvageable
  - Not helpful in the immediate diagnostic period

Diagnostic Procedures/Surgery

- Once pyonephrosis has been diagnosed, there are two possible initial interventions:
  - Antegrade nephrostomy tube placement
  - Retrograde ureteral stent placement

Pathologic Findings

- Aspiration of obstructed system will usually show:
  - WBCs
  - Bacteria or fungus
  - Sloughed urothelial cells

DIFFERENTIAL DIAGNOSIS

- Nephrolithiasis/urolithiasis
- Xanthogranulomatous pyelonephritis
- Ureteropelvic junction obstruction (UPJO)
- Urothelial carcinoma (UC) of upper tracts
- Ureteral stricture
- Extrinsic obstruction with hydronephrosis (malignancy, retroperitoneal fibrosis)

TREATMENT

GENERAL MEASURES

- Drainage of obstructed collecting system is the mainstay of treatment
  - Antegrade nephrostomy tube placement
    - Indicated in the clinically unstable patient
    - Best for maximal decompression
  - Retrograde ureteral stent placement
    - Indicated in the stable patient able to tolerate general anesthesia
    - Relatively contraindicated in setting of a large upper tract stone that will eventually need percutaneous therapy or fungus ball
- Treatment of source obstruction:
  - Once collecting system has been decompressed and appropriate antibiotic/antifungal therapy has been given for 2 wk
  - May include endoscopic, percutaneous, transurethral, laparoscopic, robotic, extracorporeal, or open approaches
  - Depends on the nature of obstruction (ie, stone, stricture) (1)
  - Clinical feasibility of intervention

MEDICATION

First Line

- Broad spectrum intravenous antibiotics (ie, piperacillin and tazobactam, gentamicin, and ampicillin) and antifungals if clinically indicated for funguria
  - Antibiotics can be focused once cultures result

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Indication for nephrectomy is controversial
  - May be indicated if source of infection is not found
  - Help to exclude malignant etiology of obstruction
  - Lack of response to percutaneous drainage and IV antibiotics/antifungals
  - Poorly functioning kidney

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Good in patients who receive prompt diagnosis and therapy

- Most patients will improve 24–48 hr after drainage of obstructed renal collecting system
- Recovery of renal function is rapid

COMPLICATIONS

- Sepsis is the most common complication of delayed treatment
- Other complications of delayed treatment include:
  - Rupture of pyonephrotic kidney resulting in:
    - Generalized peritonitis
    - Renocolic fistula
    - Renoduodenal fistula
    - Renocutaneous fistula
    - Splenic rupture
  - Rare complications:
    - Pneumoperitoneum
    - Renal vein thrombosis
    - Psoas abscess
    - Perinephric abscess
    - Rhabdomyolysis
  - Loss of renal function
- Complications from nephrostomy tube:
  - Blood transfusions
  - Hematoma
  - Nephrostomy tube replacement/revision
- Increased risk of infection if nephrectomy is not performed when indicated.

FOLLOW-UP

Patient Monitoring

- Treatment of underlying obstruction (ie, calculus, stricture, malignancy)
- Treatment and control of any predisposition to infection (ie, DM, HIV/AIDS, neurogenic bladder)

Patient Resources

- http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/
- http://www.medicinenet.com/kidney_stone/article.htm
- http://www.mayoclinic.com/health/kidney-stones/DS00282

REFERENCES

1. Peterson AC. “Pyonephrosis” Medscape Article 2013; emedicine.medscape.com/article/440548
2. Raynor MC, Carson CC. Urologic issues for the internist urinary infections in men. *Med Clin North Am.* 2011;95:43–54.
3. Hammond NA, et al. Genitourinary imaging infectious and inflammatory diseases of the kidney. *Rad Clin North Am.* 2012;50:259–270.

ADDITIONAL READING

Schaeffer AJ, Schaeffer EM. Infections of the urinary tract. In: Wein AJ, et al. eds. *Campbell-*

Walsh Urology. 10th ed. Philadelphia: Saunders; 2012.

See Also (Topic, Algorithm, Media)
- Fungal Infections, Genitourinary
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Pyonephrosis Image ☼
- Ureter, Obstruction
- Urosepsis
- Urolithiasis, Staghorn

CODES

ICD9
- 590.80 Pyelonephritis, unspecified
- 593.89 Other specified disorders of kidney and ureter
- 599.0 Urinary tract infection, site not specified

ICD10
- N13.6 Pyonephrosis
- N28.89 Other specified disorders of kidney and ureter
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS
- Patients with pyonephrosis may be asymptomatic or present with a picture of an abscess with fever and chills.
- Urolithiasis, staghorn calculi, and fungus balls are the most common clinical causes of pyonephrosis.

PYURIA

Christina Carpenter, MD
Mark L. Jordan, MD, FACS

BASICS

DESCRIPTION

- Presence of WBCs in the urine
- Normal #WBCs in a urine specimen
  - Men ≤ 2 WBC/hpf
  - Women ≤ 5 WBC/hpf
- When seen with bacteriuria, suggests inflammatory response of urothelium (ie, infection)
- When seen without bacteriuria (sterile pyuria), raises suspicion for tuberculosis, partially treated UTI, stones, and/or malignancy

EPIDEMIOLOGY

When seen in a voided urine specimen, has an 80–95% sensitivity for detecting patients with a urinary tract infection (UTI)

RISK FACTORS

- Urolithiasis
- Previous UTI
- Sexually transmitted disease
- Malignancy

PATHOPHYSIOLOGY

- Clean-catch midstream urine may contain contaminants (bacteria, squamous epithelial cells)
- Significant pyuria (at least 10 WBCs/mm^3) is uncommonly seen in patients without true infection

ALERT

60% of elderly women have significant pyuria without associated bacteriuria (1)[A].

- Can be caused by bacteria in the urinary tract provoking an inflammatory response
- Bacteria can colonize the genitourinary system in a retrograde fashion
- Certain bacteria are more frequently the cause of UTIs as they are more efficient at adhering to the mucosal cells of the urinary tract (eg, *Escherichia coli*)

ASSOCIATED CONDITIONS

- Bacteriuria
- UTI
- Pyelonephritis
- Nephrolithiasis

GENERAL PREVENTION

- Proper toileting habits
- Complete bladder emptying

- Adequate fluid intake (stone prevention)

DIAGNOSIS

HISTORY

- Common symptoms: Dysuria, frequency, urgency, malaise
- Fever (more common with upper tract infection)
- Hematuria (gross)
  - Occasional
  - More common in females
  - Rare in children
- Atypical presentations
  - Young patients
    - Difficulty with toilet training, urgency, incontinence
    - Abdominal discomfort, failure to thrive, fever, vomiting, jaundice
  - Elderly
    - Incontinence, fevers, frequency, urgency
    - May be asymptomatic
- History of recurrent childhood fevers—may imply frequent UTIs and potential congenital anomalies
- History of UTIs among female family members

PHYSICAL EXAM

- Suprapubic tenderness
- Costovertebral angle tenderness
- Fever
- Children—may have abdominal discomfort, tenderness, and/or distention

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Dipstick
  - Best screening tool
  - Leukocyte esterase (LE)
    - Produced by granulocytes that catalyze the hydrolysis of an indoxylcarbonic acid ester to indoxyl, which reacts with a diazonium salt to produce a purple color on the reagent strip
    - 75–96% sensitive for a culture-positive UTI (2)[A]
    - Sterile pyuria
      - Produces positive LE test with negative culture
      - Disease process without bacteriuria
    - Causes of false negatives
      - RBC >10 K/μL
      - Glucose >1 g/dL
      - Albumin >500 mg/dL
      - Formaldehyde
      - Medications: Cephalexin, gentamicin, tetracycline

    - Causes of false positives
        - Specimen contamination
        - Recent instrumentation of GU tract
        - Medications: Imipenem, meropenem, clavulanic acid
  - Presence of nitrites, blood, or protein suggests UTI
- Microscopic analysis—can see crystals and/or bacteria
- Gram stain—can identify type of bacteria
- Culture
  - Clean-catch midstream specimen = most common
  - Catheterized urine—required in situations in which patients are unable to collect specimen (children, incontinent adults, obese population, patients in urinary retention)
  - Segmented urine specimen
    - Sequential voided urine samples aimed to localize infection/inflammation source
    - Stamey test (see Stamey test [Three-glass test, Four-glass tests, Meares-Stamey Test])
- AFB culture—if patient has history of and/or possible exposure to TB
- Rapid in-office microbiology testing
  - 80% accurate for detecting, quantifying, and identifying specific bacteria in urine
  - Usually performed on a fresh unspun sample
- Urine cytology—if malignancy is suspected

Imaging

- Children: Ultrasound, VCUG, radionuclide cystogram, IV pyelogram
- Adult: Indicated only in the setting of suspected pathology, obstruction, stone disease, and/or hematuria
- Sterile pyuria: Imaging to identify source/evaluate cause

Diagnostic Procedures/Surgery

- Localization of bacteria
  - Segmented urine specimen
  - Ureteral catheterization in OR
  - Immunologic/antibody studies
- Isotopic function studies
- Cystogram
- CT: Localization of nidus/abnormality responsible for bacteriuria/pyuria (ie, abscess)
- Cystoscopy—indicated for symptomatic patients with persistent pyuria and negative urine cultures (3)[A]

DIFFERENTIAL DIAGNOSIS

- Specimen contamination
- Cystitis
- Epididymitis
- Pyelonephritis—acute, chronic, emphysematous, tuberculous, xanthogranulomatous
- Genitourinary TB
- Interstitial cystitis
- Interstitial nephritis
- Neoplasm

  – Urothelial carcinoma
  – Renal cell carcinoma
- Prostatitis
- Renal abscess
- Periurethral abscess
- STI/STD
- Renal transplant rejection
- Urethral diverticulum
- Urethritis
- Foreign bodies in GU tract (stents, catheters)
- Urinary tract fistula
- Vulvovaginitis
- Kawasaki disease

TREATMENT

GENERAL MEASURES
- Identify cause of inflammatory response
- Direct treatment at cause of pyuria
- UTI is most commonly the origin

MEDICATION
First Line
- In infection, should be empiric until targeted therapy can be initiated based on culture results (4)
- See “Urinary tract infection (UTI), adult female,” “Urinary tract infection (UTI), adult male” and “Urinary tract infection (UTI), pediatric”

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Correct underlying abnormality
- Treat calculus
- Remove foreign body (eg, ureteral stent)

ADDITIONAL TREATMENT
- Bacteriuria with pyuria is treated as a UTI in children and premenopausal women
- Persistent or recurrent bacteriuria may require prolonged antibiotic treatment followed by chronic low-dose prophylactic antibiosis
- High-risk patients (children with congenital abnormalities, immunocompromised adults) may need chronic suppressive antibiotic treatment
- Postmenopausal women
  – May have chronic pyuria with mild bacteriuria
    - Require treatment only if symptomatic or if associated with complicating factors
- Diabetics, patients with obstructive uropathy, and immunocompromised patients may have additional requirements to address ongoing pyuria adequately

ONGOING CARE

PROGNOSIS

Dependent upon etiology

COMPLICATIONS

- Ascending bacterial infections
- Urosepsis
- Renal failure
- Death

FOLLOW-UP

Patient Monitoring

- Repeat exam 2-wk post-UTI treatment
  - Urinalysis, urine culture
  - Reassess symptoms
- Routine periodic evaluation to check for recurrence of pyuria

Patient Resources

www.UrologyHealth.org

REFERENCES

1. Boscia JA, Kaye D. Asymptomatic bacteriuria in the elderly. *Infect Dis Clin North Am.* 1987;1:893–905.
2. Drekonja DM, Johnson JR. Urinary tract infections. *Prim Care.* 2008;35:345–367.
3. Dielubanza EJ, Schaeffer AJ. Urinary tract infections in women. *Med Clin North Am.* 2011;95:27–41.
4. Schaeffer AJ, Schaeffer EM. Infections of the urinary tract. In: Wein AJ, Kavoussi LR, Novick AC, et al. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2012.

ADDITIONAL READING

- Abrahamian FM, Moran GJ, Talan DA. Urinary tract infections in the emergency department. *Infect Dis Clin North Am.* 2008;22:73–87.
- Lin KW, Brown T. Screening for asymptomatic bacteriuria in adults. *Am Fam Physician.* 2010;81:508.
- Mulvey MA. Adhesion and entry of uropathogenic Escherichia coli. *Cell Microbiol.* 2002;4:257–271.

See Also (Topic, Algorithm, Media)

- Bacteriuria
- Pyelonephritis, Chronic
- Pyelonephritis, Emphysematous
- Pyelonephritis, Xanthogranulomatous
- Prostatitis, Chronic, Bacterial
- Prostatitis, Chronic, Nonbacterial, Inflammatory
- Prostatitis, General

- Pyuria Algorithm
- Pyuria, Image
- Tuberculosis, Genitourinary
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

791.9 Other nonspecific findings on examination of urine

ICD10

N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- Absence of pyuria should lead the clinician to question a diagnosis of UTI.
- Sterile pyuria does not suggest a benign process.
- Persistent symptomatic pyuria requires further workup, ie, cystoscopy, imaging.
- Atypical presentations in children, the elderly, and the immunocompromised require the clinician to maintain a high index of suspicion.

RECTAL INJURY DURING RADICAL PROSTATECTOMY OR RADICAL CYSTECTOMY

Debasish Sundi, MD
Misop Han, MD

BASICS

DESCRIPTION

- Rectal injury is a rare, potential complication of radical prostatectomy or radical cystoprostatectomy, with a reported incidence ranging from 0.1–1.7%
  - Reported for radical prostatectomy: Retropubic perineal, laparoscopic, and robotically assisted laparoscopic approaches
  - Reported for radical cystectomy: Open and robotically assisted approaches
- Intraoperative recognition of the rectal injury is paramount; this will allow primary repair in layers and minimize the chance of subsequent rectourethral fistula
- Occasionally the problem will not be identified until the postoperative period

EPIDEMIOLOGY

Incidence

- The rate of rectal injury during urologic pelvic procedures varies by procedure and approach
- For radical prostatectomy, rectal injury rates are quite low, ranging from 0.1–0.5% (open retropubic, pure laparoscopic, or robot assisted) (1,2)[C]
  - Rectal injury rates are higher for radical cystoprostatectomy (up to 1.7%) (3)[C], and highest for perineal prostatectomy (8–11%) (4)[C]

Prevalence

Extrapolating from the number of procedures performed annually in US, the prevalence of rectal injury for radical prostatectomy ranges from 80–400 cases per yr, and for radical cystectomy, up to 150 cases per yr

RISK FACTORS

History of pelvic radiation therapy or prior pelvic surgery

Genetics

N/A

PATHOPHYSIOLOGY

N/A

ASSOCIATED CONDITIONS

- Prior pelvic radiation or surgical procedures may increase the risk of rectal injury
- Extensive transurethral resection of bladder floor for urothelial carcinoma
- Inflammatory bowel disease
- Locally advanced malignancy

GENERAL PREVENTION

- Adequate intraoperative hemostasis to aid visualization

- Bowel preparation has not been proven to reduce the risk of intraoperative bowel injury but may limit contamination in the event of an injury
- Placement of a rectal tube at the start of the procedure may aid in the identification of the rectal wall in difficult cases (ie, salvage prostatectomy following radiation)
- Careful identification of the anterior and posterior layers of Denonvilliers fascia will aid in avoiding rectal injury

DIAGNOSIS

HISTORY

- After removal of the specimen (open surgery), inspection of the surgical bed using posterior traction to efface folds of tissue will typically reveal a rectal injury by direct visualization
  - Obtaining good hemostasis will aid visualization
  - Copious irrigation of the pelvis with sterile saline may also reveal air bubbles emanating from the rectal vault (2)[C]
- Symptoms may include abdominal or pelvic pain; nausea and vomiting may also be present

PHYSICAL EXAM

Postoperative manifestations may include exam findings that may include tenderness to palpation, fever, tachycardia, hypotension, ileus (2)[C]

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Acute injury may not manifest any lab abnormalities
- An unrecognized postoperative injury may demonstrate leukocytosis

Imaging

- Postoperatively CT ± cystourethrography
  - Free air in pelvis and/or peritoneum
  - Contrast communicating between rectum and bladder/urethra

Diagnostic Procedures/Surgery

- After removal of the specimen (laparoscopic or robotic surgery) from the prostatic fossa, a suspected rectal injury can be confirmed by flooding the pelvis with saline irrigant and gently insufflating the rectum with air injected via a Foley catheter
  - A rectal enterotomy will be evident by air bubbling through the irrigant

Pathologic Findings

A through-and-through injury will involve both the rectal serosa and mucosa

DIFFERENTIAL DIAGNOSIS

- Intraoperative differential diagnosis is limited
- Postoperative differential includes:
  - Small bowel or large perforation (iatrogenic)
  - Colonic perforation secondary to pathologic distension such as in colonic pseudoobstruction, or Ogilvie syndrome
  - Pelvic abscess

TREATMENT

GENERAL MEASURES

- When a rectal injury is diagnosed postoperatively, management depends on the patient's clinical picture
- Patients who are minimally symptomatic and have a small injury radiographically may be initially managed conservatively by indwelling urethral catheter, with reassessment by cystogram after 2–3 mo (5)[C]
- The GI tracts of patients who are symptomatic, septic, or have a history of prior pelvic radiation should be diverted with an end colostomy (5)[C]
  - These patients' GI tracts can be brought back in continuity if a cystogram and/or Gastrografin enema are negative in 2–3 mo. If these patients have persistent fistulas, they should be surgically repaired with a transrectal advancement flap (2)[C].

MEDICATION

First Line

- 7–14 days of antimicrobial therapy (4)[C]
  - Antibiotic regimen should cover both gram-negatives and anaerobes (such as ciprofloxacin and metronidazole)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- When a rectal injury is diagnosed intraoperatively, it should be repaired immediately, closing the rectal mucosa and serosa in separate layers
  - Suture choice includes mucosal layer with 3-0 chromic and the serosa with 3-0 silk or other suitable alternatives (2)
  - An additional flap of vascularized tissue (omentum or peritoneum) should be interposed between the rectal repair and the bladder/urethra. Immediate repair minimizes the risk of subsequent rectourethral fistula.
    - If a rectourethral fistula does form in spite of immediate repair, management options are conservative treatment via Foley catheterization or surgical repair via diverting colostomy and, if necessary, a transrectal advancement flap (6)[C]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Among patients undergoing immediate intraoperative repair, there is a 12.5% incidence of

subsequent rectourethral fistula (6)[C]
  – Rectal injuries of increasing length are associated with a higher risk of rectourethral fistulae, as are those recognized and repaired in delayed fashion

COMPLICATIONS

- Need for temporary colostomy diversion
- Rectourethral fistula
- With delayed rectoanastomotic fistula after radical prostatectomy: incontinence (7)
- Sepsis

FOLLOW-UP

Patient Monitoring

- After repair, routine monitoring on a regular surgical floor with daily labs is appropriate
  – Prior to routine Foley catheter removal after radical prostatectomy, perform cystogram to rule out fistula at 14 days after surgery
    - If rectourethral fistula is demonstrated, continue Foley catheter, as resolution of fistula with period of catheterization up to 9 wk has been demonstrated

Patient Resources

None

REFERENCES

1. Lepor H, Nieder AM, Ferrandino MN. Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. *J Urol*. 2001;166(5):1729–1733.
2. Evans CP. Complications of cystectomy and partial cystectomy Chapter 32. In: *Complications of Urologic Surgery*. 3rd ed. Philadelphia, PA: Saunders; 2001.
3. Lawrentschuk N, Colombo R, Hakenberg OW, et al. Prevention and management of complications following radical cystectomy for bladder cancer. *Eur Urol*. 2010;57(6):983–1001.
4. Lassen PM, Kearse WS Jr. Rectal injuries during radical perineal prostatectomy. *Urology*. 1995;77(4):266–269.
5. Borland RN, Walsh PC. The management of rectal injury during radical retropubic prostatectomy. *J Urol*. 1992;147(3):163–166.
6. Roberts WB, Tseng K, Walsh PC, et al. Critical appraisal of management of rectal injury during radical prostatectomy. *Urology*. 2010;76(5):1088–1091.
7. Pfalzgraf D, Isbarn H, Reiss P, et al. Outcomes after recto-anastomosis fistula repair in patients who underwent radical prostatectomy for prostate cancer. *BJU Int*. 2014;113(4):568–573.

ADDITIONAL READING

- Blumberg JM, Lesser T, Tran VQ, et al. Management of rectal injuries sustained during laparoscopic radical prostatectomy. *Urology*. 2009;73(1):163–166.
- Kheterpal E, Bhandari A, Siddiqui S, et al. Management of rectal injury during robotic radical prostatectomy. *Urology*. 2011;77(4):976–979.
- Sugihara T, Yasunaga H, Horiguchi H, et al. Does mechanical bowel preparation ameliorate

damage from rectal injury in radical prostatectomy? Analysis of 151 rectal injury cases. *Int J Urol.* 2014;21(6):566–570.

See Also (Topic, Algorithm, Media)

- Fistula, Enterovesical
- Fistula, Rectourethral

CODES

ICD9

- 599.1 Urethral fistula
- 863.45 Injury to rectum, without mention of open wound into cavity
- 998.2 Accidental puncture or laceration during a procedure, not elsewhere classified

ICD10

- K91.72 Acc pnctr & lac of a dgstv sys org during oth procedure
- N36.0 Urethral fistula
- S36.60XA Unspecified injury of rectum, initial encounter

CLINICAL/SURGICAL PEARLS

- Rectal injury during radical urologic pelvic surgery is a rare but serious complication.
- This injury can occur during open, laparoscopic and robotically assisted laparoscopic pelvic surgery.
- When recognized intraoperatively, immediate primary repair assures the best outcomes.
- When immediate repair is not possible or contraindicated, the patient may be temporized with a diverting colostomy until the rectal injury heals and the GI tract can be brought back into continuity.
- Rectourethral fistula is a delayed complication of rectal injury repair, the chance of which can be minimized with immediate recognition and repair of rectal injury.

RENAL AND PERIRENAL ABSCESS

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BASICS

DESCRIPTION

- Renal abscess/carbuncle:
  - Collection of purulent material confined to the renal parenchyma
- Perirenal abscess:
  - Results from extension of an acute cortical abscess into the perinephric space; confined by Gerota fascia
- Pararenal/perinephric abscess:
  - Results from the rupture of a perinephric abscess through Gerota fascia into the pararenal space

EPIDEMIOLOGY

Incidence

Perinephric and renal abscesses are uncommon but potentially lethal complications of UTI

Prevalence

- 2/3 of gram-negative abscesses are associated with renal calculi or kidneys with poor function
- Pregnant women with untreated bacteriuria are associated with a higher incidence of pyelonephritis and subsequent diagnosis of abscess
- Renal infection is among the most common sites for extrapulmonary disease in patients with TB

RISK FACTORS

Diabetes mellitus, polycystic kidney disease, hemodialysis, neurogenic bladder, IV drug users, tuberculosis, recurrent urinary tract infection and/or pyelonephritis, nephrolithiasis, vesicoureteral reflux, ureteropelvic junction obstruction or other source of obstruction, any immunocompromised state

Genetics

N/A

PATHOPHYSIOLOGY

- Gram-negative organisms have been implicated in the majority of adults with renal abscesses (*Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus aureus*) account for the majority of infections (in descending order of occurrence) (1)
- Hematogenous renal seeding by gram-negative organisms may occur, but this is not likely to be the primary pathway for gram-negative abscess formation
- Hematogenous renal seeding: Skin infection with gram-positive organisms, IV drug abuse, immunocompromised status
- Ascending infection associated with tubular obstruction from prior infections, vesicoureteral

reflux, or calculi appears to be the primary pathway for the establishment of gram-negative abscesses

ASSOCIATED CONDITIONS
See “Risk Factors" above

GENERAL PREVENTION
Increased clinical suspicion, prompt recognition, and treatment of infection, especially in the face of obstruction in high-risk patients

DIAGNOSIS

HISTORY
- Significant chronic or acute illnesses including diabetes, neurogenic bladder dysfunction, chronic renal failure, hemodialysis, and polycystic renal disease
- Renal calculi
- IV drug abuse
  - Gram-positive source of infection 1–8 wk before the onset of urinary tract symptoms
    - Preceding infection can occur in any area of the body (eg, skin lesions, dental infections)
- Patients with UTI and abdominal or flank mass
- Persistent fever with suspected genitourinary source after 3–5 days of antimicrobial therapy

PHYSICAL EXAM
- Elevated temperature
- CVA or flank tenderness
- Abdominal and/or flank mass
- Distended or palpable bladder
- Look for skin carbuncles or dermatologic evidence of IV drug abuse
- Heart murmurs

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum creatinine:
  - Variable findings, dependent on concurrent obstruction and underlying renal dysfunction
- CBC:
  - Patients typically have marked leukocytosis
- Urine analysis:
  - Pyuria and bacteria often present, although pyuria/bacteriuria may not be evident unless the abscess communicates with the collecting system
  - Sterile pyuria often seen with TB
- Urine culture:
  - When abscesses contain gram-negative organisms, urine culture often demonstrates the same organism isolated from the abscess
  - Since gram-positive organisms are most commonly blood borne, urine cultures in these cases typically show no growth or a microorganism different from that isolated from the abscess
  - Catheterized urine collection recommended for female patients

- Blood cultures:
  - Gram-negative organisms are most commonly cultured
  - Gram-positive organisms are not routinely similar to those cultured from abscess

Imaging

- Differentiation between early renal abscess and acute pyelonephritis is difficult due to small size
- Abdominal CT:
  - Diagnostic procedure of choice
  - Can often delineate the route of spread of infection into surrounding tissues
  - Abscesses are characteristically well defined both before and after contrast agent enhancement
  - Acute findings include renal enlargement and focal, rounded areas of decreased attenuation
  - Chronic findings include obliteration of adjacent tissue planes, thickening of Gerota (perinephric) fascia, a round or oval parenchymal mass of low attenuation, and a surrounding inflammatory wall of slightly higher attenuation that forms a ring when the scan is enhanced with contrast material (ring sign)
  - See Figure 1, Renal Abscess
- IV urography (if performed)
  - Abnormal in up to 80% of patients, although findings often are nonspecific
  - Generalized enlargement of involved renal unit with distortion of renal contour and collecting system
  - Absence of psoas shadow on affected side
  - Bubbles of extraluminal gas can be seen surrounding the kidney in large perinephric abscesses
- Abdominal US:
  - Quickest and least expensive diagnostic imaging study
  - Common findings include an echo-free or low-echodensity space-occupying lesion with increased transmission, which is poorly marginated during the acute phase
  - Well-defined discrete lesion during chronic stages, which is difficult to distinguish from a renal mass

ALERT
Evidence of air within renal parenchyma tissue is diagnostic for emphysematous pyelonephritis which may require urgent surgical intervention. See Section I: Emphysematous pyelonephritis.

Diagnostic Procedures/Surgery

CT- or US-guided needle aspiration may be necessary to differentiate an abscess from a hypervascular tumor; aspirated material can be collected for culture to guide appropriate antimicrobial therapy. A percutaneous drain may be left in place and clinical course can be evaluated.

Pathologic Findings

Abscess fluid will demonstrate neutrophils and gram stain will reveal bacteria

DIFFERENTIAL DIAGNOSIS

- Pyelonephritis (2)
- Pyonephrosis
- Xanthogranulomatous pyelonephritis
- Emphysematous pyelonephritis
- Renal TB
- Bowel perforation with retroperitoneal spread of infection

TREATMENT

GENERAL MEASURES (3,4)

- Hospitalization with initiation of IV antibiotics and fluid resuscitation.
- Suspected pyelonephritis treated with antibiotics for 48–72 hr without significant improvement requires radiographic evaluation to rule out obstruction and/or abscess formation.
- Recent evidence indicates that for very small (< 3-cm abscesses), careful observation and IV-tailored antimicrobial agents may obviate surgical procedures.
- Abscesses 3–5 cm in diameter and smaller abscesses in immunocompromised hosts or those that do not respond to antimicrobial therapy should be drained percutaneously.
- Surgical drainage, however, currently remains the procedure of choice for most renal abscesses > 5 cm in diameter or if perirenal extension of abscess occurs.
- Obstruction, if present, must be relieved.

MEDICATION

First Line

- Antibiotic therapy: May prevent surgical intervention unless abscess involves perinephric space.
- Initiate empiric treatment with fluid resuscitation and broad-spectrum IV antibiotics.
  - 3rd-generation cephalosporins
    - Cefotaxime—1–2 mg IV/Q8–12h
    - Ceftriaxone—1–2 mg IV/Q24h
    - Ceftazidime—1 g IV/Q8–12h
  - Aminoglycosides
    - Gentamicin—1–1.7 mg/kg IV/Q8h
    - Amikacin—7.5 mg/kg IV/Q12h
    - Tobramycin—1–1.7 mg/kg IV/Q8h
  - Antipseudomonal penicillins
    - Piperacillin/Tazobactam—3.375 g IV/Q6h
    - Ticarcillin/Clavulanate—3.1 g IV/Q4–6h
- IV antibiotics until afebrile for 24–48 hr, switch to PO for at least 2 wk based on culture.
- Adjust dose for renal function.

Second Line

- For a suspected hematogenous source, expand coverage to include penicillin-resistant Staphylococcus.
  - Vancomycin—1 g IV/Q12h

SURGERY/OTHER PROCEDURES

- Standard treatment for renal abscesses >5 cm or those that fail to respond to percutaneous drainage and IV antibiotic therapy has been rapid incision and drainage.
- Relief of coexisting obstruction is mandatory.
- Primary treatment remains drainage for all perinephric abscesses.
- Nephrectomy may be required for adequate treatment if medical therapy/incision and drainage fails.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

CT- or US-guided placement of percutaneous drains with concurrent IV antibiotic therapy is currently an accepted method of treatment for abscesses 3–5 cm in size and smaller abscesses in immunocompromised patients who fail to respond to medical therapy.

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Perinephric abscess is historically associated with mortality rates approaching 39–50%.
- Recent series with prompt implementation of IV antibiotics and subsequent percutaneous or surgical drainage report mortality rates of 5–12%.

COMPLICATIONS

- Delay in diagnosis is associated with higher mortality rate.
- Delay in diagnosis and treatment is associated with loss of renal function and, in rare circumstances, genitourinary fistulas to the pleura, colon, skin, etc.

FOLLOW-UP

Patient Monitoring

- Address the underlying medical conditions to prevent recurrent infections.
- Repeat radiographic studies to confirm complete resolution.
- Extended antibiotic therapy is often required.

Patient Resources

- Medline Patient Information:
  - http://www.nlm.nih.gov/medlineplus/ency/article/001274.htm
- Urology Care Foundation Patient Guide:
  - http://www.urologyhealth.org/urology/index.cfm?article=18

REFERENCES

1. Gardiner RA, Gwynne RA, Roberts SA. Perinephric Abscess. *BJU Int.* 2011;107(Suppl 3):20–23.
2. Shields J, Maxwell AP. Acute pyelonephritis can have serious complications. *Practitioner.* 2010;254(1728):19, 21, 23–24, 2.

3. Ko MC, Liu CC, Liu CK, et al. Incidence of renal and perinephric abscess in diabetic patients: A population-based national study. *Epidemiol Infect*. 2011;139(2):229–235.
4. Heller MT, Haarer KA, Thomas E, et al. Acute conditions affecting the perinephric space: Imaging anatomy, pathways of disease spread, and differential diagnosis. *Emerg Radiol*. 2012;19(3):245–254.

ADDITIONAL READING

• Meng MV, Mario LA, McAninch JW. Current treatment and outcomes of perinephric abscesses. *J Urol*. 2002;168(4 Pt1):1337–1340.
• Tanagho EA, McAninch JW. *Smith's General Urology*. 17th ed. New York, NY: McGraw Hill; 2008.

See Also (Topic, Algorithm, Media)

• Pyelonephritis, Acute
• Pyelonephritis, Chronic
• Pyelonephritis, Emphysematous
• Pyelonephritis, Xanthogranulomatous
• Pyonephrosis
• Renal and Perirenal Abscess Image
• Retroperitoneal Abscess

CODES

ICD9

• 590.2 Renal and perinephric abscess
• 590.80 Pyelonephritis, unspecified
• 592.0 Calculus of kidney

ICD10

• N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
• N15.1 Renal and perinephric abscess
• N20.0 Calculus of kidney

CLINICAL/SURGICAL PEARLS

• Abscesses <3 cm can be managed with medical treatment initially.
• Continued fevers require surgical drainage of abscess.
• Include gram-positive antibiotic coverage if suspect hematogenous spread (IV drug use).

RENAL ANGIOMYOLIPOMA

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BASICS

DESCRIPTION

- Angiomyolipoma (AML): Benign renal tumor composed of vascular tissue (angio), muscle (myo), and adipose (lipoma) tissue elements
- Tumors < 4 cm are less likely to be symptomatic
- Tumors > 4 cm have increased risk of spontaneous bleeding
- Can be sporadic, but is associated with tuberous sclerosis (TS) and lymphangioleiomyomatosis (LAM)
- Can be a cause of Wunderlich syndrome:
  - Spontaneous, nontraumatic renal hemorrhage
  - Bleeding usually confined to renal capsule

EPIDEMIOLOGY

Incidence

- 20–30% of cases are seen in patients with tuberous sclerosis (TS)
- Mean age:
  - Sporadic AML: 5th or 6th decade
  - Tuberous sclerosis complex (TSC) patients: Age 30
- Female > male (4:1) overall; 2:1 in TS patients
- Right side more common

Prevalence

Prevalence 0.13%, 2–3% of all renal tumors

RISK FACTORS

- TSC (50% develop AML)
- LAM (40% develop AML)
- Patients with TC tend to develop larger, bilateral, multicentric, tumors which grow more rapidly, and tend to have more spontaneous bleeds

Genetics

- TSC, AD with variable expression
- 2/3 result from sporadic mutations
- 2 genes: TSC1 (9q34), TSC2 (16p13)

PATHOPHYSIOLOGY

In rare cases, can cause: Renal failure (large volume of tumor, or solitary kidney)

ASSOCIATED CONDITIONS

- TS (1)
  - 50–80% of patients with TS develop AML

- TS: Autosomal dominant condition, comprised of mental retardation, epilepsy, angiofibromas of the face (adenoma sebaceum), hamartomas in the kidney, brain (subependymal giant-cell astrocytomas [SEGAs]), eye (retinal phakomas), heart, lung, and bone

• LAM—rare lung disease, associated with TS
- Characterized by smooth muscle growth in the lungs, resulting in obstruction of small airways. Also occurs with TS

DIAGNOSIS

HISTORY
• Most asymptomatic, discovered incidentally
• Occasionally diagnosed by flank pain, hypotension, and spontaneous hemorrhage
• History of LAM, TSC
• GI complaints due to mass effect
• Hematuria, hypertension, anemia

PHYSICAL EXAM
• Hypertension, or hypotension (in the setting of hemorrhage)
• TSC: Mental retardation, adenoma sebaceum, ungula/subungual fibromas, lung disease
• Flank pain/mass
- Up to 50% of patients who are symptomatic may have a palpable mass

DIAGNOSTIC TESTS & INTERPRETATION
Lab
• Anemia
• Gross/micro hematuria
• Renal insufficiency
• Genetic testing if TS is suspected

Imaging
• CT: AML is commonly diagnosed on CT scans that reveal solid masses with areas of fat density (Hounsfield units below −20); most reliable imaging modality; IV contrast not necessary
• Fat density is not identified on CT in some cases with reduced fat content (1)[C]
• Rare reported cases of RCC containing fat densities (finding of calcification in mass is suspicious for RCC) (2)[C]
- US: Well-circumscribed, hyperechoic mass with shadowing (other RCTs may also be echogenic)
- IVP: Similar appearance to other RCTs
- Angiogram: Increased vascularity (also seen in many malignant renal lesions); 50% of AMLs are found to have aneurysmal dilation
- MRI: Adipose tissue has high signal intensity on T1-weighted images and lower on T2-weighted images

Pathologic Findings
• Pathology findings:

  – Thick-walled vessels, smooth muscle, and adipose tissue with spindle and epithelioid cells
  – The amount of each component varies
- Epithelioid AMLs
  – Variant of AML characterized by epithelioid cells that are cytokeratin negative and HMB-45 positive. More aggressive clinical course

DIFFERENTIAL DIAGNOSIS (2)
- Renal masses:
  – Oncocytoma
  – Renal and retroperitoneal liposarcoma
  – Renal cell carcinoma
  – Renal cysts
  – Renal lipoma
  – Sarcoma (including fibrosarcoma, leiomyosarcoma, and liposarcoma)
  – Teratoma
  – Upper-tract urothelial carcinoma
  – Wilms tumor
  – Xanthogranulomatous pyelonephritis
- Renal/retroperitoneal hemorrhage:
  – Arteriovenous malformation
  – Coagulopathy
  – Hemorrhage of other renal mass such as renal cell carcinoma
  – Iatrogenic
  – Ruptured aneurysm
  – Traumatic injury
  – Vasculitis

TREATMENT

GENERAL MEASURES (3)
- Benign renal masses, rarely transform to malignant entities
- Observation unless large, or symptomatic

MEDICATION

First Line
- Medical management is not currently standard
- Everolimus (4)
  – Approved in adults with renal AML and TSC not requiring immediate surgery
  – May benefit other TSC-associated disease manifestations, such as skin manifestations, pulmonary LAM, cardiac rhabdomyomas, and epilepsy
  – An inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway
  – 10 mg once daily with or without food

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Indications: Diagnostic uncertainty, hemorrhage causing significant symptoms, pain, hematuria, risk of rupture
- Asymptomatic AML < 4 cm:
  - Observation with serial imaging at 12-mo intervals
- Asymptomatic AML > 4 cm:
  - Treatment should be considered; observation with serial imaging
  - The risk of spontaneous hemorrhage appears greatest in masses > 4 cm
  - Women of childbearing age may consider proactive treatment
- Symptomatic AML/lesion > 4 cm:
  - Selective arterial embolization or nephron-sparing surgery
- Acute hemorrhage:
  - Initially treated with embolization (stabilizes patient and often eliminates need for more intervention)
  - If explored emergently, total nephrectomy usually necessary

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Limited reports of treatment using cryoablation and radiofrequency ablation
- In patients with LAM or TS, mTOR inhibitors such as sirolimus/temsirolimus have been shown to decrease mass size by 30%

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Local recurrence rare after removal.
- Extrarenal lesions are multicentric and not metastatic.
- Extended follow-up is necessary after selective embolization due to complications and recurrence risk.
- Extremely rare case reports of malignant transformation.

COMPLICATIONS

- Flank/abdominal pain
- Hematuria
- Hemorrhage (may cause anemia or shock)
- Mass effect on surrounding organs

FOLLOW-UP

Patient Monitoring

- Controversial in patients with newly diagnosed AML; screen for TS
- Conservative management: Serial imaging (usually with CT or US) every 6–12 mo
- Growth rate typically 5% per yr for solitary AML

- TSC patients and those with multicentric AMLs have growth rate of 20% per yr

Patient Resources

- TS alliance www.tsalliance.com
- LAM Foundation www.theLAMfoundation.com

REFERENCES

1. Kennelly MJ, Grossman HB, Cho KJ. Outcome analysis of 42 cases of renal angiomyolipoma. *J Urol.* 1994;152:1988–1991.
2. Margulis V, Matin SF, Wood CG. Chapter 51: Benign Renal Tumors. In: *Campbell-Walsh Urology*. Philadelphia, PA: Elsevier; 2010:1492–1505.
3. Nelson CP, Sanda MG. Contemporary diagnosis and management of renal angiomyolipoma. *J Urol.* 2002;168:1315–1325.
4. Dabora SL, Franz DN, Aswal S, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: Kidney angiomyolipomas and other tumors regress and VEGF-D levels decrease. *PLoS One*. 2011;6(9):e23379.

ADDITIONAL READING

- Folpe AL, Mentzel T, Lehr HA, et al. Perivascular epitheliod cell neoplasms of soft tissue and gynecological origin: A clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol.* 2005;29(12):1558–1575.
- Moavero R, Coniglio A, Garaci F, et al. Is mTOR inhibition a systemic treatment for tuberous sclerosis? *Ital J Pediatr.* 2013;39:57.
- Rakowski SK, Winterkorn EB, Paul E, et al. Renal manifestations of tuberous sclerosis complex: Incidence, prognosis, and predictive factors. *Kidney Int.* 2006;70(10):1777–1782.
- Roy C, Tuchmann C, Lindner V, et al. Renal cell carcinoma with a fatty component mimicking angiomyolipoma on CT. *Br J Radiol.* 1998;71:977–979.
- Steiner MS, Goldman SM, Fishman EK, et al. The natural history of renal angiomyolipoma. *J Urol.* 1993;150:1782–1786.

See Also (Topic, Algorithm, Media)

- Renal Angiomyolipoma Image
- Renal Cell Carcinoma, General
- Renal Mass
- Retroperitoneal Hematoma
- Tuberous sclerosis

CODES

ICD9

- 223.0 Benign neoplasm of kidney, except pelvis
- 593.81 Vascular disorders of kidney
- 759.5 Tuberous sclerosis

ICD10

- D17.71 Benign lipomatous neoplasm of kidney

- N28.89 Other specified disorders of kidney and ureter
- Q85.1 Tuberous sclerosis

CLINICAL/SURGICAL PEARLS

- Benign renal tumor characterized by presence of vascular, muscle, and adipose components.
- Larger lesions have increased risk of spontaneous hemorrhage.
- Diagnosis is usually made by imaging.
- Observation for small masses, consider embolization for larger masses.
- Everolimus (mTOR inhibitor) can shrink large multifocal lesions in patients with tuberous sclerosis (TS) and lymphangioleiomyomatosis (LAM).

RENAL ARTERY STENOSIS/RENOVASCULAR HYPERTENSION

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BASICS

DESCRIPTION

- Renal artery stenosis (RAS) refers to anatomic vascular lesion that causes decreased blood flow to the kidney
- May not be associated with hypertension (HTN)
- May be atherosclerotic in nature (athersclerotic renal artery stenosis or ARAS)
- Rarely caused by fibromuscular dysplasia (FMD)
- Renovascular HTN (RVH) refers to HTN that is caused by renal hypoperfusion and is reversed by correction of the lesion or nephrectomy

EPIDEMIOLOGY

Incidence

- RAS often found incidentally
  - 33% of patients with aorto-occlusive disease
  - 20% of patients with coronary artery disease (CAD)
  - 43% of patients with diabetes
  - 7% of asymptomatic normotensive adults >65 yr (1)

Prevalence

RVH <1% of hypertensive patients

RISK FACTORS

- Atherosclerosis
- Diabetes
- CAD
- Advanced age

Genetics

N/A

PATHOPHYSIOLOGY

- Atherosclerosis
  - Accounts for 70% of all RAS
  - Nearly half of patients will have progressive obstruction within 2 yr of diagnosis
  - Usually located at the ostium or proximal renal artery
  - 10% caused by FMD, which causes primarily distal lesions
- RVH
  - Results from significant vascular stenosis which produces renal hypoperfusion
  - Hypoperfusion results in increased renin levels, which in turn increases angiotensin II levels
  - Angiotensin elevates blood pressure through several mechanisms

- Generalized vasoconstriction
- Increased aldosterone production, promoting sodium absorption and excretion of potassium and hydrogen
- Causes efferent arteriolar vasoconstriction to maintain glomerular filtration

- FMD is a nonatherosclerotic, noninflammatory process of the renal vessels
  - Intimal fibroplasia occurs in children and young adults
    - Accounts for 10% of FMD
    - Can be associated with dissection and hematoma
    - Involves proximal or midportion of artery, appears smooth on angiography
    - Invariably progressive if untreated
  - Medial fibroplasia
    - 70–80% of FMD
    - More common in women aged 25–50
    - Usually bilateral
    - "String of beads" appearance on angiography
    - Rarely associated with functional loss and may be managed medically
  - Perimedial fibroplasia
    - Women aged 15–30
    - Dense collar of collagen constricting the artery
    - Length is variable
    - Frequently associated with development of collaterals
    - Invariably progressive if not treated
  - Fibromuscular hyperplasia
    - Extremely rare (2–3% of all renal artery lesions)
    - Most commonly affects children and young adults
    - Progressive if untreated

ASSOCIATED CONDITIONS

- High-grade retinopathy
- Atherosclerosis
- Diabetes
- CAD
- Peripheral vascular disease

GENERAL PREVENTION

Reduction of risk factors for cardiovascular disease and diabetes

DIAGNOSIS

HISTORY

- Onset of HTN after age 50
- No family history of HTN
- Difficult-to-control HTN, on multiple antihypertensives
- Increase in serum creatinine with use of ACE inhibitors or angiotensin receptor blockers (ARBs)

PHYSICAL EXAM

- Blood pressure measurement
- Abdominal exam with auscultation for bruit
- Retinal exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Plasma renin activity (PRA)
  - By itself, not diagnostic of RAS or RVH
- Captopril test
  - Useful for excluding RVH
  - Diuretics and ACE inhibitors stopped 1 wk prior
  - PRA measured before and 1 hr after 25-mg dose of captopril
  - Positive test if postdose PRA >12 ng/mL/h, absolute increase of PRA >10 ng/mL/h, 4-fold increase in PRA over baseline
  - Not appropriate in children or in patients with azotemia

Imaging

- Arteriography is gold standard
  - Highly sensitive and specific (99%)
  - Provides detailed anatomy, and allows for discrimination between FMD subtypes
  - Allows for simultaneous endovascular treatment
  - Invasive
  - Recommended as initial diagnostic intervention in patients with high suspicion for RVH
- Captopril renography
  - Keep well hydrated on a liberal salt diet
  - Off ACE inhibitors for 3–5 days prior to exam
  - ^{99m}Technetium-MAG3 renal scan generally used before and 1 hr after captopril dose
  - Diagnostic criteria for RVH: Delay in maximal activity >11 min, asymmetrical peak activity, cortical retention of radionuclide, significant decrease in glomerular filtration rate
  - Recommended as initial diagnostic intervention in patients with low-to-moderate suspicion for RVH
- Duplex ultrasonography
  - Positive diagnostic criteria: Peak systolic velocity of renal artery >80 cm/s, ratio of diameter of renal artery to aorta >3.5
  - Inexpensive, noninvasive, but quality of study is operator dependent
- Magnetic resonance angiography (MRA)
  - May be more sensitive than ultrasound or renography, but inferior to conventional arteriography
  - Poorly visualizes distal arteries
  - Contraindicated in patients with met al or claustrophobia
  - Contrast must be used with caution in patients with renal insufficiency (2)
- Computed tomography angiography (CTA)
  - Uses potentially nephrotoxic contrast agents
  - More widely available and cost-effective compared to MRA

Diagnostic Procedures/Surgery

- Renal angiography
- Renal vein renin sampling
  - Useful in determining which kidney is primary contributor to RVH in patients with bilateral lesions

Pathologic Findings

- Renal biopsy indicated in patients with creatinine >4 mg/dL
  - Tubular atrophy, interstitial fibrosis, arteriosclerosis indicate functional recovery may be possible
  - Widespread glomerular hyalinization indicates irreversible injury

DIFFERENTIAL DIAGNOSIS

- Aortic aneurysm
- Essential HTN
- Functional adrenal adenoma
- Intrinsic renal disease
- Renal artery aneurysm

TREATMENT

GENERAL MEASURES

- Recognition of underlying cause is critical in guiding management
- Smoking cessation
- Weight loss
- Reduction of risk factors for cardiovascular disease and diabetes

MEDICATION

First Line

- ACE inhibitors/ARBs: Improves HTN in 96% of patients with RVH. May not prevent progression of atherosclerotic lesions.
  - Captopril: 25–50 mg PO BID-TID
  - Enalapril: 10–40 mg PO QD
  - Losartan: 25–100 mg PO divided QD-BID
  - Telmisartan: 20–80 mg PO QD
- Aspirin 81 mg PO QD
- Statins

Second Line

- Thiazide diuretics
- Loop diuretics
- Calcium channel blockers
- β-blockers

SURGERY/OTHER PROCEDURES

- Surgical intervention recommended for patients with high-grade stenosis, bilateral disease, solitary kidney, declining renal function, pulmonary edema, congestive heart failure (3)
- Angioplasty with or without endovascular stenting

  – Percutaneous access through common femoral artery
  – Selective angiography performed
  – ≥70% stenosis treated with angioplasty and deployment of balloon-mounted stent
  – Angioplasty without stenting is associated with increased risk of restenosis
- One recent clinical trial suggests that the addition of renal artery stenting to comprehensive, multifactorial medical therapy did not confer a significant benefit (4)
- Aortorenal bypass (hypogastric or saphenous vein)
- Nephrectomy (especially in patients with a poorly functioning ipsilateral renal unit)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Treatment of concomitant disease
  – Antiplatelet agents
  – Statins
  – Smoking cessation
  – Weight loss

Complementary & Alternative Therapies

Sympathetic renal denervation using radiofrequency ablation is investigational at the present time, but shows promise (5)

ONGOING CARE

PROGNOSIS

Untreated disease, except for medial fibroplasia, is often progressive and can result in renal functional loss

COMPLICATIONS

- Functional loss, worsening HTN, pulmonary edema, congestive heart failure in untreated patients
- Endovascular interventions: Access site hematoma, renal artery dissection, thrombosis, contrast-induced nephropathy
- Surgical interventions: Hemorrhage, wound infection, hematoma, anesthesia complications

FOLLOW-UP

Patient Monitoring

High-risk patients and those on medical therapy should be observed with serial metabolic and renal function studies in addition to Doppler ultrasonography

Patient Resources

http://www.nlm.nih.gov/medlineplus/ency/article/000204.htm

REFERENCES

1. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: A population-based study. *J Vasc Surg*. 2002;36:443–451.
2. Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing

dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21:1104–1108.
3. Novick AC. Options for therapy of ischemic nephropathy: Role of angioplasty and surgery. *Semin Nephrol*. 1996;16:53–60.
4. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med*. 2014;370(1):13–22.
5. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275–1281.

ADDITIONAL READING

- O'Neill WC, Bardelli M, Yevzlin AS. Imaging for renovascular disease. *Semin Nephrol*. 2011;31:272–282.
- Piecha G, Wiecek A, Januszewicz A. Epidemiology and optimal management in patients with renal artery stenosis. *J Nephrol*. 2012;25:872–878.
- Safian RD, Textor SC. Renal-artery stenosis. *N Engl J Med*. 2001;344:431–442.

See Also (Topic, Algorithm, Media)

- HTN, Urologic Considerations
- Renal Artery Aneurysm
- Renal Artery FMD
- Renin, Plasma and Renal Vein
- Renal Artery Stenosis Images ☼

CODES

ICD9

- 250.40 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
- 405.91 Unspecified renovascular hypertension
- 440.1 Atherosclerosis of renal artery

ICD10

- E11.21 Type 2 diabetes mellitus with diabetic nephropathy
- I15.0 Renovascular hypertension
- I70.1 Atherosclerosis of renal artery

CLINICAL/SURGICAL PEARLS

- RVH HTN is caused by significant stenosis of the renal artery and is reversed by correction of stenosis or nephrectomy.
- Renal angiography remains gold standard for diagnosis.
- With the exception of medial fibroplasia, untreated RVH disease often leads to progressive renal functional loss.

RENAL CAPSULAR NEOPLASMS

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BASICS

DESCRIPTION

- Predominantly mesenchymal neoplasms arising from the renal capsule encompassing a wide variety of cell progenitors
  - Tumors can be composed of fibrous, smooth muscle, vascular, adipose, nerve, or other tissue differentiation
    - Encompasses benign and malignant neoplasms

EPIDEMIOLOGY

Incidence

- Very rare tumors
- Represent up to ~1.5% of all surgically treated benign renal masses (1)
- Incidentally found at autopsy in up to ~5% of cases (1)
- Similar gender preference

Prevalence

Unknown, due to rarity of tumor

RISK FACTORS

- None known
  - Increased cross-sectional imaging use may identify incidental mass

Genetics

- No recognized genetic predisposition
- Some common genetic alterations seen in soft tissue sarcomas
  - No current clinical application for genetic alterations

PATHOPHYSIOLOGY

- Benign
  - Leiomyoma, hemangiopericytoma, hemangioma, lymphangioma, myxoma, schwannoma, solitary fibrous tumor, paraganglioma, lipoma, fibroma, myolipoma
- Malignant
  - Leiomyosarcoma, malignant fibrous histiocytoma, fibromyxoid sarcoma, hemangiosarcoma, liposarcoma, fibrosarcoma

ASSOCIATED CONDITIONS

Some renal hemangiomas may be associated with Sturge–Weber or Klippel–Trénaunay syndromes (1)

GENERAL PREVENTION

No preventive strategies identified

DIAGNOSIS

HISTORY

- Usually asymptomatic or discovered incidentally
- May present with hematuria or flank pain
- Weight loss, anorexia, malaise, or bone pain may signify metastatic disease

PHYSICAL EXAM

- Usually normal
  - Rarely, flank mass may be palpable

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Microscopic hematuria may be identified, but usually normal
- CBC
  - Anemia may be present with advanced disease or bleeding mass
- Serum chemistries usually normal

Imaging

- CT or MRI with and without contrast
  - May show enhancing mass arising from the kidney
    - Indistinguishable from renal cell carcinoma in most cases
    - Presence of fat may signify angiomyolipoma, lipoma, or liposarcoma
- Chest x-ray
  - Evaluate for metastatic disease

Diagnostic Procedures/Surgery

- Core needle biopsy
  - May be used in cases of suspected renal malignancy or if active surveillance considered
- Angiography
  - May be utilized for bleeding lesions
  - Benign lesions usually hypovascular
    - Except hemangiopericytoma, which is highly vascular

Pathologic Findings

- Leiomyoma
  - Firm, well-circumscribed, exophytic mass
  - Microscopically, composed of spindle cells arranged in fascicles typical of smooth muscle
  - Immunostaining positive for desmin, smooth muscle actin, and usually HMB-45 (1)[C]
- Hemangiopericytoma
  - Solid, encapsulated mass
  - Microscopically, varied cell shapes and sizes with morphologic variability
  - Immunostaining positive for vimentin, BCL2, CD99 and negative for S100, cytokeratins, and HMB-45 (2)[C]
- Lymphangioma
  - Well-encapsulated, multilocular cystic mass
  - Microscopically, communicating cysts seen with flattened endothelial cells

  - Immunostaining positive for D2-40
    - Labels lymphatic endothelium (1,3)[C]
- Solitary fibrous tumor
  - Well-encapsulated firm mass without necrosis, cysts, or hemorrhage
  - Microscopically, usually shows areas of spindle cells intermixed with hypocellular areas of fibrous tissue
  - Immunostaining strongly positive for CD34
    - May also stain positive for CD99 and BCL2 and can be misclassified as hemangiopericytoma (1,2)[C]
- Leiomyosarcoma
  - Usually large circumscribed mass with areas of necrosis
  - Microscopically, spindle cells with haphazard growth pattern, nuclear pleomorphism, mitoses, and necrosis
  - Immunostaining positive for SMA, desmin, and calponin (1)[C]
- Fibrosarcoma
  - Large encapsulated mass
  - Microscopically, elongated spindle cells
    - "Herringbone" pattern
  - Immunostaining positive for vimentin
    - Differentiates fibrosarcoma from sarcomatoid RCC and leiomyosarcoma (1)[C]
- Malignant fibrous histiocytoma
  - Solid, well-encapsulated mass
  - Microscopically, proliferation of fibrohistiocytes
  - Immunostaining positive for α1-antitrypsin and vimentin

DIFFERENTIAL DIAGNOSIS
- Angiomyolipoma
- Renal cysts
- Cystic nephroma
- Hemorrhagic/proteinaceous cysts
- Juxtaglomerular cell tumor
- Metastasis to kidney
- Oncocytoma
- Renal cell carcinoma
- Renal pseudotumor/scar
- Splenule (ectopic or traumatic)
- Urothelial carcinoma
- Wilms tumor
- Xanthogranulomatous pyelonephritis

TREATMENT

GENERAL MEASURES
- Surgical excision is both diagnostic and therapeutic
- Multimodal therapy generally recommended for malignancies such as sarcoma

MEDICATION

First Line

- Chemotherapy may be beneficial for certain advanced renal capsular malignancies (sarcoma) and metastatic lesions (4)[C].
  - Usually given in the adjuvant setting.
- Targeted therapies may be beneficial in certain cases.
  - Sunitinib, sorafenib, bevacizumab active in angiosarcoma, solitary fibrous tumor, and hemangiopericytoma.

SURGERY/OTHER PROCEDURES

- Surgical excision remains gold standard
  - Radical nephrectomy
    - Open or minimally invasive
  - Partial nephrectomy
    - Open or minimally invasive
    - Renal capsule margin should be excised with mass
    - Should be procedure of choice for patients with chronic kidney disease, when feasible
- Active surveillance
  - Similar surveillance protocol for patients with small renal masses

ADDITIONAL TREATMENT

Radiation Therapy

- May be beneficial in cases of renal capsular sarcoma
  - Usually given in adjuvant setting

Additional Therapies

Angioembolization for bleeding masses

Complementary & Alternative Therapies

None known

ONGOING CARE

PROGNOSIS

- Surgical excision usually curative
- Renal capsular sarcoma has poor prognosis
  - Locally advanced disease is common
  - Recurrence and metastases common
  - Overall prognosis is poor, despite adjuvant chemoradiation
    - 5-yr overall survival ~15%
    - Median survival 28 mo (4)[C]

COMPLICATIONS

- Injury to adjacent organs
- Thromboembolic event
- Delayed bleed
  - AV fistula
  - Pseudoaneurysm

• Development of metastatic disease

FOLLOW-UP

Patient Monitoring

• Periodic surveillance imaging
• Serum chemistry panel and liver function tests

Patient Resources

None due to rarity of disease

REFERENCES

1. Katabathina VS, Vikram R, Nagar AM, et al. Mesenchymal neoplasms of the kidney in adults: Imaging spectrum with radiologic-pathologic correlation. *Radiographics*. 2010;30(6):1525–1540.
2. Brescia A, Pinto F, Gardi M, et al. Renal hemangiopericytoma: Case report and review of the literature. *Urology*. 2008;71(4):755.e9–e12.
3. Kalof AN, Cooper K. D2-40 immunohisto-chemistry—so far! *Adv Anat Pathol*. 2009;16(1):62–64.
4. Wang X, Xu R, Yan L, et al. Adult renal sarcoma: Clinical features and survival in a series of patients treated at a high-volume institution. *Urology*. 2011;77(4):836–841.

ADDITIONAL READING

• MacLennan GT, Cheng L. Neoplasms of the kidney. In: Bostwick DG, Cheng L, eds. *Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008:104–106.
• Soft Tissue Sarcoma. NCCN Clinical Practice Guidelines in Oncology (www.nccn.org).

See Also (Topic, Algorithm, Media)

• Hemorrhage, Retroperitoneal and Perinephric
• Renal Capsular Neoplasms Image
• Renal Mass
• Renal Masses, Benign WHO Classification
• Renal Sarcoma, Adult and Pediatric

CODES

ICD9

• 189.0 Malignant neoplasm of kidney, except pelvis
• 223.0 Benign neoplasm of kidney, except pelvis
• 239.5 Neoplasm of unspecified nature of other genitourinary organs

ICD10

• C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
• D30.00 Benign neoplasm of unspecified kidney
• D49.5 Neoplasm of unspecified behavior of other genitourinary organs

CLINICAL/SURGICAL PEARLS

• Renal capsular neoplasms difficult to distinguish from RCC by imaging alone.

- Surgical excision (partial or radical nephrectomy) can be diagnostic and curative in most cases.
- Renal capsular sarcomas carry generally poor prognosis, despite adjuvant therapy.

RENAL CELL CARCINOMA WITH TUMOR THROMBUS

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BASICS

DESCRIPTION

- Patients with renal cell carcinoma (RCC) are at risk for developing intravenous tumor thrombus (IVTT) with tumor extending into the renal vein (RV) and inferior vena cava (IVC).
- RCC is the most common malignancy to extend into IVC.
- Tumor growth follows the path of least resistance into the venous system extending into the RV and IVC (and into the right atrium) or it can invade into the vein wall.
- Multiple staging systems exist for RCC with venous extension. 3 common staging systems include:
  - TNM
    - pT3a—RV extension
    - pT3b—IVC below diaphragm
    - pT3c—IVC above diaphragm
  - Anatomic (Hinman system)
    - Level I—RV/infrahepatic IVC
    - Level II—Intrahepatic IVC
    - Level III—Supradiaphragmatic IVC/right atrium
- Anatomic (Neves/Novick system)
  - Level 0—RV
  - Level I—IVC <2 cm above RV
  - Level II—IVC >2 cm above RV and below hepatic veins
  - Level III—IVC above hepatic veins and below diaphragm
  - Level IV—IVC above diaphragm

EPIDEMIOLOGY

Incidence

There are approximately 63,920 cases of RCC diagnosed each year; about 10% have IVTT.

Prevalence (1)

- RCC with IVTT is seen in 4–15% of cases.
  - In 50% of these cases, IVTT only extends to the RV.
  - IVTT extends into the right atrium in 1% of cases.
- Among patients that have IVTT, 29–55% will have concomitant metastatic disease.

RISK FACTORS

Risk factors for RCC with IVTT are the same for RCC and include smoking, obesity, hypertension, family history.

Genetics

No known genetic factors exist that predict IVTT.

PATHOPHYSIOLOGY

- RCC with IVTT can occur with all histologic subtypes including clear cell, papillary, and chromophobe
- RCC can occur sporadically or in a hereditary form (although there is no known genetic predisposition to IVTT)
- IVTT can cause occlusion of the IVC, which can cause lower-extremity edema, varicocele in males
- IVTT can also cause a pulmonary embolism
- Acute caval obstruction may rarely lead to disseminated intravascular coagulation, though more commonly IVTT may cause chronic venous obstruction leading to the development of collateral venous drainage

ASSOCIATED CONDITIONS

- Pulmonary embolus
- Bilateral lower-extremity edema
- Lower-extremity DVT
- Varicocele
- Caput medusa

GENERAL PREVENTION

Modification of above risk factors for RCC

DIAGNOSIS

HISTORY

- Presentation of patients with RCC with IVTT is similar to RCC without tumor thrombus, but those with tumor thrombus are more likely to be symptomatic
- Up to 95% of patients with intracaval extension present with symptoms it is an incidental finding in 23%
- Symptoms include:
  - Hematuria (35%)
  - Flank/abdominal pain (17%)
  - Constitutional symptoms including fatigue, weight loss, or paraneoplastic syndrome (9%)
  - Flank/abdominal mass (2%)

PHYSICAL EXAM

- Physical exam findings can include:
  - Bilateral lower-extremity edema
  - Varicocele (right side)
  - Dilated superficial abdominal wall veins
  - Caput medusa

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Basic lab work is necessary for preoperative workup including
  - Liver function tests

– Complete blood count
– Basic metabolic panel
– Urinalysis

Imaging

- Chest imaging (preferably CT) and bone scan should be ordered as part of staging workup
- Assessment of IVTT cephalad extension should be performed 7–14 days before surgery because it can affect the surgical approach and the need for bypass procedures
- Ultrasonography and standard CT can be used to detect the presence of IVTT, but may not be sufficient for surgical planning
- MRI (T1-weighted images) is the gold standard imaging technique used to assess the cephalad extent of the IVTT, the degree of occlusion, and its relationship to liver, diaphragm, and atrium
- Multidetector CT (MDCT) can also be used in patients who are not candidates for MRI
- Studies comparing MRI to MDCT for staging IVTT have shown comparable results
- Transesophageal echocardiography can be used intraoperatively for real-time monitoring of thrombus
- Size of tumor thrombus on imaging studies may predict vein wall invasion and need for vein reconstruction

Diagnostic Procedures/Surgery

Biopsy can be performed if urothelial cell carcinoma is suspected or patient is poor surgical candidate

Pathologic Findings

- All subtypes of RCC have been associated with IVTT
- Clear cell is the most common histologic subtype associated with IVTT

DIFFERENTIAL DIAGNOSIS

Other tumors associated (rarely) with IVTT include urothelial cell carcinoma, adrenocortical carcinoma, and angiomyolipoma

TREATMENT

GENERAL MEASURES

- For those with no evidence of distant metastatic disease, surgical resection is the gold standard for RCC with IVTT
- For patients who present with metastatic disease, biopsy may be indicated for consideration of systemic therapy
- For select patients with metastatic disease, cytoreductive nephrectomy with tumor thrombectomy may be considered, although the outcomes in this setting are usually poor

MEDICATION

First Line

- Anticoagulation (preoperatively) should be considered for patients with IVTT to prevent bland thrombus development and propagation below the tumor
- Preoperative tyrosine kinase inhibitors (TKIs)
  – Controversial

- May be utilized in the metastatic setting or when tumor felt not to be surgically resectable
- Most common TKIs used preoperatively are sorafenib and sunitinib; may decrease tumor size before surgical resection; may reduce level of IVTT, potentially altering surgical approach

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgery is the gold standard for the treatment of RCC with IVTT (2,3,4)
- Accurate assessment of the cephalad extent of the tumor thrombus is critical in determining the surgical approach and need for adjunctive procedures
- While there are some reports of robotic and laparoscopic approaches to RCC with IVTT, the mainstay is open surgery
- Midline, subcostal (chevron), or thoracoabdominal incisions can be used
- Median sternotomy or thoracoabdominal approaches can be used for IVTT above the diaphragm
- For all levels, IVC should be resected if tumor is invading into the wall and reconstruction can be performed with graft (if lumen diameter compromised >50%)
- Resection of retroperitoneal lymph nodes and/or metastasectomy can be performed as needed
- Surgical steps include:
  - Expose renal hilum, ligate renal artery
  - Expose the RV and IVC
  - Isolate venous inflow into IVC
  - Cavotomy, tumor extraction
  - Caval repair/reconstruction/ligation
- Level I Thrombus Specifics
  - Milk the thrombus into the RV and take a side bite of the IVC using a vascular clamp making sure not to occlude IVC flow
  - Incise the IVC and remove the thrombus and kidney under direct vision
  - Oversew the caval defect
- Level II Thrombus Specifics
  - Mobilize the liver and divide minor hepatic veins to expose the intrahepatic IVC
  - Place Rummel tourniquets or vascular clamps sequentially on the infrarenal vena cava, contralateral RV, and suprarenal vena cava above the thrombus
  - Incise IVC, remove the thrombus and kidney
  - Flush-exposed IVC with heparinized saline
  - Suture cavotomy; release vascular clamps
- Level III–IV Thrombus Specifics
  - A wide variety of surgical approaches have been described
  - Clamping of the IVC at the this level can compromise hemodynamic stability
  - Cardiopulmonary bypass: Used for IVTT above the diaphragm, maintains continuous arterial/venous blood flow during IVC occlusion
  - Deep hypothermic circulatory arrest (DHCA) cools the body and create a bloodless field
  - Venovenous bypass can be used for level II–IV tumors. Venovenous bypass allows for

continuous venous return to the heart while IVC is clamped.
  – Pringle maneuver (clamping of the hepatic pedicle) can be used to avoid hepatic congestion and/or IVC bleeding that may occur when IVC is clamped above the hepatic veins (limit warm hepatic ischemia to 20 min)
  – Cephalad IVC control can be obtained by exposing the intrapericardial IVC via pericardiotomy
  – Langenbuch maneuver (medial mobilization of liver) to expose retrohepatic IVC
  – Transesophageal echocardiography should be used for real-time intraoperative monitoring to identify tumor emboli
  – A multidisciplinary approach, including the involvement of cardiac, vascular, hepatic surgeons as well as a specialized anesthesia team, is highly encouraged for these complex tumors

ADDITIONAL TREATMENT

Radiation Therapy

No role, except for palliation

Additional Therapies

- IVC filter can be used to prevent pulmonary embolus, however its use is controversial
  – IVTT may become incorporated into IVC filter causing a surgical challenge
  – When IVC is chronically occluded, simple ligation of IVC below hepatic veins may be performed
- Preoperative renal artery embolization
  – Allows for early venous clamping when renal artery control may be difficult; may cause pain and complications (angioinfarction syndrome)
  – Can be used as a palliative procedure

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS

- Prognostic factors include TNM stage, nuclear grade, presence of necrosis, histologic type (worse for unclassified RCC and collecting duct carcinomas), sarcomatoid features, invasion into adjacent structures (renal sinus, perinephric fat, hepatic veins, collecting system, RV ostium), ECOG performance status, presence of lymph nodes, and distant metastasis
- Prognostic significance of tumor thrombus level remains controversial
- Median survival for nonmetastatic disease: 38–116 mo; 5-yr disease specific survival 40–60% when all gross disease is resected
- Median survival for metastatic disease: 11–20 mo and 5-yr disease specific survival is 4–30%. Patients that present with metastatic disease: 5-yr survival 0–10%.

COMPLICATIONS

- Overall complication rate is 12.5%, however, the complication rates vary greatly with level of tumor thrombus.
- Perioperative death varies from 0.8–10%. There has been a reported rate of mortality up to

40% for level IV IVTT.
- Most common complications are hemorrhage, pulmonary embolism, wound infection, acute renal failure, ileus, and need for additional surgery.
- The incidence of intraoperative tumor thrombus embolization is 1.5% and is associated with 75% mortality rate.
- Cardiopulmonary bypass is a risk factor for stroke (6% of cases) during nephrectomy for RCC with IVTT.

FOLLOW-UP

Patient Monitoring

- Surveillance based on TNM staging
- Surveillance labs include metabolic panel, liver function tests
- Surveillance imaging includes abdominal and thoracic imaging

Patient Resources

- American Cancer Society
  http://www.cancer.org/acs/groups/cid/documents/webcontent/003107-pdf.pdf
- Kidney Cancer Foundation http://www.kidneycancer.org/

REFERENCES

1. González J. Update on surgical management of renal cell carcinoma with venous extension. *Curr Urol Rep*. 2012;13(1):8–15.
2. Karnes RJ, Blute ML. Surgery insight: Management of renal cell carcinoma with associated inferior vena cava thrombus. *Nat Clin Pract Urol*. 2008;5(6):329–339.
3. Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus. *BJU Int*. 2012;110(7):926–939.
4. Pouliot F, Shuch B, Larochelle JC, et al. Contemporary management of renal tumors with venous tumor thrombus. *J Urol*. 2010;184(3):833–841.

ADDITIONAL READING

None

See Also (Topic, Algorithm, Media)

- Deep Venous Thrombosis and Pulmonary Embolus, Urologic Considerations
- RCC, General
- Renal Cell Carcinoma, Locally Advanced (T3–T4)
- Renal Cell Carcinoma with Tumor Thrombus Image
- Renal Vein Thrombosis, Adult and Pediatric

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 453.2 Other venous embolism and thrombosis of inferior vena cava
- 453.3 Other venous embolism and thrombosis of renal vein

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- I82.3 Embolism and thrombosis of renal vein
- I82.220 Acute embolism and thrombosis of inferior vena cava

CLINICAL/SURGICAL PEARLS

Preoperative assessment of cephalad extent of thrombus is critical for surgical planning.

RENAL CELL CARCINOMA, GENERAL

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BASICS

DESCRIPTION

- Renal cell carcinomas (RCC's) are malignant tumors of the kidney arising from different parts of the nephron
- Majority of renal neoplasms are RCC (80%)
- RCC is typically resistant to conventional chemotherapy and radiation, making it primarily a surgical disease

EPIDEMIOLOGY

Incidence

- 65,150 estimated new cases of RCC in 2014 in USA (39,140 in men and 24,780 in women); 12 new cases per 100,000/yr (1)[B]
- Male > Female, 3:2
- Increase in incidence since the 1970s of 3–4%/yr due to increased use of abdominal CT
- Estimated 13,860 deaths will occur in 2014 from RCC in USA (1)[B]
- Primarily occurs in 6th–7th decade of life
- 2–3% are familial; majority are sporadic

Prevalence

- 3rd most common GU malignancy in men (prostate, bladder); most common urinary tract malignancy in women
- RCC represents 2.3–6.6% of all pediatric renal tumors

RISK FACTORS

- Tobacco exposure: 1.4–2.5 times increased risk, this increases with duration, decreases after cessation (2)[C]
- Obesity
- Hypertension (HTN) has a 1.4–2-fold increase of RCC
- Family history in a 1st- or 2nd-degree relative associated with a relative risk of 2.9 of developing RCC
- Other potential environmental factors include viruses, lead compounds, and aromatic hydrocarbons

Genetics

- Clear-cell RCC is associated with chromosomal 3p deletion and/or mutations of VHL gene
- Alterations of chromosome 3p25–26 lead to clear-cell RCC in VHL syndrome (3)[A]
- Nonhereditary papillary RCC is linked to changes in chromosomes 7 and 17
- Hereditary pRCC typically involves type 1 pRCC and is due to missense mutations of the c-met proto-oncogene
- Chromophobe RCC is a result of allelic loss of chromosome 17

- Birt–Hogg–Dubé syndrome (BHD) includes cutaneous manifestations, spontaneous pneumothoraces, and chromophobe RCC, renal oncocytomas, or hybrid tumors consisting of both due to mutations in BHD gene on chromosome 17
- Translocation Xp11.2 Translocation carcinoma; predominantly younger patients

PATHOPHYSIOLOGY

- Clear cell and papillary RCC develop from the proximal convoluted tubules.
- Chromophobe and collecting-duct RCC develop from the distal convoluted tubule and collecting duct, respectively.
- VEGF and TNF-α are growth factors altered in development and progression of RCC.
- Local invasion is common; 20% of cases have invasion of the capsule or collecting system, and 10% have a tumor thrombus.
- Bilateral tumors occur 2–4% of the time with sporadic RCC, either at diagnosis or metachronously.

ASSOCIATED CONDITIONS

- For ESRD patients there is a 5–20-fold increase in risk of developing RCC, most commonly papillary subtype.
- Acquired renal cystic disease in conjunction with ESRD has a 1–2% risk of developing RCC.
- VHL-related RCC is associated with retinal angioma, pancreatic cysts, cerebellar and spinal hemangioblastomas, and neuroendocrine tumors.
- BHD-related RCC is associated with facial fibrofolliculomas in addition to lung cysts and spontaneous pneumothoraces.

GENERAL PREVENTION

- Smoking cessation reduces the relative risk of developing RCC by 20–50%
- Weight reduction: It is estimated that 40% of the cases of RCC in USA may be linked to obesity

DIAGNOSIS

HISTORY

- Most cases of localized RCC are asymptomatic and >50% of cases are detected incidentally during abdominal imaging for other reasons.
- Classic Triad: Flank pain, palpable flank mass, and hematuria. This is rarely seen except in advanced disease.
- Paraneoplastic symptoms found in 20% of patients. These include hypercalcemia (due to paraneoplastic phenomena or osteolytic bone involvement), HTN, polycythemia.
- Constitutional symptoms such as fever, weight loss, and anemia are thought to be due to paraneoplastic syndromes.

PHYSICAL EXAM

- Physical exam findings are usually absent, except in cases of advanced disease.
- Deep palpation for upper quadrant masses and auscultation for a renal artery bruit should be included in the abdominal exam.
- Assess for a varicocele with a careful testicular exam as venous outflow obstruction can occur due to a renal vein tumor thrombus. An epididymal mass may be seen in VHL-related

disease.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Initial evaluation includes CBC, electrolytes, creatinine, LFTs, and UA
- Elevated ESR is present in 56% of patients
- Stauffer syndrome found in 14.4% of patients
  - Characterized by abnormal LFTs from a paraneoplastic syndrome and not from liver metastases
  - Also find elevated alkaline phosphatase, PTT, low albumin, elevated bilirubin, or transaminases
- Hypercalcemia seen in 13% overall, and in 4.9% resulting from paraneoplastic syndromes
- Anemia may be due to blood loss

Imaging

- Thin-slice renal CT scan with and without IV contrast is the best test for diagnosing renal masses
- Any enhancing lesion on CT or MRI is RCC until proven otherwise
  - Enhancement generally defined as $\geq$20 HU increase between contrast and noncontrast phases
- R.E.N.A.L. Nephrometry score may provide a standardized system for radiologic comparison of renal masses (See RENAL Nephrometry in Section II)
- Any renal mass with a negative CT attenuation (< -20 HU) consistent with fat density is an AML
- Metastatic evaluation may include CT or MRI of the abdomen, chest x-ray for pulmonary lesions, and a bone scan in patients with elevated alkaline phosphatase or bone pain

Diagnostic Procedures/Surgery

- Biopsy of a renal mass is typically not included in the workup due to high false-negative rate, risk of bleeding, and remote possibility of seeding the biopsy tract
  - Difficult to distinguish between oncocytoma and RCC on biopsy
  - 83–90% of solid renal masses thought to be RCC are confirmed on final pathology
  - Sensitivity and specificity of FNA biopsy is 80% and 95%, which is no better than imaging alone
- Biopsy helps differentiate primary renal neoplasms from metastasis or renal lymphoma
- Biopsy is now considered more frequently in patients being considered candidates for observation vs. surgical extirpation
  - Biopsy is being used for surveillance in small RCC with $>$90% accuracy with adequate specimens

Pathologic Findings

- RCCs are adenocarcinomas, arising from renal tubular epithelial cells
- Clear cell RCC (formerly known as “conventional RCC”) 70–80% of RCC
- Papillary RCC accounts for 10–15%
  - Type 1: Associated with *Hereditary papillary renal cell carcinoma* (*HPRCC*)
  - Type 2: Aggressive, associated with *Hereditary leiomyomatosis and renal cell cancer* (*HLRCC*)
- Chromophobe 3–5% of solid renal masses, associated with a good prognosis

- Collecting duct (Bellini) RCC is rare (< 1%), but associated with a very poor prognosis. Occurs in younger patients (3rd–5th decades of life).
- Renal medullary RCC found in African Americans with sickle cell trait, and is often metastatic at the time of diagnosis
- Furhman nuclear grading: Graded 1–4 according to nuclear aberrations in RCC. Independent prognostic indicator with higher grades portending worse outcomes (4)[B]
- Sarcomatoid differentiation: Reported as presence and extent found in the primary histologic subtype; not a distinct category. Associated with a worse prognosis

DIFFERENTIAL DIAGNOSIS

- Adrenal mass
- Angiomyolipoma (fat poor)
- Collecting duct tumor (Bellini)
- Cystic nephromas (multilocular cystic nephroma)
- Cysts (hemorrhagic, infected)
- Focal pyelonephritis
- Hemangioma
- Inflammatory masses (xanthogranulomatous pyelonephritis, abscess, infected calyceal diverticulum)
- Leiomyoma
- Metanephric adenoma
- Metastasis from other primary tumor
- Oncocytoma
- Pseudotumors (hypertrophied column of Bertin, or fet al lobulations: Can mimic a central tumor, particularly in congenitally solitary kidneys)
- Renal cell carcinoma
- Renal lymphoma
- Renal medullary carcinoma (sickle cell trait)
- Renal sarcomas
- Reninoma (JG apparatus tumors)
- Urothelial carcinoma
- Wilms tumor (nephroblastoma)

TREATMENT

GENERAL MEASURES

- Surgical extirpation (radical or partial nephrectomy) is the primary treatment for solid renal masses
- Radical nephrectomy: Removal of the entire kidney, perinephric fascia, lymph nodes, and ipsilateral adrenal gland in upper pole tumors

MEDICATION

First Line

Systemic immunotherapy and targeted molecular therapies have no role in clinically localized RCC

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Partial nephrectomy is now the standard of care for clinical T1 renal masses (≤7 cm) in patients with a normal contralateral kidney who are surgical candidates. Oncologic outcomes equal to radical nephrectomy in selected patients. Renal function is preserved.
- Radical nephrectomy is the standard of care for large tumors, and for patients with metastases undergoing cytoreductive nephrectomy.
- Radiofrequency ablation/cryoablation minimally invasive; considered in selected small masses.

ADDITIONAL TREATMENT
Radiation Therapy
Radiation is limited to palliation of systemic metastases; no role in the management of clinically localized RCC

Additional Therapies
- Resection of solitary metastatic lesions (ie, lung) may be useful in selected cases
- No role for adjuvant systemic therapy in localized RCC

Complementary & Alternative Therapies
Renal masses <2 cm can be observed in many patients including those who are poor surgical candidates (~30% benign).

ONGOING CARE

PROGNOSIS
- The single most important prognostic factor for RCC is pathologic stage (5):
  - pT1a: 90–100% 5-yr survival
  - pT1b: 80–90% 5-yr survival
  - pT2: 70–80% 5-yr survival
  - pT3: 45–69% 5-yr survival in the absence of nodal or systemic metastases
  - pT4: 0–20% 5-yr survival in the absence of nodal or systemic metastases
- Direct invasion ipsilateral adrenal: 0–30% 5-yr survival; node-positive RCC: 0–20% 5-yr survival; metastatic RCC: 0–10% 5-yr survival
- Paraneoplastic syndromes, poor performance status, weight loss >10% worse outcome
- Other important prognostic factors include Fuhrman nuclear grade, histologic subtype, sarcomatoid features. Nomograms exist to predict risk of recurrence based on the above features.

COMPLICATIONS
- Surgical complications include bleeding, infection, urine leak, damage to surrounding structures including bowel, liver, spleen
- Large or locally invasive tumors may compromise GI or pulmonary function
- Bone metastases may result in pain and pathologic fractures
- Paraneoplastic syndromes causing cachexia, bleeding, HTN

FOLLOW-UP

Patient Monitoring

- See follow-up recommendations in "Renal Cell Carcinoma, Localized (T1–T2)"
- Incidence of local recurrence and the development of systemic metastases are directly associated with tumor stage (6)[B]:
  - T1: 0% local; 4% metastatic
  - T2: 2% local; 5.3% metastatic
- Surveillance is tailored to tumor stage

Patient Resources

- Kidney Cancer Association www.kidneycancer.org
- National Cancer Institute, Kidney Cancer www.cancer.gov/cancertopics/types/kidney

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9–29.
2. Parker AS, Cerhan JR, Janney CA, et al. Smoking cessation and renal cell carcinoma. *Ann Epidemiol*. 2003;13:245–251.
3. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol*. 2003;170:2163–2172.
4. Pantuck AJ, Zisman A, Belldegrun A. Biology of renal cell carcinoma: Changing concepts in classification and staging. *Semin Urol Oncol*. 2001;19:72–79.
5. Campbell SC, Lane BR. Malignant renal tumors. Chapter 49. In: Wein AJ, ed. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders/Elsevier; 2011:1413–1474.
6. Eggener S, Reiher FK, Campbell SC. Surveillance for renal cell carcinoma after surgical management. *Am Urol*. 2001;20:202–207.

ADDITIONAL READING

- Kattan MW, Reuter V, Motzer RJ, et al. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol*. 2001;166:63–67.
- Kutikov A, Uzzo RG. The R.E.N.A.L. Nephrometry Score: A comprehensive standardized system for quantitating renal tumor size, location, and depth. *J Urol*. 2009;182:844–853.

See Also (Topic, Algorithm, Media)

- Birt–Hogg–Dubé Syndrome
- Renal Cell Carcinoma, General Image
- Renal Cell Carcinoma, Localized (T1–T2)
- Renal Cell Carcinoma, Locally Advanced (T3–T4)
- Renal Cell Carcinoma, Metastatic (N+, M+)
- Renal Cell Carcinoma, Pediatric
- Renal Mass
- Reference Tables: TNM: Kidney Cancer
- Von Hippel–Lindau Disease/Syndrome

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 599.70 Hematuria, unspecified
- 789.09 Abdominal pain, other specified site

ICD10
- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- R10.9 Unspecified abdominal pain
- R31.9 Hematuria, unspecified

CLINICAL/SURGICAL PEARLS
- Most common solid renal mass is clear cell RCC.
- Most renal masses are detected incidentally.
- VHL syndrome is associated with chromosome 3p deletion and RCC, as well as other tumors.
- Surgical removal is the mainstay of treatment for RCC.
- Partial nephrectomy is increasingly utilized for larger, clinically localized tumors.

RENAL CELL CARCINOMA, LOCALIZED (T1–T2)

Reza Mehrazin, MD
Robert G. Uzzo, MD

BASICS

DESCRIPTION

- Renal cell carcinoma (RCC) refers to an adenocarcinoma and is the most common type of renal neoplasm. Stage T1 and T2 differ by size and are localized to the parenchyma with no extension outside the capsule.
- Stage T1 is further classified as T1a (tumor <4 cm) or T1b tumor (4–7 cm). Stage T2 is confined to the kidney and further classified as T2a (tumor 7–10 cm) and T2b (>10 cm).

EPIDEMIOLOGY

Incidence

- 63,920 new cases; 13,570 deaths in USA in 2014
  - Most lethal of all GU neoplasms (21% of those diagnosed will ultimately die of disease)
- Male > Female ($\sim$1.7:1)
  - 7th most frequent tumor in men (lifetime risk 1:61 in men and 1:103 in women)
- Peak incidence: 6th and 7th decades of life
- 10–20% higher incidence in African Americans
- 96% of cases are sporadic, whereas 4% are associated with familial syndromes

RISK FACTORS

- Only accepted environmental risk factor is tobacco exposure: Increases relative risk by 1.4–2.5. All forms of tobacco implicated; Risk increases with cumulative exposure
- Family history, obesity, hypertension, end stage renal disease (ESRD), autosomal dominant polycystic kideny disease (ADPCKD) and horseshoe kidney have all been implicated but not proven to be genetic or acquired risk factors

Genetics

- 3p25 (VHL gene) (tumor suppressor) implicated in $>70\%$ of all acquired (somatic mutations) cases of clear cell RCC. In cases of germ line *Von Hippel-Lindau syndrome* (VHL) mutation, additional manifestations include retinal angiomas, CNS hemangioblastomas, epididymal cystadenomas, endolymphatic sac tumors, pancreatic cysts, islet cell tumors, and pheochromocytomas.
- 7q31 (cMet gene) (oncogene) implicated in papillary type I RCC. With germ line mutations there are no known extrarenal manifestations.
- 17p11 (Birt–Hogg–Dubé/folliculin gene) (tumor suppressor) implicated in cases of chromophobe/oncocytoma. With germ line mutations can see: Cutaneous fibrofolliculomas, nevus, PTH adenomas, colonic polyps/tumors and pneumothorax.
- 1q42 (HLRCC gene) (Tumor suppressor) HLRCC syndrome (type II papillary RCC) manifestations include painful cutaneous leiomyomas, and uterine fibroids

PATHOPHYSIOLOGY

- RCC arises from the proximal convoluted tubule. Chromophobe, oncocytoma, and papillary tumors, believed to arise from the distal tubule.
- Tumors may grow locally and/or systemically concurrently. Local symptoms occur late and renal insufficiency is rare even with large tumors.
- Histology, grade, and stage are independent factors that correlate with survival
  - Lower risk: Low-grade (type I) papillary, chromophobe, and oncocytic carcinomas
  - Intermediate risk: Clear cell tumors
  - High risk: Collecting duct carcinomas, sarcomatoid clear cell carcinomas, renal medullary carcinomas associated with sickle cell
- Lesions < 4 cm: Up to 20–30% can be benign. Progression to metastasis appears to be a late event although up to 3–5% of small renal masses can present with synchronous metastases.
- In highly selected series, median radiographic growth rate during a period of active surveillance for a small renal mass is 0.08–0.58 cm/yr with mean growth rate of ~0.28 cm/yr (1)

ASSOCIATED CONDITIONS
- Extrarenal manifestations associated with RCC typically part of hereditary syndromes (such as *Von Hippel-Lindau syndrome* [VHL], *Hereditary leiomyomatosis and renal cell cancer* [*HLRCC*], Birt–Hogg–Dubé [BHD])
- Renal medullary carcinomas associated with sickle cell trait are highly aggressive (mean survival: 12–15 mo) and present during 3rd decade of life

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Most stage T1/T2 lesions are asymptomatic, incidentally discovered on cross-sectional imaging for unrelated reasons
- Symptoms of more advanced disease include hematuria, flank pain, fever, weight loss (> 10% of total body weight), bone pain

PHYSICAL EXAM
- In stage T1/T2 disease, typically few physical findings. Larger tumors may be palpable or symptomatically compressing on adjacent organs.
- Palpable abdominal mass, lymphadenopathy, nonreducing or rapid onset of varicocele may suggest advanced disease (renal vein or IVC involvement)
- Absence of symptoms or findings on physical exam does not rule out advanced disease

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC: Anemia may suggest worse prognosis, polycythemia may suggest paraneoplastic state
- Serum creatinine: eGFR clearance better estimate of renal function. Calculate CKD stage.
- Liver function tests: If abnormal consider Stauffer syndrome (reversible hepatitis), metastasis, or biliary duct obstruction
- Calcium: Elevated in paraneoplastic syndromes due to PTH-like substances

- Alkaline phosphatase: Elevation suggests bone or liver involvement

Imaging

- Pre- and postcontrast-based CT or MRI is essential (>20 Hounsfield units enhancement on CT of >20% increase in postcontrast region of interest (ROI) on MR)
- US can usually distinguish cystic from solid masses. Hyperdense cyst which may look solid and exhibit pseudoenhancement. CT or MRI (not US) is used to assign Bosniak grade.
- Extent of disease evaluation includes CXR or CT chest. Bone scan and CNS imaging performed if symptoms/signs mandate.
- FDG-PET not useful in evaluation of T1/T2 RCC due to low sensitivity and specificity

Pathologic Findings

- Staging (see "TNM Staging" section)
- Needle biopsy:
  - Appropriate if wide range of options are under consideration (focal therapy vs. observation)
  - Needle-tract seeding very uncommon
  - Good at distinguishing cancer and histologic type. Unreliable for tumor grade.

DIFFERENTIAL DIAGNOSIS

- Adrenal mass
- Angiomyolipoma (fat poor)
- Collecting duct tumor (Bellini)
- Cystic nephromas (multilocular cystic nephroma)
- Cysts (hemorrhagic, infected)
- Focal pyelonephritis
- Hemangioma
- Inflammatory masses (xanthogranulomatous pyelonephritis, abscess, infected calyceal diverticulum)
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- Pseudotumors (hypertrophied column of Bertin, or fet al lobulations: Can mimic a central tumor, particularly in congenitally solitary kidneys)
- RCC
- Renal lymphoma
- Renal medullary carcinoma (sickle cell trait)
- Renal sarcomas
- Reninoma (JG apparatus tumors)
- Urothelial carcinoma
- Wilms tumor (nephroblastoma)

TREATMENT

GENERAL MEASURES

- To avoid future renal insufficiency and metabolic disturbances, assess global renal function (eGFR) and consider nephron-sparing approaches, especially in those patients with low-to-intermediate complex renal masses and reasonable life expectancy
- For T1/T2 lesions, depending on pathology, surgery by radical or partial nephrectomy is highly likely to result in a long-term cure
- For T1 tumors radical and partial nephrectomy appear cancer equivalent. For T2 tumors partial is emerging as oncologically equivalent option (2).

MEDICATION

First Line

- Localized RCC is a surgical disease. Limited role for tyrosine kinase inhibitors and antiangiogenic therapy in localized RCC.
- Control of blood pressure, diabetes, lipids and minimization of atherosclerotic risk factors (smoking) are all important to subsequent renal function mandating physician involvement and patient counseling
- Use of ACE inhibitors or angiotensin receptor blockers may slow hyperfiltration injury

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Approach is dictated by many factors (3) including patient risks (comorbidities, underlying renal function, prior surgeries, trade-offs), tumor risk (size/location of the tumor, complexity of the mass [ie, nephrometry score—www.nephrometry.com], number of lesions), hospital and physician factors
- Excision: Partial or radical nephrectomy via open, laparoscopic, or robotic techniques
- Nephron-sparing surgery:
  - Partial nephrectomy is the standard of care for masses T1 in young otherwise healthy individuals for absolute, relative, and elective indications. Removal of mass with a small rim of normal parenchyma.
  - Other indications for partial nephrectomy: Absolute indications (patients with bilateral renal masses, a tumor in a solitary kidney) and relative indications (existing or comorbidities with potential for future renal insufficiency)
  - Enucleation (removal of mass by dissection between normal parenchyma and pseudocapsule of the tumor) is acceptable for small and/or multiple renal masses as long as negative margins are achieved
- Bilateral (synchronous) RCC: ~1–6%. Stage surgeries (Nephron sparing surgery (NSS) on easier side 1st as it provides more options for the difficult side). Can alter if there is a large discrepancy between complexity, size, and risks of the two sides.
- Ablation: Cryoablation or radio frequency ablation (RFA) by minimally invasive surgery (MIS) or percutaneous (preferred) technique:
  - Best with advanced age, significant comorbidities, and potentially amenable recurrence after prior NSS
  - Best: <3.5 cm, peripheral, solid, exophytic, remote from vessels/collecting system
  - Survival data are short term and there are no definitive data to date proving that ablation impacts tumor biologic potential

- Active surveillance: Elderly or with significant medical risks. Serial radiographic surveillance with assessment of the growth kinetics of the untreated mass and continued reassessment.

ADDITIONAL TREATMENT

Radiation Therapy

- No role in localized RCC outside of clinical trials of focal radiotherapy (CyberKnife) or HIFU
- Used for painful bony metastases and CNS metastasis in advanced RCC

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Related to stage, grade, histology. Nomograms available to calculate risk at www.cancernomograms.com.
- Local recurrence after resection is ~2–3% after radical nephrectomy and 4–6% after partial depending on pathology
- 5-yr risks of recurrence for local or regional RCC fully excised are approximately:
  - 5–9% low-risk disease
  - 20–25% intermediate-risk disease
  - 60–80% high-risk disease
- Prognosis for partial nephrectomy with a positive margin is less clear. Related to pathology and biology. Every attempt should be made intraoperatively to avoid a positive surgical margin; with focal positive margin, close observation is often indicated.

COMPLICATIONS

- Acute surgical/medical risks depend on treatments, techniques, comorbidities, and complexity of the mass. Overall perioperative death rate <0.5%. Risk of major Clavien grade 3–5 complications: 6.4%, 11.1%, 21.9% for low-, intermediate-, and high-complexity lesions (4).
- Risks after partial nephrectomy: Urinary leak/fistulas, AVF, bleeding, transient or permanent decline in renal function (5)
- Increased risk of *Nephrogenic systemic fibrosis* (*NSF*), with gadolinium (eGFR <30 mL/min per 1.73 m^2) and/or risk of contrast-induced nephropathy following use of iodinated contrast for radiographic surveillance

FOLLOW-UP

Patient Monitoring

- Periodic history, physical (including BP monitoring), and selected lab studies (calcium, hemoglobin, liver, renal profiles, urine analysis) at least yearly
- Radiographic stage/grade/histology-specific surveillance mandatory based on clinical stage and mode of treatment. Surveillance may be adjusted for other risk factors (grade/histology).

- Following ablation, initial radiographic follow-up requires lack of enhancement on pre-/postcontrast-based CT or MRI at 3–6 mo after procedure. Biopsy confirmation of successful ablation is recommended. Occasionally after cryotherapy, an area of rim enhancement can be seen that should resolve within 1st 3 mo.
- NCCN (National Comprehensive Cacner Network) guidelines (level of evidence 2B—lower level but consensus recommended)
  – Every 6 mo for 2 yr, then annually for 5 yr: History, physical, metabolic panel
  – At 2 yr (based on recurrence risk) chest and abdominal ± pelvic imaging then risk based

Patient Resources

- Kidney Cancer Association www.kidneycancer.org
- National Cancer Institute, Kidney Cancer www.cancer.gov/cancertopics/types/kidney

REFERENCES

1. Smaldone MC, Kutikov A, Egleston BL, et al. Small renal masses progressing to metastases under active surveillance: A systematic review and pooled analysis. *Cancer*. 2012;118:997–1006.
2. Long CJ, Canter DJ, Kutikov A, et al. Partial nephrectomy for renal masses ≥7 cm: Technical, oncological and functional outcomes. *BJU Int*. 2012;109(10):1450–1456.
3. Uzzo RG, Novick AC. Nephron sparing surgery for renal tumors: Indications, techniques and outcomes. *J Urol*. 2001;166:6–18.
4. Simhan J, Smaldone MC, Tsai KJ, et al. Objective measures of renal mass anatomic complexity predict rates of major complications following partial nephrectomy. *Eur Urol*. 2011;60(4):724–730.
5. Mehrazin R, Palazzi KL, Kopp RP, et al. Impact of tumor morphology on renal functional decline after partial nephrectomy. *BJU Int*. 2013;111(8):E374–E382.

ADDITIONAL READING

- AUA Guideline for Management of the Clinical Stage 1 Renal Mass, 2009: http://www.auanet.org/content/media/renalmass09.pdf
- NCCN Guidelines: www.NCCN.org

See Also (Topic, Algorithm, Media)

- Birt–Hogg–Dubé Syndrome
- Renal Cell Carcinoma, General
- Renal Cell Carcinoma, Localized (T1–T2) Image
- Renal Cell Carcinoma, Locally Advanced (T3–T4)
- Renal Cell Carcinoma, Metastatic (N+, M+)
- Renal Cell Carcinoma, Pediatric
- Renal Mass
- Reference Tables: TNM: Kidney Cancer
- Von Hippel–Lindau Disease/Syndrome

CODES

ICD9

189.0 Malignant neoplasm of kidney, except pelvis

ICD10

- C64.1 Malignant neoplasm of right kidney, except renal pelvis
- C64.2 Malignant neoplasm of left kidney, except renal pelvis
- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis

CLINICAL/SURGICAL PEARLS

- Always review the images and carefully assess the presence of the contralateral kidney and the adrenal glands.
- Do not overtreat or undertreat renal mass.

RENAL CELL CARCINOMA, LOCALLY ADVANCED (T3–T4)

Ahmad Shabsigh, MD, FACS

BASICS

DESCRIPTION

- T3 renal cell carcinoma (RCC) extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia.
  - T3a tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
  - T3b tumor grossly extends into the vena cava below the diaphragm.
  - T3c tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.
- T4 RCC invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).

EPIDEMIOLOGY

Incidence

- 63,920 new cases in USA in 2014 (39,140 in men and 24,780 in women)
- 13,860 deaths in USA in 2014
- 20% of patients present with locally advanced or node-positive RCC
- RCC with IVC involvement is seen in 4–10% of patients

Prevalence

8.3–12 new cases per 100,000 per year

RISK FACTORS

- Cigarette smoking results in a 1.4–2.5 increased risk of RCC; risk increases with higher pack/yr consumption, may not be as much of a factor for women as men.
- Obesity: 40% of RCC may be attributed to overweight or obesity.
- A positive family history of RCC in a 1st- or 2nd-degree relative carries a relative risk of 2.9 of developing RCC.
- HTN has a 1.4–2-fold increase in risk of RCC.
- Low socioeconomic status, urban background, and parity have been associated with an increased risk of RCC.

Genetics

- Nonhereditary clear cell RCC is associated with deletion of chromosome 3p and/or mutations of the VHL gene.
- VHL manifests clear cell RCC due to alterations of the VHL gene on chromosome 3p25–26.
- Nonhereditary papillary RCC has been linked with changes in both chromosome 7 and 17.
- *Hereditary papillary renal cell carcinoma* (*HPRCC*) arises from mutation of the MET protooncogene on chromosome 7p34.
- Chromophobe RCC: Loss of chromosome 17.
- Birt–Hogg–Dubé syndrome develops from changes in the BHD1 gene on chromosome

17p11.2.
- FH (fumarate hydratase) mutations on chromosome 1q42 in hereditary leiomyomatosis: Predispose to papillary Type 2 RCC.
- Mutations in the TSC1/2 genes predispose to tuberous sclerosis.

PATHOPHYSIOLOGY
- 20% of cases will have frank invasion of the capsule or collecting system.
- 10% will demonstrate venous involvement with tumor thrombus.
- Adjacent organs are usually compressed by growing tumor, whereas direct invasion of liver, spleen, colon, pancreas, diaphragm, and duodenum are rare but associated with very poor prognosis.

ASSOCIATED CONDITIONS
- Acquired renal cystic disease in conjunction with ESRD has a 1–2% risk of developing RCC, an overall 5–20-fold increase in risk of RCC for ESRD patients
- VHL-related RCC:
  - Retinal angioma
  - Cerebellar and spinal hemangioblastoma
  - Pancreatic cysts
  - Neuroendocrine tumors
- Facial fibrofolliculomas in the malar region, lung cysts, and spontaneous pneumothoraces are associated with BHD-related RCC
- Familial leiomyomatosis and RCC:
  - Type 2 papillary RCC
  - Cutaneous leiomyomas
  - Uterine leiomyomas
- Birt–Hogg–Dubé syndrome:
  - Chromophobe RCC
  - Oncocytoma
  - Occasional clear cell RCC
  - Cutaneous fibrofolliculomas
  - Lung cysts
  - Spontaneous pneumothorax
- Possibly an increased risk of RCC in individuals with TS

GENERAL PREVENTION
- Smoking cessation
- Physical activity
- Weight loss
- Questionable association with certain foods and alcohol consumption

DIAGNOSIS

HISTORY
- The classic triad of symptoms: Flank pain, palpable flank mass, and hematuria are rarely seen since the advent of CT scanning.
- Associated symptoms are due to local tumor growth, hemorrhage, paraneoplastic syndromes

(hypercalcemia, hypertension, polycythemia, Stauffer's syndrome), or metastatic disease and generally indicate advanced disease.
- Locally invasive RCC causes pain from invasion of posterior abdominal wall, nerve roots, or paraspinous muscles.
- History of pulmonary embolism should increase index of suspicion for venous thrombus in patient with kidney mass.
- Caput medusa
- Early satiety or emesis
- Varicocele, lower-extremity edema
- Lower-extremities edema

PHYSICAL EXAM
- Palpable abdominal mass
- Flank or abdominal tenderness
- Bilateral lower-extremity edema
- Isolated right-sided varicocele, or one that does not decompress
- Caput medusa (dilated abdominal veins)

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- LFTs, creatinine, electrolytes, CBC, and urine analysis are standard initial evaluation, serum calcium
- Elevated ESR is present in 55.6%
- Abnormal liver function tests (LFT's) are found in 14.4%, which is called Stauffer syndrome if elevation is due to paraneoplastic syndrome and not due to liver metastases
  - Stauffer syndrome:
    - Elevated alkaline phosphatase
    - Increased PTT
    - Low albumin, and sometimes elevated bilirubin or transaminases
- Elevated serum calcium is seen in up to 13% overall and in 4.9% as a result of paraneoplastic syndromes
- Polycythemia can be detected in 3.5%
- Elevated C-reactive protein

Imaging
- CT scan with IV contrast if renal function is acceptable.
- MRI is generally considered best for IVC tumor thrombus evaluation, although multiplanar CT with contrast is similar in accuracy.
- Transabdominal US with color Duplex imaging can be used but may not be as accurate in evaluation of the extent of thrombus (85% accuracy).
- Transesophageal echocardiography (TEE) can be helpful pre-op and intraoperatively (1).
- Venacavography is only for those who cannot have an MRI or have an indeterminate MRI.
- Nonfunction of affected kidney may indicate extensive venous thrombus formation.
- Chest CT: Evaluate for pulmonary metastasis.
- CT or MRI of the brain if symptomatic.

Diagnostic Procedures/Surgery

Biopsy or FNA has a role in differentiating RCC from a renal metastasis of another primary and from renal lymphoma; rarely used for routine diagnosis except in cases of percutaneous ablation

Pathologic Findings

- Tumors with histologic necrosis are almost twice as likely to have lymph node metastases as those without necrosis.
- All RCC are adenocarcinomas, arising from renal tubular epithelial cells.
- Clear cell RCC is 70–80%.
- Higher Fuhrman nuclear grading is linked to worse outcome and more aggressive disease.
- Papillary RCC makes up 10–15% and has 2 subtypes:
  - Type 1 associated with HPRCC: Basophilic cells with low-grade nuclei
  - Type 2 very aggressive and associated with HLRCC: Eosinophilic cells with high-grade nuclei
  - Immunohistochemistry (IHC): Low molecular weight cytokeratins (LMWCKs), CK7 (type 1 > type 2), alpha-methylacyl-CoA racemase (AMACR) positive in over 75%
- Chromophobe RCC is 3–5% of solid renal masses and may be less aggressive.
- Collecting duct RCC is rare (<1%) but very lethal.
- Medullary carcinoma associated with sickle cell trait in young African Americans, is often advanced and metastatic at the time of diagnosis; death occurs within a few months of diagnosis.
- Sarcomatoid variants of all subtypes have been described and are associated with a worse prognosis.

DIFFERENTIAL DIAGNOSIS

- Adrenal mass
- Angiomyolipoma (fat poor)
- Collecting duct tumor (Bellini)
- Cystic nephromas (multilocular cystic nephroma)
- Cysts (hemorrhagic, infected)
- Focal pyelonephritis
- Hemangioma
- Inflammatory masses (xanthogranulomatous pyelonephritis, abscess)
- Leiomyoma
- Metanephric adenoma
- Metastasis from other primary tumor
- Oncocytoma
- Renal lymphoma
- Urothelial carcinoma
- Wilms tumor (nephroblastoma)

TREATMENT

GENERAL MEASURES

- Preoperative renal artery embolization may cause the tumor thrombus to regress and reduce the morbidity of surgery as a result.

- Avoid IVC filter placement.

MEDICATION

The role of neoadjuvant targeted therapies (eg, sunitinib, sorafenib, others) for downsizing the primary tumor and the IVC thrombus is controversial: 5–10% reduction in primary site.

SURGERY/OTHER PROCEDURES

- Radical nephrectomy is standard of care.
- Nephron-sparing surgery is possible in selected patients with locally advanced RCC, with equivalent oncologic efficacy to radical nephrectomy (2).
- 45–70% of T3b patients can be cured with aggressive surgery.
- No clear survival benefit of extended lymph node dissection, except in HLRCC patients (3).
- In patients with single lymph node metastasis or micrometastasis, a regional lymphadenectomy may be beneficial.
- Open or minimally invasive surgery is acceptable.

ADDITIONAL TREATMENT

Radiation Therapy

- Role is limited; no survival benefit to preoperative treatment
- May slow growth if residual tumor left after surgery; rarely used
- May palliate symptomatic local recurrences in nonsurgical candidates

Additional Therapies

Targeted agents to growth factors are being evaluated in both an adjuvant and neoadjuvant setting for patients at high risk for recurrence (4).

Complementary & Alternative Therapies

None proven

ONGOING CARE

PROGNOSIS

- T3a: 60–80% 5-yr survival
- T3b/c: 40–60% 5-yr survival
- T4: 0–20% 5-yr survival
- Ipsilateral adrenal involvement has 0–40% 5-yr survival
- Node-positive RCC has 0–20% 5-yr survival
- For T4 tumors, the median time to recurrence is only 9.5 mo

COMPLICATIONS

- Surgical complications are bleeding, infection, injury to surrounding organs (liver, spleen, bowel, pancreas). Urine leak in partial nephrectomy.
- Pulmonary embolism from tumor thrombus
- Advanced tumors can bleed spontaneously either locally causing flank pain or into the urine resulting in hematuria and/or clot-induced urinary obstruction.
- Venous congestion resulting in bilateral lower-extremity edema, varicoceles, or portal HTN from tumor thrombi into the renal, caval, or hepatic vasculature.

FOLLOW-UP

Patient Monitoring

- T3: Every 6 mo for 2 yr then annually for 5 yr: H + P, comprehensive metabolic panel, LDH. Chest and abdomen imaging at 2–6 mo then as indicated.
- T4: Every 3 mo history and physical exam, CXR, labs; every 6 mo abdominal CT for 3 yr

Patient Resources

- Kidney Cancer Association www.kidneycancer.org
- National Cancer Institute, Kidney Cancer www.cancer.gov/cancertopics/types/kidney

REFERENCES

1. Glazer AA, Novick AC. Preoperative transesophageal echocardiography for assessment of resonance imaging. *Urology*. 1997;49:32–34.
2. Margulis V, Tamboli P, Jacobsohn KM, et al. Oncological efficacy and safety of nephron-sparing surgery for selected patients with locally advanced renal cell carcinoma. *BJU Int.* 2007;100(6):1235–1239.
3. Blute ML, Leibovich BC, Cheville JC, et al. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. *J Urol.* 2004;172:465–469.
4. Cost NG, Delacroix SE Jr, Sleeper JP, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. *Eur Urol.* 2011;59:912–918.

ADDITIONAL READING

- Hass NB, Uzzo RG. Targeted therapies for kidney cancer in urologic practice. *Urol Oncol.* 2007;25(5):420–432.
- Thillai K, Allan S, Powles T, et al. Neoadjuvant and adjuvant treatment of renal cell carcinoma. *Expert Rev Anticancer Ther*. 2012;12(6):765–776.

See Also (Topic, Algorithm, Media)

- Brit–Hogg–Dubé Syndrome
- Renal Cell Carcinoma, Localized (T1–T2)
- Renal Cell Carcinoma, Locally Advanced (T3–T4) Image
- Renal Cell Carcinoma, General
- Renal Cell Carcinoma, Metastatic (N+, M+)
- Renal Cell Carcinoma, Pediatric
- Renal Mass
- Reference Tables: TNM: Kidney Cancer
- Von Hippel–Lindau Disease/Syndrome

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 198.89 Secondary malignant neoplasm of other specified sites

ICD10

- C64.1 Malignant neoplasm of right kidney, except renal pelvis

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- C79.89 Secondary malignant neoplasm of other specified sites

CLINICAL/SURGICAL PEARLS

- Detailed evaluation of extent of the disease is critical.
- Consult vascular and/or cardiothoracic surgeon if needed.

RENAL CELL CARCINOMA, METASTATIC (N+, M+)

Jianqing Lin, MD
Wm. Kevin Kelly, DO

BASICS

DESCRIPTION

- Advanced stage of renal cell carcinoma (RCC)
  - N1: Metastasis in regional lymph node(s)
  - M1: Distant metastasis
  - Nodal involvement is now simplified to N0 vs. N1
- Other changes for staging from the *AJCC Cancer Staging Manual* (7th edition):
  - Ipsilateral adrenal involvement is reclassified as T4 if contiguous invasion and M1 if not contiguous
  - Renal vein involvement is reclassified as T3a

EPIDEMIOLOGY

Incidence

- Renal cancer increased by 2% per year for the past 65 yr. Increased by 3.1% per year from 2005–2009 primarily due to an increase in early-stage disease. Renal cancer accounts for 2–3% of all malignancies. Median age of diagnosis is 65 yr, median age of death is 70 yr.
  - 1/3 of patients with RCC present M+/N+
- 40–50% will develop metastatic disease after initial diagnosis. Male > Female (ratio is 3:2).
- Death rates for kidney cancer decreased by 0.5% per year from 2005–2009

Prevalence

N/A

RISK FACTORS

- Smoking
- Obesity
- Hypertension and chronic renal failure
  Chemicals or radiation exposure slightly increases risk.
- Rare hereditary conditions
  - Von Hippel–Lindau (VHL) disease
  - Hereditary papillary RCC

Genetics

- Majority of cases are sporadic
- VHL tumor suppressor gene (on 3p25–26) associated with clear cell RCC
- Chromosome 7q31 is associated with papillary RCC, type 1 associated with mutations in c-MET
- Fumarate hydratase (FH) associated with papillary RCC type 2
- Birt–Hogg–Dubé (BHD) syndrome associated with chromophobic RCC
- Xp11.2 translocation: Patients under 45 yr

- BRCA1-associated protein-1 (BAP1) loss associated with high tumor grade

PATHOPHYSIOLOGY
- RCCs derived from renal tubular epithelium
- Mode of spread is via direct extension, propagation into renal vein, or hematogenous
- Rare reports of spontaneous regressions, usually pulmonary, following nephrectomy

ASSOCIATED CONDITIONS
- VHL syndrome
- Chronic renal failure
- Lymphoma

GENERAL PREVENTION
Smoking cessation helps prevent primary tumor

DIAGNOSIS
HISTORY
- Usually no symptoms in early stage but incidental diagnosis of kidney mass. Metastasis may or may not cause symptoms.
- Gross hematuria
- Flank or abdominal pain
- Symptoms related to involved organ(s)
- Constitutional symptoms:
  - Fatigue, weight loss, fever, or lower-extremity edema

PHYSICAL EXAM
- With attention to abdominal mass, adenopathy, lower-extremity edema
- Varicocele (classically on left)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC: Anemia of chronic disease in up to 30%
- Urinalysis: Hematuria
- Complete metabolic panel
- Paraneoplastic syndromes (found in 20% of patients):
  - Hypercalcemia
  - Hypertension
  - Erythrocytosis
  - Elevated erythrocyte sedimentation rate (ESR)
  - Nonmetastatic hepatic dysfunction (Stauffer syndrome)
- Urine cytology: R/O urothelial carcinoma

Imaging
- MRI or CT of abdomen and pelvis (~85% of enhancing renal masses are RCC)
  - Most enlarged lymph nodes by imaging are inflammatory rather than neoplastic
- CNS imaging: In patients with symptoms or radiographic evidence of advanced disease
- Positron emission tomography (PET) has poor sensitivity and not commonly used

Diagnostic Procedures/Surgery

- Needle biopsy to the metastatic site or metastasectomy usually required to establish diagnosis
- Needle biopsy is generally safe and warranted if any uncertainty for M1 disease

Pathologic Findings

- Histologic subtypes:
  - Clear cell: 70–80%
  - Papillary: 10–15%
  - Chromophobe: 3–5%
  - Collecting duct/medullary cancer $<1\%$
  - Translocation Xp11.2: Clear and/or eosinophilic, voluminous cytoplasm
- Sarcomatoid variants all histologic subtypes:
  - Represent poorly differentiated regions
  - Portends a much more aggressive biology with recurrence/resistance to therapy

DIFFERENTIAL DIAGNOSIS

- Renal masses:
  - Angiomyolipoma (fat-poor)
  - Collecting-duct tumors
  - Cystic nephromas
  - Cysts (hemorrhagic, infected)
  - Focal pyelonephritis
  - Hemangioma
  - Inflammatory masses (xanthogranulomatous pyelonephritis, abscess)
  - Leiomyoma
  - Metanephric adenoma
  - Metastasis from other primary tumor
  - Oncocytoma
  - Pseudotumors (column of Bertin, others)
  - RCC
  - Renal lymphoma
  - Renal medullary carcinoma
  - Sarcomas
  - Reninoma (Juxtaglomerular tumors)
  - Urothelial carcinoma
  - Wilms tumor (nephroblastoma)
- Lymphadenopathy:
  - Inflammatory related to RCC
  - RCC
  - Infectious/inflammatory:
    - Granulomatous: TB, sarcoidosis, histoplasmosis, lymphogranuloma venereum, Castleman disease, etc.
    - Nongranulomatous: Viral, bacterial (if abscess in local areas), sinus histiocytosis
  - Primary lymphatic malignancy: Lymphoma (non-Hodgkin and Hodgkin, others)
  - Other metastatic malignancies:

- Gastrointestinal (GI) (carcinoid, colorectal, lymphoma), urothelial, prostate, melanoma, penile, germ cell, cervical, ovarian, uterine
- Pulmonary nodules:
  - Benign hamartoma/AVM, nonspecific granuloma, infectious granuloma (aspergillosis, coccidioidomycosis, cryptococcosis, histoplasmosis, tuberculosis, atypical mycobacterial infections), septic emboli, abscesses
  - Malignancy: Lung primary, metastasis (choriocarcinoma, RCC, melanoma, thyroid carcinoma, Kaposi's sarcoma), non-Hodgkin lymphoma

TREATMENT

GENERAL MEASURES

- Stage IV disease may also benefit from cytoreductive surgery
- Minimal regional adenopathy does not preclude surgery
- Potential candidate for nephrectomy and/or surgical metastasectomy:
  - Resectable primary RCC and a solitary resectable metastasis
  - A solitary recurrence after prolonged disease-free interval from nephrectomy
- Tends to be resistant to both traditional chemotherapy and radiation therapy
- Antiangiogenesis via targeting vascular endothelial growth factor (VEGF) pathway is the mainstay of treatment; improve survival for M1
- Multityrosine kinase inhibitors (TKI) or mTOR inhibitors or monoclonal antibody
- Data for nonclear cell RCC therapy limited
- Sarcomatoid RCC: Gemcitabine- or capecitabine- or floxuridine- or 5-FU- or doxorubicin-based chemotherapy (category 3 and limited data)
- Other immunotherapy is under development

MEDICATION

First Line

- High-dose (bolus) interleukin-2 (IL-2) (Aldesleukin, Proleukin) (1)
  - IL-2: Only agent shown to produce durable and complete responses (CR) in 6–8% of patients; Partial response 10–15%
  - 1st line. Selected patients: Mostly clear cell, <65 yr old, good cardiac, pulmonary, liver and renal function, no brain mets
  - Typical regimen 600,000–720,000 IU/kg IV Q8h for 5 days. One course as 2 cycles on days 1–5 and 15–19 of 28-day cycle. If no progression, repeat approximately every 3 mo to a max of 3 courses.
  - Systemic inflammatory response syndrome (SIRS), "capillary leak syndrome" side effects
  - "Treat as tolerated" significantly reduces treatment-related mortality
- Sunitinib: Targets VEGF receptor tyrosine kinase and other pathways (2)
  - 1st line
  - 50 mg/d PO for 4 wk of 6-wk cycle (4 wk on, 2 wk off)
- Pazopanib: Targets VEGF receptors and other pathways
  - 1st line or postcytokine: 800 mg PO daily
- Bevacizumab: VEGF antibody
  - 1st line with interferon-α 10 mg/kg IV Q2wk

- Interferon-α: Stimulates immune function
  - 1st line, only combination with bevacizumab
  - SubQ a start of 9 MU on 3 nonconsecutive days per week, with dose reduction to 6 MU and to 3 MU if toxicity
- Temsirolimus: mTOR inhibitor (3)
  - 1st line for poor-risk patients or nonclear cell histology: 25 mg IV weekly
- Sorafenib: Targets VEGF receptor and other pathways: 1st or 2nd line: 400 mg PO BID (4)

Second Line

- Agents as noted above after failure of 1st targeted therapy
- Axitinib: Potent, selective, 2nd-generation inhibitor of VEGFR 1, 2, and 3 (5):
  - 2nd line: 5 mg PO BID,10 mg PO BID max
- Everolimus: mTOR inhibitor
  - 2nd line: 10 mg PO daily

SURGERY/OTHER PROCEDURES

- Cytoreductive nephrectomy in patients with metastatic disease is generally considered standard of care (6):
  - SWOG 8949: Improved overall survival for debulking nephrectomy in interferon-treated patients with advanced RCC. However, no similar data is available in TKI era.
- Strongly consider metastasectomy for amendable and isolated solitary metastasis (synchronous or metachronous)
  - Lymphadenectomy should be performed in radiographically suspicious cases; however, ultimate role and benefit is yet to be defined.

ADDITIONAL TREATMENT

Radiation Therapy

Palliative role for osseous or CNS metastasis or pain control

Additional Therapies

- Many other agents under study and reported:
  - Nonmyeloablative allogeneic hematopoietic cell transplantation
  - Interferon-γ, vaccines, other interleukins alone and in combination
- Multiple studies under way addressing sequencing and combination of targeted therapies along with immunotherapy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 5-yr survival: Improving (7)
  - Stage III: 15–35%
  - Stage IV: 0–10%
  - Enhanced survival with the following characteristics: Long interval between nephrectomy and the appearance of distant metastases, a single metastatic site, and the absence of retroperitoneal adenopathy

COMPLICATIONS

- Related to treatment
  - High-dose IL-2: Vascular leak syndrome
  - TKIs: Fatigue, HTN, hand and foot syndrome, GI toxicity, hypothyroidism
  - mTOR inhibitors: Fatigue, rash, hyperglycemia, dyslipidemia
- Others related to disease progression

FOLLOW-UP

Patient Monitoring

- Depends on stage of disease and treatment
  - Usually chest and abdominal imaging every 3–6 mo if not being treated
  - Imaging every 3–4 cycles if underactive systemic treatment
  - Serum chemistries and liver function tests as routine

Patient Resources

- Kidney Cancer Association www.kidneycancer.org
- National Cancer Institute, Kidney Cancer www.cancer.gov/cancertopics/types/kidney

REFERENCES

1. McDermott DF, Rini BI. Immunotherapy for metastatic renal cell carcinoma. *BJU Int.* 2007;99:1282–1288.
2. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356:115–124.
3. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356:2271–2281.
4. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear cell renal-cell carcinoma. *N Engl J Med.* 2007;356:125–134.
5. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as 2nd-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol.* 2013;14(6):552–562.
6. Flanigan RC. Debulking nephrectomy in metastatic renal cell carcinoma. *Clin Cancer Res.* 2004;10:6335S–6341S.
7. Lara PN Jr, Tangen CM, Conlon SJ, et al. Predictors of survival of advanced renal cell carcinoma: Long-term results from SWOG Trial S8949. *J Urol.* 2009;181(2):512–516.

ADDITIONAL READING

- Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med.* 1996;335:865–875.
- NCCN Guidelines. Available at http://www.nccn.org/clinical.asp (Acessed August 20, 2014)

See Also (Topic, Algorithm, Media)

- Renal Cell Carcinoma, General
- Renal Cell Carcinoma, Localized (T1–T2)
- Renal Cell Carcinoma, Locally Advanced (T3–T4)
- Renal Cell Carcinoma, Metastatic (N+, M+) Image
- Renal Cell Carcinoma, Pediatric
- Reference Tables: TNM: Kidney Cancer

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 196.2 Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes

ICD10

- C64.1 Malignant neoplasm of right kidney, except renal pelvis
- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- C77.2 Secondary and unsp malignant neoplasm of intra-abd nodes

CLINICAL/SURGICAL PEARLS

- Cytoreductive surgery should be considered for M1 disease.
- Only high-dose IL-2 provide durable complete response (CR).
- No targeted agents show significant complete response (CR).
- Patients achieving response with targeted agents such as TKI have a response duration of ~8–10 mo (medium <12 mo) with continuous therapy treatment.
- Combination therapies are being explored.

RENAL CELL CARCINOMA, PEDIATRIC

Sarah M. Lambert, MD
Pasquale Casale, MD, FACS

BASICS

DESCRIPTION
Renal cell carcinoma (RCC) is a very rare tumor in childhood arising from the renal tubular epithelium

EPIDEMIOLOGY
Incidence
- 2–6% of all pediatric renal tumors
- Only ~4 cases of pediatric RCC per year
- Estimated at <0.3% of all pediatric tumors
- Just over 350 cases reported in the literature
- Mean age of presentation between 8 and 10 yr vs. <3 yr for Wilms tumor
- Equal male:female

Prevalence
N/A

RISK FACTORS
- Von Hippel–Lindau syndrome
- Tuberous sclerosis

Genetics
- Translocation type of RCC, which forms a distinct category has recently emerged as the predominant type of RCC in children and adolescents, whereas it is rarely diagnosed in adults.
- Chromosomal translocations in Xp11.3 region involving TFE3 gene (1).
- Less frequently, 6p21 translocation.
- If seen with Von Hippel–Lindau, more likely to be bilateral.

PATHOPHYSIOLOGY
- Thought to arise from renal tubular epithelium
- Most frequently papillary subtype with Xp11 translocation
  – Role of translocation at Xp11.2 region involving TFE3 gene unknown (1)
- Lung and bone are the most common distant metastases.

ASSOCIATED CONDITIONS
- Tuberous sclerosis, chronic renal failure, neuroblastoma, and teratoma with chemotherapy
- Rarely associated with adult familial RCC

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY

- Gross hematuria (~40%), flank pain, abdominal distension (2)
- Nausea, vomiting, malaise common
- Pain in up to 50%
- 30% found incidentally (2)

PHYSICAL EXAM

- Palpable abdominal mass (~40%) (2)
- Triad of hematuria, flank pain, and palpable mass found in <6% of children (3)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: Hematuria found in >40% of patients (3)
- CBC: Polycythemia is rare
- Liver and renal function tests: Baseline prior to treatment

Imaging

- Abdominal x-ray may show tumor calcifications (~25%) vs. Wilms tumor (~5%) (3)
- US demonstrates solid or cystic renal mass.
- CT or MRI with and without contrast reveal enhancing renal mass.
- Pediatric RCCs typically present as large, heterogeneous masses, commonly hemorrhage and contain internal calcifications.
- IVP can demonstrate renal mass by displacement of the collecting system.
- Chest x-ray or chest CT scan for workup of metastatic disease.
- Radionuclide bone scan is indicated based on concern for mets.

Diagnostic Procedures/Surgery

Biopsy is not indicated

Pathologic Findings

- Predominately papillary histologic features in children vs. clear cell features in adults
- Pathologic staging based on modified Robson staging system
- Up to 25% pediatric RCC cannot be clearly classified due to atypical features
- Pathologic parameters typically associated with poor outcome in adults (metastasis/high tumor stage, high Fuhrman nuclear grade, angiolymphatic invasion, tumor necrosis), do not appear to have similar implications in pediatric patients

DIFFERENTIAL DIAGNOSIS

- Benign renal mass in children:
  - Choledochal cyst, intestinal duplication cyst
  - Congenital mesoblastic nephroma
  - Hydronephrosis
  - Mesenteric cyst
  - Multicystic dysplastic kidney
  - Polycystic kidney
  - Renal abscess
  - Splenomegaly

- Malignant renal masses in children:
  - Hepatoblastoma
  - Lymphoma
  - Lymphosarcoma
  - Neuroblastoma
  - RCC
  - Rhabdomyosarcoma
  - Wilms tumor

TREATMENT

GENERAL MEASURES

Management is primarily surgical excision by either radical nephrectomy or partial nephrectomy

MEDICATION

First Line

- The use of chemotherapy, immunotherapy, or tyrosine kinase inhibitors is not adequately described in pediatric population.
- The use of tyrosine kinase inhibitors should be considered in the pediatric patient with unresectable, metastatic, or advanced-stage RCC.
- Small series of patients treated with neoadjuvant chemotherapy according to Wilms tumor protocol.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical nephrectomy (4)
  - Removal of entire kidney and portion of the ureter
  - Common approaches in children include flank and abdominal incisions
- Partial nephrectomy (5)
- Laparoscopic and robotic-assisted radical or partial nephrectomy for RCC in children are described in select cases (6,7)

ADDITIONAL TREATMENT

Radiation Therapy

Has been used for both initial treatment and recurrence but not well studied in pediatric populations

Additional Therapies

- Adjuvant chemotherapy for metastatic disease has been tried in the pediatric population but not well characterized.
- Tyrosine inhibitors have been used in children with metastatic disease but data are limited (9).

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Overall survival similar to adult RCC and depends on (Robson) stage:
  - Rest prognosis stage with stage I (>90%) and II (>80%)
  - Stage III ~75%, stage IV ~15% (2)

COMPLICATIONS

- Surgical complications (bleeding, infection, diathesis, bowel injury)
- Metastasis to lung and bone, multiple other sites

FOLLOW-UP

Patient Monitoring

- Adult protocols followed as there are no pediatric protocols
- No long-term follow-up guidelines:
  - Physical exam, chest x-ray, chemistry panel, CBC, and urinalysis every 6 mo for 5 yr
  - CT on yearly basis for 5 yr
- Risk of chronic kidney disease likely attributed to reduced renal reserve capacity should be recognized and treated with nephrologic evaluation (8)

Patient Resources

National Cancer Institute http://www.cancer.gov/cancertopics/pdq/treatment/wilms/patient

REFERENCES

1. Ramphal R, Pappo A, Zielenska M, et al. Pediatric renal cell carcinoma: Clinical, pathologic, and molecular abnormalities associated with the members of the MiT transcription factor family. *Am J Clin Pathol*. 2006;126:349–364.
2. Estrada CR, Suthar AM, Eaton SH, et al. Renal cell carcinoma: Children's Hospital Boston experience. *Urology*. 2005;66:1296–1300.
3. Undolfi P, Terenziani M, Casale F, et al. Renal cell carcinoma in children: A clinicopathologic study. *J Clin Oncol*. 2003;21:530–535.
4. Caran A, Akyuz C, Sari N, et al. Renal cell carcinoma in children: Experience of a single center. *Nephron Clin Pract*. 2007;105:c58–c61.
5. Cook A, Lorenzo AJ, Salle JL, et al. Pediatric renal cell carcinoma: Single institution 25 year case series and initial experience with partial nephrectomy. *J Urol*. 2006;175:1456–1460.
6. Perlman EJ. Pediatric renal cell carcinoma. *Surg Pathol Clin*. 2010;3(3):641–651.
7. Cost NG, Geller JI, DeFoor WR Jr, et al. A robotic-assisted laparoscopic approach for pediatric renal cell carcinoma allows for both nephron-sparing surgery and extended lymph node dissection. *J Pediatr Surg*. 2012;47(10):1946–1950.
8. Cozzi DA, Ceccanti S, Frediani S, et al. Chronic kidney disease in children with unilateral renal tumor. *J Urol*. 2012;187(5):1800–1805.
9. Chowdhury T, Prichard-Jones K, Sebire NJ, et al. Persistent complete response after single-agent sunitinib treatment in a case of TFE translocation positive relapsed metastatic pediatric renal cell carcinoma. *J Pediatr Hematol Oncol*. 2013;35(1):e1–e3.

ADDITIONAL READING

- Dome JS, Fernandez CV, Mullen EA, et al. Children's Oncology Group's 2013 blueprint for research: Renal tumors. *Pediatr Blood Cancer*. 2013;60(6):994–1000.
- Spreafico F, Collini P, Terenziani M, et al. Renal cell carcinoma in children and adolescents. *Expert Rev Anticancer Ther*. 2010;10(12):1967–1978.

See Also (Topic, Algorithm, Media)

- Neuroblastoma
- Reference Tables: TNM: Kidney Cancer
- Reference Tables: TNM: Kidney Cancer
- RCC, General
- RCC, Localized (T1, T2)
- RCC, Locally Advanced (T3–T4)
- RCC, Metastatic (N+, M+)
- Renal Mass
- Robson Staging System
- Translocation Renal Cell Carcinoma; Translocation Xp11.2
- Von Hippel–Lindau Disease/Syndrome
- Wilms Tumor

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 197.0 Secondary malignant neoplasm of lung
- 198.5 Secondary malignant neoplasm of bone and bone marrow

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- C78.00 Secondary malignant neoplasm of unspecified lung
- C79.51 Secondary malignant neoplasm of bone

CLINICAL/SURGICAL PEARLS

The most common subtypes of RCC in children are the translocation-associated tumors, papillary RCC, renal medullary carcinoma, and oncocytic RCC.

RENAL COLIC

Scott G. Hubosky, MD

BASICS

DESCRIPTION

- Renal colic is a constellation of symptoms that usually accompanies upper urinary tract obstruction (1)[C]
  - Pain
    - Involves the flank and/or groin, with radiation to the ipsilateral scrotum or labia majora
    - Pain character is colicky with patients demonstrating a restless nature, unable to stay still
    - Pain is abrupt in onset and not associated with physical activity or positions
  - Nausea/vomiting
    - Simultaneously presents with flank pain but not in all cases
  - Irritative or obstructive voiding complaints which are not present at baseline
    - Urinary frequency, feeling of incomplete emptying, hesitancy
  - Hematuria
    - Gross or microscopic
    - Presence of hematuria strongly suggests underlying urologic etiology over gastrointestinal origin

EPIDEMIOLOGY

Incidence

Renal colic accounts for about 1% of all emergency department visits (2,3)[C] representing over 1 million cases per year

Prevalence

- Renal colic caused by nephrolithiasis has an estimated prevalence of 6.3% in men and 4.1% in women over a study period of 1988–1994 (4)[C]
  - Prevalence seems to be increasing compared to past estimates

RISK FACTORS

- History of nephrolithiasis
- Recent urologic surgery
- History of ureteral stricture
  - Pelvic radiation history

Genetics

N/A

PATHOPHYSIOLOGY

- Presence of obstruction anywhere along the course of the ureter results in stretching of involuntary smooth muscle lining the ureter and renal pelvis
- This stretching of the ureteral smooth muscle is exacerbated by baseline ureteral peristalsis
- Stretching of hollow viscera, such as the ureter/renal pelvis, is a well-known stimulus for

pain as transmitted by the autonomic nervous system (1)[C]
- The kidneys, proximal ureters, and stomach are all served by the celiac ganglion thus explaining why nausea and vomiting frequently accompany renal colic

ASSOCIATED CONDITIONS
- Any process causing obstruction of the upper urinary tract
  - Ureteral stone
  - Ureteral stricture
  - Upper tract urothelial neoplasm
  - Extrinsic ureteral obstruction
  - Iatrogenic ureteral injury
    - Ureteral ligation during hysterectomy or colectomy
- Upper urinary tract infection
  - Pyelonephritis
  - Renal abscess
- Recent urologic surgery
  - Obstructing blood clots from upper tract
  - Ureteral stent in poor position
  - Presence of poorly draining percutaneous nephrostomy tube
  - Residual ureteral stone fragments after lithotripsy
- Miscellaneous
  - Renal artery embolus/infarction
  - Renal vein thrombosis

GENERAL PREVENTION
- Empiric advice for nephrolithiasis prevention
  - Adequate hydration
    - Enough fluid consumption to generate 2.5 L of urine output per day
  - Low-sodium diet
    - Daily sodium intake should be $<$2,500 mg
    - Diets high in sodium result in hypercalciuria
    - About 82% of renal stones produced have calcium as a constituent
  - Normal calcium diet
    - Daily calcium intake should range between 800 and 1,200 mg
    - Vitamins, supplements, and antacids should be considered

DIAGNOSIS

HISTORY
- Sudden onset of colicky flank pain
  - May be associated with simultaneous nausea or vomiting
  - May have associated gross or microhematuria
  - May have radiation to ipsilateral groin or scrotum/labia majora
  - Pain is colicky and intermittent
- The location and characteristics of renal colic pain relating to urolithiasis (5):
  - Stones obstructing UPJ: Mild to severe deep flank pain without radiation to the groin;

irritative voiding symptoms (eg, frequency, dysuria); suprapubic pain, urinary frequency/urgency, dysuria, stranguria, bowel symptoms
  - Stones within ureter: Abrupt, severe, colicky pain in the flank and ipsilateral lower abdomen; radiation to testicles or vulvar area; intense nausea with or without vomiting
  - Upper ureteral stones: Radiate to flank or lumbar areas
  - Midureteral calculi: Radiate anteriorly and caudally
  - Distal ureteral stones: Radiate into groin or testicle (men) or labia majora (women)
  - An objective clinical prediction rule for uncomplicated ureteral stones that uses 5 patient factors—sex, timing, origin (ie, race), nausea, and erythrocytes(STONE)—to create a score between 0 and 13 (the STONE score). With a high STONE score, patients are likely to have a kidney stone.

PHYSICAL EXAM

- General appearance is that of a restless patient unable to be still
- Usually unilateral flank pain with radiation to ipsilateral lower quadrant

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum creatinine/BUN and electrolytes
- Complete blood count
- Urinalysis
  - Look for signs of blood or infection
- Urine culture

Imaging

- CT scan of abdomen and pelvis without any contrast
  - Most sensitive way to detect urinary tract calculi (99% sensitivity to detect ureteral stones)
  - Relatively expensive and subjects patients to radiation exposure
    - Low-dose radiation stone protocol still gives 95% sensitivity for ureteral stone detection with 60% less radiation exposure
- CT urogram
  - CT scan of abdomen/pelvis with IV contrast which is useful to expand diagnostic capability when no ureteral stones are found
    - Can diagnose causes of colic not caused by stones such as UPJ obstructions or intraluminal filling defects such as neoplasms, fungus balls, or blood clots
- Renal/bladder ultrasound
  - No radiation exposure/safe in pregnancy and in pediatric patients
  - Ask for Doppler assessment of ureteral jets
    - Presence of ureteral jets rules out complete ureteral obstruction (although partial obstruction may exist)
    - Absence of ureteral jet may indicate obstruction or dehydration
  - Relies on indirect evidence to diagnosis obstruction
    - Hydronephrosis
    - Presence or absence of ureteral jets
  - Not very sensitive for detecting small ureteral stones

- KUB x-ray
  - May detect calcification along the expected course of the ureter
  - Not very sensitive or specific
  - Benefits are low-radiation dose and is inexpensive

Diagnostic Procedures/Surgery
- Relief of obstruction may be necessary
  - Ureteral stent placement
  - Percutaneous nephrostomy
- Culture-specific antibiotics
  - If infection is present
- Definitive surgical procedure as dictated by underlying condition

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Ureteral calculus
- Ureteral stricture
- UPJ obstruction
- Upper tract urothelial neoplasm
  - Upper tract urothelial carcinoma
  - Fibroepithelial polyps
- Iatrogenic ureteral obstruction
  - Ureteral ligation after hysterectomy or colon resection
  - Obstructing residual stone fragments after lithotripsy
  - Obstructing blood clots following upper tract urologic procedure
- Upper urinary tract infection
  - Pyelonephritis
  - Pyonephrosis
  - Renal abscess
  - Obstructing fungus ball
- Renal vascular etiology
  - Renal artery embolus/renal infarction
  - Renal vein thrombosis

TREATMENT

GENERAL MEASURES
- Rule out sepsis
- Treat infection
- Control pain
- Alleviate obstruction, if present

MEDICATION
First Line
- Analgesia based on degree of discomfort

  - Narcotic analgesics for more severe pain
    - Given PO or IV
    - Morphine sulfate, oxycodone/APAP, hydrocodone/APAP, meperidine, nalbuphine
  - Ketorolac
  - IV acetaminophen
    - Less dizziness and hypotension than morphine in one study
- Antiemetics (metoclopramide, ondansetron)

Second Line
- α-blockers: Tamsulosin, alfuzosin, silodosin
  - Given to relieve ureteral smooth muscle spasm patients with ureteral stones
  - Off-label use in cases of urolithiasis
    - Alfuzosin (10 mg/d)
    - Silodosin (8 mg/d)
    - Tamsulosin (start 0.4 mg to max 0.8 mg); most reported data

SURGERY/OTHER PROCEDURES
- Initial stent placement for significant obstruction
- Lithotripsy for nephrolithiasis
  - Ureteroscopy with laser lithotripsy
  - ESWL (extracorporeal shock wave lithotripsy)
  - PCNL (Percutaneous nephrolithotomy)
- Ureteral stricture treatment
  - Balloon dilation, laser incision
  - Open or laparoscopic reconstruction
- UPJ obstruction
  - Pyeloplasty (open, laparoscopic, robotic)
  - Endopyelotomy (retrograde, antegrade)
- Upper tract neoplasm
  - Ureteroscopic ablation
  - Nephroureterectomy (open or laparoscopic)

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Obtain adequate drainage if necessary, especially if the patient appears septic
  - Ureteral stenting is usually a good 1st choice
    - Chronically obstructed patients often have significant ureteral tortuosity making retrograde access challenging
  - Percutaneous drainage
    - Can be performed with conscious sedation
    - Optimal in cases of significant extrinsic ureteral compression

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

Depends on underlying etiology but usually good once obstruction is relieved and infection treated, if present

COMPLICATIONS

- Persistent obstruction if left untreated
  - Renal cortical loss
    - Could lead to nonfunctioning kidney
  - Serious infection

FOLLOW-UP

Patient Monitoring

Renal/bladder ultrasound after treatment to ensure no evidence of silent hydronephrosis or recurrent obstruction

Patient Resources

Urology Care Foundation http://www.urologyhealth.org/urology/index.cfm?article=148

REFERENCES

1. Silen W. The colics. In: *Cope's Early Diagnosis of the Acute Abdomen*. 22nd ed. New York, NY: Oxford University Press; 2010.
2. Brown J. Diagnostic and treatment patterns for renal colic in US emergency departments. *Int Uro Nephrol*. 2006;38:87–92.
3. Chauhan V, Eskin B, Allegra JR, et al. Effect of season, age and gender on renal colic incidence. *Am J Emerg Med*. 2004;22:560–563.
4. Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int*. 2003;63:1817–1823.
5. Wolf JS. Medscape practice essentials: Nephrolithiasis. Available online at http://emedicine.medscape.com/article/437096-overview. Accessed January 5, 2014.

ADDITIONAL READING

- Malo C, Audette-Côté JS, Emond M, et al. Tamsulosin for treatment of unilateral distal ureterolithiasis: A systematic review and meta-analysis. *CJEM*. 2013;15(0):1–14.
- Moore CL, Bomann S, Daniels B, et al. Derivation and validation of a clinical prediction rule for uncomplicated ureteral stone–the STONE score: retrospective and prospective observational cohort studies. *BMJ*. 2014;348:g2191.

See Also (Topic, Algorithm, Media)

- Flank Pain, General
- Pyonephrosis
- Pyelonephritis, Acute, Adult
- Renal Colic Image
- Urolithiasis, Renal
- Urolithiasis, Ureteral

CODES

ICD9

- 599.69 Urinary obstruction, not elsewhere classified
- 787.01 Nausea with vomiting
- 788.0 Renal colic

ICD10

- N13.8 Other obstructive and reflux uropathy
- N23 Unspecified renal colic
- R11.2 Nausea with vomiting, unspecified

CLINICAL/SURGICAL PEARLS

- Vast majority of patients with renal colic will have calculi.
- Young patients with hydronephrosis and no evidence of calculus likely have congenital UPJ obstruction or other upper tract narrowing.
- Support patient with medicines to alleviate the acute pain of renal colic.
- Treat infection if present.

RENAL CYSTS (INTRARENAL, PERIPELVIC, AND PARAPELVIC)

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BASICS

DESCRIPTION

- Renal cycts are fluid-filled renal structures not continuous with the nephron or collecting system
- Simple cyst
  - Arise from the renal parenchyma
  - Size varies, often <2 cm but may be significantly larger
  - Typically asymptomatic incidentally detected on CT or US
  - Can be single, multiple, and/or bilateral
  - If large, may impinge on the renal pelvis causing obstruction
  - Diagnostic US findings include a mass that is free of internal echos (anechoic), through transmission with posterior acoustic enhancement
- Complex cyst
  - Features not consistent with simple cyst; raise the possibility of malignancy
    - Increased fluid density, internal thick-walled septations, thickened wall, nodular projections into the lumen, calcifications, and contrast enhancement
- Pyogenic cysts are infected cysts
- Parapelvic cyst (aka peripelvic, parapelvic lymphatic, parapelvic lymphangiectasia, and renal sinus cysts); arise from the renal sinus

ALERT
Parapelvic cysts may be confused with hydronephrosis given their central location.

- Acquired cyst
  - Associated with chronic hemodialysis
  - Occasionally regress spontaneously
- Bosniak classification used to classify cysts based on CT complexity and likelihood of malignancy

EPIDEMIOLOGY

Incidence

- 0.22% from birth to 18 yr
- 20% by age 40
- 33% by age 60
- In autopsy series, 50% of patients >50 have ≥ 1 simple renal cysts
- Acquired cystic renal disease is more common among men
- Bilateral simple cysts infrequent <50 yr

Prevalence

N/A

RISK FACTORS

- Age, a known risk factor for simple renal cysts
- Increasing age (7-fold increase from 4th–8th decade or an increased incidence from 5–36%)
- Polycystic kidney disease (autosomal dominant and recessive types)
- Hemodialysis
  - In ESRD, cysts in 8–13% prior to hemodialysis (HD)
  - 10–20% have acquired cystic renal disease after 3 yr of dialysis, 40–60% after 5 yr, and >90% after 10 yr

Genetics

- ARPKD: PKHD1 gene, chromosome 6, protein product fibrocystin
- ADPKD: PKD1 & PKD2 genes, chromosome 16, protein products polycystin-1,-2

Other genetic cystic diseases: Juvenile nephronoph-thisis, medullary cystic kidney disease, glomerulo-cystic kidney disease, Von Hippel–Lindau syndrome (VHL), tuberous sclerosis, Birt–Hogg–Dubé syndrome

PATHOPHYSIOLOGY

- Simple cysts
  - Development of discrete fibrous saccules of clear fluid lined with cuboidal epithelium
  - Estimated growth rate: 2.18 mm/yr
  - Some will involute and disappear over time although most will not
  - It is controversial if renal cysts are causative agents of HTN
- Parapelvic cysts
  - Found on <2% of kidneys at autopsy
  - Can be confused with hydronephrosis

ASSOCIATED CONDITIONS

- ADPKD (Autosomal dominant polycystic kidney disease)
- ARPKD (Autosomal recessive polycystic kidney disease)
- Birt–Hogg–Dubé syndrome
- ESRD (end stage renal disease)
- Tuberous sclerosis
  - 50% have multiple renal angiomyolipomas
  - 20–25% of have renal cysts
- VHL disease
  - Individuals develop cysts in multiple organs (kidney, pancreas, liver, epididymis)
  - Increased risk of clear cell renal cell carcinoma (RCC) in cyst wall

GENERAL PREVENTION

Family members of patients with ADPKD and VHL should be screened

DIAGNOSIS

HISTORY

- Patients may present with an abdominal mass, pain, hematuria, or HTN but most are radiographically incidental
- Family member with polycystic kidney disease or other inherited cystic disease

PHYSICAL EXAM

- Abdominal/flank mass (rare)
- Often a benign exam

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis most often normal unless concurrent medical renal disease present
- Renal function tests—calculate eGFR and stage chronic kidney disease (CKD)

Imaging

- Ultrasound
  - Simple cyst
    - No internal echoes, distinct walls with defined margins, spherical shape with no internal echoes

ALERT
Complex renal cysts including hyperdense cysts may mimic solid renal masses. Doppler US is helpful.

- CT
  - Simple cysts
    - Have sharp walls with smooth margins, spherical shape, homogenous throughout (Hounsfield units (HU) ranging from −10 to +20); no enhancement with IV contrast
    - CT diagnosis of a simple cyst is almost 100% if study performed properly (bi- or triphasic)
    - Enhancement is defined as an increase in HU by at least 15–20
    - If cyst does not meet criteria for being simple, further workup of the lesion is necessary
  - Parapelvic cyst
    - Appears on US as a medially located cystic mass with surrounding echogenic walls (located within the fatty renal sinus)
    - On US or even CT can be confused with hydronephrosis. An excretory phase CT is most helpful in distinguishing a parapelvic cyst from a simple parcehncymal renal cyst.
- MRI:
  - Bosniak criteria can be applied to MRI (exception: Calcifications may not be well seen)
  - Low signal T1, high signal T2 is consistent with benign simple cyst
  - Hyperdense cysts can be high signal on T1 and low on T2 but appearance depends on hemoglobin breakdown
  - MRI may have a role in a subset of patients (VHL, multiple renal masses) if concern exists regarding excessive radiation due to multiple long-term imaging studies
  - May be superior in characterization of internal cyst contents (blood, mucin)
- Bi- or triphasic CT represents the gold standard for distinguishing renal cysts:
  - Discriminate between cysts and collecting system on excretory phase
  - Particularly important in assessing hydronephrotic systems
    - US may be misleading/difficult to interpret
- Bosniak classification system of cystic renal masses originally based on CT (image) (1):
  - Category I: Benign simple cysts; thin wall without septa, calcifications, or solid components, water density, and no contrast enhancement; No further imaging needed

    - Nearly all are benign
  - Category II: Benign cysts with a few thin septae; the wall or septa may contain fine calcification, sharp margins, nonenhancing
  - Category IIF: Well marginated and may have thin septae or minimal smooth thickening of the septa or wall, which may contain calcification that may also be thick and nodular; no contrast enhancement; includes totally intrarenal nonenhancing complex lesions >3 cm
    - These require follow-up (designated by the F designation)
    - 5–20% of Bosniak II/IIF cysts contain malignancy in wall
  - Category III: Indeterminate cysts with thickened irregular or smooth walls or septae; enhancement present
    - 40–60% of these are malignant (cystic RCC and multiloculated cystic RCC)
    - Other class III lesions are benign (infected cysts and multiloculated cystic nephroma)
  - Category IV: Characteristics of category III cysts plus they contain contrast-enhancing soft tissue components that are adjacent to and independent of the wall or septum
    - Risk of malignancy is 85–100%

Diagnostic Procedures/Surgery

- Cyst aspiration is rarely curative as fluid reaccumulates. Infected cysts may require aspiration and catheter placement.
  - Infected cysts often represent calyceal diverticula
- Cyst biopsy is difficult and frequently results in indeterminate pathology
- Cytologic evaluation of fluid for malignancy or culture based on the indication and characteristics of the cyst

Pathologic Findings

- Simple renal cyst
  - Single layer of cuboidal epithelium
- Not continuous with the collecting system

DIFFERENTIAL DIAGNOSIS (2)

- ADPKD (Autosomal dominant polycystic kidney disease)
- ARPKD (Autosomal recessive polycystic kidney disease)
- Calyceal diverticulum (evaluate for connection to the collecting system)
- Cystic degeneration (necrosis) of RCC
- Cystic malignancy (cystic RCC; sometimes called papillary cystadenocarcinoma)
- Hydronephrosis (parapelvic cysts)
- Juvenile nephronophthisis
- Medullary sponge kidney
- Multicystic dysplastic kidney
- Renal abscess
- Urinoma
- Pararenal (retroperitoneal or adjacent mesenteric/liver/splenic/adrenal cyst)
- Xanthogranulomatous pyelonephritis

TREATMENT

GENERAL MEASURES

- The major issue with renal cysts is differentiating a simple cyst from more serious diseases: Malignancy (RCC), polycystic kidney disease, complex cysts, and solid masses (such as a renal carcinoma or abscess)
- Risk of RCC with Bosniak III and IV lesions
- Bosniak I (benign cyst)
  - No action necessary
- Bosniak II (septae and/or wall calcifications)
  - Some clinicians consider 1 follow-up study (US) to confirm stability or if unable to differentiate from IIF cyst
- Bosniak IIF (increased, thicker walls and calcifications compared to type I)
  - Require follow-up studies for 2–3 yr
- Bosniak III (irregular thick walls with calcification)
  - Excision vs. alternative diagnostic evaluation (needle biopsy, MRI). May be observed in elderly and infirmed.
- Bosniak IV (enhancement with contrast, malignancy likely); surgical management

MEDICATION

First Line

Specific to those cystic diseases noted that cause HTN or renal insufficiency

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical or partial nephrectomy for complex or suspicious cysts
- Cyst decortication with marsupialization should be reserved for very select cases
  - Laparoscopic, open, and percutaneous approaches

ADDITIONAL TREATMENT

Additional Therapies

- Cyst aspiration and sclerotherapy (3)
  - Rarely employed for large simple symptomatic renal cysts
  - Pain often does not resolve with surgical management of renal cysts
  - Not for parapelvic/peripelvic cysts
  - Many consider this approach as primary therapy for large symptomatic cysts before surgical management; others support laparoscopic management initially
  - Simple aspiration rarely leads to resolution; reaccumulation common
  - Negative cyst fluid cytology required
  - Sclerosing agents increase success but associated with pain and infection
  - Multiple sessions are usually required, and use of indwelling percutaneous catheter may increase success rates
  - Sclerosing agents: Ethanol, bismuth phosphate, n-butyl cyanoacrylate, povidone-iodine, and tetracycline; No agent superior

ONGOING CARE

PROGNOSIS

- Up to 15% of ADPKD will require hemodialysis
- Benign simple cysts demonstrate little risk of progressing to malignancy
- Bosniak classification and risk of malignancy
  - Bosniak I: No risk
  - Bosniak II/IIF: 5–20% risk depending on imaging characteristics
  - Bosniak III: 50% risk
  - Bosniak IV: 75–90% risk

COMPLICATIONS

- Rupture and hemorrhage with simple renal cyst; usually associated with flank pain and hematuria
- Infected renal cyst
- ADPKD

ALERT

- Associated with cerebral berry aneurysms.
  - In up to 40% of patients.
  - 9% mortality (subarachnoid hemorrhage).

FOLLOW-UP

Patient Monitoring

- Follow-up imaging of Bosniak type IIF cysts
- Multicystic dysplastic kidney/VHL
  - Periodic sonography to monitor for neoplastic changes
- Acquired renal cystic disease
  - Periodic imaging (US) on dialysis

Patient Resources

http://kidney.niddk.nih.gov/kudiseases/pubs/cysts/

REFERENCES

1. Bosniak MA. The Bosniak renal cyst classification: 25 years later. *Radiology*. 2012;262(3):781–785.
2. Minor LD, Picken MM, Campbell SC, et al. Benign renal tumors. *AUA Update Series*. 2003;22:170–175. Lesson: 22.
3. Skolarikos A, Laguna MP, de la Rosette JJ. Conservative and radiological management of simple renal cysts: A comprehensive review. *BJU Int*. 2012;110(2):170–178.

ADDITIONAL READING

- Feiner HD, Katz LA, Gallo GR. Acquired renal cystic disease of kidney in chronic hemodialysis patients. *Urology*. 1981;17:260–264.
- Terada N, Ichioka K, Matsuta Y, et al. The natural history of simple renal cysts. *J Urol*. 2002;167:21–23.

See Also (Topic, Algorithm, Media)

- Acquired Renal Cystic Disease

- Birt–Hogg–Dubé Syndrome
- Cystadenocarcinoma, Genitourinary
- Medullary Sponge Kidney
- Multicystic Dysplastic Kidney
- Polycystic Kidney Disease, Autosomal Dominant
- Polycystic Kidney Disease, Autosomal Recessive
- Renal Cell Carcinoma, General
- Renal Mass
- Tuberous Sclerosis
- VHL Disease
- Renal Cysts (Intrarenal, Peripelvic, and Parapelvic) Images ☼

CODES

ICD9

- 593.2 Cyst of kidney, acquired
- 753.12 Polycystic kidney, unspecified type
- 753.16 Medullary cystic kidney

ICD10

- N28.1 Cyst of kidney, acquired
- Q61.3 Polycystic kidney, unspecified
- Q61.5 Medullary cystic kidney

CLINICAL/SURGICAL PEARLS

- Bosniak cyst type malignancy risk:
  – II/IIF (5–20%), III (50%), IV (up to 90%).

RENAL DYSPLASIA, HYPODYSPLASIA, AND HYPOPLASIA

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BASICS

DESCRIPTION

- Renal dysplasia, hypoplasia, and hypodysplasia are forms of renal dysgenesis; namely, maldevelopment of kidney size, shape, or structure
- Renal dysplasia: Chiefly a histologic diagnosis based on the presence of primitive renal components (ie, ducts) and embryonic mesenchymal cells (ie, cartilage):
  - Classification of renal dysplasia:
    - Total dysplasia: Involves both cortex and medulla; spectrum ranging from aplastic (small and solid) to multicystic (enlarged) kidneys (eg, Multicystic dysplastic kidney [MCDK])
    - Subtotal dysplasia: Segmental distribution in cortex and medulla
    - Hereditary: Zellweger and Meckel syndromes
- Renal hypoplasia: Small kidneys that have a normal nephron density with less than normal number of calyces and nephrons and are not dysplastic (1):
  - Classification:
    - With urethral obstruction
    - Prune-belly syndrome
    - True oligonephronia
    - With normal ureteral orifice
    - With abnormal ureteral orifice
    - Oligomeganephronia
    - Segmental (Ask-Upmark kidney)
- Renal hypodysplasia: Small kidneys that have normal nephron density with less than normal number of calyces and nephrons and are dysplastic:
  - Classification:
    - Normal ureteral orifice: With and without obstruction
    - Ectopic ureteral orifice with or without ureterocele: Lateral, medial, or caudal
    - With urethral obstruction
    - Prune-belly syndrome
- Renal development is dependent on the interaction between the ureteric bud and the metanephric mesenchyme

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- Renal dysplasia:
  - Unilateral or bilateral in 2–4 per 1,000 births
  - Male > Female (1.3:1)

  - Male > Female (1.9:1)
- Renal hypoplasia
  - Oligomeganephronia:
    - Male > Female (3:1)
    - Increased with low birth weight, often present by age 2
  - Ask-Upmark kidney:
    - Male < Female (1:2)
    - Commonly present ≤10 yr of age

RISK FACTORS

- Vesicoureteral reflux (VUR)
- Posterior urethral valves
- Ureteral abnormalities: Primary megaureter, Ureteropelvic junction obstruction (UPJO), ureterocele
- Prune-belly syndrome

Genetics

- A majority of dysplastic and hypoplastic kidney disorders are sporadic and nonheritable
- Genetic pathways can affect ureteric bud formation, branching morphogenesis within the metanephric blastema, and normal nephrogenesis
- Familial renal adysplasia: Heterogenous autosomal dominant inheritance of renal agenesis, renal dysplasia, MCDK, etc., within 1 family

PATHOPHYSIOLOGY

- Normal metanephric differentiation requires induction via the ureteric bud (1)
- The branching of the collecting system, as well as nephron formation, are determined by the ureteric bud
- Epithelial–mesenchymal interactions and peptide growth factors play a central role in nephrogenesis
- Dysplasia: Histologically manifests as distortion of renal architecture, immature or primitive glomeruli, cartilage, and tubules encircled by fibromuscular cells (primitive ducts):
  - Aplastic dysplasia: Region of nonfunctioning parenchyma
    - Inhibition of nephron development
    - Increased TGF-β
    - S-shaped bodies and cysts
    - Dedifferentiation of renal cells
- Hypoplasia: Normal nephron density despite smaller size, bilateral or unilateral; can be associated with reflux:
  - Oligomeganephronia:
    - Reduction in nephron number and hypertrophy of each nephron
    - Usually bilateral, but contralateral renal agenesis has been reported
    - No clear distinction between cortex and medulla, reduced number of renal segments, small renal artery, elongated nephrons
  - Ask-Upmark kidney:
    - Likely secondary to reflux nephropathy
    - Deep groove(s) on lateral convexity with underlying tubules resembling thyroid tissue

    - Underdeveloped medulla
    - Arteriosclerosis and juxtaglomerular hyperplasia
- Hypodysplasia: Most often seen in conjunction with an ectopic ureteral orifice or obstruction; extent of dysplasia correlates with degree of ureteral ectopia:
  - Normal ureteral orifice:
    - With obstruction: Primary obstructive megaureter and UPJO
    - Without obstruction: Dwarf kidney; according to bud theory is the result of deficient metanephric blastema
  - Abnormal ureteral orifice:
    - Pan-bud anomaly; abnormal budding leads to an ectopic ureteral orifice with thin renal parenchyma and ectatic calyces
    - Lateral ectopia: Often associated with reflux; rounded calyces are a result of premature termination of calyceal development
    - Medial or caudal ectopia and ureteroceles: Dilated ureter is the norm with thin renal cortex
  - Urethral obstruction:
    - Position of ureteral orifices correlates with degree of renal dysgenesis in posterior urethral valves (PUV): Orthotopic has normal histology; lateral orifice has hypoplasia; extremely lateral has hypodysplasia
    - Prune-belly syndrome: Large laterally displaced ureteral orifices with dysplastic kidneys explained by abnormal budding theory

ASSOCIATED CONDITIONS

- Branchio-oto-renal syndrome
- Ectopic ureteral orifice
- Fraser syndrome
- Jeune syndrome
- Kallmann syndrome
- Meckel–Gruber syndrome
- Oral–facial–digital syndromes
- Posterior urethral valves
- Potter syndrome
- Primary obstructing megaureter
- Prune-belly syndrome
- Pulmonary hypoplasia
- Renal coloboma syndrome
- Simpson–Golabi–Behmel syndrome
- Townes–Brocks syndrome
- Uretero pelvic junction obstruction (UPJO)
- Vesico ureteral reflux (VUR)
- Zellweger syndrome

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Systemic:
  - Failure to thrive, abnormal growth, headache, fever, chills, shortness of breath, nausea, emesis, anorexia, skin pallor, vision change, mental status change
- Renal disease:
  - Polyuria, polydipsia, abdominal pain or mass, flank pain, hematuria
- Bladder disease:
  - Lower urinary tract symptoms (LUTS), dysuria, nocturia, incontinence

PHYSICAL EXAM

- Abnormal weight or height
- Vital signs: Hypertensive
- Mental status: Encephalopathic
- HEENT: Retinopathy, papillary edema, dehydration
- Lungs: Crackles
- Abdomen: Distention, palpable mass, guarding, CVA tenderness, ascites
- Extremities: Pallor, peripheral edema

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: Proteinuria, hematuria, low specific gravity, bacteria
- Urine culture
- Electrolytes, BUN, Cr, K^+
  - Elevated Cr, hyperkalemia, uremia

Imaging

- Renal bladder ultrasound
  - Kidney number and size, pelvicaliectasis, ureteral dilation, presence of cysts or mass, hyperechoic or hypoechoic parenchyma
  - Bladder volume, ureterocele
- CT abdomen and pelvis
  - Anomalous GU anatomy, presence of dilation, calculus disease
- Static fluid and excretory MR urography
  - GU anatomy, renal function, obstruction
- Renal scan
  - Split function or obstruction
- Voiding cystourethrogram
- Retrograde pyelography:
  - Defines anatomy

Diagnostic Procedures/Surgery

- Cystoscopy may help define anatomic abnormalities
- Renal biopsy

Pathologic Findings

- Gross findings (2)

  - Smaller renal size, mass, and contour
  - Renal lobulations and cysts
  - Pale and firm kidneys
  - Duplicated kidney or ureter
  - Dilated collecting system
  - Ectopic ureteral orifice
  - Ureterocele
  - Thickened bladder wall
- Histologic findings
  - Dysplasia
    - Always with decreased nephron number
    - Embryonic mesenchyme
    - Primitive renal components
    - Distortion of renal architecture
    - Primitive glomeruli
    - Nephron precursors: Comma and S-bodies
    - Primitive ducts: Cartilage and tubules encircled by collars of fibromuscular cells
  - Hypoplasia
    - May have a normal nephron density
    - Oligomeganephronia: Reduction in nephron number with corresponding hypertrophy of the nephrons, nephron diverticula
    - Ask-Upmark kidney: Arteriosclerosis, juxtaglomerular hyperplasia, tubules resembling thyroid tissue
  - Hypodysplasia
    - Both dysplastic and hypoplastic

DIFFERENTIAL DIAGNOSIS

- Polycystic kidney disease, autosomal dominant (ADPKD)
- Polycystic kidney disease, autosomal recessive (ARPKD)
- Juvenile nephronophthisis
- Medullary sponge kidney
- Reflux nephropathy
- Renal vein thrombosis
- Simple cysts
- Sporadic glomerulocystic kidney disease
- Tuberous sclerosis
- UPJO
- Von Hippel–Lindau disease
- VUR
- Wilms tumor

TREATMENT

GENERAL MEASURES

Consultation with nephrology and multimodality management

MEDICATION

First Line

Antibiotics for UTI or as prophylaxis for VUR

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Indications for nephrectomy: Pain, chronic infection, HTN, or increasing size (3)
- Renal transplantation for end-stage renal disease
- Ureteral reimplantation: Reflux, primary megaureter
- Pyeloplasty for UPJO
- Valve ablation for posterior urethral valves

ADDITIONAL TREATMENT

Peritoneal or hemodialysis for ESRD

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Varies with degree of renal insufficiency and degree of comorbid conditions

COMPLICATIONS

Renal failure, anemia, UTI, failure to thrive

FOLLOW-UP

Patient Monitoring

- BP and growth chart annually
- Electrolytes, Cr, BUN annually
- Urinalysis and urine culture as indicated
- Bilateral disease: Renal US annually
- MCDK: Renal US every 2 yr to observe for involution

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
http://kidney.niddk.nih.gov/kudiseases/pubs/kidneydysplasia/

REFERENCES

1. Glassberg KI. Renal dysgenesis and cystic disease of the kidney. In: Wein AJ, Kavoussi LR, Novick AC, et al, eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: WB Saunders; 2007:3305–3358.
2. Grantham JJ, Winklhofer F. Cystic diseases of the kidney. In: Brenner BM, ed. *The Kidney*. 7th ed. Philadelphia, PA: Saunders; 2004:1743–1775.
3. La Scola C, Hewitt I, Pasini A, et al. Postnatal management of congenital bilateral renal hypodysplasia. *J Matern Fet al Neonatal Med*. 2010;23:97–100.

ADDITIONAL READING

- Hubert KC, Palmer JS. Current diagnosis and management of fet al genitourinary abnormalities. *Urol Clin N Am.* 2007;34:89–101.
- Weber S, Moriniere V, Knüppel T, et al. Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: Results of the ESCAPE study. *J Am Soc Nephrol.* 2006;10:2864–2870.

See Also (Topic, Algorithm, Media)

- Ask-Upmark Kidney
- Chronic Kidney Disease, Pediatric (Renal Failure, Chronic)
- Prune Belly (Eagle Barrett or Triad) Syndrome
- Renal Agenesis (Bilateral and Unilateral)
- Renal Dysplasia, Hypodysplasia and Hypoplasia Image
- Renal Malrotation
- VUR, Pediatric

CODES

ICD9

- 753.0 Renal agenesis and dysgenesis
- 753.15 Renal dysplasia
- 756.71 Prune belly syndrome

ICD10

- Q60.2 Renal agenesis, unspecified
- Q60.5 Renal hypoplasia, unspecified
- Q61.4 Renal dysplasia

CLINICAL/SURGICAL PEARLS

Prognosis varies; however, most patients have renal insufficiency and its sequelae.

RENAL ECTOPIA

Vani S. Menon, MD
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BASICS

DESCRIPTION

- Renal ectopia describes a kidney that is located outside of the normal orthotopic position within the renal fossa
- Positions for ectopia:
  - Pelvic kidney: Below aortic bifurcation; this is the most common ectopic position
  - Lumbar: Near sacral promontory
  - Abdominal: Above iliac crest
  - Cephalad: Seen in conjuncture with omphalocele when intra-abdominal organs herniate into the defect and cranial ascent of kidney is limited by the diaphragm
  - Thoracic: Above the diaphragm with vasculature arising from a cranial source
- Crossed fused renal ectopia
  - Fusion occurs in up to 90% of cases
  - Left to right crossing and more common in males
  - Solitary and bilateral crossed varieties less common
  - Type of anomaly is descriptive of the fusion anomaly
    - (inferior, lump, S-shaped [aka sigmoid], L-shaped, disc, or pancake)
  - Fused unit usually caudal to the orthotopic renal moiety
- Horseshoe kidney is a noncross-fused ectopia

EPIDEMIOLOGY

Incidence

- 1 in 500 to 1 in 1,290 in postmortem studies
  - Incidence is higher in autopsy series than in clinical studies, suggesting many clinically insignificant and not recognized
  - Left side favored over right
- Pelvic kidney 1 in 2,200 and 1 in 3,000
- Crossed renal ectopia: Extremely rare

Prevalence

N/A

RISK FACTORS

Potential relationship with maternal illnesses/teratogenic exposure

Genetics

N/A

PATHOPHYSIOLOGY

- Failure of ascent
  - Anomalous vasculature impeding ascent; possibly and abnormally situated umbilical

artery
  – Thought to occur at the 4th–8th wk of gestation
  – Normal kidney ascent to the level of L2 at the end of the 8th wk of gestation
• Abnormality of the ureteric bud or metanephric blastema
• Fusion abnormalities occur early in embryogenesis
  – Horseshoe kidney is the most common fusion anomaly
  – Two renal moieties joined at lower pole in 90% of cases
• Anatomic considerations:
  – Orthotopically located adrenal gland
  – Ureter inserts into bladder in orthotopic position
  – Renal pelvis of ectopic kidney is usually anterior to the parenchyma secondary to malrotation
  – Failure of development of fascial layers in the flanks on the side not occupied by renal tissue
• Malrotation of the ectopic kidney almost always occurs

ASSOCIATED CONDITIONS
• Vesicoureteral reflux: Estimated incidence between 20 and 30%
  – Contralateral kidney demonstrates reflux in approximately 50% of cases
  – Bilateral renal ectopia carries highest risk for reflux—>70% (1)[C]
• Hydronephrosis: Seen in over 50%
  – Half of these cases are due to either ureteropelvic junction obstruction (UPJO) or ureterovesical junction obstruction (UVJO)
  – 25% of the hydronephrotic cases are secondary to reflux and the remaining 25% due to malrotation (2)[C]
• Genital anomalies: Estimated incidence between 15 and 45%
  – 10–20% of males will have cryptorchidism, hypospadias, or duplicated urethras
  – 20–66% of females will have uterine or vaginal anomalies
• Cloacal anomalies: 14% of these patients will have an ectopic kidney
• Nephrolithiasis
• Recurrent urinary tract infections (UTIs)

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
• UTIs (30%), vague abdominal pain or renal colic
• Incidentally during pre- or postnatal screening
• Abdominal mass, hypertension, hematuria, incontinence, renal insufficiency

PHYSICAL EXAM
• Usually normal
• May find abdominal mass or flank tenderness
• Genitourinary abnormalities

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis and culture
- BUN/Cr

Imaging

- If kidney absent on ultrasound (US), radionucleotide imaging should be performed to evaluate for an ectopic kidney
  - Average differential function of ectopic kidney is 35% (1)[C]
- Diuretic renography if moderate-to-severe pelvicalyceal dilation or progressive dilation found to evaluate for obstructive process
- Voiding cystourethrogram for febrile UTI and/or pelvicalyceal dilation
- If kidney is nonfunctional, computed tomography scan or abdominal US for localization
- Recent use of magnetic resonance urogram for small, poorly functioning kidneys can be utilized

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Horseshoe kidney
- Malrotated kidney
- Ptosis of orthotopically located kidney
- Supernumerary kidney:
  - Usually caudad to orthotopic kidney

TREATMENT

GENERAL MEASURES

Specific treatment for renal ectopia itself is not indicated. However, special considerations for associated conditions may be necessary.

MEDICATION

First Line

Antibiotic prophylaxis for reflux based on clinical need

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Nephrolithiasis
  - Shock-wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, laparoscopic nephrolithotomy (3)[C]
- UPJO
  - $<$15% are due to an aberrant crossing vessel
  - Goal of management is to achieve dependent pelvic drainage

  - Dismembered pyeloplasty: Open and minimally invasive
  - Ureterocalicostomy
  - Endopylotomy could be a consideration for failed pyeloplasty but is rarely indicated as the initial surgical intervention
- Vesicoureteral reflux
  - Open vs. endoscopic repair for clinically significant reflux

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Outcomes for treatment of nephrolithiasis and UPJO are comparable to management of these entities in the orthotopic-positioned kidney
- Current literature suggests no adverse effects on blood pressure or kidney function (4)[B]
- No evidence for increased risk of malignancy

COMPLICATIONS

- Vesicoureteral reflux
- Nephrolithiasis
  - Most likely due to urinary stasis
- UPJO/UVJO
- UTIs
- Bowel laxity in the region of the empty renal fossa
- Traumatic injury to renal unit due to poor protection in ectopic location

FOLLOW-UP

Patient Monitoring

- Nephrolithiasis
  - Imaging by renal US and/or CT scans
- Vesicoureteral reflux
  - VCUG and/or DMSA
- Hydronephrosis
  - Renal US and/or nuclear scans
- Yearly blood pressure measurements
- Yearly BUN/Cr measurements

Patient Resources

- Urology Care Foundation: Ectopic Kidneys
  http://www.urologyhealth.org/urology/index.cfm?article=22

REFERENCES
1. Guarino N, Tadini B, Camardi P, et al. The incidence of associated urological abnormalities in children with renal ectopia. *J Urol*. 2004;172:1757–1759.
2. Shapiro E, Bauer S, Chow J. Anomalies of the upper urinary tract. In: *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2012.
3. Gupta M, Lee MW. Treatment of stones associated with complex or anomalous renal anatomy. *Urol Clinic N Am*. 2007;34(3):431–441.
4. van den Bosch CM, van Wijk JA, Beckers GM, et al. Urological and nephrological findings of renal ectopia. *J Urol*. 2010;183:1574–1578.

ADDITIONAL READING

Cinman NM, Okeke Z, Smith AD. Pelvic kidney: Associated diseases and treatment. *J Endourol*. 2007;21(8):836–842.

See Also (Topic, Algorithm, Media)
- Horseshoe Kidney
- Malrotated Kidney/Renal Malrotation
- Renal Dysplasia, Hypodysplasia and Hypoplasia
- Renal Ectopia Image ☼
- Renal Fusion Anomalies
- UPJO
- UTI, Complicated, Pediatric
- Urolithiasis, Pediatric, General Considerations

CODES

ICD9
753.3 Other specified anomalies of kidney

ICD10
- Q63.2 Ectopic kidney
- Q63.1 Lobulated, fused and horseshoe kidney

CLINICAL/SURGICAL PEARLS

- Renal ectopia carries an increased risk of urologic abnormalities such as reflux, hydronephrosis, and genital abnormalities.
- Over half the cases of reflux occur in the orthotopic kidney.
- >80% of ectopic kidneys will have differential function of approximately 35%.
- An anterior renal pelvis and anomalous vasculature must be a consideration prior to surgical intervention.
- Surgical interventions for nephrolithiasis have similar success rates as for orthotopic kidneys.

RENAL FUSION ANOMALIES

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Paul H. Smith III, MD

BASICS

DESCRIPTION

- Reanl fusion is a congenital condition in which the renal units are joined
- Horseshoe kidney and crossed-fused ectopia are the most common variants
  - Horseshoe kidney:
    - Most common renal fusion anomaly
    - Poles of the kidney are fused by the isthmus
    - Fusion occurs at the lower poles in 95%
- Crossed-fused ectopia:
  - 2nd most common renal fusion anomaly
    - Kidney is on opposite side of where ureter inserts (ureter crosses midline)
    - The ectopic renal unit is fused to its companion in 90% of cases
  - Crossing from left to right is the most common morphology

EPIDEMIOLOGY

Incidence

- Male > Female
- Horseshoe kidney occurs in 1 in every 400–500 live births
- Crossed-fused ectopia occurs in 1 in every 1,000–2,000 live births (1)

Prevalence

- Horseshoe Kidney: ~1:400–500
- Crossed-fused ectopia: ~1:3,000

RISK FACTORS

- Crossed-fused ectopia is frequently seen with vertebral anomalies such as myelomeningocele and sacral agenesis (1)
- Horseshoe kidney is present in 60% of female patients with Turner syndrome and 20% of patients with trisomy 18

Genetics

Specific genetic causes unknown, but renal fusion anomalies commonly seen in association with a variety of chromosomal and congenital abnormalities (Turner syndrome, trisomy 18)

PATHOPHYSIOLOGY

- Metanephric blastema is the embryologic precursor to the adult kidney
- Development of the kidney begins in the 4th–5th wk with ingrowth of the ureteric bud, an outpouching of the mesonephric duct, into the surrounding metanephric blastema
- Proper renal development is coordinated through interactions between the metanephric blastema and ureteric bud
- The developing kidney ascends and rotates medially to reach its usual anatomic position by

the 9th wk of gestation
- Several theories have been offered to explain crossed ectopia
  - One theory proposes that an aberrantly oriented ureteric bud induces renal development in the contralateral mesonephric blastema
  - An alternate theory suggests that the developing kidney is channeled/displaced to the contralateral side during its ascent by the presence of an aberrant umbilical or common iliac artery or other pelvic structures
- The developing left and right metanephric blastemas are in close proximity to each other within the pelvis and, if abutting, may merge to form a horseshoe kidney or other fusion anomaly (2)

ASSOCIATED CONDITIONS
- Other congenital anomalies are present in up to a one-third of patients with horseshoe kidney
  - Skelet al, cardiovascular, neural tube, and anorectal anomalies are the most common
- Other GU anomalies associated with horseshoe kidney
  - Cryptorchidism or hypospadias in 4% of males
  - Vesicoureteral reflux (VUR) in >50% of patients
    - Voiding cystourethrogram (VCUG) is routine part of evaluation
- 2–8 times increased risk of Wilms tumor
- 2–4 times increased risk of TCC
- Imperforate anus in 4% with crossed ectopia
- Horseshoe kidney associated with imperforate anus and Meckel's diverticulum
- Increased risk of urolithiasis due to both anatomic and metabolic factors

GENERAL PREVENTION
- Preventative measures aim to minimize risk factors for future renal deterioration:
  - Prophylactic antibiotics or surgical correction if VUR present
  - Decompression of obstructed moieties (pyeloplasty)

DIAGNOSIS
HISTORY
- Most are asymptomatic and are incidentally discovered
- May be diagnosed on prenatal ultrasound (US)
- Symptoms are usually the result of infection, stones, or obstruction of the abnormally positioned collecting system (UPJO)
  - Nonspecific abdominal pain, nausea, vomiting, hematuria

PHYSICAL EXAM
- Palpable abdominal mass (hydronephrosis)
- CVA tenderness (stone or pyelonephritis)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis (hematuria)
- Serum creatinine (elevated with obstruction)

- Metabolic evaluation for urolithiasis
  - Metabolic etiologies for stone disease common in patients with horseshoe kidney
    - Serum chemistries
    - 24-hr urinalysis

Imaging
- Renal US: Hydronephrosis
- VCUG:
  - High incidence of VUR
- Diuretic renography (MAG3):
  - If clinical or radiographic concern for obstruction
- Contrast-enhanced CT or gadolinium-enhanced MRI with delayed images can accurately characterize the renal, collecting system, and vascular anatomy for surgical planning

Diagnostic Procedures/Surgery
Karyotype in females with horseshoe kidney if dysmorphic features suggestive of Turner syndrome

Pathologic Findings
- Wilms tumor in children and TCC in adults are more common in horseshoe kidneys:
  - Unclear if carcinoma related to embryologic mechanisms, urinary sepsis, or infection

DIFFERENTIAL DIAGNOSIS
- Renal mass
- Supernumerary kidney:
  - An accessory organ with its own blood supply and collecting system
  - It may not be reniform, but possesses a distinct capsule surrounding a parenchymal mass
- Malrotated kidneys: Can look like a horseshoe kidney on radiographic imaging

TREATMENT

GENERAL MEASURES
No treatment if asymptomatic. Specific management dictated by complicating features.

MEDICATION
First Line
- Antibiotics:
  - VUR treated the same as in those without fusion anomalies
  - Antibiotic prophylaxis may be used until resolution for low-grade reflux

Second Line
N/A

SURGERY/OTHER PROCEDURES
- General operative considerations:
  - Horseshoe and ectopic kidneys often have abnormal and complex renal vasculature
    - Renal vessels may arise from the aorta, common iliac artery, or both, and typically enter the kidney anteriorly
    - Angiography (including CT and MR angiogram) may be useful to delineate renal

vascular anatomy for operative planning
  - The renal pelvis and ureteropelvic junction of the horseshoe kidney often have an abnormal configuration, which can result in urinary stasis or obstruction. This anatomic abnormality contributes to the majority of the symptoms associated with horseshoe kidney, including stone formation, infection, hydronephrosis, and frank UPJO.
  - In the horseshoe kidney, the lower poles are joined by an isthmus, which is typically situated just caudal to the inferior mesenteric artery. The isthmus may be divided if necessary during nephrectomy.
- UPJO, best managed with dismembered pyeloplasty:
  - Endoscopic management of UPJO is feasible (3)[B]
- Stone procedures:
  - PCNL:
    - Provides the highest stone-free rates for larger renal stones and is typically the primary procedure for renal calculi in the horseshoe kidney. Access to the collecting is usually best achieved through a posterior upper pole calyx. (4)[B]
  - ESWL:
    - It may be difficult to target stones for ESWL due to the abnormal location of the kidney. ESWL is most appropriate for stones <1.5 cm associated with unobstructed collecting systems. Repeat treatments may be required in order to achieve a stone-free status (4)[B].
  - Ureteroscopy:
    - Safe and effective approach for calculi associated with horseshoe or ectopic renal moieties; however, the smaller ureteroscopic instruments generally limit this approach to smaller stone burdens

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Related to complicating features. Outcomes comparable to those for anatomically normally positioned kidneys.

COMPLICATIONS

- Possible increased risk of malignancy
- UTI
- Urolithiasis
- UPJO

- VUR

FOLLOW-UP

Patient Monitoring

- Due to slight increase in incidence of Wilms tumor in children, some advocate imaging every 6 mo once the diagnosis is made
- The abnormalities and conditions for crossed-fused ectopia are similar to horseshoe kidneys, and treatment often follows similar lines

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
http://kidney.niddk.nih.gov/kudiseases/pubs/ectopicKidney/index.aspx

REFERENCES

1. Glodny B, Petersen J, Hofmann KJ, et al. Kidney fusion anomalies revisited: Clinical and radiological analysis of 209 cases of crossed fused ectopia and horseshoe kidney. *BJU Int.* 2009;103:224–235.
2. Glassberg KI. Normal and abnormal development of the kidney: A clinician's interpretation of current knowledge. *J Urol.* 2002;167:2339–2351.
3. Yohannes P, Smith AD. The endourological management of complications associated with horseshoe kidney. *J Urol.* 2002;168:5–8.
4. Gupta NP, Mishra S, Seth A, et al. Percutaneous nephrolithotomy in abnormal kidneys: Single-center experience. *Urology*. 2009;73(4):710–714.

ADDITIONAL READING

- Boyan N, Kubat H, Uzum A. Crossed renal ectopia with fusion: Report of two patients. *Clin Anat.* 2007;20:699–702.
- Decter RM. Renal duplication and fusion abnormalities. *Pediat Clin N Am.* 1997;44(5):1323–1341.

See Also (Topic, Algorithm, Media)

- Horseshoe Kidney
- Malrotated Kidney/Renal Malrotation
- Renal Ectopia
- Renal Fusion Anomalies Image
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

753.3 Other specified anomalies of kidney

ICD10

- Q63.1 Lobulated, fused and horseshoe kidney
- Q63.2 Ectopic kidney

CLINICAL/SURGICAL PEARLS

- Renal fusion anomalies often associated with other congenital anomalies.
- Ureteropelvic junction obstruction (UPJO) in up to 1/3 of patients with horseshoe kidney.
- Renal vasculature usually aberrant.
- Increased risk of urolithiasis due to medical and anatomic abnormalities.

RENAL INFARCTION

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BASICS

DESCRIPTION

- Renal infarction is a rare condition that occurs secondary to any process that interrupts or halts blood flow to the kidney causing necrosis and cessation of function
- Most commonly caused by thromboembolic phenomenon in conditions such as atrial fibrillation (a-fib), bacterial endocarditis, or cardiac mural thrombi

EPIDEMIOLOGY

Autopsy data reveal an estimated prevalence of 0.48–1.4%

RISK FACTORS

- Acute tubular necrosis
- Antiphospholipid antibody syndrome
- Atherosclerosis
- A-fib
- Chagas disease
- Cocaine abuse
- Collagen vascular disease
- Congestive heart failure
- Diabetes mellitus
- Dilated cardiomyopathy
- Endocarditis
- Hypercoagulable states (factor V Leiden)
- Hypertension
- Iatrogenic (surgical manipulation of renal vasculature)
- Intimal dissection
- Long bone fractures (fat emboli)
- Myocardial infarction
- Patent foramen ovale (paradoxical embolism)
- Pyelonephritis
- Renal artery aneurysm and stenosis
- Renal artery or vein thrombosis
- Sickle cell disease causing papillary necrosis
- Trauma: Blunt or iatrogenic
- Valvular heart disease

Genetics

- Patients with inherited hypercoagulable disorders such as factor V Leiden mutation, protein C or S deficiency, lupus, antiphospholipid antibody syndrome, neurofibromatosis, Ehler–Danlos, and other collagen vascular disorders are at increased risk

- Familial history of coronary artery disease, diabetes, or metabolic syndrome portends an increased risk for these diseases, and consequently, renal infarction

PATHOPHYSIOLOGY

- The main mechanism is embolization of the renal vasculature:
  - Clot emboli are the most common (a-fib)
  - Atherosclerotic emboli
  - Vegetative emboli (endocarditis)
  - Fat emboli
- Renal arterial occlusion is more common on the left side, due to the more acute angle of the left renal artery with the aorta (1)
- Acute infarction due to trauma may show a hematoma in the vessel wall (intimal flap); infarction due to clot emboli will reveal a clot, blocking the renal artery or its branches (2) [C]
- Renal vasoconstriction from sepsis, α-adrenergics, cocaine, others

ASSOCIATED CONDITIONS

- Aneurysms of the aorta or renal artery
- Angina
- Atrial fibrillation
- Claudication
- Collagen vascular disease (Ehlers–Danlos)
- Congestive heart failure
- Mesenteric ischemia
- Patent foramen ovale
- Prosthetic heart valve
- Sub acute bacterial endocarditis (SBE)
- Polyarteritis nodosa with vasculitis
- Sickle cell disease (papillary necrosis)

GENERAL PREVENTION

- Reduce risk factors for coronary artery disease (CAD), hypertension, and diabetes
- Appropriate anticoagulation for a-fib, deep vein thrombosis, and valvular heart disease
- Treatment of hypercholesterolemia with statins
- Measures to reduce the risk of trauma (seat belts)

DIAGNOSIS

HISTORY

- A high suspicion is mandated in patients with underlying heart disease, hypercholesterolemia, or recent trauma who present with abdominal or flank pain
- Suspect a ventricular thrombus in patients with a recent myocardial infarction
- Acute flank pain: ~75%
- Nausea/vomiting: ~50%
- Gross hematuria may be seen

ALERT

The symptoms associated with acute renal infarction closely mimic those of an acute episode of urolithiasis or pyelonephritis resulting in delayed diagnosis. This detrimentally impacts long-term renal function and potential for recovery.

PHYSICAL EXAM

- Diffuse abdominal pain without peritonitis
- CVA tenderness
- Fever
- Acute hypertension
- Flank ecchymosis in trauma patients
- Heart murmur
- Peripheral vascular disease
- Decreased urine output
- Abdominal bruit from an aneurysm

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Leukocytosis: 70% of patients
- Elevated or normal creatinine
- Microscopic hematuria: 80% of patients
- Proteinuria: 90% of patients
- Elevated LDH: 100% of patients. If LDH is elevated with normal transaminases, this is highly suggestive of renal infarction in the presence of appropriate symptoms.
- Elevated ALT: 83% of patients
- Elevated AST: 66% of patients

Imaging

- The best study is abdominal CT with and without IV contrast
- Classic CT findings of renal infarction:
  - Lack of IV contrast uptake in affected kidney
  - Areas of low attenuation secondary to local edema
  - Sharply demarcated, wedge-shaped area of devascularized infarct
  - Cortically based, hypodense areas triangular in shape, widest part at the cortex (base of infarct)
  - Cortical rim sign: Perfusion to infarcted aspect of cortex is maintained by collateral branches, showing a thin rim of enhanced cortex (3)[C]
- IVP reveals poorly or nonvisualized kidney on the affected side
- Renal ultrasound with Doppler flow

ALERT

A noncontrast CT, often obtained due to suspicion for renal colic, will fail to show a renal infarct.

Diagnostic Procedures/Surgery

- Renal angiography will diagnose any renal vascular occlusion and allow for intervention
- ECG to diagnose arrhythmias
- Echocardiography for diagnosis of mural thrombi and valvular vegetations

Pathologic Findings

- Acutely, histology demonstrates apoptosis of glomerular and renal tubular epithelial cells
- Chronic changes include necrosis and nuclear loss in glomeruli and tubules

DIFFERENTIAL DIAGNOSIS

- Acute abdominal processes (acute mesenteric ischemia, appendicitis, bowel obstruction)
- Cystic renal disease
- Pyelonephritis
- Renal artery stenosis
- Renal calculi
- Renal tumor
- Renal vein thrombosis

TREATMENT

GENERAL MEASURES

- The optimal therapy for renal infarction is not clear
- Initial therapy includes supportive measures with IV fluids and pain control
- Since thromboembolic disease is the most common cause of renal infarction, primary anticoagulation is considered 1st line
- Other acute treatment options include thrombolysis, endovascular stenting, and thrombectomy

MEDICATION

First Line

- Antihypertensives to control hypertension
- Anticoagulation therapy:
  - Heparin: Start with a bolus of 80 U/kg followed by a continuous infusion titrated to a therapeutic PTT
  - Begin warfarin therapy concurrently, goal INR of 2–3
  - Continue in patients with known causes of thromboembolic disease

Second Line

- Thrombolytic therapy may be used, especially in unstable patients
  - Direct intra-arterial infusion to limit systemic side effects
  - Many contraindications: Cerebral malignancy or AVM, history of cerebral hemorrhage, GI bleed, active hemorrhage, or aortic dissection
  - Relative contraindications: Pregnancy, major surgery within the last 3 wk, uncontrolled hypertension

SURGERY/OTHER PROCEDURES

- Surgical intervention is not considered a primary treatment for thromboembolic renal infarction. Exceptions include:
  - Young patients diagnosed within 6 hr of the infarct.
  - Bilateral infarcts or infarcts in a solitary kidney.
- For traumatic injuries leading to renal infarction (avulsion of the renal pedicle), open surgical repair may be attempted during exploration for other injuries.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Percutaneous angioplasty of the renal artery or thrombectomy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- The duration of renal ischemia is the critical factor in determining prognosis
- Prognosis also depends on the cause of the infarct and the amount of parenchyma affected
- Patients often die of illness related to the comorbid medical conditions causing the infarct

COMPLICATIONS

- Chronic renal insufficiency
- Renal atrophy
- Hypertension

FOLLOW-UP

Patient Monitoring

- Regular blood pressure monitoring to assess for new-onset hypertension following infarct
- Follow-up imaging to monitor the progression or remission of an infarct
- Medical therapy for underlying condition that led to the infarct
- Monitoring of serum creatinine

Patient Resources

N/A

REFERENCES

1. Fergany A, Novick AC. Renovascular hypertension and ischemic nephropathy Chapter 39. In: Wein AJ, ed. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elselvier/Saunders; 2012:1047–1083.
2. Rajeev TP, Köhler TS, Ryndin I, et al. Case report: Renal infarct mimicking renal mass: Further rationale for minimally invasive management. *J Endourol.* 2007;21:1065–1068.
3. Lang EK, Sullivan J, Frentz G. Renal trauma: Radiologic studies. Comparison of urographic, computerized tomography, angiography, and radionuclide studies. *Radiology*. 1985;154(1):1–6.

ADDITIONAL READING

Saeed K. Renal Infarction. *Int J Nephrol Renovasc Dis*. 2012;5:119–123.

See Also (Topic, Algorithm, Media)

- Flank Pain
- Renal Colic
- Renal Infarction Image

- Renal Trauma, Adult
- Renal Trauma, Pediatric
- Renal Artery Stenosis/Renovascular Hypertension
- Sickle Cell Disease, Urologic Considerations

CODES

ICD9

- 440.1 Atherosclerosis of renal artery
- 584.5 Acute kidney failure with lesion of tubular necrosis
- 593.81 Vascular disorders of kidney

ICD10

- I70.1 Atherosclerosis of renal artery
- N17.0 Acute kidney failure with tubular necrosis
- N28.0 Ischemia and infarction of kidney

CLINICAL/SURGICAL PEARLS

- Renal infarction is most commonly due to thromboembolic disease from underlying medical conditions.
- Prompt diagnosis is paramount for preserving renal parenchyma and function.
- Signs and symptoms may mimic more common GU or intra-abdominal pathology.
- Renal infarction should be in the initial differential diagnosis of nephrolithiasis and pyelonephritis.
- Anticoagulation therapy is the primary form of treatment for renal infarction.

BASICS

DESCRIPTION

- Masses in kidney can be benign or malignant, cystic (simple or complex) or solid, unilateral or bilateral, single or multifocal, primary or metastatic
- Most common renal mass on imaging: Benign cysts (60–70%)
- Most renal cell carcinoma (RCC) are now detected incidentally (up to 70%)
- Most common malignant renal mass is RCC (90%), urothelial (~5%), mets to kidney (~4%)
- Asymptomatic patients (CT screening for colon cancer) may have incidental renal masses 15% of time (90% determined to be benign, 10% indeterminate requiring follow-up)
- Most common renal masses in children: Hydronephrosis (a "pseudomass"), multicystic dysplastic kidney (MCDK), and Wilms tumor (WT)
- Angiomyolipoma (AML) most common benign renal tumor in addition to oncocytoma

EPIDEMIOLOGY

Incidence

- Rates of "kidney cancer" are highest in Europe, North America, and Australia, whereas low in India, Japan, Africa, and China
- 2% worldwide kidney cancer incidence increase per year stabilized in 2008
- Kidney cancer in USA incidence 63,920 with 13,860 deaths in 2014; most lethal GU malignancy
- Antenatal hydronephrosis 0.15% of all pregnancies (50% of GU abnormalities)
- AML 40–80% in tuberous sclerosis (TSC) patients; 0.13–0.03% of general population; ~80% are sporadic & ~20% are in TSC patients
- WT: 6% of all pediatric tumors, 95% of all urologic tumors, ~500 diagnosed annually

Prevalence

- On autopsy 50% of people over 50 yr old have at least one renal cyst
- Kidney cancer: 340,000 in USA

RISK FACTORS

- Kidney cancer: Male 2:1; median age 64 yr old; genetic factors; ¼ of kidney cancer occurs under age of 55; smoking increases risk by 40%; smoking cessation >10 yr almost reverses risk completely; diet effects inconsistent, occupational also conflicting but PCE (perchloroethylene also called tetrachloroethylene), solvents, wool and glass fibers, brick dust, and lead have up to 2-fold increase for RCC, end-stage renal disease (ESRD) debated
- Renal cysts: Genetic factors, age, risk factors for medical renal disease, hemodialysis

Genetics

- RCC 2–3% familial: Von Hippel–Lindau (clear cell RCC)—chromosome 3p25–26 (*VHL gene*); Hereditary papillary RCC (papillary type 1)— chromosome 7q31 (C-*met*); familial leiomyomatosis (papillary type 2)—chromosome 1q42 (*fumarate hydratase*); Birt–Hogg–Dubé (chromophobe RCC, oncocytoma)—chromosome 17p11.2 (*Folliculin*); TSC same risk for RCC as general population based on meta-analysis.
- AML: TSC—*TSC1/TSC2 (50:50),* chromosome 16 & 9 respectively, tumor suppressor genes
- Renal cysts: Autosomal dominant polycystic kidney disease (ADPKD)—PKD1 (85%)/PKD2

(polycystins-cilia, Ca^{2+} channel); autosomal recessive polycystic kidney disease (ARPKD) PKD1 (chromosomal locus 6p12.2) expressed via Potter's sequence; VHL (75%); TSC (50%) *TSC2* gene lies next to PKD1; medullary cystic kidney disease *MCKD1* (chromosome 1q21), *MCKD2* (chromosome 16p12)
- WT: *WT1 (11p13)/WT2 (11p15),* tumor suppressor gene; associated with WAGR, Denys–Drash, Beckwith–Wiedemann (BWS), mixed gonadal dysgenesis (MGD), Trisomy 18, Perlman syndrome

PATHOPHYSIOLOGY
- Renal cysts: Structural abnormalities in the nephron causing fluid to accumulate
- WT1 encodes a zinc-finger transcription factor that is expressed in the kidney and gonads and is necessary for ureteric bud outgrowth and nephrogenesis. Considered tumor suppressor gene but only 20% of Wilms have identifiable WT1 mutation. Undifferentiated blastema, epithelial, or stroma leads to cancer.
- VHL: HIF-1–mediated VEGF angiogenesis upregulated because normal VHL protein-mediated degradation of HIF-1 decreased due to mutation
- AML: Vascular component does not have normal wall, and prone to bleeding when mass size >3 cm (prophylactic intervention at 3.5–4 cm)
- RCC: Clear cell 80% (proximal tubule), papillary 15% (proximal tubule), chromophobe 5% (collecting duct), collecting duct carcinoma <1%, medullary renal carcinoma <1% (sickle cell)
- Untreated small renal masses (SRM), <4 cm, are unlikely to metastasize (~1%) at 3 yr but size and growth rates are variable and not predictive
- RCC size at diagnosis can predict synchronous mets
  - <3 cm, 0.2%
  - 3–5 cm, 2%
  - 5–7 cm, 7%
  - >7 cm ~20%

ASSOCIATED CONDITIONS
- Kidney failure (APKD, papillary RCC)
- Congenital diseases (Wilms, ARPKD, TSC, BWS, BHD, Li–Fraumeni, Cowden syndrome)
- Von Hippel–Lindau (clear cell RCC)
- Cerebral bleeds (ADPKD)
- Sickle cell disease (medullary RCC)
- Hereditary leiomyomatosis (RCC)

GENERAL PREVENTION
- Early screening if genetic predisposition high
- Eliminate modifiable risk factors
- In VHL remove only tumors >3 cm

DIAGNOSIS
HISTORY
- Most RCC patients asymptomatic (why was imaging done that detected incidental mass?)
- Cough or bone pain (mets)

- Flank pain, hematuria (2 of RCC triad of flank pain/hematuria/mass) <10% of patients with RCC

PHYSICAL EXAM

- Eye exam (TSC hamartomas; VHL angiomas)
- Skin (With TSC adenoma sebaceum & ash leaf spot & shagreen patches & finger nail fibromas); With BHD fibrofolliculomas
- Lung exam (BHD associated with pneumothorax)
- Neurologic exam (may be abnormal in TSC, VHL)
- Leg lymphedema (might suggest retroperitoneal LN mets)
- Supraclavicular lymph nodes (possibly distant mets)
- Genital exam (RCC nonreducing varicocele with renal vein thombosis due to RCC; TSC/VHL epididymal cysts/masses)
- Flank mass (part of RCC triad) <10%; more common in Wilms tumor
- Signs of comorbid conditions that will increase peri-op surgical risk (CVA, CAD, HTN, DM, COPD)
- Paraneoplastic signs:
  - Hypertension (RCC and Pheo too)
  - Cachexia, weight loss (check albumin)
  - Neuromyopathy (also part of TSC & VHL)
  - Signs of anemia

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis: Hematuria keeps RCC, UTUC, AML in the differential diagnosis; nitrite and leukocyte esterase positive suggests infection (renal abscess, etc.)
- Voided urine cytology: May detect TCC of urinary tract (not useful if "atypical")
- CBC (anemia or polycythemia in RCC), renal function tests (BUN and creatinine)
- Increased LFTs (Stauffer syndrome: Reversible hepatic dysfunction not due to liver mets)
- Serum calcium: May be elevated in RCC secondary to paraneoplastic syndrome

Imaging

- CT scan w/ and w/o contrast gold standard for renal masses (>10 Hounsfield unit (HU) increase = enhancement = 90% neoplasm) (25–35 mSv effective radiation)
- CT scan with above plus delayed excretory phase for upper-tract neoplasms
- Bosniak cyst CT classification (**1** and **2** benign, no follow-up; **2F** indeterminate, CT 6 mo [5% malignant]; **3** [50% malignant: Surgery or close obs]; **4** ~100% malignant [surgery])
- GFR for contrast-induced nephropathy (CIN)
  - CIN leading to dialysis high if GFR <30
  - CIN risk increases if GFR <60
  - CIN risk 0.6% if GFR >40 and 8% if <40 in one study (GFR 45 may be threshold)
  - 15% of patients can have normal Cr but GFR <50 so GFR better indicator of CIN risk
- If GFR between 30 and 60 gadolinium is safe so consider MRI for these renal masses
  - Gadolinium not safe if GFR <30 (nephrogenic systemic fibrosis—NSF)
- MRI optimal for assessing IVC thrombus and anomalous renal hilar vessels (no radiation)
- Patients on dialysis can get CT contrast without need for immediate dialysis

- Consider CT chest no contrast in patients at risk for mets (CXR misses 10%)
- Nuclear medicine for split functional differentiation rarely needed if Cr <1.5 and kidney size and shape similar to contralateral side
- Brain/bone imaging for mets if symptomatic

Diagnostic Procedures/Surgery

Biopsy necessary for metastatic disease prior to initiation of systemic therapy and if concern for mets *to* the kidney. Indeterminate biopsy occurs 10–20%. Biopsy not routinely needed due to high positive predictive value of enhanced imaging but has role in ablation.

DIFFERENTIAL DIAGNOSIS

- Adults: A solid primary renal mass in adult is most likely to be a RCC, although UCC or metastatic disease is an important consideration
  - AML: Fat in a renal mass strongly suggests AML; fat-poor AML may resemble RCC
  - Carcinoid tumors
  - Collecting duct tumor (Bellini)
  - Cystic nephromas
  - Cysts (simple, hemorrhagic, infected)
  - Focal pyelonephritis
  - Hemangioma
  - Inflammatory masses (xanthogranulomatous pyelonephritis, abscess)
  - Leiomyoma: Usually in renal capsule
  - Metanephric adenoma
  - Metastasis: Lung, gastric, breast cancers most common; melanoma and others
  - Oncocytoma: Benign; cannot be reliably differentiated from RCC on imaging studies
  - Pseudotumors (column of Bertin, others)
  - Renal capsule neoplasm
  - RCC
  - Renal cortical adenoma: Controversial entity; cannot be distinguished from RCC on imaging: <2 cm, metastasis exceedingly rare
  - Renal lymphoma
  - Renal medullary carcinoma
  - Renal sarcomas: 1–2% of all renal masses (leiomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, anaplastic sarcoma)
  - Reninoma (JG apparatus tumors)
  - Urothelial carcinoma upper tract (UTUC)
- Benign renal mass in children:
  - Choledochal cyst, intestinal duplication cyst
  - Congenital mesoblastic nephroma
  - Crossed-fused ectopia
  - Cystic nephroma (multiloculated cystic nephroma)
  - Hydronephrosis
  - Mesenteric cyst
  - MCDK—involuted nonfunctional kidney
  - Polycystic kidney disease
  - Renal abscess

  – Splenomegaly
- Malignant renal masses in children:
  – Lymphoma, lymphosarcoma
  – Neuroblastoma (actually adrenal origin)
  – Ossifying renal tumor of infancy
  – RCC (rare in children)
  – Sarcomas (clear cell, rhabdomyosarcoma)
  – WT (nephroblastoma): Renal mass in a child is WT until proven otherwise

TREATMENT

GENERAL MEASURES

- Renal lesions suspicious for RCC are treated surgically (laparoscopically or open) usually with radical nephrectomy or partial nephrectomy (PNx). PNx use dependent on surgeon experience and location of tumor to hilum; most <3–4 cm (1).
- PNx decreases long-term risk of CVD mortality and ESRD vs. nephrectomy
- Most recommend surgery for Bosniak III (50% malignant) and IV cysts ($\sim$100%)
- TCC of the renal pelvis: By endoscopic ablation for small superficial lesions (low-grade Ta), or radical nephroureterectomy
- Asymptomatic AML >3.5 cm or small symptomatic lesions are treated by embolization, partial nephrectomy, or nephrectomy
- Painful simple renal cysts and infected cysts: Percutaneous aspiration and sclerotherapy
- Although cytoreductive nephrectomy is debated in post-IL-2 era, FDA approval of TKI & mTOR inhibitors based on studies where almost half patients had received a nephrectomy

MEDICATION

First Line

- Usually used for advanced mRCC
- Sunitinib or bevacizumab + IFN-α: 1st line in low/intermediate risk
- Temsirolimus: 1st line in high risk
- Pazopanib: 1st line and after cytokine failure
- Interleukin-2 has more side effects than INF-α. High-dose IL-2 gives durable complete responders in a limited number of patients. IL-2 can be monotherapy in selected good prognosis.

Second Line

- Sorafenib: 2nd line after cytokine failure
- Everolimus: 2nd line after TKI

ADDITIONAL TREATMENT

Radiation Therapy

- Radiation used in pediatric tumors: Wilms stage 3–4, all clear cell and rhabdoid stages
- Metastatic RCC for pain/CNS mets in adults

Additional Therapies

- RCC: Embolization prior to nephrectomy not beneficial but can be palliative for pain and bleeding if nonsurgical candidate

- Ablation (cryotherapy or radio frequency) of smaller renal masses (<3 cm) may be considered in selected cases (elderly, poor surgical risk) (1)

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- MSKCC (Motzer) criteria to predict survival of patients with advanced RCC; for RCC, Kattan and UCLA nomograms popular (based on 2002 TNM)
- RCC 5-yr cancer-specific survival (2010) is 88–100% stage T1–T2, T3 45–75%, T4 <5–30%; +LN 0–30%, or +mets 0–10%
- Wilms: 4-yr survival stage 1–4 favorable histology (FH): 90–98%, stage 5 FH ~56–87%; stage 1–5 unfavorable histology ~66%; clear cell RCC any stage ~75%; rhabdoid sarcoma any stage ~25%

COMPLICATIONS

Surgical complications include hematoma, pneumothorax, infection, adjacent organ injury (liver, spleen, pancreas, duodenum, and bowel), urinary leak, myocardial infarction, thromboembolism, positive surgical margins

FOLLOW-UP

Patient Monitoring

- AML: Renal US every 6–12 mo
- Poor surgical candidate with SRM imaging every 6 mo alternating with renal US and CT scan with yearly CXR or chest CT
- Stage 1–3 RCC, 20–30% relapse, lung most common (50–60%), median relapse 1–2 yr, evaluate every 6 mo for 2 yr, then annually. Stage 4 RCC f/u dependent on primary treatment and provider dependent.

Patient Resources

Kidney Cancer Association www.kidneycancer.org/

REFERENCE

1. Buethe DD, Spiess PE. Current management considerations for the incidentally detected small renal mass. *Cancer Control*. 2013;20(3):211–221.

ADDITIONAL READING

- 2012 EUA Guidelines: http://www.uroweb.org/gls/pdf/10_Renal_Cell_Carcinoma_LRV2.pdf
- NCCN Guidelines: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

See Also (Topic, Algorithm, Media)

- RCC, General Considerations
- Renal Capsule Neoplasm
- Renal Mass, Algorithm
- Renal Mass Image
- Renal Mass, Intraoperative Consultation

- Renal Masses, Benign WHO, Classification
- Renal Pseudotumors
- Renal Sarcoma, Adult and Pediatric
- Reference Tables: TNM: Kidney Cancer

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 593.9 Unspecified disorder of kidney and ureter

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- N28.89 Other specified disorders of kidney and ureter

CLINICAL/SURGICAL PEARLS

- Much less than 10% of patients with RCC present with the “classic triad” of hematuria, flank pain, and a renal mass.
- A solid renal mass in childhood is WT until proven otherwise.

RENAL MASS, INTRAOPERATIVE CONSULTATION

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BASICS

DESCRIPTION

- Most renal masses are incidentally found preoperatively on routine axial imaging (eg, CT or MRI of the abdomen)
- Although rare today, some renal masses are 1st identified intraoperatively
  - Typically associated with trauma or urgent cases where preoperative imaging was either not done or inadequate for renal visualization

EPIDEMIOLOGY

Incidence

- Renal cell carcinoma (RCC)
  - 63,920 estimated new cases in 2014 (NCI data)
  - Primarily occurs in 6th or 7th decade
  - Male > Female (3:2)
  - 4% of RCC are familial; majority are sporadic
  - 10–20% higher incidence in African Americans

Prevalence

N/A

RISK FACTORS

- RCC
  - Family history, smoking, obesity, hypertension, end stage renal disease (ESRD)
- For intraoperative renal mass consult, risk factors include:
  - Pre-existing nonrenal primary cancer
    - Possible metastatic lesion on kidney
  - Inheritable tumor syndrome
    - Associated renal tumor component
  - Renal insufficiency preventing use of contrast during imaging
  - Centrally located or small tumors initially missed on imaging

PATHOPHYSIOLOGY

N/A

ASSOCIATED CONDITIONS

- Polycystic kidney disease
  - Autosomal dominant (autosomal dominant polycystic kidney disease) or recessive (autosomal recessive polycystic kidney disease)
- Inheritable tumor syndromes with renal and extrarenal manifestations
  - Birt–Hogg–Dubé (BHD gene; 17p11)

- Cutaneous lesions, lung cysts, spontaneous pneumothorax, colonic polyps, or cancer
- Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC gene; 1q42) (aka: Reed's syndrome)
  - Uterine leiomyoma and leiomyosarcoma, cutaneous leiomyoma and leiomyosarcoma
- Hereditary hyperparathyroidism-jaw tumor syndrome (CDC23 gene; 1q24–32)
  - Parathyroid tumor, fibroosseous mandibular and maxillary tumor, uterine tumor
- Papillary thyroid carcinoma with associated papillary renal neoplasia (1q21)
  - Papillary thyroid cancer, nodular thyroid disease
- Tuberous sclerosis complex (TSC1, 9q34)
  - Facial angiofibroma, subungual fibroma, hypopigmentation and café au lait spots, cardiac rhabdomyoma, seizure, mental retardation, CNS tubers, lymphangioleiomyomatosis
- VHL (VHL gene; 3p25)
  - Retinal and CNS hemangioblastomas, pheochromocytoma, pancreatic cyst and endocrine tumor, endolymphatic sac tumor, epididymal and broad ligament cystadenomas

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Obtain history from operative team and review available medical and radiographic records
  - Prior or current cancers
  - Inheritable tumor syndromes
  - History of renal or abdominal trauma

PHYSICAL EXAM
- Intraoperative evaluation—location of mass
  - Check adrenal
  - Intrarenal
  - Extrarenal within Gerota fascia
  - Perirenal
  - Renal pelvis

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Serum creatinine and eGFR

Imaging
- Review all preoperative ultrasound (US), contrast-enhanced CT, and/or MR if available
  - If serial images available, determine growth rate to help define risk (1)[B]
    - Average yearly linear growth rate of 0.3 cm for all masses vs. 0.8 cm found in patients with progression
    - Masses with no growth under surveillance unlikely to metastasize
- Intraoperative US with color Doppler (use laparoscopic or finger probe in open surgery)
  - Features suggesting malignant pathology

- Purely cystic lesions without septation can be observed
- Remove lesions with solid elements

– Color Doppler also useful to:
- Assess flow to ipsilateral and contralateral kidney
- Differentiate an isoechoic lesion with renal parenchyma since vessels are displaced around solid renal masses
- Identifies deep vessels near the wall of the lesion that may be encountered during excision

ALERT

Obtain all available informatIon on renal function.

• Calculate overall renal function (GFR—Cockcroft–Gault equation; calculators available online) and classify CKD status.
• Status of contralateral renal unit presence, flow, and function.
• Enhancement characteristics on imaging.

Objectify risk:

• Overall survival vs. competing risks of death.
– Competing risks nomogram operationalized online at www.cancernomograms.com (2) [B].
• Remaining renal function.
– Can estimate percent functional volume preservation if partial nephrectomy planned as volume loss correlates well with ultimate renal function after partial nephrectomy (3)[B].

Diagnostic Procedures/Surgery

• Diagnostic procedures
– Consider intraoperative renal mass biopsy and frozen section analysis
- Obtain core biopsy with biopsy gun
- ~20% of intraoperative frozen sections of renal lesions nondiagnostic (4)[B]
- Management options include active surveillance, ablation, or extirpation (Note: Renal biopsy and frozen section analysis yield poor tumor grade information)

Pathologic Findings

• Approximately 14% of incidentally found renal masses are benign depending on size (5)[B]
– 68% clear cell RCC
– Positive association between tumor size and:
- Rates of clear cell RCC
- Fuhrman grade for clear cell RCC
- Tumor stage

DIFFERENTIAL DIAGNOSIS

• Renal masses (see Section I “Renal Mass” for more information)
– Abscess (acute or chronic)—consider history and available labs
– Angiomyolipoma (AML)—check for fat on imaging
– Adrenal lesion—check for presence of contralateral gland prior to removal—if unable beware of postoperative insufficiency
– Benign lesion—oncocytoma, etc.

- Calyceal diverticulum (chronic and infected can cause mass-like appearance with heavy perinephric reaction)
- Hemorrhagic cyst—may appear solid and pseudoenhance
- Lymphoma—may cause renomegaly
- Metastatic lesion from other primary tumor
- Pseudotumor (column of Bertin)
- Renal lobulations
- RCC, Wilms tumor
- Renal cysts
- Sarcoma (renal or retroperitoneal—including leiomyosarcoma and liposarcoma)
- Subcapsular hematoma—may be chronic especially with old trauma or extracorporeal shock wave lithotripsy
- Upper-tract urothelial carcinoma
- Vascular—hemangioma, renal artery aneurysm, malformation

• Perirenal
- Adrenal lesion or adrenocortical carcinoma
- Mesothelial cyst
- Teratoma

TREATMENT

GENERAL MEASURES

• What to do if called to the operating room emergen-tly to evaluate a renal mass (See Section III: Renal Mass, Intraoperative Consultation Algorithm)
• If patient unstable and involved kidney uninjured, defer to later date
• If films unavailable, safely defer if possible
• If unable to defer treatment—assess presence, function, and anatomy of both kidneys and consider biopsy
• Look at available films to see if pre-/postcontrast phases available
- If preoperative imaging suggests a solid, enhancing mass amenable to partial nephrectomy
  - Consider intraoperative biopsy and frozen section analysis
  - Reasonable to perform partial nephrectomy after family discussion (if present)
- Do not get fooled by hyperdense cyst or pseudotumor—see clinical pearls

• If no films, and cannot postpone intervention, consider biopsy
- If solid elements with flow on Doppler US, normal contralateral kidney and amenable to partial nephrectomy, then intervene
- If radical required for technical reasons, perform biopsy with frozen section pathologic analysis and possibly deferring intervention until permanent section results obtained
  - Unless absolute indication for radical nephrectomy (≥cT3, adjacent organ involvement, vascular compromise)

• Avoid the following:
- Rely on US as only test for radical nephrectomy (get biopsy)
- Rely solely on intraoperative single shot IVP to evaluate contralateral kidney
- Perform a radical nephrectomy because technically easier
- Assume presence, flow, or function of contralateral kidney

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Extirpative procedures
  - Partial nephrectomy
    - Tumor enucleation may yield equivalent oncologic outcomes. Best used when mass locally confined on preoperative imaging, easily delineated intraoperatively, and do not appear to grossly invade beyond the pseudocapsule.
    - Frozen section analysis on margin if in question
  - Radical nephrectomy
  - Resection of mass adjacent to kidney ± partial or radical nephrectomy, if only way to get specimen out safely
- Surgical approach
  - Attempt to use existing approach (laparoscopic/robotic) or incision
    - Convert from laparoscopic to open if needed for imperative indications only, otherwise may defer if oncologic risk low
    - If nephron sparing requires conversion for technical reasons, consider performing at later date with patient consent
- Remember to place perirenal closed suction drain for most nephron-sparing procedures

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Investigate adjuvant therapies or eligibility for adjuvant clinical trials based on pathology
- Follow functional (nephrologic) results
- If adrenalectomy was performed—beware of postoperative adrenal insufficiency

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Influenced by stage, grade, histology
- Margin status appears not to portend an adverse prognosis or increased local recurrence
- Local recurrence after resection is ~2–3% after partial or radical nephrectomy
- 5-yr risks of recurrence for local or regional RCC fully excised are approximately:
  - >95% for pT1, ~85% for pT2, range from 40–60% for pT3b

COMPLICATIONS

- For partial and radical nephrectomy: Acute renal failure, need for dialysis

- Long-term risk of chronic renal insufficiency after radical nephrectomy associated with increased cardio- and cerebrovascular morbidity
- For partial nephrectomy: Urinary fistulas, and bleeding
- Major complications, including urine leak, increase with increasing tumor complexity
  - Low complexity—6%
  - Moderate complexity—11%
  - High complexity—22%

FOLLOW-UP

Patient Monitoring

- NCCN guidelines (level of evidence 2B—lower level but consensus recommended)
  - Every 6 mo for 2 yr, then annually for 5 yr
    - History and physical exam
    - Comprehensive metabolic panel
  - At 2 yr as indicated based on recurrence risk
    - Chest and abdominal ± pelvic imaging
    - Risk-based follow-up clinical practice guidelines operationalized at www.cancernomograms.com

Patient Resources

N/A

REFERENCES

1. Smaldone MC, Kutikov A, Egleston BL, et al. Small renal masses progressing to metastases under active surveillance: A systematic review and pooled analysis. *Cancer.* 2012;118:997–1006.
2. Kutikov A, Egleston BL, Wong YN, et al. Evaluating overall survival and competing risks of death in patients with localized renal cell carcinoma using a comprehensive nomogram. *J Clin Oncol.* 2010;28:311–317.
3. Simmons MN, Hillyer SP, Lee BH, et al. Functional recovery after partial nephrectomy: Effects of volume loss and ischemic injury. *J Urol.* 2012;187:1667–1673.
4. Krishnan B, Lechago J, Ayala G, et al. Intraoperative consultation for renal lesions. Implications and diagnostic pitfalls in 324 cases. *Am J Clin Pathol.* 2003;120:528–535.
5. Corcoran A, Russo P, Lowrance WT, et al. A review of contemporary data on renal masses—benign or malignant? *Urology.* 2013;81(4):707–713.

ADDITIONAL READING

NCCN guidelines: http://www.nccn.org/

See Also (Topic, Algorithm, Media)

- Birt–Hogg–Dubé Syndrome
- Renal Cell Carcinoma, General
- Renal Cell Carcinoma, Localized (T1–T2)
- Renal Cell Carcinoma, Locally advanced (T3–T4)
- Renal Cell Carcinoma, Metastatic (N^+, M^+)
- Renal Cell Carcinoma, Pediatric

- Renal Mass
- Renal Mass, Intraoperative Consultation Algorithm
- Renal Masses, Benign, WHO Classification
- Von Hippel–Lindau Disease/Syndrome

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 593.9 Unspecified disorder of kidney and ureter
- 753.10 Cystic kidney disease, unspecified

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- N28.89 Other specified disorders of kidney and ureter
- Q61.9 Cystic kidney disease, unspecified

CLINICAL/SURGICAL PEARLS

- Traumatic hemorrhage into a cyst can mimic a hypoechoic, solid renal mass. Color Doppler can establish blood flow ruling out hemorrhagic cysts.
- Failing to check preoperative films if available as AML can often be distinguished by macroscopic fat on CT/MR.
- Avoid getting fooled by renal pseudotumor or adrenal lesion.
- Avoid expanding the goals of planned operation without consent or clearly thought out plan.

RENAL ONCOCYTOMA

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BASICS

DESCRIPTION
- Renal oncocytoma is the most common benign solid renal tumor in adults
- Usually asymptomatic at time of presentation
- Frequently detected incidentally at time of CT scan

EPIDEMIOLOGY
Incidence
- 3–7% of all renal masses
- Epidemiology similar to renal cell carcinoma (RCC)
- Male > female (2:1)
- Median age of diagnosis 62 yr
- 6% occur bilaterally
- 17% multifocal

Prevalence
N/A

RISK FACTORS
- Familial renal oncocytoma syndrome
  - Described rarely to date
- Birt–Hogg–Dubé (BHD)

Genetics
- Most frequent abnormalities (1,2):
  - Loss of chromosome 1p
  - Loss of chromosome Y (males)
- Less frequent translocations
  - Breakpoint region on 11q13
  - Region encoding mDNA
  - Loss of heterozygosity at chromosomes 1,14,21
    - May reflect progression of oncocytoma to chromophobe RCC

PATHOPHYSIOLOGY
- Arise from intercalated cells in collecting duct of kidney (like chromophobe RCC)
- Occasionally oncocytoma and RCC may be found in the same kidney

ASSOCIATED CONDITIONS
- Most usually sporadic
- BHD
  - Autosomal dominant

- Mutation in gene for folliculin
- Renal tumors
  - Chromophobe/oncocytoma
- Spontaneous pneumothorax, lung cysts
- Fibrofolliculomas, especially on face

GENERAL PREVENTION

No preventative strategies have been described. Relatives of those with genetic syndromes may be screened.

DIAGNOSIS

HISTORY

- Most patients asymptomatic
- Incidentally detected
- Gross hematuria/flank pain/flank mass rare
- Family history of renal tumors, fibrofolliculomas, lung cysts/pneumothorax—rule out BHD

PHYSICAL EXAM

- No specific findings for sporadic oncocytoma
- Palpable flank mass rare
- Dermatologic exam if suspected BHD

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- No lab test can identify renal tumor as oncocytoma
- Lab panel as with any newly diagnosed renal mass
  - CBC, chemistry panel, LFTs

Imaging

- Cannot be used to reliably distinguish oncocytoma from RCC
- CT with and without IV contrast
  - Diagnostic test of choice for solid renal mass
  - Central scar within mass often seen in oncocytoma, but this can be confused with necrosis, commonly seen with RCC
- MRI
  - Solid enhancing renal mass ± central scar
  - Test of choice with IV contrast allergy, renal insufficiency
- Renal US
  - Not typically helpful for identification of mass as oncocytoma
- Renal angiogram
  - Spoke wheel pattern of feeding vessels
    - Not definitive for diagnosis
  - Usually not helpful in evaluation of renal mass
- Metastatic evaluation for solid renal mass
  - Chest x-ray vs. chest CT
- Additional studies may be indicated clinically

Diagnostic Procedures/Surgery

- Percutaneous biopsy
  - May be useful to exclude metastasis to kidney based on patient history
  - May guide management of poor surgical candidates
- Pitfalls of biopsy
  - Difficult to distinguish oncocytoma from chromophobe RCC
  - Coexistence of RCC and oncocytoma in up to 10% cases

Pathological-Findings (3,4)

- The term "oncocytoma" is a general descriptor of an epithelial tumor that consists of oncocytes. Oncocytes are large eosinophilic cells with small, round, benign-appearing nuclei without nucleoli.
  - Oncocytomas can arise in a number of different organs
- Renal oncocytoma: Gross findings
  - Well-circumscribed mass, mahogany brown, often with pseudocapsule
  - Average size 6–7 cm
  - 33% with central stellate scar
  - 20% demonstrate extension into perinephric fat
  - Calcifications and necrosis rarely seen
- Renal oncocytoma: Microscopic findings
  - Round to polygonal eosinophilic cells
  - Abundance of mitochondria seen on electron microscopy
  - Mitotic figures rare
  - Regular nuclei
  - Cells arranged in distinct nests
  - May be difficult to distinguish from chromophobe RCC
    - Colloidal iron stain positive in chromophobe RCC but not oncocytoma
    - Chromophobe RCC is vimentin, cytokeratin 7 positive
    - CD82 and epithelial-related antigen (MOC31) may be helpful in the distinction between chromophobe RCC and renal oncocytoma
    - Gene expression differences are being explored
    - The World Health Organization (2004) renal tumor classification indicates renal oncocytomas are benign neoplasms. In the past some renal oncocytomas were classified as malignant.
    - This may have resulted from confusion with clear cell renal carcinomas with eosinophilic component or due to eosinophilic chromophobe RCC (low metastatic potential)

ALERT

Although oncocytoma has "Classic Findings" on imaging, no radiographic studies exist to differentiate benign oncocytoma from malignant RCC.

DIFFERENTIAL DIAGNOSIS

- Adrenal mass
- Angiomyolipoma
- Carcinoid tumor

- Collecting duct tumor
- Cystic nephroma
- Cysts
- Focal pyelonephritis
- Hemangioma
- Inflammatory masses (xanthogranulomatous pyelonephritis (XGP), abscess)
- Leiomyoma
- Metanephric adenoma
- Metastasis
- Pseudotumor (column of Bertin)
- RCC
- Renal cortical adenoma
- Renal lymphoma
- Renal medullary carcinoma
- Renal sarcoma
- Reninoma
- Urothelial carcinoma
- Wilms tumor

TREATMENT

GENERAL MEASURES
Mainstay of treatment is surgical

MEDICATION
First Line
No medical treatment exists

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Establishes diagnosis of oncocytoma
- Partial nephrectomy whenever feasible based on size and location
- Radical nephrectomy rarely indicated unless very large, uncertain diagnosis or partial not possible

ADDITIONAL TREATMENT
Radiation Therapy
No role

Additional Therapies
N/A

Complementary & Alternative Therapies
- Renal cryotherapy and radiofrequency ablation (5)
  - Being studied as treatment option
  - Unable to differentiate between oncocytoma and RCC due to lack of tissue for histology

  - Primarily for smaller lesions (< 3 cm)
  - May be done laparoscopically or percutaneously
  - No long-term follow-up exists
  - Usually considered for poor surgical candidates
- Active surveillance
  - Good for select patients with solid renal masses, but no size can reliably differentiate between benign and malignant processes
    - 3 cm usually used as cutoff in BHD

ONGOING CARE

PROGNOSIS

- Oncocytoma is uniformly considered a benign tumor and surgical removal is curative
- Multiple series report no metastases or death from oncocytoma on long-term follow-up
- Older, rare reports of metastases may represent unrecognized, low-grade RCC (6,7)
- Risk of metachronous oncocytoma 4–6%

COMPLICATIONS

- Perioperative for partial/radical nephrectomy
  - Bleeding, infection, urine leak
- Long term after nephrectomy depends on renal reserve
  - Chronic renal insufficiency/dialysis

FOLLOW-UP

Patient Monitoring

- Patient monitoring
  - Long-term surveillance of renal units recommended annually to semiannually
  - Metachronous ipsilateral and bilateral oncocytomas have been reported
- Renal US preferred modality
  - Minimizes radiation exposure
  - No need for IV contrast
- Urinalysis
  - Hematuria/proteinuria
- Serum creatinine

Patient Resources

- Kidney Cancer Association
  www.kidneycancer.org/

REFERENCES

1. Al-Saleem T, Cairns P, Dulaimi EA, et al. The genetics of renal oncocytosis: A possible model for neoplastic progression. *Cancer Genet Cytogenet.* 2004;152:23–28.
2. Boris RS, Benhammou J, Merino M, et al. The impact of germline BHD mutation on histological concordance and clinical treatment of patients with bilateral renal masses and known unilateral oncocytoma. *J Urol.* 2011;185(6):2050–2055.
3. Gudbjartsson T, Hardarson S, Petursdottir V, et al. Renal oncocytoma: A clinicopathological analysis of 45 consecutive cases. *BJU Int.* 2005;96:1275–1279.

4. Kuroda N, Tanaka A, Ohe C, et al. Review of renal oncocytosis (multiple oncocytic lesions) with focus on clinical and pathobiological aspects. *Histol Histopathol.* 2012;27(11):1407–1412.
5. Breen DJ, Bryant TJ, Abbas A, et al. Percutaneous cryoablation of renal tumours: Outcomes from 171 tumours in 147 patients. *BJU Int.* 2013;112(6):758–765.
6. Romis L, Cindolo L, Patard JJ, et al. Frequency, clinical presentation, and evolution of renal oncocytomas: Multicentric experience from a european database. *Eur Urol.* 2004;45:53–57.
7. Van der Kwast T, Perez-Ordoñez B. Renal oncocytoma, yet another tumour that does not fit in the dualistic benign/malignant paradigm. *J Clin Pathol.* 2007;60(6):585–586.

ADDITIONAL READING

- Chen YT, Tu JJ, Kao J, et al. Messenger RNA expression ratios among 4 genes predict subtypes of renal cell carcinoma and distinguish oncocytoma from carcinoma. *Clin Cancer Res.* 2005;11:6558–6566.
- Dechet CB, Bostwick DG, Blute ML, et al. Renal oncocytoma: Multifocality, bilateralism, metachronous tumor development and coexistent renal cell carcinoma. *J Urol.* 1999;162:40–42.
- Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol.* 2003;170:2163–2172.

See Also (Topic, Algorithm, Media)

- BHD
- Reference Tables: TNM: Kidney Cancer
- Renal Cell Carcinoma, Chromophobe
- Renal Cell Carcinoma, General Considerations
- Renal Mass, Algorithm
- Renal Mass, Intraoperative Consultation
- Renal Masses, Benign WHO, Classification
- Renal Oncocytoma Image
- Renal Pseudotumors

CODES

ICD9

223.0 Benign neoplasm of kidney, except pelvis

ICD10

- D30.00 Benign neoplasm of unspecified kidney
- D30.01 Benign neoplasm of right kidney
- D30.02 Benign neoplasm of left kidney

CLINICAL/SURGICAL PEARLS

- Oncocytoma is a benign solid renal lesion.
- No imaging study reliably differentiates oncocytoma from RCC. The CT finding of a central

scar, previously felt to be specific for oncocytoma, has been found with RCCs, and this finding is not specific.

RENAL SARCOMA, ADULT AND PEDIATRIC

Adam O. Kadlec, MD
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BASICS

DESCRIPTION

- Sarcomas of the kidney are rare solid tumors that arise from the embryonic mesoderm
  - Sarcomas of the renal parenchyma itself are very rare. More commonly, "renal sarcomas" represent a soft tissue sarcoma that either invades or abuts the kidney.
  - In large case series of adult patients, leiomyosarcoma and liposarcoma are the most common histologic subtypes
- Renal sarcomas are more likely to be seen in childhood than adulthood
- Childhood sarcomas
  - Represented almost exclusively (approximately 95%) by Wilms tumor (historically called nephroblastoma) (1)[A]
  - Other sarcomas of childhood include clear cell sarcoma, rhabdomyosarcoma, congenital mesoblastic nephroma, and fibrosarcoma

EPIDEMIOLOGY

Incidence

- Adults: 1–2% of genitourinary cancer with peak incidence in 5th decade
- Children: 6–7% of childhood cancers represented mainly by Wilms tumor
- Wilms tumor occurs equally in boys and girls, with a median age of onset of 3.5 yr

Prevalence

N/A

RISK FACTORS

- Specific etiologies are not known
- HIV is associated with Kaposi sarcoma of the kidney
- Wilms tumor does have a small component of family history

Genetics

- Adult renal sarcomas unknown; suggestion of familial tendency with angiosarcoma
  - Possible role of DNA mismatch repair pathway
- 1–2% of Wilms tumor patients have an inherited genetic predisposition
  - Most common loss or inactivation of a tumor suppressor gene called WT1 on chromosome 11
  - WT1 located at 11p13 and is associated with renal and gonadal development
  - WT2 located at 11p15 and is associated with Beckwith–Wiedemann syndrome
  - 90% of Wilms tumors arise from somatic mutations with overall genetic paradigm remaining unknown

PATHOPHYSIOLOGY

- Most common adult renal sarcomas are leiomyosarcomas, representing as many as 50–60%

of such tumors. A wide variety of other types, such as liposarcoma and fibrosarcoma, are also found (2)[B].

- Sarcomas exhibit aggressive local growth with high rate of local recurrence, even in the event of negative surgical margins, due to a tendency for "skip lesions."
- RCC with sarcomatoid features is an increasingly recognized variant of RCC (<5% of all cases) that contains regions of mesenchymal-appearing malignant cells adjacent to or within another typical RCC histology
- Later metastasis to the lung and liver can occur
- Wilms tumor is categorized into favorable or unfavorable histology; this has important implications regarding treatment (1)[A]

ASSOCIATED CONDITIONS

Wilms tumor is associated with aniridia, hemihypertrophy, Beckwith–Wiedemann syndrome, Denys–Drash, and GU abnormalities (hypospadias and cryptorchidism)

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Age and sex of patient
- Family history
- History of mental retardation or GU anomalies
- Noticeable abdominal mass (esp. Wilms)
- Shortness of breath, lethargy, abd pain, weight loss, and other systemic symptoms may be present

PHYSICAL EXAM

- Abdominal exam for mass
  – In children, a palpable mass will be seen with Wilms tumor in >80% of cases
- Assess for associated lymphadenopathy
- GU exam to assess for GU anomalies such as hypospadias or undescended testis, which may alert to syndromes such as Denys–Drash

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Comprehensive metabolic panel to include liver function tests
- CBC
- UA (microhematuria, pyuria)
- No reliable tumor markers for sarcoma

Imaging

- CXR or CT to evaluate for metastatic disease in the chest or abdomen
- CT/MRI to assess local extent of tumor may aid surgical planning
- On MRA, sarcomas tend to be avascular
- Renal US may be helpful in evaluation of cystic renal mass

Diagnostic Procedures/Surgery
Biopsy of limited utility

Pathologic Findings
- Morphologically, renal sarcomas are similar to their extrarenal counterparts
- In adults they can arise from both the parenchyma and the renal capsule
- Wilms tumor
  - Generally soft and friable with hemorrhage and necrosis
  - Classic: Coexistence of blastemal, epithelial, and stromal cells
  - Unfavorable histology is associated with nuclear enlargement, hyperchromasia, and abnormal mitotic figures
- Leiomyosarcoma (most common)
  - Cell origin is smooth muscle of capsule or the perinephric structures
  - Displaces rather than invade parenchyma
- Fibrosarcoma, malignant fibrous histiocytomas, anaplastic sarcoma of the kidney are other histologic types

DIFFERENTIAL DIAGNOSIS
- Adults: A solid primary renal mass in adult is most likely to be a RCC, although urothelial carcinoma or metastatic diseases are other considerations
  - AML: Fat in a renal mass strongly suggests AML; fat-poor AML may resemble RCC
  - Carcinoid tumors
  - Collecting duct tumor (Bellini)
  - Cystic nephromas
  - Cysts (simple, hemorrhagic, infected)
  - Focal pyelonephritis
  - Hemangioma
  - Inflammatory masses (xanthogranulomatous pyelonephritis, abscess)
  - Leiomyoma: Usually in renal capsule
  - Metanephric adenoma
  - Metastasis: Lung, gastric, breast cancers most common; melanoma and others
  - Oncocytoma: Benign; cannot be reliably differentiated from RCC on imaging studies
  - Pseudotumors (column of Bertin, others)
  - Renal capsule neoplasm
  - Renal cell carcinoma (RCC)
  - Renal cortical adenoma: Controversial; cannot be distinguished from RCC on imaging: <2 cm
  - Renal lymphoma
  - Renal medullary carcinoma
  - Renal sarcomas
    - Angiosarcoma
    - Chondrosarcoma
    - Clear cell sarcoma
    - Ewing sarcoma/primitive neuroectodermal tumor
    - Fibrosarcoma
    - Kaposi sarcoma

- Leiomyosarcoma (including the myxoid types)
- Liposarcoma
- Malignant fibrous histiocytoma
- Malignant hemangiopericytoma
- Malignant mesenchymoma
- Malignant schwannoma
- Osteogenic sarcoma
- Rhabdomyosarcoma
- Sarcomatoid renal cell carcinoma
- Synovial sarcoma
- Wilms tumor

– Reninoma (JG apparatus tumors)
– Urothelial carcinoma upper tract (UTUC)

• Benign renal mass in children:
– Choledochal cyst, intestinal duplication cyst
– Congenital mesoblastic nephroma
– Crossed-fused ectopia
– Cystic nephroma (multiloculated cystic nephroma)
– Hydronephrosis
– Mesenteric cyst
– Multicystic dysplastic kidney (MCDK): involuted nonfunctional kidney
– Polycystic kidney disease
– Renal abscess
– Splenomegaly

• Malignant renal masses in children:
– Lymphoma, lymphosarcoma
– Neuroblastoma (actually adrenal origin)
– Ossifying renal tumor of infancy
– RCC (rare in children)
– Sarcomas (clear cell, rhabdomyosarcoma)
– Wilms tumor (nephroblastoma): A renal mass in childhood is Wilms until proven otherwise

ALERT
Primary renal sarcoma is extremely rare. Primary retroperitoneal soft tissue sarcoma (such as leiomyosarcoma or liposarcoma) with secondary renal invasion is the more common clinical presentation.

TREATMENT

GENERAL MEASURES

• In adults, the lesions are usually approached as for RCC, with surgical excision being 1st-line therapy, as the histology of lesion is rarely known preoperatively (3)[B]
• Masses tend to be quite large, presumably due to rapid growth pattern
• The primary treatment of renal sarcomas is surgical excision. Local recurrences should be

resected when feasible.
- The role of adjuvant and neoadjuvant therapy in the adult population is poorly understood

MEDICATION

First Line

- Dactinomycin and vincristine are used for more favorable stages of Wilms, with the addition of doxorubicin and abdominal radiation for more advanced stages
- Doxorubicin for clear cell sarcoma in children
- Doxorubicin, dacarbazine, and ifosfamide have been used with adult sarcomas; however, response rates at best are poor

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Mainstay of treatment for all sarcomas involving the kidney is radical nephrectomy with excision of entire tumor mass, which may require resection of adjacent organs. In some cases, partial nephrectomy may be possible (2)[B].
- Wide excision is the preferred approach due to sarcomas' tendencies toward skip lesions
- Sarcomas tend to surround the renal vasculature as well as surrounding vascular structures
- No defined role for lymphadenectomy
- Preoperative chemotherapy is given in advanced cases of Wilms to downstage prior to surgery, usually with external radiation therapy. In bilateral disease, nephron sparing is indicated.

ADDITIONAL TREATMENT

Radiation Therapy

- Sometimes employed in management of Wilms tumor postoperatively. Radiation of the tumor bed is indicated if the tumor extended beyond the renal capsule to involve adjacent organs or lymph nodes or with intraoperative tumor spillage.
- Radiation therapy after surgery in adult sarcomas may reduce local recurrence.

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Adult sarcomas, especially high grade, have a generally poor prognosis, with 5-yr survival rates of approximately 50%
  - Poor prognostic variables include high-grade histology, metastases at presentation, large tumor size, and incomplete resection/margin positivity
- Local recurrence alone is associated with a better survival rate than local recurrence with concomitant metastasis
- Pediatric patients with Wilms tumors can expect a >90% cure rate, but prognosis for clear

cell sarcoma and especially rhabdoid tumors is much worse

COMPLICATIONS

Children should be monitored for long-term effects of radiation and/or chemotherapy (such as cardiac dysfunction, HTN, secondary malignancies, endocrinologic abnormalities, and ovarian or testicular failure)

FOLLOW-UP

- Careful patient monitoring is essential due to the high recurrence rate
  - Adults: Close follow-up for 2–5 yr
    - CXR every 3–6 months
    - Abd MRI or CT screening every 3–6 min
    - No specific tumor markers to follow
  - Children: Same as adults. Try to limit studies such as CT due to long-term ionizing radiation risks.

Patient Resources

Kidney Cancer Association www.kidneycancer.org/

REFERENCES

1. Davidoff AM. Wilms tumor. *Adv Pediatr*. 2012;59(1):247–267.
2. Wang X, Xu R, Yan L, et al. Adult renal sarcoma: Clinical features and survival in a series of patients treated at a high-volume institution. *Urology*. 2011;77(4):836–841.
3. Dotan ZA, Tal R, Golijanin D, et al. Adult genitourinary sarcoma: The 25-year Memorial Sloan-Kettering experience. *J Urol*. 2006;176(5):2033–2038.

ADDITIONAL READING

- Buckley K. Pediatric genitourinary tumors. *Curr Opin Oncol*. 2012;24(3):291–296.
- Russo P, Brady MS, Conlon K, et al. Adult urological sarcoma. *J Urol*. 1992;147(4):1032–1036.

See Also (Topic, Algorithm, Media)

- Ossifying Renal Tumor of Infancy
- Renal Capsular Neoplasms
- Renal Cell Carcinoma, General Considerations
- Renal Cell Carcinoma, Sarcomatoid
- Renal Leiomyosarcoma
- Renal Mass
- Renal Sarcoma, Adult and Pediatric Image ☼
- Wilms Tumor

CODES

ICD9

- 171.5 Malignant neoplasm of connective and other soft tissue of abdomen
- 236.91 Neoplasm of uncertain behavior of kidney and ureter

ICD10

- C49.4 Malignant neoplasm of connective and soft tissue of abdomen
- D41.00 Neoplasm of uncertain behavior of unspecified kidney
- D41.01 Neoplasm of uncertain behavior of right kidney

CLINICAL/SURGICAL PEARLS

- Primary renal sarcomas are very rare. Soft tissue sarcomas that involve the kidney are the more common presentation.
- Renal sarcomas are more likely to be seen in childhood than adulthood. Wilms tumor is the most common pediatric renal sarcoma and has a distinct treatment algorithm.
- The primary treatment of renal sarcomas is surgical excision. Wide excision is the preferred approach due to sarcomas' tendencies toward skip lesions. Local recurrences should be resected when feasible.
- It is important to differentiate renal or soft tissue sarcomas from RCC with sarcomatoid features, which is an aggressive variant of RCC, *not* a primary sarcoma.

RENAL TRAUMA, ADULT

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BASICS

DESCRIPTION

- Renal injuries can occur by either blunt or penetrating trauma
  - Renal contusions, renal laceration, and renal vascular injury are the general categories
- Renal injury classification: Based on American Association for the Surgery of Trauma (AAST) renal injury grading system (1)
  - Grade I: Subcapsular hematoma
  - Grade II: Laceration <1 cm deep into cortex, small hematoma with Gerota's fascia
  - Grade III: Laceration >1 cm into medulla, no collecting system injury
  - Grade IV: Laceration into collecting system, vascular segmental vein or artery injury, renal pelvis laceration and/or complete ureteral pelvic disruption
  - Grade V: Main renal artery or vein injury or thrombosis
  - Substratification of grade IV injuries (2)[B]
    - Grade IVb: Higher risk of intervention (angioembolization or exploration) if 2 or more
      - Active vascular extravasation
      - Perinephric hematoma >3.5 cm
      - Medial/complex laceration

EPIDEMIOLOGY

Incidence

- 1–3% of all traumatic injuries
- Most commonly injured GU organ

Prevalence

Estimated 245,000 cases of traumatic renal injuries per year, world wide

RISK FACTORS

- Blunt trauma
  - Rapid deceleration
    - Motor vehicle
    - Falls
    - Direct strike to abdomen or flank (sports injury related, bicycle accident, pedestrian in motor vehicle accident [MVA])
- Penetrating trauma
  - Upper abdominal
    - Stab, gunshot, or industrial injury
- Iatrogenic injury
  - Laparoscopic, endourologic, renal biopsy, percutaneous procedures

PATHOPHYSIOLOGY

- Kidneys are well protected in the retroperitoneum
  - Deceleration can lead to intimal tearing of renal artery and thrombosis

ASSOCIATED CONDITIONS
- Rib fractures
- Injury to other organ systems

GENERAL PREVENTION
- General trauma preventative measures
  - Restraints in motor vehicles

DIAGNOSIS
HISTORY
- Ample trauma history:
  - Allergies
  - Medications
  - Past medical history
  - Last meal
  - Event
- Contrast allergy, previous renal surgeries, stones, trauma, cancer

PHYSICAL EXAM
- Tachycardia and hypotension suggest major bleeding
- Primary survey
  - Flank contusion
  - Abdominal tenderness

ALERT
Degree of hematuria does not correlate with degree of injury.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
  - Hematuria >90% of renal injuries
  - Hematuria absent in 36% renal vasculature injuries
  - Hematuria with hypotension predictor for major renal injury
- Basic labs: Hgb, Hct, Cr, electrolytes

Imaging
- Indications for imaging
  - Blunt trauma
    - Hypotension (SBP < 90) and hematuria
    - Gross hematuria
    - Clinical indicators of renal injury from mechanism or associated injury
  - Penetrating trauma
    - Any degree of hematuria
- US

- Focused abdominal sonography for trauma (FAST) used in some centers for detection of hemoperitoneum
- CT
  - Contrast enhanced is best
  - Delayed films to evaluate urine leak and collecting system
  - Medial urine extravasation
- IV urography (IVP)
  - While mostly replaced by CT scan, single shot intraoperative IVP when pre-op imaging is not available before abdominal exploration in the OR with a film under patient on OR table
    - Single plain film 10 min after 2 mL/kg of IV contrast (max 150 mL)

Diagnostic Procedures/Surgery

Angiography may be performed if embolization is being considered

DIFFERENTIAL DIAGNOSIS

- Spontaneous hemorrhage in patients with renal mass: Traumatic or atraumatic
  - Renal angiomyolipoma
  - Renal cell carcinoma
  - Wunderlich syndrome: Atraumatic renal hemorrhage
- Injury to other organs

TREATMENT

GENERAL MEASURES

- Supportive care
- Assessment of associated injuries
- Decision for nonoperative or operative management of renal injuries (for operative management see “Surgery/Other Procedures” below)
- Nonoperative management: Blunt trauma
  - Hemodynamically stable patients with well-staged renal injury may be managed nonoperatively
  - 97% blunt renal injuries can be managed nonoperatively (1)[B]
  - Monitor with serial Hct and imaging
  - Consider angiography and embolization as alternative to renal exploration
    - Large perinephric hematoma and extravasation of contrast predictive for need of angiographic embolization (3)[B]
  - Isolated renal injuries
    - Most managed nonoperatively except for grade V pedicle avulsion
    - Consider placement of ureteral stent for persistent urine extravasation
- Nonoperative management: Penetrating trauma
  - 55% of stab wounds and 24% of GSW can be managed nonoperatively
  - If laparotomy is required for other reasons explore the retroperitoneum for pulsatile, expanding hematoma

MEDICATION

First Line
- Basic fluid and transfusion management
- Broad-spectrum antibiotics for penetrating injury and blunt trauma with urinary extravasation or large retroperitoneal hematoma

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Indications for operative management
  - Absolute: Persistent bleeding, expanding and pulsatile retroperitoneal hematoma
  - Relative: Urine extravasation, urinoma, nonviable parenchyma, delayed diagnosis, segmental arterial injury
  - Isolated urine extravasation can be managed nonoperatively with expectation of >90% resolution (4)[B]
    - Stent placement if no resolution after 3–7 days
  - Nonviable tissue >20%, then complications are greater
- Renal exploration: Transperitoneal approach
  - Early isolation of vessels
  - Retroperitoneal exploration for expanding and pulsatile hematoma
- Renal reconstruction
  - Debridement of nonviable tissue, closure of collecting system, coverage of parenchymal defect
  - For polar injury, consider partial nephrectomy with removal of devitalized tissue

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
Bed rest for nonoperative management

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
Most blunt trauma does not require surgical intervention and prognosis is excellent

COMPLICATIONS
- Urinoma/urinary extravasation
  - May require internal stent or external drainage
- Urinary fistula
- Delayed bleeding
- Perinephric abscess
- Sepsis
- Calculus formation

- Hydronephrosis
- Hypertension
  - Due to renal vessel injury
  - Compression of kidney
  - Posttraumatic AV fistula
- Pseudoaneurysm

FOLLOW-UP

Patient Monitoring

- Bed rest for continued hematuria
- Repeat CT scan
- Serial Hct

Patient Resources

- Urology Care Foundation: Kidney (renal) Trauma
  http://www.urologyhealth.org/urology/index.cfm?article=61

REFERENCES

1. Buckley JC, McAninch JW. Revision of current American Association for the Surgery of Trauma Renal Injury grading system. *J Trauma*. 2011;70:35–37.
2. Dugi DD, Morey AF, Gupta A, et al. American Association for the Surgery of Trauma grade 4 renal injury substratification into grades 4a (low risk) and 4b (high risk). *J Urol*. 2010;183:592–597.
3. Nuss GR, Morey AF, Jenkins AC, et al. Radiographic predictors of need for angiographic embolization after traumatic renal injury. *J Trauma*. 2009;67:578–582.
4. Alsikafi NF, McAninch JW, Elliott SP, et al. Nonoperative management outcomes of isolated urinary extravasation following renal lacerations due to external trauma. *J Urol*. 2006;176:2494–2497.

ADDITIONAL READING

- Alsikafi NF, Rosenstein DI. Staging, evaluation, and nonoperative management of renal injuries. *Urol Clin N Am*. 2006;33:13–19.
- American Association for the Surgery of Trauma (AAST) Injury Scoring Scale. http://www.aast.org/Library/TraumaTools/InjuryScoringScales.aspx. Accessed January 26, 2014.

See Also (Topic, Algorithm, Media)

- Bladder Trauma
- Renal Trauma, Adult Algorithm
- Renal Trauma, Adult Images
- Renal Trauma, Pediatric
- Retroperitoneal Hematoma
- Ureter, Trauma
- Wunderlich Syndrome

CODES

ICD9

- 866.00 Injury to kidney without mention of open wound into cavity, unspecified injury
- 866.01 Injury to kidney without mention of open wound into cavity, hematoma without rupture of capsule
- 866.02 Injury to kidney without mention of open wound into cavity, laceration

ICD10

- S37.009A Unspecified injury of unspecified kidney, initial encounter
- S37.019A Minor contusion of unspecified kidney, initial encounter
- S37.039A Laceration of unsp kidney, unspecified degree, init encntr

CLINICAL/SURGICAL PEARLS

- CT with IV contrast is single best study.
- Most blunt renal trauma is managed nonoperatively.
- Angioembolization should be considered for stable patients with isolated renal laceration and renal vascular laceration.
- Renal vascular avulsions should be explored.
- Grade IV renal injuries may be substratified by additional findings of active vascular extravasation, perinephric hematoma, medial/complex laceration.

RENAL TRAUMA, PEDIATRIC

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BASICS

DESCRIPTION

- Traumatic injury overall is the leading cause of childhood death in the United States.
- Pediatric renal trauma is subdivided into blunt and penetrating mechanisms of injury.
- The pediatric kidney is believed to be more susceptible to trauma vs. the adult kidney.
- Over the past 2 decades, the management of pediatric renal trauma has shifted from operative intervention to conservative management.

EPIDEMIOLOGY

Incidence

- 10–20% of all abdominal blunt trauma involves a renal injury.
- 90% of GU injuries are from blunt trauma.
- Nearly 90% of patients with GU injuries have coexisting injuries to the thorax, spine, pelvis, or intra-abdominal organs.

Prevalence

N/A

RISK FACTORS

- Pre-existing GU abnormalities (ie, ureteropelvic junction obstruction horseshoe kidney vs. pelvic kidney):
  - 3–5-fold more common in pediatric patients undergoing CT for trauma
  - Classically presents with a history of hematuria disproportionate to the severity of trauma
- Decrease in physical renal protective mechanisms:
  - More pliable thoracic cage and weaker abdominal muscles
  - Less renal fat
  - Position of the kidney within the abdomen

Genetics

Disorders that lead to an increase in GU anomalies have a greater risk for traumatic injury

PATHOPHYSIOLOGY

- Tissue or organ injury from external source of energy
- Grading system:
  - Grade I: Subcapsular hematoma, microscopic or gross hematuria, normal radiographic studies
  - Grade II: Nonexpanding perirenal hematoma or cortical laceration <1 cm deep
  - Grade III: Laceration >1 cm in parenchyma without collecting system rupture or urine extravasation
  - Grade IV: Parenchymal laceration through renal cortex, medulla, collecting system; contained main renal artery or vein hemorrhage

– Grade V (shattered kidney): Renal pedicle avulsion, multiple parenchymal lacerations, major injury to the renal vessels, urinary extravasation

ASSOCIATED CONDITIONS
Injury to other organ systems

GENERAL PREVENTION
Measures that decrease traumatic injury in general, such as seat belts, air bags

DIAGNOSIS

HISTORY
- Mechanism of injury: Degree of actual traumatic injury may not correlate with the mechanism
  – Blunt: Falls, automobile collision, sporting injuries, etc.
  – Penetrating: Gunshot wound, stabbing, etc.
- Vital signs in the field:
  – Hypotension: Children will often have a normal BP despite a significant blood loss.
- Hematuria: Unlike adults, an unreliable indicator of underlying renal injury in children:
  – Up to 70% of children with grade II or higher renal injury may have neither gross nor microscopic hematuria.
- Medical history: Any acute or chronic medical conditions and any previous GU abnormality
- Surgical history: Previous urologic procedure for reflux, stone, hypospadias, etc.
- Iodine or latex allergy
- Loss of consciousness

PHYSICAL EXAM
- Vital signs and ABCD of resuscitation to stabilize patient
- BP is often normal in severely hypovolemic children
- Exposure: Observe for obvious signs of abdominal/flank/thoracic trauma, abdominal/flank tenderness, flank ecchymosis, gross hematuria, pelvic instability
- DRE: Observe for perineal ecchymosis
- If blood at the urethral meatus, do not insert catheter

ALERT
Degree of hematuria does not correlate with degree of injury.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC, basic metabolic profile, coagulation profile
- Urinalysis
  – Unreliable in determining the extent of GU trauma
  – Up to 70% of children with grade II renal trauma will have neither gross nor microscopic hematuria.

ALERT
The patient's hemodynamic status determines when and what type of imaging modality is indicated.

Imaging

- Indications for radiographic imaging: All penetrating abdominal trauma or blunt trauma victims with 1 of the following criteria (1):
  - Significant deceleration or high-velocity injury: MVA, fall from >15 ft
  - Trauma resulting in fracture of the thoracic cage, spine, pelvis, or femur, or bruising of the torso/perineum
  - Acute peritonitis
  - Gross hematuria
  - Microscopic hematuria (>50 RBC/HPF) associated with shock (SBP <90 mm Hg)
  - Delayed hemorrhage following renal trauma
- CT:
  - Currently the most commonly used imaging modality in these patients
  - Triphasic abdominal and pelvic CT (ideally): Clinically stable patients; most sensitive method for diagnosing and classifying GU trauma, precontrast phase, nephrogram phase after injection of contrast, and delayed images at 15 min. The downside of this is radiation exposure.
  - Single-phase CT: Clinically labile patients; allows for determination of renal perfusion and major renal fractures. This can be followed by a KUB to assess renal integrity.
  - Delayed CT: Obtained postoperatively after patient is stabilized or after patient is resuscitated in the ICU for full trauma evaluation; used to assess grade 3–5 renal injuries 2–3 days posttrauma to assess for baseline hematoma or urinoma
- Focused assessment with sonography for trauma (FAST):
  - Often combined with serial physical exams as a screening modality after blunt trauma
  - Sensitivity ranges from 70–85% and specificity ranges from 93–100%; operator dependent
  - Option in areas with limited radiologic resources
- Arteriography:
  - Used for diagnosis of arteriovenous fistula in the setting of delayed hemorrhage following renal trauma
- Retrograde pyelography:
  - Rule out presence of partial/total ureteral disruption
  - Management of symptomatic urinoma with placement of ureteral stent
- Single-shot IVP:
  - Increasingly limited role
  - Done after patient is hemodynamically stable following trauma-exploratory laparotomy; allows for visualization of functioning contralateral kidney when considering unilateral nephrectomy
- DMSA scan:
  - Allows for quantification of renal function for grade 3–5 injuries; obtain at least 1 wk after traumatic injury, also indicated
- Follow-up imaging:
  - Triphasic CT is indicated for patients with persistent fever, worsening flank pain, or gross hematuria >72 hr after injury

Diagnostic Procedures/Surgery

N/A

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
Injury to other major abdominal viscera in the setting of acute trauma

TREATMENT

GENERAL MEASURES
- The major challenge facing the urologist in evaluating pediatric renal trauma is in determining when to surgically intervene.
- The decision to intervene operatively is based on 3 clinical indicators: Hemodynamic stability, accurate radiographic staging, presence of associated organ injuries (2).
- In general:
  - Irrespective of the mechanism of injury and provided there are no absolute indications for abdominal exploration then all renal trauma can be observed.
  - Renal exploration and renorrhaphy for grade III or higher renal injuries should be carried out if laparotomy is necessary for coexisting intra-abdominal injuries.
  - Renal exploration may be excluded in patients with concurrent intra-abdominal injuries if the urinary tract is separated from the enteric tract by omentum or other tissue, and adequate drains are left in place.
- Renal injury classification: Based on American Association for the Surgery of Trauma (AAST) renal injury grading system (see “Renal Trauma, Adult”)

MEDICATION
First Line
- Basic fluid and transfusion management
- Broad-spectrum antibiotics for penetrating injury and blunt trauma with urinary extravasation or large retroperitoneal hematoma

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Absolute indications for renal exploration:
  - Hemodynamic instability from a renal source
  - Expanding or pulsatile retroperitoneal hematoma
  - Inability to stop persistent or delayed hemorrhage via selective vascular embolization
- Relative indications for renal exploration:
  - Patients with vascular instability resulting in an inability to obtain adequate preoperative radiographic studies
  - Retroperitoneal hematoma found at the time of surgical exploration
  - Known grade III or higher renal injury during concomitant abdominal exploration: Either perform renal exploration with renorrhaphy or separation of GI from GU tract and drain placement
- Renal salvage via renorrhaphy or partial nephrectomy requires complete exposure of the injured kidney, debridement of nonviable tissue, repair of the collecting system, and ligation

of all bleeding vessels.
  – Renal pelvic or ureteral injuries should be closed watertight; if not, then ureteral stents or nephrostomy tube may be necessary.
  – Nephrectomy should be considered in the setting of irreparable grade IV–V injures and in cases where nephrectomy would help control bleeding in the coagulopathic or hypothermic patient.
  – Renal vascular injuries: The kidney is an end organ; segmental renal vessel repair should not be attempted, main renal artery reconstruction should only be considered if patients are hemodynamically stable and have either a solitary kidney or bilateral renal injuries.
  – Endoscopic stent placement and/or percutaneous placement of perirenal drain or nephrostomy tube in cases of expanding urinoma

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Nonoperative management (3)
  – Initially only for if hemodynamically stable
  – Admission to ICU for monitoring is warranted:
    - Bed rest, monitor urine output, serial abdominal exams, serial hemoglobin/HCT, resuscitate and transfuse as necessary
- Ideal candidate will have grade I–II injury
- Patients with isolated grade III, IV, and V renal injuries are candidates for nonoperative treatment:
  – Conservative management of isolated grade III–IV renal injuries will prevent 95% of patients from requiring operative intervention
  – Angiographic, endoscopic, or percutaneous intervention will be required in up to 55% of patients

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Based on the overall renal function following the traumatic injury
- Renal vascular HTN
  – Usually develops within 36 mo after injury
  – DMSA scan is indicated to determine differential renal function
  – CT angiogram may be necessary to rule out arteriovenous fistula as the source of HTN
- End-stage renal disease
  – Bilateral renal injury
  – May require peritoneal or hemodialysis

FOLLOW-UP

Patient Monitoring

- Repeat CT of the kidney 2–3 days after trauma for grade III or higher renal injuries.
  - Have low threshold for repeat CT if patient has decreasing hemoglobin/HCT despite blood transfusion or if child is hemodynamically unstable.
- Ambulation should resume when gross hematuria resolves.
  - Strenuous physical activity should be avoided for 6 wk.

REFERENCES

1. Buckley JC, McAninch JW. The diagnosis, management, and outcomes of pediatric renal injuries. *Urol Clin N Am.* 2006;33:33–40.
2. Husmann D. Pediatric genitourinary trauma. In: Wein AJ, Kavoussi LR, Novick AC, et al, eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007:3929–3945.
3. Jacobs MA, Hotaling JM, Mueller BA, et al. Conservative management vs early surgery for high grade pediatric renal trauma–do nephrectomy rates differ? *J Urol.* 2012;187(5):1817–1822.

ADDITIONAL READING

- Kawashima A, Sandler CM, Corl FM, et al. Imaging of renal trauma: A comprehensive review. *Radiographics.* 2001;21:557–574.

See Also (Topic, Algorithm, Media)

- Bladder Trauma
- Renal Trauma, Adult
- Renal Trauma, Adult Algorithm
- Renal Trauma, Adult Images
- Retroperitoneal Hematoma
- Ureter, Trauma
- Wunderlich Syndrome

CODES

ICD9

- 866.00 Injury to kidney without mention of open wound into cavity, unspecified injury
- 866.01 Injury to kidney without mention of open wound into cavity, hematoma without rupture of capsule
- 866.02 Injury to kidney without mention of open wound into cavity, laceration

ICD10

- S37.009A Unspecified injury of unspecified kidney, initial encounter
- S37.019A Minor contusion of unspecified kidney, initial encounter
- S37.039A Laceration of unsp kidney, unspecified degree, init encntr

CLINICAL/SURGICAL PEARLS

Hemodynamically stable patients can be managed conservatively.

RENAL TUBULAR ACIDOSIS

Steve Dong, MD

BASICS

DESCRIPTION

- Renal tubular acidosis (RTA) is a metabolic condition characterized by abnormal urinary acidification due to a defect in renal tubules, resulting in hyperchloremic nonanion gap metabolic acidosis, increased pH of the urine
- 4 major types of RTA are now considered to be only 3:
  - Type I (distal): Defective distal tubular H+ secretion
  - Type II (proximal): Defective proximal tubular bicarbonate reabsorption
  - Type III (mixed): No longer considered as a distinct entity
  - Type IV: Aldosterone deficiency/resistance

EPIDEMIOLOGY

Incidence

- RTA I: More common in adults (2/3 adults, 1/3 children) and women; endemic in certain regions of Thailand
- RTA II: Usually more predominant in males associated with Fanconi syndrome; urinary loss of glucose, amino acids, uric acid, phosphate, and bicarbonates
- Most RTAs are sporadic occurring at any age. Familial RTA are rare and usually occurs in childhood.

RISK FACTORS

- Genetic disorders
- Secondary to systemic disease. See "Commonly Associated Conditions."

Genetics

- Familial RTA I (1):
  - Autosomal dominant (AD) form is associated with mutation in anion exchanger 1 gene
  - Autosomal recessive (AR) form is due to a mutation in the B1 or H^+-ATPase (V-ATPase) gene and associated with sensorineural deafness
- Familial RTA II:
  - AD form is rare
  - AR form associated with ocular abnormalities and mental retardation
  - AR form associated with osteopetrosis and cerebral calcification
  - AR form associated with Fanconi syndrome
- Familial RTA IV: Associated with pseudohypoaldosteronism type 1

PATHOPHYSIOLOGY

- Type I (distal) tubular acidosis: Secondary to impaired ability to secrete hydrogen ions into the distal tubule or collecting duct. Urine pH $>$ 5.5.
- Type II (proximal) tubular acidosis: Impaired bicarbonate absorption in the proximal tubule. Urine pH may be $<$5.5.

- Type IV: Presence of aldosterone resistance or deficiency leading to hyperkalemia (not seen in type I and II) along with acidosis. Urine pH may be <5.5.

ASSOCIATED CONDITIONS

- Acquired RTA type I:
  - Autoimmune disease: Systemic lupus erythematosus (SLE), Sjögren syndrome, primary biliary cirrhosis, chronic active hepatitis
  - Chronic pyelonephritis
  - Diseases causing nephrocalcinosis
  - Drugs (amphotericin B, lithium, analgesics)
  - Ehlers–Danlos syndrome
  - Fabry disease
  - Glycogenosis type III
  - Hepatic cirrhosis
  - Hypercalciuria
  - Hypergammaglobulinemic syndrome
  - Leprosy
  - Malnutrition
  - Medullary cystic disease
  - Obstructive uropathy
  - Sickle cell disease, hereditary elliptocytosis
  - Toxins (toluene, glue)
  - Vitamin D intoxication
  - Wilson disease
- Acquired RTA type II:
  - Fanconi syndrome due to toxin-related or immunologic nephrotoxic damage
  - Tubular toxicity causing acute tubular necrosis:
    - Sepsis
    - Rhabdomyolysis
    - Hypotension
    - Nephrotoxins: Intravenous (IV) contrast, aminoglycoside antibiotics
  - Interstitial renal disease:
    - Multiple myeloma
    - Heavy met al poisoning (cadmium, lead, mercury)
    - Medications (methicillin, cisplatin, adefovir, tenofovir, COX-2 inhibitors, cimetidine, acetazolamide, sulfanilamide, ifosfamide, tetracycline, Topamax)
    - Infections: Leptospirosis, corynebacterium, diptheria, polyomavirus, cytomegalovirus
    - Autoimmune disease: SLE, Sjögren's syndrome, sarcoidosis
  - Amyloidosis
- Acquired RTA type IV:
  - Addison disease
  - Diabetic nephropathy
  - Hypertension
  - Lupus nephropathy
  - Obstructive nephropathy

– Tubulointerstitial nephropathies
• Gordon syndrome
• Sickle cell nephropathy

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY
• Failure to thrive, rickets, and osteomalacia in children
• Anorexia, nausea, vomiting
• Weakness and polyuria due to potassium loss
• Constipation
• Polydipsia
• History of hematuria, urinary tract infections (UTIs), passage of stones in urine
• History of recurrent, familial, or childhood renal stone disease
• Ask about systemic diseases causing RTA

PHYSICAL EXAM
• Urologic exam of genitalia, suprapubic area for swelling and tenderness
• Exam for osteomalacia, hypokalemic muscle weakness, and growth retardation
• Exam for other systemic diseases

DIAGNOSTIC TESTS & INTERPRETATION
Lab
• Renal function test usually normal
• Electrolytes and blood gas reveal hyperchloremic, nonanion gap metabolic acidosis:
– Hypokalemia or normokalemia in type I and II
– Hyperkalemia in type IV
• Urine pH (fasting, under oil, pH meter):
– pH > 5.5: Complete type I RTA
– pH > 5.5, but systemic acidosis mild or absent: Ammonium chloride loading test and measure urinary bicarbonates; failure of urine pH to go below 5.5 is diagnostic of RTA (1) [C]
• RTA II is diagnosed by bicarbonate loading test: After IV bicarbonate infusion, fractional excretion of bicarbonate >15% is diagnostic (1)[C]
• Urine calcium: High in type I, normal in type II
• Phosphaturia, glycosuria, and aminoaciduria in Fanconi's syndrome

Imaging
• Plain x-ray and computed tomography (CT) urogram:
– Likely to demonstrate nephrocalcinosis and nephrolithiasis

Pathologic Findings
• Nephrocalcinosis
• Nephrolithiasis
• Osteomalacia

DIFFERENTIAL DIAGNOSIS

- Other causes of metabolic acidosis (2)[C]
  - Lactic and ketoacidosis, chronic renal failure, chronic diarrhea, etc.
- Azotemia
- Bilateral stones
- Calcium phosphate stones
- Chronic pyelonephritis
- Hypocitraturia < 0.5 mmol/24 h
- Hypokalemia
- Medullary nephrocalcinosis
- Medullary sponge kidney
- Recurrent stones: >2/yr

TREATMENT

GENERAL MEASURES

- Identifiable causes, such as obstructive uropathy or drug-induced RTA, should be corrected or eliminated
- If there is no identifiable etiology, then direct treatment to correction of acidosis

MEDICATION

First Line

- Alkali therapy decreases stone formation and growth, prevents nephrocalcinosis, normalizes growth retardation in children, and corrects hypokalemia in most cases:
  - Oral alkali therapy: In both type I and type II RTA with the goal of treatment to restore urinary citrate to high-normal levels, and not simply correct the metabolic acidosis (3)[C]
    - Sodium bicarbonate (7.7 mEq HCO_3/tab)
    - Bicitra (1 mEq Na, 1 mEq citrate/mL)
    - Polycitra (1 mEq Na, 1 mEq K, 2 mEq citrate/mL)
  - Type I RTA generally requires lifelong treatment:
    - 1–4 mEq/kg/d of oral bicarbonate or citrate in 2–3 divided doses in adults (4)[C]
    - May require potassium supplementation for hypokalemia
- Type II (proximal) RTA:
  - 5–20 mEq/kg/d in 4–6 doses/d due to the severe bicarbonate wasting.
  - Adults with bicarbonate levels >10 mEq/mL and no evidence of bone disease may not require treatment.
  - Supplemental potassium, calcium, vitamin D, and phosphate may become necessary.
- Type IV RTA treatment is directed toward correction of hyperkalemia rather than acidosis:
  - Dietary potassium restriction
  - Thiazide or loop diuretics
  - Mineralocorticoid replacement in cases of adrenal disease or hyporeninemia (fludrocortisone 0.1 mg/d)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Management of stone by shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy, and rarely, open surgery
- Management of obstructive uropathy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Monitor osteoporosis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Primary RTA I: Although a permanent disease, prognosis is excellent if diagnosis and treatment initiated early.
- Prognosis of other RTAs depends on associated disease

COMPLICATIONS

- Hypercalciuria
- Hyperkalemia or hypokalemia
- Nephrocalcinosis
- Nephrolithiasis
- Osteomalacia/osteoporosis

FOLLOW-UP

Patient Monitoring

- Spot urine testing for NAG (N-acetyl-β-D-glucosaminidase) has eliminated the need for 24-hr urine collection. Levels increased secondary to renal tubular cell damage and hypercalciuria.
- Urinary calcium excretion should be kept <0.05 mmol/kg/d in infants and children
- Potassium levels should be monitored during alkali therapy and replaced appropriately
- Monitor underlying disease as indicated

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC)
http://kidney.niddk.nih.gov/kudiseases/pubs/tubularacidosis/

REFERENCES

1. Laing CM, Unwin RJ. Renal tubular acidosis. *J Nephrol*. 2006;19(suppl 9):S46–S52.
2. Casaletto JJ. Differential diagnosis of metabolic acidosis. *Emerg Med Clin North Am*. 2005;23:771–787, ix.
3. Rodriguez SJ. Renal tubular acidosis: The clinical entity. *J Am Soc Nephrol*. 2002;13:2160–2170.
4. Domrongkitchaiporn S, Khositseth S, Stitchantrakul W, et al. Dosage of potassium citrate in

the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis*. 2002;39:383–391.

ADDITIONAL READING

Haque SK, Ariceta G, Batlle D. Proximal renal tubular acidosis: A not so rare disorder of multiple etiologies. *Nephrol Dial Transplant*. 2012;27(12):4273–4287.

See Also (Topic, Algorithm, Media)

- Calcifications, Renal
- Fanconi Syndrome
- Nephrocalcinosis
- Osteoporosis and Osteopenia, Urologic Considerations
- Urolithiasis, Renal

CODES

ICD9

- 255.42 Mineralocorticoid deficiency
- 276.7 Hyperpotassemia
- 588.89 Other specified disorders resulting from impaired renal function

ICD10

- E27.40 Unspecified adrenocortical insufficiency
- E87.5 Hyperkalemia
- N25.89 Oth disorders resulting from impaired renal tubular function

CLINICAL/SURGICAL PEARLS

- Type I RTA is the only type associated with increased stone formation, nephrocalcinosis.
- Potassium levels should be monitored during alkali therapy for RTA and replaced appropriately.
- A young person with multiple stones with systemic acidosis and high urine pH, a diagnosis of type I RTA should be considered.

RENAL VEIN THROMBOSIS, ADULT AND PEDIATRIC

Adonteng A. Kwakye, MD

BASICS

DESCRIPTION

- Renal vein thrombosis (RVT) is an acute or chronic thrombosis in the renal vein leading to a reduction in venous drainage of the kidney.
- In infants, RVT typically presents as a severe illness, occasionally with colicky pain:
  - 60% have enlarged kidneys on physical exam; gross hematuria and microangiopathic hemolytic anemia and thrombocytopenia can also be present
- In the adult, RVT presentation depends on onset of RVT:
  - Acute RVT: Triad of sudden flank pain
  - Costovertebral angle tenderness and gross hematuria only present in minority of cases.
  - Chronic RVT: Generally asymptomatic;
    - Can have proteinuria and microscopic or gross hematuria.

EPIDEMIOLOGY

Incidence

- Newborns and infants:
  - Commonly associated with hypoxia, dehydration, shock, and/or sepsis
  - Usually acute and unilateral (more common on the left side); although 30% bilateral
  - Male-to-female ratio 2:1 in the neonate, with no sex predilection beyond age 1
  - Accounts for approximately 10% of venous thrombosis in newborns
  - Most common form of thrombosis not associated with a vascular catheter (1)
- Adults:
  - Associated with nephrotic syndrome (reported incidence of RVT in patients with nephrotic syndrome ranges from 5–62%), renal cell carcinoma, or renal transplantation
  - More often chronic and unilateral

Prevalence

N/A

RISK FACTORS

- Newborn/infant:
  - Acute hypoxia
  - Birth trauma
  - Cyanotic congenital heart disease with polycythemia
  - Cytomegalovirus infection
  - Dehydration from diarrhea/vomiting
  - Maternal diabetes, polyhydramnios
  - Hyperosmolar state form angiocardiography
  - Preterm (<36 wk) infants at greater risk
  - Sickle cell disease
- Adult:

- Abdominal tumors, especially renal cell carcinoma
- Endothelial damage
- Intrinsic hypercoagulability (eg, Factor V Leiden deficiency)
- Nephrotic syndrome:
- Membranous nephropathy: Lesion most frequently associated with nephrotic syndrome–related RVT; also reported in many other nephropathies.
- Use of oral contraceptives, steroids
- Renal transplantation, particularly in those taking OKT-3 and cyclosporine for immunosupression
- Shock, sepsis, dehydration
- Trauma
- Use of IV contrast agents
- Vasculitis
- Compression from aortic aneurysm, lymphadenopathy, retroperitoneal fibrosis (2)

Genetics

Unknown

PATHOPHYSIOLOGY

- Newborn/infant:
  - Diminished intrarenal blood flow due to hypovolemia (sepsis, dehydration, diarrhea)
  - Creates prothrombotic state
  - Clot can then propagate in antegrade and/or retrograde manner, resulting in RVT
  - May become bilateral, produce vena caval occlusion and/or renal artery thrombosis
  - 65% in neonates, 30% beyond 1 yr age
  - Associated with adrenal hemorrhage in 15% of cases
- Adults: Most often unilateral; acute and chronic forms described:
  - Acute RVT: Severe dehydration, sudden hypercoagulability, renal vein obstruction from tumor or transplant rejection
  - Chronic RVT:
    - Nephrotic syndrome leads to alterations in coagulation pathway that creates prothrombotic conditions (3)
    - RVT is a result of nephrotic syndrome and not the cause
    - Slow onset allows the development of collateral venous kidney drainage

ASSOCIATED CONDITIONS

- DVT in patients with nephrotic syndrome
- Pulmonary embolus

GENERAL PREVENTION

- Adults: Long-term anticoagulation is appropriate if RVT has recurred when patients discontinued anticoagulation
- Treatment of underlying cause

DIAGNOSIS

HISTORY

- Newborn/infant:
  - Risk factors: Mother's history, birth, and early postnatal course
  - Gross hematuria
- Adult:
  - Sudden onset of hematuria and flank pain should raise the question of RVT, as should a history of nephrotic syndrome in the presence of hematuria

PHYSICAL EXAM

- Newborn/infant:
  - Unilateral, or often bilateral, flank masses
  - Evidence of dehydration
  - Evidence of cyanotic heart disease
  - If the thrombosis is bilateral, oliguria may be present; urine output may be normal with a unilateral thrombus (4)
- Adult:
  - Evidence of blunt trauma, abdominal mass
  - Edema or anasarca suggestive of nephrotic syndrome

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Newborn/infant:
  - Thrombocytopenia, leukocytosis, hemolytic anemia
  - Consumptive coagulopathy (prolonged clotting time, elevated fibrinogen and fibrin split products)
  - Proteinuria
  - Elevated BUN and creatinine
- Adult:
  - Proteinuria and microscopic hematuria
  - Hemolytic anemia, consumptive coagulopathy, and thrombocytopenia may be present
  - Elevated BUN and creatinine
  - Hypoalbuminemia
  - Marked elevation in LDH with normal transaminases

Imaging

- Newborn/infant:
  - The extent of thrombus may be assessed by duplex ultrasonography, and only rarely will CT, MRI, or renal venography be required for confirmation of the diagnosis or determination of the extent of thrombus
  - Ultrasonography: Enlarged and echogenic kidneys (90%) with attenuation or loss of corticomedullary differentiation
    - Doppler studies may detect increased resistance or absence of flow in renal venous branches; increased resistance in the renal artery may be present
    - Doppler ultrasonography is the primary modality for the detection of RVT; however, its utility is operator specific (3)
  - IVP: Delayed opacification and renomegaly
  - A renal scan may be obtained to assess the function of the involved kidney.

  - MRI is more expensive and requires sedation in pediatric patients (6)
- Adult:
  - Inferior vena cavography with selective catheterization of the renal vein is the gold standard for the diagnosis.
  - CT findings are similar in noninvasive evaluation of acute RVT.
    - Sensitivity of CT angiography approaches 100%; considered current imaging modality of choice
    - Low attenuation within the renal vein; proximal venous enlargement
    - Capsular venous collaterals, thickened Gerota's fascia and pericapsular stranding
  - Doppler ultrasonography is helpful, especially in a transplanted kidney.
  - MRI: Excellent imaging; avoids iodinated contrast, but concerns with gadolinium in patients with renal insufficiency
  - IVP
    - Faint or absent excretion of contrast
    - Enlarged kidney due to congestion
    - Collateral circulation may cause collecting system opacification and/or notching of ureter
    - Renal pelvis is often distorted

Diagnostic Procedures/Surgery

Renal biopsy in the setting of nephrotic syndrome and RVT confirms etiology and may guide therapy

Pathologic Findings

- Membranous nephropathy is the most common finding in the setting of nephrotic syndrome and RVT.
- In infants the condition is pathologically more correctly described as "renal venous thrombosis" as the interlobular and arcuate renal veins are primarily affected rather than the main renal vein in adults.

DIFFERENTIAL DIAGNOSIS

- Other causes of flank pain (eg, urolithiasis, pyelonephritis, renal infarction)
- Renal cell carcinoma with direct compression or tumor thrombus
- Renal vein leiomyosarcoma (filling defect)

TREATMENT

GENERAL MEASURES

- Evaluate and treat all underlying causes
- Aggressive rehydration and treatment of sepsis, diarrhea, and electrolyte abnormalities

MEDICATION

First Line

- Newborn/infant:
  - Use of thrombolytic agents is reported, but controversial
  - Systemic heparinization:
    - Prevents thrombus propagation into vena cava (risk of propagation low with fluid and

electrolyte repletion).
  - Used in neonates with bilateral RVT
  - Equivocal results regarding long-term preservation of renal function
- Adult:
  – Unilateral RVT: Heparin anticoagulation and long-term anticoagulation with warfarin:
  – Optimum duration of anti-coagulation unknown
  – Most experts feel that warfarin should be continued for as long as nephrotic syndrome persists (3).

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Infants: No role for surgical thrombectomy
- Thrombectomy in adults:
  – Rarely used, because neither renal preservation nor improvement in survival demonstrated
  – Surgical thrombectomy (either open or percutaneous) in patients with acute bilateral RVT with poor prognosis
  – Postoperative posttransplant RVT
- Nephrectomy in highly selected patients for lifesaving measures
- Radical nephrectomy and thrombectomy in renal cell carcinoma

ADDITIONAL TREATMENT
- Infants with renal failure—dialysis if needed
- IVC filters are indicated in high-risk adult patients for pulmonary embolism.

Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Neonates: Mortality rate of 3%
- The kidney may recover completely, atrophy, or recover partially, resulting in renovascular hypertension or chronic tubular dysfunction.
- Nephrectomy may be required if renovascular hypertension or chronic infection develops.
- ACE inhibitors and/or angiotensin II receptor blockers may decrease proteinuria from nephrotic syndrome as decreased urinary protein loss decreases hypercoagulability.

COMPLICATIONS (5)
- Consumptive coagulopathy
- Pulmonary embolism

- Renal failure
- Loss of graft in transplant patient

FOLLOW-UP

Patient Monitoring

- Newborn/infant:
  - Renal function may be followed using nuclear scanning. Atrophy is often detected long term. About 5% of affected neonates progress to dialysis or transplantation.
  - Monitor blood pressure, as renovascular hypertension may occur after RVT in ~20%, even with normal renal function.
- Adult:
  - Treat cause of nephrotic syndrome
  - Long-term anticoagulation as preventive measure in nephrotic syndrome not supported
  - Because RVT may be asymptomatic, all patients with nephrotic syndrome should be monitored for symptoms of RVT

Patient Resources

MedlinePlus: Renal vein thrombosishttp://www.nlm.nih.gov/medlineplus/ency/article/000513.htm

REFERENCES

1. Schmidt B, Andrew M. Neonatal thrombosis: Report of a prospective Canadian and international registry. *Pediatrics*. 1995;96:939–943.
2. Ferri F. Ferri's clinical advisor 2013. R - Renal vein thrombosis. 1st ed. Philadelphia, PA: Elsevier; 2013.
3. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: Pathophysiology and clinical management. *Throm Res*. 2006;118:397–407.
4. Lum GM. Kidney & urinary tract. In: Hay WW Jr., Levin MJ, Deterding RR, et al., eds. *Current Diagnosis & Treatment: Pediatrics*. 21st ed. Chapter 24. New York, NY: McGraw-Hill; 2012.
5. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome.*Kidney Int*. 1985;28(3):429–439.
6. Textor SC, Leung N. Chapter 286. Vascular injury to the kidney. In: Longo DL, Fauci AS, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.

ADDITIONAL READING

- Asghar M, Ahmed K, Shah SS, et al. Renal vein thrombosis. *Eur J Vasc Endovasc Surg*. 2007;34(2):217–223.
- Lau KK, Stoffman JM, Williams S, et al. Neonatal renal vein thrombosis: Review of the English-language literature between 1992 and 2006. *Pediatrics*. 2007;120(5):e1278–e1284.

See Also (Topic, Algorithm, Media)

- Nephrotic Syndrome
- Renal Cell Carcinoma with Tumor Thrombus
- Renal Vein Thrombosis, Adult and Pediatric Image

• Renal Vein, Leiomyosarcoma

CODES

ICD9

• 453.3 Other venous embolism and thrombosis of renal vein
• 581.9 Nephrotic syndrome with unspecified pathological lesion in kidney
• 788.0 Renal colic

ICD10

• I82.3 Embolism and thrombosis of renal vein
• N04.9 Nephrotic syndrome with unspecified morphologic changes
• N23 Unspecified renal colic

CLINICAL/SURGICAL PEARLS

• Renal vein thrombosis (RVT) is associated with nephrotic syndrome in adults.
• Membranous nephropathy is most common pathology in RVT with nephrotic syndrome.
• Newborns and infants more likely than adults to have bilateral RVT.

RETROGRADE EJACULATION

Pravin K. Rao, MD

BASICS

DESCRIPTION

- Expulsion of semen from posterior urethra into bladder with low- or zero-volume antegrade ejaculate.
- Suspected in men with symptoms or semen analysis findings suggesting low or absent ejaculate volume.
- Primary implications are for infertility.
  - Also: Sexual function/satisfaction.
- No other known medical health effects.
- Men with failure of emissions are often labeled as having "retrograde ejaculation."
  - Failed deposition of ejaculate contents into posterior urethra before expulsion.

EPIDEMIOLOGY

Incidence

- 74–78% incidence after transurethral prostate surgery (1)[B]
- 4–26% incidence with α-blocker tamsulosin (2,3)[A]
- As low as 14% incidence after bilateral nerve-sparing retroperitoneal lymph node dissection (RPLND) (4)[B]

Prevalence

N/A

RISK FACTORS

- Bladder neck/prostate procedures
  - Transurethral resection of the prostate
  - Transurethral incision of the prostate (TUIP)
  - Bladder neck incision (BNI)
- Surgical/traumatic/congenital neuropathy
  - Retroperitoneal surgery
    - eg, RPLND
  - Pelvic surgery
    - eg, abdominoperineal resection
  - Spinal cord injury (SCI)/surgery
  - Spina bifida/myelomeningocele
- Medical neuropathy
  - Diabetes mellitus (DM)
  - Multiple sclerosis (MS)
- Iatrogenic from medications
  - α-blockers
    - Reduce bladder neck muscle tone

- Reduce seminal emissions
- Tamsulosin, terazosin, doxazosin

– Antipsychotic and psychotropic medications
- Risperidone

– Antidepressants
- Selective serotonin reuptake inhibitors

Genetics

N/A

PATHOPHYSIOLOGY

- Normal ejaculation requires:
  – Seminal emission
  – Bladder neck closure
  – Antegrade expulsion from urethra
- Neurologic control:
  – Central control in multiple brain regions
    - Can promote or inhibit ejaculation
  – Sympathetic (T12–L3):
    - Hypogastric nerve (thoracolumbar)
    - Seminal "emission" into posterior urethra by contraction of epididymis, vas deferens/ampulla, seminal vesicle (SV), and prostate smooth muscle
    - Bladder neck closure preventing retrograde ejaculation
  – Parasympathetic (S2–S4):
    - Pelvic nerve
    - Gland secretions of prostate SV
  – Somatic (S2–S4):
    - Pudendal nerve
    - Efferents from sacral cord
    - Contraction of bulbocavernosal and ischiocavernosal muscles
    - Relaxation of external urethral sphincter
    - Projectile expulsion of ejaculate
  – Sensory
    - Pudendal nerve
    - Tactile stimulation of penis can activate ejaculatory reflex
- Retrograde ejaculation occurs from impaired bladder neck closure due to various causes
  – Poor coaptation of bladder neck
    - Medication side effect
    - Prostate surgery
    - Idiopathic
  – Neural disruption
    - Spinal cord injury (SCI)
    - Diabetes mellitus (DM)
    - Retroperitoneal lymphnode dissection (RPLND)
    - Pelvic surgery

ASSOCIATED CONDITIONS
- See risks factors
- Benign prostatic hyperplasia (BPH)
- Bladder neck dysfunction
- Diabetes mellitus (DM)
- Multiple sclerosis (MS)
- Rectal cancer
- Testicular cancer

GENERAL PREVENTION
- Avoidance of iatrogenic causes
- Nerve sparing during RPLND

DIAGNOSIS
HISTORY
- Absence or presence of orgasm
- Presence of erectile dysfunction
- Cloudy urine after sex/orgasm
- Symptoms of hypogonadism
- Medical history (see risk factors)
- Surgical history (see risk factors)
- Medications (see risk factors)
- Accuracy of semen analysis findings:
  - Low measured volume may be due to spillage
  - Some patients report subjective low volume only at time of sample collection
    - Anxiety due to lab/atmosphere
    - Anxiety related to medical condition

PHYSICAL EXAM
- Usually normal physical exam findings
- Absent vasa suggests congenital absence of the vas deferens
- Small testes may suggest hypogonadism
- Seminal vesical (SV) dilation may suggest ejaculatory duct obstruction (EDO)
- Muscle weakness or focal neurologic deficit may suggest primary neurologic cause

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- If ejaculate volume <1.5 cc, consider postejaculatory urinalysis (PEU)
- PEU
  - >10–15 sperm/HPF is diagnostic for retrograde ejaculation
  - Small number of sperm may be normal
  - Technique:
    - Abstain from ejaculation 2–3 days
    - Empty bladder
    - Collect/attempt antegrade ejaculate
    - Collect urine by void or catheter

- Endocrine evaluation if clinical suspicion for hypogonadism

Imaging

Only performed for concurrent medical conditions

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Anejaculation
- Anorgasmia (inability to reach orgasm)
- Aspermia due to failure of emission
- Congenital bilateral/unilateral absence of the vas deferens
- EDO
- Erectile dysfunction
  - Failure to reach orgasm
  - Poor expulsion of ejaculate through flaccid penile urethra
- Hypogonadism
- Semen spillage in lab
- Poor semen collection technique

TREATMENT

GENERAL MEASURES

- Treatment typically reserved for fertility purposes
- Treat reversible causes
- Modify causative medications
  - Change or discontinue causative medications
  - Some clinicians favor alfuzosin for BPH (possibly less RE than other α-blockers)

MEDICATION

First Line

- α-adrenergic agents
  - Dosing structure highly variable:
    - Pseudoephedrine 60 mg
    - Ephedrine 25–50 mg
    - Imipramine 25–50 mg (may cause dizziness and nausea)
    - Frequency ranges from QD to QID
    - Duration ranges from 2–14 days
    - Side effects: HTN, tachycardia
- Author recommendation: Pseudoephedrine 60 mg QID × 2–7 days prior to ejaculation (titrate to effectiveness)
- Medical therapy less likely to be effective after bladder neck injury or surgery

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Sperm retrieval
  - For use with assisted reproductive techniques
    - IUI (intrauterine insemination)
    - IVF In vitro fertilization
    - ICSI Intracytoplasmic sperm injection
- Sperm retrieval technique
  - Prior to collection, alkalinize urine to pH 7
    - Sodium bicarbonate 650 mg QID or 1–3 tablespoons of baking soda, 12–48 hr before collection
  - Catheterize or void for collection
- Sperm retrieval from the testis and epididymis, an option for unsuccessful retrograde collection
  - Adoption and use of donor sperm can prevent the need for IVF/ICSI

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Success rates with assisted reproductive techniques largely dependent on female factors
- 44% pregnancy rates with intrauterine insemination (5)[C]

COMPLICATIONS

- Main issue is infertility
- Emotional distress

FOLLOW-UP

Patient Monitoring

Follow up semen analysis to determine effectiveness of medical therapy

Patient Resources

MedlinePlus: Retrograde Ejaculation
http://www.nlm.nih.gov/medlineplus/ency/article/001282.htm

REFERENCES

1. Briganti A, Naspro R, Gallina A, et al. Impact on sexual function of holmium laser enucleation versus transurethral resection of the prostate: Results of a prospective, 2-center, randomized trial. *J Urol*. 2006;175(5):1817–1821.

2. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2003;(1):CD002081.
3. Lepor H. Long-term evaluation of tamsulosin in benign prostatic hyperplasia: Placebo-controlled, double-blind extension of phase III trial. Tamsulosin Investigator Group. *Urology*. 1998;51:901–906.
4. Steiner H, Zangerl F, Stöhr B, et al. Results of bilateral nerve sparing laparoscopic retroperitoneal lymph node dissection for testicular cancer. *J Urol*. 2008;180(4):1348–1352.
5. van der Linden PJ, Nan PM, te Velde ER, et al. Retrograde ejaculation: Successful treatment with artificial insemination. *Obstet Gynecol*. 1992;79:126–128.

ADDITIONAL READING

Ohl DA, Quallich SA, Sønksen J, et al. Anejaculation and retrograde ejaculation. *Urol Clin North Am*. 2008;35:211–220.

See Also (Topic, Algorithm, Media)

- Anorgasmia/Dysorgasmia
- Ejaculatory Disturbances
- Infertility, Urologic Considerations
- Semen Analysis, Abnormal Findings and Terminology
- Semen Analysis, Technical and Normal Value

CODES

ICD9

- 355.9 Mononeuritis of unspecified site
- 608.87 Retrograde ejaculation
- 606.9 Male infertility, unspecified

ICD10

- G62.9 Polyneuropathy, unspecified
- N46.8 Other male infertility
- N53.14 Retrograde ejaculation

CLINICAL/SURGICAL PEARLS

In men with spinal cord injury (SCI) or history of retroperitoneal surgery, men may have failure of seminal emission, so sperm retrieval from the bladder may not be feasible.

RETROPERITONEAL ABSCESS

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BASICS

DESCRIPTION

- A retroperitoneal abscess is an infectious process that involves the retroperitoneum.
- The retroperitoneum spans anteroposteriorly from the peritoneum to posterior pariet al wall of the abdominal cavity and craniocaudally from the diaphragm to the pelvic floor.
- Most common source of infection is from renal diseases.

EPIDEMIOLOGY

Incidence

Reported highest incidence in 3rd–6th decades.

Prevalence

N/A

RISK FACTORS

- Appendicitis
- Diabetes
- Diverticulitis
- Existing osteomyelitis or epidural infection
- GU tract obstruction
- Immunosuppression
- Inflammatory bowel disease (Crohn's disease)
- Malignancy
- Osteomyelitis
- Pyelonephritis
- Recent instrumentation or surgery of the GU or GI tract
- Systemic infection (ie, hematogenous spread from remote infection)
- Trauma
- Tuberculosis

PATHOPHYSIOLOGY

- Retroperitoneal abscess is an infectious process that can be found in 1 of 4 retroperitoneal compartments (1):
  - Anterior retroperitoneum:
    - Esophagus, duodenum, pancreas, bile duct, portal and splenic veins, appendix, ascending/descending colon, rectosigmoid
  - Posterior retroperitoneum (aka perinephric/perirenal):
    - Kidneys, ureters, gonadal vessels, aorta, inferior vena cava, lymphatics
    - See "Renal and Perirenal Abscess"
  - Retrofascial (aka iliopsoas):

    - 12th rib, spine, paraspinous muscles
  - Pelvic retroperitoneal:
    - Prevesical, retrovesical, presacral, perirectal spaces
- Primary infection if spread is hematogenous (75–90% *Staphylococcus aureus*)
- Secondary infection if spread is from infected adjacent organs (78% enteric bacteria).
- Most common source is from renal diseases accounting for 47% of retroperitoneal abscesses.
- Infection seeds a contained space in retroperitoneum:
  - Depending on the source, anaerobic and aerobic organisms may be present.
  - Usual source is normal flora from a nearby organ site (eg, GI, GU, female reproductive tract).
  - Multimicrobial infections are common.
  - Malignancy frequently violates fascial barriers, whereas abscesses tend to be contained by the fascia.
  - Hypoxia and lack of appropriate blood supply limit effective immune response.
  - If untreated, bacteremia, followed by shock ensues.
- TB and *Staphylococcus* (skin source) were previously major pathogens, but are less common today.
- *Proteus* and *Escherichia coli* are the most commonly cultured bacteria in retroperitoneal abscesses.
- Common pathogens (aerobic and anaerobic) (2,3):
  - Enterobacteriaceae:
    - *E. coli*
    - *Klebsiella pneumonia*
    - *Proteus* sp.
    - *Pseudomonas aeruginosa*
  - Anaerobes:
    - *Peptostreptococcus* sp.
    - *Bacteroides fragilis*
    - *Prevotella* sp.
    - *Clostridium* sp.
  - *Enterococcus* sp.
  - *Streptococcus* sp.
  - *S. aureus*
- Site-specific pathogens:
  - Pancreatic abscess:
    - *S. aureus*
    - *K. pneumoniae*
    - *P. aeruginosa*
  - Pelvic retroperitoneal:
    - *Neisseria gonorrhoeae*
    - Streptococcus B
  - Anterior retroperitoneal:
    - *Clostridium* sp.
    - *Fusobacterium nucleatum*

ASSOCIATED CONDITIONS
- Diabetes, liver disease, renal insufficiency, immunosuppression, retroperitoneal hematoma
- GU specific: Urinary tract infection (UTI), urolithiasis, instrumentation/surgery, malignancy
- GI specific: Malignancy, surgery, pancreatic pathology

GENERAL PREVENTION
Perioperative antibiotic prophylaxis

DIAGNOSIS
HISTORY
- Abdominal or flank pain (60–75%)
- Sweats, fever, and chills (30–90%)
- Malaise (10–22%)
- Nausea/vomiting
- Altered bowel habits
- Dysuria
- Weight loss (12%)
- Duration of symptoms is typically longer than 1 wk
- Recent instrumentation/surgery/trauma
- Recent treatment for UTI
- History of urolithiasis, inflammatory bowel disease, pancreatitis, diverticulitis, appendicitis, osteomyelitis, malignancy, TB
- Medical comorbidities: Diabetes, renal insufficiency, immunosuppression (ie, HIV)

PHYSICAL EXAM
- General vital signs:
  - Fever
  - Tachycardia
  - Tachypnea
- Unlike peritoneal cavity, retroperitoneum is relatively concealed on exam.
- Assess for:
  - Tenderness: Usually localized, dull, and mild
  - Costovertebral angle tenderness
  - Palpable flank/abdominal mass
  - Lower abdominal, groin, and/or upper thigh referred pain due to irritation of retroperitoneal nerves
  - Psoas sign: Increased pain when flexing patient's thigh against examiner's hand; suggests involvement of psoas muscle

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Lab findings often nonspecific (ie, elevated ESR)
- Obtain CBC (leukocytosis)
- BMP: Serum glucose often elevated
- Urinalysis
  - Approximately 30% will have microscopic hematuria.

  – Pyuria is also very common.
• Urine/blood/abscess cultures

Imaging
• Cross-sectional CT or MRI is most helpful:
  – CT (100% sensitivity, 77% specificity):
    ○ Low-density mass in retroperitoneum with surrounding inflammation
    ○ Gas may be present in approximately 33% of cases
    ○ Evaluates surrounding organs (ie, possible sources)
• MRI:
  – Thick purulent collections have high-intensity signal on T1-weighted images
  – Edema in surrounding fat seen as high signal on T2-weighted images
  – High soft tissue contrast resolution sensitive for detecting psoas muscle pathology and intervertebral disc involvement
  – May not show calcifications or gas collections
• US: Can reveal gas/fluid collections
• KUB: May show psoas shadow, loss of renal outline, displacement of organs, gas, or urolithiasis
• Gallium^{67} citrate and indium^{111} chloride scanning can be helpful:
  – False positives: Pyelonephritis, acute tubular necrosis, vasculitis, and neoplasms
• Chest x-ray may show elevation of hemidiaphragm, pleural effusions, secondary pneumonia

Diagnostic Procedures/Surgery
• CT, MRI, or US-guided aspiration and drainage of abscess cavity
• Specimens must be sent for both aerobic and anaerobic cultures
• Consider sending for AFB culture

Pathologic Findings
Coagulation necrosis

DIFFERENTIAL DIAGNOSIS
• Malignancy
• Necrotizing fasciitis
• Osteomyelitis
• Pancreatitis
• Perforated viscus (ie, duodenal ulcer)
• Perinephric aneurysm/pseudoaneurysm
• Perinephric/perirenal abscess
• Psoas abscess
• Pyelonephritis
• Ruptured aortic aneurysm
• TB
• Trauma/retroperitoneal hematoma
• Urinoma

TREATMENT

GENERAL MEASURES

- Supportive care
- DVT prophylaxis

MEDICATION

First Line

- Broad-spectrum antibiotics to empirically cover most likely pathogens (ampicillin, gentamicin, and metronidazole) (4)
  - Refine antibiotic coverage based on culture results
  - Tailor duration of treatment to clinical progress

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Early percutaneous drainage (5)
  - Essential in lesions >3 cm
  - May consider antibiotics only in abscesses <3 cm
- Surgical drainage must be considered if:
  - Safe percutaneous drainage not possible
  - Percutaneous drainage has failed
  - Multiple abscesses
  - Multiloculated abscesses
  - Purulent material too thick to be drained
  - If patient is persistently febrile after 48–72 hr of appropriate antibiotics
  - If primary cause must be addressed surgically (ie, xanthogranulomatous pyelonephritis (XGP), malignancy, urolithiasis)
- Surgical approach should be retroperitoneal unless pancreatic pathology is present:
  - Obtain cultures
  - Irrigate abscess cavity aggressively
  - Use drains liberally

ADDITIONAL TREATMENT

Radiation Therapy

No role

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Mortality is considerable (5–50%) despite modern management that combines antibiotics, drainage, and intensive care support.
- High success with antibiotics and percutaneous drainage (>80%):

- Only 1–4% recurrence with percutaneous drainage
- If abscess is not drained and only antibiotics are used, mortality approaches 100%

COMPLICATIONS
- Abscess crossing the midline to opposite side or tracking into the ipsilateral thigh
- DVT
- GI bleed
- Organ failure
- Pneumonia
- Secondary infections: Osteomyelitis, involvement of psoas muscle, fistulization to the skin

FOLLOW-UP

Patient Monitoring
- Reimaging necessary
  - CT or MRI (MRI avoids radiation)
  - Timing depends on clinical progress
- Drains:
  - Must be monitored carefully and irrigated appropriately
- Can be removed when:
  - Patient is clinically improved
  - Drainage stops (<10 mL/d) or becomes serous
  - Abscess cavity involution is documented on imaging

PATIENT RESOURCES

N/A

REFERENCES

1. Solomkin JS. Peritonitis, pancreatitis and intra-abdominal abscesses. In: Cohen J, Powderly WG, eds. *Cohen & Powderly: Infectious Diseases*. 2nd ed. Philadelphia, PA: Mosby; 2004:517–527.
2. Anaya DA, Dellinger EP. Surgical infections and choice of antibiotics. In: Townsend CM Jr, Beauchamp RD, Evers M, et al., eds. *Sabiston Textbook of Surgery*. 18th ed. Philadelphia, PA: Saunders Elsevier; 2008.
3. Brook I, Frazier EH. Aerobic and anaerobic microbiology of retroperitoneal abscesses. *Clin Infect Dis*. 1998;26:938–941.
4. Crepps JT, Welch JP, Orlando R 3rd. Management and outcome of retroperitoneal abscesses. *Ann Surg*. 1987;205:276–281.
5. Tunuguntla A, Raza R, Hudgins L. Diagnostic and therapeutic difficulties in retroperitoneal abscess. *South Med J*. 2004;97:1107–1109.

ADDITIONAL READING

- Brook I. Microbiology and management of abdominal infections. *Dig Dis Sci*. 2008;53:2585–2591.
- Heller MT, Haarer KA, Thomas E, et al. Acute conditions affecting the perinephric space: Imaging anatomy, pathways of disease spread, and differential diagnosis. *Emerg Radiol*. 2012;19:245–254.

• Negus S, Sidhu PS. MRI of retroperitoneal collections: A comparison with CT. *Br J Radiol.* 2000;73:907–912.

See Also (Topic, Algorithm, Media)
• Psoas Abscess, Urologic Considerations
• Renal and Perirenal Abscess
• Retroperitoneal Abscess Image ☼
• Retroperitoneal Hematoma
• Retroperitoneal Mass and Cysts

CODES

ICD9
• 567.31 Psoas muscle abscess
• 567.38 Other retroperitoneal abscess
• 998.59 Other postoperative infection

ICD10
• K68.11 Postprocedural retroperitoneal abscess
• K68.12 Psoas muscle abscess
• K68.19 Other retroperitoneal abscess

CLINICAL/SURGICAL PEARLS

• Nonspecific signs and symptoms frequently lead to a delay in diagnosis and treatment.
• Early percutaneous drainage is essential in lesions >3 cm.

RETROPERITONEAL FIBROSIS (RPF, ORMOND DISEASE)

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BASICS

DESCRIPTION

- Retroperitoneal fibrosis (RPF) also refered to as Ormond disease, is characterized by sclerotic tissue from inflammatory processes causing encasement of the retroperitoneal structures including the ureters, aorta, and inferior vena cava. The main manifestation is obstructive uropathy.
- Exhibits a perivascular distribution, typically including the periaortic, pericaval, and peri-iliac retroperitoneum.
- Generally classified as either primary (idiopathic) or secondary RPF.
- Hallmark is medial deviation of the ureters on imaging with or without hydronephrosis.

EPIDEMIOLOGY

Incidence

- In Finland, incidence is 0.1:100,000/yr
- Unknown, but estimated at 1:200,000–1:500,000/yr

Prevalence

1–38 per 100,000

RISK FACTORS

- Asbestos exposure
- Associated with autoimmune disorders
- Abdominal aortic aneurysm
- Male > Female (2–3:1)
- RPF most common in the 5th–6th decades, but can occur at any age
- Use of implicated medications (see below)
- Malignancy

Genetics

- Evidence suggests an immunogenetic role with certain HLA haplotypes:
  – HLA-DRB1*03 and HLA-B*08

PATHOPHYSIOLOGY

- Idiopathic RPF recently identified as a immunoglobulin G4-related disease (IgG4-RD) and is a multisystem, fibroinflammatory condition (1)
- Most commonly, the retroperitoneal thickening is located between L5 and S1, close to the aortic bifurcation
- Mechanical obstruction of the ureters is usual presentation; may also cause venous or arterial occlusion
- Primary RPF:
  – 70% of cases are idiopathic, and the exact pathogenesis is unclear

- Mitchinson and Parums classify idiopathic RPF in a range of diseases collectively termed chronic periaortitis
  - Immune-mediated reaction to antigens (ceroid and low-density lipoprotein) within atherosclerotic plaques
  - Often have autoantibodies, and thus overlap with many autoimmune disorders
  - IgG4-bearing plasma cells may also be involved in the pathogenesis of RPF
- Secondary RPF: 30% of patients with RPF have an identifiable cause of their RPF:
  - Medications:
    - Prolonged therapy with ergot alkaloids such as methylsergide (Sansert, once widely used for migraine headaches)
    - Others include LSD, methyldopa, phenacetin, β-blockers, amphetamines, hydralazine, and analgesics
  - Malignancy:
    - Lymphoma (most common), multiple myeloma, carcinoid, pancreatic tumors, prostate cancer, testicular cancer, and sarcoma
  - Radiotherapy for malignancies such as seminoma, colon, or pancreatic cancer
  - Infections: Tuberculosis, actinomycosis, histoplasmosis
  - Others: Trauma (hemorrhage, urinary extravasation), surgical injury, Crohn disease, inflammatory bowel disease, asbestos exposure, fat necrosis, collagen vascular disease, perianeurysmal inflammation

ASSOCIATED CONDITIONS

- Atherosclerotic disease (abdominal aortic aneurysm)
- Autoimmune diseases: Ankylosing spondylitis and Wegener granulomatosis
- Membranous glomerulonephritis
- Multifocal fibrosclerosis: RPF may present as part of a systemic sclerosis
  - Presentation may include sclerosing mediastinitis, sclerosing cholangitis, orbital pseudotumor, and Riedel thyroiditis

GENERAL PREVENTION

Avoid medication implicated in RPF (see above)

DIAGNOSIS

HISTORY

- Constitutional symptoms (fatigue, weight loss, anorexia, low-grade fever)
- Pain (back, flank, abdominal) and duration
- Signs of vascular obstruction:
  - Testicular pain, varicocele, hydrocele, leg edema, deep vein thrombosis, claudication
- GI symptoms such as weight loss, nausea, anorexia, constipation, or vomiting
- Urinary symptoms, including frequency, and dysuria, also oliguria if severe
- Medication history especially ergot alkaloids
- History of malignancies, other autoimmune or collagen vascular diseases, fibrotic processes, inflammatory bowel diseases, asbestos exposure, radiation exposure
- Surgical history:
  - Abdominal, vascular, or endoscopic procedures

PHYSICAL EXAM

- Patient can appear pale, ill, and has malaise if significant azotemia is present
- Low-grade fevers and hypertension
- Abdominal exam: Mass, abdominal bruit, costovertebral angle tenderness
- Testicular masses
- Lower-extremity edema, varicosities

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- No tests are diagnostic
- Metabolic profile: Electrolyte abnormalities will depend upon the degree of ureteral obstruction
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated
- Ferritin and other acute phase reactants are often high
- Polyclonal hypergammaglobulinemia
- ANA is positive in 60% of patients along with other autoantibodies including antismooth muscle antibodies and rheumatoid factor

Imaging

- Excretory Urography (2):
  - Medial deviation of the ureters with tapering of the middle 1/3 of the ureter beginning at the 3rd or 4th lumbar vertebra
  - Varying degrees of hydronephrosis; may see a nonfunctioning kidney
  - Encasement of ureters may prevent dilation of middle and distal ureteral segments
- Ultrasound (US)
  - More useful for following the response to therapy
- Computed tomography (CT)
  - Imaging modality of choice
  - Typically shows a symmetric, geometrically shaped mass encasing the retroperitoneal structures
  - Demonstrates the medial deviation of the ureters and extrinsic compression with hydronephrosis
  - Mass is often isodense to muscle with contrast enhancement
- Magnetic resonance imaging (MRI)
  - Hypodensity on T1 images but high intensity on T2-weighted images
- Positron emission tomography (PET):
  - Investigational; may visualize other disease sites
  - May reveal neoplastic or infectious processes to which the RPF may be secondary

Diagnostic Procedures/Surgery

- Retrograde pyelography may be indicated in patients with severe azotemia prohibiting the use of contrast-enhanced imaging. Usually shows medial deviation of ureters.
- CT-guided biopsy may be necessary to rule out a malignant process.

Pathologic Findings

- Gross findings secondary RPF:
  - Smooth, flat, firm, grayish/tan-colored mass

– Extends from the origin of the renal vessels to the distal extent of the common iliac vessels
– May also involve the thoracic aorta and other atypical areas
• Microscopic findings
– Early findings: Collagen bundles with capillary proliferation and inflammatory cells
– Later acellular and avascular mass with sheets of hypocellular collagen
– Vasculitis of small retroperitoneal vessels with plasma cells staining for IgG4 (rarest IgG subclass)

DIFFERENTIAL DIAGNOSIS
• Medial deviation of the ureters
– Malignancies, aneurysms, bladder diverticulum, and prior surgery
– 20% of normal individuals have medial deviation of the ureters, especially on the right
• Retroperitoneal mass: See also Section I "Retroperitoneal masses, fluid, and cysts"
– Malignant processes; inflammatory myofibroblastic tumors
– Desmoid-type fibromatosis; associated with Gardner syndrome; presents as soft tissue mass with mass effect

TREATMENT

• Discontinue any offending medications
• Relieve urinary obstruction:
– Monitor for postobstructive diuresis after the urinary system is decompressed
• Biopsy to rule out malignancy
• Unclear if trial of steroids or immediate ureterolysis is optimal therapy

MEDICATION
First Line
• After ureteral obstruction has been relieved, 1st-line therapy is generally glucocorticoids (prednisone). No consensus as to duration of therapy:
– Prednisone 60 mg every other day for 2 mo, then tapered over 5 mo to 5 mg/d
– Alternate regimen: 60 mg/d for 6 wk, and tapered over the next 2–3 mo to 10 mg/d for a total of 1 yr

Second Line
• In patients with glucocorticoid-resistant RPF or who have recurrent disease, immunosuppressive agents may also be helpful:
– Prednisone in combination with cyclophosphamide or azathioprine for 6–12 mo
– Mycophenolate mofetil has also been used in combination with glucocorticoids

SURGERY/OTHER PROCEDURES
• Relief of ureteral obstruction:
– Ureteral stents may be helpful during subsequent ureterolysis
– Usually not difficult; often elect to stent both sides even if not bilaterally obstructed to prevent obstruction or provide guide for surgery
• Percutaneous nephrostomy undertaken only in acutely ill patients; rarely necessary
• Ureterolysis:
– May be performed via an open approach (transabdominal) or laparoscopically (hand-

assisted or standard) (3)
  – Ureters are often wrapped in omentum or intraperitonealized to prevent further fibrous entrapment
- Other procedures: May require ileal interposition graft, autotransplantation, nephrectomy, or urinary diversion in complicated or severe cases

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Observation:
  – There may be a role in patients on methylsergide after discontinuation of the medication if normal renal function.
  – These patients should be monitored for resolution of hydronephrosis. If the hydronephrosis does not resolve, then the standard combination of medical and surgical therapy should be administered.
- Tamoxifen has been used
- Low-protein, sodium-restricted diet for patients with renal insufficiency

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Prognosis is excellent with combined medical and surgical therapy

COMPLICATIONS

- Recurrence of RPF: Typically in 1st yr; usually limited to those treated with medical therapy
- Ureteral injury, requiring further surgical management
- Vascular injury
- Postoperative adhesions due to intraperitoneal procedure

FOLLOW-UP

Patient Monitoring

- Patients can be monitored at regular intervals with symptom check, ESR/CRP levels, creatinine, and degree of hydronephrosis on US
- CT/MRI is usually performed 2–4 mo after the beginning of the steroid treatment (1)
- Patients treated with definitive surgical intervention require less frequent follow-up

Patient Resources

- Medline Plus: Retroperitoneal Fibrosis
  http://www.nlm.nih.gov/medlineplus/ency/article/000463.htm

REFERENCES

1. Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking ormond's disease: "Idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine (Baltimore)*. 2013;92(2):82–91.

2. Caiafa RO, Vinuesa AS, Izquierdo RS, et al. Retroperitoneal fibrosis: Role of imaging in diagnosis and follow-up. *Radiographics*. 2013;33(2):535–552.
3. Brown JA, Garlitz CJ, Hubosky SG, et al. Hand-assisted laparoscopic ureterolysis to treat ureteral obstruction secondary to idiopathic retroperitoneal fibrosis: Assessment of a novel technique and initial series. *Urology*. 2006;68(1):46–49.

ADDITIONAL READING

• Scheel PJ Jr, Feeley N. Retroperitoneal fibrosis. *Rheum Dis Clin North Am*. 2013;39(2):365–381.
• Vaglio A, Palmisano A, Corradi D, et al. Retroperitoneal fibrosis: Evolving concepts. *Rheum Dis Clin N Am*. 2007;33:803–817.
• Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet*. 2006;367:241–251.

See Also (Topic, Algorithm, Media)

• Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Adult
• Retroperitoneal fibrosis (RPF, Ormond Disease) Image ☼
• Retroperitoneal Hematoma
• Retroperitoneal Masses, Fluids and Cysts

CODES

ICD9

• 590.80 Pyelonephritis, unspecified
• 593.4 Other ureteric obstruction
• 599.60 Urinary obstruction, unspecified

ICD10

• N13.5 Crossing vessel and stricture of ureter w/o hydronephrosis.
• N13.6 Pyonephrosis.
• N13.9 Obstructive and reflux uropathy, unspecified.

CLINICAL/SURGICAL PEARLS

• Although no tests are diagnostic of RPF, most will present with medial deviation of the ureters on imaging.
• CT is the image modality of choice.
• Stents are often placed for relief of obstruction.
• Patients who fail steroid treatment without evidence of malignancy should undergo ureterolysis.

RETROPERITONEAL MASSES, FLUID, AND CYSTS

Mark R. Anderson, MD, MSc
Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Retroperitoneal masses and cysts can originate from retroperitoneal organs or nonorgan tissue. The latter are relatively rare.
- 70–80% of primary retroperitoneal neoplasms are malignant in nature, and these account for 0.1–0.2% of all malignancies in the body.
- Most cystic lesions within the retroperitoneum are benign; unless the lesion is mostly solid then suspect malignancy.
- Metastatic disease is the most common etiology of a solid retroperitoneal mass.
- Liposarcomas are among the most common of primary retroperitoneal tumors and are distinguished by their often large dimensions and range of subtypes.
  - Peak incidence: Ages 40–60.
  - 10–15% of sarcomas, and approximately 20% of these lesions arise in the retroperitoneum.
  - Often recur usually within the 1st 6 mo after surgery.

EPIDEMIOLOGY

Incidence

Retroperitoneal sarcoma: Accounts for $<1\%$ of all adult malignancy, or 9,500 new diagnoses per year, ~ 2.7 cases per million per year of retroperitoneal sarcoma

Prevalence

N/A

RISK FACTORS

- Primary, solid/cystic retroperitoneal mass: Previous radiotherapy (dose dependant), chemical exposure (vinyl chloride, arsenic), HIV/AIDS
- Primary, cystic retroperitoneal mass: Parasitic infection, embryonic remnants, prior lymphadenectomy

Genetics

- Tuberous sclerosis (TS1, TS2 mutation, tumor suppressor loss)
- Werner syndrome (chromosome 8 alteration, premature aging)
- Li–Fraumeni syndrome (p53 mutation, tumor suppressor loss)
- Neurofibromatosis (NF1, NF2 mutation)
- Liposarcomas are being reclassified based on a molecular basis. Well-differentiated and dedifferentiated lesions are a continuum of lesions based on the genetic abnormality of giant and ring chromosomes usually involving chromosome 12.
- Gene amplification, particularly of *MDM2,* drives their pathology.
- Myxoid and round-cell lesions are another continuum that have fusion transcripts caused by

translocations in chromosomes 16 and 12.
- Alveolar rhabdomyosarcoma t(2;13) (q35;q14) PAX3-FKHR, and t(1;13) (p36;q14) PAX7-FKHR
- Sporadic gastrointestinal stromal tumor activating kinase mutations KIT or PDGFRA

PATHOPHYSIOLOGY
- The retroperitoneum extends from the diaphragm superiorly to the pelvis inferiorly and is situated between the posterior pariet al peritoneum anteriorly and the transversalis fascia posteriorly (1).
- The anterior pararenal space is bordered anteriorly by the posterior pariet al peritoneum, posteriorly by the anterior renal fascia (Gerota fascia), and laterally by the lateroconal fascia.
- The anterior pararenal space is subdivided into the pancreaticoduodenal space (contains the pancreas and duodenum) and the pericolonic space (contains ascending and descending colon).
- The posterior pararenal space is situated between the posterior renal fascia (Zuckerkandl fascia) and the transversalis fascia.
- The perirenal space is located between the anterior renal fascia and the posterior renal fascia.
- The great vessel space is the fat-containing region that surrounds the aorta and the inferior vena cava (IVC) and lies anterior to the vertebral bodies and psoas muscles.
- Below the kidneys, the anterior and posterior pararenal spaces merge to form the infrarenal retroperitoneal space, which communicates inferiorly with the prevesical space and extraperitoneal compartments of the pelvis.
- Due to the loose connective tissue in the retroperitoneum, tumors can have widespread growth and extension before clinical presentation.

ASSOCIATED CONDITIONS
N/A

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Headaches, palpitations, etc. for hypertension secondary to pheochromocytoma
- Unexplained weight loss
- Constitutional symptoms
- Night sweats
- History of chemotherapy, radiation therapy
- Back or bone pain
- Medications: Methysergide, methyldopa, LSD
- GI complaints: Nausea, vomiting, pain, constipation, increasing abdominal girth

PHYSICAL EXAM
- Vitals for hypertension

- Cachexia
- Lymphadenopathy
- Neurologic deficits from paraneoplastic syndrome
- Lower-extremity lymphedema
- Breast exam
- Testicular exam
- Abdominal mass
- Signs of virilization

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC: Leukocytosis (infection or lymphoma), leukopenia, anemia
- Serum chemistry: Elevated serum creatinine, azotemia (obstructive uropathy), transaminitis (biliary obstruction), and elevated alkaline phosphatase (bone involvement).
- AFP, LDH, and β-HCG: Testicular tumor markers
- ESR: Elevated in retroperitoneal fibrosis
- Urinalysis: Hematuria, pyuria
- Urine cytology: Evidence of a malignant urothelial source
- Blood and urine culture
- Adrenal mass: Pheochromocytoma screen
  - Plasma metanephrines
    - 96–100% sensitivity, 85–89% specificity
  - 24-hr urine-fractionated metanephrines
    - 91–98% sensitivity and specificity

Imaging

- Adrenal: CT washout for adenoma, MRI “light bulb” sign/T2 bright for carcinoma and pheochromocytoma, MIBG scan for pheochromocytoma (2)
- CT urogram for RCC and urothelial carcinoma
- CT can show enhancement, fat density, water density to help characterize underlying components
- MRI better at defining local invasion
- Ultrasound can differentiate between solid and fluid-filled masses but not good at determining malignant potential or regional mets.
- CT with contrast has relative contraindication if GFR <60, MRI has relative contraindication if GFR <30.
- MAG-3 diuretic renal scan can determine relative differential function between each kidney and urine obstruction.
- Testicular sonogram for mass
- Bone scan, mammogram if needed
- Cystogram if pelvic lipomatosis

Diagnostic Procedures/Surgery

- Image-guided biopsy: CT- or US-guided fine-needle aspiration is usually feasible, but core-needle biopsy improves diagnostic capability
- Open surgical biopsy: Best option if the mass is small and inconveniently located for needle

biopsy
- Be prepared to complete the resection if sarcoma identified
- Aspiration of cyst: Fluid for cytology, culture, creatinine
- Angiogram: To delineate relationship of tumor to vascular anatomy or to determine extent of aneurysm

Pathologic Findings
- Metastasis pathology is consistent with primary tumor pathology.
- Determination of benign vs. malignant tissue is not always possible, leaving final determination to the surgical pathology.
- Well-differentiated liposarcomas mostly resemble lipomas and are typically low grade.
- Pleomorphic liposarcomas comprise 10–15% defined as high-grade malignant variants with very bizarre nuclei and huge lipoblasts and carry poor prognosis.
- Liposarcoma is most common (35%), followed by leiomyosarcoma (30%), malignant fibrous histiocytoma (20%), rhabdomyosarcoma, and peripheral nerve neoplasm.
- Lymphoma: Diffuse, monomorphous proliferation of lymphocytes.
- Fibrosis: Cellular and acellular variants coexist; fibroblast and collagen proliferation.

DIFFERENTIAL DIAGNOSIS
- Solid masses—Benign (malignant variant in parenthesis)
  - Lipoma (liposarcoma)
  - Leiomyoma (leiomyosarcoma)
  - Fibroma (chondro-, synovial cell-, fibrosarcoma)
  - Rhabdomyoma (rhabdomyosarcoma)
  - Hemangioma (angiosarcoma)
  - Perivascular epithelioid cell tumor (PECT): Angiomyolipoma, lymphangioleiomyomatosis, clear cell "sugar" tumor, clear cell myomelanocytic tumor, pigmented melanotic tumor (sarcoma variants)
  - Gastrointestinal stromal tumor, aka GIST
  - Myxoma (myxosarcoma)
  - Chordoma
  - Schwannoma, neurofibroma
  - Ganglioneuroma, ganglioneuroblastoma (neuroblastoma)
  - Paraganglioma, pheochromocytoma (pheochromocytoma)
  - Mature teratoma (seminoma, nonseminoma germ cell tumors; choriocarcinoma, malignant teratoma, yolk sac, embryonal, mixed)
  - Sex cord: Granulose, thecoma, Sertoli–Leydig (rarely malignant)
  - Malignant lymphoma, extramedullary plasmacytoma, fibrous histiocytoma
- Cystic malignant masses
  - Mucinous cystadenoma or cystadenocarcinoma
  - Mesothelioma
  - Cystic teratoma
  - Paraganglioma, neurilemmoma, sarcoma
- Cystic nonmalignant mass
  - Hematoma
  - Urinoma

– Lymphocele
– Pancreatic cyst and pseudocyst
– Lymphangioma
– Postoperative seroma

TREATMENT

GENERAL MEASURES

- Need tissue diagnosis via primary excision or needle biopsy
- Core biopsy better than fine needle if possible

MEDICATION

First Line

- Metastatic lesions and lymphoproliferative cancers are best treated with systemic, tumor-specific chemotherapy (in most cases).
- Sarcomas respond variably to chemotherapy, depending on the histology, and generally do not influence survival.
- Pheochromocytoma needs α-blocking blood pressure control, followed by β-blockade. Some advocate single agent calcium channel blockade.
- May need stress steroids if functional adrenal tumor suppresses contralateral function.
- Infected retroperitoneal cysts are treated with broad-spectrum (gram positive and negative) antibiotics until culture sensitivities are known:
  – Ampicillin 1 g IV q6h (gram positive)
  – Gentamicin 5–7 mg/kg/d (gram negative)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Metastatic site resection may be beneficial for prognosis and/or symptoms for RCC and testicular tumors
- Liposarcoma needs primary excision
- Extensive lymph node resection commonly needed in liposarcoma and testicular cancer (modified templates used in some instances)
- Benign cysts can be aspirated and sclerosed

ADDITIONAL TREATMENT

Radiation Therapy

- Retroperitoneal sarcoma is typically radiation resistant.
- Intraoperative radiotherapy for sarcoma has been shown to improve local control rates, but does not improve survival.

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 5- and 10-yr survival following surgical resection of retroperitoneal sarcoma is 45% and 29%.
- Poorly differentiated liposarcoma metastasize.
- Completely resected, nonmetastatic, and low-grade sarcomas are associated with improved survival.
- Leiomyosarcoma is an independent predictor of poor outcome.
- Adrenal carcinoma typically presents late stage and has poor prognosis even with complete resection.
- Pheochromocytoma has good prognosis.
- RCC has good prognosis though is most lethal GU cancer and present with mets ~25% of time.

COMPLICATIONS

- Bowel injury
- Adjacent organ injury (liver, spleen, pancreas)
- Lymphocele
- Deep vein thrombosis
- Wound infection
- Transfusion-dependent anemia

FOLLOW-UP

Patient Monitoring

Schedule imaging that is intensive during 1st 2 yr (q3–6mo) followed by biannual, migrating to annual by year 5 is generally recommended for most retroperitoneal masses.

Patient Resources

N/A

REFERENCES

1. Osman S, Lehnert BE, Elojeimy S, et al. A comprehensive review of the retroperitoneal anatomy, neoplasms, and pattern of disease spread. *Curr Probl Diagn Radiol.* 2013;42(5):191–208.
2. Rajiah P, Sinha R, Cuevas C, et al. Imaging of uncommon retroperitoneal mass. *Radiographics*. 2011;31:949–976.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Retroperitoneal Abscess
- Retroperitoneal Fibrosis (RPF, Ormond Disease)
- Retroperitoneal Hematoma
- Retroperitoneal Liposarcoma
- Retroperitoneal Lymphoma

- Retroperitoneal Masses, Fluids, and Cysts Image
- Retroperitoneal Rheumatoid Nodules
- Retroperitoneal Sarcoma
- Retroperitoneum, Fat Necrosis

CODES

ICD9

- 158.0 Malignant neoplasm of retroperitoneum
- 568.89 Other specified disorders of peritoneum
- 789.39 Abdominal or pelvic swelling, mass, or lump, other specified site

ICD10

- C48.0 Malignant neoplasm of retroperitoneum
- K68.9 Other disorders of retroperitoneum
- R19.09 Other intra-abdominal and pelvic swelling, mass and lump

CLINICAL/SURGICAL PEARLS

Most solid retroperitoneal masses are malignant.

RHABDOMYOLYSIS

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BASICS

DESCRIPTION

- Rhabdomyolysis is muscle necrosis resulting in the egress of cellular muscle particles (namely myoglobin, potassium, creatine kinase [CK], and lactic acid dehydrogenase [LDH]) into the blood stream.
- In particular myoglobin is harmful to the kidney and often causes acute kidney injury.
  – Up to 15% of patients who have rhabdomyolysis can have renal failure.
- There are many causes for rhabdomyolysis; this section primarily focuses on operative causes.

EPIDEMIOLOGY

Incidence

- 2,600 cases per year (likely underreported)
- Overall incidence of 0–4.9% in the laparoscopic nephrectomy data

RISK FACTORS

- Trauma and immobilization (1)
  – Lying unconscious on hard surface under the influence of alcohol or drugs
  – Crush injury
  – Prolonged compression as seen in excessive operating times (esp. males)
    - Laparoscopic, robotic, and open
    - Dorsal lithotomy positioning
- Elevated BMI (esp. muscle mass)
- Sepsis and shock
- Toxins (spider and snake venom [mostly in South America, Asia, Africa])
- Medications (cocaine, Ecstasy [MDMA] LSD, amphetamines, statins [especially in combination with fibrate-derived lipid-lowering agents such as niacin], cyclosporin, itraconazole, colchicine, steroids)
- Infections (HIV, influenza)
- Excessive muscle use (status epilepticus, prolonged exercise)
- Electrolyte and endocrine abnormalities (hyponatremia, hyperthyroidism, ketoacidosis)
- Electrical shock injury, lightning strike
- 3rd-degree burns
- High body temperature, heat stroke, malignant hyperthermia
- Myopathy (eg, Duchenne muscular dystrophy)

Genetics

- Suspect a genetic disorder with recurrent rhabdomyolysis after minimal to moderate exertion or after viral infections starting in childhood
  – Glycogen and lipid disorders (McArdle disease, carnitine deficiency, others)

- Duchenne muscular dystrophy

PATHOPHYSIOLOGY

- Muscle cell destruction
  - Pressure or crush
  - Cellular hypoxia
- Reperfusion injury results in large quantities of potassium, phosphate, myoglobin, CK, and urate leak into the circulation
  - Electrolyte alterations further impact cellular integrity
- Normal plasma myoglobin is very low (0–0.003 mg/dL)
  - With >100 g of skelet al muscle damaged, serum haptoglobin binding capacity becomes saturated
  - At this point circulating myoglobin becomes "free" and is filtered by the glomeruli
  - Myoglobin precipitates in the kidney and cause renal tubular obstruction, potentially leading to acute kidney injury
- Myoglobin levels return to normal values in 1–6 hr after injury due to hepatic metabolism and renal excretion
- Up to 12 L of fluid may be sequestered in the necrotic muscle tissues
  - This relative hypovolemia is an additional cause of renal failure in rhabdomyolysis
  - Free iron, which catalyses free radical production further enhances ischemic renal tubule damage
- Compartment syndrome
  - Caused by insufficient blood supply to muscles due to increased pressure within a body compartment (arm, leg, any enclosed space within the body)
  - 6 "Ps" associated with compartment syndrome: Pain out of proportion based on exam, paresthesia, pallor, paralysis, pulselessness, and pressure
  - For most prolonged operative cases the paraspinous muscles and the extremities are at risk for compartment syndrome

ASSOCIATED CONDITIONS

- Acidosis
- Cardiac arrest (hyperkalemia)
- Compartment syndrome
- Disseminated intravascular coagulation (DIC)
  - Activation of the coagulation cascade by the substances released from damaged muscle cells
- Hepatic dysfunction
- Myoglobinuric acute renal failure

GENERAL PREVENTION

- Avoid immobilization or prolonged operating times
- Appropriate patient padding in the operating room
- Some reports of using pulse oximetry monitoring of lower extremity to monitor for compartment syndrome
- Monitor for malignant hyperthermia

DIAGNOSIS

HISTORY

- Trauma
- Sepsis
- New medication
- Toxin exposure, drug use or infection
- Excessive muscle use
- Electrolyte or endocrine disorder
- Prolonged operating room time—most common reason in urology (2,3,4)
  - Most commonly reported in the laparoscopic nephrectomy data when patients are in flank or modified flank position for >6 hr but also seen in exaggerated lithotomy and steep Trendelenburg
  - Male sex predominates
  - Elevated BMI, reported mean BMI of 33.2 in review of the laparoscopic nephrectomy data

PHYSICAL EXAM

- Generalized fatigue, nausea, fevers
- Mental status changes
- Skin discoloration
- Muscular pain and swelling (symptoms may be out of proportion with exam)
- Muscle weakness
- Symptoms may be absent in 50% of patients
- Reddish-brown urine
- Classic triad of muscle pain, weakness, and dark urine

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Myoglobinuria:
  - Myoglobin only appears in the urine when serum level >1.5 mg/dL
    - Red-brown urine when urine levels >100 mg/dL
  - Positive for blood on urine dipstick but no RBCs suggests myoglobinuria (5)
  - Short half-life only 2–3 hr, so it may return to normal if muscle damage is limited
- Elevated CK levels (5× upper limit of normal which is about >1,000 U/L)
  - CK half-life of 26 hr and remains elevated longer than myoglobin, peaks at 1–3 days and declines at 3–5 days after all muscle injury has stopped
- Basic metabolic panel
  - Monitor for acute renal failure and hyperkalemia
- Calcium level:
  - Can be hypocalcemic early, then hypercalcemic later
- Uric acid:
  - Conversion of purines from lysed muscle cells
- CBC/clotting studies (for DIC)
- LFTs, ABG
- Microscopic urine: Pigmented casts, dysmorphic red cells

Imaging

- Often unnecessary
- MRI with gadolinium best modality for muscle injury
  - Sensitivity of 100% vs. 42% for US and 62% for CT scan

Diagnostic Procedures/Surgery
- Muscle biopsy is unnecessary
- Forearm ischemic test to differentiate genetic causes of rhabdomyolysis (6)
  - Relies on forearm compression with exercise and determination of ammonia and lactate levels

Pathologic Findings
- Though muscle biopsy is not needed, one would see noninflammatory loss of the nucleus and muscular stria.
- Renal biopsy: Myoglobin precipitates and forms obstructive casts.

DIFFERENTIAL DIAGNOSIS
- Acidotic states
- Compartment syndrome
- DIC
- Nephritic syndromes
- Rhabdomyolysis can be the result of another process (ie, sepsis) and result in other complications (ie, compartment syndrome, DIC)

TREATMENT

GENERAL MEASURES
- Prevention of acute renal failure (ARF)
- Recognition of compartment syndrome
- Elderly patients and those with comorbidities should be treated in an intensive care unit

MEDICATION

First Line (6,7)
- Aggressive hydration initially with normal saline
  - Urine output should be maintained at (goal of 2 mg/kg/h of urine output) until myoglobinuria has ceased
  - High rates of IV fluid administration should be used at least until the CK level decreases to or below 1,000 U/L
- Consider mannitol for osmotic diuresis to purge nephrotoxic agents
- Diuretics should not be used as they may worsen the condition
- Alkalinize urine to prevent ARF:
  - Bicarbonate: 1 ampule in 1 L of normal saline
    - Goal: Urine pH >6.5 and serum pH 7.4–7.45
- There are retrospective data to suggest aggressive hydration is sufficient for treatment and that mannitol and bicarbonate are not needed
- Avoid correction of early hypocalcemia as hypercalcemia can develop later

Second Line

May need to correct acidosis, DIC, and hyperkalemia, if present

SURGERY/OTHER PROCEDURES

- Fasciotomy for compartment syndrome.
  - For the extremity such as the leg recommendations for fasciotomy vary. In general an intracompartmental pressure of >30 mmHg or a >30 mm Hg difference between diastolic blood pressure and the compartment pressure.
- Dialysis for hyperkalemia, acidosis, and/or fluid overload.
  - In general, only 4% of patients require dialysis, but up to 55% in the laparoscopic nephrectomy data

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Monitor osteoporosis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Overall survival rate of 78.6% at 14 yr
- Initial mortality rate as high as 8%
- ARF develops in 33% of patients
  - In review of the laparoscopic nephrectomy data, patients who developed ARF had a higher peak CK than those who did not (46,780 U/L vs. 25,650 U/L)

COMPLICATIONS

- Long-term weakness, pain, and numbness; may have permanent disability
- Morbidity associated with dialysis and fasciotomy

FOLLOW-UP

Patient Monitoring

- Check for return of renal function
- Physical therapy as needed

Patient Resources

- Medline Plus: Rhabdomyolysis
  http://www.nlm.nih.gov/medlineplus/ency/article/000473.htm

REFERENCES

1. Khan FY. Rhabdomyolysis: A review of the literature. *Neth J Med*. 2009;67(9):272–283.
2. Glassman DT, Merriam WG, Trabulsi EJ, et al. Rhabdomyolysis after laparoscopic nephrectomy. *JSLS*. 2007;11(4):432–437.
3. Wolf JS Jr, Marcovich R, Gill IS, et al. Survey of neuromuscular injuries to the patient and surgeon during urologic laparoscopic surgery. *Urology*. 2000;55(6):831–836.
4. Reisiger KE, Landman J, Kibel A, et al. Laparoscopic renal surgery and the risk of rhabdomyolysis: Diagnosis and treatment. *Urology*. 2005;66(suppl 5):29–35.

5. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. *Intern Emerg Med.* 2007;2(3):210–218.
6. Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. *Am Fam Physician.* 2002;65(5):907–913.
7. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis–an overview for clinicians. *Crit Care.* 2005;9(2):158–169.

ADDITIONAL READING

Wen T, Deibert CM, Siringo FS, et al. Positioning-related complications of minimally invasive radical prostatectomies. *J Endourol.* 2014;28(6):660–667.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult
- Acute Tubular Necrosis (ATN)
- Compartment Syndrome, Urologic Considerations
- Myoglobin Nephrotoxicity
- Myoglobinuria
- Urine, Abnormal Color

CODES

ICD9

- 728.88 Rhabdomyolysis
- 929.9 Crushing injury of unspecified site
- 958.5 Traumatic anuria

ICD10

- M62.82 Rhabdomyolysis
- T79.5XXA Traumatic anuria, initial encounter
- T79.6XXA Traumatic ischemia of muscle, initial encounter

CLINICAL/SURGICAL PEARLS

- The classic triad of muscle pain, weakness, and dark urine suggests rhabdomyolysis.
- Limit operative times especially in obese and muscular patients. Consider high BMI as a risk factor for intraoperative rhabdomyolysis.
- Some advocate not using a kidney rest/bar during laparoscopic surgery to help prevent rhabdomyolysis.
- Appropriately pad all pressure points in the operating room.
- Early recognition and aggressive hydration (better outcomes within the 1st 6 hr of presentation).

RHABDOMYOSARCOMA, PEDIATRIC (SARCOMA BOTRYOIDES)

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BASICS

DESCRIPTION

- Rhabdomyosarcoma (RMS) (sarcoma botryoides) is a malignancy arising from embryonal mesenchyme that tends to occur mostlyin children (Sometimes also called Embryonal Rhabdomyosarcoma)
- Most common soft tissue sarcoma in children
- Sarcoma botryoides describes a polypoid variant of RMS originating in a hollow viscus (vagina, bladder)
- Of all types of pediatric RMS15–20% involve GU system:
  - Paratesticular
  - Bladder
  - Prostate
  - Uterus
  - Vagina

EPIDEMIOLOGY

Incidence

- 0.5–0.7 cases per million children <15 yr
- Bimodal age distribution:
  - 1st peak: 2–4 yr
  - 2nd peak: 15–19 yr
- 3rd most common solid tumor in children (behind neuroblastoma and Wilms tumor)

Prevalence

N/A

RISK FACTORS

See genetics

Genetics

- Li–Fraumeni syndrome:
  - Mutation of p53 tumor suppressor gene
  - Higher incidence of RMS
- Neurofibromatosis:
  - Higher incidence of RMS
- Cytogenetic abnormalities:
  - Alveolar histology subtype:
    - 1;13 translocation (favorable prognosis)
    - 2;13 translocation (unfavorable prognosis)

  - Embryonal histology subtype:
    - Loss of heterozygosity on chromosome 11

PATHOPHYSIOLOGY

- The Latin word “botryoides” refers to the polypoid or “grape-like lesion” appearance of the tumor beneath the mucosa
  - Some sources refer to this as “embryonal RMS”
- Rapid growth with local invasion
- Can spread by lymphatic and hematogenous routes
- Thought to arise from immature cells that are destined to form striated skelet al muscle:
  - However, may arise in locations where skelet al muscle is not typically found, such as the bladder
- Defect in regulatory mechanism that controls proliferation and differentiation of skelet al muscle
- Prognosis and pattern of spread depends on histologic subtype and clinical staging
- Lymph nodes (LNs) and lungs are the most common sites of distant metastasis

ASSOCIATED CONDITIONS

See Genetics

GENERAL PREVENTION

None

DIAGNOSIS

HISTORY

- Family history of malignancy or genetic syndromes (Li–Fraumeni, neurofibromatosis)
- Bladder/prostate:
  - Urinary frequency
  - Stranguria
  - Urinary retention
  - Hematuria
- Paratesticular:
  - Scrotal swelling or pain
  - Back pain
- Vaginal/uterine:
  - Vaginal discharge/bleeding

PHYSICAL EXAM

- Bladder/prostate
  - Abdominal mass
  - Bladder distention
  - Firm prostate or mass on rectal exam
- Paratesticular
  - Scrotal mass
- Vagina/uterine
  - Vaginal mass (may be prolapsing)

- Abdominal mass

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Basic metabolic panel: BUN/Cr may be elevated with ureteral obstruction
- Complete blood count: May see anemia due to vaginal bleeding or hematuria
- β-HCG or AFP: Evaluate for testicular tumors

Imaging

- CT/MRI of abdomen/pelvis: Evaluate local extent of tumor, pelvic or retroperitoneal LN involvement, distant metastasis
- Chest x-ray/CT: Evaluate for pulmonary metastases
- PET scan: Evaluate the metabolic activity of the primary for future comparison after therapy, as well as assess for metastasis
- Bone scan: Evaluate for osseous metastasis
- Scrotal US: Characterize paratesticular mass

Diagnostic Procedures/Surgery

- Bone marrow aspirate/biopsy: Evaluate for metastases for all primary sites of RMS
- Bladder/prostate
  - Cystoscopy: Transurethral resection/biopsy for pathologic diagnosis
  - Image-guided needle biopsy: Pathologic diagnosis
- Paratesticular
  - Radical inguinal orchiectomy: Diagnostic and therapeutic
- Vagina/uterine
  - Cystoscopy/vaginoscopy: Evaluate extent of tumor, biopsy for pathologic diagnosis

Pathologic Findings

- Embryonal:
  - Most common subtype
  - Accounts for majority of GU RMS
  - Embryonal variants associated with excellent prognosis:
    - Sarcoma botryoides
    - Spindle cell/leiomyomatous
- Alveolar:
  - Less common in GU RMS
  - More common in trunk/extremity RMS
  - Higher rates of local recurrence, LN spread, and distant metastasis
- Pleomorphic:
  - Undifferentiated/anaplastic variant
  - Poor prognosis

DIFFERENTIAL DIAGNOSIS

- Bladder/prostate
  - TCC of bladder
  - Inflammatory pseudotumor of bladder
  - Nephrogenic adenoma of bladder

  - Fibroepithelial polyps of prostatic urethra
- Testis
  - Primary testicular tumor
  - Benign adnexal mass
- Vagina/uterine
  - Prolapse of ureterocele, urethra, vagina

TREATMENT

GENERAL MEASURES

- Pre- and post-op staging and risk classification are critical in evaluation and treatment planning
  - Preoperative staging: Intergroup Rhabdomyosarcoma Study Group (IRSG) staging/classification system based on TNM and primary location
  - Postoperative grouping: IRSG grouping based on primary resection
  - Risk classification: Combines stage, group, and histology—helps determine therapy and prognosis
- Preoperative staging: TNM system
  - T1: Confined to organ of origin
    - (a) ≤5 cm in diameter
    - (b) >5 cm in diameter
  - T2: Extension or fixed to surrounding tissue
    - (a) ≤5 cm in diameter
    - (b) >5cm in diameter
  - N0: Regional LNs clinically negative
  - N1: Regional LNs clinically positive
  - Nx: Unknown
  - M0: No distant metastasis
  - M1: Metastasis present
- Preoperative staging: IRSG
  - Stage 1: Vaginal and paratesticular, any T, any N, M0
  - Stage 2: Bladder/prostate, T1/T2a, N0/Nx, M0
  - Stage 3 Bladder/prostate, T1/T2a and N1, *OR* T1b/T2b, any N, M0
  - Stage 4: Any T, M1
- Postoperative grouping
  - Group I: Localized disease, completely excised, no microscopic residual
    - (a) Confined to site of origin, completely resected
    - (b) Infiltrating beyond site of origin, completely resected
  - Group II: Total gross resection
    - (a) Gross resection with microscopic local residual
    - (b) Regional disease with involved LNs, completely resected, no microscopic residual
    - (c) Microscopic local or nodal residual
  - Group III: Incomplete resection with gross residual disease or biopsy only for diagnosis
  - Group IV: Distant metastasis
- Risk grouping

  - Low risk
    - Embryonal histology, Stage 1, all groups
    - Embryonal histology, Stage 2/3, Group I/II
  - Intermediate risk
    - Embryonal histology, Stage 2/3, Group III
    - Alveolar histology, Stage 1/2/3, Group I/II/III
  - High risk
    - Any histology, Stage 4, Group IV
- All sites of GU RMS require a multidisciplinary approach to curative therapy including appropriate surgical excision, chemotherapy, and radiation (1)
- For bladder/prostate and vaginal/uterine RMS, chemotherapy is 1st-line therapy after biopsy and before radiation or extirpative surgery in all cases except rare instances amenable to immediate partial cystectomy with negative margins
- For paratesticular RMS, retroperitoneal staging is critical. Any boys <10 yr with radiologic evidence of enlargedretroperitoneal LNs, and all patients >10 yr should have an ipsilateral retroperitoneal LN dissection (RPLND). Thisshould be done to complete staging and must be done before chemotherapy or radiation (1).

MEDICATION

First Line

- Bladder/prostate
  - Low risk: Vincristine, actinomycin-D (VA)
  - Low-risk N1, intermediate risk, high-risk: VA + Cyclophosphamide (VAC)
- Paratesticular
  - VA: Stage 1, <10 yr, no evidence of LN involvement on imaging (1)
  - VAC: Positive LNs on RPLND
- Vagina/uterine (1)
  - VAC: Chemotherapy followed by repeat biopsy to assess residual disease

Second Line

- 2nd-line chemotherapy with addition of carboplatin, etoposide, irinotecan, or topotecan
- Phase I studies

SURGERY/OTHER PROCEDURES

- Bladder/prostate:
  - Partial cystectomy: Primary treatment in rare cases at dome/lateral wall where adequate margins can be obtained
  - Radical cystectomy: Performed after chemotherapy or chemoradiation if tumor not amenable to bladder-sparing options
  - Urinary diversion: Both temporary and permanent reconstructive options
  - Radical prostatectomy: Performed for isolated prostatic tumors after chemoradiotherapy
- Paratesticular:
  - Radical inguinal orchiectomy: All cases should be approached inguinally with radical resection
  - RPLND (2):
    - All >10 yr regardless of imaging

- <10 yr if evidence of LN involvement on imaging, prior to chemotherapy
- Vagina/uterine:
  - Vaginectomy: If evidence of residual disease on postchemotherapy biopsy

ADDITIONAL TREATMENT

Radiation Therapy

- Bladder/prostate:
  - Postdiagnostic biopsy, in addition to chemotherapy: Most cases (Group III)
  - Following initial attempted resection initial resection with residual margins, in addition to chemotherapy: Group II
- Paratesticular:
  - Positive LNs on RPLND
- Vagina/uterus:
  - After chemotherapy or surgical resection unless an initial upfront resection (Group I)

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Bladder/prostate:
  - 3-yr disease-free survival (3)
    - Embryonal: 83% (Botryoid variant: 92%) (4)
    - Alveolar: 40%
- Paratesticular:
  - 3-yr disease-free survival: 81% (3)
  - Overall survival: 96%
- Vagina/uterine:
  - 5-yr disease-free survival: 69% (3)
  - Overall survival: 82% (94%in those <10 yr, 76% in those >10 yr) (5)

COMPLICATIONS

- Bladder/prostate
  - Bladder dysfunction
  - Hematuria/dysuria
  - Secondary malignancy
  - Incontinence
- Paratesticular
  - Complications of RPLND
    - Bowel obstruction
    - Ejaculatory dysfunction
- Vaginal/uterine
  - Infertility

  – Sexual dysfunction
- Chemotherapy-related toxicity
  – Neurotoxicity
  – Secondary malignancy

FOLLOW-UP

Patient Monitoring

- Follow up imaging to assess for recurrent disease
- Assessment of residual bladder/vaginal function (exam, labs, urodynamics)

Patient Resources

http://www.curesearch.org/

REFERENCES

1. Wu HY, Snyder HM 3rd. Pediatric urologic oncology: Bladder, prostate, testis. *Urol Clin North Am.* 2004;31:619–627.
2. Wiener ES, Anderson JR, Ojimba JI, et al. Controversies in the management of paratesticular rhabdomyosarcoma: Is staging retroperitoneal lymph node dissection necessary for adolescents with resected paratesticular rhabdomyosarcoma? *Semin Pediatr Surg.* 2001;10:146–152.
3. Wu HY, Snyder HM 3rd, Womer RB. Genitourinary rhabdomyosarcoma: Which treatment, how much, and when? *J Pediatr Urol.* 2009;5:501–506.
4. Leuschner I, Harms D, Mattke A, et al. Rhabdomyosarcoma of the urinary bladder and vagina: A clinicopathologic study with emphasis on recurrent disease. A report from the Kiel Pediatric Tumor Registry and the German CWS Study. *Am J Surg Pathol.* 2001;25:856–864.
5. Arndt CA, Donaldson SS, Anderson JR, et al. What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? *Cancer.* 2001;91:2454–2468.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Bladder Mass, Differential Diagnosis
- Bladder Tumors, Benign and Malignant, General Considerations
- IRS (Intergroup Rhabdomyosarcoma Study) Clinical Classification
- Rhabdomyosarcoma, Pediatric (Sarcoma Botryoides) Images ☼
- Testis, Tumor, and Mass, Pediatric, General
- Vaginal Mass, Newborn

CODES

ICD9

- 171.6 Malignant neoplasm of connective and other soft tissue of pelvis
- 171.9 Malignant neoplasm of connective and other soft tissue, site unspecified
- 184.9 Malignant neoplasm of female genital organ, site unspecified

ICD10

- C49.5 Malignant neoplasm of connective and soft tissue of pelvis
- C49.9 Malignant neoplasm of connective and soft tissue, unsp
- C57.9 Malignant neoplasm of female genital organ, unspecified

CLINICAL/SURGICAL PEARLS

- Radical upfront surgery should be avoided with the goal of organ preservation.
- Small residual masses may not require resection if such surgery would lead to morbidity.

SACRAL AGENESIS, UROLOGIC CONSIDERATION

Nicholas G. Cost, MD
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BASICS

DESCRIPTION

- The partial or complete absence of 2 or more lower vertebral bodies
- May be occult or associated with voiding dysfunction

EPIDEMIOLOGY

Incidence

- 1 in 25,000 live births
- 16% of children with sacral agenesis (SA) have a diabetic mother (1)
- 80% of cases are detected during infancy
- 20% of cases go undetected until difficulty with toilet training (at 3–4 yr of age) (1)

Prevalence

None

RISK FACTORS

- Maternal insulin-dependent diabetes
- Maternal drug exposure (Minoxidil noted in case reports) (2)
- Genetic predispositions, see "Genetics"

Genetics

- Mutations in HLXB9 gene on chromosome 7 involved in neural plate infolding (3)
- Deletion of chromosome 7q
- Currarino syndrome (4)
  - Autosomal dominant
  - Mutation in HLXB9 on chromosome 7
  - Presacral mass, sacral agenesis, anorectal malformation

PATHOPHYSIOLOGY

- Failure of fusion or formation of lower vertebral bodies—ie, caudal regression syndrome
- Spectrum of anomalies including meningocele and anorectal malformations
- Urologic manifestations (5):
  - Upper motor neuron (UMN) lesions (35%)
    - Detrusor hyperreflexia
    - Detrusor sphincter dyssynergia (DSD)
  - Lower motor neuron (LMN) lesions (40%)
  - No neurologic deficit (25%)

ASSOCIATED CONDITIONS

- Maternal diabetes
- Tethered cord/tethered cord syndrome

- VACTERL/VATER Association
- Currarino syndrome
  - Form of caudal regression syndrome
  - Hemisacrum, anorectal malformations, and a presacral mass

GENERAL PREVENTION
Avoid maternal exposures to potentially causative agents

DIAGNOSIS
HISTORY
- Urinary tract infections (UTIs) in 75% of affected children
- Gestational/birth history
- Maternal drug exposure
- Gestational diabetes
- Toilet training history
- Bowel function/constipation

PHYSICAL EXAM
- Sacral dermatome sensation is usually intact
- Lower extremity strength is usually normal
- High arched feet, claw/hammer toes are possible findings
- Flat buttocks
- Low-riding, short gluteal cleft
- Palpation of coccyx and sacrum for abnormalities
- Assess for anal location and reflex
  - Bulbocavernosal reflex: Gently squeeze head of penis or clitoris and observe for anal wink
    - Present in most UMN lesion, absent in most LMN lesions

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Assess metabolic panel

Imaging
- Lateral x-ray of lower spine
  - Confirms absence of lower vertebral bodies
  - Eliminates obscured image due to bowel gas on an anterior–posterior view
- Prenatal/postnatal ultrasound (US)
  - Can detect defect after ossification is complete at 18-wk gestation
  - Can be used to evaluate kidneys and bladder once diagnosis is confirmed
- Magnetic resonance imaging (fet al or postnatal)
  - Confirms diagnosis, often shows sharp cutoff of conus medullaris at T12

Diagnostic Procedures/Surgery
- Video urodynamics/voiding cystourethrogram
  - UMN lesion: Detrusor overactivity, exaggerated sacral reflexes, no voluntary sphincter control, detrusor sphincter dyssnergia (DSD), no evidence of sphincter denervation (5)
    - Bladder may appear thick walled with closed bladder neck (1)

- LMN lesion: Detrusor acontractility, diminished sacral reflexes, denervation of sphincter
  - Bladder appears smoothed walls with open bladder neck
- Vesicoureteral reflux (VUR) in 37% (1)

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Spectrum of anomalies that include myelomeningocele and other spinal dysraphisms
- Anorectal malformations
- Sacrococcygeal teratoma
- Presacral mass

TREATMENT

GENERAL MEASURES

- Bladder management
  - Consideration for clean intermittent catheterization regimen depending on status of ability to empty bladder and low pressure, state of the upper urinary tracts, and renal function status
  - Potentially utilizing anticholinergics in the setting of high-pressure neurogenic bladder
- Bowel management
  - Identify and treat constipation
  - Anorectal manometry
- Orthopedics consultation

MEDICATION

First Line

- UMN Lesions: Anticholinergics
  - Oxybutynin (Ditropan)
    - 1 yr: No dose established
    - 1–5 yr: 0.2 mg/kg PO BID–QID
    - 5–12 yr: 5 mg PO BID–TID (15 mg/d max)
    - >12 yr: Adult dose: 5 mg PO BID–QID
    - XL form: 5–20 mg/d

Second Line

- UMN lesions
  - Alternate anticholinergics, many not approved for children but used “off-label”

SURGERY/OTHER PROCEDURES

- UMN lesions
  - Augmentation cystoplasty may be necessary depending on bladder capacity and compliance
  - Done in conjunction with continent catheterizable channel (ie, Mitrofanoff)
  - May require reconstructive surgery for the bladder outlet if there is concomitant incontinence from an open bladder neck.
- LMN Lesions

  - Endoscopic injections of bulking agents to help with bladder neck continence
  - May require reconstructive surgery for the bladder outlet if there is concomitant incontinence from an open bladder neck
  - May require continent catheterizable channel (ie, Mitrofanoff) to reliably empty the bladder
- Ureteral reimplantation or endoscopic bulking agent at the ureteral orifices for persistent VUR
- Bowel management may require enemas and even include the creation of a continent catheterizable channel for antegrade enemas (MACE [Malone antegrade continence enema])

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Best prognosis for successful toilet training and management of sequelae is when defect is detected early and when the child has normal lowerextremity function.

COMPLICATIONS

- Renal function deterioration
  - Potential for high-pressure urinary storage transmitted to the kidneys which is deleterious for renal function
  - Scarring from VUR and recurrent UTI
- Social and developmental difficulties associated with fecal/urinary incontinence

FOLLOW-UP

Patient Monitoring

- Renal/bladder US at regular intervals
  - Monitor status of upper urinary tracts
- Basic metabolic panel
  - Monitor renal function by a calculated glomerular filtration rate using serum creatinine
- Voiding cystourethrogram to follow status of VUR as needed
- Urodynamics every year or every other year to ensure bladder is of a safe capacity and compliance to avoid a setup detrimental to renal health

Patient Resources

- The International Sacral Agenesis Caudal Regression Association (iSACRA)
  - https://sites.google.com/site/caudalregressionsyndrome/

REFERENCES

1. Wilmshurst JM, Kelly R, Borzyskowski M. Presentation and outcome of sacral agenesis: 20

years' experience. *Dev Med Child Neurol.* 1999;41:806–812.
2. Rojansky N, Fasouliotis SJ, Ariel I, et al. Extreme caudal agenesis. *J Reprod Med.* 2002;47:241–245.
3. Ross AJ, Ruiz-Perez V, Wang Y, et al. A homeobox gene, HLXB9, is the major locus for dominantly inherited sacral agenesis. *Nat Genet.* 1998;20(4):358–361.
4. Lynch SA, Wang Y, Strachan T, et al. Autosomal dominant sacral agenesis: Currarino syndrome. *J Med Genet.* 2000;37(8):561–566.
5. Boemers TM, van Gool JD, de Jong TP, et al. Urodynamic evaluation of children with caudal regression syndrome (caudal dysplasia sequence). *J Urol.* 1994;151:1038–1040.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Caudal Regression Syndrome
- MACE (Malone Antegrade Continence Enema)
- Myelodysplasia (Spinal Dysraphism), Urologic Considerations
- Neurogenic Bladder, General
- Sacral Agenesis Image ☼
- Spina Bifida/Spina Bifida Occulta, Urologic Considerations
- Tethered cord/Tethered Cord Syndrome
- VACTERL/VATER Association

CODES

ICD9

- 344.61 Cauda equina syndrome with neurogenic bladder
- 596.55 Detrusor sphincter dyssynergia
- 756.13 Absence of vertebra, congenital

ICD10

- N32.81 Overactive bladder
- N32.89 Other specified disorders of bladder
- Q76.49 Other congenital malformations of spine, not associated with scoliosis

CLINICAL/SURGICAL PEARLS

- There is variability in the level of neurologic insult and resulting in bladder dysfunction. This ranges from a UMN lesion with bladderhyperreflexia to an LMN lesion with areflexia.
- Aggressive medical management with anticholinergics and CIC may prevent renal damage and the need for major reconstructive surgery.

SARCOIDOSIS, UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Sarcoidosis is a systemic granulomatous disease with unknown etiology; it is characterized by the formation of noncaseating granulomas, primarily in the lungs, but also throughout the rest of the body.
- Hypercalcuria is more common than hypercalcemia.
  - Renal stones secondary to hypercalcuria can be associated in up to 14% of patients. Occasionally, this can be the presenting complaint that leads to the diagnosis of sarcoidosis.
- Other urologic manifestations of sarcoidosis are rare. These include acute interstitial nephritis, neurogenic bladder dysfunction secondary to neurosarcoidosis, renal pseudotumors, bladder sarcoidosis with gross hematuria, and ureteral obstruction due to retroperitoneal adenopathy or fibrosis.

EPIDEMIOLOGY

Incidence

- In US, sarcoidosis is 10 times more common in African Americans than in whites (AA: 35–64/100,000; whites: 10–14/100,000)
  - African Americans have a 2.4% lifetime risk of developing the disease, whereas in Caucasian Americans and Europeans, the incidence is lower
- Female > Male
- Onset is most often before age 50. Peak is age 20–39 (1)[A]
- Sarcoidosis affects both men and women, but it seems to be most prevalent among African American women

Prevalence

1–40 cases per 100,000 population

RISK FACTORS

- Many organisms have been linked, including *Mycoplasma* sp., fungi, *Histoplasma* and *Cryptococcus* spp.; viruses, and Propionibacterium (2)[B].
- Environmental exposures to noninfectious agents, such as aluminum, zirconium, talc, pine tree pollen, and clay, have also been implicated.

Genetics

- Familial clustering of cases has been reported. Monozygotic twins who have sarcoidosis are 2–4 times as likely to have the disease as dizygotic twins.
- Most common allele found in sarcoidosis is HLA-B8. Other associated alleles include HLA-A1 and HLA-DR3.

PATHOPHYSIOLOGY

- The cause of sarcoidosis is unknown. Symptoms are extensive and can involve pulmonary, arthritic, skin lesions, and manifestations relative to specific organ involvement.
- It is suspected that the granulomas of sarcoidosis are caused by an abnormal immunologic response to a stimulus.
- The most common presentation is pulmonary: Bilateral hilar adenopathy (50%). Less common is bilateral hilar adenopathy and pulmonary infiltrate (25%) and pulmonary infiltrate alone (15%). Other presenting manifestations include cough, wheezing, fever, malaise, fatigue, hepatomegaly, splenomegaly, night sweats, and uveitis.
- Hypercalcemia:
  - Present in at least 20–30% of patients with sarcoidosis.
  - Sarcoidosis may cause resorptive hypercalciuria and urolithiasis.
  - The sarcoid granuloma produces 1,25 $(OH)_2D_3$ (calcitriol), causing increased intestinal absorption of calcium, hypercalcemia. 60% develop hypercalciuria (3)[A].
  - Pulmonary alveolar cells and lymph node in patients with sarcoidosis are capable of synthesizing vitamin D; this is usually a function limited to the kidney.
  - Most patients with sarcoidosis have a suppressed level of PTH secondary to hypercalcemia.
  - Secondary hyperoxaluria can be seen.
  - Most sarcoidosis stones are calcium oxalate.
- Glomerular involvement is very rare and may include:
  - Membranous nephropathy, IgA nephropathy, minimal-change disease, proliferative or crescentic glomerulonephritis, and focal glomerulosclerosis.
  - Interstitial nephritis with granuloma formation is relatively common in sarcoidosis.
- Tubulointerstitial nephritis and uveitis (TINU) syndrome is idiopathic; these patients should be evaluated for sarcoidosis and Sjögren syndrome.
- Prostatic involvement has been reported.

ALERT
A diagnosis of sarcoidosis should always be considered when patients present with renal calculi of unknown origin.

ASSOCIATED CONDITIONS

Erythema nodosum

GENERAL PREVENTION

N/A

DIAGNOSIS

HISTORY

- Sarcoidosis can involve any organ system; the clinical presentation is variable and insidious.
- Patients most commonly present in winter and early spring, which suggests a possible environmental trigger.
- Cutaneous involvement is seen in 25% of patients with sarcoidosis. It may accompany systemic involvement.

- Fever, anorexia, and polyarthralgias.
- Dyspnea on exertion, cough, chest pain, and occasionally hemoptysis.

PHYSICAL EXAM
- Cutaneous involvement may be present (lupus pernio, erythema nodosum)
  - Most common sites are face, upper back, trunk, or extremities (3)[A]
- Wheezing
- Adenopathy
- Some cases of involvement of testis and epididymis, range from induration to painless mass
- Neurologic symptoms

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Sterile pyuria and mild proteinuria
- Leukopenia and/or thrombocytopenia are common.
- Eosinophilia: 24%
- Anemia: 5%
- Hypercalciuria: 49%
- Hypercalcemia: 13%
- Elevated calcitriol levels
- Serum ACE level is elevated in 60% of patients; therefore, this test is not sensitive in diagnosing sarcoidosis.
- BUN and Cr may be elevated if there is renal involvement.

Imaging
- Chest imaging may demonstrate hilar adenopathy or pulmonary infiltrate present in 90% of sarcoidosis patients.
- Abdominal imaging may show hepatomegaly, retroperitoneal adenopathy, and retroperitoneal fibrosis.
- Stones and nephrocalcinosis secondary to hypercalcemia can be seen on CT.
- Sarcoid renal pseudotumors can mimic renal cell carcinoma, and more diffuse enlargement may mimic lymphoma. Retroperitoneal lymph nodes may enlarge sufficiently in sarcoidosis to cause obstruction.
- In rare cases of urinary involvement, ureterohydronephrosis may be seen from urolithiasis or obstruction.

Diagnostic Procedures/Surgery
- Many physicians prefer a biopsy to confirm the diagnosis of sarcoidosis.
  - Mediastinoscopy is utilized to assess hilar adenopathy.
  - Fiberoptic bronchoscopy with transbronchial biopsy is used for biopsy documentation of pulmonary sarcoidosis.
  - Biopsy of renal mass (especially atypical in appearance) in patient with sarcoid to distinguish from RCC.
- Bladder involvement confirmation requires transurethral bladder resection.
- Sarcoidosis can also be differentiated from other diagnoses by the rapid resolution of hypercalcemia with initiation of corticosteroid therapy.
- In cases of bilateral testicular masses in man with sarcoid and negative markers, consider

testes sparing approach (3)[C].

Pathologic Findings

Typical sarcoid lesions are characterized by the presence of circumscribed granulomas of epithelioid cells with little or no necrosis (noncaseating granuloma).

DIFFERENTIAL DIAGNOSIS

- Interstitial lung diseases:
  - Medications (nitrofurantoin, methotrexate), idiopathic pulmonary fibrosis, collagen vascular diseases, amyloidosis, hypersensitivity pneumonitis, granulomatous vasculitis, collagen vascular diseases
  - Other granulomatous diseases: TB, brucellosis, Q fever, biliary cirrhosis, Wegener granulomatosis, Hodgkin disease
- Other skin and arthritic disorders
- Other causes of hypercalcemia/hypercalcuria:
  - PTH-related malignancy, vitamin D-related mediations (eg, lithium), endocrine disorders, immobilization
- Causes of interstitial nephritis:
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Wegener granulomatosis
  - Behçet disease

TREATMENT

GENERAL MEASURES

- Sarcoidosis remains a diagnosis of exclusion. Before a definitive diagnosis can be made, multiple other conditions that can share similar symptomatology and pathologic findings must be ruled out (See “Differential diagnosis” above).
- Coordination of care is suggested with experts in the management of the systemic and pulmonary manifestations of the disease.
- Corticosteroids are the mainstay of therapy for most manifestations of sarcoidosis.
- For sarcoidosis-related renal disease, the primary management is steroid therapy. Although many have poor renal function on presentation, patients may respond dramatically to steroid therapy. The steroids are given at high dose for 1–2 mo then reduced for the remainder of the course, which should be at least 1 yr.
- Hydration and limiting sodium intake can reduce hypercalcuria.

MEDICATION

First Line

- Oral corticosteroids are the treatment of choice for patients with hypercalcemia and systemic involvement.
  - Initial prednisone 40 mg/d, PO which is tapered to every other day over several weeks for long-term therapy; typically 10–15 mg PO every other day
- Nephropathy due to sarcoidosis appears to respond to steroid therapy.

Second Line

- Inhaled steroids
- Methotrexate
- Chloroquine

SURGERY/OTHER PROCEDURES
- Biopsy is necessary for diagnosis.
- Obstruction may require diversion.
- Surgical management of urolithiasis

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
- The course of the disease is variable.
- Spontaneous remission occurs in 50% of patients.
- 1/3 of patients have eventual improvement.
- 10–30% of patients have chronic or progressive disease.

COMPLICATIONS
- Renal lithiasis, gross hematuria, ureteral obstruction, neurogenic bladder dysfunction
- Renal failure is rare and is due to hypercalcemic nephropathy.

FOLLOW-UP
Patient Monitoring
History, physical exam, chest x-ray, pulmonary function tests, and serum chemistry

Patient Resources
- National Heart Lung and Blood Institute. http://www.nhlbi.nih.gov/health/health-topics/topics/sarc/
- UpToDate. http://www.uptodate.com/contents/sarcoidosis-beyond-the-basics

REFERENCES
1. Rybicki BA, Major M, Popovich J Jr, et al. Racial differences in sarcoidosis incidence: A 5 year study in a health maintenance organization. *Am J Epidemiol*. 1997;145:234–241.
2. Culver DA. Sarcoidosis. *Immunol Allergy Clin N Am*. 2012;32:487–511.
3. La Rochelle JC, Coogan CL. Urological manifestations of sarcoidosis. *J Urol*. 2012;187:18–24.

ADDITIONAL READING
- Fitzpatrick KJ, Chancellor MB, Rivas DA, et al. Urologic manifestations of spinal cord

sarcoidosis. *J Spinal Cord Med.* 1996;19(3):201–203.
- Koyama T, et al. Radiologic manifestations of sarcoidosis in various organs. *Radiographics.* 2004;24:87–104.
- Rao PK. Sabanegh ES. Genitoruinary sarcoidosis. *Rev Urol.* 2009;11:108–113.
- Rehman J, Rizkala ER, Chughtai B, et al. Hypoechoic testicular mass: A case of testicular and epididymal sarcoidosis. *Urology.* 2005;66(3):657.

See Also (Topic, Algorithm, Media)
- Hypercalcemia, Urologic Considerations
- Urolithiasis, Adult, General

CODES

ICD9
- 135 Sarcoidosis
- 275.40 Unspecified disorder of calcium metabolism
- 592.0 Calculus of kidney

ICD10
- D86.9 Sarcoidosis, unspecified
- E83.52 Hypercalcemia
- N20.0 Calculus of kidney

CLINICAL/SURGICAL PEARLS
- Sarcoidosis may cause resorptive hypercalciuria and urolithiasis.
- Retroperitoneal lymph nodes may enlarge sufficiently in sarcoidosis to cause obstruction..
- Consider a diagnosis of sarcoidosis in patients presenting with nephrolithiasis of unknown etiology, especially in an African American female.
- For sarcoidosis-related renal disease, oral corticosteroids is the mainstay of treatment.

SCROTUM AND TESTICLE, MASS

Jay Simhan, MD
Jack H. Mydlo, MD

BASICS

DESCRIPTION
- A mass in the scrotum or testicle can be noted by the patient or during physical exam
- Lesions can be in scrotal wall, testicle, or paratesticular tissues
- Testicular masses can be distinguished from other common intrascrotal masses (hydrocele, varicocele, spermatocele, epididymal cyst, hernia) based on exam or imaging studies
- Most palpable testicular tumors in adults are malignant; 80% nonpalpable lesions are benign.
- Children with testicular tumors are more likely to have benign lesions (20–40% benign).

EPIDEMIOLOGY
Incidence
8,820 cases of testicular cancer in the US in 2014 with 380 deaths

Prevalence
- Testicular tumors: 0.05–2/100,000 children
- Lifetime risk 1/270

RISK FACTORS
- Malignancy: Cryptorchidism, prior testicular neoplasm or hematopoietic malignancy, HIV, family history of testicular cancer, marijuana use
- Benign mass: Recent trauma, UTI, STDs, viral illness, urethral instrumentation, congenital anomalies, previous history of scrotal surgery

Genetics
- Chromosome 12 alterations in testicular cancer:
  – Genetics associated in 33% of cases
  – 2.2% incidence in brothers of patients with testicular cancer

PATHOPHYSIOLOGY
- Depends upon the etiology of the mass
- Differential diagnosis can be narrowed based on patient's age and history

ASSOCIATED CONDITIONS
Inguinal hernia in pediatric hydrocele

GENERAL PREVENTION
None (testicular self-exam may help diagnose)

DIAGNOSIS

HISTORY
- Age of the patient

  - Tumor types are age-specific
  - Torsion usually in prepubertal age group
- Description of the mass
  - Small, discrete mass commonly neoplastic
  - Diffuse enlargement with tenderness seen with infection, torsion, or trauma
- Associated pain
  - Torsion: Sudden, severe, unilateral pain with nausea and vomiting. If torsion intermittent, pain may wax and wane; may have pain during sleep
  - Neoplasms rarely cause severe pain, usually described as dull ache or fullness
  - Orchitis pain may gradually increase as infection causes increased inflammation
- Referred pain to the scrotum without a mass can be due to renal colic, or nerve root irritation
- Prior scrotal surgery: Orchidopexy for cryptorchidism; increased risk of cancer; malignancy; postvasectomy granuloma
- History of trauma, surgery, any radiation
- Previous UTI or current lower UTI complaints suggests orchitis ± epididymitis
- Urethral discharge suggests STD-concurrent *epididymo-orchitis* (*Chlamydia* and gonorrhea are most common in men < 35 yr of age).
- Urethral instrumentation: Ascending infection
- Current illnesses: Mumps, UTI
- Medical problems: Diabetes mellitus, immunodeficiency, neurologic disorders, autoimmune disorders, others
- Fever, weight loss, nausea, vomiting, hemoptysis, shortness of breath, and back pain can all be clues to possible metastatic testicular neoplasm.
- Nausea and vomiting in torsion or orchitis

ALERT
- Evaluate scrotal swelling and testicular masses urgently.
- Solid, firm testicular mass must be considered testicular cancer until proven otherwise.
- Patients may present with complaint of testicular mass when they have paratesticular mass instead.

PHYSICAL EXAM
- Fever can be marker for infection, tumor necrosis, or testicular necrosis
- Mumps orchitis: 30% with mumps parotitis, onset 3–7 days following the parotitis
- Gynecomastia: Germ cell or Leydig cell tumor
- Abdomen:
  - Retroperitoneal lymphadenopathy from metastatic tumors can sometimes be palpated
  - Palpate for signs of hernia
- Testes:
  - Evaluate if testicular vs. paratesticular mass
  - Evaluate for associated pain on palpation
  - Neoplastic/cystic processes usually painless
  - Torsion or epididymoorchitis is exquisitely tender
  - Phren sign: Scrotal elevation relieves pain in epididymitis, but worsens pain or no effect

with torsion; not reliable
- Discrete lesion vs. diffuse swelling:
  – Most early-stage neoplasms or cysts are palpable discrete masses
  – Orchitis and torsion lead to generalized testicular enlargement
- Position of mass in testicle:
  – May be high riding or in altered position in torsion
  – Bell clapper deformity: In torsion, occurs when the testicle is situated in a horizontal lie with the long axis in the anteroposterior direction
- Scrotum:
  – Evaluate if the mass is within testicle, epididymis, spermatic cord, or scrotal wall
  – Edema and erythema: Torsion or orchitis
  – Evaluate for prior scrotal scars/past surgery
  – Transilluminate to evaluate for hydrocele
  – Valsalva maneuver to elicit varicocele
  – Cremasteric reflex: Stroke upper thigh and observe ipsilateral testicle/scrotum for contraction (absent in torsion)
- Penis: Ulcers, induration, or discharge can be seen in epididymoorchitis (STD)
- Epididymis:
  – Normally located posterior to testicle
  – Pain or swelling helps make diagnosis of *epididymo-orchitis.* If severe, difficult to demarcate epididymis from testicle
- Extremities:
  – Swelling due to malignant retroperitoneal lymphadenopathy or venous thrombosis
- Neurologic exam
- Lymphatics:
  – Testicular tumor metastasizes to pelvic and retroperitoneal nodes, not inguinal nodes; tender or enlarged inguinal nodes are associated with infection
- Rectal exam: Evidence of prostatitis
- Skin: Signs of cellulitis, swelling, discoloration, or breaks in skin:
  – Blue dot sign: Torsion of the appendix testes

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- WBC count to evaluate for infection or leukemia/lymphoma
- HCT to evaluate for anemia associated with malignancy
- Urine analysis and urine culture: May suggest the diagnosis of orchitis or epididymitis
- Hematuria and proteinuria: Viral infection
- Pyuria and bacteriuria: Bacterial infection
- Tumor markers:
  – AFP: Elevated in embryonal cell carcinomas, teratocarcinoma, yolk sac tumors, or combined tumors, but never increased in pure seminomas
  – β-hCG: Elevated in all choriocarcinomas and some embryonal cell carcinomas, yolk sac carcinomas, and seminomas
  – LDH: Nonspecific; elevated in metastatic disease
- Urethral swab to rule out gonorrhea/Chlamydia

Imaging (1)

- Ultrasound, US (diagnostic procedure of choice):
  - 95% sensitivity for testicular tumor diagnosis
  - Specificity for malignancies is lower since US detects benign lesions as well
  - Most testicular tumors have hypoechoic areas, but overall heterogeneity of the lesion is common
  - Color flow Doppler is essential for the differentiation of torsion from *epididymo-orchitis:*
    - Decreased blood flow with torsion
    - Increased blood flow with *epididymo-orchitis*
    - Will also sometimes show increased vascularity in testicular neoplasms
- MRI: Minor role in testicular masses; can help evaluate intratesticular masses that are difficult to visualize or characterize on US
- Nuclear scintigraphy is most useful for testicular torsion, but is less convenient than US

Diagnostic Procedures/Surgery

Biopsy is avoided if there is suspicion for testicular neoplasm.

Pathologic Findings

See specific Section I and II topics.

DIFFERENTIAL DIAGNOSIS

- Adult/pediatric painful mass:
  - *Epididymo-orchitis:* bacterial, STD, mumps, TB
  - Fournier gangrene
  - Henoch–Schönlein purpura (usually no mass)
  - Incarcerated/strangulated hernia
  - Post-vasectomy syndrome (usually no mass)
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle, testicular, or epididymal appendage)
  - Tumor (infrequent unless traumatized or rapidly growing; see differential diagnosis below)
- Adult painless mass:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Adenocarcinoma of the rete testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea
  - Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of the cord
  - Lipoma of the cord
  - Mesothelioma of tunica vaginalis
  - Polyorchidism
  - Paratesticular sarcomas: Rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma
  - Scrotal edema (insect bite, nephrotic syndrome, acute idiopathic scrotal edema)
  - Scrotal wall: Sebaceous and inclusion cysts, idiopathic calcinosis, fat necrosis, malignancy
  - Sperm granuloma following vasectomy
  - Spermatocele (epididymal cyst)

- Testicular cysts (simple, tunica albuginea, epidermoid)
- Testicular tumor:
  - Germ cell tumors (95% of testicular malignancies): Seminoma, embryonal cell carcinoma, choriocarcinoma, yolk sac carcinoma teratoma (1–5%), teratocarcinoma
  - Gonadal stromal tumors: Leydig tumor, Sertoli cell, granulosa cell tumors
  - Metastatic tumors: Prostate, lung, and GI tract; rare kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Mixed germ cell and stromal tumor (gonadoblastoma)
  - Angioma, fibroma, leiomyoma, hamartoma, carcinoid, mesothelioma, and neurofibroma
  - Malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)
  - Leukemia or lymphoma
- Varicocele

• Pediatric painless mass:
- Similar to adult list; most common are: Hydrocele, hernia, varicocele, testicular teratoma, adrenal rest tumors, rhabdomyosarcoma

TREATMENT

GENERAL MEASURES

• Scrotal ultrasound is indicated in most cases of scrotal mass
• Testicular torsion is an emergency and requires immediate evaluation

MEDICATION

First Line

• Cause-specific treatment, as well as supportive care, should be applied to cases of orchitis: Bed rest, scrotal support, ice bags, and analgesics.
• Broad-spectrum antibiotics should be administered if a bacterial source is suspected.
• A patient's sexual partners should be treated if STD is the cause.

Second Line

N/A

SURGERY/OTHER PROCEDURES

• Testicular neoplasms: Radical orchiectomy with high ligation of the spermatic cord; inguinal incision:
- Testicular biopsy or orchiectomy through a scrotal approach is contraindicated if there is the possibility of neoplasm.

• Cystic lesions are difficult to differentiate from neoplastic lesions and are usually removed as above for testicular neoplasms.
• In children, testis-sparing surgery for benign lesions such as teratoma, Leydig cell tumor, and epidermoid cyst based on frozen biopsy findings.

ADDITIONAL TREATMENT

Radiation Therapy

Seminoma or some sarcomas

Additional Therapies

Chemotherapy for advanced testicular tumors

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS

- Neoplasms: See tumor types in Section I or II.
- Cystic lesions: Simple periodic exam.
- Torsion: Evaluation in 6–12 mo to check for testicular atrophy and presence of new masses:
  – Infertility noted as a long-term problem.
- Orchitis: If primary cause resolved, no follow-up needed.
  – In prepubertal patients, *epididymo-orchitis* may be due to underlying urinary tract anomaly. These patients need structural evaluation of their urinary tracts.
- Trauma: After documentation of adequate healing, no follow-up is required.

COMPLICATIONS

Infertility; complications secondary to radiation or chemotherapy

FOLLOW-UP

Patient Monitoring

- Patients should be advised to perform monthly testicular self-exams.
- Patients diagnosed with cancer should have disease-specific follow-up.

Patient Resources

Medline Plus: Scrotal masses.
http://www.nlm.nih.gov/medlineplus/ency/article/001283.htm

REFERENCES

1. Rybenstein RA, Dogra VS, Seftel AD, et al. Benign intrascrotal lesions. *J Urol.* 2004;171:1765–1772.
2. Chandra RV, Dowling RJ, Ulubasoglu M, et al. Rational approach to diagnosis and management of blunt scrotal trauma. *Urology.* 2007;70(2):230–234.
3. Tiemstra J, Shailendra K. Evaluation of scrotal masses. *Fam Physician.* 2008;78(10):1165–1170.

ADDITIONAL READING

- Khoubehi B, Mishra V, Ali M, et al. Adult paratesticular tumours. *BJU Int.* 2002;90(7):707–715.
- Park SB, Lee WC, Kim JK, et al. Imaging features of benign solid testicular and paratesticular lesions. *Eur Radiol.* 2011;21:2226–2234

See Also (Topic, Algorithm, Media)

- Paratesticular Tumors, General
- Scrotal and Testicle Trauma
- Scrotum and Testicle Mass Algorithm
- Scrotum and Testicle, Mass Image
- Scrotum Tumors General

- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs]), General
- Spermatic Cord Mass and Tumors
- Testicle Pain (Orchalgia)
- Testis, Tumor and Mass, Adult, General
- Testis, Tumor and Mass, Pediatric, General
- Torsion, Testis or Testicular/Epididymal Appendages

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 222.0 Benign neoplasm of testis
- 608.89 Other specified disorders of male genital organs

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- D29.20 Benign neoplasm of unspecified testis
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

- Evaluate acute scrotal swelling or testicular masses urgently.
- A solid, firm testicular mass in an adult is cancer until proven otherwise.

SCROTUM AND TESTICLE, TRAUMA

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BASICS

DESCRIPTION

- Injury to the scrotum and testicle can occur through a variety of mechanisms—blunt, penetrating, avulsion, ischemic, burn
- American Association for the Surgery of Trauma (AAST) injury severity scale for the scrotum
  - Grade 1 contusion
  - Grade 2 laceration < 25% of scrotal diameter
  - Grade 3 laceration > 25% of scrotal diameter
  - Grade 4 avulsion < 50%
  - Grade 5 avulsion > 50%
- AAST injury severity scale for the testis (with bilateral testicular injury advance 1 grade up to Grade 5)
  - Grade 1 contusion or hematoma
  - Grade 2 subclinical laceration of tunica albuginea
  - Grade 3 laceration of tunica albuginea with < 50% parenchymal loss
  - Grade 4 major laceration of tunica albuginea with > 50% parenchymal loss
  - Grade 5 total testicular destruction or avulsion

EPIDEMIOLOGY

Incidence/Prevalence

- < 1% of all civilian traumas
- < 5% of battlefield injuries
  - More frequently caused by fragmentation devices
- < 5% of all burn victims

RISK FACTORS

- High-speed trauma
- Contact or "extreme" sports
- Industrial workers
- Bicycling recently recognized as leading sport associated with injury to the external genitalia

PATHOPHYSIOLOGY

- Blunt injury
- Penetrating injury
  - Gunshot wound (GSW), stab wound, human or animal bite
- Avulsion or ischemic injury
  - Industrial injury, self-mutilation
- Burn injury
  - Flame, electrical, chemical

ASSOCIATED CONDITIONS
- Associated injuries
  - Urethra, corpora spongiosum
  - Corpora cavernosa
- Testicular torsion
- Testicular tumor

GENERAL PREVENTION
- Protective equipment during contact sports
- Proper safety training for industrial machinery
- Military services are developing devices for ballistic protection of the external genitalia

DIAGNOSIS
HISTORY
- Trauma
  - Determine type of injury and magnitude of force infected
  - Investigate contamination of objects used in stab injuries
  - Determine species of animal in bite injuries
- Timing, severity, progression of pain, swelling, discoloration
  - Testicular rupture is usually immediately painful followed by acute onset of swelling
  - Minor trauma is associated with delayed onset of pain, swelling, and discoloration
  - Tumors typically have more insidious progression of symptoms
- Associated abdominal pain, nausea, emesis

PHYSICAL EXAM
- Evaluate for other trauma, including penile injury
- Document size of laceration or percentage of degloving injury
- Transilluminate any palpable scrotal mass
  - Hydrocele will transilluminate
  - Hematocele or tumor will not transilluminate
- Blood at meatus: Rule out urethral injury
- Absence of cremasteric reflex is a possible sign of testicular torsion
- Assess for inguinal hernia

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
- Urine culture if infection suspected
- CBC
- For delayed presentation with abscess formation, culture abscess contents

Imaging
- Scrotal ultrasound
  - Highly sensitive and specific for hematocele, avulsion, and rupture (1)[B]
  - Evaluate integrity of tunica albuginea
  - Heterogeneous areas within testicular parenchyma is suggestive of testicular rupture

– Doppler US may rule out torsion

DIFFERENTIAL DIAGNOSIS

- Torsion of the testicle or one of its appendages
- Infection (epididymitis, orchitis)
- Ruptured varicocele resulting in discoloration or tenderness
- Pelvic fracture resulting in scrotal swelling

TREATMENT

GENERAL MEASURES

- Select cases of blunt injury can be managed conservatively
  – Intact scrotal skin and nonruptured, viable testis on US
  – Small hematoceles
- Tetanus and/or rabies immunization for penetrating injuries
- For bilateral testicular injury, or injury to solitary testis, consider sperm extraction for cryopreservation, if available

MEDICATION

First Line

- Narcotics as needed: Oral and IV
- Avoid NSAIDs and aspirin

SURGERY/OTHER PROCEDURES

- Blunt trauma: Ruptured testis, expanding hematocele
- Irrigation, debridement of devascularized skin
  – Noninfected wound: Primary closure
  – Infected wound: Wet-to-dry dressing changes, broad-spectrum antibiotic
- Scrotal exploration and early repair is better for testicular rupture
- Penetrating trauma
  – Surgical exploration recommended for penetrating scrotal injuries
  – For testicular injury
    - Most are salvageable (2)[B]
    - Debride nonviable tissue
    - Primary closure with fine absorbable suture
    - Free graft of tunica vaginalis may be used (3)[B]
    - Drain placement may reduce postoperative hematoma
    - Layered closure of deep fascia and skin
- Burn
  – Flame or electrical:
    - Debridement of eschar and devascularized tissue
    - Split-thickness skin graft
    - Silver sulfadiazine cream for partial thickness
  – Chemical
    - Do not irrigate a chemical burn with water as this can exacerbate damage
    - Irrigate with saline if chemical is unknown

- Alkaline burns: Irrigate with dilute acetic acid
- Acidic burns: Irrigate with sodium bicarbonate

- Avulsion injury:
  - Small injuries may be managed with irrigation, debridement, and primary closure
  - Complex injuries: Debridement, delayed rotational scrotal flaps and/or split-thickness skin graft
- Animal or human bite
  - Treat as penetrating trauma with addition of antibiotics
  - Dicloxacillin or cephalexin (500 mg PO QID)
  - Dog bites: Add penicillin V 500 mg PO QID for coverage of Pasteurella multocida

ADDITIONAL TREATMENT

Additional Therapies

- Scrotal elevation
- Ice packs

ONGOING CARE

PROGNOSIS

- Early exploration and repair of testicular injury results in >90% testicular salvage
- Fertility is not compromised by repair (4)[C]
- Antisperm antibodies are not prevalent after trauma
- Nonoperative management of testicular rupture will result in 45% chance of delayed exploration and orchiectomy

COMPLICATIONS

- Abscess
- Fistula
- Fournier gangrene
- Hematoma
- Infertility and hormonal dysfunction
- Ischemic injury to testicle

FOLLOW-UP

Patient Monitoring

- Repeat US for conservatively managed patients
- Serum testosterone and fertility testing for patients with bilateral testicular injuries

REFERENCES

1. Buckley JC, McAninch JW. Use of ultrasonography for the diagnosis of testicular injuries in blunt scrotal trauma. *J Urol*. 2006;175(1):175–178.
2. Bjurlin MA, Kim DY, Zhao LC, et al. Clinical characteristics and surgical outcomes of penetrating external genital injuries. *J Trauma Acute Care Surg*. 2013;74:839–844.
3. Ferguson GG, Brandes SB. Gunshot wound injury of the testis: The use of tunical vaginalis and polytetrafluoroethylene grafts for reconstruction. *J Urol*. 2007;178:2462–2465.
4. Lin WW, Kim ED, Quesada ET, et al. Unilateral testicular injury from external trauma: Evaluation of semen. *J Urol*. 1998;159:841–843.

ADDITIONAL READING

- American Association for the Surgery of Trauma (AAST) Injury Scoring Scale http://www.aast.org/Library/TraumaTools/InjuryScoringScales.aspx (Accessed January 11, 2014).
- Morey AF, Metro MJ, Carney KJ, et al. Consensus on genitourinary trauma: External genitalia. *BJU Int.* 2004;94:507–515.
- Lewis EA, Pigott MA, Randall A, et al. The development and introduction of ballistic protection of the external genitalia and perineum. *J R Army Med Corps*. 2013;159 (suppl 1):i15–i17.
- Morey AF, Brandes S, Dugi DD, et al. Urotrauma: AUA Guideline (https://www.auanet.org/common/pdf/education/clinical-guidance/Urotrauma.pdf Accessed August 21, 2014)

See Also (Topic, Algorithm, Media)

- Burns, External Genitalia and Perineum
- Edema, External Genitalia
- Penis, Trauma
- Scrotum and Testicle, Trauma Algorithm
- Scrotum and Testicle, Trauma Images
- Testis Pain
- Torsion, Testis, and Testicular Appendages
- Urethra, Trauma (Anterior and Posterior)

CODES

ICD9

- 878.2 Open wound of scrotum and testes, without mention of complication
- 922.4 Contusion of genital organs
- 959.14 Other injury of external genitals

ICD10

- S30.22XA Contusion of scrotum and testes, initial encounter
- S31.31XA Laceration w/o foreign body of scrotum and testes, init
- S39.94XA Unspecified injury of external genitals, initial encounter

CLINICAL/SURGICAL PEARLS

- Sonogram is the best technique to evaluate for testicular rupture.
- Heterogeneous areas within testicular parenchyma are more often suggestive of testicular rupture than defect in tunica albuginea on ultrasound.
- Repair testicular rupture whenever possible.
- Early exploration and repair of testicular injury is highly efficacious. Rupture of tunica albuginea of testicle in as many of 50% of blunt scrotal trauma presenting for evaluation. Prompt exploration and repair leads to improved salvage rates.
- In pediatric patients, painless hematocele after abdominal injury is a concern for ruptured viscera (especially spleen).

SCROTUM, SQUAMOUS CELL CARCINOMA

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BASICS

DESCRIPTION

- Squamous cell carcinoma (SCC) of the scrotum is a very rare, environmentally induced cancer with high metastatic potential
- The first reported occupational cancer
  – Initially described in 1775 by Sir Percivall Pott in chimney sweeps
- Synonyms: Chimney sweeps cancer, Mule-spinners' disease, Pott cancer

EPIDEMIOLOGY

Incidence

- 1.5–3/10 million men in US(1); similar rates noted in Dutch series (2)
- Increasing incidence in US may be related to increases in HPV infection, Psoralen plus ultraviolet light A (*PUVA*) treatment for psoriasis, and also due to improved reporting
- Lower incidence among black men in older series, though increased risk in black men in more recent SEER database analysis (1)
- Most reported in men >50 yr; median age in SEER series: 68

Prevalence

N/A

RISK FACTORS

- Chemical/mechanical irritation
- Classically described in chimney sweeps: Related to soot or chemical exposure, poor hygiene
- Oil/petroleum: Machine workers (lathe workers, mule-spinners [men and boys who worked on cotton spinning machines])
- Poor hygiene
- Repeated trauma
- Rarely in patients with prior scrotal incision/scar
- PUVA: Ultraviolet A radiation for psoriasis. Effect is dose dependent.
- Associated with HPV 16, 18 in limited case reports
- Chronic immunosuppression

Genetics

N/A

PATHOPHYSIOLOGY

- SCC is a malignant tumor of epidermal keratinocytes thought to occur mainly from chronic irritation from a mechanical or chemical source.
- 3,4-benzpyrene, a polycyclic aromatic hydrocarbon, is a common occupational carcinogen in these men
- Associations with many other carcinogens have been described

ASSOCIATED CONDITIONS
- Psoriasis
- HPV/condylomata
- Sexually transmitted infections

GENERAL PREVENTION
- Decrease exposure to carcinogenic agents:
  - Protective clothing for those with occupational risk
  - Prevention of HPV transmission
  - Shielding of area during PUVA treatment
- Improve hygiene

DIAGNOSIS

HISTORY
- Occupational exposure to chemical and/or mechanical irritants
- History of treatment for psoriasis
- History of HPV, HIV
- History of scrotal trauma, scrotal surgery
- Inflammatory conditions involving the scrotum
- Change in size of lesion or ulceration
- Fever
- Nonhealing nodule or ulcer

PHYSICAL EXAM
- Exam of external genitalia, inguinal and distant lymph nodes:
  - Usually a solitary, slow-growing nodule with or without ulceration usually on the anterolateral aspect of the scrotum
  - Starts as a small pimple or nodule which gradually develops ulceration, raised or rolled edges, purulent discharge
  - Lesion may persist for 6 mo before ulcerating
  - May have associated condylomata of penis, scrotum, perianal region
- May lead to lymphadenopathy due to malignancy or infection
  - 30–60% have palpable lymphadenopathy at presentation
  - 25% have inguinal metastases at presentation

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- WBC count to rule out acute infection
- Urinalysis and urine culture if indicated

Imaging
- CT may help to assess size, extent of lymphadenopathy but cannot differentiate inflammation vs. malignancy
- MRI
  - Improved accuracy in diagnosis and staging
  - Can assess infiltrative vs. inflammatory process

- Lymphangiography is accurate in delineating metastatic vs. inflammatory nodes, but cannot detect micrometastases

Diagnostic Procedures/Surgery

Excisional biopsy of primary lesion

Pathologic Findings

- SCC:
  - Most are well or moderately differentiated and contain focal areas of keratosis
  - Surrounding epidermis demonstrates hyperkeratosis, acanthosis, dyskeratosis
  - Diffuse lymphocytic infiltrate may be present
- Staging (staging for all scrotal carcinoma, not only SCC, no TNM classification exists) (3)
  - Stage A1: Localized to scrotal wall
  - Stage A2: Locally invasive involving adjacent structures (testis, spermatic cord, penis, pubis, and perineum)
  - Stage B: Metastatic disease to the inguinal lymph nodes only
  - Stage C: Metastatic disease to the pelvic lymph nodes without evidence of distant spread
  - Stage D: Metastatic disease beyond the pelvis involving distant organs
  - In SEER series, 76% presented with localized disease, 20% with regional metastases, and 4% with distant metastases (4)

DIFFERENTIAL DIAGNOSIS

- Benign scrotal lesions:
  - Condyloma
  - Eczema
  - Hidradenitis suppurativa
  - Folliculitis
  - Nevus
  - Periurethral abscess
  - Psoriasis
  - Sebaceous cysts/epidermal inclusion cyst
  - Syphilis
  - Tuberculous epididymitis with a draining sinus
- Malignant scrotal lesions:
  - Basal cell carcinoma
  - Malignant melanoma
  - Paget disease
  - Marjolin ulcer: Cancer arising from site of prior inflammation
  - Kaposi sarcoma: A purple, papular, plaque-like, or ulcerated lesion on the penis or scrotum
  - Sarcoma: Leiomyosarcoma from the Dartos layer of the scrotum is most common, though still very rare
  - Metastatic lesion

TREATMENT

GENERAL MEASURES

- Management is primarily surgical.
- Local wide excision is diagnostic and therapeutic.

MEDICATION

First Line

- Broad-spectrum antibiotics for 4–6 wk in patients with lymphadenopathy
- Chemotherapy has not demonstrated success for primary treatment (single agent or combination therapy)
  - Methotrexate, bleomycin, and cisplatin have been used with radiotherapy in 1 case report, but the patient later required surgical resection
  - Bleomycin has been reported as successful in 2 cases
  - Multiple case reports exist in the literature of combined adjuvant chemotherapy and radiotherapy
- Topical 5-FU has not been successful in treating carcinoma in situ of the scrotum

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Primary lesion:
  - Wide local excision of lesion with a 2-cm margin of skin and dartos fascia.
  - Small lesions may be closed primarily.
  - Large lesions may require split-thickness skin grafting or local flaps.
  - If hemiscrotectomy is performed, the ipsilateral testis may be placed in a thigh pouch or moved to the contralateral hemiscrotum.
  - Excision of all scrotal contents is required only when structures are directly involved by tumor.
- Regional lymph nodes
  - If palpable adenopathy resolves after antibiotics or was never present, then a superficial inguinal lymph node biopsy should be performed:
    - Ipsilaterally if lesion is lateral.
    - Bilaterally if lesion at the median raphe
  - If palpable lymphadenopathy persists after antibiotics, then a bilateral superficial lymph node biopsy should be performed.
  - Full ilioinguinal lymphadenectomy should be performed only on the side of the positive biopsy:
    - If performing a unilateral ilioinguinal lymphadenectomy, a contralateral superficial inguinal lymph node biopsy should also be performed.
    - If there is a positive frozen section, then perform a bilateral ilioinguinal lymphadenectomy.
- Laser vaporization of the primary lesion has been used in poor surgical candidates or those who refused surgery.
- Mohs micrographic surgery has also been used for primary lesions.

ADDITIONAL TREATMENT

Radiation Therapy

- Has not been effective and is reserved for recurrences and poor surgical candidates.
- Has been described in multiple case reports as adjuvant therapy.

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Scrotal cancer survival is worse for SCC histology than all other histologies except melanoma (4)
- Survival at 5 yr (1):
  - Stage A: 70–80%
  - Stage B: 40–50%
  - Stage C: Rare
  - Stage D: Rare
- Local recurrence rates:
  - 21–40%
  - May require additional excision
  - Patients with industrial exposure may be at higher risk for recurrence

COMPLICATIONS
- Femoral hernias after ilioinguinal lymphadenectomy
- Lymphedema
- Lymphoceles
- Wound infections

FOLLOW-UP
Patient Monitoring
- Patient Monitoring
  - Self-exams for local recurrence of lesion or lymphadenopathy
  - Periodic follow-up by physician for monitoring of local recurrence or lymphadenopathy
- Follow-up is required for life

Patient Resources
N/A

REFERENCES

1. Wright JL, Morgan TM, Lin DW. Primary scrotal cancer: Disease characteristics and increasing incidence. *Urology*. 2008;72(5):1139–1143.
2. Verhoeven RH, Louwman WJ, Koldewijn EL, et al. Scrotal cancer: Incidence, survival and second primary tumours in the Netherlands since 1989. *Br J Cancer*. 2010;103(9):1462–1466.
3. Ray B, Whitmore WF Jr. Experience with carcinoma of the scrotum. *J Urol*. 1977;117(6):741–745.

4. Johnson TV, Hsiao W, Delman KA, et al. Scrotal cancer survival is influenced by histology: A SEER study. *World J Urol*. 2013;31(3):585–590.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Scrotum and Testicle Mass
- Scrotum, Epidermal Inclusion Cyst
- Scrotum, Hemangioma
- Scrotum, Idiopathic Calcinosis
- Scrotum, Tumors, Benign and Malignant
- Seborrheic Dermatitis
- Skin Tags, External Genitalia (Acrochordon, Pedunculated Papilloma)

CODES

ICD9

187.7 Malignant neoplasm of scrotum

ICD10

C63.2 Malignant neoplasm of scrotum

CLINICAL/SURGICAL PEARLS

A nonhealing ulcer or nodule on the scrotum should raise suspicion for squamous cell carcinoma.

SEMINAL VESICLE, CYSTS AND MASSES

Mark W. Ball, MD
Arthur L. Burnett, II, MD, MBA, FACS

BASICS

DESCRIPTION

- The most common seminal vesicle (SV) masses are secondary malignancies
- Cystic masses are the 2nd most common, followed by primary seminal vesical malignancies.
- Cysts
  - Rare; either congenital or acquired
  - Age at diagnosis, 20–50 yr
  - Usually unilateral; size varies considerably from small (5 mm) to huge cysts that fill the pelvis.
- Neoplasms
  - Primary malignant neoplasms of the seminal vesicles are exceedingly rare
  - SV solid mass is more likely from local invasion by another malignancy such as prostate cancer

EPIDEMIOLOGY

Incidence

- Cysts: Incidence peaks at age 20–30 yr.
- Primary SV malignancy: Exceedingly rare. Only case reports and small series reported.

Prevalence

N/A

RISK FACTORS

- Secondary malignancies
- Prior transurethral surgery causing scarring at the ejaculatory duct

Genetics

- SV formation occurs at the 12th wk of gestation. Abnormal branching of the ureteral bud from the mesonephric duct can disrupt SV formation and result in an ectopic ureteral orifice:
  - The abnormal ureter and metanephrogenic blastema results in a dysplastic kidney.
- A basement membrane defect that is seen in multiple organs (as in autosomal dominant polycystic kidney disease [ADPKD]) is believed to also affect SV cysts.

PATHOPHYSIOLOGY

- Normal anatomy:
  - SVs are elongated, flat, paired structures that lie between the rectum and bladder, superior to the prostate.
  - Mean normal length is 3.1 cm and width is 1.5 cm; contributes 50–80% of total seminal ejaculatory volume
  - Blood supply: Vesiculodeferential artery, a branch of the umbilical artery

- Cystic disease of the SVs can be either congenital or acquired; congenital cysts are associated with anomalies of the ipsilateral mesonephric duct.
- Acquired SV cysts result from ejaculatory duct obstruction, inflammation, or other abnormality.
- Cysts are filled with seminal fluid (nonmotile spermatozoa, red and white blood cells, and epithelial cells).
- Congenital SV cysts are typically associated with an ipsilateral ectopic ureter and/or ipsilateral renal abnormalities:
  - Lesions <5 cm are rarely symptomatic.
  - Lesions >12 cm have been described as giant cysts and are often associated with symptoms related to bladder outlet or colonic obstruction.
- In men, 30% of ectopic ureters insert into the SV.
- 3 patterns of spread of prostate cancer into SV
  - Direct spread along the ejaculatory duct
  - Prostatic capsular perforation followed by extension into the periprostatic tissues and the SV
  - Isolated deposits
- Direct invasion of the SVs can also occur in malignancies of the bladder and rectum

ASSOCIATED CONDITIONS
- Bladder cancer
- Ectopic ureter
- Ipsilateral renal dysplasia or agenesis
- Prostate cancer
- Rectal cancer

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Most SV cysts are asymptomatic
- When symptomatic, typical symptoms are:
  - Dysuria, irritative voiding
  - Perineal discomfort
  - Recurrent epididymitis
  - Painful ejaculation
  - Hematuria
  - Hematospermia
  - Infertility
- Determine history of other malignancy such as prostate, bladder, or rectal cancer.

PHYSICAL EXAM

ALERT
Normal seminal vesicles are not palpable on DRE. A palpable SV is abnormal.

- SV tumors are often palpable and nontender hard areas on digital rectal exam (DRE), just cranial to the base of the prostate.
- Primary tumors are usually unilateral and not contiguous with the prostate.
- Secondary tumors are usually bilateral and contiguous with a prostate or bladder tumor.
- SV cysts (when large) can usually be palpated on DRE as a ballotable mass.
- Indurated and/or tender epididymis and ductus deferens: Evidence of chronic epididymitis or obstruction

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Low semen volume and lack of fructose and liquefaction implies SV absence or ejaculatory duct occlusion.
- PSA elevation may suggest prostate cancer.

Imaging

- TRUS (transrectal ultrasound):
  - 1st-line imaging for suspected SV abnormality or SV mass on DRE
  - SV cystic lesions: Echopenic center with echogenic luminal folds
  - SV tumors: Isoechoic to the prostate, but hyperechoic to normal SV
- CT:
  - SV tumors: Enlarged SV, with a high-attenuation lesion and a normal bladder and prostate. Can be cystic if there is significant tumor necrosis
  - Cannot distinguish benign from malignant tumors. Obliterated tissue planes suggest a secondary tumor by direct extension
- MRI:
  - Cannot distinguish benign from malignant tumors
  - SV cyst: T1, low signal intensity; T2, unilocular smooth wall with uniform high intensity and well-defined margin
  - Hemorrhagic SV cyst: High intensity on both T1 and T2; heterogeneous intensity

Diagnostic Procedures/Surgery

- Cystoscopy
  - Hemitrigone with absent ipsilateral orifice
  - Intravesical cyst protrusion often noted with congenital SV cysts
- TRUS-guided needle placement for SV aspiration or biopsy for pathologic diagnosis
- Vasovesiculography: Limited value and use today in imaging the SV. Can help determine duct obstruction in azoospermic men; also helps distinguish SV cyst from a müllerian or other wolffian duct cyst

Pathologic Findings

Most primary SV masses are benign and rarely neoplastic.

DIFFERENTIAL DIAGNOSIS

- Müllerian duct cysts and ejaculatory duct cysts:
  - Both are midline in location
  - Spermatozoa in the aspirate may differentiate seminal vesicle cysts from müllerian duct cysts

- Prostatic cysts
- Diverticulosis of the ampulla of the vas deferens
- Ectopic ureterocele
- SV calcifications/masses can occur from chronic bilharziasis, TB, or old bacterial abscess (commonly from colonic flora):
  - Symptoms may include hematospermia, infertility, and pelvic pain
- SV cysts:
  - Seminal vesiculitis: SV infection is uncommon:
    - May occur as a consequence of prostatitis or epididymitis
  - SV abscess: Best imaged on MRI or US.
    - Predisposing factors include diabetes or chronic catheterization
    - Patients often have pelvic pain, fullness, and fever
  - SV calculi: Often present with pain, infection, or hematospermia; usually the result of infection and ejaculatory duct obstruction
  - Congenital vs. acquired cysts: Congenital cysts are typically associated with ipsilateral ectopic ureter and/or ipsilateral renal dysplasia
- Benign SV tumors:
  - Papillary adenoma or cystadenoma: Middle-aged men; mimics a simple cyst in presentation and on imaging
  - Amyloid: Subendothelial deposits of amyloid:
    - Usually presents in the elderly
    - Often concomitant with bladder or prostate cancer
  - Other rare tumors: Carcinoid
- Mixed SV tumors are extremely rare:
  - Only 15 cases reported
  - Variously described as cystadenoma, cystomyoma, low-grade phyllodes tumor, benign mesen-chymoma, adenomyosis, and mesonephric hamartoma
- Malignant SV tumors:
  - Most SV neoplasms are from secondary invasion from prostate, bladder, or rectal cancer, or lymphoma:
    - Direct extension into the SV can often be mistaken for primary SV cancer
  - Primary adenocarcinoma of the SV:
    - Age >50 yr; incidence is rare
    - Serum PSA and PAP are normal, and CEA elevated.
    - Stains positive for CA125 and negative for PSA
  - Primary sarcoma:
    - Extremely rare aggressive tumor; usually diagnosed late in disease course
    - Variants: Leiomyosarcoma, angiosarcoma, and müllerian adenosarcoma

TREATMENT

GENERAL MEASURES

- Asymptomatic cystic lesions do not require any specific intervention. Imaging of the urinary tract may reveal renal agenesis.
- Solid lesions require biopsy.

• Adjuvant therapy has no demonstrated efficacy in primary malignancy of the SV.

MEDICATION

First Line

Seminal vesiculitis is treated with standard antibiotic regimens used to treat prostatitis (eg, ciprofloxacin, ofloxacin)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Symptomatic cysts
  - For small cysts, percutaneous transperineal or TRUS-guided aspiration/drainage (cysts typically recur)
  - Marsupialization (unroof into the prostate/bladder by TUR or TUI)
  - Laparoscopic or robotic-assisted laparoscopic excision. Laparoscopy has good efficacy with minimized morbidity (1)
  - Open surgical excision (by the transperineal, coccygeal, intravesical vesical, or retroperitoneal routes) is rarely performed today
  - If associated with a congenital ectopic ureter and dysplastic kidney: An ipsilateral nephroureterectomy, along with the SV, should be performed
  - SV duct stones: Lithopaxy is feasible in select patients via a ureteroscope
- SV tumors
  - All solid or noncystic SV masses on TRUS should undergo a US-guided biopsy:
    - If tumor is confirmed: Further stage with CT and/or MRI
  - Enlarging asymptomatic benign tumors are treated with simple seminal vesiculectomy
  - Historically, small benign tumors were excised transperineally or retrovesically, and large tumors, transvesically or transcoccygeally
  - Today, excisions are typically by transperitoneal laparoscopy (case series are small)
  - A diagnosis of malignancy (large in size or poorly differentiated) warrants radical cystoprostatectomy and regional lymph node dissection, en bloc with adherent surrounding structures
  - SV invasion by another malignancy: Directed at the primary tumor type

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Primary SV malignancies due to their rarity, typically present at an advanced stage and are

diagnosed late.
• Local invasion of SVs by secondary cancers are a poor prognostic sign.

COMPLICATIONS
ED can occur after SV excision since the neurovascular bundle lies lateral to the tip of the SV.

FOLLOW-UP
Patient Monitoring
Asymptomatic benign tumors: Close follow-up with DRE and TRUS. After radical surgery for malignancy, no clear follow-up consensus exists.

Patient Resources
N/A

REFERENCE
1. Cherullo EE, Meraney AM, Bernstein LH, et al. Laparoscopic management of congenital seminal vesical cysts associated with ipsilateral renal agenesis. *J Urol.* 2002;167:1263–1267.

ADDITIONAL READING
Van den Ouden D, Blom JH, Bangma C, et al. Diagnosis and management of seminal vesical cysts associated with ipsilateral renal agenesis: A pooled analysis of 52 cases. *Eur Urol.* 1998;33:433–440.

See Also (Topic, Algorithm, Media)
• Prostate Nodule
• Renal Dysplasia, Hypodysplasia, and Hypoplasia
• Renal Ectopia
• Seminal Vesicle, Amyloidosis
• Seminal Vesicle, Mass and Cysts Image ☼
• Seminal Vesiculitis (Pyospermia)

CODES

ICD9
• 198.82 Secondary malignant neoplasm of genital organs
• 608.0 Seminal vesiculitis
• 608.89 Other specified disorders of male genital organs

ICD10
• C79.82 Secondary malignant neoplasm of genital organs
• N49.0 Inflammatory disorders of seminal vesicle
• N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS
• Seminal vesical masses are most commonly secondary malignancies.
• During seminal vesiculectomy, limit cautery during dissection to limit damage to the

neurovascular bundle.

- Asymptomatic cystic lesions should be observed.

SEXUAL ABUSE, PEDIATRIC

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BASICS

DESCRIPTION

- Sexual activity involving a child or a minor
- Spectrum of pediatric sexual abuse includes intercourse, fondling, pornography, and exhibitionism

EPIDEMIOLOGY

Incidence

~1% of children sexually abused each year

Prevalence

- 12–25% of girls and 8–10% of boys have been sexually abused by age 18 (12–40% overall)
- Of girls reporting abuse (1)
  - 65% reported abuse occurred more than once
  - 57% reported that abuser was family member
  - 53% reported that the abuse occurred at home

RISK FACTORS

- Occurs in all socioeconomic levels
- Increased risk with:
  - Parents who were abused
  - Poverty
  - Drug or alcohol abuse
  - Teen parents
  - Parental violence
  - Mental illness
  - Multiple child caretakers

PATHOPHYSIOLOGY

- American Academy of Pediatrics definition (2):
  - Child sexual abuse is the engaging of a child in sexual activities that the child cannot comprehend, for which the child is developmentally unprepared and cannot give informed consent, and that violate the social taboos of society.
  - Children cannot consent to any sexual activity, but note that the legal age of consent may vary on a state-by-state basis.

ASSOCIATED CONDITIONS

- Physical abuse
- Emotional abuse

GENERAL PREVENTION

- Education
- Social services

DIAGNOSIS

ALERT
Findings in the evaluation of children with straddle injuries to the external genitalia that should raise concern for sexual abuse include:
- Presence of other nonurogenital trauma.
- Patient < 9 mo.
- Perianal, rectal, injury without history of penetrating trauma.
- Findings of more extensive or severe trauma.
- Lack of correlation between reported history and physical findings.

HISTORY
- Child may make a statement of abuse, or abuse is witnessed
- Child brought by law enforcement/social services for evaluation for possible abuse as part of investigation
- Caregiver suspects child may have been abused
- Suspicious findings on routine exam
- Suspicious complaints: Rectal or vaginal bleeding or discharge, especially in prepubertal child
- Presenting symptoms may be general and nonspecific:
  - Sleep disturbances
  - Abdominal pain, enuresis, encopresis
  - Dysuria
- Consider evaluation by trained forensic interviewer
- Avoid leading questions or showing strong emotions/shock: Use “tell me more” or “and then what happened” approach?”
- Parent/caregiver should be interviewed separately to avoid influences/distraction
- Questions asked and verbatim answers in quotation marks should be documented as accurately as possible

PHYSICAL EXAM
- Be familiar with the normal appearance of the prepubertal introitus and hymen (image).
- Do not force exam on uncooperative children.
- Do not use speculum in prepubertal child.
- Do not touch hymen with swabs or other objects.
- Do not perform a digital rectal exam (DRE).
- Educate caretaker and patient that most sexually abused children have a normal physical exam. Absence of physical findings does not exclude abuse.
- Perform complete physical exam including skin, oropharynx, genitalia, and anal area.
- Use frog-leg position with gentle labial traction to visualize female anatomy.
- Consider exam in chest-knee position to confirm suspected abnormalities.
- Consult specialists as appropriate.
- Document thoroughly detailed exam findings and descriptions, using drawings or photos if

feasible.
- When severe rectal injury suspected, persistent bleeding or full thickness lacerations, consider exam under anesthesia.
- Exam findings of concern:
  – Abrasions or bruising of genitalia.
  – Acute or healed tear in posterior aspect of hymen.
  – A markedly decreased amount of hymenal tissue.
  – Injury or scarring of posterior fourchette, fossa navicularis, or hymen.
  – Anal bruising or lacerations.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Culture for gonorrhea and Chlamydia.
- Vesicles should be tested for HSV.
- All postmenarchal females should have pregnancy test.
- Presence of semen, sperm, or acid phosphatase; positive culture for gonorrhea or Chlamydia, or a positive test for syphilis or HIV (if prenatal transmission excluded for the STDs) makes sexual abuse a near medical certainty.

Imaging

None needed unless more extensive physical abuse is suspected

Diagnostic Procedures/Surgery

Consider exam under anesthesia

DIFFERENTIAL DIAGNOSIS

- Accidental trauma (straddle injuries, toilet-lid injury to penis, masturbation injuries)
- Anal fissure
- Hemangioma
- Hematochezia
- Henoch–Schönlein purpura
- Lichen planus
- Nonspecific vaginitis
- Normal anatomic variants (perihymenal bands, prominent linea vestibularis)
- Physical abuse
- Poor hygiene
- Urethral prolapse
- Vaginitis
- Vaginal foreign body

TREATMENT

GENERAL MEASURES

- Mental health evaluation is essential (3)
- Acute evaluation and treatment of injuries

MEDICATION

First Line

- Varies with presentation
  - Pain medication as appropriate
  - Postexposure prophylaxis (PEP) for prevention of pregnancy and STDs should be offered to adolescents
  - PEP generally not indicated for prepubertal children

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Consider exam under anesthesia
- Depends upon findings/injuries

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Need for mental health support, especially in:
  - Patients reporting suicidal or self-injurious thoughts
  - More intrusive forms of assault
  - More violent assaults
  - Longer period of molestation
  - Closer relationship of perpetrator to victim

COMPLICATIONS

- Psychological
  - Eating disorders
  - Depression and anxiety
    - Suicidal behaviors
    - Self-injury
  - Posttraumatic stress disorder
  - Sexual dysfunction
- Pregnancy
- STDs/STI's

FOLLOW-UP

Patient Monitoring

- Follow-up exams for healing of injuries
- Evaluation for development of STDs/STIs
- Evaluation for development of pregnancy and discussion of this possibility with the

postpubertal child
- Emotional support/therapy

Patient Resources
- Darkness to Light: National Resources Related to Child Sexual Abuse. http://www.d2l.org/site/c.4dICIJOkGcISE/b.6069289/
- Safehorizon. http://www.safehorizon.org/?gclid=CL-kg7OT5LkCFVGi4AodQXwA6w
- The National Child Traumatic Stress. Network http://www.nctsn.org/trauma-types/sexual-abuse

REFERENCES

1. Schoen C, Karen Davis, Karen Scott Collins, et al. *The Commonwealth Fund survey of the health of adolescent girls*. New York, NY: Commonwealth Fund; 1997. Available at: http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/1997/Nov/The%20Commonwealth%20Fund
2. American Academy of Pediatrics. Guidelines for the evaluation of sexual abuse of children: Subject review. American Academy of Pediatrics Committee on Child Abuse and Neglect. *Pediatrics*. 1999;103(1):186–191.
3. Adams J, Kaplan RA, Starling SP, et al. Guidelines for medical care of children who may have been sexually abused. *J Pediatr Adolesc Gynecol.* 2007;20(3):163–172.

ADDITIONAL READING

- Bernard D, Peters M, Makoroff K. The evaluation of suspected pediatric sexual abuse. *Clin Pediatr Emerg Med*. 2006;7:161–169.
- Buckingham ET, Daniolos P. Longitudinal outcomes for victims of child abuse. *Curr Psychiatry Rep.* 2013;15:342.
- Flaherty EG, Sege R. Barriers to physician identification and reporting of child abuse. *Pediatr Ann.* 2005;34:349–356.
- Kellogg N, American Academy of Pediatrics Committee on child abuse and neglect. The evaluation of sexual abuse in children. *Pediatrics*. 2005;116(2):506–512.

See Also (Topic, Algorithm, Media)
Sexual Abuse, Pediatric Image

CODES

ICD9
- 995.53 Child sexual abuse
- V15.41 History of physical abuse

ICD10
- T74.22XA Child sexual abuse, confirmed, initial encounter
- T76.22XA Child sexual abuse, suspected, initial encounter
- Z62.810 Personal history of physical and sexual abuse in childhood

CLINICAL/SURGICAL PEARLS

- Pediatric providers should remain alert to signs and symptoms that suggest the possibility of sexual abuse.
- The clinician is obligated to report any suspected case of childhood sexual abuse.
- Sensitivity during the history and exam and providing the victim access to psychological and social work support are key factors in the case of children who have been sexually abused.

SEXUAL DYSFUNCTION, FEMALE

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BASICS

DESCRIPTION

- Sexual dysfunction is a disorder involving sexual desire, orgasm, arousal, or sexual pain in females that results in significant personal distress. It includes the following:
  - Hypoactive sexual desire disorder
  - Subjective sexual arousal disorder
  - Genital sexual arousal disorder
  - Combined genital and subjective arousal disorder
  - Persistent sexual arousal disorder
  - Sexual aversion disorder
  - Women's orgasmic disorder
  - Dyspareunia
  - Vaginismus
  - DSM-IV defines femal sexual dysfunction (FSD) (formerly, inhibited female orgasm) as persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase
- Often multifactorial etiology

EPIDEMIOLOGY

Incidence

25–76% of adult women

Prevalence

N/A

RISK FACTORS

- Age
- Cardiovascular disease
- Depression, alcoholism, or drug abuse
- Diabetes mellitus
- Hyperlipidemia
- HTN
- Menopause
- Pelvic trauma or radiation
- Pelvic surgery for incontinence or prolapse
- Spinal cord injury (SCI)

Genetics

N/A

PATHOPHYSIOLOGY

- Vascular causes: Vascular insufficiency often secondary to atherosclerosis, causes diminished genital blood flow leading to vaginal and clitoral smooth muscle fibrosis (1,2)
- Hormonal influences: Estrogen plays a significant role in regulating sexual function and maintains the vaginal smooth muscle epithelium and lubrication
- Testosterone is the predominant female androgen that also supports sexual arousal and libido. Low estrogen or testosterone levels are associated with sexual dysfunction
- Neurogenic causes: SCI or disruption of the sacral reflex arcs interfere with vaginal sensation or the ability to reach orgasm
- Psychogenic causes: Emotional issues or psychological stressors such as depression, fatigue, or sexual abuse can negatively affect the female sexual response
- Iatrogenic:
  - Various medications such as antidepressants can decrease sexual desire and function
  - Prior pelvic surgery such as hysterectomy or cystectomy can disrupt the autonomic nerve plexus, thus contributing to sexual dysfunction
  - OCP: Exogenous estrogens

ASSOCIATED CONDITIONS

- Depression
- Endometriosis, vulvodynia, etc.
- Urinary incontinence
- Interstitial cystitis
- Menopause
- Multiple sclerosis
- Any disease that causes decreased estrogen or androgens

GENERAL PREVENTION

- Lifestyle modification to reduce CV disease or psychosocial stressors
- Improvements in surgical technique during pelvic surgery have lessened damage to nerves important in sexual arousal

DIAGNOSIS

HISTORY

- Age: Higher prevalence of sexual dysfunction in older women:
  - Physical and psychological factors associated with aging affect sexual desire and response
  - Decreased estrogen and testosterone after menopause decreases libido and promotes dryness and atrophy
- Sexual history
- Psychosocial history
- Self-administered, validated questionnaires such as the Female Sexual Function Index (FSFI) are useful objection tools to assess sexual function
- Childbirth: Short-term sexual dysfunction is common postpartum (22–86%) with loss of desire and dyspareunia
- Past medical history:
  - Hypertension (HTN), hyperprolactinemia (HPL), or diabetes mellitus

  - Thyroid disorders can also affect sexual dysfunction
  - Previous history of endometriosis, infections, or tumors should also be elucidated
- Past surgical history: Previous pelvic trauma, pelvic surgery, or radiation
- Medications:
  - Antidepressants such as seletive serotonin receptor inhibitors (SSRIs) or tricyclics can decrease libido
  - Oral contraceptives and tamoxifen can interfere with testosterone binding
  - Spironolactone or ketoconazole have antiandrogen properties
  - Antihypertensives and chemotherapeutic agents can also contribute to female sexual dysfunction
- Social history: Sexual, alcohol, or drug abuse; pertinent psychosocial factors or interpersonal relationships are also important

PHYSICAL EXAM
- A thorough physical and pelvic/bimanual exam:
  - Assess for vaginal atrophy, lichen sclerosis, vaginal depth, genital/perineal sensation
  - Examine for trigger points, scarring, or narrowing from prior surgery
  - Assess for prolapse, masses
- If neurologic signs are present, a more detailed neurologic assessment is then warranted including anal and vaginal tone, bulbocavernosal reflex, and voluntary tightening of the anus

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Basic chemistry panel, CBC, TSH, and lipid profile to help identify chronic medical conditions, renal failure, diabetes, or hyperlipidemia
- Hormonal profile
- Serum total and free testosterone
- Estradiol level
- LH, FSH, prolactin
- Sex hormone binding globulin (SHBG)

Imaging

Vaginal and clitoral plethysmography, duplex US, and selective pudendal arteriography can be used to assess genital blood flow.

Diagnostic Procedures/Surgery

Genital vibratory sensation threshold testing, genital temperature sensation, and the bulbocavernosal reflex can be evaluated to help rule out associated neurologic dysfunction

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS
- Desire phase disorders (3)
  - Hypoactive sexual desire (low sex drive)
  - Sexual aversion disorder: Panic disorder; active repulsion from sexual stimulation
- Impaired female sexual arousal

  - Failure to achieve or maintain vaginal lubrication
  - Swelling of genitalia; dyspareunia may result
- Orgasmic phase dysfunction
  - Orgasm in response to indirect stimulation: kissing, fantasy, breast stimulation
  - Orgasm only in response to clitoral stimulation
  - Lack of orgasm (Anorgasmy)
- Coital pain problems
  - Dyspareunia
  - Vaginismus
  - Reduced genital sensation
- Others
  - Urinary incontinence
  - Pelvic organ prolapse
  - Vascular causes
  - Surgical (Hysterectomy, oophorectomy, etc.)
  - Medication related
    - CNS depressants
    - Illicit drug abuse
    - Antihypertensives
    - Antiandrogens (cimetidine, ranitidine)
    - Chemotherapy

TREATMENT

GENERAL MEASURES

- Attempt to identify a correctable cause and treat when present.
- Exercise and pelvic floor training/massage can improve sexual function.
- Treat prolapse and incontinence in affected patients, as female sexual dysfunction may be in part related to inhibition due to leakage during sexual relations.

MEDICATION

First Line

- Hormone replacement therapy (HRT) is the mainstay of treatment in postmenopausal women or oophorectomized women (4)
  - Oral estrogen or topical vaginal estrogen may improve libido and ameliorate symptoms of dryness or irritation
  - Ospemifene is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
    - One tablet (60 mg) taken orally once daily with food
    - Do not use estrogens or estrogen agonist/antagonist or fluconazole concomitantly
  - Topical steroids for lichen sclerosis
  - Androgen replacement therapy can be considered in patients with androgen deficiency:
    - Combined estrogen and testosterone replacement therapy can be used or testosterone alone can be applied topically or with a patch (counsel patient on risks of virilization including: Acne, hirsutism, male pattern baldness, and clitoral hypertrophy)

  – Testosterone replacement is controversial and not FDA approved despite being one of the most commonly prescribed off label drugs for desire disorders
- Tibolone (synthetic steroid) is commonly used in Europe in postmenopausal women with desire and arousal disorders

Second Line
- Arousal disorders have been treated with several different classes of medications:
  – Alprostadil
  – Bupropion
  – Estrogen
  – Phentolamine and yohimbine
  – Sildenafil
  – Zestra

SURGERY/OTHER PROCEDURES
InterStim therapy is currently under investigation to treat sexual arousal disorders

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Eros Clitoral Therapy Device is a handheld mechanical device that has been FDA approved for the treatment of sexual arousal and orgasmic disorders in women.
- Several other pharmacologic agents are under investigation for treatment of female sexual dysfunction:
- PDE-5 inhibitors are thought to enhance vaginal lubrication and engorgement in postmenopausal women; however, the benefit is not well established.
- α-Adrenergic antagonists such as phentolamine and yohimbine produce vasodilation of the smooth muscle, increasing vaginal blood flow and lubrication.

Complementary & Alternative Therapies
- Education, sex therapy, psychotherapy, and cognitive behavioral therapy are also important in the multidisciplinary management of sexual dysfunction including those with a history of sexual abuse.
- Currently there are limited studies on the effectiveness of herbal remedies to aid female sexual dysfunction.

ONGOING CARE

PROGNOSIS
Outcome is improved if a specific cause can be identified.

COMPLICATIONS
Patients on HRT should be appropriately counseled on its risks and benefits.

FOLLOW-UP
Patient Monitoring
Close monitoring of progress and compliance is necessary.

Patient Resources
Medline Plus. http://www.nlm.nih.gov/medlineplus/sexualproblemsinwomen.html

REFERENCES

1. Jha S, Thakar R. Female sexual dysfunction. *Eur J Obstet Gynecol Reprod Biol*. 2010;153(2):117–123.
2. Graziottin A, Serafini A, Palacios S. Aetiology, diagnostic algorithms and prognosis of female sexual dysfunction. *Maturitas*. 2009;63(2):128–34.
3. Female Sexual Dysfunction. Family Practice Notebook: www.fpnotebook.com/Gyn/Psych/FmlSxlDysfnctn.htm. Accessed January 28, 2014.
4. Fooladi E, Davis SR: An update on the pharmacological management of female sexual dysfunction. *Expert Opin Pharmacother*. 2012;13(15):2131–2142.

ADDITIONAL READING
ACOG Practice Bulletin No. 119: Female sexual dysfunction. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology. *Obstet Gynec*. 2011;117(4):996–1007.

See Also (Topic, Algorithm, Media)
- Dyspareunia, Female
- Erectile Dysfunction/Impotence, General Considerations
- Female Hypoactive Sexual Desire Disorder
- Female Sex Function Index (FSFI)
- Incontinence, Urinary, Adult Female
- Libido, diminished, female
- Pelvic Organ Prolapse (Cystocele and Enterocoele)
- Pelvic Pain, Female
- Vaginal Atrophy, Urologic Considerations

CODES
ICD9
- 302.70 Psychosexual dysfunction, unspecified
- 302.73 Female orgasmic disorder
- 625.0 Dyspareunia

ICD10
- F52.22 Female sexual arousal disorder
- F52.31 Female orgasmic disorder
- N94.1 Dyspareunia

CLINICAL/SURGICAL PEARLS
- FSD is a complex condition with many etiologies.
- A multidisciplinary approach is often necessary.
- Search for reversible cause such as incontinence or prolapse and treat accordingly.

SEXUALLY TRANSMITTED INFECTIONS (STIs) (SEXUALLY TRANSMITTED DISEASES [STDs]), GENERAL

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Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Sexually transmitted infections (STIs) are viral, bacterial, or parasitic disease typically transmitted via exposure to infected secretions or infested genitalia.
  - Transmission is predominantly via sexual contact.
  - Nonsexual transmission: Mother–infant, blood transfusions, accidental needle injury.
  - STIs has generally replaced the term Sexually Transmitted Diseases (STDs)

EPIDEMIOLOGY

Incidence

- 20 million new infections yearly (1)[A]
  - Relative frequency of cases by disease: HPV > Chlamydia > Trichomonas > Gonorrhea > HSV-2 > syphilis > HIV > Hep B
  - 50% of new STIs in patients 15–24 yr old

Prevalence

- 110 million STIs estimated by the Centers for Disease Control and Prevention (CDC) (1)[A]
  - Most prevalent STI is human papilloma virus (HPV)
  - 25% STIs are incurable (HIV, HSV-2, Hep B)

RISK FACTORS

- Multiple sex partners, sexual contact with infected partner, unprotected sex
- Low socioeconomic status, drug abuse
- Exposure at delivery and/or in utero

Genetics

- CCR5 mutation provides relative protection against HIV infection (2)[C]

PATHOPHYSIOLOGY

- Ulcerative lesions
  - HSV-1 and HSV-2
    - Type 1: 85–90% of genital cases
    - Type 2: 10–15% usually oral to genital contact
    - Painful ulcer of genitalia or anus and concomitant painful inguinal lymphadenopathy
    - Prodrome (initial infection and recurrent flares): Flu-like symptoms
  - Chancroid (*Haemophilus ducreyi*)
    - Painful ulcer; tender inguinal adenopathy, suppurative with fistula to the skin
  - Syphilis (*Treponema pallidum*)
    - Primary syphillis presents with painless ulcer, may last 4–6 wk. ± nontender

adenopathy if untreated
    - Secondary syphillis presents with maculopapular rash of body and arms (including palms and soles of feet). If untreated 1/3 progress to 3° syphilis
    - Tertiary syphillis can affect any organ and can lead to aortitis, eye involvement, meningitis, spinal column (tabes dorsalis), and skin gummas
  - Granuloma inguinale (*Klebsiella granulomatis* or Donovanosis)
    - Painless ulcer without lymphadenopathy
    - Intracellular Donovan bodies (hairpin intracellular inclusions)
  - Lymphogranuloma venereum (LGV: *Chlamydia trachomatis* types L1–L3)
    - Transient genital ulcer
    - Tender inguinal/femoral lymphadenopathy
    - If untreated, may progress to a systemic infection or secondary bacterial infection
- Urethritis/cervicitis
  - *Neisseria gonorrhea*
    - May present as urethritis, epididymitis, proctitis, or prostatitis
    - Male: Purulent discharge, dysuria
    - Female: Usually asymptomatic, but may have pelvic discomfort, dysuria, dyspareunia
  - Nongonococcal *(C. trachomatis, Mycoplasma, Ureaplasma urealyticum*)
    - Chlamydia: Frequently asymptomatic, may present with urethritis, epididymitis, or prostatitis. Gonorrhea may coexist
    - 25% of women are symptomatic, and can have a mucopurulent cervical discharge
    - 40% of untreated women will develop pelvic inflammatory disease (PID). PID is associated with infertility and ectopic pregnancy
- Vaginal discharge
  - *Trichomonas vaginalis*
    - Male: Presents with urethritis but often asymptomatic
    - Female: Malodorous, yellow-green vaginal discharge with vulvar irritation
- Genital warts
  - Condyloma acuminata (HPV)
    - HPV 6 and 11 tend to cause warts, HPV 16, 18, 31, 33, and 35 are high risk for cellular dysplasia and increase cancer risk
  - Condyloma lata (*T. pallidum*)
    - Occurs in 10% of patients with 2° syphilis.
    - Moist, broad, wart-like, highly infectious lesions that may ulcer
- Parasites
  - Pubic lice (*Phthirus pubis*)
    - Presents with genital pruritus, insects may be visible on hair or clothing
  - Scabies (*Sarcoptes scabiei*)
    - Mites burrow under skin and lay eggs, pruritus results from an inflammatory reaction to excreta

ASSOCIATED CONDITIONS

- Coinfection is common (ie, gonorrhea and chlamydia)
- HPV may be associated with carcinomas (cervical, penile, vulvar)
- PID: (Chlamydia and gonorrhea), infertility, tuboovarian abscess, Fitz-Hugh–Curtis

syndrome
- Reiter syndrome: HLA B27
- Septic arthritis: Disseminated gonococcal infection

GENERAL PREVENTION
- Abstinence
- Female and male condoms
- Education and awareness of risky behavior
- HPV vaccine (Cervarix—against HPV 16, 18; Gardasil—against HPV 6, 11, 16, 18) (3)[A]

DIAGNOSIS
HISTORY
- Symptoms, duration, onset, quality, severity, related conditions
  - Especially: Dysuria, dyspareunia, urethral discharge, genital lesions
- Screen for IV drug use, drug/alcohol abuse
- Sexual history: Prior STIs, number partners, use of protection

ALERT
Rule out sexual abuse in children with a potential STI.

PHYSICAL EXAM
- Vitals: Fever, tachycardia
- Skin: Maculopapular rash (syphilis), examine soles and palms, linear burrows (scabies)
- Cardiac: Murmur (aortic insufficiency—syphilis)
- Abdomen: Tenderness, rebound, guarding
- GU: Ulcerations, vesicles, urethral discharge, warts (GU and anal)
- Pelvic: Cervical tenderness, petechial hemorrhages (Trichomonas), uterine tenderness
- Neuro: Tabes dorsalis, Argyll Robertson pupil (syphilis)

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- HSV (3)[A]
  - Growth of HSV in culture with serologic subtyping is gold standard
  - PCR assay for HSV DNA most sensitive for diagnosis: FDA approved only for vaginal swabs in symptomatic women
  - Cytologic detection (Tzanck smear) is not sensitive and should not be relied upon
- Syphilis (3)[A]
  - Dark field microscopy or direct fluorescence antibody of lesion exudate is diagnostic
  - Serologic: Nonspecific treponemal test
    - Rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL): Sensitivity is ~80% in primary syphilis, 100% in secondary, and over 95% in tertiary syphilis
    - Must confirm with a specific treponemal test
    - Will revert to normal after therapy
  - Serologic: Specific treponemal test
    - FTA-ABS (fluorescent treponemal antibody absorbed) and TP-PA (*T. pallidum* particle agglutination)—detects antibodies against spirochetes

- Positive for life

- HIV (3)[A]
  - ELISA (an enzyme immunoassay): Rapid, sensitivity—99.7%, specificity—98.5%
  - Confirm ELISA + results by Western blot
- Chlamydia/Gonorrhea (3)[A]
  - Nucleic acid amplified test (NAAT) of urine: 1st 10–30 cc voided
  - Culture: Gonorrhea in Thayer–Martin or chocolate agar
- LGV: Swab lesion or aspirate node for culture (3)[A]
- Chancroid (3)[A]
  - *H. ducreyi* can be grown on culture, although sensitivity is $<80\%$
  - PCR is available, but not FDA approved
- Granuloma inguinale (3)[A]
  - Difficult to culture; requires visualization of dark-staining Donovan bodies in sample
- Trichomonas (3)[A]
  - Wet prep reveals flagellated protozoans
  - In men, wet prep not sensitive: Thus, culture urine, urethral swab, or semen
- Pubic lice/scabies
  - Detectable on low-power microscopy

Imaging

N/A

Diagnostic Procedures/Surgery

- HPV: Aceto-white test for occult disease
  - 3–5% acetic acid (white vinegar) application to HPV-infected mucosa turns white
  - Questionable utility: Not validated

Pathologic Findings

See “Lab” section

DIFFERENTIAL DIAGNOSIS

- Genital ulcer mnemonic **CHISEL**
  - **C**hancroid (painful)
  - **H**erpes genitalis (painful)
  - **I**nguinale (granuloma inguinale)
  - **S**yphilis (painless)
  - **E**ruption secondary to drugs
  - **L**GV
- Genital ulcer: Other causes
  - Behçet disease
  - Excoriations
  - Fixed drug eruption
  - Genital trauma
  - Pyoderma
  - Scabies
- Urethral discharge

  - Gonorrhea
  - Nongonococcal urethritis: *C. trachomatis* (35–45%), *Ureaplasma urealyticum* (15–25%), *Trichomonas vaginalis*
- Nonulcerative STDs
  - PID: *C. trachomatis, N. gonorrhea, Mycoplasma hominis*, facultative or anaerobic organisms
  - Syphilis (secondary/tertiary)
  - HIV, hepatitis B and C

TREATMENT

GENERAL MEASURES

- Screen for coinfection (including HIV)
- Educate for prevention of transmission
- Screen partner

MEDICATION

First Line

- HSV: Acyclovir 400 mg PO TID for 7–10 days, or famciclovir 250 mg PO TID for 7–10 days, or valacyclovir 1 g PO BID for 7–10 days (3)[A]
- Chancroid: Azithromycin 1 g PO in 1 dose or ceftriaxone 250 mg IM in 1 dose
- Syphilis
  - Primary: Benzathine penicillin G 2.4 million units IM in 1 dose
  - Latent: Early—benzathine penicillin G 2.4 million units IM once. Late—Benzathine penicillin G 2.4 million units IM weekly × 3 wk
  - Tertiary: Nonneurosyphilis - benzathine penicillin G 2.4 million units IM weekly × 3 wk. Neurosyphilis—aqueous crystalline penicillin G, 3–4 million units IV q4h for 10–14 days
- Granuloma Inguinale: Doxycycline 100 mg PO BID for 21 days or until all lesions are healed
- LGV: Doxycycline 100 mg PO BID for 3 wk
- Gonorrhea: Ceftriaxone 250 mg IM in 1 dose, or cefixime 400 mg PO in 1 dose; also treat for *Chlamydia*
- Chlamydia: Azithromycin 1 g PO in 1 dose or doxycycline 100 mg PO BID for 7 days
- Trichomoniasis: Metronidazole 2 g PO 1 dose
- Genital warts (condyloma)
  - Observation
  - Podofilox 0.5% solution or gel (lesion <10 cm) q12h for 3 days then off for 4 days; cycle may be repeated 4 times
- Pubic lice: Permethrin cream (1%) to affected areas and washed off after 10 min

Second Line

Please refer to the CDC's published Sexually Transmitted Diseases Treatment Guidelines 2010 for updates and alternatives

SURGERY/OTHER PROCEDURES

- Surgical intervention may be necessary secondary to complications from STIs
  - Urethritis: Urethral stricture
  - Gonorrhea/chlamydia: PID (tuboovarian abscess, ectopic pregnancy)

– HIV: Kaposi sarcomas
– Genital warts (condyloma): Ablation with laser, electrosurgery

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Many STIs cured with treatment
- HSV: Outbreaks reduced by prophylactic therapies
- HIV: Medical management portends long survival

COMPLICATIONS

Urethral stricture, carcinomas, PID, infertility, neurologic, and cardiovascular disease

FOLLOW-UP

Patient Monitoring

Screen nonpregnant females <25 yr old for gonorrhea/chlamydia. Screen nonpregnant females with risky behavior for gonorrhea/chlamydia/HIV/syphilis (4)[A]

Patient Resources

CDC. http://www.cdc.gov/std

REFERENCES

1. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among U.S. women and men: Prevalence and incidence estimates, 2008. *Sex Transm Dis.* 2013;40(3):187–193.
2. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell.* 1996;86(3):367–377.
3. Workowski KA, Berman S. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1–110.
4. Meyers D, Wolff T, Gregory K, et al. USPSTF Recommendations for STI Screening. *Am Fam Physician.* 2008;77:819–824.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Genital Ulcers
- Lymphadenopathy, Inguinal

- Sexually Transmitted Infections (STI) (Sexually Transmitted Diseases [STD]), General Images
- See Section I and Section II “Specific STD/STI"
- Urethra, Discharge

CODES

ICD9

- 042 Human immunodeficiency virus [HIV] disease
- 099.41 Other nongonococcal urethritis, chlamydia trachomatis
- 099.9 Venereal disease, unspecified

ICD10

- A56.8 Sexually transmitted chlamydial infection of other sites
- A64 Unspecified sexually transmitted disease
- B20 Human immunodeficiency virus [HIV] disease

CLINICAL/SURGICAL PEARLS

- When treating gonorrhea treat for chlamydia as these often coexist.
- HPV vaccine recommended for Either HPV vaccine is recommended (by the CDC) for 11–12-year-old girls. Quadrivalent HPV vaccine is recommended for 11–12-year-old boys. Start series at age 9 years. Vaccination is also recommended for 13–26-year-old females and13–21-year-old males who have not completed the vaccine series. Quadrivalent HPV vaccine may be given to 22–26-year-old males and is routinely recommended for both men who have sex with men (MSM) and immunocompromised persons aged 22 through 26 years.
- Urethritis may lead to urethral stricture in males.

SICKLE CELL DISEASE, UROLOGIC CONSIDERATIONS

Philip J. Dorsey, Jr., MD, MPH
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BASICS

DESCRIPTION

- Sickle cell (SC) disease is a chronic hemoglobinopathy transmitted genetically and marked by severe chronic hemolytic anemia and periodic acute painful episodes.
- The heterozygote is termed SC trait and usually has no symptoms.
- Major GU complications can include priapism and a spectrum of renal disorders from hematuria and decreased renal concentrating ability through renal medullary carcinoma and renal failure.

EPIDEMIOLOGY

Incidence

- 1:500 African American births
- 1:1,000 Hispanic American births
- 2 million Americans, or 1 in 12 African Americans, carry the SC trait.
- ~4,000–5,000 pregnancies are at risk of SC disease.
- Life expectancy: Men, 42 yr; women, 48 yr

Prevalence

- Prevalence estimated at 8% of African Americans
- 8–10% of African Americans have SC trait
- 25–30% of Western Africans have SC trait

RISK FACTORS

Family history of disease

Genetics

- Autosomal codominant inheritance pattern
- Allele is on chromosome 11
- Several haplotypes; allelic with β-thalassemia
- SC disease: Inheritance of 2 alleles, all RBCs contain hemoglobin (Hb)S
- SC trait: From 1 allele, 40% of Hb is HbS

PATHOPHYSIOLOGY

- Sickling of RBCs caused by HbS in ischemic state leading to vaso-occlusive state and causing most complications of SC disease:
  – Substitution of valine for glutamate at 6th amino acid position
- HbS tetramer: The deoxygenated state polymerizes into double-stranded filaments and bundles
- Chronic anemia is the hallmark of the disease; RBC mean lifespan: 17 days
- SC trait (heterozygote) usually asymptomatic
- Decreased renal concentrating ability is common and results in polyuria and nocturia

- Hematuria is due to chronic papillary infarctions:
- Predominantly left-sided
- Renal infarction due to ischemia; may present with nausea, vomiting, abdominal and flank pain, and HTN
- Renal papillary necrosis due to ischemia; may cause secondary infection or obstruction
- Progressive renal failure and proteinuria due to glomerular injury; renal failure in ~10%
- Renal medullary carcinoma:
  – An aggressive malignancy
  – Almost exclusively found in young African American patients with SC trait, or SC disease

ASSOCIATED CONDITIONS
- Acute papillary necrosis
- Anemia
- Hepatitis C and HIV (increased risk for these and other transfusion-associated infections)
- Priapism
- Renal medullary carcinoma
- Hyposthenuria (Urine with low specific gravity)
- Urinary tract infections

GENERAL PREVENTION
Avoid situations that precipitate sickling episodes (dehydration, hypoxia, cold, infections, fever, acidosis).

DIAGNOSIS
HISTORY
- Prior episodes of SC complications and outcomes
- Timing of sexual maturation (delayed puberty)
- Determine time length of any priapism episodes
- Painful crisis brought on by cold or dehydration
- Nocturnal enuresis

PHYSICAL EXAM
- HTN is unusual.
- Look for staging of sexual maturation.
- Palpate testes in men to check for atrophy.
- In cases of priapism, examine the glans to determine bi- or tricorporal involvement.
- Splenic sequestration causes painful enlargement of the spleen.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Complete blood count (CBC): Note degree of anemia
- Peripheral blood smear: Presence of sickled or deformed RBCs with high reticulocyte count
- Hb electrophoresis: Types and percentages of Hb present
- SC prep: Rapid determination of SC disease vs. trait vs. normal. Check fet al Hb level
- Urine analysis: Hematuria, proteinuria, or infection
- Urine culture: Infection if indicated by urine analysis or symptoms

- Serum creatinine
- Monitor for renal insufficiency, and calculate GFR as needed. The creatinine clearance may overestimate the GFR.
- Hyperphosphatemia may be present
- Blood Gas (BG) measurement on corporal blood aspirates in priapism setting to assess high- vs. low-flow state:
  – pH <7.10 (acidotic) suggests a low-flow state.

Imaging
- CT urogram using low osmolar contrast, as indicated for hematuria:
  – May not be useful in progressive renal insufficiency (poor concentrating ability limits visualization)
  – Papillary necrosis may be present
- Renal medullary carcinoma may present as a centrally located infiltrative lesion invading the renal sinus with peripheral caliectasis
- US: Noninvasive; look for renal source of hematuria if renal insufficiency precludes contrast use
- MRI when indicated

Diagnostic Procedures/Surgery
- Cystoscopy: As needed for hematuria
- Retrograde pyelograms: Upper-tract sources of bleeding if IVP limited or suspect papillary necrosis
- Ureteroscopy: For hematuria as indicated
- Renal biopsy: As needed for specific glomerulopathies
- Impotence evaluation with duplex blood flow studies. (Preferred over nocturnal penile tumesence (NPT) monitoring).

Pathologic Findings
- Peripheral blood smear: Presence of sickled or deformed RBCs
- Penile corporal fibrosis seen in patients with stuttering or recurrent priapism
- Hb electrophoresis: Types and percentage of Hb present
- Renal biopsy:
  – Early: Glomerular hypertrophy, hemosiderin deposits, focal areas of hemorrhage or necrosis
  – Late: Interstitial inflammation, edema, fibrosis, tubular atrophy, and papillary infarcts

DIFFERENTIAL DIAGNOSIS
- Other SC diseases: SC trait, sickle-β thalassemia, etc.
- Hematuria (see Section I topic)
- Papillary necrosis (see Section I topic)
- Priapism (see Section I topic)

TREATMENT

GENERAL MEASURES
- For acute SC crisis:

- Oxygenation, nasal canula
- Aggressive hydration: Counters dehydration, increases perfusion, and improves blood rheology
- Metabolic alkalinization limits further sickling
- Pain control
- Narcotics for pain: Risk of addiction is negligible in the acute setting
  - Patient controlled analgesia (PCA) for inpatients

MEDICATION

First Line

- Simple transfusion:
  - Transfusion performed to increase proportion of RBCs with normal Hb to decrease sludging
  - Blood transfusion performed less liberally than in past because of risks of exposure to antigens
  - Indications for transfusion:
    - Acutely: Persistent, recurrent priapism after failure of corporal irrigation, injection of vasoactive medications and other measures before shunting procedure or if life-threatening hemorrhage
    - Preoperative transfusion if significant anemia or if indicated by procedure
- Exchange transfusion:
  - Used when needed to remove RBCs and replace with transfused blood products if simple transfusion fails
  - Risk of cerebrovascular accidents with increased hematocrit, causing a relative hyperviscosity (ASPEN syndrome)
- Antibiotics: As needed for infections
- Hematuria:
  - Diuresis with IV hydration is standard
  - Alkalization decreases sickling and hematuria
  - Aminocaproic acid is used to induce thrombosis and control persistent and threatening hematuria, but can cause clot formation in the urinary tract
  - Persistent or life-threatening hematuria may rarely necessitate nephrectomy
  - High-dose urea in selected cases
- Priapism (see Section I “Priapism”):
  - Prompt corporal irrigation to induce detumescence and remove old clotted blood
  - Use α-adrenergic agents for corporal injection to decrease inflow to corpora for detumescence
  - Impotence due to fibrosis can be managed with penile prosthesis after 6 mo
- Delayed sexual maturation:
  - Cautious supplementation of testosterone

Second Line

NA

SURGERY/OTHER PROCEDURES

May be needed in the acute setting for priapism or urinary tract obstruction due to sloughed

papilla

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Follow-up and monitoring by hematologist
- Hydroxyurea
- α-Adrenergic medication (ie, pseudoephedrine) and low-dose PDE-5 inhibitors used for prevention of stuttering priapism
- Folic acid and penicillin in pediatrics
- Genetic counseling

Complementary & Alternative Therapies

NA

ONGOING CARE

PROGNOSIS

Several factors aside from genetic inheritance determine prognosis, including frequency, severity, and nature of specific complications.

COMPLICATIONS

- Nephropathy:
  - Renal insufficiency
  - Vaso-occlusion in renal medulla secondary to hypertonicity, inducing HbS sickling
  - Progressive cortical infarction leads to CRF; average age of onset is 23 yr
  - Hyposthenuria: Inability to maximally concentrate urine in the face of dehydration or vasopressin
  - Usually associated with renal insufficiency; able to dilute urine
  - Associated impairment of K excretion
    - Renal biopsy: Focal and segmental glomerulosclerosis, membranous glomerulopathy, or MPGN
    - Proteinuria can progress to full-blown nephrotic syndrome
- Hematuria:
  - Microscopic or gross hematuria; mechanism unknown. Source rarely identified; possibly due to papillary necrosis
  - Usually unilateral (left-sided)
  - Male > female
  - Usually remits with conservative measures (eg, bedrest, hydration) with 50% recurrence
- Papillary necrosis:
  - Due to medullary ischemia from sickling in vasa recta (see in 40% of patients with SCD)
  - Radiologic diagnosis can be difficult due to poor concentrating ability of kidneys
  - Can cause hematuria
  - Can obstruct, if sloughed papillae blocks the UPJ or ureter
- Priapism:

  - Affects ~66% of SC disease patients
  - 2 age peaks; onset usually after puberty
  - 5–13 yr, then at 21–29 yr
  - Initiating factors: Nocturnal penile tumescence and sexual arousal
  - Typically, bicorporal involvement
  - Pathophysiology: Engorgement and sludging of the corpora, with no outflow and low flow
  - Major risk is fibrosis and subsequent impotence; children have greater chance of recovery and subsequent erectile function
- Impotence:
  - Fibrosis from recurrent episodes of priapism
- Delayed sexual maturation:
  - Primary hypogonadism, due to testicular ischemia or infarction, hypopituitarism, or hypothalamic insufficiency
  - Correlates with severity of sickle disease
- Infertility:
  - Complication of hypogonadism and direct testicular insult by ischemia and infarction
- UTI:
  - Usually *Escherichia coli*, or other gram-negative bacteria
  - Can lead to more serious infections or bacteremia
- RTA:
  - Incomplete distal RTA (type IV) from progressive medullary infarction
  - Inability to lower urine pH to <5
  - Can develop hyperchloremic metabolic acidosis in SC disease and renal insufficiency
  - Not associated with nephrolithiasis
- Acute urinary retention:
  - Related to acute, painful SC; transient, resolves with resolution of the acute episode
- Renal medullary carcinoma:
  - Median age 13 yr
  - High mortality

FOLLOW-UP

Patient Monitoring

- Renal function over time
- Regular follow-up

Patient Resources

- http://www.cdc.gov/ncbddd/sicklecell/freematerials.html

REFERENCES

1. Morrison BF, Burnett AL. Urological complications of sickle cell disease. *AUA Update Series*. 2012;31(29):289–296.
2. Panepinto JA, Bonner M. Health-related quality of life in sickle cell disease: Past, present, and future. *Pediatric Blood Cancer*. 2012;59(2):377–385.
3. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet*. 2010;376(9757):2018–2031.

ADDITIONAL READING

- Levey HR, Kutlu O, Bivalacqua TJ. Medical management of ischemic stuttering priapism: A contemporary review of the literature. *Asian J Androl.* 2012;14(1):156–163.
- Brawley OW, Cornelius LJ, Edwards LR. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. *Ann Intern Med.* 2008;148(12):932–938.

See Also (Topic, Algorithm, Media)

- Papillary Necrosis, Renal
- Priapism
- Priapism, stuttering (intermittent priapism)
- Renal Medullary Carcinoma (Renomedullary Interstitial Cell Tumor)

CODES

ICD9

- 282.60 Sickle-cell disease, unspecified
- 599.70 Hematuria, unspecified
- 607.3 Priapism

ICD10

- D57.1 Sickle-cell disease without crisis
- N48.30 Priapism, unspecified
- R31.9 Hematuria, unspecified

CLINICAL/SURGICAL PEARLS

Urologic complications are common in SC disease.

SPERMATIC CORD MASS AND TUMORS

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BASICS

DESCRIPTION

- The spermatic cord extends from the internal inguinal ring to the testicle, passing through the inguinal canal.
- Cord structures consist of vas deferens, internal and external spermatic arteries, artery to the vas deferens, pampiniform plexus, lymphatics, nerves, investing layer of fascia, and cremaster muscle.
- Considered paratesticular tissue
- Masses or swelling can be cystic or solid:
  - Most cystic (70–75%)
  - Most benign (75–80%)
  - Usually asymptomatic
  - Most solid spermatic cord masses are also benign

EPIDEMIOLOGY

Incidence

Varies by type (see Pathophysiology)

Prevalence

Varies by type (see Pathophysiology)

RISK FACTORS

Varies by type (see Pathophysiology)

Genetics

Varies by type (see Pathophysiology)

PATHOPHYSIOLOGY

- Cord mass can arise from cord contents or from structures above or below the cord
- Generally nonacute and benign
- Most common malignant tumors are sarcoma
- Varicocele
  - Enlarged, tortuous spermatic veins above the testis; most common on the left side
  - Isolated right-sided varicocele is rare and may suggest retroperitoneal pathology
  - Asymptomatic, often found on routine exam
  - Grade I: Palpable, grade II: Palpable without Valsalva, grade III: Visible
  - May cause infertility; likely increasing scrotal temperature, impairing spermatogenesis
- Hydrocele
  - Patent processus vaginalis causes collection of peritoneal fluid between the visceral and pariet al layers of tunica vaginalis
  - Painless groin mass contiguous with the cord structures that transilluminates

- Communicating hydrocele with “indirect hernia”; more commonly seen in infancy
- Congenital; incidence of 4%, seen in early adolescence. May have associated inguinal hernia (usually children)

- Spermatic cord hydrocele
  - Loculated fluid collection along the spermatic cord, separated from and located above the testicle and the epididymis
  - Rare congenital anomaly from abnormal closure of the processus vaginalis distally and in some cases proximally; 2 types:
    - Encysted hydrocele of the cord: The fluid collection does not communicate with the peritoneum/tunica vaginalis
    - Funicular hydrocele of the cord: Distal closure of the processus vaginalis with fluid collection along the cord, communicating with the peritoneum at the internal ring
- Spermatocele:
  - Cloudy fluid and sperm-filled cyst arising from epididymal tubules; usually at the head of epididymis
  - Very common (up to 30% of general population), usually asymptomatic; incidental finding on ultrasound
- Inguinal hernia in adults:
  - Late-onset communicating “indirect” hernia in adults
  - “Direct” through the floor of the inguinal canal
  - Indirect presents as mass in inguinal cord or extends through external ring into scrotum
- Lipoma of the cord:
  - Benign; most common tumor of the cord and paratesticular tissues
  - From adipose tissue of the cord; fat collections around hernia sac; not true lipomas
- Adenomatoid tumor:
  - Benign neoplasms; most common epididymal tumor; no reliable echo pattern for diagnosis; can involve the spermatic cord
- Sarcomas:
  - Rare lesions of spermatic cord, epididymis, and paratesticular soft tissue, from muscle, adipose, or connective tissue
  - Incidence peaks: Adolescence and >40.
  - Rhabdomyosarcoma and leiomyosarcoma most common
  - High rate of recurrence after excision
- Other malignant tumors of spermatic cord:
  - Melanoma and metastatic cancers are rare.
- TB of spermatic cord:
  - Rare; 70% of cases have history of TB; usually in young, sexually active males
  - Presents as TB epididymitis; difficult to differentiate from acute epididymoorchitis
  - Usually secondary to infection of epididymis via direct extension
- Sarcoidosis:
  - Systemic granulomatous disease; increased intestinal adsorption of calcium; hypercalcemia and hypercalciuria
- Funiculitis:
  - Inflammation of spermatic cord secondary to severe epididymitis or due to trauma

- Filarial hydroceles:
  – Caused by *Wuchereria bancrofti*; often have a thickened spermatic cord and epididymis
- Undescended testicle
- Retractile testicle

ASSOCIATED CONDITIONS
- Renal tumor invading renal vein or retroperitoneal mass compressing right gonadal vein with isolated right-sided varicocele or any acute onset of varicocele
- TB with spermatic cord involvement
- Filariasis

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Patients present with symptomatic or asymptomatic mass with or without swelling.
- Most masses are painless at onset.
- Presence or absence of pain does not differentiate benign or malignant mass.
- Scrotal elevation may provide relief.
- Recumbent position may resolve mass and pain in varicocele and communicating hydrocele.
- History of cryptorchidism is important.

ALERT
Always rule out torsion of cord if pain is acute.

PHYSICAL EXAM
- Examine patient in warm room in both upright and supine positions (1).
- Cord mass can be palpated in the inguinal region or the upper scrotum.
- Palpate mass with thumb and 1st 2 fingers of both hands and note character (hard, firm, cystic).
- Transillumination signifies cystic mass:
  – Cystic mass may not transilluminate if thick wall, chronic inflammation, or blood present.
- Spermatic cord can be followed to the internal inguinal ring by palpitation.
- Verify both testicles present in scrotum.
- The vas deferens can be felt in the scrotum by 1st encircling the cord with the fingers and allowing small amounts of cord to pass through.
- Valsalva maneuver performed with patient in supine and standing positions for varicocele or hernia:
  – Usually palpable posterior to and above the testicle and can mimic solid mass.
  – Crucial to assess testicular volume and consistency in boys with varicocele.
  – Ipsilateral testis may be atrophic.
  – Palpation can determine superior and inferior extent of mass (unlike inguinal hernia).
- Communicating hydrocele:
  – Enlarges when upright and with activities that increase intra-abdominal pressure.
  – Supine position drains fluid into peritoneal cavity and decreases size.

  – Abdominal contents may be found in the sac: Small intestine, omentum, or bladder.
  – Proximal limit not palpable since contents extend through internal ring.
- Adult inguinal hernia:
  – May be direct or indirect, reducible or incarcerated.
  – Superior extent of the mass not palpable.
  – May have bowel sounds over the mass.
  – Attempt to reduce hernia with gentle pressure in supine or Trendelenburg position.
  – After reduction, insert finger through external ring into inguinal canal.
  – Cough or Valsalva maneuver produces impulse, caused by abdominal contents felt at fingertip.
- Lipoma of the cord is palpated as smooth, firm mass in inguinal canal or upper scrotum:
  – Nontender; does not transilluminate.
  – Usually incidental finding during inguinal procedures.
  – Important to rule out concomitant inguinal hernia by noting the intact external inguinal ring on exam.
- Adenomatoid tumors found on routine exam:
  – Painless, well-circumscribed, hard; nearly 50% at the head of the epididymis
  – Most common solid paratesticular mass.
  – Usually asymptomatic and slow growing.
- Sarcomas present as firm to hard mass, occasionally tender:
  – May be distinct and well circumscribed or invade the surrounding tissues.
  – Explore all solid masses for malignancy.

ALERT
No clinical signs or symptoms reliably distinguish between benign or malignant solid mass.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Urinalysis to rule out infectious processes

Imaging

- Scrotal US: Solid vs. cystic mass (2)
  – Cannot differentiate benign or malignant mass
- MRI or CT in certain clinical scenarios

Diagnostic Procedures/Surgery

Solid masses: Biopsy (mostly excisional) with surgical exposure

Pathologic Findings

Distinguish leiomyosarcoma from leiomyoma based on occasional or absent mitotic figures and uniform cellular arrangement

DIFFERENTIAL DIAGNOSIS

- Adenomatoid tumor of the cord (1,2)
- Epidermoid cyst, epididymitis/epididymo-orchitis, funiculitis, tuberculoma
- Hernia
- Hydrocele
- Hydrocele of the cord

- Hemangioma
- Inguinal lymphadenopathy
- Leiomyoma
- Malignant tumor: Liposarcoma, rhabdomyosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, metastatic melanoma, and others
- Undescended/retractile testicle, polyorchidism
- Sperm granuloma, spermatocele
- Testis tumor
- Varicocele
- Vasitis and vasitis nodosa (usually associated with epididymitis)

ALERT
Torsion of the cord or incarcerated/strangulated hernia is surgical emergency.

TREATMENT

GENERAL MEASURES
- Distinguish testis and epididymis (physical exam, transillumination, scrotal US).
- Most cystic masses do not need treatment.
- Investigate pain as presenting feature; sarcoma is often misdiagnosed as inflammatory lesion.

MEDICATION
First Line
Anti-TB drug therapy for 6–9 mo for TB (tuberculoma) in spermatic cord

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Spermatocelectomy if painful or symptomatic
- Hydrocelectomy (only if large or symptomatic)
- In children, repair hydrocele by age 2 if it does not resolve; usually associated with indirect hernia
  – Communicating hydrocele often resolves in children within 1st yr
- Inguinal hernia (adults): Herniorrhaphy
- Communicating hydrocele with hernia:
  – Explore through inguinal incision
  – Exploration of asymptomatic contralateral inguinal canal in children with inguinal hernia or communicating hydrocele is controversial
- Varicocele:
  – Varicocelectomy *may* relieve pain and improve fertility
  – Standard testis volume measurements are mainstay of assessing need for surgical management of varicocele
- Explore solid masses for malignancy:
  – Inguinal incision; testis is delivered and inspected
  – Early control of cord at internal ring

– Biopsy to confirm diagnosis
- TB of cord: Excision of the mass
- Sarcoma: Radical orchiectomy with high ligation of the cord (wide resection margins if possible); possible flaps to reconstruct large anatomic defects

ADDITIONAL TREATMENT

Radiation Therapy

Retroperitoneal lymphadenopathy with adjuvant radiation or chemotherapy indicated for malignant tumor

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Excellent for benign lesions

COMPLICATIONS

Risk of infertility in varicocele

FOLLOW-UP

Patient Monitoring

- None for benign masses
- Liposarcoma, leiomyosarcoma, and rhabdomyosarcoma may recur; closely monitor (physical exam, imaging)

Patient Resources

N/A

REFERENCES

1. Eble JN, Sauter G, Epstein JI, et al., eds. Pathology and genetics of tumours of the urinary system and male genital organs. *World Health Organization classification of tumours*. Lyon, France: IARC Press; 2004.
2. Dogra V, Gottlieb RH, Oka M. Sonography of the scrotum. *Radiology*. 2003;227:18–36.

ADDITIONAL READING

Wieder J, Hu J, Bui M, et al. Case scenario: 69-year-old male with left spermatic cord mass. *Rev Urol*. 2002 Summer;4(3):153–156.

See Also (Topic, Algorithm, Media)

- Groin/Inguinal Mass, Male and Female
- Lipoma, Spermatic Cord
- Paratesticular Tumors
- Scrotum and Testicle, Mass
- Spermatic Cord Mass and Tumors Images ☼

- Varicocele, Adult
- Varicocele, Pediatric

CODES

ICD9

- 171.6 Malignant neoplasm of connective and other soft tissue of pelvis
- 222.8 Benign neoplasm of other specified sites of male genital organs
- 608.9 Unspecified disorder of male genital organs

ICD10

- C49.5 Malignant neoplasm of connective and soft tissue of pelvis
- D29.8 Benign neoplasm of other specified male genital organs
- N50.9 Disorder of male genital organs, unspecified

CLINICAL/SURGICAL PEARLS

- Pain may be attributed to emergencies such as torsion.
- Ultrasound is a valuable diagnostic tool.

SPERMATOCELE

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BASICS

DESCRIPTION

- Spermatocele is a benign, fluid-filled cystic mass most often in the head (caput) of the epididymis. The spermatocele can occur in other areas of the epididymis, rete testis, or along the vas deferens.
- Sometimes referred to a "spermatic cyst" or "acquired epididymal cyst."
- Clinically, spermatocele is differentiated from a hydrocele in that the spermatocele may contain viable or nonviable spermatozoa.
- Usually not a cause of epididymal obstruction.
- Also called an epididymal cyst or acquired epididymal cyst in the literature (1):
  - Some sources state that the epididymal cyst is congenital and represents the most common epididymal mass.
  - The origin of the epididymal cyst is thought to be lymphatic.
  - Epididymal cyst fluid does not contain spermatozoa.
  - Clinical management is similar, so the differentiation between spermatocele and epididymal cyst may not be significant.

EPIDEMIOLOGY

Incidence

- Peak incidence in 4th–5th decades
- Rare in children
- No racial or ethnic predilection
- Reported in 30–70% of postpubertal males undergoing high-resolution scrotal US

Prevalence

N/A

RISK FACTORS

- Diethylstilbesterol (DES) exposure in utero
- Inflammation
- Not clearly related to prior vasectomy, prior epididymitis, or herniorrhaphy
- Trauma
- Von-Hippel Lindau (VHL) syndrome
  - Mostly epididymal cystadenomas with simple cysts less common

Genetics

- VHL syndrome:
  - Mutations of the VHL suppressor gene on 3p.
  - Increased incidence of epididymal cysts and papillary cystadenomas of the epididymis

PATHOPHYSIOLOGY

- Main concern is usually that of confusion with a true testicular mass.
- Precise mechanism is unknown.
  - Cystic dilatations of tubules of the epididymis
  - The efferent ductules in the head of the epididymis.
- The distinction between a spermatocele and an epididymal cyst is based on size; epididymal cystic masses >2 cm are spermatoceles. Spermatoceles are always located superior to the testis and are palpated as distinct from the testis, which differentiates them from hydroceles.
- Spermatoceles generally range in size from 2 to 5 cm.
- Trauma and inflammation may result in obstructed efferent ductules or epididymal tubules, resulting in a dilated spermatocele.
- No effect on fertility.
- Most are idiopathic.
- Most ≤ 1 cm in size.

ASSOCIATED CONDITIONS
- Epididymal obstruction may rarely be present
- Prior vasectomy
- High association with tubular ectasia of the rete testis

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Typical presentation is a painless, asymptomatic, intrascrotal mass found on testicular self-exam or on routine office exam.
- Occasionally may present with orchialgia or scrotal heaviness.
- No associated urinary symptoms

PHYSICAL EXAM
- Palpation shows a smooth, soft, spherical nontender mass at the head (caput) of the epididymis.
- Lies just superior and posterior to the testis but is distinct from testis.
- A cystic mass above the testis is usually demonstrated on scrotal transillumination.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urine analysis
- Urine culture
- Serum AFP, hCG, LDH if there is concern over testis tumor

Imaging
- Scrotal US is diagnostic:
  - Lesion is hypoechoic with posterior acoustic enhancement
  - May have internal echoes
  - MRI if US is indeterminate

Diagnostic Procedures/Surgery

Needle aspiration for diagnosis is not usually indicated. If indicated, a 30-gauge needle can be used to aspirate the cyst fluid.

Pathologic Findings

- Clear or opaque fluid-filled mass
- Fluid contains spermatozoa (live or dead), lymphocytes, and cellular debris
  - Hydrocele, the other common cystic lesion is devoid of spermatozoa
- Fibromuscular wall lined by cuboidal epithelium

DIFFERENTIAL DIAGNOSIS

- Adenomatoid tumor of the epididymis:
  - Most common solid tumor of the epididymis
- Ectopic tissues:
  - Adrenal cortical rests
  - Splenogonadal fusion
- Epidermoid cyst
- Epididymal calcinosis
- Epididymal cystadenoma/papillary cystadenoma;
  - 2/3 associated with von Hippel–Lindau syndrome
  - 1/3 of all epididymal tumors
  - 2/3 associated with VHL syndrome
  - On US, most common appearance is 15–20-mm solid mass with small cystic components.
- Epididymitis Epididymo-orchitis:
  - Acute; very tender on exam
  - Chronic; may have secondary calcification
  - Common cause of epididymal pain
- Fibroma of epididymis
- Fibrous pseudotumor
- Funiculitis
- Granulomas: Sarcoidosis, TB, histoplasmosis
- Hernia
- Hydrocele
- Hydrocele of the cord
- Leiomyoma
- Malignant epididymal tumor:
  - Primary (very rare): Liposarcoma, rhabdomyosarcoma (high on differential in children), leiomyosarcoma, adenocarcinoma, lymphoma
  - Metastatic: Prostate, kidney, stomach most common
- Papillary cystadenoma:
- Polyorchidism
- Sarcoid
- Sperm granuloma:
  - Seen in 40% post vasectomy or 2.5% idiopathic in general population
  - Granulomatous lesion with few giant cells
  - Consequence of extravasation of spermatozoa generally post vasectomy (of vasectomized men and of general population)

- Testis tumor
- TB of the epididymis
- Varicocele
- Vasitis and vasitis nodosa (usually associated with epididymitis)
- Young syndrome (obstructive azoospermia, sinusitis, bronchiectasis)

TREATMENT

GENERAL MEASURES

- Most do not require treatment unless symptomatic.
- Supportive care is usually sufficient:
  - Scrotal supporter
  - Heat
  - NSAIDs
  - Continued testicular self-exam

MEDICATION

First Line

Oral analgesics or NSAIDs

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Spermatocelectomy is elective and indicated for progressive enlargement or persistent pain
- Performed by magnified or microsurgical dissection of cyst from epididymal bed to preserve arterial supply and avoid injury to the epididymal tubules and resultant epididymal obstruction (2)
- Ligation of spermatocele at its stalk
- Surgery should be deferred in men seeking fertility since the spermatocelectomy can occasionally cause epididymal obstruction

ADDITIONAL TREATMENT

- Transscrotal cyst aspiration with or without sclerotherapy:
  - Agents used have included tetracycline, fibrin glue, phenol, talc powder, and others
  - Not usually recommended due to high recurrence rate and chemical epididymitis
  - Spermatocele aspiration may provide a sperm source for azoospermic men treated by IVF or ICSI

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Most require no intervention and do not lead to epididymal obstruction.

- Recurrence rate is low postoperatively.

COMPLICATIONS
- Orchalgia
- Concern for cancer
- Postoperative spermatocelectomy:
  - Regrowth of spermatocele
  - Vascular injury during spermatocelectomy causing testicular atrophy
  - Infection
  - Epididymal obstruction: Very concerning in cases of bilateral spermatocele surgical repair. Some authors recommend sperm cryopreservation in this setting

FOLLOW-UP

Patient Monitoring
- Periodic scrotal/testicular self-exam
- Subsequent scrotal US if symptoms recur

Patient Resources
- Urology Care Foundation (AUA). http://www.urologyhealth.org/urology/index.cfm?article=117

REFERENCES

1. Walsh TJ, Seeger KT, Turek PJ. Spermatoceles in adults: When does size matter? *Arch Androl*. 2007;53(6):345–348.
2. Kauffman EC, Kim HH, Tanrikut C, et al. Microsurgical spermatocelectomy: Technique and outcomes of a novel surgical approach. *J Urol*. 2011;185(1):238–242.

ADDITIONAL READING

- Algaba F, Mikuz G, Boccon-Gibod L, et al. Pseudoneoplastic lesions of the testis and paratesticular structures. *Virchows Arch*. 2007;451:987–997.
- Gray CL, Powell CR, Amling CL. Outcomes for surgical management of orchalgia in patients with identifiable intrascrotal lesions. *Eur Urol*. 2001;39(4):455–459.
- Vohra S, Morgentaler A. Congenital anomalies of the vas deferens, epididymis and seminal vesicles. *Urology*. 1997;49:313–321.
- Woodward PJ, Schwab CM, Sesterhenn IA. From the archives of the AFIP: Extratesticular scrotal masses: Radiologic-pathologic correlation. *RadioGraphics*. 2003;23:215–240.

See Also (Topic, Algorithm, Media)
- Epididymal Cyst
- Epididymal Cystadenomas
- Epididymis, Mass (Epididymal Tumor and Cysts)
- Hydrocele
- Paratesticular Tumors, General
- Scrotum and testicle, Mass
- Sperm Granuloma
- Spermatic Cord Mass and Tumors
- Spermatocele, Images

- Testis, Pain (Orchalgia)

CODES

ICD9

608.1 Spermatocele

ICD10

- N43.40 Spermatocele of epididymis, unspecified
- N43.41 Spermatocele of epididymis, single
- N43.42 Spermatocele of epididymis, multiple

CLINICAL/SURGICAL PEARLS

- A common pitfall is the failure to distinguish between hydrocele and spermatocele preoperatively.
- Spermatoceles are always located superior to the testis and are palpated as distinct from the testis, which differentiates them from hydroceles.
- Ideal surgical approach: Incise the tunica vaginalis over the tunica albuginea testis to maintain the spermatoceles definition throughout its excision.

SPINAL CORD INJURY, UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Spinal cord injury (SCI) may result from damage to the spinal column secondary to trauma, vascular injury, infection, or disc prolapse
- SCI can impact lower urinary tract and sexual function and varies based on level and completeness of injury
- Upper and lower urinary tract dysfunction due to SCI can lead to significant morbidity/mortality
  - Increased risk for renal failure, UTI (urinary tract infection), renal/bladder calculi, and malignancy

EPIDEMIOLOGY

Incidence

40 cases per million in US; 12,000 new cases per year (1)

Prevalence

- 270,000 people alive in US in 2012 with SCIs
- Extent of lesion
  - SCI are graded using the ASIA scale (American Spinal Injury Association)
  - 45% of injuries are neurologically complete (ASIA grade A), 55% incomplete (ASIA B-D)
- Age: SCI previously affected young adults with most injuries occurring between the ages of 16 and 30. Since 2005, the average age of injury is 41 yr
- 53% tetraplegia, 46% paraplegia, and less than 1% experience complete neurologic recovery
- Gender: 80.6% of spinal cord injured patients in US are male
- Race/ethnicity: Since 2005, 66% of SCI patients are Caucasian, 26.2% African American, 2.1% Asian, and 0.9% Native American

RISK FACTORS

- Trauma
  - Since 2005, motor vehicle accidents account for nearly 40% of SCI cases, followed by falls and acts of violence (primarily gunshot wounds)
- Vascular injury
- Disc prolapse
- Spinal cord tumors

Genetics

Congenital malformations (myelodysplasia)

PATHOPHYSIOLOGY

- Spinal control of micturition is located at the S2–S4 level of the spinal cord
- The sacral cord begins at spinal column level T12–L1. The cord terminates in the cauda

equina at approximately spinal column level L2
- Spinal shock = a period of decreased excitability of spinal cord segments at or below the level of the lesion
  - Involves suppression of autonomic and somatic activity resulting in an acontractile, areflexic bladder
  - Bladder neck (smooth sphincter) generally remains competent/closed
  - Urinary retention is generally the rule
  - Generally lasts 6–12 wk after injury
- A significant association exists between the level of a spinal cord lesion and the corresponding bladder and sphincter behavior
- Most patients with complete SCI show clinical signs and symptoms of bladder dysfunction; incomplete SCI demonstrates variable function
  - Suprasacral lesions generally result in an upper motor neuron deficit with NDO (neurogenic detrusor overactivity) with or without DSD (detrusor sphincter dyssynergia)
  - Sacral lesions generally produce a lower motor neuron deficit with resulting detrusor areflexia
- NDO: Involuntary detrusor contraction during the filling and storage phase
  - Symptoms: Urinary urgency, frequency, incontinence
  - Can lead to upper tract damage due to detrusor hypertonicity, high voiding pressures, high-pressure reflux, recurrent UTIs and their sequelae
- DSD: Abnormal reflexive sphincter contraction during involuntary detrusor contraction
  - Causes bladder outflow obstruction, increased post void residuals (PVRs) and elevated intravesical pressures
  - Can lead to damage to upper tracts, UTIs, urolithiasis
  - Intravesical pressure >40 cm H_2O is responsible for sequelae of NDO-DSD
  - DO (detrusor overactivity) must be present for DSD, but NDO may occur without DSD
  - 10–20% of patients have internal (bladder neck) sphincter dyssynergia with external sphincter dyssynergia
- Detrusor areflexia
  - Results from damage to sacral reflex arc which results in absent detrusor contraction
  - Results in low-pressure storage (volumes up to 500 mL)
  - Decreased risk of upper tract damage

ASSOCIATED CONDITIONS
Arachnoiditis, Guillain–Barré, multiple sclerosis, spinal stenosis, transverse myelitis, tumor, or malignancy

GENERAL PREVENTION
- Drive safely, wear seatbelt, prevent falls
- Prevent secondary complications of SCI

DIAGNOSIS
HISTORY
- Onset, duration, etiology of injury
- Voiding symptoms

  – Irritative or obstructive
  – Incontinence: Stress, urge, overflow
- Method of urinary management
  – Voluntary voiding, clean intermittent catheterization (CIC), indwelling catheter or Credé/Valsalva voiding with or without external catheter
- Urinary tract infection (UTI)
  – Associated symptoms, severity, and frequency of recurrence
- Urolithiasis episodes, interventions, calculus composition
- Erectile dysfunction

PHYSICAL EXAM
- Temperature, blood pressure
- Palpable flank mass/tenderness
- Suprapubic fullness: Distended bladder
- Evaluate incontinence; spontaneous or with stress maneuvers
- GU exam for testicular or prostate abnormality
- Complete Neurologic exam: Sensation, tone, and sphincter control
- Bulbocavernosus reflex: Contraction of anal sphincter with stimulation of glans penis/clitoris

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Blood studies:
  – Serum chemistry: Basic metabolic panel (BMP) (assess renal function and acidosis), CBC
  – Urinalysis

Imaging
- Renal US (ultrasound): To screen for calculi, hydronephrosis, masses
- VCUG (voiding cystourethrogram)
  – Trabeculation, diverticulum, incomplete emptying, vesicoureteral reflux
- Nuclear medicine renal scan:
  – Performed to evaluate for compromised function or presence of obstructive element

Diagnostic Procedures/Surgery
- PVR: To ensure complete bladder emptying
- Video urodynamics: Essential to assess and follow bladder dynamics and anatomical changes so that effective urologic management can be tailored appropriately

Pathologic Findings

Bladder wall thickening and fibrosis common

DIFFERENTIAL DIAGNOSIS
- Infection
- Intervertebral disc disease
- Malignancy (metastasis)
- Spinal cord vascular disease
- Traumatic
- Vertebral body injury

TREATMENT

GENERAL MEASURES

- Goal of treatment: Optimize intravesical bladder pressures to protect upper urinary tract
- Spontaneous voiding with continence
- Indwelling catheterization should be avoided when possible to avoid complications (urethral strictures, UTIs, calculi, malignancy)
  - Indwelling urethral catheter or suprapubic tube (SPT)
- Intermittent self-catheterization: Most effective treatment, requires manual dexterity
  - If unable to self-catheterize urethra
    - Males: External catheter, outlet obstruction procedure, urinary diversion, or creation of continent catheterizable stoma
    - Females: Urinary diversion or creation of continent catheterizable stoma
  - Incontinence between catheterizations may suggest elevated intravesical pressure due to poor compliance or DO
    - Reduce storage pressure: Increase frequency of catheterizations, anticholinergics, or augmentation cystoplasty
- Lower urinary tracts that cannot be reconstructed require urinary diversion with or without cystectomy
  - Incontinent urostomy
  - Continent urinary reservoir

MEDICATION

First Line

- Anticholinergics improve urinary storage pressure and decrease involuntary contraction
  - Oxybutynin 5 mg PO BID–TID
  - Tolterodine 2 mg PO BID, others
- α-adrenergic blockers: Decrease internal sphincter function, lower voiding pressures; ineffective for DSD
  - Agents include: doxazosin 1–8 mg PO QD, terazosin 1–10 mg PO QHS, tamsulosin 0.4 mg PO QD

Second Line

Botulinum toxin injected into detrusor

SURGERY/OTHER PROCEDURES

- Sphincterotomy: Requires external catheter
- Augmentation cystoplasty: Use of intestinal segment to enlarge the bladder, increasing bladder volume to decrease intravesical pressure
  - Usually requires clean intermittent catheterization (CIC)
- Ileovesicostomy
  - Useful for those unable to perform CIC
- Sacral neuromodulation
  - Deafferentation with dorsal rhizotomy abolishes spontaneous detrusor contraction, improving urinary storage
  - Nerve root stimulation allows for control over detrusor contraction

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Sacral nerve root stimulator

Complementary & Alternative Therapies

Vanilloid agents (capsaicin and resiniferatoxin) suppress uninhibited detrusor contraction

ONGOING CARE

PROGNOSIS

- Proper urologic care improves morbidity, mortality, and quality of life in SCI individuals
- Early data suggested renal disease was major cause of death in the paraplegic patient. However more recent data has revealed that pneumonia, septicemia, heart attack, accidents, and suicides are now leading causes of morbidity (2)

COMPLICATIONS

- UTI/sepsis (3)
- Urolithiasis
  - Due to urinary stasis, chronic infection, acidosis associated with immobility, bladder calculi related to chronic indwelling catheters
- Upper urinary tract deterioration
  - Hydroureteronephrosis due to elevated intravesical pressure
- Lower urinary tract deterioration
  - Detrusor hypertrophy, decreased compliance
  - Urethral erosion, fistula with chronic catheterization
- Autonomic dysreflexia
  - Can occur with SCI at T6 level or higher, with complete/incomplete spinal cord lesions
  - Triggered by a noxious stimuli below the level of the lesion; bladder and bowel manipulation are the most common causes
  - Unopposed sympathetic activity results in vasoconstriction and HTN (hypertension)
  - HTN sensed by baroreceptors in carotid and aortic arch activating parasympathetics above lesion to counter the sympathetic response. However, the SCI inhibits parasympathetic activity below the level of the lesion
  - Signs and symptoms include HTN, headache, bradycardia, flushing, diaphoresis, blurred vision
    - Treatment: Remove offending stimuli
    - Address HTN with rapid onset/short duration agent (nifedipine, captopril, hydralazine)
- Neoplastic transformation
  - Associated with chronic catheter
- Depression
- Skin complications (related to incontinence)

FOLLOW-UP

Patient Monitoring

- UTI screening: Routine urine cultures are unnecessary in healthy, asymptomatic individuals.
- UDS: Completed periodically. However, no consensus exists regarding frequency. Obtain UDS after resolution of spinal shock and every 5 yr in stable patients. If a change in bladder-related symptoms (incontinence) is noted, UDS should be repeated to evaluate for change in bladder dynamics.
- Renal US: Useful, noninvasive screening method to monitor upper and lower tracts.
  – Recommended initially and annually for 5–10 yr, then every other year.
- Basic metabolic panel: Biennially.
- Renal function scan: In setting of progressive hydroureteronephrosis on renal US.
- Bladder cancer surveillance: Cystoscopy is recommended annually for patients with chronic indwelling catheters or augmentation cystoplasty.

Patient Resources

None

REFERENCES

1. National Spinal Cord Injury Statistical Center. Spinal cord injury facts and figures at a glance. *J Spinal Cord Med.* 2013;36(1):1–2.
2. Cameron AP, Rodriguez GM, Schomer KG. Systematic review of urological follow-up after spinal cord injury. *J Urol.* 2012;187:391–397.
3. Patki P, Woodhouse J, Hamid R, et al. Lower urinary tract dysfunction in ambulatory patients with incomplete spinal cord injury. *J Urol.* 2006;175:1784–1787.

ADDITIONAL READING

Tapia C, Khalaf K, Berenson K, et al. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: A systematic review. *Health Qual Life Outcomes.* 2013;11:13.

See Also (Topic, Algorithm, Media)

- Autonomic Dysreflexia
- Bladder Areflexia (Detrusor Areflexia)
- Detrusor-Sphincter Dyssynergia (DSD)
- Neurogenic Bladder, General
- Neurogenic Detrusor Overactivity (NDO)
- Spinal Cord Injury, Urologic Considerations Images
- Urodynamics, Indications and Normal Values

CODES

ICD9

- 586 Renal failure, unspecified
- 599.0 Urinary tract infection, site not specified
- 952.9 Unspecified site of spinal cord injury without evidence of spinal bone injury

ICD10

- N19 Unspecified kidney failure

- N39.0 Urinary tract infection, site not specified
- S34.109A Unsp injury to unsp level of lumbar spinal cord, init encntr

CLINICAL/SURGICAL PEARLS

- Suprasacral lesions generally result in an upper motor neuron deficit with NDO.
- Sacral lesions generally produce a lower motor neuron deficit with resulting detrusor areflexia.
- UDS should be obtained at least 6 wk after injury and repeated when appropriate.

STRESS URINARY INCONTINENCE, FEMALE

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BASICS

DESCRIPTION

- Stress urinary incontinence (SUI) is subjectively defined by the International Continence Society as the"the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing" (1)
- Urinary incontinence (UI) should be further described by specifying: Type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, the measures used to contain the leakage and whether or not the individual seeks or desires help because of urinary incontinence (1)

EPIDEMIOLOGY

Incidence

Annual incidence of any type of new UI ranges from 3 to 11% and increases with age, with approximately 50–70% attributed to SUI alone or in association with urge incontinence (mixed urinary incontinence or MUI)

Prevalence

~30% of women aged 30 to 60 have urinary incontinence, with approximately 50–70% attributed to SUI with or without urge urinary incontinence (UUI). Significant variation is seen in specific populations, eg, community dwelling vs. long-term facility occupants, and nulliparous vs. postpartum females.

RISK FACTORS

Aging, obesity, smoking, pregnancy, and child birth

Genetics

Deficient collagen structures

PATHOPHYSIOLOGY

- Anatomical: Weakness of urethral supportive structures (vaginal wall and surrounding connective tissue) leads to hypermobility and loss of urethral compression (1)
- Intrinsic sphincter deficiency: Loss of intrinsic urethral closure, coaptation, and function
- Neurologic: Rarely, loss of spinal sympathetic reflex and/or pudendal nerve efferents leading to relaxation of the extrinsic and intrinsic closure forces of the urethra.

ASSOCIATED CONDITIONS

- Chronic cough, COPD, obesity
- Pelvic organ prolapse (cystocele, rectocele) and/or anal incontinence
- 40% of women with urethral sphincter incompetence will have a cystocele
- Occult incontinence: Urethral sphincteric incompetence masked by the presence of pelvic

prolapse

GENERAL PREVENTION
See treatment

DIAGNOSIS

HISTORY
- Subjective characterization of UI (aggravating factors)
- Duration of symptoms
- Impact on life
- Daytime vs. nocturnal UI
- Urinary frequency, urgency, nocturia
- UTI history
- Pad use
- Past medical/surgical history
  - Neurologic conditions (Parkinson, MS, back surgery, etc.)
  - Medical conditions (DM, dementia, etc.)
  - Radiation and trauma
  - Gynecologic history (parity, hormonal status)
  - Previous pelvic surgery
- Medications (sympatholytics and diuretics)

PHYSICAL EXAM
- Focused pelvic exam and evaluation of estrogen status (urethral caruncle/prolapse and labial adhesions indicate deficiency)
- Cough stress test to visualize and confirm SUI
- Evaluation of urethral position and mobility
- Presence of pelvic organ prolapse
- Neurologic exam: Gait, cognitive status, sensation, motor, and reflexes (bulbocavernous reflex)
- Digital rectal exam

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
- Routine renal function evaluation unnecessary

Imaging
Diagnosis is mainly based on history and physical exam

Diagnostic Procedures/Surgery
- Postvoid residual measurement
- Voiding diary
- Quality-of-life questionnaires
- Pad test
  - A preweighed sanitary pad is examined after a defined period of time
  - 1-g increase in weight = 1 mL of urine

- The International Continence Society: Weight change of <1 g during its standardized 1-hr test to be negative.

- Cystoscopy in the presence of urinary urgency, hematuria, UTI, or other irritative symptoms, particularly if they have previously undergone a previous anti-incontinence procedure, pelvic radiation, or pelvic prolapse repair
- Urodynamics indicated especially in patients who have failed previous pelvic floor reconstruction or with mixed incontinence, urinary urgency, or obstructive symptoms, and in those who have elevated PVRs or neurologic disease

Pathologic Findings

- Sphincter muscle deficiency is the main pathology.
- SUI may occur in the absence of urethral hypermobility.

DIFFERENTIAL DIAGNOSIS

- Enuresis means any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective "nocturnal"
- Fistula: Vesicovaginal, urethrovaginal
- Mixed urinary incontinence (MUI) is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
- Neurogenic bladder (CNS and spinal cord lesions)
- Pelvic organ prolapse
- Polyuria/polydipsia
- Potentially reversible conditions (DIAPERS):
  - **D**rugs
  - **I**nfection
  - **A**trophic vaginitis
  - **P**sychological (depression, delirium, dementia)
  - **E**ndocrine (hyperglycemia, hypercalcemia)
  - **R**estricted mobility
  - **S**tool impaction
- Situational incontinence: eg, the report of incontinence during sexual intercourse, or giggle incontinence.
- Urethral abnormalities (diverticulum)
- Urge vs. stress vs. overflow incontinence
  - Urge urinary incontinence: Involuntary leakage accompanied by or immediately preceded by urgency
- Urinary leakage may need to be distinguished from sweating or vaginal discharge
- Urinary tract infection
- Vaginal voiding

TREATMENT

GENERAL MEASURES

- Initial therapy includes behavioral modification and pelvic floor exercise
- Lifestyle modifications
- Weight loss, smoke cessation, moderation of fluid intake, caffeine and/or alcohol

MEDICATION

First Line

- Treatment for pure SUI is generally nonpharmacologic in US.
  - However medication may be indicated in MUI when predominant symptoms of OAB or urge incontinence coexist and in such cases antimuscarinic therapy is utilized (see Section I "Overactive Bladder").

Second Line

- In rare cases an α-adrenergic receptor agonist (phenylpropanolamine) or tricyclic antidepressant (imipramine) may be utilized but this is an off-label use.
- Duloxetine is a serotonin and norepinephrine reuptake inhibitor approved for major depression and other indications and is approved for treatment of SUI in Europe but not in US.

SURGERY/OTHER PROCEDURES

- Surgery is the single most effective long-term treatment (2,3)
- Suburethral slings:
  - Midurethral slings:
    - Currently these are the procedure of choice for primary surgical treatment of SUI
    - Made from synthetic material (mesh)
    - As effective as other surgical therapies but associated with less operative time and shorter convalescence rate
    - 3 types include: Retropubic including tension-free vaginal tape (TVT), transobturator, single incision ("mini-sling")
  - Bladder neck (proximal urethral) sling generally fashioned from autologous rectus abdominis fascia or fascia lata (leg)
- Transurethral injectable bulking agents
- Retropubic colposuspension (Burch procedure)
- Artificial urinary sphincter
  - Rarely used in US and only reserved for patients with severe intrinsic sphincter deficiency

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Behavioral therapy (4)
  - Patient education
  - Fluid and dietary management
  - Timed voiding
  - Patient compliance and periodic reinforcement are essential
- Pelvic floor muscle training (PFMT)
  - Strong pelvic floor contraction increases intraurethral pressure against increased intra-abdominal pressure
  - Inhibits detrusor contractions
- Adjunctive measures for PFMT
  - Vaginal cones and weights

– Biofeedback: Helps patients identify and isolate correct pelvic muscles
– Pelvic floor electrical stimulation
– Magnetic therapy
- Intra- or extraurethral and intravaginal support and occlusive devices (pessaries, plugs, urethral inserts, etc.)

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Nonsurgical therapy can be effective in carefully selected, highly motivated, and compliant individuals and in such individuals may improve symptoms and subsequent quality of life in up to 50–80% of mild–moderate cases.
- Excellent outcomes are expected with the use of 1st-line surgical options in uncomplicated patients with all degrees of SUI with success rates in excess of 85–90% at 5–10 yr of follow-up.

COMPLICATIONS
- Untreated SUI may result in skin rash and chronic irritation
- Complications of sling procedures include: Urethral/bladder perforation, mesh exposure in the vagina and erosion into the urinary tract, voiding dysfunction (due to obstruction), UTI, pain, and dyspareunia
- Vaginal, urethral, and intravesical erosion of the midurethral slings is a particularly feared complication
- Vascular injury or intestinal perforations are rare and associated with slings, as well as open abdominal approaches.

FOLLOW-UP
Patient Monitoring
Conservative management requires regular reinforcement and education

Patient Resources
National Association for Continence. http://www.nafc.org

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: Report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167–178.
2. Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol*. 2010;183(5):1906–1914.
3. Rovner ES, Lebed BD. Stress incontinence surgery: Which operation when? *Curr Opin Urol*. 2009;19(4):362–367.
4. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev*. 2010;(1):CD005654.

ADDITIONAL READING

- Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: A randomized controlled trial. *JAMA*. 1998;280(23):1995–2000.
- Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2009;(4):CD006375.

See Also (Topic, Algorithm, Media)

- ICIQ (International Consultation on Incontinence Questionnaire), ICIQ-MLUTS
- Incontinence Impact Questionnaire (IIQ-7)
- Incontinence, Urinary, Adult Female
- Pad Test
- SEAPI Incontinence Classification System
- Stress Urinary Incontinence, Female Images
- Urge Incontinence
- Urinary Retention Following Stress Incontinence Surgery

CODES

ICD9

625.6 Stress incontinence, female

ICD10

N39.3 Stress incontinence (female) (male)

CLINICAL/SURGICAL PEARLS

- It is imperative to distinguish different types of urinary incontinence in female.
- Lifestyle modification and conservative treatment is the 1st step in management.
- Midurethral slings are the standard surgical treatment and are highly effective in properly selected patients.

STRESS URINARY INCONTINENCE, MALE

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BASICS

DESCRIPTION

- Stress urinary incontinence (SUI) is subjectively defined by the International Continence Society (ICS) as the "the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing" (1).
- SUI is also seen objectively on pressure flow urodynamics (UDS) as unintended leakage of urine during an increase in intra-abdominal pressure.

EPIDEMIOLOGY

Incidence

True SUI is rare in young men, but the incidence increases as men age. This predominance in the elderly mirrors the increased likelihood of having undergone prostate surgery as men age.

Prevalence

- The prevalence of UI in women is approximately twice that in men; however this gap narrows over time (2)
- Overall prevalence of moderate–severe urinary incontinence in men 20 yr of age and older is approximately 4.5% (3)
  - 0.7% for men aged 20–34 yr
  - 16% for men aged ≥75 yr
  - SUI accounts for only 12.5% of moderate to severe UI, the remainder predominantly urge or mixed incontinence

RISK FACTORS

- Urologic procedures are the primary risk factor for male SUI
  - Radical prostatectomy (RP)
    - Leading cause of male SUI, especially in older men
    - Postprostatectomy incontinence (PPI) has widely variable rates reported, from 3–89% depending on the timeframe and definition used for incontinence
    - Rates appear similar regardless of technique (retropubic, laparoscopic, or robotically assisted laparoscopic)
  - Transurethral resection of the prostate:
    - Uncommonly results in sphincteric injury leading to SUI
- Urethral distraction injuries involving the membranous urethra
- Acquired or traumatic spinal cord pathology
- Congenital malformations
  - Spinal dysraphism
  - Exstrophy/epispadias complex

Genetics

N/A

PATHOPHYSIOLOGY

- Male continence relies on an intact internal and external urinary sphincter and a compliant bladder for storage of urine
  - Internal sphincter
    - Bladder neck and prostate
    - Smooth muscle/involuntary
  - External sphincter
    - Rhabdosphincter/voluntary
- Internal sphincter dysfunction can be caused by:
  - Prior pelvic surgery, such as RP
  - Traumatic or iatrogenic injury to the bladder neck or prostate
  - Injury or dysfunction of the sympathetic innervation to the internal sphincter
  - Congenital internal sphincter dysfunction
- Dysfunction or the external sphincter is termed intrinsic sphincter deficiency (ISD) and most frequently occurs following radical prostatectomy (RP) (5)
- A noncompliant bladder may exacerbate UI, however, by definition sphincteric dysfunction is required for SUI to be present

ASSOCIATED CONDITIONS

- Urinary incontinence negatively affects a man's quality of life, even in those with minimal urine leakage (6)
- Depression is consistently associated with UI. It is unclear whether this incontinence is cause by depression and meds used to treat it or whether UI is actually causing the depression (3)
- Neurologic diseases
- Pelvic trauma
- Benign prostatic hypertrophy (BPH)
- Prostate cancer
  - Prostate surgery, usually RP
- Pelvic radiation for urologic and nonurologic malignancy

GENERAL PREVENTION

- Careful surgical technique in avoiding damage to the external sphincter during RP.
- If postoperative radiation is used for adverse pathology following RP it is desirable to have the patient continent before radiation since this can adversely affect the return of continence postop.
- Patients with neurogenic bladder such as spina bifida, incontinence episodes can be limited through the use of intermittent catheterization and anticholinergics.

DIAGNOSIS

HISTORY

- Incontinence history
  - Duration
  - Severity (pads, diapers, tissues, etc.)
    - The nature of the absorptive device helps with the assessment of the degree of leakage

  – Precipitating events (cough, sneeze, etc.)
- Presence/absence of urge symptoms
  – Suggests pharmacologic therapy may benefit
- Frequency of urination
- Fluid intake, including use of caffeine, alcohol
- Use of medications such as diuretics or antihypertensive medications
- Neurologic or spinal cord disease or injury
- Voiding diary
- Prior pelvic surgery or other urologic surgery
- Prior pelvic radiation
- Prior anti-incontinence procedures
- AUA symptom score
- ICIQ (International Consultation on Incontinence Questionnaire), ICIQ-MLUTS

PHYSICAL EXAM
- Abdominal exam
  – Surgical scars
  – Palpable suprapubic mass suggests retention
- External genitalia and groin
  – Skin breakdown or fungal/bacterial infection secondary to UI
  – Scrotal exam to rule out hydrocele or testicular mass
  – Digital rectal exam for assessment of the prostate as well as rectal tone
  – Inguinal hernia
- Spine/back for deformity
- Cutaneous signs for spinal dysraphism
  – Subcutaneous lipoma
  – Vascular malformation
  – Tuft of hair
  – Skin dimple
- Reflexes
  – Anal reflex (S2–S5)
    - Stroking circumanal skin leads to visible contraction; absence suggests peripheral or sacral nerve dysfunction
  – Bulbocavernosus reflex (S2–S4)
    - Squeezing the glans leads to anal contraction
    - Absence suggests sacral nerve dysfunction

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis and urine culture
- PSA if known history of prostate cancer or has had a prostatectomy

Imaging
- Postvoid residual urine (PVR) measurement to rule out urinary retention
- Other routine imaging not indicated

Diagnostic Procedures/Surgery

- Pressure flow UDS are helpful to confirm stress incontinence and rule out other complicating factors such as urge incontinence/detrusor overactivity, detrusor underactivity, bladder outlet obstruction, and poor bladder compliance.
- Cystoscopy to rule out urethrovesical anastomotic stenosis (most often after radical prostatectomy) or urethral stricture is essential prior to any planned surgical intervention.

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Stress urinary incontinence
- Urge urinary incontinence: Involuntary leakage accompanied by or immediately preceded by urgency
- Mixed urinary incontinence
- Overflow incontinence/urinary retention
- Postvoid dribbling (urine retained in the urethra)
- Situational incontinence: eg, the report of incontinence during sexual intercourse
- Urethrocutaneous fistula
- Urinary leakage may need to be distinguished from sweating

TREATMENT

GENERAL MEASURES

- Pelvic floor physical therapy ("Kegel" exercises)
  - Efficacious following RP to allow quicker return of continence, though not found to improve overall continence (7)
  - May also be used in men with SUI from other causes to strengthen the pelvic floor
- Lifestyle changes
  - Limiting fluid intake
  - Decreasing certain activities that cause SUI
- Penile clamps
- Condom catheter

MEDICATION

First Line

- Medication generally is not efficacious for male SUI. However, medical therapy is sometimes used in this population. None are officially FDA approved for this indication
  - Tricyclic antidepressants
    - Imipramine 10–25 mg PO BID–TID
  - Duloxetine 30–60 mg PO QD (8)

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Post prostatectomy incontinence (PPI)
  - Artificial urinary sphincter (AUS)
    - Gold standard

- Excellent long-term outcomes and high patient satisfaction (9)
- Urethral slings
  - Transobturator
  - Bone-anchored
  - Combined prepubic and transobturator
- Urethral bulking agents
  - Least effective and generally not used as a 1st-line surgical treatment
  - May be useful in the salvage setting after a failed sling

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Generally speaking SUI is stable or progressive in nature. It is not likely spontaneously resolved.
- PPI differs from other causes of SUI in that it has been shown to improve over time. However, a plateau is seen after approximately 2 yr and further improvements are not anticipated (4).
- With surgical treatment, and occasionally medical management, male SUI can be expected to improve dramatically in most cases.

COMPLICATIONS

- Urinary incontinence
  - Social isolation/embarrassment
  - Dermatitis
  - Candidiasis
  - Skin breakdown
  - Foul odor
- Artificial urinary sphincter (AUS)
  - Urinary retention
  - Device infection or malfunction
  - Urethral erosion
  - Urethral atrophy
- Urethral slings
  - Urinary retention
  - Perineal pain
  - Infection/sling erosion (rare)
  - Osteitis pubis or chronic pain from bone-anchored slings

FOLLOW-UP

Patient Monitoring

- Following surgical or medical treatments patients should be followed with standardized questionnaires, such as the International Consultation on Incontinence Questionnaire Short Form.
- Patients may also be followed with 1-hr or 24-hr pad weight testing, but this can be burdensome to obtain regularly in the office.
- Self-reported pad counts are easier to obtain, but not as accurate as a pad weight test.
- No routine labs or imaging are required unless complicating factors in the initial history and physical were identified.

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse.
http://kidney.niddk.nih.gov/kudiseases/pubs/uimen/

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: Report from the Standardization Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167–178.
2. Landefeld CS, Bowers BJ, Feld AD, et al. National Institutes of Health state-of-the-science conference statement: Prevention of fecal and urinary incontinence in adults. *Ann Intern Med*. 2008;148(6):449–458.
3. Markland AD, Goode PS, Redden DT, et al. Prevalence of urinary incontinence in men: Results from the national health and nutrition examination survey. *J Urol*. 2010;184(3):1022–1027.
4. Smither AR, Guralnick ML, Davis NB, et al. Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test data. *BMC Urol*. 2007;7:2.
5. Chao R, Mayo ME. Incontinence after radical prostatectomy: Detrusor or sphincter causes. *J Urol*. 1995;154(1):16–18.
6. Liss MA, Osann K, Canvasser N, et al. Continence definition after radical prostatectomy using urinary quality of life: Evaluation of patient reported validated questionnaires. *J Urol*. 2010;183(4):1464–1468.
7. Hunter KF, Moore KN, Cody DJ, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev*. 2004;(2):CD001843.
8. Collado Serra A, Rubio-Briones J, Puyol Payás M, et al. Postprostatectomy established stress urinary incontinence treated with duloxetine. *Urology*. 2011;78(2):261–266.
9. Montague DK. Artificial urinary sphincter: Long-term results and patient satisfaction. *Adv Urol*. 2012;2012:835290.

ADDITIONAL READING

Burden H, Warren K, Abrams P. Diagnosis of male incontinence. *Curr Opin Urol*. 2013;23(6):509–514.

See Also (Topic, Algorithm, Media)

- Bulking Agents, Injectable
- Incontinence, Urinary, Adult Male

- Incontinence, Urinary, Following Radical Prostatectomy
- Intrinsic Sphincteric Deficiency
- ICIQ (International Consultation on Incontinence Questionnaire), ICIQ-MLUTS
- Overactive Bladder (OAB)

CODES

ICD9

788.32 Stress incontinence, male

ICD10

N39.3 Stress incontinence (female) (male)

CLINICAL/SURGICAL PEARLS

- SUI is uncommon in young men, but becomes more common with age as more patients are undergoing urologic procedures.
- Most effective treatments are surgical, though medical therapy may be helpful in men with very mild incontinence.
- The artificial urinary sphincter (AUS) remains the gold standard procedure for male SUI, however urethral slings are now commonly used with success approaching that of the AUS with proper patient selection.

STROKE (CVA), UROLOGIC CONSIDERATIONS

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BASICS

DESCRIPTION

- Stroke (CVA-cerebovascular accident) is the 3rd leading cause of death, and the leading cause of chronic morbidity in the United States
- Stroke can be ischemic or hemorrhagic
- Stroke can lead to urinary tract disturbances
- Initially, transient (occasionally permanent) urinary retention ± overflow incontinence
- Likelihood of voiding disturbances is directly associated with stroke severity
- May eventually develop bladder overactivity and urgency with or without incontinence
- Urinary symptoms post-CVA are very common
  - 25% of people have urinary incontinence at time of discharge and 15% have these issues at 1 yr post-CVA (1)[A]

EPIDEMIOLOGY

- 270/100,000 Americans experience a stroke each year
- Mean age 72 yr

RISK FACTORS

- Urinary disturbances after stroke are common, the risk factor is stroke and extent of hemorrhage or ischemia
  - Those with dysphagia, >75 yr, motor weakness, and visual field defects were more likely to have long-term incontinence issues (2)[A]

Genetics

N/A

PATHOPHYSIOLOGY

- Urinary retention due to cerebral shock and detrusor areflexia
- Incontinence-multifactorial (4)[B]
  - Overflow urinary incontinence from retention
  - Detrusor overactivity (DO) with urge urinary incontinence (UUI)
  - Functional incontinence due to mobility and/or cognitive impairment

ASSOCIATED CONDITIONS

- Prostatic hyperplasia
- Underlying urinary incontinence
- Fecal incontinence and/or constipation
- Depression
- See also Differential Diagnosis

GENERAL PREVENTION

- Stroke prevention measures
  - Smoking cessation
  - Blood pressure control
  - Cholesterol control
  - Diabetic control
  - Avoid hormonal replacement therapy in older women
  - Identify and control atrial fibrillation
  - Balanced diet and exercise
  - Low-dose aspirin if appropriate

DIAGNOSIS

HISTORY

- Based on diagnosis of CVA
- Evaluate for previous or underlying urologic issues or complaints
- Obtain medication history
- Detailed past surgical history

PHYSICAL EXAM

- Abdominal exam for bladder distention
- Neurologic exam (usually already done by primary team during initial diagnosis)
- Digital rectal exam (DRE) to evaluate rectal tone and prostate size in males
- Pelvic exam in females

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis with or without urine culture as clinically appropriate
- Creatinine to evaluate renal function

Imaging

- Postvoid residual bladder scan
- Abdominal imaging
  - Renal/bladder ultrasound
  - KUB

Diagnostic Procedures/Surgery

- Voiding/fluid intake diaries
  - Bladder capacity
  - Daily/nightly trends
- Urodynamic studies: Should not be performed until after stability in neurologic symptoms following stroke (not immediately)
  - Typically 3–6 mo following stroke
  - Evaluate bladder function and detrusor function vs. bladder outlet obstruction
  - May be used for surgical guidance and management if necessary

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Urinary Retention (see Section I "Urinary Retention, Adult Male," "Urinary Retention, Adult Female")
- Urge incontinence
  - Loss of urine accompanied by urgency; often related to triggers such as sounds of running water, cold weather, passing a restroom
- Stress incontinence
  - Urinary leakage associated with exertion, lifting, coughing, sneezing
- Mixed incontinence
  - Urinary leakage associated with both stress and urge incontinence
- Low bladder compliance resulting in overflow incontinence
- Continuous urinary incontinence is the continuous loss of urine
- Postmicturition dribble
  - The involuntary loss of urine immediately after passing urine, usually after leaving the toilet
- Mobility or cognitive impairment post stroke

TREATMENT

GENERAL MEASURES

- General stroke rehabilitation interventions (3)
  - Physical therapy
  - Occupational therapy
- Initially and short term
  - Ensure bladder drainage with Foley catheter vs. clean intermittent catheterization (CIC)
- Long term
  - CIC, Foley or suprapubic catheter for urinary retention and elevated post void residuals
  - Caution to avoid long-term indwelling urethral catheter to avoid risk of bladder neck erosion or urethral injury
  - Bladder overactivity
    - Behavioral modifications regarding voiding habits and fluid intake
    - See medication therapy below

MEDICATION

First Line

- Antimuscarinics or β_3-agonists: Decrease detrusor overactivity (DO) that is demonstrated as urinary frequency and urgency ($\pm$ incontinence)
  - Side effects
    - Dry mouth, constipation, blurred vision, confusion
    - Use cautiously in geriatric patients secondary to potential central nervous system effects

Second Line

- α-Blockers for prostatic hyperplasia and retention related to BPH if necessary
- 5α-reductase inhibitors for BPH especially in those men with large prostate glands

SURGERY/OTHER PROCEDURES

- Suprapubic catheter placement if long-term urinary retention
- Intravesical botulinum toxin injections for DO
  - Temporary effect and may require patients to perform CIC
- Neuromodulation
- Transurethral resection of prostate if concomitant BPH with clinical obstruction
- Urinary diversion

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Psychological support and re-enforcement

Complementary & Alternative Therapies

- Absorbent pads and products
- Pelvic floor physical therapy with or without biofeedback
- Acupuncture

ONGOING CARE

PROGNOSIS

- Health-related quality of life is impaired in general in those with urgency incontinence post neurologic event (4)[B]
- Urinary symptom outcome is proportional to the extent of resolution of other stroke sequelae
  - Those who resolve cognitive and/or motor function often resolve urinary issues

COMPLICATIONS

- Short term
  - Acute renal failure if acute urinary retention
  - Urinary tract infection if not draining bladder appropriately
  - Urinary incontinence because of overflow incontinence in retention
  - Depression
- Long term
  - Renal dysfunction and possible renal failure
  - Urinary tract infections—recurrent
  - Decreased quality of life
  - Depression

FOLLOW-UP

Patient Monitoring

- Detrusor overactivity (DO): yearly checkups, medicine monitoring
- Neurogenic bladder and performing CIC
  - Evaluate renal function with yearly (or more often if clinically indicated) creatinine and renal ultrasound
  - Urodynamic evaluation for significant change in clinical symptoms
  - If indwelling catheter dependent, needs regular cystoscopy to visualize bladder and

monitor for cancer or stones
  - Increased risk of bladder cancer is secondary to chronic foreign body in urinary tract

Patient Resources

www.stroke.org/site/DocServer/NSAFactSheet_BowelandBladder.pdf?docID=984 (National STROKE Association)

REFERENCES

1. Thomas LH, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. *Cochrane Database Syst Rev*. 2008;(1):CD004462.
2. Patel M, Coshall C, Rudd AG, et al. Natural history and effects on a 2-year outcomes of urinary incontinence after stroke. *Stroke*. 2001;32:122–127.
3. Brittain KR, Peet SM, Castleden CM. Stroke and incontinence: Review.*Stroke*. 1998;29:524–528.
4. Tapia CL, Khalaf K, Berenson K, et al. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurological condition: A systematic review. *Health Qual Life Outcomes*. 2013;11:13.

ADDITIONAL READING

www.stroke.org (National Stroke Association)

See Also (Topic, Algorithm, Media)

- Detrusor Overactivity
- Neurogenic Bladder, General Considerations
- Urinary Retention, Adult Female
- Urinary Retention, Adult Male
- Urinary Retention, Pediatric

CODES

ICD9

- 434.91 Cerebral artery occlusion, unspecified with cerebral infarction
- 788.29 Other specified retention of urine
- 788.38 Overflow incontinence

ICD10

- I63.9 Cerebral infarction, unspecified
- R33.8 Other retention of urine
- N39.490 Overflow incontinence

CLINICAL/SURGICAL PEARLS

- Important to determine residual urinary effects after near full recovery from stroke.
- Prior to operation, ensure stability of urinary function.

SUPRAPUBIC PAIN, GENERAL CONSIDERATIONS

Kristin A. Greco, MD
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BASICS

DESCRIPTION

- Suprapubic pain describes a pain located in the midline of the abdomen, above the pubic symphysis and below the umbilicus.
- Multiple organ systems can cause suprapubic pain including urologic, gastrointestinal, gynecologic, and other rare causes.

RISK FACTORS

- History of urinary tract infections (UTIs)
- BPH as it may cause urinary retention
- Urolithiasis
- Immunocompromised patients have increased susceptibility to infections
- Pelvic radiation treatment
- Chronic pain syndromes
- Strenuous athletic activity

PATHOPHYSIOLOGY

- The pathophysiology of suprapubic pain is dependent on the etiology and various reproductive, GI, urologic, and neuromuscular disorders may cause pain in this area. This section will focus on urologic pathophysiology.
- Suprapubic pain resulting from the urinary tract is usually associated with inflammation or obstruction such as in UTI or acute urinary retention.
  - Bacterial cystitis causes a sharp and stabbing pain that is worse at the end of micturition. The pain is often referred to the distal urethra and is associated with the symptoms of frequency and urgency of urination.
    - UTI also causes intermittent suprapubic discomfort secondary to inflammation of the urothelium. This is often more severe with a full bladder and improves when the bladder is relieved of distention.
  - Acute urinary retention causes suprapubic pain by overdistention of the bladder (1). In contrast, chronic, slowly progressing urinary retention is usually asymptomatic despite large residual volumes.
- Malignancies in the urinary tract generally do not produce pain unless they cause obstruction or extend into adjacent nerves. Pain can be a late manifestation of malignancy.
- Prostatitis typically causes pain in the perineum, but this pain is frequently referred to the suprapubic area. Pain is secondary to inflammation with resulting edema and distention of prostatic capsule.
- Interstitial cystitis or painful bladder syndrome (IC/PBS) is defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6-wk duration, in the absence of

infection of other identifiable causes.
  – The pathophysiology of this disorder is currently under investigation. It is associated with other chronic systemic pain syndromes.

ASSOCIATED CONDITIONS
- BPH with urinary retention
- IC/PBS
- Prostatitis
- UTI
- Urolithiasis

DIAGNOSIS
HISTORY
- History taking in the patient presenting with suprapubic pain should be broad and consider all possible organ systems involved. A thorough history can lead the clinician to appropriate diagnostic tests in this patient
- Associated urinary symptoms such as frequency, urgency, dysuria, nocturia, and ability to empty the bladder
- Onset and duration of suprapubic pain
- Perineal pain
- Gross hematuria or hematospermia
- History of urinary retention
- Benign prostatic hypertrophy (BPH)
- Urolithiasis
- History of pelvic malignancy
- Trauma
- Radiation treatment for cancer
- History of diarrhea or bowel disease
- Last menstrual period and possibility of pregnancy
- History of STI/STD
- Dyspareunia

PHYSICAL EXAM
- Abdominal exam:
  – Palpable bladder suggests urinary retention
  – Suprapubic tenderness is common with inflammation and infection of the genitourinary system
  – Umbilical discharge with urachal abnormality
- Pelvic exam:
  – Chandelier sign (tenderness with movement of the cervix) with PID
  – Cervical discharge
  – Pelvic masses
- Rectal exam:
  – Tender, swollen, or boggy prostate during palpation may indicate prostatitis
  – Evidence of masses or blood with GI tract disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis and culture:
  - Pyuria, nitrite, and bacteria with infection
  - pH, crystals/calcium, uric acid, oxalate, citrate, 24-hr excretion with urolithiasis
- CBC: Leukocytosis with left-shift; nonspecific infection and inflammation
- Urine cytology for malignancy
- Pregnancy testing in women

Imaging

- Plain x-ray: Important for evaluation of bowels, urolithiasis, or foreign body.
- CT pelvis: Useful for diagnosing GI etiology, urolithiasis, or pelvic masses. Has no role in uncomplicated infections of the GU tract.
- US bladder: Assess postvoid residual volume, calculi, or mass.
- Pelvic US for gynecologic causes. Transvaginal US is best for uterine or ovarian evaluation.

Diagnostic Procedures/Surgery

- Cystoscopy:
  - Evaluate for bladder tumor, stone, outlet obstruction, urethral stricture and IC/PBS (may see inflammatory lesions or Hunner's ulcers).
  - Contraindicated during acute GU infection such as UTI or prostatitis.
- Mears–Stamey 4-glass test for prostatitis evaluation.
- Urodynamics:
  - Assess bladder capacity, bladder contraction, pressure, and outlet obstruction. Not indicated for acute suprapubic pain.

Pathologic Findings

Based on the specific entity

DIFFERENTIAL DIAGNOSIS

- Urologic:
  - UTI
    - Cystitis
    - Prostatitis, acute bacterial
    - Pyelonephritis
  - Urinary Retention
  - Urolithiasis (bladder or distal ureter)
  - Prostatitis including acute bacterial, chronic nonbacterial, inflammatory and noninflammatory (NIH CP/CPPS III A and B)
  - Bladder perforation
  - IC/PBS
  - Malignancy (bladder, prostate)
  - Urachal abnormality
- Gastrointestinal:
  - Acute appendicitis
  - Colitis
  - Diverticulitis

- Inflammatory bowel disease
- Gynecologic:
  - Dysmenorrhea
  - Endometriosis
  - Malignancy (uterine, ovarian)
  - Miscarriage
  - Mittelschmerz
  - Ovarian cyst (hemorrhagic or ruptured)
  - Ovarian torsion/ovarian vein thrombosis
  - Pelvic Inflammatory disease
  - Pregnancy (including ectopic)
  - Uterine fibroids
- Other:
  - Trauma
  - Sexual abuse
  - Osteitis pubis
  - Abdominal wall myofascial pain
  - In athletes (2):
    - Sports hernia (athletic pubalgia, Sportsman's hernia)
    - Adductor strain
    - Muscle tears
    - Avulsion injuries
    - Stress fractures
    - Tears of acetabular labrum

TREATMENT

- The focus of this discussion is on urologic pathologic processes.
- Some common urologic conditions and interventions are noted below. Other conditions are beyond the scope of this section.

MEDICATION

First Line

- Acute uncomplicated UTI in women (3,4):
  - Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days is appropriate due to minimal resistance and propensity for collateral damage.)
  - Trimethoprim–sulfamethoxazole (160/800 mg [1 double-strength tablet] twice daily for 3 days) given its efficacy in numerous clinical trials.
- Complicated UTI: Treat for 7–14 days with culture-specific antibiotics.
  - Risk factors that make a UTI complicated include:
    - Indwelling catheter
    - Immunosuppression
    - Male sex
    - Urinary retention
    - Functional or anatomical abnormality of the urinary tract

- History of urinary tract surgery

- Prostatitis
  - Antibiotics empirically for 2 wk. If cultures are positive or the patient has improved clinical symptoms then continue antibiotics for 4–6 wk. Antibiotics with excellent prostatic penetration include fluoroquinolones (so they should not be used with concomitant UTI).
- BPH/urinary retention
  - α-Blockers, such as tamsulosin, may be used. 5α-reductase inhibitors, such as finasteride can be added if the prostate gland is estimated to be over 40 g.
- Bladder calculi
  - Often require surgical removal. Medical therapy can be considered for uric acid stones.
- Interstitial cystitis/painful bladder syndrome (IC/PBS) (5)
  - 1st-line treatment is behavioral modifications, counseling and stress management, and coping techniques.
  - 2nd-line treatment includes manual physical therapy techniques that resolve pelvic, abdominal and hip muscular trigger points, and lengthen muscle contractures.
  - Amitriptyline, cimetidine, hydroxyzine or pentosan polysulfate may be used as 2nd-line oral medications.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- BPH/urinary retention
  - Transurethral catheterization to relieve acute obstruction; if unable to perform then suprapubic catheter should be considered.
  - Transurethral resection of prostate or other ablative procedure (laser, microwave) if appropriate.
- Bladder calculi
  - Remove transurethrally and fragment manually with lithotrite or with Holmium laser
  - Open cystolithotomy rarely needed
- IC/PBS
  - 3rd-line treatment of IC/PBS can involve cystoscopy under anesthesia with short-duration, low-pressure hydrodistention
  - If Hunner's lesions are present, then fulguration with laser or electrocautery and/or injection of triamcinolone should be performed.
- Bladder cancer
  - Superficial tumors:
    - TURBT ± intravesical BCG
  - Invasive tumors: Radical cystectomy with urinary diversion

ONGOING CARE

PROGNOSIS

Good prognosis with treatment of a clearly identified problem. Patients with IC/PBS often have a chronic course with flares that can last days to weeks to months. These patients

require a multimodal treatment approach.

FOLLOW-UP

Patient Monitoring

- Patient monitoring and follow-up is dependent on the specific pathologic process.
- Assessment of postobstructive diuresis following relief of urinary obstruction includes measurement of serum electrolytes.
- Urine culture following treatment of complicated UTI should be performed to ensure adequate treatment. This is not needed for uncomplicated UTI in women.

REFERENCES

1. Selius BA, Subedi R. Urinary retention in adults: Diagnosis and initial management. *Am Fam Physician*. 2008;77(5):643–650.
2. Weber MA, Rehnitz C, Ott H, et al. Groin pain in athletes. *Rofo*. 2013;185(12):1139–1148.
3. Wagenlehner FM, Wullt B, Perletti G. Antimicrobials in urogenital infections. *Int J Antimicrob Agents*. 2011;385:3–10.
4. Hummers-Pradier E, Kochen MM. Urinary tract infections in adult general practice patients. *Br J Gen Pract*. 2002;52:752–761.
5. Faubion SS, Shuster LT, Bharucha AE. Recognition and management of nonrelaxing pelvic floor dysfunction. *Mayo Clin Proc*. 2012;87(2):187–193.

ADDITIONAL READING

Edwards JL. Diagnosis and management of benign prostatic hyperplasia. *Am Fam Physician*. 2008;77(10):1403–1410.

See Also (Topic, Algorithm, Media)

- Bladder Calculi
- Cystitis, General
- Interstitial cystitis (IC)/Painful Bladder syndrome (PBS)
- Osteitis Pubis
- Prostate, Benign Hyperplasia/hypertrophy (BPH)
- Prostatitis, General
- Stamey Test (Meares–Stamey Test)
- Urethra Stricture, Male
- Urethral Stenosis/Stricture, Female
- Urinary Retention, General

CODES

ICD9

- 592.9 Urinary calculus, unspecified
- 599.0 Urinary tract infection, site not specified
- 789.09 Abdominal pain, other specified site

ICD10

- N20.9 Urinary calculus, unspecified

- N39.0 Urinary tract infection, site not specified
- R10.8 Other abdominal pain

CLINICAL/SURGICAL PEARLS

- Multiple organ systems can cause suprapubic pain including urologic, gastrointestinal, gynecologic, neuromuscular and other rare causes.
- Bacterial cystitis typically causes a sharp and stabbing pain that is worse at the end of micturition. This is secondary to inflammation of the urothelium.
- Acute urinary retention causes suprapubic pain by overdistention of the bladder.
- CT imaging can be useful for diagnosing GI etiology, urolithiasis or pelvic masses, but CT has no role in uncomplicated infections of the GU tract.
- Cystoscopy can be used to evaluate for bladder tumor, stone, outlet obstruction or urethral stricture.
- 1st-line treatment for interstitial cystitis/painful bladder syndrome (IC/PBS) involves behavioral modifications, counseling and stress management and coping techniques.

SYPHILIS

John L. Phillips, MD, FACS
Dawud Lankford, MD, MPH

BASICS

DESCRIPTION

- "Syphilis" coined by Fracastoro in 1500s
- Describes infection by the spirochete *Treponema pallidum,* 1st discovered in 1905 by Hoffman
- Primary, secondary, and tertiary forms
- Congenital or acquired
- Often there is an asymptomatic, latent period (serology positive without clinical disease) between forms

EPIDEMIOLOGY

Incidence

- 2011 CDC data
  - In US, 55,400 new cases (est.) per year
  - 1/3 of new cases primary (P) or secondary (S)
  - From 2004 to 2008, rates increased most in 15–20-yr-old men and women
  - Rates highest in men who have sex with men (MSM), accounting for 2/3 of primary and secondary cases
  - Minorities make up majority of new P & S cases
  - Congenital syphilis now more common than perinatal HIV infection (3.4–15.0 times higher in blacks/Hispanics than in whites)

Prevalence

- US (NHNE) (1)
  - 0.71% seropositive (SP) in 18–49 yr olds
  - 4.1% SP in non-Hispanic blacks
  - 0.07% SP in non-Hispanic whites
- China (2) SP rates
  - Low-risk groups
    - Antenatal women (0.45%)
    - Food & service employees (0.3%)
  - High-risk groups
    - Female sex workers 12.49%
    - Drug users 6.81%
    - MSM 14.56%

RISK FACTORS

- Unprotected sex
- Sex with infected partner
- History of other STDs

- High-risk behaviors
  - Multiple partners
  - Prostitution
  - Illicit drug use
  - MSM

PATHOPHYSIOLOGY

- Contact inoculation through fluids, in utero; rare dissemination through transfusion
- Incubation 10–90 days
- Primary syphilis
  - Chancre: A dry, *painless*, erosion with raised border (not a true ulcer)
    - Glans, penile shaft, foreskin
    - Vulva, cervix
  - Regional lymphadenopathy: *Painless, nonsuppurating*
- Secondary syphilis: Develops 4–10 wk later if primary untreated
  - Flu-like symptoms (eg, fatigue, fever, headache)
  - Generalized lymphadenopathy
  - Generalized eruption
    - Diffuse, pale, red papules, usually <1 cm
    - Scaling
    - Plaques, can be >1 cm
    - Symmetric on palms, soles of feet, and trunk
  - Condyloma lata: Highly infectious, hypertrophic intertriginous genital lesions
- Latent period
  - Early <1 yr
  - Late >1 yr
  - Typically precedes tertiary disease but can take years
- Tertiary syphilis may take 10–20 yr
  - Central nervous system involvement: 6–10%
    - Tabes dorsalis (syphilitic myelopathy); demylenation of dorsal/posterior column of the spinal cord; causes problems with proprioception
    - Dementia
    - Seizures
    - Argyll Robertson pupils (constricting with accommodation but not to light)
  - Cardiac Involvement: 10% over 10–30 yr
    - Aortitis
    - Aortic aneurysms
    - Fatal hemorrhage
  - Gummatous syphilis: 15% over 45 yr where soft, inflammatory gummas destroy local tissues of:
    - Bone
    - Face
    - Skin
    - Legs
- Congenital Syphilis: Infection occurs in utero or during vaginal delivery. Nearly 2/3 of

neonates asymptomatic but can develop as children:
- Hepatosplenomegaly (75%)
- Fever, chills, rash (50%)
- Pneumonitis (20%)
- Late congenital syphilis (40%)
  - Saddle nose deformity
  - Hutchinson teeth (peg-shaped incisors)
  - Frontal bossing
  - Higoumenakis sign (unilateral enlargement of sternoclavicular joint)
  - Painless synovitis (Clutton joints)
  - Neurosyphilis

ASSOCIATED CONDITIONS
- Other sexually transmitted conditions
  - HIV
  - Gonorrhea
  - Hepatitis B and C
  - Chlamydia

GENERAL PREVENTION
- Protected sex
- Early Diagnosis and Treatment

DIAGNOSIS
HISTORY
- Genital lesion
- Risk behavior
- Urethritis, urinary symptoms, burning
- Known history of other STDs
- Drug allergies (which may cause fixed eruptions)
- Vision changes, dyspnea, fever/headache, paresis, neurologic impairment

PHYSICAL EXAM
- Primary syphilis
  - Classic *painless* chancre
    - Small, solid, raised lesion <1 cm across that becomes a red open sore with a scooped-out appearance. It usually does not bleed
    - Can be on the genitalia, anus, or mouth
  - Painless regional lymph nodes
- Secondary syphilis
  - Maculopapular and *symmetric* rash on trunk, arms, especially soles of feet
  - Lymphadenopathy painless
- Tertiary Syphilis
  - Hemiparesis
  - Tabes dorsalis (ie, decreased proprioception, touch)
  - Cardiac murmur

- Pulmonary edema
- Generalized dementia

DIAGNOSTIC TESTS & INTERPRETATION

- Lab: Critical to diagnosis (2,3)
- Indirect tests (ie, measure serologic response to treponemes)
  - *Non–treponemal-based tests* (screening or preliminary)
    - Rapid, cheap, simple
    - Can monitor for reinfection
    - Reduced sensitivity in primary and late disease
    - False positivity due to cross-reactions
    - False negatives due to high antibody levels
    - Examples: Venereal Disease Research Lab (VDRL); rapid plasma reagin (RPR); unheated serum reagin (USR)
  - *Treponemal-based tests* (confirmatory)
    - Expensive, technically difficult
    - Fluorescent anti-treponemal antibody absorption (FTA-ABS) (manually read)
    - Treponema pallidum particle agglutination (TP-PA) (manually read but simpler than FTA-ABS)
    - Enzyme immunoassay (EIA) (automated, rapid)
    - Western blot (helps resolve ambiguity)
- Direct tests (ie, measure treponemes or treponemal antigens directly)
  - Dark field microscopy of fresh lesion fluid
    - Simple, reliable
    - Requires expertise, limited sensitivity
  - Fluorescent antibody against *T. pallidum*
    - Most specific test when lesions present
    - False positive for other treponemes (eg, yaws, pinta)
  - Nonfluorescent staining (IHC [immunohistochemistry] + H&E)
  - PCR amplification (in development)
    - For congenital and neurosyphilis
    - Better sensitivity than traditional tests
- Culture: *T. pallidum* cannot be cultured

Imaging

Chest x-ray (eg, assess cardiac shadow in late syphilis)

Diagnostic Procedures/Surgery

- Serologic indirect testing
- Wound fluid microscopy
- Confirmatory direct testing
- Spinal tap to assess for neurosyphilis
- Biopsy of atypical lesions

Pathologic Findings

- Tertiary syphilis
  - Gummas: Nonspecific granulomatous reaction destroying involved tissue

- Cardiac: Endarteritis obliterans of vasa vasorum with consequent aortic aneurysm formation

DIFFERENTIAL DIAGNOSIS

ALERT
Syphilis is often called the "Great Pretender" as it can resemble other diseases.

- Rule out chancroid (painful ulcer and lymphadenopathy)
- Rule out lymphogranuloma venereum (nodes classically suppurate)
- Rule out granuloma inguinale (painless, beefy red raised ulcer, "pseudobubos" without nodes)
- Rule out herpes (usually clusters of vesicles in varying stages, burning pain)
- Annular syphilis can resemble cutaneous sarcoid (especially in African Americans)
- Condyloma lata do not have the digitate elevations seen in viral condyloma acuminata
- Pityriasis rosea may appear like secondary syphilis
- Psoriasis guttate (follow strep infections, drop-like raised plaques)
- Rule out fixed drug reaction (usually itchy)
- Bacterial meningitis
- Stroke
- Multiple sclerosis

TREATMENT

GENERAL MEASURES
- Antibiotic therapy is mainstay
- Serologic monitoring thereafter
- Contact public health service

MEDICATION
First Line
- Penicillin: 2.4 MU Benzathine PCN G IM × 1 (4)
- PCN-allergy: Tetracycline 500 mg PO q6h or doxycycline 100 mg PO q12 × 2 wk
- If pregnant: Ceftriaxone 1 g IM
- Widespread erythromycin resistance noted

Second Line
- Latent cardiovascular syphilis (duration over 1 yr)
  - Benzathine PCN G 2.4 MU IM qwk × 3 wk
  - If PCN allergic: Tetracycline 500 mg PO QID × 4 wk or doxycycline 100 mg PO bid × 4 wk

SURGERY/OTHER PROCEDURES
Aortic graft replacement has been used for late syphilitic aortic dissection.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies

- Postexposure prophylaxis
  - Ceftriaxone 250 mg IM and Doxycycline 100 mg for 14 days
  - or Azithromycin (Zithromax) 1 g PO × 1
- Treat partners (chance of infection within 30 days of sex with infected partner is 15–30%)
- Retreatment if titers rise

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent in primary syphilis
- Good in asymptomatic neurosyphilis
- Poor if symptomatic tabes dorsalis
- Syphilic aneuryms can cause death within 6 mo
- 1/3 of patients treated for above have a negative FTA-ABS by 36 mo

COMPLICATIONS

- Jarisch–Herxheimer reaction to treponemolysis after penicillin therapy begun
  - In up to 60% with initial therapy; 90% with secondary syphilis
  - Minor: Fever, flu-like symptoms, inflammation of affected structures (watch if cardiac involvement)
  - Major: Tachycardia, premature labor, transient paralysis (in tertiary syphilis), iritis, aortitis
  - Treatment is supportive
    - Undertreatment and development of late disease
    - Tabes dorsalis (poor prognosis)
    - Aortic aneurysm rupture

FOLLOW-UP

Patient Monitoring

- Repeat serologic testing q3mo × 4 then q6mo × 2
- Yearly thereafter
- 4-fold decrease should be seen in 12–24 mo
- Treatment failure: 4-fold increase in titer
  - Check CNS/spinal fluid
  - Check HIV status
  - Retreatment

Patient Resources

- CDC fact sheet. www.cdc.gov/std/syphilis/syphilis-Fact-Sheet.pdf
- NIH fact sheets. www.niaid.nih.gov and type in “syphilis” in search function

REFERENCES

1. Gottlieb SL, Pope V, Sternberg MR, et al. Prevalence of syphilis seroreactivity in the US:

Data from the National Health and Nutrition Examination Surveys (NHANES) 2001–2004. *Sex Transm Dis*. 2008;35:507–511.
2. Lin CC, Gao X, Chen XS, et al. China's syphilis epidemic: A systematic review of seroprevalence studies. *Sex Transm Dis*. 2006;33:726–736.
3. Ratnam S. The laboratory diagnosis of syphilis. *Can J Infect Dis Med Microbiol*. 2005;16(1):45–51.
4. Sexually Transmitted Diseases Treatment Guidelines, 2012 MMWR December 17, 2010/Vol. 59/No. RR-12.

ADDITIONAL READING

James WD, Berger TG, Elston DM. Syphilis, yaws, bejel, and pinta. In: *Andrews' Disease of the Skin: Clinical Dermatology*. 11th ed. New York, NY: Elsevier, Inc., 2011.

See Also (Topic, Algorithm, Media)

- Genital ulcers
- Lymphadenopathy, inguinal Sexually Transmitted Infections (STI) (Sexually Transmitted Diseases [STD]), general
- Syphilis Image ☼

CODES

ICD9

- 091.2 Other primary syphilis
- 091.9 Unspecified secondary syphilis
- 097.9 Syphilis, unspecified

ICD10

- A51.0 Primary genital syphilis
- A51.49 Other secondary syphilitic conditions
- A53.9 Syphilis, unspecified

CLINICAL/SURGICAL PEARLS

- Screen pregnant women for syphilis (USPSTF grade A recommendation).
- Screen people-at-risk for syphilis (USPSTF grade A recommendation).
- Pregnancy is an absolute contraindication for doxycycline or tetracycline.
- Nonpenicillin, Nontetracyline alternatives are inferior to PCN but include ceftriaxone.
- Patients with syphilis, or being screened for syphilis, should be counseled to undergo HIV testing.
- Late syphilis may be asymptomatic.
- Condyloma lata are highly infectious and must be differentiated from HPV-related condyloma acuminate largely on physical exam.

TESTIS CANCER, ADULT GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Testicular cancer is a malignancy of germ cell origin originating in the testis and is the most common malignancy in males 15–35 yr of age.
- Testicular cancer must always be considered in males presenting with testicular swelling.
- Patients with testicular cancer may present with a testicular mass, gynecomastia, infertility, abdominal mass, or symptoms related to metastatic disease such as back pain or cough.

EPIDEMIOLOGY

Incidence

- It is projected that in US, 8,820 new cases of testicular cancer would be diagnosed and 380 men would die of this disease in 2014.
- Germ cell tumors (GCTs) of the testis occur predominantly in Caucasian males.
- Lifetime risk of developing testis cancer is ~1 in 270, and the lifetime risk of dying of testicular cancer is 1 in 5,000.

Prevalence

N/A

RISK FACTORS

- Risk factors associated with the development of testicular cancer:
  - Cryptorchidism 4–6 fold increased risk
  - Family history 8–12 fold risk if affected brother
  - Testicular atrophy
  - Infertility
  - Klinefelter syndrome
- Cannabis use controversial

Genetics

Identification of isochromosome 12p amplification.

PATHOPHYSIOLOGY (1)

- GCTs of the testis can be divided into 2 major subgroups based on histology: Seminoma and nonseminoma germ cell tumor (NSGCT).
  - Seminoma: ~50% of all testicular cancers most frequently appear in the 4th decade of life.
  - ~10–15% of will produce the serum tumor marker, human chorionic gonadotropin (HCG).
  - The remainder of GCTs is comprised of nonseminomatous histology (embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, and teratoma) and frequently present in the 3rd decade of life.
    - ~50–70% of nonseminomas will produce α-fetoprotein (AFP) and/or HCG.

- Most nonseminomatous tumors are mixed, composed of 2 or more cell types of which seminoma may be a component
  - The definition of a pure seminoma excludes the presence of any nonseminomatous elements or an elevated serum AFP.

ASSOCIATED CONDITIONS
- Infertility
- Cryptorchidism
- Gynecomastia

GENERAL PREVENTION
- Possibly early orchidopexy for undescended testicle
- USPSTF: Against routine screening for testicular cancer in asymptomatic adolescent and adults including routine testicular self-exams.
- American Cancer Society suggests that men with family history do monthly self-exams.
- American Urological Association (AUA): Monthly self-exams for all young men.

DIAGNOSIS
HISTORY
- The most common symptom at the time of diagnosis is painless swelling or enlargement of the testis.
- Acute testicular pain is reported to occur in ~10% of patients with testicular cancer and often represents infarction or hemorrhage within the tumor.
- At initial presentation, symptoms manifesting secondary to metastatic disease occur in ~20% of patients and include:
  - A mass in the left neck, pulmonary complaints such as hemoptysis or dyspnea, an abdominal mass, or back pain that can often be disabling.
- In ~5% of patients, gynecomastia or tenderness of the breast is reported.

PHYSICAL EXAM
- The most common finding on physical exam is a solid intratesticular mass or swelling.
- Patients should undergo a complete physical exam with emphasizing palpation of the cervical lymph nodes (lymphadenopathy), breasts (gynecomastia), abdomen (retroperitoneal masses/lymphadenopathy, liver masses), and the contralateral testis (bilateral testicular tumors).

ALERT
Markers must be drawn prior to radical orchiectomy.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum tumor markers (AFP, HCG, LDH) should be obtained prior to and following radical orchiectomy. The serum tumor markers are necessary for diagnosis, staging, and risk classification.
- Tumor markers obtained prior to orchiectomy:
  - 1 or more elevated in 85–90% of NSGCT
- β-hCG:

  - Half-life: 24–36 hr
  - Elevated in 40–60% with testis cancer; 100% of choriocarcinomas;10–15% pure seminomas
- AFP:
  - Half-life: 5–7 days
  - Produced by yolk sac tumors, embryonal cell carcinoma, and teratocarcinomas
  - Not produced in pure seminoma or pure choriocarcinoma. If AFP elevated in case of pure seminoma, NSGCT elements are present.
- LDH
  - Nonspecific marker for GCT
  - Elevated in 20% of low-stage and 50% of high-stage GCT
  - Useful in prognosis as magnitude of elevation correlates with disease bulk
  - Half-life: 1 day
- Serum and urine estrogens may be elevated in Leydig cell tumors
- While normal postorchiectomy serum tumor markers does not preclude the finding of metastatic disease, an elevation of either AFP or HCG does signify the presence of metastasis.

Imaging

- Testicular ultrasonography is the initial imaging modality of choice with a $>95\%$ sensitivity/specificity in identifying intratesticular lesions.
- Testicular ultrasonography often reveals a solid hypoechoic mass present within the testis.
- The contralateral testis should also be imaged as $\sim 2\%$ of patients will have bilateral testicular cancers.
- The initial staging evaluation should include a CT scan of the chest, abdomen, and pelvis with and without contrast.
  - CT is the most effective radiographic technique for identifying metastatic disease both above and below the diaphragm.
  - No evidence of metastases in $\sim 70\%$ of patients with seminoma and 30% of patients with nonseminoma.

Diagnostic Procedures/Surgery

A radical orchiectomy with high ligation of the spermatic cord at the level of the inguinal ring provides histopathologic diagnosis, primary tumor staging, and excellent local control of the tumor, with minimal morbidity and no mortality.

Pathologic Findings

- Histologic findings of seminoma, embryonal carcinoma, choriocarcinoma, yolk sac tumor, teratoma.
- Documentation of lymphovascular invasion.
- Pathologic and clinical staging follows the TNMS classification and risk assessment if performed using the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification.

ALERT

18–33% of patients with testicular cancer were initially treated for epididymitis resulting in a delay in diagnosis of testicular cancer.

DIFFERENTIAL DIAGNOSIS

- Benign lesions
  - Epididymitis/orchitis: Bacterial, STD, mumps
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle or appendages)
  - Incarcerated/strangulated hernia
  - Cysts (simple, tunica albuginea, epidermoid)
  - Adrenal rest tumors: In general benign, but can contribute to infertility in patients with congenital adrenal hyperplasia
  - Fibrous pseudotumor of the tunica albuginea: Painless fibrous mass often associated with prior history of trauma or infection
  - Adenomatoid tumor of testis or epididymis
  - Other rare benign lesions: Angioma, fibroma, leiomyoma, hamartoma, carcinoid, neurofibroma
- Malignant lesions
  - Testicular primary tumors (GCT, stromal and mixed as discussed above)
  - Leukemia involving testis: Testis can be a site of solitary recurrence of leukemia posttreatment (sanctuary site). Biopsy to confirm diagnosis. Treat with testis-sparing radiation, treat bilaterally.
  - Lymphoma involving testis: Usually represents extension from extratesticular sites, rarely can represent a primary lymphoma site (1% of lymphoma cases); can present bilaterally one-third of the time; mostly involves older men >60 yr; constitutional symptoms commonly present (fever, chills, night sweats, weight loss).
  - Metastatic solid tumors: Common: Prostate, lung, GI tract; more rare: Kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Adenocarcinoma of the rete testis: Arises in the testis collecting system, high-stage presentation, poor response to chemotherapy and radiation, with median survival of 1 yr.
  - Mesothelioma of tunica vaginalis: Rare, similar to the more common pleural histology, associated with asbestos exposure
  - Paratesticular sarcomas: Rhabdomyosarcoma, malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)

TREATMENT

GENERAL MEASURES

- Inguinal radical orchiectomy/high ligation of the spermatic cord is diagnostic and therapeutic.
- Patients are then staged based on TNM classification (see Section VII: "Reference tables: TNM: Testis Cancer")

ALERT
Discuss sperm banking prior to treatment.

MEDICATION

First Line (1,2)

- Regardless of histology, patients with advanced GCTs (cIIB–cIII) and with persistently

elevated tumor markers following radical orchiectomy (cIS), are initially treated with platinum-based chemotherapy according to the IGCCCG risk stratification.
  – Good risk disease: 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP).
  – Intermediate-risk or high-risk disease: 4 cycles of BEP; ~30–40% of patients with poor-risk disease fail to achieve a durable response to conventional chemotherapy.

Second Line

Second-line chemo: Reserved for advanced testicular cancer in whom serum tumor markers do not normalize following initial chemo.

SURGERY/OTHER PROCEDURES

- Radical orchiectomy should be performed for diagnosis and treatment of the primary tumor.
- In US, the preferred management for patients at high risk for relapse in the retroperitoneum, ie, predominant embryonal carcinoma, lymphovascular invasion, or extension into the tunica or scrotum, is primary RPLND if serum tumor markers have normalized.
- Postchemotherapy RPLND (PC-RPLND) and resection of residual masses should be done. Following chemo, 40% undergoing RPLND will have teratoma; 10–15% have GCT.

ADDITIONAL TREATMENT

Radiation Therapy

In US, radiation therapy to the retroperitoneum remains the treatment of choice for patients with clinical stage I and IIa seminoma.

Additional Therapies

- Surveillance, with serial imaging and tumor markers, in well-selected low-risk patients:
  – Stage I seminoma
  – Stage I NSGCT: No teratomatous elements, no lymphovascular invasion, and no embryonal cell carcinoma in the primary specimens. Patients must be reliable

Complementary & Alternative Therapies

Discuss sperm banking before therapy

ONGOING CARE

PROGNOSIS

- Prognosis is dependent on initial clinical stage, risk stratification, and histology.
- The multidisciplinary approach to GCTs has survival rates at >90%.

COMPLICATIONS

- Radical orchiectomy: Wound infection, scrotal and/or retroperitoneal hematoma
- RPLND: Wound infection, pancreatitis, venous thrombosis, chylous ascites, anejaculation, and small-bowel obstruction.
- Chemotherapy: Neutropenia, gastrointestinal symptoms, alopecia, pulmonary fibrosis, and cardiovascular events.

FOLLOW-UP

Patient Monitoring

History and physical exam, serum tumor markers, chest x-ray, and periodic CT imaging of the

chest, abdomen, and pelvis for life. Follow-up according NCCN guidelines.

Patient Resources

MedlinePlus: Testicular cancer.
http://www.nlm.nih.gov/medlineplus/ency/article/001288.htm

REFERENCES

1. Bosl G, Bajorin DF, Sheinfeld J et al. Cancer of the testis. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia: PA, JB Lippincott; 2000:1491–1518.
2. Carver BS, Sheinfeld J. Germ cell tumors of the testis. *Ann Surg Oncol.* 2005;12(11):871–880.

ADDITIONAL READING

NCCN Guidelines for the Treatment of Testis Cancer (www.nccn.org)

See Also (Topic, Algorithm, Media)

- International Germ Cell Cancer Collaborative Group (IGCCCG)
- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Adult General Considerations Images
- Testis Cancer, Choriocarcinoma
- Testis Cancer, Embryonal Carcinoma
- Testis Cancer, Endodermal Sinus Tumors (Yolk Sac Tumors)
- Testis Cancer, Pediatric, General Considerations
- Testis Cancer, Seminoma
- Testis, Cancer Nonseminomatous Germ Cell Tumors, General
- Testis, Leydig Cell Tumor
- Testis, Sertoli Cell Tumor
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Pediatric, General Considerations

CODES

ICD9

- 186.0 Malignant neoplasm of undescended testis
- 186.9 Malignant neoplasm of other and unspecified testis
- 608.3 Atrophy of testis

ICD10

- C62.00 Malignant neoplasm of unspecified undescended testis
- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- N50.0 Atrophy of testis

CLINICAL/SURGICAL PEARLS

- All intratesticular masses should be assumed to be testicular cancer until proven otherwise.
- Elevated AFP is diagnostic for nonseminomatous GCT.

- Inguinal radical orchiectomy with high ligation of the spermatic cord is the initial treatment.

TESTIS CANCER, CHORIOCARCINOMA

Brett S. Carver, MD

BASICS

DESCRIPTION

- Choriocarcinoma is a type of germ cell tumor (GCT) composed of syncytiotrophoblastic, cytotrophoblastic, and other trophoblastic cells.
- Histologic cell type for nonseminomatous GCTs.
- Pure choriocarcinomas are commonly associated with metastatic disease and high levels of β-hCG at the time of presentation

EPIDEMIOLOGY

Incidence

- It is projected that in US, 8,820 new cases of testicular cancer would be diagnosed and 380 men would die of this disease in 2014.
- Pure choriocarcinoma compromises <1% of testicular GCT.
- Choriocarcinoma is a histologic cell type in ~10% of nonseminomas.

Prevalence

N/A

RISK FACTORS

- Risk factors associated with the development of testicular cancer include:
  - Cryptorchidism, family history, testicular atrophy, infertility.

Genetics

Identification of isochromosome 12p amplification.

PATHOPHYSIOLOGY

- Choriocarcinoma is a histologic subtype of nonseminomatous GCTs composed primarily of syncytiotrophoblasts and cytotrophoblasts.
- Syncytiotrophoblastic cells produce human chorionic gonadotropin (HCG) which may be detected by immunohistochemistry or measurement of serum levels.
- Pure choriocarcinoma is associated with significantly elevated levels of serum HCG. Choriocarcinoma represents a germ cell transformed through extraembryonic differentiation.
- Relationship between size of primary tumor and metastatic disease may seem paradoxical, with widespread disease associated with a relatively small primary tumor.
- Route of metastatic spread is variable compared to other GCTs, which are often stepwise and predictable. Choriocarcinoma is associated with a greater propensity for hematogenous dissemination.
- β-hCG is produced by syncytiotrophoblasts and is elevated in 100% of choriocarcinomas. The serum half-life of β-hCG is 24–36 hr.
  - Elevated serum levels of β-hCG are also noted in 40–60% of embryonal carcinomas and 5–10% of pure seminomas.

ASSOCIATED CONDITIONS
- Infertility
- Cryptorchidism
- Gynecomastia

GENERAL PREVENTION
Conflicting data if early orchiopexy reduces testis cancer risk in cryptorchidism

DIAGNOSIS
HISTORY
- Past medical history focusing on history of cryptorchidism
- The most common symptom at the time of diagnosis is painless swelling or enlargement of the testis.
  - Acute testicular pain is reported to occur in ~10% of patients with testicular cancer and often represents infarction or hemorrhage within the tumor.
- At initial presentation, symptoms manifesting secondary to metastatic disease occur in ~20% of patients and include, a mass in the left neck, pulmonary complaints such as hemoptysis or dyspnea, an abdominal mass, or back pain that can often be disabling.
  - Patients with choriocarcinoma may present with gynecomastia or tenderness of the breast secondary to elevated serum HCG.
- Neurologic symptoms related to brain metastases may be present in patients with advanced pure choriocarcinoma.

PHYSICAL EXAM
- The most common finding on physical exam is a solid intratesticular mass or swelling.
- Thorough exam of both gonads
  - Careful palpation of surrounding spermatic cord structures on involved side to evaluate extent of disease
  - Transillumination of scrotal contents if hydrocele is associated or suspected.
- Exam for metastatic disease including inguinal, abdominal, thoracic, neurologic exams.
  - Cervical lymph nodes (lymphadenopathy), breasts (gynecomastia), abdomen (retroperitoneal masses/lymphadenopathy, liver masses)
- Gynecomastia can be noted in ~5% of patients with GCT:
  - β-hCG can stimulate estrogen production from Leydig cells, leading to breast enlargement and tenderness, and the contralateral testis (bilateral testicular tumors).

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum tumor markers (AFP, HCG, LDH) should be obtained prior to and following radical orchiectomy. The serum tumor markers are necessary for diagnosis, staging, and risk classification. While normal postorchiectomy serum tumor markers does not preclude the finding of metastatic disease, an elevation of either AFP or HCG does signify the presence of metastasis.
- Pure choriocarcinomas are often associated with significantly high levels of serum HCG.

Imaging

- Testicular ultrasonography is the initial imaging modality of choice with a >95% sensitivity and specificity in identifying intratesticular lesions.
- Testicular ultrasonography often reveals a solid hypoechoic mass present within the testis.
- The initial staging evaluation should include a CT scan of the chest, abdomen, and pelvis. CT is the most effective radiographic technique for identifying metastatic disease both above and below the diaphragm.
- MRI of the brain should be performed to evaluate for metastases in patients with pure choriocarcinoma.

Diagnostic Procedures/Surgery

A radical orchiectomy with high ligation of the spermatic cord at the level of the inguinal ring provides histopathologic diagnosis, primary tumor staging, and excellent local control of the tumor, with minimal morbidity and no mortality.

Pathologic Findings

- Choriocarcinoma may be associated with other nonseminomatous germ cell histologies, as well as seminomatous histologies.
- Histology revealing syncytiotrophoblasts and cytotrophoblasts.
  - Macroscopically, tumors are often hemorrhagic with areas of necrosis, and can be associated with areas of fibrosis and tumor regression. Hemorrhage is usually central with viable tumor located peripherally.
- Mix of mononuclear cells with lightly staining cytoplasm (cytotrophoblasts) combined with multinucleated cells with smudged/degenerating nuclei and densely eosinophilic cytoplasm (syncytiotrophoblasts)
- Multiple fields need to be examined to clearly identify the cytotrophoblasts. Syncytiotrophoblasts stain strongly with HCG
- Pathologic and clinical staging follows the TNM classification and risk assessment if performed using the IGCCCG risk classification.

DIFFERENTIAL DIAGNOSIS

- These are a delineation of testicular masses only. For a complete listing of intrascrotal and testicular masses see Section I: “Scrotum and Testicle Mass”:
- Benign lesions
  - Epididymitis/orchitis: Bacterial, STD, mumps, TB
    - Often delayed testicular cancer diagnosis due to treatment of presumed epididymitis
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle or appendages)
  - Incarcerated/strangulated hernia
  - Cysts (simple, tunica albuginea, epidermoid)
  - Adrenal rest tumors: In general benign, but can contribute to infertility in patients with congenital adrenal hyperplasia
  - Fibrous pseudotumor of the tunica albuginea: Painless fibrous mass often associated with prior history of trauma or infection
  - Adenomatoid tumor of testis or epididymis
  - Other rare benign lesions: Angioma, fibroma, leiomyoma, hamartoma, carcinoid, neurofibroma

- Malignant lesions
  - Testicular primary tumors (seminoma and nonseminomatous GCT, stromal and mixed as discussed above)
  - Leukemia involving testis—testis can be a site of solitary recurrence of leukemia posttreatment (sanctuary site). Biopsy can be utilized to confirm diagnosis in a patient with history of leukemia.
    - Treatment can be testis-sparing with radiation, though contralateral testis should be treated as bilateral disease can be present.
  - Lymphoma involving testis—usually represents extension from extratesticular sites, rarely can represent a primary lymphoma site (1% of lymphoma cases); can present bilaterally one-third of the time; mostly involves older men >60 yr; constitutional symptoms commonly present (fever, chills, night sweats, weight loss).
  - Metastatic solid tumors: More common—prostate, lung, GI tract; more rare—kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Adenocarcinoma of the rete testis: Arises in the testis collecting system, high-stage presentation, poor response to chemotherapy and radiation, with median survival of 1 yr.
  - Mesothelioma of tunica vaginalis: Rare, similar to the more common pleural histology, associated with asbestos exposure
  - Paratesticular sarcomas: Rhabdomyosarcoma, malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)

TREATMENT

GENERAL MEASURES (1)

- Inguinal radical orchiectomy with high ligation of the spermatic cord is diagnostic and therapeutic.
- Treatment options are based on clinical staging. Staging following removal of the primary tumor is similar to all GCT and is based on physical exam, radiographic studies, serum tumor markers, and histologic tumor features according the TNMS staging system.

MEDICATION

First Line (2)

- Regardless of histology, patients with advanced GCTs (cIIB–cIII) and those with persistently elevated tumor markers following radical orchiectomy (cIS), are initially treated with platinum-based chemotherapy according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification.
  - Patients with good-risk disease are treated with 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP).
  - While patients with intermediate-risk or high-risk disease receive 4 cycles of BEP.
- Choriocarcinomas are often associated with hemorrhage, neurologic and pulmonary monitoring is critical following chemotherapy.

Second Line

Second-line chemotherapy is reserved for patients with advanced testicular cancer in whom serum tumor markers do not normalize following initial chemotherapy regimen.

SURGERY/OTHER PROCEDURES

- Radical orchiectomy should be performed for diagnosis and treatment of the primary tumor.
- In US, the preferred management for patients at high risk for relapse in the retroperitoneum, ie, predominant embryonal carcinoma, lymphovascular invasion, or extension into the tunica or scrotum, is primary RPLND if serum tumor markers have normalized.
- Postchemotherapy RPLND (PC-RPLND) and resection of residual masses are an integral component in the management of advanced nonseminoma.

ADDITIONAL TREATMENT

Radiation Therapy

Occasionally radiation therapy for cerebral metastases is utilized, but systemic therapy remains the initial treatment of choice for the management of metastatic disease including cerebral metastasis.

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- The multidisciplinary approach to the management of GCTs of the testis has resulted in survival rates of >90% overall.
- The prognosis for patients with testicular cancer including choriocarcinoma depends on stage, risk stratification, and histology.
- Prognosis for patients with metastatic disease estimated using the IGCCC system for NSGCT:
  - Good prognosis: Testis or retroperitoneal primary, no nonpulmonary visceral metastases, AFP <1,000, β-hCG <5,000, and LDH <1.5 for upper limit of normal (ULN)
  - Intermediate prognosis: Testis or retroperitoneal primary, no nonpulmonary visceral metastases, AFP 1,000–10,000, β-hCG 5,000–50,000, or LDH 1.5–10 ULN
  - Poor prognosis: Mediastinal primary, nonpulmonary visceral metastases, AFP >10,000, β-hCG >50,000, or LDH >10 ULN

COMPLICATIONS

- The complications of radical orchiectomy include: Wound infection, scrotal hematoma, and retroperitoneal hematoma.
- Complications of RPLND: Wound infection, pancreatitis, venous thrombosis, chylous ascites, anejaculation, and small-bowel obstruction.
- Complications of chemotherapy: Neutropenia, gastrointestinal symptoms, alopecia, pulmonary fibrosis, and cardiovascular events; propensity for choriocarcinomas to hemorrhage

FOLLOW-UP

Patient Monitoring

Following management of GCTs, patients should be followed with history and physical exam, serum tumor markers, chest x-ray, and periodic CT imaging of the chest, abdomen, and pelvis

for life. Follow-up protocols should be followed according to guidelines established by the National Comprehensive Cancer Network.

Patient Resources

American Cancer Society: http://www.cancer.org/cancer/testicularcancer/index

REFERENCES

1. Bosl G, Bajorin D, Sheinfeld J, et al. Cancer of the testis. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia: PA, JB Lippincott; 2000:1491–1518.
2. Carver BS, Sheinfeld J. Germ cell tumors of the testis. *Ann Surg Oncol*. 2005;12(11):871–880.

ADDITIONAL READING

NCCN Guidelines for the Treatment of Testis Cancer (www.nccn.org)

See Also (Topic, Algorithm, Media)

- International Germ Cell Cancer Collaborative Group (IGCCCG)
- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Adult General Considerations
- Testis Cancer, Choriocarcinoma Image ☼
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis Cancer, Pediatric, General Considerations

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 608.3 Atrophy of testis
- 752.51 Undescended testis

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- N50.0 Atrophy of testis
- Q53.9 Undescended testicle, unspecified

CLINICAL/SURGICAL PEARLS

- All intratesticular masses should be assumed to be testicular cancer until proven otherwise.
- Choriocarcinomas are associated with production of HCG.
- Choriocarcinomas have a predilection for brain metastases.
- Inguinal radical orchiectomy with high ligation of the spermatic cord is the initial treatment.

TESTIS CANCER, EMBRYONAL CARCINOMA

Nicholas J. Kuntz, MD
Judd W. Moul, MD, FACS

BASICS

DESCRIPTION

- Embryonal carcinoma (EC) is the most common (43%) nonseminoma germ cell tumor (NSGCT) histologic subtype of the testis (1)[B]
- Pure EC histology is present in 2–4% of all germ cell tumors (GCTs)
- EC is present in 85% of mixed GCTs
- Most common in age 20–40 yr
- Right more common, bilateral in 2–3%

EPIDEMIOLOGY

Incidence

- US age-adjusted incidence (SEER data)
  - 5.5 per 100,000/yr (all testicular cancers)
- 2014 estimated new cases of testicular cancer
  - 8,820 with 380 deaths
- Lifetime risk of developing testicular cancer:
  - 1 in 270

Prevalence

Testicular cancer: 221,020 US men in 2010

RISK FACTORS

- Cryptorchidism
  - 4–6-fold increased risk for all GCTs
  - Increased risk in contralateral testes
- Previous testicular malignancy
  - 12-fold increases risk to develop cancer in the contralateral testicle
- Family history
  - 8–12-fold increased risk with affected brother
- Intratubular germ cell neoplasia (ITGCN)
- Testicular atrophy
  - Nonspecific or mumps-associated
- Klinefelter syndrome

Genetics

- Isochromosome of the short arm of chromosome 12–i(12p) (2)[B]
- ITGCN
  - p53 alterations found in 66% (3)[B]

PATHOPHYSIOLOGY

- EC is an aggressive GCT subtype
- 74% have metastases at presentation (1)[B]
- Predominant EC component (>50%) increases the risk of occult metastasis (3)[A]
- High associated relapse rate (35–40%)
- Predictable lymphatic spread
  - Retroperitoneum (primary site)
    - Left-sided tumors spread to preaortic and para-aortic lymph nodes; left-to-right spread is rare.
    - Right-sided tumors spread to precaval, interaortocaval, and then may spread to preaortic and para-aortic nodes.
  - Most common visceral sites
    - Lungs, liver

ASSOCIATED CONDITIONS
- Infertility
- Cryptorchidism
- Seminoma

GENERAL PREVENTION
- Possibly early orchidopexy for undescended testicle
- Testicular self-exam

DIAGNOSIS
HISTORY
- Signs and symptoms
  - Painless testicular mass (50–60%)
  - Testicular pain or dull ache (30–40%)
  - Symptomatic metastases (10%)
    - Cough, dyspnea, supraclavicular nodal
  - Gynecomastia (2%)
  - Trauma (4%)
  - Infertility
- History of undescended testes in 10%

PHYSICAL EXAM
- Thorough genital, lymph node, abdominal, chest, and neurologic exam
  - 2–3% of patients with disseminated testicular cancer present with central nervous system (CNS) metastasis.
  - Gynecomastia noted in 7% of GCTs (2)[B]
- Include palpation of spermatic cord structures
- Scrotal ultrasound (US) (see “Imaging”)
- Transillumination test
  - Reactive hydrocele may be secondary to underlying malignancy

DIAGNOSTIC TESTS & INTERPRETATION
Lab

- Tumor markers (4)[A] (drawn at diagnosis and following orchiectomy according to half-life)
  - α-Fetoprotein (AFP)
    - Produced by fet al gut, liver, and yolk sac
    - Half-life of ~5 days.
    - Elevated in 80% of EC
    - Absent in pure seminoma and choriocarcinoma.
  - Human chorionic gonadotropin (hCG)
    - Normally secreted by placental syncytiotrophoblasts
    - Half-life of ~24–36 hr. Consists of α- and β-chains: α-chain analogous to luteinizing hormone and thyroid-stimulating hormone.
    - Elevated in 60% of all NSGCT, 30% of seminomas, and all choriocarcinomas.
  - Lactate dehydrogenase (LDH)
    - Most useful when other markers are negative.
    - Relates to tumor bulk.
- Chemistry profile
  - Renal function (future chemo, ureteral obstruction from RP disease)

Imaging

- Scrotal US (4)[A]
  - Well circumscribed, heterogeneous, hypoechoic mass is highly suspicious for cancer
  - Cannot distinguish subtypes on imaging
- Clinical staging
  - Computed tomography (CT) of chest abdomen and pelvis (4)[A]
  - Head magnetic resonance imaging (MRI) if:
    - Neurologic symptoms
    - High risk for CNS disease (mets, high hCG, or choriocarcinoma)
  - Positron emission tomography (PET): Not indicated for NSGCT (2)[B]

Diagnostic Procedures/Surgery

- Biopsy of primary mass is contraindicated
  - Contamination of lymph drainage
- Consider inguinal biopsy of contralateral testis if (2)[B]:
  - Concerning US findings
  - Cryptorchid testis
  - Significant atrophy

Pathologic Findings

- Gross
  - Tan to yellow, fleshy tumor
  - Areas of necrosis or hemorrhage
  - Poorly defined capsule
- Histologic
  - Epithelioid cells arranged in glands or tubules, indistinct cell borders
  - Pale or vacuolated cytoplasm
  - Rounded nuclei with coarse chromatin

- Large nucleoli; pleomorphism, mitotic figures, and giant cells
- Staining:
  - Positive: AE1/AE3, PLAP, and OCT3/4
  - Negative: c-KIT

DIFFERENTIAL DIAGNOSIS

See Section I "Testis, Tumor and Mass, Adult, General Considerations" and Testis, tumor and mass, pediatric, general considerations

ALERT
Up to 33% of testicular tumors are initially misdiagnosed

TREATMENT

ALERT
Discuss sperm banking prior to treatment, due the increased risk of infertility following treatment (4)[A].

GENERAL MEASURES

- Surgery (radical inguinal orchiectomy) is the primary treatment for all testicular malignancies (4)[A]
- Chemotherapy prior to orchiectomy may be warranted in severe cases (4)[A]
- Subsequent primary treatments include chemo, radiation, or retroperitoneal lymph node dissection (RPLND)
- Treatment options for EC are based on clinical stage (4)[A]. (see Table "TNM: Testis Cancer")
  - Stage IA, IB:
    - Surveillance (IA or IB T2 only)
    - RPLND
    - Chemotherapy (2 cycles bleomycin, etoposide, cisplatinum (BEP) × 2 or BEP × 1
  - Stage IIA and IIB:
    - RPLND
    - Chemotherapy (EP × 4, or BEP × 3)
  - Stage IIc or stage III:
    - Good risk (EP × 4 or BEP × 3)
    - Intermediate risk (BEP × 4)
    - Poor risk (BEP × 4, clinical trial, VIP × 4)

MEDICATION

First Line

- BEP or EP regimens
- See Section I: "Testis, Cancer, Adult General Considerations" for specific regimens

Second Line

- Vinblastine, ifosfamide, cisplatinum (VIP)
  - Poor tolerance to bleomycin

  – Salvage protocol
  – Pretreat with MESNA to reduce incidence of hemorrhagic cystitis
- Paclitaxel, ifosfamide, cisplatin (TIP)
- High-dose chemotherapy

SURGERY/OTHER PROCEDURES
- Radical inguinal orchiectomy
  – Recommended first-line treatment for testicular tumors (4)[A]
- Partial orchiectomy
  – Small tumor (< 30% of testicular volume), solitary testes, or bilateral tumors
  – Adjuvant radiation at some point (16–20 Gy) given high rate of associated ICGCN (2)[B]
- RPLND
  – Nerve-sparing approach minimizes ejaculatory dysfunction
  – stage IIa, IIb, or high-risk stage I (4)[A]
- Salvage RPLND
  – Consider referral to high-volume center
  – Full bilateral template recommended in this setting

ADDITIONAL TREATMENT

Radiation Therapy

No role in treatment of NSGCT

Additional Therapies

Palliative chemotherapy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS
- Stage I:
  – > 30% relapse with observation alone
- Stage II and III:
  – > 60% have complete response following adjuvant treatment

COMPLICATIONS
- RPLND:
  – Loss of seminal emission: 10%
  – Bowel obstruction: 1–3% lifetime risk
  – ARDS: Patients previously been treated with bleomycin
- Chemotherapy:
  – Bleomycin: Pulmonary fibrosis, ARDS
  – Etoposide: Myelosuppression, alopecia secondary leukemia
  – Cisplatin: Renal insufficiency, nausea/vomiting, neuropathy
  – Ifosfamide: Hemorrhagic cystitis
  – Vinblastine: Neuromuscular toxicity

FOLLOW-UP

Patient Monitoring

- Primary surveillance
  - ~30% recurrence, most common 1st 2 yr
  - NCCN follow-up protocol:
    - Year 1: Tumor markers and chest x-ray every 1–2 mo; abdominal CT every 3–4 mo
    - Year 2: Tumor markers and chest x-ray every 2 mo; abdominal CT every 4–6 mo
    - Years 3–5: Tumor markers and chest x-ray every 3–6 mo; abdominal CT every 6–12 mo
    - After year 5: Tumor markers and chest x-ray once a year; abdominal CT every 1–2 yr
- RPLND
  - Most likely site of recurrence is the chest (3)
  - NCCN follow-up protocol:
    - Year 1: Tumor markers and chest x-ray every 2–3 mo, baseline abdominal/pelvic CT
    - Year 2: Tumor markers and chest x-ray every 2–3 mo, abdominal/pelvic CT as indicated
    - Years 3–5: Tumor markers and chest x-ray every 3–12 mo, abdominal/pelvic CT as indicated.
    - After year 5: Tumor markers and chest x-ray once a year
- Chemotherapy and RPLND
  - NCCN follow-up protocol:
    - Year 1: Tumor markers and chest x-ray every 2–3 mo; abdominal/pelvic CT every 6 mo
    - Year 2: Tumor markers and chest x-ray every 2–3 mo; abdominal/pelvic CT every 6–12 mo
    - Years 3–5: Tumor markers and chest x-ray every 3–12 mo; abdominal/pelvic CT every year
    - After year 5: Tumor markers and chest x-ray once a year; abdominal/pelvic CT as indicated

Patient Resources

- NCI 1-800-4-CANCER. http://www.cancer.gov/cancertopics/pdq/treatment/testicular/Patient
- American Cancer Society. http://www.cancer.org/cancer/testicularcancer/index

REFERENCES

1. Vugrin D, Chen A, Feigl P, et al. Embryonal carcinoma of the testis. *Cancer*. 1988;61(11):2348–2352.
2. Albers P, Albrecht W, Algaba F, et al. EAU guidelines on testicular cancer: 2011 update. *Eur Urol*. 2011;60(2):304–319.
3. Albers P, Siener N, Kliesch S, et al. Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: Results of the German Testicular Cancer Study Group Trial. *J Clin Oncol*. 2003;21(8):1505–1512.
4. National Guideline Clearinghouse. Guidelines on testicular cancer Rockville MD: Agency for Healthcare Research and Quality (AHRQ); [5/15/2013]. www.guideline.gov/content.aspx?id=34061&search=embryonal+carcinoma.

ADDITIONAL READING

• National Cancer Institute. www.cancer.gov/cancertopics/types/testicular/ (Accessed August 20, 2014)
• National Comprehensive Cancer Network. Available at www.nccn.org (Accessed August 20, 2014)

See Also (Topic, Algorithm, Media)
• International Germ Cell Cancer Collaborative Group (IGCCCG)
• Reference Tables: TNM: Testis Cancer
• Scrotum and Testicle, Mass
• Testis Cancer, Adult General Considerations
• Testis Cancer, Embryonal Carcinoma Image ☼
• Testis Cancer, Pediatric, General Considerations
• Testis, Tumor and Mass, Adult, General Considerations

CODES

ICD9
• 186.9 Malignant neoplasm of other and unspecified testis
• 608.3 Atrophy of testis
• 752.51 Undescended testis

ICD10
• C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
• Q53.9 Undescended testicle, unspecified
• N50.0 Atrophy of testis

CLINICAL/SURGICAL PEARLS

• Painless testicular mass is testicular cancer until proven otherwise.
• Transscrotal orchiectomy or biopsy is contraindicated.
• EC is aggressive histologic subtype with increased risk of occult disease.
• Second opinion of pathologic specimens by experienced pathologists is encouraged.
• Current treatment approaches achieve excellent long-term survival rates.

TESTIS CANCER, ENDODERMAL SINUS TUMORS (YOLK SAC TUMORS)

Elizabeth V. Dray, MD
Marcus L. Quek, MD, FACS

BASICS

DESCRIPTION

- Endodermal sinus tumors (yolk sac tumors [YSTs]) are germ cell tumor (GCT) that resembles cells of allantois, yolk sac, and mesenchyme
  - AKA endodermal sinus tumors, Teilum tumor, orchioblastoma, juvenile embryonal
- Bimodal age distribution
  - Children < 3 yr, young adults
- Staging
  - Adults: Per TNM staging for non seminomtous germ cell tumors (NSGCT) (See Section VI: Reference tables: TNM: Testis Cancer)
  - Children: Children's Oncology Group Staging
    - Stage I: Tumor limited to the testis, completely resected by high inguinal orchiectomy with negative margins. No clinical, radiographic or histologic evidence of disease beyond the testis. Tumor markers negative after appropriate half-life decline.
    - Stage II: Microscopic residual disease present in the scrotum or spermatic cord (< 5 cm from proximal end). Tumor markers elevated after appropriate half-life. Tumor rupture or scrotal biopsy prior to completion orchiectomy.
    - Stage III: Retroperitoneal lymph node involvement (LN > 4 cm on CT).
    - Stage IV: Distant metastases.
- 85% of children present with stage I disease, compared to 35% of postpubertal cases

EPIDEMIOLOGY

Incidence

- Children
  - Incidence of pediatric testis tumors is 0.5–2 per 100,000.
  - YST comprise 62% of all testicular tumors in childhood based on AAP tumor registry.
- Adults
  - In US, ~8,820 new cases of testicular cancer would be diagnosed and 380 men would die of this disease in 2014.
  - Lifetime risk of developing testis cancer is ~1 in 270, and the lifetime risk of dying of testicular cancer is 1 in 5,000
  - Pure YST is extremely rare, but found in 42% of mixed GCTs.

Prevalence

N/A

RISK FACTORS

- General risk for testicular cancer

- Cryptorchidism
- Klinefelter's syndrome.
- Family history.
- Male infertility
- Low birthweight, young maternal age, young paternal age, multiparity, breech delivery
- Infant hernia.
- Height-taller men
- Testicular microlithiasis

Genetics

Heredity unknown

PATHOPHYSIOLOGY

- Associated with gains in chromosome 12p in adults, RUNX promotor methylation on chromosome 1p in children (1)
- ITGCN precursor lesion in adults, unclear relationship in children.
- Lymphatic and hematogenous spread
  - Up to 20% of children present with lung metastases compared to 4–6% of adults

ASSOCIATED CONDITIONS

- Adults
  - Cryptorchidism
    - Later age at orchiopexy associated with higher relative risk of cancer.
    - Risk also increased with intra-abdominal testis and bilateral cryptorchidism.
- Children
  - Disorders of sex development

DIAGNOSIS

HISTORY

- Presents as painless testicular mass
  - May also present as retroperitoneal mass in mediastinal GCT
  - Incidentally associated with trauma in $<10\%$ of cases.

PHYSICAL EXAM

- Painless testicular mass
  - 15–50% have associated hydrocele

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum tumor markers
  - β-hCG never elevated in pure YST.
  - 90% of YST produce AFP
    - Also produced by liver and GI tract.
    - Half-life 5–7 days.
    - AFP often elevated in infants. Normal adult levels not reached until 8 mo of age.

Imaging

- Scrotal US

- Hyperechoic or heterogenous mass with increased blood flow on Doppler
  - Note: In children, anechoic cystic lesions with normal AFP suggestive of benign mass, can attempt testis-sparing surgery.
- CT chest/abdomen/pelvis with PO and IV contrast
  - For staging in all age groups.

Diagnostic Procedures/Surgery

Inguinal orchiectomy with high ligation of spermatic cord within 1–2 wk of presumed diagnosis.

Pathologic Findings

- Gross
  - Endodermal sinus tumors appear firm, yellow-white mass
- Microscopic
  - Resemble cells of allantois, yolk sac, mesenchyme arranged in glandular, papillary, or microcytic pattern with hyaline globules.
  - Schiller–Duval bodies characteristic finding
  - Stains positive for AFP.

DIFFERENTIAL DIAGNOSIS

- Adults: See Section I "Testis, Tumor and Mass, Adult, General Considerations"
- Painful childhood testicular masses:
  - Epididymitis/orchitis; bacterial, mumps
  - Henoch–Schönlein purpura (usually no mass)
  - Incarcerated/strangulated hernia
  - Testicular or paratesticular tumor
  - Testis trauma: Contusion, hematocele
  - Torsion (testicle, testicular, or epididymal appendage); more common after puberty
- Painless childhood testicular masses:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Cystic dysplasia of the testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea
  - Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of cord
  - Hernia
  - Lipoma of the cord
  - Polyorchidism
  - Scrotal edema (insect bite, nephrotic syndrome, acute idiopathic scrotal edema)
  - Spermatocele (epididymal cyst)
  - Testicular cysts
  - Testicular tumors:
    - GCTs: YST, teratoma, seminoma, embryonal, choriocarcinoma, mixed tumors
    - Gonadal stromal tumors: Leydig tumor, Sertoli cell, granulosa cell tumors
    - Metastatic tumors
    - Hamartoma, carcinoid, and neurofibroma

- Testis tumor of adrenogenital syndrome
- Leukemia or lymphoma

• Varicocele

TREATMENT

GENERAL MEASURES

• Adults
  – Management I handled as for nonseminomatous GCT: Section I "Testis Cancer, Nonseminomatous Germ Cell Tumors, General."
• Children (2,3)
  – Inguinal orchiectomy curative in 80% of children with stage I disease
  – Adjuvant chemotherapy recommended for stage II–IV disease.

MEDICATION

First Line (4)

• Chemotherapy: Bleomycin, etoposide, cisplatin (BEP)
  – Carboplatin may have equivalent outcomes compared to cisplatin with decreased ototoxicity and nephrotoxicity.

Second Line

• Etoposide, ifosfamide, cisplatin (VIP)
  – High-dose chemotherapy regimens for treatment failures.

SURGERY/OTHER PROCEDURES

• In children: LN >2 cm and <4 cm in size at diagnosis should undergo excisional or interventional radiologybiopsy biopsy to confirm histology.
• Postchemotherapy residual retroperitoneal disease should undergo retroperitoneal lymphadenectomy.

ADDITIONAL TREATMENT

Radiation Therapy

No role for radiation in endodermal sinus tumor.

Additional Therapies

• Sperm banking should be offered prior to chemotherapy in adolescents and adults.
  – Fertility-sparing procedure for prepubertal boys are controversial, but include Testicular sperm extraction (*TESE*) and cryopreservation of testicular tissue

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

• Adults: See "NSGCT"
• Children
  – Survival for all stages approaches 100% at 6 yr.
  – 20% of children with stage I disease will relapse during surveillance; however, excellent

cure rates with chemotherapy.

COMPLICATIONS

- Chemotherapy toxicity
  - Bleomycin: Pulmonary fibrosis
  - Cisplatin: Ototoxicity, nephrotoxicity, neuropathy.
  - Etoposide: Pancytopenia
- Infertility

FOLLOW-UP

Patient Monitoring

- Children
  - CXR, CT or MRI, AFP, and history and physical exam monthly for 3 mo, then at 6 mo postoperatively, and subsequently every 6 mo for 36 mo.
    - Note: Imaging guidelines evolving in light of increasing awareness of the impact of radiation on pediatric populations.

Patient Resources

- Urology Care Foundation: Testicular cancer in children. http://www.urologyhealth.org/urology/index.cfm?article=37
- Children's Oncology Group. http://www.childrensoncologygroup.org

REFERENCES

1. Kato N, Tamura G, Fukase M, et al. Hypermethylation of the RUNX3 gene promoter in testicular yolk sac tumor of infants. *Am J Pathol.* 2003;163(2):387–391.
2. Ahmed HU, Arya M, Muneer A, et al. Testicular and paratesticular tumor in prepubertal populations. *Lancet Oncol.* 2010;11(5):476–483.
3. Ross JH, Rybicki L, Kay R, et al. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: A summary of the Prepubertal Testis Tumor Registry. *J Urol.* 2002;168:1675–1679.
4. Wu HY, Snyder H. Pediatric urologic oncology: Bladder, prostate, testis. *Urol Clin North Am.* 2004;31(3):619–627.

ADDITIONAL READING

- Carver BS, Sheinfeld J. Germ cell tumors of the testis. *Ann Surg Oncol.* 2005;12(11):871–880.
- National Comprehensive Cancer Network Guideline Recommendations. http://www.nccn.org/clinical.asp (Accessed August 21, 2014).

See Also (Topic, Algorithm, Media)

- Paratesticular Tumors
- Reference Tables: TNM: Testis Cancer
- Rhabdomyosarcoma, Pediatric
- Scrotum and Testicle, Mass
- Testis Cancer, Adult General Considerations
- Testis Cancer, Endodermal Sinus Tumors (Yolk Sac Tumors) Image
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General

• Torsion, Testis and Testicular Appendages

CODES

ICD9

• 186.9 Malignant neoplasm of other and unspecified testis
• 608.89 Other specified disorders of male genital organs
• 752.51 Undescended testis

ICD10

• C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
• N50.8 Other specified disorders of male genital organs
• Q53.9 Undescended testicle, unspecified

CLINICAL/SURGICAL PEARLS

• Endodermal sinus tumor is the most common GCT of childhood.
• Inguinal orchiectomy with high ligation of spermatic cord mainstay of therapy.
• Excellent prognosis for all stages in children.

TESTIS CANCER, NONSEMINOMATOUS GERM CELL TUMORS, GENERAL

Robert H. Blackwell, MD
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BASICS

DESCRIPTION

- Nonseminomatous germ cell tumors (NSGCTs) are malignant neoplasms of the testicle originating from germ cells, excluding seminoma
- 4 histologic types: Choriocarcinoma, embryonal cell, teratoma, and yolk sac
- >50% of NSGCT have a mixed histology; may also include a seminoma component (mixed GCT)
- Testicular cancer accounts for 1–1.5% of male cancer, of which GCTs make up 90–95%
- This section provides an overview of NSGCT. Details on each subtype can be found in their respective chapters

EPIDEMIOLOGY

Incidence

- SEER age-adjusted incidence of testicular cancer in US is 5.5 per 100,000 men
- In US (2014), ~8,820 new cases will be diagnosed with about 370 deaths

Prevalence

SEER prevalence of testicular cancer in US in 2010 was 221,020

RISK FACTORS

- Family history: ~1.4% of patients with newly diagnosed GCTs report a family history
  - Sons have a 4–6× increased risk of GCT, siblings have a 8–10× increased risk
- Cryptorchidism: ~3.7× increased risk of GCT
  - 7–10% incidence in cryptorchid patients in the ipsilateral undescended testicle, ~5% in the contralateral testicle
- Environment: Higher incidence in Northern Europe > North America > Africa/Asia
- Prior testicular tumor: 2% incidence of malignancy in the contralateral testicle
- ITGCN: 70% progresses to GCT over 7 yr

Genetics

- Identification of isochromosome 12p amplification; found in nearly all GCTs
- 2–3% incidence of bilateral testis tumors may suggest congenital predisposition

PATHOPHYSIOLOGY

- ITGCN (intracellular germ cell neoplasia also referred to as CIS) is believed to be the precursor lesion of all GCTs, excluding spermatocytic seminoma
  - ~2.5% of patients with a GCT will have ITGCN in the contralateral testicle
- GCTs typically spread in a predictive manner via the retroperitoneal lymph nodes (although choriocarcinoma also spreads hematogenously)

  - Left-sided tumors typically spread to para-aortic lymph nodes, right-sided tumors spread to interaortocaval lymph nodes. Tumor may spread right-to-left, but usually not left-to-right
  - Subsequent drainage through the cisterna chyli, thoracic duct, and supraclavicular nodes (usually left) or retrograde to iliac/inguinal nodes
- Nearly 60% of NSGCTs contain >1 histologic subtype in varying amounts (mixed GCTs)
- Choriocarcinoma
  - Expected presenting age: 20–30 yr
  - Tumor markers: Markedly elevated HCG, normal AFP
  - Rare in pure form (1%)
  - Often presents as small primary tumor
  - Can spread hematogenously to lung/brain
- Embryonal cell carcinoma
  - Expected presenting age: 25–35 yr
  - Tumor markers: Elevated or normal HCG/AFP
  - Present in up to 85% of mixed GCTs
  - Only pure embryonal in 2–3% of cases
  - >40% of embryonal component in primary tumor puts patient at high risk for relapse
- Teratoma
  - Expected presenting age: 25–35 yr
  - Tumor markers: Normal AFP and HCG
  - Composed of 2 or more germ cell layers: Endoderm, mesoderm, ectoderm
  - Benign lesions when prepubertal, malignant lesions after puberty
  - May be mature (completely differentiated cell types and somatic tissue) or immature (incompletely differentiated) teratoma
  - Areas may undergo malignant transformation according to which layer transforms (eg, endoderm to adenocarcinoma).
- Yolk sac (endodermal sinus)
  - Expected presenting age: 0–10 yr
  - Tumor markers: Markedly elevated AFP, normal HCG
  - Most common prepubertal testicular tumor
  - Absence of yolk sac elements in mixed GCT is a predictor of relapse

ASSOCIATED CONDITIONS

- Cryptorchidism
- Infertility

GENERAL PREVENTION

- In cases of cryptorchidism, orchiopexy does not decrease incidence of malignancy, but allows for earlier detection
- USPSTF: Against routine screening for testicular cancer in asymptomatic adolescent and adults including routine testicular self-exams.
- American Cancer Society suggests that men with family history do monthly self-exams.
- American Urological Association (AUA): Monthly self-exams for all young men.

DIAGNOSIS

HISTORY

- Presents as painless mass or swollen testicle
- May be initially detected following testicular trauma, but not associated with trauma
- Back or flank pain present in ~10% of cases

PHYSICAL EXAM

- Scrotal exam including both testes, epididymis, and cord structures
- Abdominal exam with attention to palpable lymphadenopathy and/or viscera
- Supraclavicular nodes
- Gynecomastia (present in ~7%)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Tumor markers: Used preop, postop, surveillance
  - β-HCG: Produced by syncytiotrophoblasts. Half-life 24–36 hr
  - AFP: Produced by epithelial lining of endodermal sinus. Half-life 5–7 days
  - LDH: Elevated with increased tumor burden. Half-life 4–4.5 days

Imaging

- Scrotal US: Tumors tend to be hypoechoic, with blood flow seen within the tumor
  - Microlithiasis: Prevalence of ~6% in patients undergoing testicular ultrasound, although controversial if associated with malignancy

Diagnostic Procedures/Surgery

- No role for percutaneous biopsy for intratesticular masses
- Radical inguinal orchiectomy for histologic confirmation and may be therapeutic
- Metastatic evaluation: Abdominal/pelvic CT with CXR or chest CT
- MRI of brain and bone scan indicated only for suspicious symptoms or if choriocarcinoma

Pathologic Findings

- Choriocarcinoma: Have both syncytiotrophoblasts and cytotrophoblasts
- Embryonal: Distinct cell arrangements and vascular invasion often present
- Teratoma: At least 2 germ cell layers present
- Yolk sac: Schiller–Duval bodies are present in 50% of cases (resemble a glomerulus)

DIFFERENTIAL DIAGNOSIS

See Section I “Testis Cancer, Adult General Considerations” and “Testis Cancer, Pediatric, General Considerations”

ALERT

Encourage sperm banking prior to any definitive treatment.

TREATMENT

GENERAL-MEASURES (1)

- Radical inguinal orchiectomy standard of care
  - Risk altering lymphatic drainage patterns with scrotal incision

– Additional therapy for NSGCTs depend on staging (TNM staging, risk stratification based on International Germ Cell Consensus Collaborative Group (IGCCCG) system

MEDICATION

First Line (2,3)

- Regardless of histology, patients with advanced germ cell tumors (cIIB—cIII) and those with persistently elevated tumor markers following radical orchiectomy (cIS), are initially treated with platinum-based chemotherapy according to the IGCCCG risk stratification.
  – Patients with good-risk disease are treated with 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP). While patients with intermediate-risk or high-risk disease receive 4 cycles of BEP, ~30–40% of patients with poor-risk disease fail to achieve a durable response to conventional chemotherapy.

Second Line

Chemotherapy is reserved for patients with advanced disease where serum tumor markers do not normalize following initial chemotherapy.

SURGERY/OTHER PROCEDURES

- Radical inguinal orchiectomy for treatment and pathologic diagnosis
  – Follow serum tumor markers and compare to preoperative values
  – Pathologic risk factors for relapse
    - ≥T2 disease
    - Lymphovascular invasion (50% chance of relapse)
    - >40% embryonal component
    - Absence of yolk sac component
- Testicular-sparing surgery can be selectively considered in patients with bilateral testicular tumors or a solitary testicle
- RPLND—if necessary (see below)
  – For low-stage disease a unilateral sympathetic nerve-sparing template may be used
    - Superior boundary: Renal hilum bilaterally
    - Lateral boundary: Ipsilateral ureter down to level where it crosses the ipsilateral common iliac artery. The ipsilateral gonadal vessels and spermatic cord stump are included in the specimen.
    - Right-sided template medial boundary: Lateral edge of aorta down to level of IMA, then from aorta down along the right common iliac artery to where the right ureter crosses
    - Left-sided template medial boundary: Lateral edge of the IVC down to level of the IMA, then from the aorta down along the left common iliac artery to left ureter crossing
  – Postchemotherapy: A full bilateral template is utilized with prospective nerve sparing
  – The templates should not be strictly upheld should palpable disease be found.

ADDITIONAL TREATMENT

Radiation Therapy

Unlike seminomas, NSGCTs are not treated with radiation (teratoma is radioresistant).

Additional Therapies

- See Section III “Testis Cancer: Nonseminomatous Germ Cell Tumor” for treatment algorithm
- Stage Ia/Ib disease treatment options

- Surveillance: In reliable patients with no risk factors (no teratomatous elements, no lymphovascular invasion, and no embryonal cell carcinoma in the primary). Reliable patient; cure rate >95% with close follow-up
  - 20–30% relapse rate; these patients can be salvaged with subsequent chemotherapy
- RPLND: Modified unilateral template/nerve-sparing. 70–75% will have no tumor (pN0)
  - Perform within 4 wk of CT and 7–10 days of tumor for accurate clinical staging
  - >95% cure rate if nodes negative, but may be curative for low-volume nodal disease
  - 5% relapse rate
- Chemotherapy: 95% cure rate with BEP

• Stage IS disease: Elevated tumor markers postorchiectomy without radiographic evidence of disease. Treat with chemotherapy. Preferable to RPLND given suspected disseminated disease

• Stage IIa/IIb disease
- Postorchiectomy tumor markers positive; induction chemotherapy
- Postorchiectomy tumor markers negative; either RPLND or chemotherapy
  - No viable tumor (pN0), observe patient
  - Low-volume tumor, surgery curative in 60–90%; surveillance or chemotherapy
  - High-volume disease (pN2–3—risk of relapse >50%) or tumor left behind; adjuvant BEP chemotherapy decreases relapse to <1%

• Stage IIc or III disease
- Either 3 or 4 cycles of BEP chemotherapy
- Complete response, observe
- Partial response with residual masses, full bilateral RPLND (nerve sparing if applicable)
  - Residual masses: 40% fibrosis, 40% teratoma, 20% viable malignancy
  - Teratoma/fibrosis on pathology: Observe
  - Viable tumor and tumor markers are elevated or tumor is left behind; consider salvage chemotherapy
- If no response to primary chemotherapy consider second-line chemotherapy (ifosfamide, vinblastine, cisplatin) or bone marrow transplant

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

• Has been divided into good, intermediate, and poor prognosis based on stage and risk factors.

• See Section I “International Germ Cell Cancer Collaborative Group (ICGCCCG)”
- Good: 5-yr survival 94%.
- Intermediate: 5-yr survival 83%
- Poor: 5-yr survival 71%.

COMPLICATIONS

• Surveillance: Risk of recurrence, risk for secondary malignancy due to repeat CT imaging

• RPLND

  - Ejaculatory dysfunction can impair fertility; a nerve-sparing template can preserve antegrade ejaculation in more than 90% of cases.
  - Morbidity (atelectasis, ileus, lymphocele, pancreatitis, chylous ascites); rate 5–25%, late bowel obstruction rate 1–2%, mortality rate < 1%
- Chemotherapy
  - Bleomycin: Pulmonary fibrosis. Need to limit IV fluid hydration and supplemental oxygenation
  - Cisplatin: Nephrotoxicity, ototoxicity, peripheral neuropathy
  - Secondary malignancy, especially leukemias, skin malignancies, and lymphomas
  - Metabolic syndrome
  - Infertility (50% with normal semen 2 yr after chemotherapy, 25% remain azoospermic)

FOLLOW-UP

Patient Monitoring

- Physical exam, tumor markers, and imaging (CXR, abdominal/pelvic CT)
- Frequency of follow-up may be tailored depending on therapy, stage, and disease risk

Patient Resources

NCI Testicular Cancer Information. www.cancer.gov/cancertopics/types/testicular

REFERENCES

1. Albers P, Albrecht W, Algaba F, et al. EAU guidelines on testicular cancer: 2011 update. *Eur Urol.* 2011;60:304–319.
2. Mannuel HD, Mitikiri N, Hussain A. Update on testicular germ cell tumors. *Curr Opin Oncol.* 2011;23:265–270.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: testicular cancer. www.nccn.org. Version 1.2013. (Accessed January 21, 2014)

ADDITIONAL READING

Stephenson AJ, Sheinfeld K. The role of retroperitoneal lymph node dissection in the management of testicular cancer. *Urol Oncol.* 2004;22:335–235.

See Also (Topic, Algorithm, Media)

- International Germ Cell Cancer Collaborative Group (IGCCCG)
- Reference Tables: TNM: Testis Cancer Codes
- Scrotum and Testicle, Mass
- Testis Cancer, Nonseminomatous Germ Cell Tumor Algorithm
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General Images
- Testis Cancer, Pediatric, General Considerations
- Testis, Tumor and Mass, Adult, General

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 752.51 Undescended testis

- V16.43 Family history of malignant neoplasm of testis

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- Q53.9 Undescended testicle, unspecified
- Z80.43 Family history of malignant neoplasm of testis

CLINICAL/SURGICAL PEARLS

- At radical inguinal orchiectomy, tag the residual spermatic cord stump with a long silk suture for identification at future RPLND.
- Lymphatic drainage is predictable unless there is a history of scrotal/inguinal surgery.
- Tumor marker half-lives can be followed to assess if they fall appropriately after treatment (should nadir after 5 half-lives).

TESTIS CANCER, PEDIATRIC, GENERAL CONSIDERATIONS

Mark R. Anderson, MD, MSc
Sherry S. Ross, MD

BASICS

DESCRIPTION

- In contrast to adults, testicular tumors in children are often benign including teratoma, dermoid, and epidermoid cyst.
- The majority of malignant germ cell tumors in children are yolk sac tumors
- Differentiate testicular mass from scrotal wall and paratesticular mass with scrotal US.
- The most common causes of scrotal swelling or mass in pediatrics include hernias (organ protrusion required) and hydrocele (likely communicating in younger children), with lesions such as varicocele (see incidence section), scrotal wall swelling (insect bite or nephrotic syndrome), with testicular neoplasms less common (peak incidence at 2 yr old and adolescence).
- Though very rare, most common malignant paratesticular tumor is rhabdomyosarcoma.

EPIDEMIOLOGY

Incidence

- Testicular tumors (tumor-registry data not presented due to reporting bias toward yolk sac):
  - Total 0.5–2/100,000 males; 2% of
    - Teratoma (well differentiated): ~66%
    - Yolk sac (endodermal sinus) tumor 15%
    - Stromal tumors: ~15%
    - Gonadoblastoma: 1%
    - Lymphoma testicular primary: Rare
    - Epidermoid cysts: <1%

Prevalence

N/A

RISK FACTORS

- Cryptorchidism: Postpubertal germ cell tumors
- Congenital adrenal hyperplasia (CAH): In boys often presents with precocious puberty. Adrenal rests, commonly present along the spermatic cord and in the testicular hilum, may hypertrophy in patients with CAH, leading to testicular nodules that are clinically indistinguishable from testicular tumors.
- Kleinfelters syndrome
- Family history of testicular cancer
- More common in white men than black men

Genetics

- Gonadoblastoma is associated with gonadal dysgenesis and a 45XO/46XY karyotype.
- Yolk sac tumors: Abnormalities: 1p, 6q, 3p

- Large-cell calcifying Leydig tumor is associated with Peutz–Jeghers syndrome and Carney complex.
- No clear genetic etiology exists for teratoma, Leydig cell tumor, and granulosa cell tumor.

PATHOPHYSIOLOGY

- Non–germ cell and germ cell tumors originate from the celomic epithelium and primordial germ cells, respectively
- Totipotent germ cells can evolve into seminoma or embryonal carcinoma
- Embryonal carcinoma is capable of differentiating into embryonic structures, such as mature (peds) or immature (adults) teratomas and extraembryonic structures such as yolk sac and choriocarcinoma tumors.
- Seminoma (dysgerminoma) is a primitive germ cell neoplasm that cannot further differentiate (unusual in childhood, except with gonadal dysgenesis).
- Teratoma: Monodermal (epidermoid cyst) or multiple histologic types present (nerve, cartilage, intestinal epithelium, etc.). Benign and no prepubertal metastasis
- Yolk sac tumors characterized by Schiller–Duval bodies (glomerulus in appearance, contain AFP)
- Leydig tumors which can secrete testosterone are malignant 10% of time. (Reinke crystals—40%, increased mitotic figures absent in peds), Sertoli (10% malignant) can secrete estrogen or testosterone, and granulosa cells (75% diagnosed within 1 mo of birth) have a common embryologic origin from a mesenchymal stem cell
- Gonadoblastomas are small benign tumors found in patients with gonadal dysgenesis, including those who have at least a portion of the Y chromosome. Although benign have high risk of malignant transformation.
- 15–20% of all RMS arise from the genitourinary system.
  - Most common genitourinary sites are the prostate, bladder, and paratesticular (vagina and uterus are relatively unusual sites).
  - Survival rates vary with site (vagina and paratesticular have a better prognosis than bladder/prostate primaries).
- 2 main histologic types of RMS
  - Embryonal RMS is the most common subtype of RMS and accounts for most of the genitourinary tumors.
  - Alveolar RMS occurs more commonly in the trunk and extremities than in GU; worse prognosis than embryonal tumors
- Epididymitis usually not infectious in pediatrics; likely due to refluxing fluid from urethra. Obtain urinalysis and culture. If infected need renal ultrasound to rule out ectopic ureter.
- Varicocele pathogenesis not known. Body habitus (tall, thin), genetics (risk increased if brother or 1st-degree relative has varicocele), or intrinsic venous anomalies (“nutcracker” by SMA, left renal vein insertion), and rarely central outflow obstruction from tumor.
- In neonates and young children “hernia” will be used to describe a communicating hydrocele with a “hernia sac” present though no organ protrusion present: Patent process vaginalis

ASSOCIATED CONDITIONS

- Hernia: Prematurity
- Testicular tumor: Undescended testicle (UDT), gonadal dysgenesis, precocious puberty in

non–germ cell tumors (NGCT).
- Hernia: 1–5% newborns, 3-fold increase in preterm infants, 15% bilateral, clinical synchronous hydrocele 20% ; asymptomatic patent process vaginalis present ~66% of time.
- Varicoceles: ~0% <10 yr old, increasing to 15% through puberty into adulthood
- Paratesticular tumors: Very rare, bimodal—mo & adolescence
- Epididymitis: Less common than adults

GENERAL PREVENTION
- Unclear if orchidopexy reduces risk in undescended testicles
- USPSTF: Against routine screening for testicular cancer in asymptomatic adolescent and adults including routine testicular self-exams.
- American Cancer Society suggests that men with family history do monthly self-exams.
- American Urological Association (AUA): Monthly self-exams for all young men.

DIAGNOSIS

HISTORY
- Painless testicular mass (testicular tumor)
- Acute onset of pain (torsion, epididymitis)
- Symptoms of precocious puberty (non–germ cell testicular tumors)
- Subacute achy pain (varicocele)
- Past history of UDT
- Flank pain from kidney obstruction secondary to enlarged retroperitoneal nodes

PHYSICAL EXAM
- Systematic exam identifying intrascrotal structures (testicular mass vs. intrascrotal mass)
- Testicle should be smooth and firm and within 20% size of contralateral testicle (use orchiometer or ultrasound measurements)
- Epididymis: Posterolateral adjacent to testicle
- Hydrocele transilluminates (communicating if fluid manipulated back into abdomen)
- Solid masses do not transilluminate
- Varicoceles (“bag of worms”)
  – If does not diminish when supine/under manual pressure may be due to tumor
- Lymph nodes: Lymphoma or metastasis
- Breast exam, signs of virilization (consider adrenal tumor) for NGCT tumors

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Order tumor markers immediately, but *post* orchiectomy markers determine staging
- AFP: Elevated postnatal up to 8 mo; AFP >1,000 ng/mL almost always due to yolk sac tumor (vs. teratoma) at any prepubertal age; only 15% of yolk sac tumors have AFP <100 ng/mL under age of 5.
  – AFP <100 ng/mL and >5 yo suspect teratoma
  – AFP never elevated in pure seminoma, choriocarcinoma, or teratoma
- β-HCG always elevated with choriocarcinoma (rarely pediatric), <10% of pure seminomas, and never elevated in pure teratoma
  – Rarely falsely elevated (increases with marijuana use or LH cross-reactivity)

- Embryonal and yolk sac: May secrete both AFP/HCG
- Half lives: HCG ~24 hr, AFP ~5–7 days, LDH ~4–5 days
- Testosterone/estrogen levels for NGCT
- LDH: Elevated if large tumor burden

Imaging
- Scrotal ultrasound very helpful (use color Doppler) for any scrotal or testicular concern
- No reliable sonographic features that can distinguish benign from malignant testis tumors
- Anechoic cysts trend toward benign
- Epidermoid cyst "onion skin" appearance
- Paratesticular RMS appears large, hypervascular and ipsilateral testicle may not be visualized
- Testicular microlithiasis not associated with increased risk of cancer
- Indeterminate lesions on US that resemble testicular neoplasm include tubular ectasia of the rete testis, inflammation, infarction, fibrosis, and traumatic hematoma.
- CT scan of abdomen and chest can be done before or after orchiectomy but reactive lymph nodes may appear postoperatively

Diagnostic Procedures/Surgery
Biopsy not indicated. The diagnostic procedure of choice is the radical orchiectomy.

Pathologic Findings
See Section I and II "Individual Tumor Types"

DIFFERENTIAL DIAGNOSIS
- Painful scrotum:
  - Torsion (testicle, testicular, or epididymal appendages); more common after puberty
  - Epididymitis/orchitis; bacterial, mumps
  - Fournier gangrene
  - Henoch–Schönlein purpura (usually no mass)
  - Incarcerated/strangulated hernia
  - Testis trauma: Contusion, rupture; hematocele
  - Tumor (pain infrequent unless traumatized or rapidly growing; see below)
- Painless mass:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Cystic dysplasia of the testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea
  - Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of cord
  - Hernia; lipoma of the cord
  - Polyorchidism
  - Paratesticular rhabdomyosarcoma (bimodal age 3–4 and teens)
  - Scrotal edema (insect bite, nephrotic syndrome, acute idiopathic scrotal edema)
  - Spermatocele (epididymal cyst): Uncommon
  - Testicular cysts
  - Testicular tumor: Germ cell tumors: Yolk sac carcinoma, teratoma, seminoma, embryonal

cell carcinoma, choriocarcinoma; Gonadal stromal tumors: Leydig, Sertoli cell, granulosa cell.
- Metastatic tumors: Unusual in childhood
- Mixed germ cell and stromal tumor (gonadoblastoma)
- Hamartoma, carcinoid, and neurofibroma
- Testis tumor of adrenogenital syndrome
- Leukemia or lymphoma
- Varicocele: Fullness and not a firm mass; changes with position

TREATMENT

GENERAL MEASURES

- If concern for tumor obtain tumor markers pre- and postoperatively (1–4 wk)
- Discuss sperm banking, especially if chemotherapy needed
- Do not make incision through scrotum (inguinal incision only)
- Use long tag nonabsorbable suture when ligating cord to help with lymph node dissection in future if necessary
- Open inguinal fascia so cord ligated as cephalad as possible
- International Germ Cell Cancer Collaborative Group (IGCCCG) staging:
  - Stage 1: Limited to testis, markers normalize in the half-life. Normal markers at diagnosis require normal imaging and a negative ipsilateral retroperitoneal node dissection.
  - Stage 2: Microscopic residual disease is present in the scrotum or high in spermatic cord (<5 cm from proximal end). Markers elevated after appropriate half-life interval. Tumor rupture or scrotal biopsy prior to complete orchiectomy.
  - Stage 3: Retroperitoneal lymph node involvement. Nodes >4 cm by CT are considered metastases. Nodes 2–4 cm need biopsy to document nodal metastases.
  - Stage 4: Distant metastases

MEDICATION

First Line

- Chemotherapy for all yolk sac tumor stage II or greater or other germ cell tumor
- Platinum-based as for other nonseminomas (cisplatin, etoposide, and bleomycin); see Section I: "Testis, Cancer General"
- Rhabdomyosarcoma: Adriamycin and dactinomycin chemotherapy

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Testis preservation with benign lesions most common in children as opposed to adults.
- Prepubertal testicular teratomas, Leydig and Sertoli cell tumors are benign; orchiectomy or testicular-sparing surgery is curative and no additional therapy is indicated in benign lesions.
- Yolk sac tumor or other malignant tumor; radical orchiectomy and observation if low stage
- Retroperitoneal lymph node dissection (RPLND):
  - Postchemotherapy with residual mass.

– Rarely indicated: 90% of yolk sac tumors are stage 1 at presentation.
– 60–80% of paratesticular RMS are stage I at diagnosis. Patients >10 yr have a higher risk for retroperitoneal relapse and should undergo ipsilateral RPLND before chemo.

ADDITIONAL TREATMENT

Radiation Therapy

Used in rhabdomyosarcoma

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prepubertal teratoma is uniformly benign
- 90% of yolk sac tumors are stage I at presentation;85% 6-yr survival in stage 4 patients
- Paratesticular RMS: Variable survival rates; modern surgical technique, and chemotherapy 90% overall survival in most patients.

COMPLICATIONS

- Chemotherapy toxicity
- Iatrogenic secondary cancers
- Infertility
- RPLND: Retrograde ejaculation, lymphocele

FOLLOW-UP

Patient Monitoring

Testicular and paratesticular cancer varies. Refer to NCCN guidelines@www.nccn.org

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Adult General Considerations
- Testis, Cancer Nonseminomatous Germ Cell Tumors, General
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Adult, General Considerations
- Testis, Tumor and Mass, Pediatric, General Considerations

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 608.89 Other specified disorders of male genital organs

- 171.6 Malignant neoplasm of connective and other soft tissue of pelvis

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- N50.8 Other specified disorders of male genital organs
- C49.6 Malignant neoplasm of conn and soft tissue of trunk, unsp

CLINICAL/SURGICAL PEARLS

- The presence or absence of pain or tenderness alone cannot reliably rule in or out benign vs. malignant processes in the scrotum.
- Acute onset of testicular pain in a child is most likely torsion, and emergent evaluation is indicated, early surgical intervention; do not delay surgery for imaging.
- Painless testicular mass is highly suspicious for tumor and should be confirmed with imaging.

TESTIS CANCER, SEMINOMA

Robert B. Den, MD
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BASICS

DESCRIPTION

- Seminoma is a GCT (germ cell tumor) of the testicle composed of cells that are considered the malignant counterpart of gonocytes
- These tumors are generally very sensitive to both chemotherapy and radiation therapy.
- GCTs account for 95% of testicular cancer and are broadly classified as seminoma or NSGCT.
  - Seminoma accounts for 50% of GCTs
  - Represents 20% of mixed GCTs (combinations of seminomatous and NSGCT)
- Histologic subtypes:
  - Classic seminoma (peak age 35–39)
  - Spermatocytic seminoma typically found in men >50–60
  - Anaplastic seminoma is no longer recognized as distinct entity.

EPIDEMIOLOGY

Incidence

- Peak incidence among men aged 20–40
- 4–5 times more common among white than African American men.
- Patients who have had 1 seminoma are at an increased risk of developing a contralateral seminoma.

Prevalence

N/A

RISK FACTORS

- Cryptorchidism; 3–14 times the normal incidence
- HIV infection
- Gonadal dysgenesis with Y chromosome
- Testicular feminization >30 yr of age

Genetics

- Genetic changes in the form of amplifications and deletions are observed mainly in the 12p11.2–p12.1 chromosomal regions (1).
- A gain of 12p sequences is associated with invasive growth of both seminomas and NSGCTs.
- In contrast, spermatocytic seminoma shows a gain of chromosome 9, whereas most infantile yolk sac tumors and teratomas show no chromosomal changes.
- p53 mutations are also seen with seminoma.

PATHOPHYSIOLOGY

- The slow growth characteristics of most seminomas result in them most commonly being diagnosed at an early stage (≥85% stage I) (2).

- Right-sided tumors tend to spread in the following sequence: Interaortocaval nodes, precaval zone, and para-aortic nodes.
- Left-sided tumors spread in the following order: The para-aortic, preaortic, and renal hilar nodes. Interaortocaval nodes are involved with typically higher-stage disease.
- Rarely presents as an extragonadal GCT in a site remote from the testicle.
- Hematogenous dissemination is much less common than in NSGCT.
- β-hCG elevation can sometimes be seen in seminoma.
- The presence of elevated AFP during evaluation usually suggests nonseminomatous elements
- Due to slower growth pattern, relapses tend to be later than with NSGCT, and many can occur 2–3 yr after therapy.

ASSOCIATED CONDITIONS
Increased risk in patients with cryptorchidism; risk is >35 times the general population

GENERAL PREVENTION
Unclear if orchidopexy reduces risk in undescended testicles

DIAGNOSIS
HISTORY
- Painless mass or swelling in the testes
- History of undescended testicle or inguinal surgical procedure as a child

PHYSICAL EXAM
- Palpate the testes bilaterally.
- Transilluminate the mass.
- Examine the groin for evidence of surgical scar (prior orchiopexy).
- Inspect for lymphedema of the groin or lower extremities.
- Lymphatic spread is not typically inguinal; however, prior scrotal surgery may change lymphatic drainage.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC and chemistry
- β-hCG and AFP to rule out NSGCT:
  – Seminoma never have elevated AFP.
  – 10–20% may have elevated β-hCG.
- Placental alkaline phosphatase: Pulmonary and renal function tests for patients who may receive chemotherapy

Imaging (3)
- Scrotal US: Often diagnostic, characterizes solid vs. cystic lesions, flow
- Chest x-ray: To rule out metastatic lesions
- CT of chest, abdomen, and pelvis to evaluate for lymphatic spread:
  – Studies suggest that in seminoma patients treated for retroperitoneal adenopathy, up to 50% will resolve on subsequent imaging.
  – Bipedal lymphangiography was once the standard of care to identify retroperitoneal nodes to direct radiation planning. It is no longer routinely used.

- PET: Limited role in patients with postchemotherapy residual masses to determine the presence of viable tumor.

Diagnostic Procedures/Surgery

Biopsy not indicated. The diagnostic procedure of choice is the radical orchiectomy.

Pathologic Findings

- Classic seminoma (most common):
  - Large cells or uniform size with clear cytoplasm and distinct cell borders
  - Stains positive for PLAP
- Spermatocytic seminoma (up to 4%):
  - Cells of varying size that resemble maturing spermatogonia (peak age >50)
  - Does not stain for PLAP
- Anaplastic seminoma is no longer considered a distinct subtype of seminoma:
  - Same histology as classic seminoma, with high mitotic activity and unchanged prognosis using current treatment standards
  - Histologically, must differentiate from lymphoma and embryonal carcinoma

DIFFERENTIAL DIAGNOSIS

- Adult/pediatric painful mass:
  - Epididymitis/orchitis; bacterial, STD, mumps, TB
  - Incarcerated/strangulated hernia
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle, testicular, or epididymal appendage)
  - Tumor (pain infrequent unless traumatized or rapidly growing; see below)
- Adult painless mass:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Adenocarcinoma of the rete testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea
  - Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of the cord
  - Lipoma of the cord
  - Mesothelioma of tunica vaginalis
  - Polyorchidism
  - Paratesticular sarcomas: Rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma
  - Scrotal edema (insect bite, nephrotic syndrome, acute idiopathic scrotal edema)
  - Scrotal wall: Sebaceous and inclusion cysts, idiopathic calcinosis, fat necrosis, malignancy
  - Sperm granuloma following vasectomy
  - Spermatocele (epididymal cyst)
  - Testicular cysts (simple, tunica albuginea, epidermoid)
  - Testicular tumor:
    - GCTs (95% of testicular malignancies): Seminoma, embryonal cell carcinoma, choriocarcinoma, yolk sac carcinoma teratoma (1–5%), teratocarcinoma
    - Gonadal stromal tumors: Leydig tumor, Sertoli cell, granulosa cell tumors
    - Metastatic tumors: Prostate, lung, and GI tract; rare kidney, malignant melanoma,

pancreas, bladder, and thyroid.
    - Mixed germ cell and stromal tumor (gonadoblastoma)
    - Angioma, fibroma, leiomyoma, hamartoma, carcinoid, mesothelioma, and neurofibroma
    - Malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)
    - Leukemia or lymphoma
  - Varicocele
- Pediatric painless mass:
  - Similar to adult list; most/more common are: Hydrocele, hernia, varicocele, testicular teratoma, adrenal rest tumors, rhabdomyosarcoma, endodermal sinus tumor

TREATMENT

GENERAL-MEASURES (4)

- Discuss sperm banking
- Stage IA,B: Radical orchiectomy and adjuvant RT in low stage most common treatment:
  - Close surveillance with CT scanning in lieu of RT for low-stage seminoma is gaining acceptance.
  - Single-agent chemotherapy (carboplatin)
- Stage IS: RT as adjuvant therapy
- Stage II: Radical orchiectomy and adjuvant therapy:
  - Nonbulky retroperitoneal nodes: RT 35 Gy or chemotherapy
  - Bulky lymphadenopathy (>5–7 cm nodes) or higher visceral metastasis (retroperitoneal adenopathy) and is treated with standard platinum-based chemotherapy (BEP = bleomycin/etoposide/cisplatinum or EP = etopiside/cisplatinum).

MEDICATION

First Line

- Regardless of histology, patients with advanced germ cell tumors (cIIB–cIII) and those with persistently elevated tumor markers following radical orchiectomy (cIS), are initially treated with platinum-based chemotherapy according to the IGCCCG risk stratification.
  - Patients with good-risk disease are treated with 3 cycles of bleomycin, etoposide, and cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP). While patients with intermediate-risk or high-risk disease receive 4 cycles of BEP, ~30–40% of patients with poor-risk disease fail to achieve a durable response to conventional chemotherapy.

Second Line

High-dose chemotherapy or clinical trial

SURGERY/OTHER PROCEDURES

- Radical inguinal orchiectomy
- RPLND is not usually for seminoma.

ADDITIONAL TREATMENT

Radiation Therapy

- Stage I:
  - Standard RT is para-aortic field to 20–25 Gy following surgery
  - If prior ipsilateral pelvic surgery, treat para-aortic and ipsilateral iliac lymph nodes.

- Shield contralateral testis
- Stage II:
  - Subdiaphragmatic radiation to 35 Gy to the para-aortic and ipsilateral iliac lymph nodes following radical orchiectomy (hockey stick template).
- Prophylactic mediastinal RT has generally been abandoned due to side-effect profile (cardiovascular) and failure to significantly improve outcomes. It also interferes with ability to administer salvage chemotherapy.

Additional Therapies

- Active surveillance for low-risk, early disease:
  - Avoids unnecessary treatment and related side effects
  - CT every 4–6 mo; reduce interval after ~5 yr
  - Traditional risk factors that increase the recurrence risk: Tumor >4 cm, invasion of the rete testis, anaplastic features, small vessel invasion
- The role of salvage chemotherapy, surgical removal, or RT of persistent masses detected by CT continues to be controversial.

Complementary & Alternative Therapies

Patients should consider sperm banking prior to treatment to aid in avoiding risk of infertility.

ONGOING CARE

PROGNOSIS

- Elevation of LDH, hCG, or both and number of metastatic sites are the most important prognostic factors in patients with GCTs
- ~75% have localized disease (stage I) at diagnosis. ~15% have metastatic disease to the regional lymph nodes, and 5–10% have involvement of regional nodes or visceral metastases.
- All stages have at least a 90% cure rate:
  - Stage I: 98–100%
  - Stage II (B1/B2 nonbulky): 98–100%
  - Stage II (B3 bulky) and stage III: >90% complete response to chemotherapy and 86% durable response rate to chemotherapy
- Response rates to chemotherapy seem to be slightly better without prior radiation.

COMPLICATIONS

- Infertility, GI complications, and possible induction of secondary malignancies are a concern following adjuvant RT.
- Involvement of retroperitoneal lymph nodes may produce backache.

FOLLOW-UP

Patient Monitoring

- Surveillance:
  - H&P, AFP, β-hCG, LDH:
    - Every 3–4 mo for years 1–2
    - Every 6–12 mo for years 3–4, then annually

  - Abdominal/pelvic CT every 6 mo for yr 1–2, every 6–12 mo for yr 3, then annually for yr 4–5
  - CXR as clinically indicated for yr 1–5
- Carboplatin:
  - H&P, AFP, β-hCG, LDH:
    - Every 3 mo for yr 1
    - Every 4 mo for yr 2
    - Every 6 mo for yr 3, then annually
  - Abdominal/pelvic CT annually for yr 1–3
  - CXR as clinically indicated
- RT:
  - H&P, AFP, β-hCG, LDH:
    - Every 4 mo for yr 1–2, then annually
    - Abdominal/pelvic CT annually for yr 1–3 (for patients post only para-aortic RT)
  - CXR as clinically indicated

REFERENCES

1. Bosl GJ, Ilson DH, Rodriguez E, et al. Clinical relevance of the i(12p) marker chromosome in germ cell tumors. *J Natl Cancer Inst.* 1994;86(5):349–355.
2. Mannuel HD, Mitikiri N, Khan M, et al. Testicular germ cell tumors: Biology and clinical update. *Curr Opin Oncol.* 2012;24(3):266–271.
3. Chung PW, Bedard P. Stage II seminomas and nonseminomas. *Hematol Oncol Clin North Am.* 2011;25(3):529–541.
4. Mok G, Warde P. Management of stage I testicular seminoma. *Hematol Oncol Clin North Am.* 2011;25(3):503–516.

ADDITIONAL READING

- Huddart R, Kataja V; ESMO Guidelines Working Group. Testicular seminoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2008;19(suppl 2):ii49–ii51.
- International Germ Cell Consensus Classification. A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15:594–603.

See Also (Topic, Algorithm, Media)

- International Germ Cell Cancer Collaborative Group (IGCCCG)
- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Pediatric, General Considerations
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis Cancer, Seminoma Image
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Adult, General Considerations
- Testis, Tumor and Mass, Pediatric, General Considerations

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 608.89 Other specified disorders of male genital organs

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- C62.92 Malig neoplasm of left testis, unsp descended or undescended
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

Anaplastic seminoma is no longer recognized as distinct entity.

TESTIS, LEYDIG CELL TUMOR

Austin R. Younger, MD
James S. Rosoff, MD

BASICS

DESCRIPTION

- Leydig cell tumors (LCTs) are hormonally active steroid secreting tumors that may produce feminizing/virilizing syndromes
- Most common sex cord/stromal tumors
  - (Neoplasms containing Leydig, Sertoli, granulosa, or thecal cells) commonly referred to as nongerm cell tumors
- Usually benign, 10% malignant variants reported in adults only (1)
- TNM staging follows current NCCN Guidelines for Testis Cancer

EPIDEMIOLOGY (1)

Incidence

- An estimated 8,820 new cases of testicular cancer were diagnosed in 2014
- LCTs represent 1–3% of all testicular neoplasms (90% of nongerm cell tumors)
- Bimodal distribution with peak incidences occurring between ages 4–5 and 30–60
- Equal incidence between right and left testis with 4–10% occurring bilaterally

Prevalence

Roughly 25% of cases of LCT occur in the pediatric population

RISK FACTORS

- No association with cryptorchidism
- Increased prevalence in Caucasians

Genetics

- No documented familial inheritance pattern or associated syndromes
- Association with specific activating mutation of luteinizing hormone receptor (LHR) gene (2)
  - LHR is a stimulatory G-protein–coupled receptor present on surface of Leydig cell
- Hypothesized that oncogenesis is increased by (1) hyperstimulation of LHR and (2) Long-term estrogen exposure from aromatase conversion (seen in animal studies only)

PATHOPHYSIOLOGY

- Leydig cells are located in the interstitium of testicle between seminiferous tubules; produce testosterone in response to stimulation by luteinizing hormone
  - Hypothalamic–pituitary axis is directly involved in Leydig cell stimulation and testosterone production
    - Vital role in development of male secondary sex characteristics and spermatogenesis
    - In neoplasia, feedback regulation is disrupted resulting in uncontrolled hormone production.
- LCTs usually secrete testosterone, may also secrete other androgens, corticosteroid, estrogen,

and progesterone.
- Feminization may result directly from estradiol producing tumors or from peripheral conversion of testosterone to estrogens by aromatase
- Virilization occurs due to unopposed testosterone/androgen production independent of LH stimulation.

ALERT
- Virilizing signs are often not observed in adults.
- More frequently present with feminizing signs due to peripheral conversion of testosterone to estrogens.

ASSOCIATED CONDITIONS
- Adrenogenital syndromes—adrenal rest tumors are often misdiagnosed as LCTs.
  - 80% of these are bilateral whereas only 4–10% of LCT are bilateral (1)
  - Hyperplastic nodules will resolve with appropriate steroid replacement
- LCTs are not associated with cryptorchidism

GENERAL PREVENTION
- Routine self-exam in adult population
- Regular pediatric office visit during childhood development to identify any deviation in normal growth and maturation

DIAGNOSIS
- Low estradiol, increased testosterone, gynecomastia, and hypoechoic lesion on ultrasound are highly suspicious for LCT
- Histopathology confirms diagnosis

HISTORY
- Children commonly present with:
  - Precocious puberty due to androgen secreting tumors; irreversible and profound physical changes—early diagnosis is critical
  - Feminization from estrogen-secreting tumors
- Adults commonly present with:
  - Nontender testicular mass/nodule
  - Incidental finding on imaging for other conditions
  - Feminization symptoms—low energy, anhedonia, gynecomastia, infertility

PHYSICAL EXAM
- A unilateral mass is palpable in 90% of cases with careful exam
- Hormonal imbalance responsible for physical changes
  - Virilizing changes
    - Children: Precocious puberty, early growth, early change in penile length, deepened voice, increased muscle mass
    - Adults: Usually asymptomatic
  - Feminizing change
    - Children: Delayed maturation, testicular atrophy, gynecomastia
    - Adults: Female hair distribution, gynecomastia, testicular atrophy

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Increased testosterone (with normal LH and FSH) is most common positive lab finding. With feminization syndrome, serum estradiol may be elevated
  - All other tests should be within normal limits if leaning toward diagnosis of pure LCT
- Testicular mass work-up (AFP, β-hCG, LDH, testosterone, basic chemistry panel)
- Precocious puberty work-up (LH, FSH, testosterone, serum cortisol, urinary ketosteroids, 17-OH progesterone, ACTH stimulation test, dexamethasone suppression)
  - Rule out:
    - Pituitary lesions—increased LH and FSH
    - Leydig cell hyperplasia—normal urinary ketosteroids, histopathology
    - Congenital adrenal hyperplasia (CAH): Elevated 17-OH progesterone, elevated urinary ketosteroids

Imaging

- CXR
- Testicular ultrasound—preferred imaging if mass is palpable (3)
  - Solid hypoechoic mass
- MRI: May detect smaller nonpalpable lesions (4)
- CT chest/abdomen/pelvis: If concern for malignancy, lungs and retroperitoneal nodes are common metastatic sites

Diagnostic Procedures/Surgery

- Historically, radical inguinal orchiectomy was gold standard treatment
- Testis-sparing surgery (TSS): Enucleation of tumor and frozen-section analysis is acceptable option in some cases; no evidence of local recurrence or metastases on long-term follow-up (3,5)

Pathologic Findings

- Gross pathology
  - Benign LCT: 3–5 cm, sharply delineated, solid mass, embedded within testicle, displaces normal stromal/tubular architecture (1)
    - Brown to yellow-white depending on total lipid content
  - Malignant LCT: Larger, >5 cm, infiltrative margins, hemorrhage/necrosis present, replace or spread beyond testicular parenchyma
- Microscopic pathology (1)
  - Tumor cells in nests/sheets, large polygonal cells with eosinophilic/granular cytoplasm, round regular nuclei, rare mitotic figures, prominent nucleoli
  - Reinke crystals: Pathognomonic for LCT, rhomboid/cylindrical crystals, pale staining within cytoplasm and nucleus.
    - Confirms diagnosis but are only present in 40% of tumors
- Findings that correlate with malignancy
  - Cytologic/nuclear atypia, increased mitotic activity 3–5 per 10 hpf, DNA aneuploidy
  - Coagulative tumor necrosis, lymphovascular invasion
  - Extension of the tumor to the spermatic cord, invasion of the capsule
  - Abscence of Reinke's crystals

- Immunohistochemistry (IHC)—beneficial if challenging diagnosis. May stain for inhibin A, calretinin, melan-A (1)

DIFFERENTIAL DIAGNOSIS

- Testicular masses (see Section I: "Testis Cancer, Adult General Considerations" and "Testis Cancer, Pediatric, General Considerations")
- Precocious puberty
  - Adrenocortical syndromes: CAH
  - Large-cell Sertoli cell tumors
  - Leydig cell hyperplasia
  - Pituitary lesions
- Gynecomastia/feminization
  - Pituitary lesions
  - Paraneoplastic syndromes
  - Marijuana use

TREATMENT

GENERAL MEASURES

- Management is primarily surgical
- Radical orchiectomy is the gold standard
- TSS is being performed more frequently with good results (5)
  - Especially applies to cases of bilateral testicular tumors, subfertility, monorchidism, and in children where preservation of testicular function is of high importance
  - There is no evidence for increased risk of local recurrence on long-term follow-up (3)
  - TSS is a safe procedure in patients with LCT < 25 mm (5)
- Malignant disease
  - 3–10% of cases
  - RPLND is indicated if concerned for malignancy based on histopathologic findings or presentation
  - Malignant LCT responds poorly to radiation and chemotherapy
  - Elevated serum estrogen after resection may indicate micrometastatic disease and requires monitoring
  - Median survival: 2–4 yr

MEDICATION

First Line

Chemotherapy regimens using standard bleomycin-etoposide-platinum regimens for germ cell tumors have limited efficacy for malignant Leydig cell tumors

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Radical inguinal orchiectomy:
  - Definitive method of diagnosis and treatment for stages I, II neoplasm
- Enucleation of mass with TSS:

  - Inguinal exploration as for radical orchiectomy with use of intraoperative US and frozen-section confirmation of benign Leydig cell tumor
  - May have a role in children and younger adults to preserve fertility.
- RPLND if suspicion of malignancy by CT criteria

ADDITIONAL TREATMENT

Radiation Therapy

Responds poorly to radiation

Additional Therapies

N/A

Complementary & Alternative Therapies

Patients should consider sperm banking prior to treatment to aid in avoiding risk of infertility.

ONGOING CARE

PROGNOSIS

Benign/local disease in the majority of patients portends a good prognosis

COMPLICATIONS

- Residual gynecomastia
- Physical changes of precocious puberty are permanent

FOLLOW-UP

Patient Monitoring

- Focused physical exam: Remaining testis, regional lymph nodes, abdomen
- Tumor markers, serum testosterone, estradiol
- CBC, electrolytes, and endocrine markers
- CT imaging of the chest and abdomen may be indicated
- RPLND patients should be evaluated every 3 mo for 2 yr, then every 6 mo for 3 yr, then yearly.

Patient Resources

Testicular Cancer Society. www.testicularcancersociety.org

REFERENCES

1. Al-Agha OM, Axiotis CA. An in-depth look at Leydig cell tumor of the testis. *Arch Pathol Lab Med*. 2007;131(2):311–317.
2. Fowler KA, Gill K, Kirma N, et al. Overexpression of aromatase leads to development of testicular Leydig cell tumors: An in vivo model for hormone-mediated testicular cancer. *Am J Pathol*. 2000;156(1):347–353.
3. Bozzini G, Picozzi S, Gadda F, et al. Long-term follow-up using testicle-sparing surgery for Leydig cell tumor. *Clin Genitourin Cancer*. 2013;11:321–324.
4. Leonhartsberger N, Ramoner R, Aigner F, et al. Increased incidence of Leydig cell tumours of the testis in the era of improved imaging techniques. *BJU Int*. 2011;108(10):1603–1607.
5. Loeser A, Vergho DC, Katzenberger T, et al. Testis-sparing surgery versus radical orchiectomy in patients with Leydig cell tumors. *Urology*. 2009;74:370–372.

ADDITIONAL READING

Olivier P, Simoneau-Roy J, Francoeur D, et al. Leydig cell tumors in children: contrasting clinical, hormonal, anatomical, and molecular characteristics in boys and girls. *J Pediatr*. 2012;161:1147–1152.

See Also (Topic, Algorithm, Media)

- Precocious Puberty
- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Adult General Considerations Images
- Testis Cancer, Pediatric, General Considerations
- Testis Cancer, Seminoma
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis, Leydig Cell Tumor Images
- Testis, Sertoli Cell Tumor
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Pediatric, General Considerations

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 222.0 Benign neoplasm of testis
- 259.51 Androgen insensitivity syndrome

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- D29.20 Benign neoplasm of unspecified testis
- E34.50 Androgen insensitivity syndrome, unspecified

CLINICAL/SURGICAL PEARLS

- Leydig cell tumors (LCT's) are hormonally active steroid-secreting tumors that may produce feminizing/virilizing syndromes.
- LCTs are usually benign, 10% malignant variants reported in adults only.
- Low estradiol, increased testosterone, gynecomastia, and hypoechoic lesion on ultrasound are highly suspicious for LCT.
- Scrotal exploration with frozen section is reliable in diagnosing LCT.
- Testicular sparing surgery (TSS) is a reasonable option in certain cases and has no reported increased risk of local recurrence or metastasis compared with radical orchiectomy.

TESTIS, PAIN (ORCHALGIA)

Alosh Madala, MD
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BASICS

DESCRIPTION

- Orchalgia is scrotal or testicular pain
  - Acute or chronic
  - Intermittent or constant
  - Unilateral, bilateral, or alternating
- Characteristics:
  - Localized to scrotum
  - May radiate to groin, perineum, back, or legs
  - Chronic orchalgia
    - Lasting >3 mo
    - Constant or intermittent pain.
    - No specific cause is identified in most cases.
  - Synonym(s) for chronic testicular pain: Orchalgia; idiopathic testicular pain; orchiodynia; chronic scrotal pain syndrome

EPIDEMIOLOGY

Incidence

- Majority in mid to late 30s
- Increased in men with psychological issues

Prevalence

- Chronic testicular pain
  - Idiopathic 25–50%
  - Postvasectomy chronic orchalgia
    - ~15%

RISK FACTORS

- Organic risk factors
  - Previous trauma or surgery
    - Post-vasectomy pain syndrome in 5–43% of men who have undergone this procedure (1)
    - Posthernia repair
  - Scrotal masses
    - Testicular tumors
    - Varicocele
    - Hydrocele
    - Epididymal cysts or spermatoceles
  - Infections
    - Chronic epididymitis
  - Neuropathic conditions

    - Diabetic neuropathy
    - Withdrawal from imipramine
- Psychological risk factors
  – Life stressors
  – Depression
  – Secondary gain with malingering

Genetics

No studies exist at this time

PATHOPHYSIOLOGY

- Poorly understood
- Idiopathic in most cases
- Testis innervation
  – Sympathetic nerve supply from T10–T12 segments
  – Accompany the internal spermatic vessels
  – Penetrate the tunica albuginea
  – Distributed between the seminiferous tubules
  – Stimulates smooth muscles of the tunica albuginea
  – Testis shares innervations with the epididymis
- Epididymis and vas deferens innervation
  – Sympathetic fibers from T10–L1.
  – Supply smooth muscles of vas deferens and epididymis.

ASSOCIATED CONDITIONS

- Often idiopathic (~25%)
- Can be associated with:
  – Previous surgery (vasectomy, hernia repair)
  – Trauma
  – Intermittent torsion
  – Hydrocele, varicocele, spermatocele
  – Tumor
  – Infection
  – Herniated intervertebral disc
  – Vasculitis (polyarteritis nodosa)

GENERAL PREVENTION

- USPSTF: Against routine screening for testicular cancer in asymptomatic adolescent and adults including routine testicular self-exams.
- American Cancer Society suggests that men with family history do monthly self-exams.
- American Urological Association (AUA): Monthly self-exams for all young men.

ALERT

Acute onset of testicular pain in a child is most likely torsion, and emergent evaluation is indicated, early surgical intervention; do not delay surgery for imaging.

DIAGNOSIS

HISTORY

- Onset, location, duration, quality, aggravating (exercise, sexual intercourse, or ejaculation) and relieving factors.
- Visual analogue scale (VAS) of 0–10 helps quantify degree of pain
- Consult with multiple physicians including urologists
- Multiple treatments (antibiotics, anti-inflammatory drugs)
  - Little or no relief
- Previous surgery
  - Scrotal/inguinal
  - Vasectomy
  - Retroperitoneal/pelvic
- Social/psychological history
  - Current life stressors
  - Social support
  - Sexual function
  - Mood and anxiety
  - Sexual abuse, relationship stress
- Back injuries or spinal trauma

PHYSICAL EXAM

- Often does not reveal abnormality
- Evaluate genitalia for reversible causes
  - Testicular torsion
  - Scrotal mass
  - Hernia
  - Infection
  - Varicocele
  - Spermatocele
- Sperm granuloma following vasectomy
- Digital rectal exam
  - Evaluate prostate and rectum.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis and culture
  - Before and after prostatic massage
- Semen analysis (for chronic epididymitis)
- Consider STD/STI screening

Imaging

- Scrotal US exam with color flow doppler
  - Evaluate scrotal contents
  - Rule out testicular torsion and tumor

Diagnostic Procedures/Surgery

Cystoscopy and urodynamics are of limited value

Pathologic Findings
Based on etiology

DIFFERENTIAL DIAGNOSIS (2)
- Chronic pelvic pain syndrome (CPPS)
- Cremasteric spasm
- Hydrocele, spermatocele
- Idiopathic orchalgia
- Infection
  - Epididymitis and epididymo-orchitis
  - Urethritis
  - Prostatitis
  - Viral orchitis
  - Testicular abscess
- Inguinal hernia (incarcerated, other)
- Nerve entrapment (ilioinguinal or genitofemoral)
- Medical causes: Diabetic neuropathy, polyarteritis nodosa
- Paratesticular tumor
- Postoperative (vasectomy, inguinal herniorrhaphy)
- Psychogenic
- Referred pain (nerve root irritation)
  - Disk herniation, back injury, other
- Testicular torsion
- Testicular/scrotal trauma
- Testicular tumor
- Testicular vasocongestion from sexual arousal without ejaculation
- Torsion of testicular/epididymal appendices
- Varicocele

TREATMENT

GENERAL MEASURES
- For acute testicular pain: See Section I “Acute Scrotum”
- For chronic testicular pain
  - Scrotal support
  - Restrict physical activity
  - Sitz baths

MEDICATION
First Line
- NSAIDs
  - Variable and usually temporary relief
  - Regimens described include ibuprofen 400–600 mg PO q6h for 1 mo
- Antibiotics
  - Usually empiric unless specific agent such as STD/STI (chlamydia, etc.) identified
  - Often prescribed, rarely beneficial

- Common regimens
  - Doxycycline 100 mg PO BID or ciprofloxin 250–500 mg PO BID for 2–3 wk

Second-Line (5,6)

- Antidepressants and anticonvulsants
  - Demonstrated benefit in chronic idiopathic orchalgia
  - Poor response to postvasectomy pain
- Tricyclic antidepressants
  - Amitriptyline 10–25 mg qhs
  - Nortriptyline 10–150 mg daily
- Anticonvulsants
  - Gabapentin 300 mg titrated up to 3,600 mg/d daily
- α-Adrenergic antagonists
  - Tamsulosin; no proven benefit

SURGERY/OTHER PROCEDURES

- Acute testicular pain in a child: See Section I "Torsion, Testis or Testicular/Epididymal Appendages".
- The following are used for the management of chronic pain in an adult.
- Minimally invasive treatment options (7,8)
  - Enucleation of cystic lesions
  - Local anesthetic infiltration
    - Spermatic cord
    - Pelvic plexus under TRUS guidance
- Denervation of spermatic cord (3,9)
  - Division of ilioinguinal nerve and its branches
  - Microscopic or laparoscopic or robotic
  - Best outcome is initial response to spermatic cord block with local anesthetic
- Orchiectomy
  - Last resort: Many will continue to have pain
  - Inguinal approach superior to scrotal
  - >75% patients have relief after surgical removal of varicocele, hydrocele, spermatocele, or intermittent torsion.
- Epididymectomy
  - Poor results except in the setting of postvasectomy pain syndrome
- Vasovasostomy in the setting of postvasectomy pain

ADDITIONAL TREATMENT

- Physical therapy
  - May be helpful in patients with spinal disk and back problems with nerve root irritation

Radiation Therapy

N/A

Additional Therapies (10,11)

- Pulsed radiofrequency denervation of the spermatic cord (4)
  - Not well studied

- Sacral nerve stimulation
  - 80% decrease in pain

Complementary & Alternative Therapies

- Mental health consult
  - Psychological evaluation
  - Psychotherapy
  - Should be strongly considered before surgical intervention
- Pelvic muscle exercises

ONGOING CARE

PROGNOSIS

Depends on etiology

COMPLICATIONS

- Surgery
  - Epididymectomy may result in loss of testicle or infertility

FOLLOW-UP

Patient Monitoring

Periodic follow-up with urology or other providers depending on etiology (if known)

Patient Resources

Urology Care Foundation: Epididymitis and Orchitis.
http://www.urologyhealth.org/urology/index.cfm?article=114&display=1

REFERENCES

1. McConaghy P, Reid M, Loughlin V, et al. Pain after vasectomy. *Anaesthesia.* 1998;53(1):83–86.
2. Granitsiotis P, Kirk D. Chronic testicular pain: An overview. *Eur Urol.* 2004;45(4):430–436.
3. Levine LA, Matkov TG, Lubenow TR. Microsurgical denervation of the spermatic cord: A surgical alternative in the treatment of chronic orchialgia. *J Urol.* 1996;155(3):1005–1007.
4. Cohen SP, Foster A. Pulsed radiofrequency as a treatment for groin pain and orchialgia. *Urology.* 2003;61(3):645.
5. Sinclair AM, Miller B, Lee LK. Chronic orchialgia: Consider gabapentin or nortriptyline before considering surgery. *Int J Urol.* 2007;14(7):622–625.
6. Sasaki K, Smith CP, Chuang YC, et al. Oral gabapentin (neurontin) treatment of refractory genitourinary tract pain. *Tech Urol.* 2001;7(1):47–49.
7. Levine L. Chronic orchialgia: Evaluation and discussion of treatment options. *Ther Adv Urol.* 2010;2(5-06):209–214.
8. Kumar P, Mehta V, Nargund VH, et al. Clinical management of chronic testicular pain. *Urol Int.* 2010;84(2):125–131.
9. Strom KH, Levine LA. Microsurgical denervation of the spermatic cord for chronic orchialgia: Long-term results from a single center. *J Urol.* 2008;180(3):949–953.
10. Basal S, Ergin A, Yildirim I, et al. A novel treatment of chronic orchialgia. *J Androl.* 2012;33(1):22–26.

11. McJunkin TL, Wuollet AL, Lynch PJ. Sacral nerve stimulation as a treatment modality for intractable neuropathic testicular pain. *Pain Physician*. 2009;12(6):991–995.

ADDITIONAL READING

Strebel RT, Schmidt C, Beatrice J, et al. Chronic scrotal pain syndrome (CSPS): The widespread use of antibiotics is not justified. *Andrology*. 2013;1(1):155–159.

See Also (Topic, Algorithm, Media)

- Acute Scrotum
- Chronic Pelvic Pain Syndrome (CPPS)
- Epididymitis
- Paratesticular Tumors
- Prostatitis, Chronic Nonbacterial, Inflammatory & Noninflammatory (NIH CP/CPPS III A and B)
- Scrotal Pain Syndrome (Chronic Scrotal Pain Syndrome [CSPS])
- Scrotum and Testicle, Mass
- Sperm Granuloma
- Spermatocele
- Testis, Pain (Orchalgia) Image ☼
- Testis, Tumor and Mass, Adult, General Considerations
- Torsion, Testis or Testicular/Epididymal Appendages
- Varicocele, Adult
- Vasectomy and Postvasectomy Pain Syndrome

CODES

ICD9

- 307.89 Other pain disorders related to psychological factors
- 608.89 Other specified disorders of male genital organs
- 959.14 Other injury of external genitals

ICD10

- F45.41 Pain disorder exclusively related to psychological factors
- N50.8 Other specified disorders of male genital organs
- S39.94XA Unspecified injury of external genitals, initial encounter

CLINICAL/SURGICAL PEARLS

- The presence or absence of pain or tenderness alone cannot reliably rule in or out benign vs. malignant processes in the scrotum or testis.
- Physical exam is often normal with testicular pain.
- Ultrasound is the most valuable study.
- Surgical options should only be considered after medical and conservative management fails for chronic testicular pain.

TESTIS, SERTOLI CELL TUMOR

Tariq A. Khemees, MD
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BASICS

DESCRIPTION

- Sertoli cell tumor is a rare sex cord stromal tumor; 90% are benign
  - No reliable criteria for malignancy
  - Presence of metastasis indicate malignancy
- 3 different subtypes has been described with distinctive clinical, histologic, and prognostic characteristics:
  - Classic "tumors that are not otherwise specified"
  - Large-cell calcifying Sertoli cell tumor (LCCSCT)
  - Sclerosing

EPIDEMIOLOGY

Incidence

- Comprise <1% of testicular neoplasms
- Majority are sporadic
- Classic and sclerosing subtypes are mainly reported in young adult with rare occurrence in prepubertal boys
- LCCST has bimodal age incidence:
  - Early onset: Prepubertal
  - Late onset: Adulthood

Prevalence

< 1/1,000,000

RISK FACTORS

Usually arise in normal intrascrotal testes; however, may occur in cryptorchid or maldescended testes

Genetics

- 40% of LCCSCT are hereditary and are associated with multiple neoplasia syndromes (MNSs) namely:
  - Carney complex (CNC): Autosomal dominant; often caused by PRKAR1A gene mutations and characterized by
    - Spotty skin pigmentation
    - Myxomas (cardiac, cutaneuos, and mucosal)
    - Primary pigmented nodular adrenocortical disease
    - Thyroid tumors
    - Acromegaly due to growth hormone-producing adenoma
    - LCCSCTs
  - Peutz–Jeghers syndrome (PJS): Autosomal dominant; mainly caused by STK11 gene

mutations and characterized by
  - Multiple hamartomatous polyps along the whole gastrointestinal tract
  - Mucocutaneous hyperpigmented macules
- Tuberous sclerosis (TS) (possible): Autosomal dominant caused by TSCI and TSC2 mutations and characterized by
  - Mental retardation
  - Cutaneuos lesions
  - Nonmalignant brain tumors
  - Malformation of internal organs

PATHOPHYSIOLOGY

- Sertoli cells are supporting cells of the testis
  - During fet al development: Secrete anti-Mullerian hormone, which lead to regression of Mullerian ducts.
  - During adulthood: Promote differentiating of spermatocyte.
- Normally, Sertoli cells do not have aromatase activity (the enzyme that converts testosterone to estradiol); however, neoplastic Sertoli cells may express aromatase.
- Excess estrogens in prepubertal boy will lead to accelerated skelet al maturation and gynecomastia

ASSOCIATED CONDITIONS

- Gynecomastia
- Carney complex (CNC)
- Peutz–Jeghers syndrome (PJS)
- Tuberous sclerosis (TS)

GENERAL PREVENTION

In familial cases and in those who present with bilateral testicular Sertoli cell tumor, periodic screening for other tumors and associated conditions with MNS is highly recommended

DIAGNOSIS

HISTORY

- Painless or painful testicular mass/enlargement
- Breast pain and/or gynecomastia
- Growth spurt
- Family history of MNS
- Fertility

PHYSICAL EXAM

- General physical exam: Look for
  - Feminization, hair pattern, and other signs of estrogen access
  - Stigmata of MNS
- Testicular exam: Look for
  - Mass
    - Bilateral in 20% of LCCSCT with occasional coarse irregularities due to macrocalcifications

- Breast exam: Look for
  - Tenderness
  - Gynecomastia

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Sex steroid: Check for age-appropriate levels of
  - FSH
  - LH
  - Androgens
  - Estrogen
  - Progesterone
- Tumor markers:
  - AFP is usually negative
  - β-hCG is usually negative.
  - Placental alkaline phosphatase is usually negative.

Imaging

- Testicular US
  - Usually appear as solid, well-circumscribed, and hypervascularized mass
  - Bilateral increase in testicular volume
  - Occasionally cysts are seen
  - Calcifications: Microcalcifications within the tumor mass
    - Christmas tree–like appearance of multiple calcifications in syndromic LCCSCT is almost always pathognomonic for this tumor
- Metastatic workup: Includes
  - Chest x-ray
  - CT pelvis and abdomen
  - Bone scan

Diagnostic Procedures/Surgery

- Excisional biopsy usually by radical orchiectomy, can be curative
- Fine needle biopsy or nonexcisional biopsy of mass should never be done due to the risk of spread of the more common malignant tumors such as embryonal cell carcinoma or seminoma
- Partial orchiectomy, inguinal approach for patient with familial syndrome

Pathologic Findings

- Gross: Generally well circumscribed, yellow-gray, and lobulated on cut-surface
- Histologically:
  - Solid, tubular, or cord-like growth pattern of stromal epithelial tumor cells
  - Ovoid or spindle-shaped nuclei
  - Eosinophilic or clear cytoplasm
  - Variably scanty, edematous, hyalinized, or sclerotic connective tissue stroma
  - Call-Exner-like bodies sometimes seen
- Immunopathology:
  - Positive for vimentin, cytokeratin, and epithelial membrane antigen stains

  - Negative or focally positive for CD30, OCT3/4, and placental alkaline phosphates
- Histologic subtypes:
  - Classic or tumors that are not otherwise specified:
    - Low malignant potential (around 10–20%)
    - Mean age of 45 yr
    - No hereditary or MNS association
    - Occasionally causes access estrogen
    - Medium-size cells, scanty stroma with no calcifications
  - LCCSCT:
    - Mostly have benign clinical course, but malignancy can occur especially in older ages
    - Bimodal age: Early and late onset
    - Frequently associated with MNS
    - Occasionally causes access estrogen
    - Bilateral in 20% of reported cases, especially in syndromic disease
    - Often multifocal
    - Large eosinophilic cells surrounded by myxoid to collagenous stroma with occasional neutrophilic infiltrate
    - Necrosis and calcifications are common
  - Sclerosing:
    - Malignancy has never been reported
    - Affects young adults mainly
    - No hereditary association
    - Unilateral affection only
    - No hormonal imbalances
    - Usually small in size, <4 cm
    - Small pale cells with scanty cytoplasm surrounded by dense fibrous stroma

DIFFERENTIAL DIAGNOSIS

- Always rule out precocious puberty in any child who present with testicular enlargement and accelerated growth pattern
- Adult/pediatric painful mass:
  - Epididymitis/orchitis; bacterial, STD, mumps, TB
  - Fournier gangrene
  - Henoch–Schönlein purpura (usually no mass)
  - Incarcerated/strangulated hernia
  - Postvasectomy syndrome (usually no mass)
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle, testicular, or epididymal appendage)
  - Tumor (infrequent unless traumatized or rapidly growing; see below)
- Adult painless mass:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Adenocarcinoma of the rete testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea

- Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of the cord
- Lipoma of the cord
- Mesothelioma of tunica vaginalis
- Polyorchidism
- Paratesticular sarcomas: Rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma
- Scrotal edema (insect bite, nephritic syndrome, acute idiopathic scrotal edema)
- Scrotal wall: Sebaceous and inclusion cysts, idiopathic calcinosis, fat necrosis, malignancy
- Sperm granuloma following vasectomy
- Spermatocele (epididymal cyst)
- Testicular cysts (simple, tunica albuginea, epidermoid)
- Testicular tumor:
  - Germ cell tumors (95% of testicular malignancies): Seminoma, embryonal cell carcinoma, choriocarcinoma, yolk sac carcinoma teratoma (1–5%), teratocarcinoma
  - Gonadal stromal tumors: Leydig tumor, granulosa cell tumors
  - Metastatic tumors: Prostate, lung, and GI tract; rare kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Mixed germ cell and stromal tumor (gonadoblastoma)
  - Angioma, fibroma, leiomyoma, hamartoma, carcinoid, mesothelioma, and neurofibroma
  - Malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)
  - Leukemia or lymphoma
- Varicocele

• Pediatric painless mass:
- Similar to adult list; most/more common are: Hydrocele, hernia, varicocele, testicular teratoma, adrenal rest tumors, rhabdomyosarcoma

TREATMENT

GENERAL MEASURES

• Radical inguinal orchiectomy is the primary procedure of choice as these rare tumors are usually thought to be a more common malignancy of the testicle
• LCCSCT in the setting of CNC in children and young adults are typically benign and can be treated with pharmacotherapy for symptomatic relief of gynecomastia and/or advanced puberty

MEDICATION

First Line

• Platinum-based chemotherapy
- Used in metastatic disease, but unproven benefit

Second Line

N/A

SURGERY/OTHER PROCEDURES

• Radical inguinal orchiectomy
• In prepubertal boys, testis-sparing local excision has been reported (none are malignant) after frozen-section biopsy confirms the diagnosis

- Testis-sparing (partial orchiectomy) inguinal approach for patient with familial syndrome
- Retroperitoneal lymph node dissection: Reported but unproven efficacy

ADDITIONAL TREATMENT

Radiation Therapy

No proven role

Additional Therapies

Aromatase inhibitors may be an effective mode of therapy for patients with increased aromatization; currently, only limited number of patients has been treated and no definite recommendations can be made

Complementary & Alternative Therapies

Used in metastatic disease, but unproven benefit

ONGOING CARE

PROGNOSIS

- Benign, completely excised: Excellent
- Malignant, poor

COMPLICATIONS

- Recurrence: Rare
- Metastasis: Uncommon
- Infertility/subfertility
  - Bilateral LCCSTs can gradually increase in size, block the seminiferous tubules, and decrease fertility
  - Effect of treatment
  - Inhibin: Has been proposed as marker for LCCST cell activity and can inhibit FSH, but larger studies are needed to confirm the finding

FOLLOW-UP

Patient Monitoring

- Benign tumors: Periodic scrotal exam
- Malignant tumors: Imaging for metastasis
- Periodic screening for conditions associated with MNS is necessary in syndromic LCCSCT

Patient Resources

MedlinePlus: Sertoli-Leydig cell tumor.
http://www.nlm.nih.gov/medlineplus/ency/article/001172.htm

REFERENCES

1. Gourgari E, Saloustros E, Stratakis CA. Large-cell calcifying Sertoli cell tumors of the testes in pediatrics. *Curr Opin Pediatr*. 2012;24:518–522.
2. Giglio M, Medica M, De Rose AF, et al. Testicular Sertoli cell tumours and relative subtypes. Analysis of clinical and prognostic features. *Urol Int*. 2003;70:205–210.
3. Young RH. Testicular tumors–some new and a few perennial problems. *Arch Pathol Lab Med*. 2008;132:548–564.
4. Lodish MB, Stratakis CA. Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis

and related syndromes. *Best Pract Res Clin Endocrinol Metab*. 2010;24(3):439–449.

ADDITIONAL READING

Brunocilla E, Pultrone CV, Schiavina R, et al. Testicular sclerosing Sertoli cell tumor: An additional case and review of the literature. *Anticancer Res*. 2012;32(11):5127–5130.

See Also (Topic, Algorithm, Media)

- Gynecomastia
- Testis Cancer, Adult General Considerations
- Testis Cancer, Pediatric, General Considerations
- Testis, Tumor and Mass, Adult, General
- Testis, Tumor and Mass, Pediatric, General

CODES

ICD9

222.0 Benign neoplasm of testis

ICD10

- D29.20 Benign neoplasm of unspecified testis
- D29.21 Benign neoplasm of right testis
- D29.22 Benign neoplasm of left testis

CLINICAL/SURGICAL PEARLS

- Consider hereditary syndromes.
- Most Sertoli cell tumors are benign.

TESTIS, TERATOMA, MATURE AND IMMATURE

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BASICS

DESCRIPTION

- Testicular teratomas (TTs) are germ cell tumors (GCTs) which form somatic tissues in varying stages of maturity (ie, differentiation)
  - Mature (M) = well-differentiated endoderm, mesoderm, and/or ectoderm germ cell (GC) layers
  - Immature (I) = fet al or embryonal GC layers
- Most common GCT in childhood
- Adult TT, mature and immature: Consider as malignant
- Pediatric TT, mature and immature: Behave in general as benign lesions

EPIDEMIOLOGY

Incidence

- 8,820 cases of testicular cancer in the US in 2014
- 5.2 cases 100,000 men
- Adults: 2nd to 4th decade
- Mature: Immature types 10:1 (1)
- Pure teratoma (T) in 5% of adult GCTs but 35–40% of pediatric GCT
- T + GCT (ie, mixed) more common in adults (up to 50% of cases)
- Pure T more common in children
- T found in retroperitoneum in
  - 22% stage IIa
  - 1/3 of patients after chemo for NSGCT (2)

Prevalence

- US has 195,000 survivors of testicular cancer
- 5-yr survival
  - 99% when confined to testis
  - 96% for stage II
  - 40% 4-yr survival with malignant transformation of teratoma (3)

RISK FACTORS

- Same for all GCTs
  - Cryptorchidism
  - Klinefelter syndrome
  - Cannabis use controversial
  - Family history
  - Testicular atrophy/maldevelopment
  - DDT exposure (see http://www.cancer.gov/cancertopics/causes/testicular/pesticides0408 Accessed August 22, 2014)

Genetics
- Isochromosome 12p
- Adult tumors hypotriploid
- pRB expressed in epithelial component

PATHOPHYSIOLOGY
- GC tumor model
  - Initiation possibly in utero
  - Intratubular GC neoplasia unclassified (ITGCNU) undergoes progression
  - Differentiation of malignant embryonal GCs into mature teratoma thus mixed elements may occur
  - Adult and not pediatric TT genetically unstable
  - Adult and not pediatric TT has transforming capability
- Dermoid cysts are different in that they may differentiate from nonmalignant GCs

ASSOCIATED CONDITIONS
- Infertility and oligospermia
- Cryptorchidism
- Gynecomastia

GENERAL PREVENTION
- Self-exam for early diagnosis and treatment
- Possibly early orchidopexy for undescended testicle

DIAGNOSIS

ALERT
Identify symptoms of metastatic disease.

HISTORY
- The most common symptom at the time of diagnosis is painless swelling or enlargement of the testis.
- Scrotal injury
- Cryptorchidism
- Symptoms of metastatic disease may include:
  - Weight loss
  - Inanition
  - Abdominal distention
  - Joint, neck, or back pain
  - Sweats, lethargy

PHYSICAL EXAM
- Most common: Painless scrotal mass
  - Assess for tenderness, mobility, fixation
- Abdominal exam
- Breast exam
- Lymph node evaluation

- Document normal contralateral testis

DIAGNOSTIC TESTS & INTERPRETATION

ALERT
Markers must be drawn prior to orchiectomy.

Lab

- Tumor markers
  - α-Fetoprotein (AFP) (10%, can be made seen if hepatoid differentiation has occurred)
  - β-hCG (only elevated if chorio- or seminomatous elements present)
  - LDH
  - CEA (rare, can be seen if GI tissues present)
- Complete metabolic profile
  - Electrolytes
  - Liver function tests
- Complete blood count
- PT/INR

Imaging

- Ultrasound is critical in assessing for intratesticular mass, typically hypoechoic
- Microlithiasis in contralateral testis should be documented and followed; role of biopsy is controversial, more common in Europe
- Chest x-ray or better chest CT
- Abdomen–pelvis CT scan with and without contrast (if creatinine normal)
- PET scan not usually indicated; may have a role in the postchemotherapy setting

Diagnostic Procedures/Surgery

- Inguinal orchiectomy, radical, is standard of care for a solid testicular mass in adults
- Stage patient per TNMS
  - Document tumor markers: Important for staging
  - Document presence of nonteratomatous elements: Important for treatment algorithm

Pathologic Findings

- Large (5–10 cm), multinodular, heterogenous (solid, cartilaginous, cystic)
- May contain teeth, hair, bone, cartilage
- Cystic areas mixed with solid
- Mature teratoma
  - Mixture of elements of ectoderm (eg, hair), endoderm (eg, GI), and mesoderm (eg, bone)
- Immature teratoma
  - Neuroepithelium with embryonic features,
  - Poorly formed cartilage
  - Primitive glandular structures
  - High grade if mitotically active
- Dermoid cysts
  - Truly benign, no atypia or mitoses
  - Keratin, hair, dermatoectoderm

DIFFERENTIAL DIAGNOSIS

- These are a delineation of testicular masses only. For a complete listing of intrascrotal and testicular masses see Section I: "Scrotum and Testicle Mass"
- Benign lesions
  - Epididymitis/orchitis: Bacterial, STD/STI, mumps, TB
    - Often delayed testicular cancer diagnosis due to treatment of presumed epididymitis
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle or appendages)
  - Incarcerated/strangulated hernia
  - Cysts (simple, tunica albuginea, epidermoid)
  - Adrenal rest tumors: In general benign, but can contribute to infertility in patients with congenital adrenal hyperplasia
  - Fibrous pseudotumor of the tunica albuginea: Painless fibrous mass often associated with prior history of trauma or infection
  - Adenomatoid tumor of testis or epididymis
  - Other rare benign lesions: Angioma, fibroma, leiomyoma, hamartoma, carcinoid, neurofibroma
- Malignant lesions
  - Testicular primary tumors (seminoma and nonseminomatous GCT)
  - Leukemia involving testis—testis can be a site of solitary recurrence of leukemia posttreatment (sanctuary site). Biopsy can be utilized to confirm diagnosis in a patient with history of leukemia.
    - Treatment can be testis sparing with radiation, though contralateral testis should be treated as bilateral disease can be present.
  - Lymphoma involving testis—usually represents extension from extratesticular sites, rarely can represent a primary lymphoma site (1% of lymphoma cases); can present bilaterally 1/3 of the time; mostly involves older men >60 yr; constitutional symptoms commonly present (fever, chills, night sweats, weight loss).
  - Metastatic solid tumors: More common—prostate, lung, GI tract; more rare—kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Adenocarcinoma of the rete testis: Arises in the testis collecting system, high-stage presentation, poor response to chemotherapy and radiation, with median survival of 1 yr.
  - Mesothelioma of tunica vaginalis: Rare, similar to the more common pleural histology, associated with asbestos exposure
  - Paratesticular sarcomas: Rhabdomyosarcoma, malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)

TREATMENT

GENERAL MEASURES

- Radical orchiectomy for adult solid testicular mass
  - Staging and then treatment based on histology and stage
  - Treat most aggressive subelement
- Chemo for high-stage disease followed by retroperitoneal lymph node dissection (RPLND)
- Prior to systemic therapy, discuss sperm banking

MEDICATION

First Line

- Teratomas are *not* chemosensitive
- Platinum-based chemotherapy used in teratoma only to treat the non-teratomatous elements, eg, embryonal, choriocarcinoma
- RPLND is only treatment to address teratoma in retroperitoneum, esp. after chemo

Second Line

N/A

SURGERY/OTHER PROCEDURES

- RPLND important in teratoma
  - Primary (no prior treatment)
    - 20% of stage I teratomas have retroperitoneal (retroperitoneum) disease and the retroperitoneum nodes should be resected
  - Secondary (after chemotherapy/RT)
    - 20–30% of residual retroperitoneum masses after chemotherapy in NSGCT may harbor teratoma and should be resected
  - Tertiary (ie, "growing teratoma syndrome")
    - Recurrent retroperitoneal teratoma after RPLND may occur after incomplete resection or recurrent differentiated tumor
    - Retroperitoneal lymph node reresection best option if feasible

ADDITIONAL TREATMENT

Radiation Therapy

- Teratomas are *not* radiosensitive
- In stage I seminomatous GCT, radiation to the retroperitoneum may be used for patients at risk of occult stage II disease but must be monitored for retroperitoneum teratoma

Additional Therapies

Discuss sperm banking before treatment

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent with low stage & complete resection
  - 95–100% cure rate in adults
  - 100% cure rate in children
- Fair to poor if metastatic/incomplete resection
  - 86% 2-yr survival for retroperitoneal disease only
  - 40% 2-yr survival for retroperitoneal + multiple sites

COMPLICATIONS

- Infertility
  - Preorchiectomy oligospermia

  – Post-RPLND loss of emission (infertility)
- Chemotherapy toxicity
  – Platinum: Renal
  – Bleomycin: Pulmonary toxicity and fibrosis (watch for ARDS)
  – Etoposide: Myelosuppression

FOLLOW-UP

Patient Monitoring

- Surveillance not good option in primary teratoma because of occult GC elements in retorperitoneum
- If markers elevated, look for occult nonteratoma elements or, rarely, GI elements within teratoma.
- NCCN guidelines for teratoma *after* RPLND
  – Year 1–2
    ◦ Chest x-ray (CXR) + markers q3mo
    ◦ CT abdomen/pelvis baselines and q6mo
  – Year 3–4
    ◦ CXR + markers q3–6mo
    ◦ CT annual
  – Year 4–6, 6+
    ◦ CXR + markers q6–12mo
    ◦ CT biannual

Patient Resources

- National Cancer Institute. www.cancer.gov/cancertopics/types/testicular
- Testicular Cancer Awareness Foundation. www.testicularcancerawarenessfoundation.org
- Teratoma Support Foundation. www.Teratoma.weebly.com

REFERENCES

1. Pohl HG, Shukla AR, Metcalf PD, et al. Prepubertal testis tumors: Actual prevalence rate of histological types. *J Urol.* 2004;172:2370–2372.
2. Sheinfeld J, Motzer RJ, Rabbani F, et al. Incidence and clinical outcome of patients with teratoma in the retroperitoneum following primary retroperitoneal lymph node dissection for clinical stages I and IIA nonseminomatous germ cell tumors. *J Urol.* 2003;170:1159–1162.
3. Comiter CV, Kibel AS, Richie JP, et al. Prognostic features of teratomas with malignant transformation: A clinicopathological study of 21 cases. *J Urol.* 1998;159:859–863.

ADDITIONAL READING

- Beck SD, Foster RS, Bihrle R, et al. Long-term outcome for patients with high volume retroperitoneal teratoma undergoing post-chemotherapy surgery. *J Urol.* 2009;181:2526–2532.
- Simmonds PD, Lee AH, Theaker JM, et al. Primary pure teratoma of the testis. *J Urol.* 1996;155:939–942.
- Vaughn DJ, Flaherty K, Lal P, et al. Treatment of growing teratoma syndrome. *N Engl J Med.* 2009;360:423–424.

See Also (Topic, Algorithm, Media)

- Growing Teratoma Syndrome
- International Germ Cell Cancer Collaborative Group (IGCCCG)
- Reference Tables: TNM: Testis Cancer
- Testis Cancer, Pediatric, General Considerations
- Testis Cancer, Seminoma
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis, Teratoma, Mature and Immature Images ☼
- Testis, Tumor and Mass, Pediatric, General Considerations

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 222.0 Benign neoplasm of testis
- 752.51 Undescended testis

ICD10

- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended
- D29.20 Benign neoplasm of unspecified testis
- Q53.9 Undescended testicle, unspecified

CLINICAL/SURGICAL PEARLS

- Teratomas are resistant to chemotherapy and radiotherapy.
- Metastatic embryonal germ cell tumor may mature into teratoma in adult cases. Therefore, mature teratomas in adults should be treated aggressively.
- Immature and mature teratomas in children are benign.
- Pure teratomas do not secrete AFP (but may harbor GI elements that do).
- Pure teratomas do not secrete β-hCG (but may harbor choriocarcinomatous or seminomatous elements that do).
- Postchemo RPLND has double the rate of teratomas than RPLND for stage I tumors.

TESTIS, TUMOR AND MASS, ADULT, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Testis cancer is the most common malignancy in men aged 20–40 yr in US.
- Mortality has dropped from >50% in the 1970s to <5% today, due to improved imaging, better tumor markers, and multidrug chemotherapy.
- 95% of testicular tumors are germ cell tumors, other types are rare (sex cord/stromal)
- While benign lesions can be found in the testis (see section on "Differential Diagnosis"), all solid lesions should be considered cancer until definitively proven otherwise

EPIDEMIOLOGY

Incidence (1)

- ~8,820 new cases of testis cancer in US in 2014, and 380 men will die of this disease.
- Median age at diagnosis was 33 (2006–2010)
- Incidence rate was 5.5/100,000 men per year:
  - By race/100,000 men/yr: White men 6.6; black men 1.4, Asian men 1.9; Hispanic men 4.7

Prevalence

In 2010, in US there were ~221,020 men alive with history of testicular cancer.

RISK FACTORS (2)

- History of cryptorchidism:
  - 7–10% of cases; 4–6 times more likely to develop testicular cancer
  - Seminoma is most common tumor type
  - Orchiopexy reduces relative risk (RR) from 3 to 2 if performed prior to onset of puberty
- Family history (affected 1st-degree relative):
  - Father with testis cancer—RR 4.63
  - Brother with testis cancer—RR 8.3
  - Son with testis cancer—RR 5.23
- Cannabis use controversial
- Testicular atrophy
- Infertility
- Klinefelter syndrome

Genetics

Isochromosome 12p amplification seen in the majority of tumors

PATHOPHYSIOLOGY

- Germ cell tumors (seminoma, embryonal cell carcinoma, teratoma, choriocarcinoma, and yolk sac tumor) comprise 90–95% of testicular tumors.

  – Mixed germ cell tumors common (60% of all)
- Seminoma: 35–65% of germ cell tumors; classified into 3 subtypes:
  – Typical (classic) seminoma: 82–85% of seminomas; most commonly men in 30s; less common in men in 40s–50s
    - Syncytiotrophoblast in 10–15% of typical seminomas and makes to β-hCG.
  – Spermatocytic seminoma:
    - 2–12%; roughly 1/2 in men >50 yr
  – Lower malignant potential
- Embryonal cell carcinoma:
  – Occurs in 40% of germ cell tumors
- Choriocarcinoma
  – Rarely found in pure form; pure form is often advanced, with a small primary tumor.
  – Prognosis for pure choriocarcinoma is poor.
- Yolk sac tumor: 92% stain for AFP
- Teratoma:
  – Frequently found at metastatic sites
  – Locally invasive, chemotherapy resistant
- Nongerm cell tumors (5–7%):
  – Leydig cell tumors: 2–3% of tumors; not associated with cryptorchidism;10% malignant
  – Sertoli cell tumors:
    - 1% of testicular tumors; 90% benign
  – Gonadoblastoma: Rare; most in men <30 yr

ASSOCIATED CONDITIONS
- Cryptorchidism
- Infertility seen in men upon diagnosis (half with oligospermia, 1/10th with azoospermia)

GENERAL PREVENTION
Testicular self-exam should be performed monthly for earlier diagnosis.

DIAGNOSIS
HISTORY
- Local symptoms: Change in testicular size or texture; testicular pain (uncommon)
- Systemic symptoms: Weight loss; abdominal pain/discomfort; fevers; mastodynia or other changes in secondary sex characteristics:
- History: Cryptorchidism, infertility, orchiopexy

PHYSICAL EXAM
- Check all lymph nodes, including supraclavicular nodes.
- Abdominal exam for masses
- Examine for gynecomastia (5% of cases).
- Testicular exam: Examine both testes:
  – Any firm or hard area in the testis should be evaluated; determine if mass is distinct from epididymis. Note consistency of testis, whether it is fixed to scrotum, and size of lesion
  – Palpate for hydrocele, hernia.

ALERT
Markers must be drawn prior to orchiectomy.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Tumor markers obtained prior to orchiectomy:
  - 1 or more elevated in 85–90% of non-seminomatous germ cell tumor (NSGCT)
- β-hCG:
  - Half-life: 24–36 hr
  - Elevated in 40–60% with testis cancer; 100% of choriocarcinomas;10–15% pure seminomas
- AFP:
  - Half-life: 5–7 days
  - Produced by yolk sac tumors, embryonal cell carcinoma, and teratocarcinomas
  - Not produced in pure seminoma or pure choriocarcinoma. If AFP elevated in case of pure seminoma, NSGCT elements are present.
- LDH
  - Nonspecific marker for GCT
  - Elevated in 20% of low stage and 50% of high-stage GCT
  - Useful in prognosis as magnitude of elevation correlates with disease bulk
  - Half-life: 1 day
- Serum and urine estrogens may be elevated in Leydig cell tumors

Imaging

- Scrotal US:
  - Diagnostic imaging mainstay for identifying testicular tumors
  - Any hypoechoic lesion within the testicular parenchyma should be considered cancer until proven otherwise.
  - 80% of testicular tumors are hypoechoic.
- Abdominal CT:
  - Critical for staging of testicular tumors
  - Should be performed prior to orchiectomy if possible, as postoperative retroperitoneal hematoma can distort imaging.
  - Accuracy is 70–90%, depending upon stage.
  - Cannot detect micrometastasis in normal-sized lymph nodes
- Chest x-ray: Staging for metastases; if abnormal, chest CT is obtained.

Diagnostic Procedures/Surgery

- Radical inguinal orchiectomy:
  - Important for determining pathology of primary tumor. Is also therapeutic in that chemotherapy does not penetrate testis well.
- Transscrotal testicular biopsy or orchiectomy should NOT be performed.

DIFFERENTIAL DIAGNOSIS

These are a delineation of testicular masses only. For a complete listing of intrascrotal and testicular masses see Section I “Scrotum and Testicle Mass”:

- Benign lesions
  - Epididymitis/orchitis: Bacterial, STD/STI, mumps, TB
    - Often delayed testicular cancer diagnosis due to treatment of presumed epididymitis
  - Testicular trauma: Usually blunt; contusion, rupture; usually associated hematocele
  - Torsion (testicle or appendages)
  - Incarcerated/strangulated hernia
  - Cysts (simple, tunica albuginea, epidermoid)
  - Adrenal rest tumors: In general benign, but can contribute to infertility in patients with congenital adrenal hyperplasia
  - Fibrous pseudotumor of the tunica albuginea: Painless fibrous mass often associated with prior history of trauma or infection
  - Adenomatoid tumor of testis or epididymis
  - Other rare benign lesions: Angioma, fibroma, leiomyoma, hamartoma, carcinoid, neurofibroma
- Malignant lesions
  - Testicular primary tumors (seminoma and nonseminomatous GCT)
  - Leukemia involving testis—testis can be a site of solitary recurrence of leukemia post-treatment (sanctuary site). Biopsy can be utilized to confirm diagnosis in a patient with history of leukemia.
    - Treatment can be testis sparing with radiation, though contralateral testis should be treated as bilateral disease can be present.
  - Lymphoma involving testis—usually represents extension from extratesticular sites, rarely can represent a primary lymphoma site (1% of lymphoma cases); can present bilaterally one-third of the time; mostly involves older men >60 yr; constitutional symptoms commonly present (fever, chills, night sweats, weight loss).
  - Metastatic solid tumors: More common—prostate, lung, GI tract; more rare—kidney, malignant melanoma, pancreas, bladder, and thyroid
  - Adenocarcinoma of the rete testis: Arises in the testis collecting system, high-stage presentation, poor response to chemotherapy and radiation, with median survival of 1 yr.
  - Mesothelioma of tunica vaginalis: Rare, similar to the more common pleural histology, associated with asbestos exposure
  - Paratesticular sarcomas: Rhabdomyosarcoma, malignant fibrous histiocytoma (most common soft tissue sarcoma in late adult life)

TREATMENT

GENERAL MEASURES

- Radical inguinal orchiectomy is considered standard of care for initial management.
- Additional therapy depends on staging. Commonly used staging system is the TNM staging and group staging by the AJCC.
  - For NSGCT: RPLND, primary chemotherapy (platinum based), or surveillance
- For seminoma: Surveillance, primary radiotherapy, or primary chemotherapy (single-agent carboplatin)
- Surveillance, with serial imaging and tumor markers, is appropriate in well-selected low-risk patients:

- Stage I seminoma
- Stage I NSGCT: No teratomatous elements, no lymphovascular invasion, and no embryonal cell carcinoma in the primary specimens. Patients must be reliable.

MEDICATION

First Line

- Treatment depends upon primary cell type of tumor and stage at presentation.
- Cisplatin-based chemotherapy is the 1st-line regimen for treating testicular cancer:
  - Commonly used for stage IIc and higher seminoma; numerous regimens used.
  - 2 cycles of BEP (bleomycin/etoposide/cisplatinum) in stage I NSGCT
  - 3 cycles of BEP commonly used for stage IIa, IIb; good-risk stage IIc and III disease
  - Poor-risk stage IIc and II disease: 4 cycles of BEP have been used:
    - Some centers have replaced etoposide with ifosfamide and some use advocated 4 cycles of vinblastine, ifosfamide, and cisplatin.

Second Line

High-dose chemotherapy with autologous bone marrow transplantation in patients with residual disease and or recurrent disease or rather, enrollment in a clinical trial

SURGERY/OTHER PROCEDURES

- Radical orchiectomy:
  - Inguinal approach is used to prevent violation of tissue planes
  - May be adequate treatment for stage I seminoma and certain stage I NSGCTs
- Retorperitoneal lymph node dissection (RPLND):
  - Indicated in patients with stage I and IIa NSGCT, particularly those with teratoma in the primary specimen
  - With residual mass after chemotherapy
    - For low-stage disease, a modified nerve-sparing template is normally used.
  - For RPLND description, see Section I: “Testis Cancer, Nonseminomatous Germ Cell Tumors”

ADDITIONAL TREATMENT

Radiation Therapy

- Commonly used in stage I and IIa seminomas
- External beam radiation to retroperitoneal and ipsilateral ilioinguinal lymph nodes
- Contralateral inguinal region is included if history of inguinal or scrotal procedures

Additional Therapies

Patients should consider sperm banking prior to treatment to aid in avoiding risk of infertility.

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Depending upon stage and cell type of primary tumor, prognosis is excellent, with 95% of

patients experiencing a long-term cure.

COMPLICATIONS

- Infertility
- RPLND: Retrograde ejaculation, ileus, atelectasis, chylous ascites, chylothorax, pneumonitis, lymphocele, pancreatitis, and vascular or bowel injury
- Increased risk of secondary malignancies in patients undergoing chemotherapy or radiation

FOLLOW-UP

Patient Monitoring

- In patients who underwent RPLND:
  - Serial monitoring with chest x-ray, physical exam, and tumor markers. Retroperitoneal recurrence is rare, so imaging of this region is not usually needed.
  - Follow-up depends upon initial stage and cell type of primary tumor and response to therapy.
- In patients who did not undergo RPLND:
  - Follow-up similar; serial monitoring of retroperitoneum using CT scanning
  - Frequency of follow-up is based on initial stage and cell type and the response to therapy.

Patient Resources

- NCI 1-800-4-CANCER. http://www.cancer.gov/cancertopics/pdq/treatment/testicular/Patient
- American Cancer Society. http://www.cancer.org/cancer/testicularcancer/index

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9–29.
2. Nordsborg RB, Meliker JR, Wohlfahrt J, et al. Cancer in first-degree relatives and risk of testicular cancer in Denmark. *Int J Cancer*. 2011;129(10):2485–2491.

ADDITIONAL READING

- Feldman DR, Bosl GJ, Sheinfeld J, et al. Medical treatment of advanced testicular cancer. *JAMA*. 2008;299:672–684.
- National Comprehensive Cancer Network Guideline Recommendations. http://www.nccn.org/clinical.asp

See Also (Topic, Algorithm, Media)

- Reference Tables: TNM: Testis Cancer
- Scrotum and Testicle, Mass
- Testis Cancer, Adult General Considerations
- Testis Cancer, Choriocarcinoma
- Testis Cancer, Embryonal Carcinoma
- Testis Cancer, Endodermal Sinus Tumors (Yolk Sac Tumors)
- Testis Cancer, Pediatric, General Considerations
- Testis Cancer, Seminoma
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis, Leydig Cell Tumor
- Testis, Pain (Orchalgia)

- Testis, Sertoli Cell Tumor
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Adult, General Considerations Images
- Testis, Tumor and Mass, Pediatric, General Considerations
- Torsion, Testis or Testicular/Epididymal Appendages

CODES

ICD9

- 186.9 Malignant neoplasm of other and unspecified testis
- 239.5 Neoplasm of unspecified nature of other genitourinary organs
- 608.89 Other specified disorders of male genital organs

ICD10

- D49.5 Neoplasm of unspecified behavior of other genitourinary organs
- N50.8 Other specified disorders of male genital organs
- C62.90 Malig neoplasm of unsp testis, unsp descended or undescended

CLINICAL/SURGICAL PEARLS

- Increased risk of malignancy in patients with history of cryptorchidism and family history of testis cancer.
- Ultrasound should be performed to resolve any concerns of abnormal scrotal exam.
- Initial diagnosis of radical orchiectomy using an inguinal approach to avoid scrotal violation.
- All testis masses in adults should be considered malignant until proven otherwise.

TESTIS, TUMOR AND MASS, PEDIATRIC, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Important to distinguish prepubertal "pediatric" testis tumors from the postpubertal "adolescent" testis tumors (1).
- Prepubertal testicular tumors in children are much more often benign than the postpubertal tumors which are more often malignant.
- Must differentiate a true testicular tumor or mass from paratesticular and scrotal masses
- The most common causes of painless scrotal swelling in a child include hernias, hydrocele, varicocele, and scrotal wall swelling
- Testis accounts for 2% of pediatric tumors

EPIDEMIOLOGY

Incidence

- 0.5–2 per 100,000 children/yr
- Peak age of 2 yr
- Lower incidence of germ cell tumors (GCTs) when compared to adults
- 25–30% of pediatric tumors are malignant (2).
- Rare in black and Asian children
- Testicular tumors in children (2):
  - Teratoma: 40–50%
  - Epidermoid cyst: 10–15%
  - Yolk sac tumor (YST): 25–35%
  - Gonadal stromal tumors: 10–15%
  - Others: Gonadoblastoma: 1–2% (3), leukemia: 1–2%, cystic dysplasia: $<1\%$

Prevalence

N/A

RISK FACTORS

- Risk factors for GCTs:
  - Cryptorchidism (4)
  - Family history
  - Intratubular germ cell neoplasia
  - Past personal history
- Congenital adrenal hyperplasia (CAH) increases risk for intratesticular adrenal rests

Genetics

- Gonadoblastoma is associated with gonadal dysgenesis and a 45XO/46XY karyotype.
- YST: Abnormalities in 1p, 6q, and 3p

- GCTs: Excess genetic material from the short arm of chr 12, including isochromosome 12p.
- Large-cell calcifying Leydig tumor is associated with Peutz–Jeghers syndrome and Carney complex.

PATHOPHYSIOLOGY

- GCTs typically develop from a precursor lesion, which, in turn, appears to develop from arrested primordial germ cells or gonocytes
- Teratoma: Monodermal (epidermoid cyst) or multiple histologic types present
  - Not associated with an elevated AFP
  - Metastasis not reported before puberty
  - Testis-sparing enucleation via an inguinal incision is possible in prepubertal patients and normal serum tumor markers.
- YST (also called endodermal sinus tumor):
  - AFP elevated in 80% of YST, and normally elevated in a neonate (physiologic).
    - AFP half-life is 5–7 days; elevation after orchiectomy implies metastatic disease.
  - Yolk sac elements stain positive for AFP
  - β-hCG produced by syncytiotrophoblast indicates a mixed GCT.
- Gonadoblastoma:
  - Most common tumor in disorders of sexual development; germ cell component prone to malignant degeneration
- Seminomas and mixed GCT rare in prepubertal children.
- Gonadal stromal tumors (3):
  - Leydig cell tumors:
    - Peak age of 4–5 yr; increased testosterone production with normal LH
    - Differential diagnosis includes pituitary lesions, Leydig cell hyperplasia, CAH based on hormonal production
    - Reinke crystals classically described in adults, rare in children on histology
    - Malignancy not reported in Leydig cell tumors in children
  - Sertoli cell tumor:
    - Peak age <4; most not hormonally active
    - Gynecomastia when hormonally active
    - Retroperitoneal spread rarely reported
  - Granulosa cell tumor:
    - Rarely metastasizes
- Testis tumor of adrenogenital syndrome:
  - Benign, suppressible with glucocorticoids
- Lymphoma, leukemia
  - May serve as a sanctuary site of these malignancies because of blood–testis barrier
- Cystic dysplasia of the testis:
  - Irregular cysts in rete testis; associated with renal agenesis and multicystic dysplasia
- Children's Oncology Group (COG) staging:
  - Stage 1: Limited to testis, markers normalize according to half-life. No radiologic evidence of metastatic disease
  - Stage 2: Transscrotal orchiectomy or tumor rupture during orchiectomy, persistent elevated markers, residual disease in scrotum or disease on pathology <5 cm from

testicular cord margin
  – Stage 3: Nodes >4 cm, no visceral or distant disease. Nodes 2–4 cm require biopsy.
  – Stage 4: Distant metastases
- Postpubertal GCTs staged and managed according to adult testicular cancer guidelines

ASSOCIATED CONDITIONS
- Disorders of sexual development with a dysgenetic gonad and the presence of a Y chromosome
- Congenital adrenal hyperplasia (CAH)
- Cryptorchidism
- Precocious puberty

GENERAL PREVENTION
- Orchidopexy does not eliminate the risk of developing testicular cancer in cryptorchidism, but early intervention may reduce the risk (4).
- Early orchidopexy permits earlier detection of testicular masses. Other benefits include improved fertility and a reduced risk of torsion.
- Routine exam of the scrotal contents

DIAGNOSIS

HISTORY
- Asymptomatic scrotal mass or asymmetry
- Acute pain or fever with hemorrhage, trauma, rapid growth of the tumor, infection
- Precocious sexual development
- Breast tenderness with gynecomastia
- Undescended testicle or hernia repair
- Family history of testicular tumors

PHYSICAL EXAM
- Scrotal asymmetry
- Abnormality intratesticular vs. intrascrotal, testicular vs. paratesticular
- Diffusely enlarged testicle or palpable nodularity in the testicle
- Does not transilluminate (solid)
- Inguinal canal and cord structures are usually normal in a boy with a testicular tumor
- Signs of precocious puberty

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum markers AFP and β-hCG:
  – Obtain prior to orchiectomy in all patients with a testicular mass
  – Marked AFP elevations present in newborn; may be detectable up to 8 mo of age
- Serum testosterone, LH, and FSH levels if a gonadal stromal tumor is suspected.

Imaging
- Scrotal ultrasound (US):
  – Differentiate intratesticular vs. extratesticular
  – Does not differentiate benign from malignant

  - Paratesticular rhabdomyosarcoma (PT-RMS):
    - Hypervascular, solid extratesticular mass
    - Often large; testicle not seen on US
  - Indeterminate lesions on US that resemble testicular neoplasm include tubular ectasia of the rete testis, inflammation, and hematoma.
- Chest x-ray: Evaluate for metastatic YST
- Abdominal and pelvic CT or MRI:
  - Obtained after histology confirms malignancy
  - Evaluate retroperitoneum for lymph node metastases and liver for metastases
- MRI may have utility in the evaluation of indeterminate lesions seen on US.

Diagnostic Procedures/Surgery

- All suspicious testicular and paratesticular lesions should be approached inguinally.
- Prepubertal patients with a primary testicular lesion and normal tumor markers may be considered for testis-sparing surgery (TSS).
  - Such approaches require intraoperative assessment including immediate frozen-section analysis to ensure complete resection
  - If frozen section reveals GCT elements or concern for incomplete resection, radical orchiectomy should be performed
  - Intraoperative US may be helpful
  - Postpubertal patients with a normal contralateral testicle should undergo radical inguinal orchiectomy.
  - Paratesticular lesions consistent with malignancy should be managed with radical inguinal orchiectomy

Pathologic Findings

- GCTs
  - Teratoma: Contain elements of at least 2 of the 3 germ cell layers of endoderm, mesoderm, and ectoderm.
  - YST: Epithelioid cells that form glandular and ductal structures arranged in columns, papillary projections, or solid islands within a primitive mesenchymal stroma. The cells have poorly defined cell borders and vacuolated cytoplasm with glycogen and fat.
  - Seminoma: Islands or sheets of relatively large cells with clear cytoplasm and densely staining nuclei.
  - Embryonal carcinoma: Malignant epithelioid cells arranged in glands or tubules. Cell borders indistinct, cytoplasm pale or vacuolated, and nuclei rounded with coarse chromatin.
  - Choriocarcinoma: 2 distinct cell types must be demonstrated to satisfy the histologic diagnosis of choriocarcinoma: Syncytiotrophoblasts and cytotrophoblasts.
  - Gonadoblastoma: Must have 3 elements: Sertoli cells, interstitial tissue, and germ cells
- Stromal tumors
  - Leydig cell tumors: Uniform, closely packed cells with round, slightly eccentric nuclei and eosinophilic granular cytoplasm with lipoid vacuoles, brownish pigmentation, and inclusions known as Reinke crystals.
  - Sertoli cell tumors: Epithelial elements resembling Sertoli cells and varying stroma.
  - Granulosa cell tumors: Characteristic Call–Exner bodies may be identified, consisting of

PAS-positive material similar to that seen in the basement membrane of the tubules.

DIFFERENTIAL DIAGNOSIS

- Painful childhood testicular masses:
  - Epididymitis/orchitis; bacterial, mumps
  - Henoch–Schönlein purpura (usually no mass)
  - Incarcerated/strangulated hernia
  - Testicular or paratesticular tumor
  - Testis trauma: Contusion, hematocele
  - Torsion (testicle, testicular or epididymal appendage); more common after puberty
- Painless childhood testicular masses:
  - Adenomatoid tumor of testis or epididymis
  - Adrenal rest tumors
  - Cystic dysplasia of the testis
  - Chylocele: Usually associated with filariasis
  - Fibrous pseudotumor of the tunica albuginea
  - Hydrocele, primary or due to trauma, torsion, tumor, epididymitis; hydrocele of cord
  - Hernia
  - Lipoma of the cord
  - Polyorchidism
  - Rhabdomyosarcoma (RMS) (bimodal age 3–4 and adolescence)
  - Scrotal edema (insect bite, nephrotic syndrome, acute idiopathic scrotal edema)
  - Spermatocele (epididymal cyst)
  - Testicular cysts
  - Testicular tumors:
    - GCTs: YST, teratoma, seminoma, embryonal, choriocarcinoma, mixed tumors
    - Gonadal stromal tumors: Leydig tumor, Sertoli cell, granulosa cell tumors
    - Metastatic tumors
    - Hamartoma, carcinoid, and neurofibroma
    - Testis tumor of adrenogenital syndrome
    - Leukemia or lymphoma
  - Varicocele

TREATMENT

GENERAL MEASURES

- TSS for most lesions in prepubertal children
- Prepubertal testicular teratomas, and Leydig and Sertoli cell tumors are benign; orchiectomy or TSS is curative and no additional therapy is indicated.
- YST or other malignant tumor; radical orchiectomy and observation if low stage
- PT-RMS require specific RMS management

MEDICATION

First Line

- Chemotherapy for all GCTs stage II or greater
  - Bleomycin, etoposide, cisplatin

SURGERY/OTHER PROCEDURES

- Inguinal approach for primary lesion in all patients regardless of age
- RPLND
  - Postchemotherapy for residual retroperitoneal mass
    - Rare given the rarity of metastatic disease and exquisite sensitivity to chemotherapy
  - Staging RPLND in all boys >10 yr with PT-RMS regardless of staging imaging and those <10 yr with abnormalities on staging imaging

ADDITIONAL TREATMENT

Radiation Therapy

As indicated for PT-RMS depending on stage and histology

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Prepubertal teratoma is uniformly benign
- GCTs (5)
  - 100% 6-yr overall survival for Stages I–III
  - 91% 6-yr overall survival for Stage IV

COMPLICATIONS

Long-term complications after chemotherapy

FOLLOW-UP

Patient Monitoring

- Routine follow-up not necessary for teratoma
- Surveillance for malignancy based on stage of disease and adjuvant therapy

Patient Resources

Urology Care Foundation: Testicular cancer in children.
http://www.urologyhealth.org/urology/index.cfm?article=37

REFERENCES

1. Agarwal PK, Palmer JS. Testicular and paratesticular neoplasms in prepubertal males. *J Urol.* 2006;176:875–881.
2. Pohl HG, Shukla AR, Metcalf PD, et al. Prepubertal testis tumors: Actual prevalence rates of histologic types. *J Urol.* 2004;172:2370–2372.
3. Schultz KA, Schneider DT, Pashankar F, et al. Management of ovarian and testicular sex cord-stromal tumors in children and adolescents. *J Pediatr Hematol Oncol.* 2012;34 (suppl 2):S55–S63.
4. Wood HM, Elder JS. Cryptorchidism and testicular cancer: Separating fact from fiction. *J Urol.* 2009;181:452–461.
5. Schlatter M, Rescorla F, Giller R, et al. Excellent outcome in patients with stage I germ cell

tumors of the testes: A study of the Children's Cancer Group/Pediatric Oncology Group. *J Pediatr Surg.* 2003;38(3):319–324.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Paratesticular Tumors
- Reference Tables: TNM: Testis Cancer
- Rhabdomyosarcoma, Pediatric
- Scrotum and Testicle, Mass
- Testis Cancer, Adult General Considerations
- Testis Cancer, Nonseminomatous Germ Cell Tumors, General
- Testis, Cancer, General
- Testis, Leydig Cell Tumor
- Testis, Sertoli Cell Tumor
- Testis, Teratoma, Mature and Immature
- Testis, Tumor and Mass, Pediatric, General Considerations Images
- Torsion, Testis and Testicular Appendages

CODES

ICD9

- 222.0 Benign neoplasm of testis
- 239.5 Neoplasm of unspecified nature of other genitourinary organs
- 608.89 Other specified disorders of male genital organs

ICD10

- D29.20 Benign neoplasm of unspecified testis
- D49.5 Neoplasm of unspecified behavior of other genitourinary organs
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

- Scrotal US can generally distinguish a tumor from other causes of testicular swelling or pain and discriminate between a testicular and paratesticular mass.
- While infant and prepubertal boys with a testicular mass and normal serum tumor markers may be treated with attempted testis sparing surgery (TSS), peripubertal boys should be managed with a radical inguinal orchiectomy.

TESTOSTERONE REPLACEMENT THERAPY, GENERAL PRINCIPLES

Robert L. Segal, MD, FRCS(C)
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BASICS

DESCRIPTION

- Hypogonadism is the clinical syndrome associated with low serum testosterone (T)
  - Can occur in early age (early onset), although most commonly seen in aging males
  - Late-onset male hypogonadism may also be referred to as andropause, androgen deficiency in the aging male, or androgen deficiency syndrome

EPIDEMIOLOGY

Incidence

N/A

Prevalence

- 2–4 million men in US
- Hypogonadism increases with age
  - Overall 5.6–38.7% men are affected, depending on study
  - 6th decade: 12%; 7th: 19%; 8th: 29%; 9th: 49%

RISK FACTORS

- Medical comorbidities (chronic liver disease, chronic renal failure/hemodialysis, HIV/AIDS, hyperthyroidism, obesity)
- Medication (GnRH agonists/antagonists, androgen antagonists, estrogen, opiates, ketoconazole, amiodarone, thiazide diuretics, cimetidine)
- Low protein diet

Genetics

N/A

PATHOPHYSIOLOGY

- As age increases, there is:
  - Decreased number of Leydig cells within the testicle (site of T production)
  - Decreased testicular responsiveness to LH
  - Dampening in the amplitude of circadian release of T
  - Increased serum sex hormone binding globulin (SHBG); binds T, therefore less bioavailable (functionally active) T

ASSOCIATED CONDITIONS

- Metabolic syndrome (obesity, hypertension, dyslipidemia)
- Impaired fasting glucose/insulin resistance/diabetes mellitus type II (DMII)
- Asthma/chronic obstructive pulmonary disease/obstructive sleep apnea (OSA)
- Osteoporosis

GENERAL PREVENTION
N/A

DIAGNOSIS

HISTORY
- Low energy level/daytime sleepiness (2)[B]
- Decreased sexual interest/libido (2)[A]
- Erectile dysfunction (ED)/absence of spontaneous erections/delayed ejaculation (2)[A]
- Diminished mood/memory/concentration
- Hot flushes/sweats
- Loss of muscle mass/visceral obesity
- Visual field defects
- Several validated questionnaires to screen for T deficiency have been developed, but are unreliable with low specificity (1)[C]

PHYSICAL EXAM
- May not be contributory (2)[B]
- Small testicular size/soft consistency (2)[B]
- Hair distribution and pattern (2)[B]
- Gynecomastia (2)[B]
- Digital rectal exam (DRE) to rule out palpable prostate abnormality

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Total serum T (best before 11:00 am) (1)[A]
- Free T
- Bioavailable T
  - No universally accepted lower limit of normal serum T
  - It is generally agreed that serum T >12 nmol/L (3.5 ng/mL, 350 ng/dL) does not usually need replacement (2)[A]
  - If T <8 nmol/L (2.3 ng/mL, 230 ng/dL) replacement is typically beneficial (2) [A]
- FDA research trial definition: Hypogonadism is total T levels of ≤ 300 ng/dL
- Serum albumin
- SHBG
- If secondary hypogonadism is suspected:
  - Serum prolactin; Serum gonadotropins (LH); thyroid function

Imaging
- Cranial imaging (MRI, CT) if prolactinoma suspected
- Dexa scan for the assessment of bone mineral density if at risk for osteopenia/osteoporosis (1)[B]

Diagnostic Procedures/Surgery
N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Acute critical illness (surgery, head trauma)
- Age-related decline ("andropause")
- Alcoholism
- Chronic illness (liver failure, chronic renal failure, hypertension, hypothyroidism, diabetes, sleep apnea, obesity, anorexia nervosa, depression, HIV)
- Hematologic (sickle cell disease, thalassemia)
- Hemochromatosis of the pituitary, Leydig cells
- Hypopituitarism (hypothalamic/pituitary)
- Kallmann, Klinefelter, or Noonan syndrome
- Medications: LHRH analogues/antagonists, glucocorticoids, androgens, estrogens, progestins (eg, megestrol), chronic opioids, marijuana (controversial)
- Pituitary infections, infiltration, trauma, radiation (decreased LH/FSH production)
- Pituitary tumors, macroadenomas, hyperprolactinemia
- Syndromes Prader–Willi and Sertoli only
- Testicular failure (primary): Congenital or acquired anorchia, cryptorchidism, mumps orchitis, radiation therapy, chemotherapy
- Testicular tumors

TREATMENT

GENERAL MEASURES

- Treatment is warranted for men with clinical symptoms associated with objective biochemical findings of low T (2)[C]
  - In the context of significant symptoms and normal or borderline T levels, a trial of TRT is acceptable with appropriate follow-up to ensure improvement in symptoms (2)[C]. If no improvement is noted, further workup to delineate cause is warranted
- In the presence of visceral obesity, weight loss through regular exercise and low-caloric intake is recommended (2)[A]
- Appropriate glycemic, blood pressure, and lipid management is recommended
- TRT contraindications include:
  - Known prostate cancer (absolute)
  - Known breast cancer (absolute)
  - Unexplained prostate-specific antigen (PSA) elevation/suspicious DRE finding (absolute)
  - Severe lower urinary tract symptoms (LUTS) associated with BPH
  - Erythrocytosis (hematocrit >52–54%)
  - Uncontrolled/poorly controlled heart failure
  - Untreated OSA, although no scientific evidence exists demonstrating a direct causal relationship between T and OSA
  - Men seeking fertility
- Improvement is expected in:
  - Reduction of body fat/visceral obesity (2)[A]
  - Increase in fat-free mass/possibly muscle strength (1)[A]

- Insulin resistance/glycemic control in men with DMII (2)[A]
- Bone mineral density at lumbar spine (1)[A]
- Hypoactive sexual desire/ED/delayed ejaculation (1)[B]

- Considerations in the older male: The American Geriatrics Society (AGS) lists T as a medication to generally avoid in older adults because of potential for cardiac problems and men with personal history of prostate cancer.
- TRT agents/options outlined below
  - Transdermal agents may have best compliance; all provide uniform T level for 24 hr
  - Topical agents: Interpersonal transfer possible and should be avoided, especially for women and children
  - Gels should be dry before putting on clothes over application site; delay swimming
  - Brand names provided to avoid patient confusion; see FDA label for details

MEDICATION

First Line

- Buccal (Striant) 30 mg T/tab system
  - Dose: 30 mg BID
  - Avoids 1st-pass effect of hepatic inactivation
  - Apply to gum over incisor; do not chew/swallow
- Transdermal (Androderm): Apply to nonscrotal skin (back, abdomen, upper arms, thighs); avoid bony prominences; delivery 2 mg or 4 mg T/patch
  - Dose: Based on patch; start one 4 mg/patch/24 h; adjust to 1 or more patch combinations for desired effect
  - Skin irritation may be noted; remove for MRI
- Transdermal gels; product-specific dosing; apply clean dry: Shoulder, upper arm, or abdomen
  - (AndroGel 1%)
    - Dose: Topical daily 5–10 g (max)
  - (AndroGel 1.62%)
    - Dose: Topical 2 pump activations or 40.5-mg pack; adjust from 1 activation 20.25 mg or single 20.25 mg pack; 81 mg/d (max)
  - [Fortesta] 10 mg T/0.5 mg gel/activation; apply to inner thigh area only
    - Dose: Start 4 pump activations (40 mg) QAM; adjust 1–7 pump activations (10 mg–70 mg daily; 70 mg max
  - (Testim 1%) 50 mg T/5 g gel; 50 mg/unit dose tube; apply shoulder or upper arm
    - Dose: Topical 5–10 g/d/2 tubes MAX
- Transdermal solution
  - (Axiron) 30 mg T/1.5 mL of solution
    - Dose 60 mg T (1 pump = 30 mg of T solution to each axilla) daily; adjust based on levels
- IM short-acting formulations; may be associated with fluctuations in serum T (supraphysiologic 2–5 d after injection, subphysiologic 10–14 d after injection) which may be associated with symptom fluctuation
  - T cypionate (Depo-Testosterone) 200–400 mg IM every 3–4 wk or 100–150 mg
  - every 2 wk preferred

  - T enanthate (Delatestryl) 100–400 mg IM every 4 wk or 100–150 mg every 2 wk preferred
  - *Prepubertal boys*: 50–100 mg IM agent monthly or 25–50 mg every 2 wk, increase to 50–100 mg every 2 wk and then adult dose over 2–4 yr or until pubertal development occurs
- T implant
  - Pellets (Testopel) (75 mg/each) 150–450 mg SC implant every 3–6 mo
  - 2 pellets for each 25 mg T required weekly; in upper buttock with local anesthesia
  - Local symptoms such as pain, bleeding
  - Pellet infection and extrusion (up to 10%)
- Parenteral T undecanoate (Aveed): 750 mg IM (3 mL) initially, at 4 wk, then 750 mg every 10 wk
- T nasal gel (Natesto) 2 pumps each nostril (11 mg testosterone) one in each nostril TID (total 33 mg/day)
- T formulations outside the US:
  - Oral T undecanoate: 40–80 mg PO with meals BID to TID
  - T-in-adhesive matrix patch: 2 patches (4.8 mg T/d) applied every 2 days
  - T gel 2%: 3–4 g (60–80 mg of T) applied to abdomen or both inner thighs daily

Second Line

Any agent form the Frist Line medication can be used as second line if the product is ineffective or there are proactical use issues with an individual patient

SURGERY/OTHER PROCEDURES

Insertion of subdermal T pellets (see above MEDICATION: First Line)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- There may be therapeutic synergism with combined TRT and phosphodiesterase-5 inhibitors in men with low T and ED (2)[A]
- Other forms of androgen therapy include the usage of dehydroepiandrosterone (DHEA), dihydrotesto-sterone (DHT), although their use has not been proven effective (2)[B]
- Human chorionic gonadotropin (hCG) may preserve spermatogenesis in young men with hypogonadism (1)[B] (See Section I “Testosterone, Decreased [Hypogonadism]”)
- Antiestrogens and aromatase inhibitors may raise endogenous T in secondary hypogonadism if the hypothalamic–pituitary–testicular axis is intact
- Selective androgen receptor modulators (SARMs) may have a role in hypogonadism

Complementary & Alternative Therapies

There are no alternative therapies that will cure low T. Some stress management techniques can relieve the stress and anxiety associated with hypogonadism: Yoga, meditation techniques, emotional support/counseling, healthy lifestyle (nutritious diet, active exercise, adequate rest)

ONGOING CARE

PROGNOSIS

- Goal is for the restoration of serum T within normal lab limits; supraphysiologic levels should be avoided (2)[C]
- Target serum T should be 40–70% of upper limit of normal serum T (2)[C]
- There is no evidence of benefit for maintaining a circadian rhythm of serum T (2)[C]

COMPLICATIONS

- Erythrocytosis; gynecomastia; fluid retention
- No conclusive evidence that TRT increases the risk of or worsens pre-existing prostate cancer or LUTS secondary to BPH. Men effectively treated for prostate cancer, after sufficient period of surveillance has elapsed (at least 1 yr), may be candidates for symptomatic TRT (1)[B]
  - TRT should be reserved for patients with low-risk prostate cancer (Gleason grade <8, pT1-2, PSA <10 ng/mL)
  - Men considering TRT in this context must be counseled and understand the theoretical risks and the fact that T medications carry prostate cancer risk labeling

FOLLOW-UP

Patient Monitoring

- Clinical and biochemical verification of treatment effect should occur 1–6 mo after initiating TRT (depending on TRT modality) (1)[C]
  - Repeat assessment of serum T parameters
  - Dosage may be adjusted if still subphysiologic
  - Once the proper dose established, annual T measurements are usually sufficient
- Monitor hematocrit 3, 6, and 12 mo after initiating TRT, then annually (1)[A]
- Monitor prostate heath (DRE/PSA) 3, 6, and 12 mo after initiating TRT, then annually (1)[A]
- In men with known osteopenia or osteoporosis, bone mineral density should be verified after 6, 12, or 24 mo of TRT (1)[C]
- Monitoring lipids and glycemia is not routinely required for safety but should be done as part of general health maintenance

Patient Resources

Urology Care Foundation AUA. www.urologyhealth.org/urology/index.cfm?article=132

REFERENCES

1. Dohle GR, Arver S, Bettocchi C, et al. Guidelines on male hypogonadism. Uroweb. 2012. Available at: http://www.uroweb.org/gls/pdf/16_Male_Hypogonadism_LR%20II.pdf (Accessed May 13, 2014)
2. Buvat J, Maggi M, Guay A, et al. Testosterone deficiency in men: Systematic review and standard operating procedures for diagnosis and treatment. *J Sex Med*. 2013;10:245–284.

ADDITIONAL READING

Hsiao W, et al. The role of testosterone replacement therapy in contemporary urological practice. *AUA Update*. 2008;27 Lesson 40.

See Also (Topic, Algorithm, Media)

- Andropause (Late-Onset Male Hypogonadism)
- Erectile Dysfunction/Impotence, General Considerations
- Hyperprolactinemia
- Hypogonadism, Society Definitions
- Infertility
- See Specific Syndromes: Kallmann, Klinefelter, Laurence–Moon, Prader–Willi, Sertoli only
- Testosterone (Free and Total) Lab Testing
- Testosterone Replacement Following Localized Prostate Cancer Therapy
- Testosterone Replacement Therapy, Prostate Cancer Risk
- Testosterone, decreased (hypogonadism)
- Testosterone, decreased (hypogonadism) Algorithm ↕

CODES

ICD9

- 257.2 Other testicular hypofunction
- V07.4 Hormone replacement therapy (postmenopausal)

ICD10

- E29.1 Testicular hypofunction
- Z79.890 Hormone replacement therapy (postmenopausal)

CLINICAL/SURGICAL PEARLS

- Treatment is usually indicated for men with both symptoms and lab evidence of low serum T.
- The risks and benefits of each TRT modality should be thoroughly discussed.
- Post-TRT initiation, patient monitoring for treatment effect, biochemical resolution, and development of adverse effects is critical.
- Patients who have completed prostate cancer treatment for localized disease cancer treatment may cautiously be initiated on TRT in certain circumstances.

TESTOSTERONE, DECREASED (HYPOGONADISM)

Philip T. Zhao, MD
Allen D. Seftel, MD

BASICS

DESCRIPTION

- Hypogonadism is the clinical syndrome associated with low serum testosterone (T)
  - Can occur in early age (early onset), although most commonly seen in aging males
  - Late-onset male hypogonadism may also be referred to as andropause, androgen deficiency in the aging male, or androgen deficiency syndrome
  - Usually associated with impaired sperm production; or with an isolated impairment of sperm production or function with normal T production.
- T is essential for:
  - Normal sexual function, growth and development of male sexual organs, and maintenance of male secondary sexual characteristics
- Normal levels and function result in:
  - Enhanced libido, increased energy, and production of RBCs; osteoporosis protection
- In utero hypogonadism
  - Ambiguous genitalia, normal female genitalia, microphallus, pseudovaginal perineoscrotal hypospadias, bifid scrotum, cryptorchidism
- Prepubertal hypogonadism:
  - Delayed puberty, microphallus, small testes, no male hair pattern, disproportionately long arms/legs, high-pitched voice, poor muscle mass
- Postpubertal/adult hypogonadism:
  - Lack of libido, erectile dysfunction (ED), hot flushes/sweats, gynecomastia, spermarche, infertility (oligospermia/azoospermia), poor vitality, depression, increased body fat/BMI, osteopenia/osteoporosis, hypercholesterolemia

EPIDEMIOLOGY

Incidence

N/A

Prevalence (1)

- 2–4 million men in US Hypogonadism increases with age
  - Overall 5.6–38.7% men are affected, depending on study
  - 6th decade: 12%; 7th: 19%; 8th: 29%; 9th: 49%

RISK FACTORS

- Testicular trauma/orchiectomy
- Medications
  - Decreased T production: Dopamine antagonists, corticosteroids, ethanol, ketoconazole, GnRH analogues/antagonists, metoclopramide
  - Decreased conversion of T to dihydrotestosterone (DHT): 5α-Reductase inhibitors
  - Androgen receptor blockade: Flutamide, spironolactone, cyproterone, cimetidine

- Infections (mumps orchitis, HIV)
- Medical conditions:
  - Iron toxicity to pituitary gonadotrophs, autoimmune diseases, endstage renal disease (ESRD)/uremia, histiocytosis X, pituitary apoplexy, myotonic dystrophy

Genetics

- Klinefelter syndrome
- Kallmann syndrome; mutation in Dax-1
- Laurence–Moon–Bardet–Biedl syndrome
- Prader–Willi syndrome
- Y chromosome microdeletion
- Congenital androgen resistance/insensitivity
- Alstrom, Rud, Bloom syndromes; mutations in leptin

PATHOPHYSIOLOGY

- T is regulated by the hypothalamic–pituitary–testicular axis
- Gonadotropin-releasing hormone (GnRH) neurons originate in the olfactory placode and migrate through the cribriform plate of the ethmoid to localize in the hypothalamus.
- Hypothalamus secretes GnRH, stimulates the pituitary to secrete leuteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- GnRH pulse amplitude and frequency activate intracellular signalling mechanisms, which results in differential gene expression of the 2 subunits forming LH and FSH.
- LH stimulates testis Leydig cells to produce T. Feedback inhibition by T on the hypothalamus and pituitary maintains hormonal balance.
- FSH stimulates Sertoli cells to support spermatogenesis and secrete inhibin, which provides feedback on the pituitary
- Week long night/day shift work does not seem to change T levels
- T levels decrease 0.8–1.6% per year in men aged 40–70

ASSOCIATED CONDITIONS

- Increased risk for developing type 2 diabetes mellitus, metabolic syndrome, cardiac events, and a general reduction in survival
  - Impact on cardiac events is controversial with most publications supporting a protective effect of “normal” T levels

GENERAL PREVENTION

Screening: The Endocrine Society in US recommends against screening for androgen deficiency in the general population.

DIAGNOSIS

HISTORY

- Development:
  - Genital abnormalities (eg, hypospadias, microphallus, cryptorchidism); delayed sexual development/growth; need for hormone therapy; family history of delayed puberty or reproductive disorders; psychological impact of delayed puberty or growth; difficulty in school or learning disability; inability or reduced ability to smell

- Sexual function:
  - Poor erections; reduced spontaneous, nighttime, morning erections; inability to perform sexually; decreased sexual activity; inability to father children despite unprotected sexual relations (>1 yr); small or shrinking testes
- Brain function:
  - Poor general well-being; reduced sexual desire, interest, and motivation (libido); poor energy/vitality; excessive fatigue; poor motivation and initiative, passivity, low self-confidence/self-esteem; depressed mood; irritability; difficulty sleeping; hot flushes/sweats; poor concentration and memory
- Body function
  - Decreased muscle bulk/strength; reduced physical activity or performance; breast enlargement/tenderness, especially if recent in onset; height loss, history of low trauma or vertebral compression fractures, osteopenia, or osteoporosis; body hair loss; reduced beard growth and shaving frequency.

PHYSICAL EXAM

- Assess height and eunuchoidal proportions:
  - Arm span >2 cm > height; heel–pubis >2 cm > pubis–crown normal
- Secondary sexual characteristics, gynecomastia, bone age determination
- External genitalia: Testis and phallus
  - Testis volume
    - Measure with a Prader orchidometer (normal adult 15–25 mL)
    - <6 mL characteristic of prepubertal hypogonadism
    - Soft and atrophic but normal sized suggestive of postpubertal hypogonadism
    - Small, firm suggests Klinefelter syndrome
  - Genital ambiguity; hypospadias/micropenis

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- There is no consensus among specialists (endocrinologists, urologists, pathologists) as to what lab values define a “low” T level.
- The Food and Drug Administration (FDA) uses a cutoff value of 300 ng/dL to define hypogonadism for clinical trial development and enrollment.
- Society definitions of T levels and hypogonadism are summarized in Section II: “Hypogonadism, Society Definitions”.
- Total T concentrations are affected by alterations in sex hormone-binding globulin (SHBG), and T levels may be suppressed transiently with illness, certain medications, and some nutritional deficiencies
- If an isolated serum T is low, measure an early morning total serum T, bioavailable T (useful in equivocal cases), and LH.
- If the morning T is low, check serum prolactin:
  - Prolactin elevated: Obtain MRI and consult with an endocrinologist
  - Prolactin normal/low: 1) LH elevated: Primary hypogonadism; 2) LH normal/low: Obtain serum FSH and evaluate causes of secondary hypogonadism in consultation with an endocrinologist

Imaging
MRI if lab suggests pituitary tumor

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
Atrophic testes in primary hypogonadism

DIFFERENTIAL DIAGNOSIS
- Hypergonadotropic hypogonadism (primary testicular failure); inadequate production of T despite adequate/elevated levels of LH/FSH:
  – Klinefelter syndrome (most common); congenital XXY karyotype (1 in 576 male births)
  – Impaired secretion of T and spermatogenesis
  – Cryptorchidism, varicocele, bilateral anorchia
  – Gonadal failure (chemotherapy/radiotherapy)
  – Inactivating mutations of GnRH or gonadotropin receptor
- Hypogonadotropic hypogonadism (secondary hypogonadism): Inadequate stimulation of production of testicular androgen/spermatogenesis (low FSH/LH associated with low T)
  – Kallmann syndrome: Abnormal migration of the GnRH neurons; anosmia and small testes
  – Adrenal hypoplasia congenita: Constitutional delay of growth and puberty
  – Chronic illness (celiac disease, Crohn disease, sickle cell, cystic fibrosis, diabetes)
  – Malnutrition, hyperprolactinemia, hypothyroidism
  – Hypopituitarism: Congenital vs. acquired (radiotherapy, CNS malignancy, infection, trauma)
  – Isolated gonadotropin deficiency
  – Congenital: Kallmann syndrome
  – Acquired: Intracranial neoplasm (craniopharyngiomas, gliomas, prolactinomas)
  – Syndromes with hypogonadotropism: See “Genetics” above

TREATMENT

GENERAL MEASURES
- Treatment should be guided by the intentions and desires of the patient.
- Avoid T replacement in a man with infertility seeking to regain fertility.
- Consider whether low serum T might be transient suppression caused by a critical, acute/subacute illness, or recovery from an acute illness; short-term use of certain medications; transient malnutrition; or excessive and chronic strenuous endurance exercise.
- A consensus statement from a group of professional societies (ISA, ISSAM, EAU, EAA, and ASA see Section II: “Hypogonadism, Society Definitions”) recommended (2,3):
  – T >350 ng/dL do not treat
  – T <230 ng/dL (with symptoms) may require T replacement therapy (TRT)
  – Levels between 230–350 ng/dL, the recommendation is to repeat the T with SHBG for calculation of free testosterone or direct measurement of free testosterone by equilibrium dialysis.
  – It has been previously recommended that men with T <200 ng/dL be treated as

hypogonadal; T >400 ng/dL be considered normal and those with TT 200–400 ng/dL be treated based on their clinical presentation if symptomatic.

- Hypogonadotropic hypogonadism:
  - Treat the underlying cause
  - TRT may still be required
- Hyperprolactinemia:
  - Discontinue offending medications
  - Dopamine agonists (bromocriptine)
- If fertility is not desired, TRT may be instituted.
- Obtain baseline digital rectal exam (DRE), CBC, lipid profile, PSA
  - T replacement may be associated with lipid abnormalities, polycythemia, azoospermia, sleep apnea, and possible prostatic changes.
- The overall goal of TRT is to correct or improve the clinical manifestations of androgen deficiency in men
- TRT agents/options outlined below
  - Transdermal agents may have best compliance; all provide uniform T level for 24 hr
  - Topical agents: Interpersonal transfer possible and should be avoided, especially for women and children
  - Gels should be dry before putting on clothes over application site; delay swimming
  - Brand names provided to avoid patient confusion; see FDA label for details

MEDICATION

First Line

- Buccal (Striant) 30-mg T/tab system
  - Dose: 30 mg BID
  - Avoids 1st-pass effect of hepatic inactivation
  - Apply to gum over incisor; do not chew/swallow
- Transdermal (Androderm): Apply to nonscrotal skin (back, abdomen, upper arms, thighs); avoid bony prominences; delivers 2- or 4-mg T/patch
  - Dose: Based on patch; start one 4 mg/patch/24 h; adjust to 1 or more patch combinations for desired effect
  - Skin irritation may be noted; remove for MRI
- Transdermal gels; product-specific dosing; apply clean dry: Shoulder, upper arm, or abdomen
  - (AndroGel 1%)
    - Dose: Topical daily 5–10 g (max)
  - (AndroGel 1.62%)
    - Dose: Topical 2 pump activations or 40.5-mg pack; adjust from 1 activation 20.25 mg or single 20.25-mg pack; 81 mg/d (max)
  - (Fortesta) 10-mg T/0.5 mg gel/activation; apply to inner thigh area only
    - Dose: Start 4 pump activations (40 mg) QAM; adjust 1–7 pump activations (10–70 mg daily; 70 mg max
  - (Testim 1%) 50-mg T/ 5 g gel; 50 mg/unit dose tube; apply shoulder or upper arm
    - Dose: Topical 5–10 g/d/2 tubes MAX
- Transdermal solution

- (Axiron) 30-mg T/1.5 mL of solution
  - Dose 60-mg T (1 pump = 30 mg of T solution to each axilla) daily; adjust based on levels

- IM short acting formulations; may be associated with fluctuations in serum T (supraphysiologic 2–5 days after injection, subphysiologic 10–14 days after injection) which may be associated with symptom fluctuation
  - T cypionate (Depo-Testosterone) 200–400 mg IM every 3–4 wk or 100–150 mg every 2 wk preferred
  - T enanthate (Delatestryl) 100–400 mg IM every 4 wk or 100–150 mg every 2 wk preferred
  - *Prepubertal boys*: 50–100 mg IM agent monthly or 25–50 mg every 2 wk, increase to 50–100 mg every 2 wk and then adult dose over 2–4 yr or until pubertal development occurs
- T implant
  - (Testopel) pellets (75 mg/each) 150–450 mg SC implant every 3–6 mo
  - 2 pellets for each 25-mg T required weekly; in upper buttock with local anesthesia
  - Local symptoms such as pain, bleeding
  - Pellet infection and extrusion (up to 10%)
  - T nasal gel (Natesto) 2 pumps each nostril (11 mg testosterone) one in each nostril TID (total 33 mg/day)
- T formulations outside US:
  - Oral T undecanoate: 40–80 mg PO with meals BID to TID
  - Parenteral T undecanoate: 1,000 mg IM initially, at 6 wk, then 1,000 mg every 10–14 wk; long lasting
  - T-in-adhesive matrix patch: 2 patches (4.8-mg T/d) applied every 2 days
  - T gel 2%: 3–4 g (60–80 mg of T) applied to abdomen or both inner thighs daily

Second Line

Any of the agents noted as First line can be potentially used a second line alternative agents

SURGERY/OTHER PROCEDURES

Pituitary adenoma: Transsphenoidal resection

ADDITIONAL TREATMENT

Radiation Therapy

- Pituitary microadenoma or macroadenoma (>1.0 cm):
  - Transsphenoidal resection ± radiation therapy

Additional Therapies

- If hypogonadotropic: May provide GnRH/gonadotropins to stimulate testicular production of androgen
- To initially stimulate T and sperm production:
  - Human chorionic gonadotropin (hCG): 500–2,000 IU given SQ 2–3x weekly to maintain serum T levels within the normal range for 6–12 mo
- Added to hCG to stimulate sperm production:
  - FSH/human menopausal gonadotropin (hMG), human FSH (hFSH), recombinant human FSH (rhFSH): After 6–12 mo of hCG treatment alone resulting in normal T levels, add FSH 75–300 IU is given SQ 3 times weekly for an additional 6–12 mo or longer
- To stimulate T/sperm production:

– GnRH: 5–25 ng/kg SQ every 2 hr by programmable infusion pump for 6–12 mo

Complementary & Alternative Therapies

- There are no alternative therapies that will cure hypogonadism
  – No data to support the use of over the counter or direct to consumer "natural" T supplements.
- Some stress management techniques can relieve the stress and anxiety associated with hypogonadism:
  – Yoga, meditation techniques, emotional support/counseling, healthy lifestyle (nutritious diet, active exercise, adequate rest)

ONGOING CARE

PROGNOSIS

Excellent ability to restore T levels to the normal range by adjusting dosage of medication and improve symptoms of hypogonadism (4)

COMPLICATIONS

- Hypogonadism (5):
  – "Metabolic syndrome": Anemia, increased fasting blood sugar, increased uric acid, increased cholesterol, increased body fat
  – Appetite changes (increased or decreased)
  – Balance problems
  – Body hair loss
  – Dry eyes
  – Edema or leg pain
  – Fatigue
  – GI and/or respiratory disturbances
  – Gynecomastia/breast tenderness
  – Hot flushes/flashes/sweats
  – Loss of libido/impotence
  – Muscle weakness/wasting
  – Osteoporosis
  – Psychologic: Depression, memory difficulties, emotional lability
  – Testicular atrophy
  – Weight gain/increased body fat
- T replacement:
  – Fluid retention
  – Gynecomastia
  – Hepatotoxicity
  – Sleep apnea
  – Theoretical risk of progression of prostate cancer: Unsubstantiated in recent studies

FOLLOW-UP

Patient Monitoring

- Every 3 mo (CBC, PSA, DRE) after starting treatment annually for response and adverse effects

- In men with known osteopenia or osteoporosis, bone mineral density should be verified after 6, 12, or 24 mo of TRT
- Monitoring lipids and glycemia is not routinely required for safety but should be done as part of general health maintenance

Patient Resources

- Guidelines on male hypogonadism (U.S. Department of Health & Human Services). http://guideline.gov/content.aspx?id=37626
- Urology Care Foundation AUA. www.urologyhealth.org/urology/index.cfm?article=132

REFERENCES

1. Morales A. Androgen deficiency in the aging male. In: Melmed S, Polonsky KS, Larsen PR, et al., eds. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, PA: Saunders; 2011:688–777.
2. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536–2559.
3. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol*. 2008;159:507–514.
4. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007;92:4241–4247.
5. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab*. 2008;93:68–75.

ADDITIONAL READING

Paduch DA, Brannigan RE, Fuchs EF, et al. The Laboratory Diagnosis of Testosterone Deficiency: AUA White Paper. Available at http://www.auanet.org/common/pdf/education/clinical-guidance/testosterone-deficiency-whitepaper.pdf. Accessed March 27, 2014.

See Also (Topic, Algorithm, Media)

- Hyperprolactinemia
- Hypogonadism, Society Definitions
- Infertility
- Kallmann Syndrome
- Klinefelter Syndrome
- Laurence–Moon–Bardet–Biedl Syndrome
- Prader–Willi Syndrome
- Testosterone (Free and Total) Lab Testing
- Testosterone Replacement Therapy, General Principles
- Testosterone, Decreased (Hypogonadism) Algorithm

CODES

ICD9

- 257.2 Other testicular hypofunction
- 792.2 Nonspecific abnormal findings in semen
- 799.81 Decreased libido

ICD10
- E29.1 Testicular hypofunction
- R68.82 Decreased libido
- R86.9 Unsp abnormal finding in specimens from male genital organs

CLINICAL/SURGICAL PEARLS

- Early morning serum total T below 300 ng/dL on at least 2 occasions in a symptomatic man usually confirms hypogonadism.
- Gonadotropins (LH and FSH) distinguish between a primary and a secondary cause.
- When caused by pituitary adenoma, patients can have additional symptoms due to mass effects, such as headaches or peripheral visual disturbance. There may also be signs and symptoms of other pituitary hormone deficiencies.
- Low T might be transient suppression (critical, acute/subacute illness, short-term use of certain medications; transient malnutrition; or excessive and chronic strenuous endurance exercise).

TORSION, TESTIS OR TESTICULAR/EPIDIDYMAL APPENDAGES

Julia S. Barthold, MD, FACS

BASICS

DESCRIPTION

- Torsion of the testicle or testicular/epididymal appendages results in vascular compromise to the testicle or 1 of the appendages.
- Impaired perfusion of the testis, appendix testis, or appendix epididymis is caused by spermatic cord (testicular) torsion or appendix torsion
- Presents as acute scrotal and/or inguinal pain with or without scrotal erythema and swelling
- Occurs primarily in children

EPIDEMIOLOGY

Incidence

- Most scrotal pain occurs at age 12–18
- Bimodal age distribution
  - Perinatal: Extravaginal testicular torsion
  - Prepubertal:
    - More commonly appendix torsion
    - Some data suggests this may be the most common cause of acute scrotal pain in children
  - Puberty: Peak incidence of intravaginal testicular torsion, but can occur at any age

Prevalence

1:4,000 males < 25 yo

RISK FACTORS

- Usually none
- Cryptorchidism
- History of contralateral torsion
- Familial clustering has been reported

Genetics

- Testicular torsion reported in 10% of family members; may be autosomal or X-linked recessive (1)
- No specific genetic defects identified

PATHOPHYSIOLOGY

- Testicular torsion can be either intravaginal or extravaginal
  - Intravaginal testicular torsion
    - Twisting of the spermatic cord *within* the tunica vaginalis
    - Due to congenital incomplete fixation of testis within the tunica vaginalis (bell-clapper deformity, see image)
    - Intermittent or sustained

- Impaired venous outflow, impaired arterial inflow, ischemia, potential testicular necrosis
- May progress to compartment syndrome
- Ischemia/reperfusion injury causes impaired spermatogenesis in animal models

• Extravaginal testicular torsion
– Twisting of both the spermatic cord *and* tunica vaginalis
– Due to incomplete fixation of the tunica vaginalis to the scrotum in the perinatal period
• Appendix torsion: Vascular compromise may be related to pedunculated anatomy of the appendage (image)
– Appendix testis (also known as hydatid of Morgagni)
- A vestigial Müllerian duct remnant present in majority of males (92%)
- Typical position: The superior testicular pole in the groove between the testicle and the epididymis.
- Accounts for 95% of appendage torsions

– Appendix epididymis
- A vestigial Wolffian duct remnant is less commonly present

– The paradidymis (organ of Giraldes) and the vas aberrans (organ of Haller) are 2 other appendages that are not clinically important.

ASSOCIATED CONDITIONS
• Bell-clapper deformity: 10–15% of males
• Cryptorchidism

GENERAL PREVENTION
• Reduce testicular necrosis risk by:
– Early diagnosis and treatment
– Community awareness about testis pain
– Elective bilateral orchidopexy for intermittent pain or contralateral orchidopexy at surgery for an episode of acute torsion

DIAGNOSIS

HISTORY
• Intravaginal testicular torsion
– Usually severe pain, sudden onset
– Nausea/vomiting more common
– May be recurrent usually same side
• Extravaginal testicular torsion
– Usually painless and asymptomatic
• Appendix torsion
– Usually more gradual but may be acute
– Pain may be mild or severe
– Nausea/vomiting uncommon
– No prior episodes
• Inguinal or abdominal pain may be associated or may be only site of pain in younger boys
• Irritative voiding symptoms possible
• History alone is suggestive only and often not reliable in differentiating testicular torsion,

appendix torsion, and other causes of scrotal pain

PHYSICAL EXAM

- Note: Phren sign (elevation of scrotum relieves pain in epididymitis but in torsion it is no longer considered reliable)
- Intravaginal testicular torsion: These are possible findings but these may be highly variable.
  - Early
    - Generalized testicular tenderness
    - Loss of ipsilateral cremasteric reflex
    - Elevated ipsilateral testis or transverse lie (look for this in intermittent testicular torsion cases)
    - Anterior epididymis
  - Late
    - Any of the above; increasing scrotal swelling and erythema
    - Loss of scrotal rugation ± hydrocele
    - Inability to distinguish epididymal landmarks
- Extravaginal testicular torsion
  - Firm to hard nontender testis
  - Scrotal discoloration
- Appendix torsion
  - Early
    - Localized tenderness superior to testis
    - Supratesticular nodule
    - Preserved ipsilateral cremasteric reflex
    - Normal testicular position and orientation
    - Blue dot sign: Rare, more likely in prepubertal boys; tender nodule with blue discoloration on the upper pole of the testis and more easily see in light-skinned individuals
  - Late
    - Any of the above
    - Generalized tenderness
    - Increasing scrotal swelling and erythema
    - Hydrocele

ALERT

- No H&P findings are completely reliable in diagnosis of the acute scrotum.
- Urgent surgery always needed if evaluation does not rule out the possibility of spermatic cord torsion.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - If pyuria suspect epididymitis/UTI
  - If hematuria consider renal or ureteral source of pain (eg, stone)
- Urine culture if indicated
- Additional labs not needed

Imaging

- Scrotal US with Doppler
  - Need to identify **waveforms** that originate in the central parenchyma
  - Intravaginal testicular torsion findings:
    - Usually shows decreased or absent arterial flow but may be normal
    - Increased flow possible in intermittent testicular torsion
    - Increased or mixed echogenicity suggests torsion: Compare both sides
    - Hydrocele and/or enlarged epididymis may be present
    - Visible twist of cord: Requires expertise but highly specific if present
  - Extravaginal testicular torsion findings:
    - Heterogeneous appearance typical
    - Doppler flow may be hard to demonstrate in neonatal testes
    - Calcification may be present
  - Appendix torsion findings:
    - Normal exam most common
    - Supratesticular complex mass w/o vascular flow may be present
    - Enlarged epididymis reported as “epididymitis” often present
    - Doppler flow normal or increased
  - Doppler flow normal
  - Thickened scrotal skin and hydrocele are nonspecific findings in acute scrotum cases
- Nuclear scan: Rarely performed

Diagnostic Procedures/Surgery

Exploration for diagnosis if equivocal findings on exam and/or US, suspicion of testicular rupture, or tumor

Pathologic Findings

- Testicular necrosis (intravaginal) or subtotal loss of tubules with calcification (extravaginal) testicular torsion
- Severity of injury depends on age, duration of testicular torsion, number of twists/thickness of spermatic cord
- In cases of appendicular torsion the necrotic tissue is reabsorbed usually without any sequelae

DIFFERENTIAL DIAGNOSIS

- Acute testicular pain
  - Appendix torsion most common in prepubertal boys
  - Testicular torsion most common in peripubertal boys but can occur at any age; less common than appendix torsion
  - Epididymitis due to UTI or STD: Rare or uncommon in pediatric age group; more likely in adult
  - Communicating hydrocele ± meconium
  - Incarcerated inguinal hernia
  - Trauma and possible testicular rupture
    - Hematocele present
  - Orchitis (eg, mumps)

- Henoch–Schönlein purpura
  - Rash usually present
- Fournier gangrene (rare in children)
- Referred pain from urolithiasis or intra-abdominal process such as appendicitis
- Orchalgia; consider voiding dysfunction

TREATMENT

GENERAL MEASURES

- Testicular torsion: Consider manual detorsion in ER
  - Not routine; consider if surgical delay
  - Most likely to be effective early in course
  - Sedation recommended
  - External rotation of testis when viewed from the feet ("opening a book")
  - Not always effective, 1/3 of cases may rotate laterally
  - Does not preclude need for immediate surgery
- Appendix torsion: Rest until pain resolves
  - Urgent re-evaluation if pain worsens or is recurrent

MEDICATION

First Line

- Ibuprofen to reduce inflammation in appendix torsion
- Antibiotics for UTI, STDs

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Testicular torsion
  - Emergent exploration indicated if evaluation suggests intravaginal testicular torsion or diagnosis is equivocal
  - Detorsion, observation for reperfusion, and bilateral orchidopexy via scrotal approach with fixation of testis extravaginally
  - Consider capsulotomy; if flow improves with placement of tunica vaginalis patch
  - Urgent exploration, bilateral fixation for extravaginal testicular torsion to avoid asynchronous contralateral torsion (2)
  - Avoid imaging/delay if findings are classic
  - Elective surgery for resolved intermittent testicular torsion (3)
  - Orchiectomy in antenatal extravaginal testicular torsion or if testis appears nonviable after detorsion ± capsulotomy
  - Consider delayed prosthesis placement for monorchia
- Appendix torsion
  - Prolonged pain not responsive to conservative measures
  - Recurrent episodes (rare) or diagnostic uncertainty

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Experimental agents such as nitric oxide (NOS) inhibitors to reduce reperfusion injury in testicular torsion not used clinically

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Intravaginal testicular torsion
  - Risk of postoperative atrophy increases with duration of torsion
  - Testicular loss 1st seen at 4 hr, increasing after 6 hr, 80% after 12 hr and essentially universal after 24 hr
  - Risk of subfertility unclear but probably higher after postpubertal torsion
- Extravaginal testicular torsion
  - No salvage in cases of antenatal torsion
  - Risk of contralateral torsion in the neonatal period low but present with contralateral fixation recommended
  - Long-term risks unknown but fertility potential presumed normal

COMPLICATIONS

- Recurrent testicular torsion: Rare, occurs with failure of absorbable or nonabsorbable suture fixation of a testis that remains within an intact tunica vaginalis
- Testicular atrophy

FOLLOW-UP

Patient Monitoring

- Follow for at least 6 mo to determine risk of atrophy
- Monitor for recurrent testicular pain
- Scrotal protection in contact sports
- Education of healthy adolescent populations about the signs/symptoms of testicular torsion and the benefits of early evaluation and treatment
- Specific educational focus on family members of affected individuals

Patient Resources

MedlinePlus: Testicular torsion.
http://www.nlm.nih.gov/medlineplus/ency/article/000517.htm

REFERENCES

1. Cubillos J, Palmer JS, Friedman SC, et al. Familial testicular torsion. *J Urol.* 2011;185:2469–2472.
2. Nandi B, Murphy FL. Neonatal testicular torsion: A systematic literature review. *Pediatr Surg Int.* 2011;27:1037–1040.
3. Eaton SH, Cendron MA, Estrada CR, et al. Intermittent testicular torsion: Diagnostic features and management outcomes. *J Urol.* 2005;174:1532–1535.

ADDITIONAL READING

- Mellick LB. Torsion of the testicle: It is time to stop tossing the dice. *Pediatr Emerg Care*. 2012;28:80–86.
- Sells H, Moretti KL, Burfield GD. Recurrent torsion after previous testicular fixation. *ANZ J Surg*. 2002;72:46–48.

See Also (Topic, Algorithm, Media)

- Appendix Testis and Appendix Epididymis, Torsion
- Scrotum, Tumors, Benign and Malignant
- Testis, Pain (Orchalgia)
- Testis, Tumor and Mass, Adult, General
- Testis, Tumor and Mass, Pediatric, General
- Torsion, Testis or Testicular/Epididymal Appendages Images ☼

CODES

ICD9

- 608.20 Torsion of testis, unspecified
- 608.23 Torsion of appendix testis
- 608.24 Torsion of appendix epididymis

ICD10

- N44.00 Torsion of testis, unspecified
- N44.03 Torsion of appendix testis
- N44.04 Torsion of appendix epididymis

CLINICAL/SURGICAL PEARLS

- Diagnosis of spermatic cord torsion requires a high index of suspicion, particularly in patients with intermittent testicular pain.
- Emergent surgery is indicated for all cases of suspected spermatic cord torsion.
- The risk of testicular loss increases after 4–6 hr of untreated spermatic cord torsion.

TRANSPLANT REJECTION, RENAL

Eric Langewisch, MD
Jason C. Hedges, MD, PhD

BASICS

DESCRIPTION

- The hallmark of renal transplant rejection is immunologic damage to the transplanted kidney due to donor-specific response by recipient immune system
- Classification of rejection:
  - Hyperacute (immediately after revascularization of the kidney graft)
    - Kidney becomes mottled and cyanotic usually in the OR
  - Accelerated (days to weeks after transplantation)
  - Acute (weeks to months after transplantation)
  - Chronic (months to years after transplantation)

EPIDEMIOLOGY

Incidence

15% rejection rate in 1st yr for those rejection-free at hospital discharge after transplantation

Prevalence

N/A

RISK FACTORS

- Presence of preformed human leukocyte antigen (HLA) antibodies
- Positive crossmatch between donor and recipient
- Previous transplant, pregnancy, blood transfusion
- Prior rejection episodes
- Delayed graft function
- African American race
- Noncompliance with immunosuppressant medications

Genetics

Greater degree of HLA mismatch between donor and recipient increases risk of rejection

PATHOPHYSIOLOGY (1)

- Hyperacute rejection: Mediated by preformed cytotoxic antibodies against kidney graft (develop after prior transfusion, transplantation, and child birth)
- Acute rejection: Most cases are acute cellular rejection (ACR) mediated by T-cell recognition of donor major histocompatibility (MHC) proteins that are presented by antigen-presenting cells (APCs) and T-cell activation. This results in mononuclear cell infiltration of interstitium, tubules (tubulitis), and endothelium (vasculitis)
- Acute antibody-mediated rejection (AMR) is mediated by circulating donor-specific antibodies (DSAs) to foreign donor HLA. Recipient antibodies bind to donor HLA, activate complement, and recruit inflammatory mediators.
- Chronic rejection: Fibrosis and atrophy from chronic allograft damage. Limited viable

allograft with active inflammation.

ASSOCIATED CONDITIONS

Common causes of end-stage renal disease: Diabetes, hypertension, glomerulonephritis, cystic renal disease

GENERAL PREVENTION

- Avoid incompatible donors for kidney transplant recipient. Avoid transplants across a positive crossmatch or with preformed DSAs.
- Induction immunosuppression with lymphocyte-depleting agents, especially for high immunologic risk recipients
- Compliance with immunosuppressant medications
- Monitor renal function and maintain therapeutic immunosuppressant drug levels
- Minimize sensitizing events (eg, blood transfusions and pregnancies)

DIAGNOSIS

HISTORY

- Medication noncompliance or tapering off immunosuppression for a failed allograft
- Often asymptomatic with plasma creatinine elevation as sole abnormality.
- Severe rejection may result in decreased urine output and pain over kidney transplant.
- Fluid retention/weight gain

PHYSICAL EXAM

- May be normal
- Increased blood pressure
- Volume overload
- May have tenderness over kidney transplant

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Rising BUN/plasma creatinine
  - Otherwise unexplained plasma creatinine rise >20% over baseline is suggestive of rejection.
- Urinalysis and urine culture
  - Rule out pyelonephritis.
- Determine drug levels (tacrolimus or cyclosporine)
  - 12-hr trough level (usually before morning dose)
  - Suspect calcineurin inhibitor (CNI: Tacrolimus or cyclosporine) toxicity if abnormally high levels
  - Target levels vary by patient and assay
- If antibody-mediated rejection (AMR) is suspected, test for donor-specific antibodies (DSAs)

Imaging

- Renal ultrasound
  - Rule out obstructive uropathy or stone.
  - Assess for diminished renal blood flow.
    - Color flow Doppler evaluates vascular status

– Detect graft swelling (with acute rejection; graft may be small with chronic rejection).
- Nuclear medicine renal scan:
  – Rejection: Decreased renal blood flow/glomerular filtration rate
  – Arterial or venous thrombosis: Decreased or absent perfusion. With complete obstruction, a reniform photopenic area can be seen
  – Acute rejection/acute tubular necrosis: Marked parenchymal retention with normal or mildly reduced perfusion. Rejection will show progressive decrease in function over time.

Diagnostic Procedures/Surgery
- Needle biopsy of transplant kidney (confirmation of rejection)
  – Usually under ultrasound guidance
  – Automated biopsy gun device, needle sizes 14–18 gauge
  – Adequate sample
    - ≥2 cores of cortex, ≥7 glomeruli, and ≥2 arteries required

Pathologic Findings
- Acute cellular rejection
  – Interstitial mononuclear cell infiltrate
  – Tubulitis
  – Vasculitis (in more severe cases)
- Acute antibody-mediated rejection
  – Pathology variable
  – Acute tubular necrosis (ATN)
  – Glomerulitis
  – Peritubular capillaritis
  – Fibrin thrombi
  – C4d staining (C4d is a complement split product that covalently binds to tissue indicating antibody-mediated complement activation)
- Chronic rejection
  – Interstitial fibrosis
  – Tubular atrophy

DIFFERENTIAL DIAGNOSIS
- Prerenal: volume depletion or hypotension
- CNI (calcineurin inhibitor) toxicity (tacrolimus or cyclosporine)
- Pyelonephritis
- ATN
- Technical complications
  – Arterial or venous thrombus,
  – Arterial stenosis
  – Ureteral obstruction or urine leak (early posttransplant)
- Obstructive uropathy
- Recurrence of original renal disease

TREATMENT

GENERAL MEASURES

- Attempt to reverse rejection with medical therapy
- Graft removal may be necessary in severe rejection eg, hyperacute rejection.

MEDICATION

First Line

- Acute cellular rejection: High-dose glucocorticoids
  - Methyl prednisolone IV or high-dose oral prednisone (eg, 5 mg/kg) for 3–5 days followed by taper to maintenance dosing
- Antibody-mediated rejection: Plasmapheresis and intravenous immune globulin (IVIG) ± rituximab in attempt to remove, neutralize, or prevent the production of DSAs, respectively
- Chronic rejection: No effective therapy.
- Hyperacute rejection: Remove transplanted kidney (2)[A]
  - Can result in DIC if not removed promptly

Second Line

- Acute cellular rejection: Lymphocyte-depleting agents such as antithymocyte globulin (ATG) or alemtuzumab may be given for severe rejection or rejection refractory to high-dose glucocorticoid therapy (3)[A].
  - Significant reactions possible with 1st doses including anaphylaxis, pulmonary edema, fever, hemodynamic instability
  - Must be inpatient for initiation of therapy
  - Pretreat with glucocorticoids, diphenhydramine, and acetaminophen
  - Monitor CBC for therapy-related leukopenia or thrombocytopenia (may be severe)
  - Consider prophylaxis against cytomegalovirus (CMV) (eg valganciclovir)
  - Continue maintenance immunosuppression

SURGERY/OTHER PROCEDURES

- Allograft nephrectomy
  - Remove a symptomatic, irreversibly rejected kidney transplant.
  - Remove an asymptomatic, chronically rejected kidney to withdraw immunosuppression and prevent further development of anti-HLA antibodies

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Severe rejection and graft failure may require acute dialysis

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Repeated episodes of acute rejection reduce allograft survival
- Relative risk of graft failure is 1.8 for patients who have had 1 episode of rejection

compared to none (4)

COMPLICATIONS

- DIC can accompany hyperacute rejection
- Graft loss can result from untreated or unrecognized rejection episode
- Cyclosporin toxicity can resemble mild acute rejection.
- Need to resume dialysis

FOLLOW-UP

Patient Monitoring (5)

- Compliance with anti rejection critical
- Therapeutic drug levels: Including monitoring of CNI toxicity
- Plasma creatinine
- Monitor for recurrence of native kidney disease (ie, diabetes, hypertension, etc.)
- Protocol transplant biopsies (optional)

Patient Resources

National Kidney Foundation. http://www.kidney.org/atoz/content/kidneytransnewlease.cfm

REFERENCES

1. Sunthanthiran M. Acute rejection of renal allografts: Mechanistic insights and therapeutic options. *Kidney Int*. 1997;51:1289–1304.
2. Sunthanthiran M, Strom TB. Mechanisms and management of acute renal allograft rejection. *Surg Clin North Am*. 1998;78(1):77–94.
3. Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: Updates and future directions. *Am J Transplant*. 2008;8(4):753–760.
4. Pallardó Mateu LM, Sancho Calabuig A, Capdevila Plaza L, et al. Acute rejection and late renal transplant failure: risk factors and prognosis. *Nephrol Dial Transplant*. 2004;19:iii38–iii42.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(suppl 3):S1–S155.

ADDITIONAL READING

- Brown ED, Chen MY, Wolfman NT, et al. Complications of renal transplantation: Evaluation with US and radionuclide imaging. *Radiographics*. 2000;20(3):607–622.
- Danovitch G. *Handbook of Renal Transplantation*. 5th ed. Lippincott Williams & Wilkins; 2009.

See Also (Topic, Algorithm, Media)

- Acute Kidney Injury, Adult (Renal Failure, Acute)
- Acute Kidney Injury, Pediatric (Renal Failure, Acute)
- Chronic Kidney Disease, Adult (Renal Failure, Chronic)
- Chronic Kidney Disease, Pediatric (Renal Failure, Chronic)
- Pyelonephritis, Adult

CODES

ICD9

996.81 Complications of transplanted kidney

ICD10

- T86.11 Kidney transplant rejection
- T86.12 Kidney transplant failure

CLINICAL/SURGICAL PEARLS

- Don’t confuse kidney transplant rejection with pyelonephritis.
- Cyclosporin toxicity can resemble mild acute rejection.

TRANSURETHRAL RESECTION (TUR) SYNDROME

Philip J. Dorsey, Jr., MD, MPH
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BASICS

DESCRIPTION

- Transurethral resection (TUR) syndrome is classically associated with TUR of the prostate (TURP) and is characterized by confusion, hypertension (HTN), bradycardia, and visual disturbances.
- Symptoms are caused by hypervolemia, dilutional hyponatremia, and solute effects from irrigant absorption during resection.
- While traditionally associated with prostate resection, it can also be seen in TUR of bladder tumor (TURBT) and has also been described for procedures such as hysteroscopy.
- Use of bipolar TURP and laser TURP techniques with normal saline irrigant has led to decreased incidence of TUR syndrome.
- Synonym(s): TURP syndrome

EPIDEMIOLOGY

Incidence

- 0.3–2% incidence (1)[B]
- Can occur as early as 15 min into resection or up to 24 hr after a TUR procedure
- Higher risk when hypotonic irrigation is used
- The declining use of TURP, because of medical management options, for the management of benign prostatic hypertrophy (BPH) has led to a reduction in the incidence of this syndrome

Prevalence

N/A

RISK FACTORS

- Resection time >60 min
- Gland size >45 g
- Intravesical pressures >30 mm Hg
- Operative technique (open venous sinuses, capsular perforations increase risk)
- Sympathetic blockade associated with spinal anesthesia may contribute to late hypotension.

Genetics

N/A

PATHOPHYSIOLOGY

- Irrigants used are osmotically active.
- Osmolarity of TUR irrigant solutions:
  - Normal serum: 280–310 mOsm/L
  - 5% mannitol: 275 mOsm/L
  - 1.5% glycine: 200 mOsm/L
  - 2.7% sorbitol/0.5% mannitol: 178 mOsm/L

  – 3% sorbitol: 165 mOsm/L
- Irrigant is absorbed by venous sinuses opened during resection or by slow absorption from the periprostatic and perivesical spaces in case of capsular perforation.
- As osmotically active solute enters the intravascular space, the plasma sodium concentration drops, leading to hypo-osmolality.

Volume effects:

- Increase in intravascular volume initially leads to hypervolemia, HTN, and reflex bradycardia; later hypotension can occur.
- Volume overload of the left ventricle may also lead to PE and respiratory failure.

ALERT
After 30–40 min of resection, flow from the intravascular space to peripheral tissues increases and can cause hypovolemia and hypotension (2)[B].

- Hyponatremia:
  – Caused by loading the intravascular space with nonelectrolyte solution
  – Contributes to CNS disturbances
  – If serum sodium levels rapidly decrease to <120 mEq/L, negative inotropic effects are manifested as hypotension and ECG changes of widened QRS complexes, ventricular ectopy, ST-segment depression, or T-wave inversions

Sodium Concentration	Symptoms
130–135 mEq/L	Asymptomatic
120–130 mEq/L	Restlessness, confusion
115–120 mEq/L	Nausea
<115 mEq/L	Seizures, coma

- Hypo-osmolality:
  – Blood–brain barrier is basically impermeable to sodium, but water crosses freely.
  – Osmotic gradient causes uptake of water by CNS tissue.
  – Resulting cerebral edema can exacerbate HTN and bradycardia via the Cushing reflex.
- Hypo-osmolar plasma results in RBCs taking on water, causing hemolysis.
- Renal failure secondary to hypotension and hemoglobinemia
- Hyperglycemia:
  – Glycine is a GABA-like inhibitory neurotransmitter.
  – Serum levels of glycine 17 times that of normal adults have been recorded in patients after TURP using glycine irrigant.

ALERT
Signs of glycine toxicity mimic the hyponatremic symptoms of the TUR syndrome (visual disturbances, nausea, vomiting, headache, malaise, and weakness) (3)[B].

- Glycine can cause visual disturbances and even transient blindness independent of hyponatremic or hypo-osmolar effects.
- Glycine may also have direct toxic effects on the kidney, possibly via metabolism to oxalate.
- Hyperammonemia:
  – Glycine is metabolized by the liver and kidneys to 2 potential toxins, glyoxylic acid and ammonia.

– Elevated serum ammonia may contribute to CNS derangement.

ASSOCIATED CONDITIONS

- BPH
- Bladder tumors

GENERAL PREVENTION

- Using irrigants such as glycine, sorbitol, and mannitol solutions reduces the hemolytic effects associated with sterile water irrigation.
  – Glycine is no longer recommended as an irrigation fluid.
- Intravesical pressure can be reduced by using continuous-flow equipment, draining the bladder with a suprapubic tube, or lowering the fluid height to <60 cm.
- If a significant extraperitoneal perforation occurs during the TURP or TURBT, it may be best to abandon the procedure after achieving hemostasis to prevent excessive fluid absorption.
- Appropriate selection of patients for TURP is based on gland size:
  – Limit resection time to <60–90 min.
  – Consider open prostatectomy, or other appropriate options, for adenoma >100 g measured by imaging studies.
- Judicious use of IV diuretics
- Use of bipolar resectoscopes to perform TURP allows for saline irrigation:
  – Reduces the hypo-osmotic effect of the absorbed fluid
- Use of laser energy sources for TUR management also decreases occurrence of TUR syndrome.

DIAGNOSIS

A patient who is slow to awaken from anesthesia or complains of visual disturbances should be considered to have the TUR syndrome following TURP.

HISTORY

- During TUR procedure: HTN and brachycardia may be a prodrome to rapid reduction in BP
- Postoperatively: No classic presentation, but patient may complain of any of the following:
  – Chest pain
  – Confusion
  – Headache
  – Itching
  – Lethargy
  – Nausea and vomiting
  – Shortness of breath

PHYSICAL EXAM

- Nonspecific physical findings: Although skin may be clammy
- Neurologic exam will reveal altered sensorium and confusion, but no focal signs

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum sodium <125 mEq/L
- Serum ammonia and glycine may be elevated if glycine solution is used

- Determine measured and calculated plasma osmolality:
  - Posm = 2 × plasma Na + (glucose)/18 + BUN/2.8
  - The difference between measured osmolality and calculated osmolality is known as the osmolality gap.
  - Normal osmolality gap: <5–10 mOsm/kg
  - Clinically significant gap is usually >14 and may be due to the presence of substances such as ethanol, ethylene glycol, or in this case irrigating solutions.
  - Osmolality gap can be >30–60 mOsm/kg following TUR due to the accumulation of glycine or sorbitol.

Imaging
- Cystogram or computed tomography (CT) cystogram in cases where perforation suspected to be cause of excess fluid absorption
- CT/MRI of brain to r/o cerebrovascular accident when other causes have been excluded

Diagnostic Procedures/Surgery
- ECG changes as noted above
- Arterial blood gas (ABG)

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Cerebrovascular accident
- Myocardial infarction
- Narcotic overdose
- Pulmonary embolism (PE)
- Seizure

TREATMENT

GENERAL MEASURES
- No specific therapy is necessary in the absence of symptomatology.
- Patients with normal renal function need no intervention to correct mild hyponatremia.
- Hemodynamic and cardiopulmonary support should be provided as needed.
- Vasoactive agents may be required to increase systemic vascular resistance in case of severe hypotension and circulatory collapse.

MEDICATION
First Line
- Furosemide:
  - Indicated to treat PE and hypervolemia when diuresis does not occur spontaneously
  - Furosemide: 20–100 mg IV
  - Water diuresis outpaces sodium diuresis, correcting both hypervolemia and hyponatremia.
  - Routine use to counteract fluid absorption is not supported by the literature.

Second Line
- Hypertonic saline:

  - Indicated for serum Na^+ <120 mEq/L or multiple symptoms
  - Na^+ deficit is calculated: (preop Na^+ - postop Na^+) for total body water (TBW)
  - TBW in males = 0.6 for weight in kg
  - Determine amount of 3% hypertonic saline (513 mEq/L) needed to correct deficit
  - Increasing serum Na by 0.5–1 mEq/L/h is considered a safe rate to avoid central pontine myelinolysis.
- In case of cerebral edema, more rapid correction is indicated, as the risk of brainstem herniation exceeds that of osmotic demyelination.

ALERT
Correcting sodium too quickly in hyponatremia can lead to central pontine myelinolysis and permanent neurologic injury. Recommended correction for life-threatening hyponatremia is no more than 1 mmoL/L/h in the ICU setting (4)[B].

SURGERY/OTHER PROCEDURES
Very rarely, decompression of a large retroperitoneal or pelvic irrigant collection is indicated in order to prevent further absorption of hypo-osmolar fluid.

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE
PROGNOSIS
- When recognized and treated early, prognosis is favorable.
- Mortality 0.2–0.8%
- If therapy is delayed and hyponatremia is severe, risk of significant morbidity and mortality.

COMPLICATIONS
- Cardiopulmonary collapse
- Central pontine myelinolysis
- Cerebral edema and brainstem herniation
- Seizures
- Transient blindness

FOLLOW-UP
Patient Monitoring
- Hemodynamic monitoring and close attention to serum electrolytes, especially sodium, is essential during and after procedure.
- Serial neurologic exams/mental status exams should be performed until symptoms improve.

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=144

REFERENCES

1. Mebust WK, et al. Transurethral prostatectomy: Immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol.* 1989;141:243–247.
2. Hahn RG. Fluid and electrolyte dynamics during development of the TURP syndrome. *Br J Urol.* 1990;66:79–84.
3. Hahn RG, Sandfeldt L, Nyman CR. Double-blind randomized study of symptoms associated with absorption of glycine 1.5% or mannitol 3% during transurethral resection of the prostate. *J Urol.* 1998;160:397–401.
4. Weissman JD, Weissman BM. Pontine myelinolysis and delayed encephalopathy following the rapid correction of acute hyponatremia. *Arch Neurol.* 1989;46:926–927.

ADDITIONAL READING

- Borboroglu PG, Kane CJ, Ward JF, et al. Immediate and postoperative complications of transurethral prostatectomy in the 1990s. *J Urol.* 1999;162:1307–1310.
- Hong JY, Yang SC, Ahn S, et al. Preoperative comorbidities and relationship of comorbidities With postoperative complications in patients undergoing transurethral prostate resection. *J Urol.* 2011;185:1374–1378.
- Mamoulakis C, Skolarikos A, Schulze M, et al. Results from an international multicenter double-blind randomized controlled trial on the perioperative efficacy and safety of bipolar vs monopolar transurethral resection of the prostate. *BJU Int.* 2012;109:240–248.

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Hyponatremia, Urologic Considerations
- Prostate, Benign Hyperplasia/Hypertrophy (BPH)

CODES

ICD9

- 276.1 Hyposmolality and/or hyponatremia
- 276.69 Other fluid overload
- 997.5 Urinary complications, not elsewhere classified

ICD10

- E87.1 Hypo-osmolality and hyponatremia
- E87.70 Fluid overload, unspecified
- N99.89 Oth postprocedural complications and disorders of GU sys

CLINICAL/SURGICAL PEARLS

- Diagnosis of the TUR syndrome requires high clinical suspicion.
- Prompt diagnosis, evaluation, and management are essential to prevent adverse events.
- If a significant extraperitoneal perforation occurs during the TUR, consider abandoning

procedure after achieving hemostasis to prevent excessive fluid absorption.

- Limit resection time to <60–90 min.
- Consider open prostatectomy, or other appropriate options (eg, laser assisted techniques), for adenoma >100 g.
- Use of bipolar resectoscopes to perform TURP permits use of saline irrigation reducing risk of TUR syndrome.

TROCAR INJURY DURING LAPAROSCOPY

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BASICS

DESCRIPTION

- Vascular or visceral injury during placement of trocars in laparoscopic surgery commonly referred to as "access injuries."
- Initial trocar placement is generally considered the most hazardous portion of minimally invasive surgery.
- Hemorrhage due to vessel injury and infection secondary to bowel injury, especially when diagnosis is delayed, are the most serious complications and the most likely to result in death.

EPIDEMIOLOGY

Incidence

- Vascular injury: 0.04–0.5%
- Visceral: 0.06%

Prevalence

N/A

RISK FACTORS

- Blind port placement
- Dilated viscus
- Inexperienced surgeon
- Prior intra-abdominal surgery
- Thin patient

Genetics

N/A

PATHOPHYSIOLOGY (1,2,3)

- During transperitoneal laparoscopy at risk structures are in proximity to port:
  - Umbilicus: Right common iliac artery
  - Upper midline: Aorta or vena cava
  - Right upper quadrant: Liver or gall bladder
  - Left upper quadrant (LUQ): Spleen or stomach
  - Pelvis: Bladder
  - Right and left lower quadrant: Epigastric vessels
- Bifurcation of the aorta and vena cava is generally at the level of the umbilicus or at the level of the anterior-superior iliac spine.
  - Direct perpendicular trocar or Veress needle entry created a situation whereby a great vessel (aorta, vena cava, common iliac artery, and vein) can be injured.
- Life-threatening gas embolism is rare and most often caused by direct insufflation of CO_2 gas

into a vessel by the Veress needle.
  – The 1st sign of intravascular insufflation is acute cardiovascular collapse. The diagnosis is usually made by the anesthesiologist based on an abrupt increase of end-tidal CO_2 accompanied by a sudden decline in oxygen saturation and then a marked decrease in end-tidal CO_2
- The bladder is most likely injured during initial trocar placement.
- Extraperitoneal laparoscopy decreases the risk of visceral and vascular injury.

ASSOCIATED CONDITIONS

- For urologic laparoscopy the underlying indication for the laparoscopy:
  – Malignancy (kidney, prostate, testicular, ureteral, bladder)
  – Obstruction: Ureteropelvic junction obstruction
  – Masses: Adrenal, retroperitoneal
  – Others: Lymphocele, hernia

GENERAL PREVENTION

- Hasson technique ("cut down," or "open trocar placement") for initial access; allows direct visualization of peritoneum.
- Use of visual obturator trocar for primary port placement.
- Use of a nonbladed port for all ports.
- Utilization of confirmatory testing to insure proper placement of initial Veress needle before full insufflation (4):
  – Aspiration of colored (red, yellow, green, brown) or malodorous fluid suggests improper placement.
  – *Drop test*: Apply a drop of saline inside the hub of the needle and lift the abdominal wall. If in proper position, the drop will enter the abdomen due to the negative intraperitoneal pressure.
  – *Advancement test*: If the needle has truly just entered the peritoneal cavity, then the surgeon ought to be able to advance the needle 1 cm deeper without the tip meeting any resistance.
  – *Modified Palmer test*: Inject 10 mL of saline into the needle and attempt to aspirate. Inability to aspirate the fluid suggests that the fluid has dispersed into the abdomen and the needle is in correct position.
  – *Initial pressure reading <8 mm Hg*. The insufflator is turned on with no flow to obtain a pressure reading.
    ◦ A decrease in pressure with elevation of the abdominal wall.
  – If perforation of a viscus occurs, the needle should be removed and discarded. A new needle may then be inserted at another location or the surgeon may choose to obtain open access using the Hasson technique. The injury should be observed laparoscopically or through open intervention if there is any concern over the degree of injury
- Utilizing a LUQ insertion site (Palmer point), located 3 cm below the middle of the left costal margin, for primary port
  – Patients with a history of prior abdominal surgery should be a 1st-line option to eliminate major vessel injury and entry injuries into the bowel which might adhere to a previously made lower abdominal incision

- Angle ports at insertion to 45° into the pelvis; critically important in very thin patients
- Increase pneumoperitoneum to 20–25 mm Hg during port placement to increase tension of abdominal wall and decrease posterior displacement during trocar insertion
- Ensure adequate skin incision for trocar size to avoid excess insertion pressure
- Stabilize abdominal wall when inserting trocar
- Direct vision of secondary port placement and transillumination of abdominal wall to avoid more superficial vessels.
- Bladder catheter placement
- Nasogastric tube placement
- Surgeons should completely familiarize themselves with a new trocar device or design before 1st-time use.
- Visualization of port removal can help identify unrecognized anterior abdominal wall vascular injury.

DIAGNOSIS

HISTORY

Prior abdominal surgery records should be reviewed if appropriate

PHYSICAL EXAM

- Intraoperative findings that suggest trocar injury:
  - Blood in the port after initial placement
  - Bile in the port after initial placement
  - Retroperitoneal hematoma on initial abdominal inspection
  - Air in the bladder catheter bag after initial trocar
  - Drip of blood form trocar
    - Visualization of port removal can help identify unrecognized anterior abdominal wall vascular injury
  - Drop pneumoperitoneum to 5 mm Hg at the end of the case to uncover possible significant small vessel or venous bleeding.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Sudden unexplained drop in blood pressure at the beginning of the case consistent with unrecognized major vascular injury
  - Need to differentiate from insufflation causing compromised blood pressure

Imaging

Not usually used acutely

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

Serosal tear in viscera without mucosal violation

TREATMENT

GENERAL MEASURES

- In general Veress needle injuries often heal with conservative management whereas trocar injuries or gross spillage of bowel contents require formal repair
- Direct injury may be observed laparoscopically or during conversion laparotomy
- Abdominal wall/epigastric vessel bleeding may be recognized after ports are removed under direct visualization
- If a port is placed into a major vessel, do not remove but keep in place during laparotomy
  - During an emergent open conversion, use anteriorly deflected port or laparoscope to cut down into abdomen (unless in major vessel)

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Laparoscopic or open repair of injury
  - Always have open tray available for each case
- If the Veress needle aspiration returns frank blood or other fluid (5)
  - Consider leaving the needle in place to help tamponade and identify the injury site
  - If the patient is unstable due to a presumed major vascular injury, immediate laparotomy is indicated
  - If the patient is stable, consider an alternate access site and laparoscopically evaluate the site.
- For abdominal wall bleeding:
  - Clip or electrocautery
  - Intra-abdominal suture placement under laparoscopic guidance.
  - Transcutaneous suture placement using Endo Close or other technique used to close the fascia.
  - Acute placement of Foley inflated to tamponade bleeding.
- For gas embolism (4):
  - Immediate cessation of insufflation and prompt desufflation of the peritoneal cavity.
  - The patient is turned into a left lateral decubitus position and hyperventilated with 100% oxygen.
  - Advancement of a central venous line into the right heart with subsequent attempts to aspirate gas may sometimes be helpful.
- Bladder injury:
  - Veress needle injury can usually be managed by bladder catheter for 7–10 days.
  - More significant injury requires 2-layer closure with absorbable suture and catheter drainage.
- Bowel injury:
  - Requires further inspection and repair either laparoscopically or via laparotomy.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Correction of any coagulopathy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent if injury is recognized and managed quickly.
- Delayed or unrecognized visceral injury can lead to significant morbidity or mortality.
  - Many bowel injuries are not recognized initially and typically present with peritonitis.

COMPLICATIONS

Unrecognized injury can lead to ongoing hemorrhage, infection

FOLLOW-UP

Patient Monitoring

Dependent on injury and management.

Patient Resources

MedlinePlus: Diagnostic laparoscopy.
http://www.nlm.nih.gov/medlineplus/ency/article/003918.htm

REFERENCES

1. Ghavamian R, ed. Complications of Laparoscopic and Robotic Urologic Surgery. New York, NY: Springer. 2010. ISBN 978-1-60761-675-7
2. Ahmad G, O'Flynn H, Duffy JM, et al. Laparoscopic entry techniques. *Cochrane Database Syst Rev*. 2012;2:CD006583.
3. Pickett SD, Rodewald KJ, Billow MR, et al. Avoiding major vessel injury during laparoscopic instrument insertion. *Obstet Gynecol Clin North Am*. 2010;37(3):387–397.
4. Bandi G, Gomella LG. Basic Laparoscopy In: Graham S, ed. *Glenn's Operative Urology*. 7th ed. Philadelphia, PA: LWW; 2010.
5. Ponsky L, Matin SF. Chapter 28. Special considerations in laparoscopy. In: Taneja SS, ed. *Complications of Urologic Surgery*. 4th ed. Philadelpia, PA: Saunders; 2010.

ADDITIONAL READING

Chandler JG, Corson SL, Way LW, et al. Three spectra of laparoscopic entry access injuries. *J Am Coll Surg*. 2001;192(4):478–490.

See Also (Topic, Algorithm, Media)

- Hypercarbia During Laparoscopy
- Rectal Injury During Radical Prostatectomy or Radical Cystectomy
- Trocar Injury During Laparoscopy Image

CODES

ICD9

- 868.19 Injury to other and multiple intra-abdominal organs, with open wound into cavity
- 902.9 Injury to unspecified blood vessel of abdomen and pelvis
- 998.2 Accidental puncture or laceration during a procedure, not elsewhere classified

ICD10

- K91.72 Acc pnctr & lac of a dgstv sys org during oth procedure
- S35.91XA Laceration of unspecified blood vessel at abdomen, lower back and pelvis level, initial encounter
- S36.90XA Unspecified injury of unspecified intra-abdominal organ, initial encounter

CLINICAL/SURGICAL PEARLS

- Drop pneumoperitoneum to 5 mm Hg at the end of the case to uncover possible significant small vessel or venous bleeding.
- Remove ports under direct visualization to detect latent abdominal wall/epigastric vessel bleeding.
- During an emergent open conversion, use anteriorly deflected port to cut down into abdomen (unless port in major vessel).
- Have open tray available for each laparoscopy case.

TUBERCULOSIS, GENITOURINARY, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Genitourinary tuberculosis (TB) refers to urinary and GU infection with *Mycobacterium tuberculosis*. Common GU sites include the kidney, ureter, bladder, prostate, and testis/epididymis.
- GU tract is 2nd most common site after lungs for tuberculous infection. Urogenital TB represents 27% of extrapulmonary cases (1).
- Tubercle bacilli found in 7–29% of urine in patients with extrarenal TB.
- In 1882, the bacillus causing TB, *M. tuberculosis,* was 1st identified and described by Robert Koch.
- 10% of TB is extrapulmonary with GU locations accounting for 33% of these sites and these rates double in developing countries.
- TB is 2nd only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent.
- In 2010, there were about 10 million orphan children as a result of TB deaths among parents.
- TB is a leading killer of people living with HIV causing one-quarter of all deaths.
- Although declining, multidrug-resistant TB (MDR-TB) is present in virtually all countries surveyed.
- The world is on track to achieve the Millennium Development Goal to reverse the spread of TB by 2015.
- The TB death rate dropped 41% between 1990 and 2011.

EPIDEMIOLOGY

Incidence

- 1/3 of the world's population are infected with TB.
- In 2011, 8.7 million people fell ill with TB and 1.4 million died from TB.
- Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 3 causes of death for women aged 15–44.
- About 1/3 of the world's population has *latent* TB and can transmit infection.

Prevalence

In US, the peak surge in 1992 of reported TB cases has steadily declined to about half its peak value.

RISK FACTORS

- Health care providers
- Immunosuppression (eg, HIV)
- TB is spread from person to person through the air.

- Smoking

PATHOPHYSIOLOGY

- Hematogenous spread to kidneys from pulmonary disease proved by Medlar, et al. in 1949
- 2–12 wk often ensue before mycobacterial numbers are sufficient to mount a clinically detectable cellular immune response.
- *M. tuberculosis* infections acquired by inhalation of aerosolized droplet nuclei (1–5 μm), which reach pulmonary alveoli
- Invasion of GU organs by ascent (prostate to bladder) or descent (kidney to bladder, prostate to epididymis)
- Kidney and epididymis are primary sites of TB infection in the GU tract in men, and fallopian tubes in women.
- Tuberculomas develop in glomerular capillaries as a result of hematogenous seeding from lungs.
- Renal TB may take years to develop in patients with normal immune system.
- Normal renal parenchyma is slowly replaced by caseous material; calcium is laid down as part of the reparative process.
- Adrenal TB is seen in $<6\%$ of active TB cases (up to 56% of patients with adrenal TB will have a subnormal cortisol response to corticotrophin stimulation).

ASSOCIATED CONDITIONS

- Chronic TB infection
- Immunocompromised states (eg, AIDS)
- Malnutrition
- Poor living conditions/poverty/drug use

GENERAL PREVENTION

- Diagnose and treat patients with TB before development of active disease.
- Take careful precautions with patients hospitalized with TB (N95 mask, negative pressure room flow)
- Test annually with PPD if at high risk for exposure.
- Females of the childbearing age should be advised to avoid pregnancy while on antituberculous treatment.

DIAGNOSIS

HISTORY

- Initial symptoms may be minimal, even in presence of extensive disease. No classical clinical picture, most symptoms are of bladder/lower urinary origin.
- History or exposure to TB; determine last PPD testing results; latency can be >20 yr after primary TB.
- Vague, intermittent, nonspecific complaints such as malaise, lethargy, weight loss, and low-grade fevers common.
- Men commonly present with epididymitis.
- Bacterial cystitis may be superimposed on bladder TB. Common to see recurrent UTIs with *Escherichia coli*
- Dysuria from seeding of the bladder with TB

- Chronic cystitis unresponsive to therapy
- Urinary tract involvement occurs in up to 50% of transplant recipient cases. PPD skin testing may be falsely negative in 70% of cases due to anergy.

PHYSICAL EXAM

- Physical exam is often of limited value in the diagnostic process, because physical signs develop late in the disease. The most common physical finding is an abnormal scrotal exam in about half the patients.
- Suprapubic pain when disease is extensive
- Painful swollen testis
- Chronic draining scrotal sinuses should be considered TB until proven otherwise.
- Nontender, enlarged epididymis with beaded or thickened vas deferens
- Nodular, indurated prostate and thickened seminal vesicles on rectal exam mimic neoplasm.
- Upper abdominal bruit may be indication of advanced renal disease.
- Up to 25% of patients will present only with sterile pyuria and 13% might have gross or microscopic hematuria as their only presentation

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Routine urine analysis (13% might have gross or microscopic hematuria as their only presentation), plus standard culture
- Sterile pyuria classic finding (25%); typically >20 WBC/HPF.
- 20% of patients will also have bacterial cystitis or urinary tract infection with *E. coli.*
- Specific staining of urine for acid-fast bacteria and mycobacterial culture is gold standard:
  - Ziehl–Neelsen or Kinyoun acid-fast stain; more rapid fluorochrome (fluorescence microscopy) procedure 1st morning specimen has highest yield of tubercle bacilli.
- Minimum 3 and up to 6 early-morning urine specimens are recommended, as TB organisms shed into urine intermittently.
- Acid-fast stains from 24-hr urine specimen are positive in 60% of cases.
- High index of suspicion for persistent pyuria without bacteria on repeated cultures (stain with methylene blue)
- PCR assay may identify organisms
- CBC, electrolytes, ESR: Measure monthly as indicator of response to therapy
- 88% have positive skin tests of PPD
- Heavy proteinuria in a patient with TB suggests secondary involvement of the kidney with amyloid.

Imaging

- Chest x-ray: Abnormal in 75%
- KUB: Enlargement of 1 kidney
- Punctuate calcifications in renal parenchyma
- Large calcified structures in prostate
- Renal stones in 10%
- Obliteration of psoas shadow due to perinephric abscess
- Excretory urogram: Considered a mandatory study; moth-eaten appearance in ulcerated calyces; dilation of upper tract secondary to ureteral stricture; obliteration of calyces

- Loss of kidney function due to complete occlusion or renal destruction
- Retrograde pyelography with selective culture for TB; assessment of ureteral stricture
- CT is an option if IVP contraindicated: Useful in delineating disease in seminal vesicles; limited value in early management

Diagnostic Procedures/Surgery

- Tuberculin skin test: Induration >10 mm in diameter is considered positive reaction; >5 mm in high-risk patient. Positive reaction indicates exposure, not necessarily active disease; – May be negative in a patient with miliary TB, AIDS, or advanced age.
- Negative tuberculin skin test makes diagnosis of TB unlikely.
- Must not have had BCG vaccine or therapy in the past due to false-positive effect
- Cystoscopy: TB appears as a patchy erythematous ulceration with exudate.
- TB may mimic urothelial carcinoma including carcinoma in situ (CIS).

Pathologic Findings

- Microscopically, the inflammation produced with TB infection is granulomatous, with epithelioid macrophages and Langhans giant cells along with lymphocytes, plasma cells, maybe a few PMN's, fibroblasts with collagen, and characteristic caseous necrosis in the center.
- The inflammatory response is mediated by a type IV hypersensitivity reaction which can be utilized as a basis for diagnosis by a TB skin test.
- An acid-fast stain (Ziehl–Neelsen or Kinyoun acid-fast stains) will show the organisms as slender red rods.
- An auramine stain of the organisms as viewed under fluorescence microscopy will be easier to screen and more organisms will be apparent.

DIFFERENTIAL DIAGNOSIS

- Amicrobic cystitis
- BCG sepsis/BCGosis
- Chronic nonspecific cystitis or pyelonephritis
- Disseminated coccidioidomycosis
- Granulomatous prostatitis; prostate cancer
- Medullary sponge kidney
- Necrotizing papillitis
- Nonspecific epididymitis
- Renal stones or nephrocalcinosis
- Urinary bilharziasis (schistosomiasis)

TREATMENT

GENERAL MEASURES

- Quarantine until on appropriate medications
- Screen close contacts

MEDICATION

First Line (2)

- Antituberculous drugs are 1st choice: Isoniazide, rifampicin, pirazinamide, ethambutol, and

streptomycin.
- Patient with uncomplicated TB infection: Isoniazid (300 mg/d), rifampin (450–600 mg/d), and pyrazinamide (25 mg/kg/d) once a day in the morning, 3 times a week, for 2–4 mo, followed by isoniazid and rifampin once a day, 3 times a week, for an additional 2–4 mo. (add 1 g of vitamin C, 3 times a week, for 4 mo with above regimen).

Second Line
- Patient with complicated TB infection: Add streptomycin to the above for severe infection or severe bladder symptoms.
- Drug resistance is increasing and necessitates tight therapy control, expanded antibiotic regimen of 4 of the following: Ethionamide, prothionamide, quinolones, clarithromycin, cycloserine, kanamycin, viomycin, capreomycin, thiacetazone, and para-aminosalicylate.
- Steroids: No role in initial therapy but can be used for acute TB cystitis or stricture at distal ureter (prednisone 20 mg PO TID)

SURGERY/OTHER PROCEDURES
- Nephrectomy for symptomatic (HTN, obstruction, pyelonephritis) nonfunctioning kidney with extensive disease or coexistent renal cell carcinoma.
- Perform 4–6 wk after start of antituberculous drugs
- Epididymectomy: Indicated for caseating abscess unresponsive to chemotherapy
- Ureteral strictures: Stenting vs. reconstruction
- Bladder augmentation: Small capacity, fibrotic bladder.
- Surgery not necessary for TB abscesses: Treat medically

ONGOING CARE

PROGNOSIS
- Awareness of renal TB is urgently needed by physicians to suspect this disease in patients with unexplained urinary tract abnormalities, mainly in those with any immunosuppression and those coming from TB-endemic areas (1).
- No specific statistics, but overall patients can do well with appropriate, early antituberculosis medications and surgical interventions.

COMPLICATIONS
- Ureteral TB: Stricture formation, hydronephrosis
- Complete nonfunctioning of an affected kidney (“autonephrectomy”) described
- Renal TB: Obliteration of the renal and psoas shadow on plain radiographs, perinephric abscess may cause an enlarging mass in the flank.
- Genital TB: Sterility a consequence
- An abscess of the epididymis may erode through the scrotal wall or testis, creating a sinus tract and drainage.
- Bladder TB: Stenosis of ureterovesical junction, fibrosis, and contraction of bladder
- Nephrotoxicity induced by antimicrobial agents (especially rifampin)

FOLLOW-UP
- Completion of TB regimens long term is essential.
- Strictures can evolve after organism is eradicated.

- Follow regularly after completion of therapy as stricturing can continue: 3, 6, 9, 12 mo with urine culture and TB staining and excretory urography.
- Need long-term imaging follow-up of calcifications if present.

REFERENCES

1. Daher Ede F, da Silva GB Jr, Barros EJ. Renal tuberculosis in the modern era. *Am J Trop Med Hyg.* 2013;88(1):54–64.
2. The Medical Letter: Drugs for tuberculosis. *Treat Guidel Med Lett.* 2004;2(28):83–88.

ADDITIONAL READING

- de Figueiredo AA, Lucon AM, Srougi M. Bladder augmentation for the treatment of chronic tuberculous cystitis. Clinical and urodynamic evaluation of 25 patients after long term follow-up. *Neurourol Urodyn.* 2006;25(5):433–440.
- Fischer M, Flamm J: The value of surgical therapy in the treatment of urogenital tuberculosis. *Urologe A.* 1990;29(5):261–264.
- Gow JG, Barbosa S. Genitourinary tuberculosis. A study of 1117 cases over a period of 34 years. *Br J Urol.* 1984;56(5):449–455.
- Wise GJ, Marella VK. Genitourinary manifestations of tuberculosis. *Urol Clin North Am.* 2003;30:111–121.

See Also (Topic, Algorithm, Media)

- Bacteruria and Pyuria
- BCG Sepsis/BCGosis
- Prostatitis, Granulomatous
- Prostatitis, Tuberculous
- Tuberculosis, Bladder, and Urethra
- Tuberculosis, Genitourinary, General Considerations Image
- Tuberculosis, Kidney, and Ureter
- Tuberculosis, Male External Genitalia

CODES

ICD9

- 016.00 Tuberculosis of kidney, unspecified
- 016.10 Tuberculosis of bladder, unspecified
- 016.90 Genitourinary tuberculosis, unspecified, unspecified

ICD10

- A18.10 Tuberculosis of genitourinary system, unspecified
- A18.11 Tuberculosis of kidney and ureter
- A18.12 Tuberculosis of bladder

CLINICAL/SURGICAL PEARLS

- Chronic draining scrotal sinuses should be considered TB until proven otherwise.
- Sterile pyuria is the classic finding, typically >20 WBC/HPF.

- Renal involvement by TB infection is underdiagnosed in most health care centers.
- Posttreatment follow-up is essential as strictures can evolve after organism is eradicated.

TUBERCULOSIS, KIDNEY AND URETER

Mohamed S. Ismail, MBChB, MRCS, PhD
Jayram Krishnan, DO, MBA

BASICS

DESCRIPTION

- *Mycobacterium tuberculosis* (TB) may affect the urinary system including the kidney and ureter
- Most TB occurs in the lung but 15% occurs in extrapulmonary sites
  - GU system is the most common extrapulmonary site
    - Kidneys are the most common GU site

EPIDEMIOLOGY

Incidence

- Worldwide—9.27 million worldwide (140 per 100,000) (2007)
- US—12,904 cases (4.2 per 100,000) (2008)

Prevalence

- GU TB:
  - Developed countries—2–10%
  - Developing countries—15–20%
- Male > female (2:1) (1)[C]
- Mean age 40.7 yr (1)[C]

RISK FACTORS

- Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)
- Chronic dialysis patients
- Immunocompromised states (renal transplants)
- Foreign travel

PATHOPHYSIOLOGY

- *M. tuberculosis* infections are acquired by inhalation of aerosolized droplet nuclei which reach the pulmonary alveoli
- Hematogenous spread to kidneys from pulmonary disease
  - Tuberculomas develop in glomerular capillaries as a result of hematogenous seeding
  - Normal renal parenchyma is slowly replaced by caseous material and calcium is laid down as part of the reparative process
  - Renal papilla involvement results in sloughing and caseous material gaining access to the collecting system by calyceal ulceration
  - Extensive fibrosis with healing tubercles results in disfiguration and hydronephrosis with obstruction
- Ureteral involvement is almost always from direct extension from the kidney
  - Mycobacteria caseous material leads to tubercle formation within the ureteric mucosa
  - This usually affects the lower ureter and the ureterovesical junction with the middle and

upper ureter less commonly affected (2)[C]
  - Dense fibrosis on the ureteric serosa leads to stricture formation and/or shortening in 50% of patients with renal involvement
- Secondary amyloidosis can be found; often resulting in proteinuria and nephrotic syndrome

ASSOCIATED CONDITIONS
- Chronic TB infection
- Immunocompromised states (HIV/AIDS)
- Malnutrition
- Poor living conditions/poverty

GENERAL PREVENTION
- Diagnose and treat patients with TB before development of active disease
- Take careful precautions with patients hospitalized with TB
- Test annually with the purified protein derivative (PPD) skin test if at high risk for exposure

DIAGNOSIS
HISTORY
- Often mimics a wide range of nonspecific urologic symptoms and are often minimal even with extensive disease
- History or exposure to TB; determine last PPD test results; latency can be >20 yr after primary TB
- Vague, intermittent, nonspecific complaints such as malaise, lethargy, weight loss, and low-grade fevers common
- Men commonly present with epididymitis
- Bacterial cystitis may be superimposed on bladder TB. Common to see recurrent urinary tract infections with *Escherichia coli*
- Dysuria from seeding of the bladder with TB
- Chronic cystitis unresponsive to therapy

PHYSICAL EXAM
- Significant physical signs develop late and with extensive disease
- Storage symptoms are the most common overall presentation (50.5%) (1)[C]
  - Hematuria (35.6%) (1)[C]
  - Lumbar pain (34.4%) (1)[C])
  - Most common physical finding in men is an abnormal scrotal exam (49.8%) (1)[C]
    - Scrotal lumps, epididymal hardening, or draining scrotal fistulas
- Upper abdominal bruits may indicate advanced renal disease

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis and culture:
  - Classic finding: Sterile pyuria (>20 white blood cells/high power field)
  - 20% of patients will also have bacterial cystitis or urinary tract infection with *E. coli*
  - 13% of patients will present with gross or microscopic hematuria (3)[C]
- **GOLD STANDARD:** Specific staining of urine for acid-fast bacteria and mycobacterial

culture
  - Nonpathogenic mycobacteria can also stain positive, so culture more useful
  - Ziehl–Neelsen or Kinyoun acid-fast stain; more rapid fluorochrome (fluorescence microscopy) procedure
  - 1st morning urine specimen has highest yield of tubercle bacilli
  - Minimum 3 and up to 6 early-morning urine specimens are recommended, as TB organisms shed into urine intermittently
  - 64.2% of patients had *M. tuberculosis* in their urine (1)[C]
  - High index of suspicion for persistent pyuria without bacteria on repeated cultures (stain with methylene blue)
- Polymerase chain reaction (PCR) assay may identify organisms
- Complete blood count and electrolytes
  - Renal failure is present in 7.4% of cases (creatinine >1.5) (1)[C]
    - Functional loss of the affected kidney can be present in up to 25% of cases (1)[C]
- Erythrocyte sedimentation rate (ESR):
  - Measure monthly as indicator of response to therapy
- Heavy proteinuria may suggest secondary involvement of the kidney with amyloid

Imaging
- Chest radiograph: Abnormal in 75%
- Abdominal radiograph:
  - Enlargement of 1 kidney
  - Renal stones in 10%
  - Focal punctate calcifications occur within the caseating lesions in renal parenchyma
  - Obliteration of psoas shadow due to perinephric abscess
  - Characteristic diffuse, uniform, extensive parenchymal calcifications are present with lobar cast of the kidney (autonephrectomy)
- Excretory urogram:
  - Moth-eaten appearance in ulcerated calyces (4)[C]
  - Dilation of upper tract secondary to ureteral stricture (4)[C]
  - Obliteration of calyces
  - Loss of kidney function due to complete occlusion or renal destruction
- Computed tomography (4)[C]:
  - Most common finding: Renal parenchymal scarring (76%)
  - Hydrocalycosis, hydronephrosis, or hydroureter due to stricture (67%)
  - Thick walls of the renal pelvis, ureters, or bladder (61%)

Diagnostic Procedures/Surgery
- Tuberculin skin test (PPD):
  - 88% patients have positive skin tests
  - 5 mm or more of induration is considered positive in persons with the highest likelihood of developing active disease
    - HIV, immunosuppression, organ transplants
  - 10 mm or more of induration is considered positive in those who are at high risk for TB
    - Drug abuse, health care workers, family members
  - 15 mm or more of induration is considered positive in any patient

  - Positive reaction indicates exposure, not necessarily active disease
  - May be negative in a patient with miliary TB, AIDS, or advanced age
  - Negative tuberculin skin test makes diagnosis of TB unlikely
  - Not used in patients with history of Bacille Calmette–Guérin (BCG) vaccine or therapy
- Retrograde pyelography
  - Obtain selective cultures for TB
  - Assessment of ureteral stricture
- Cystoscopy and ureteroscopy play a limited role

Pathologic Findings

Tubercles replaced by caseating necrosis

DIFFERENTIAL DIAGNOSIS

- Amicrobic cystitis
- Systemic BCG infection
- Chronic nonspecific cystitis or pyelonephritis
- Disseminated coccidioidomycosis
- Medullary sponge kidney
- Necrotizing papillitis
- Nonspecific epididymitis
- Renal stones or nephrocalcinosis
- Urinary bilharziasis (schistosomiasis)

TREATMENT

GENERAL MEASURES

- Early diagnosis of active disease is imperative and requires prompt initiation of adequate drug regimens
  - Surgical treatment is reserved for advanced cases and with the goal of renal preservation
  - Correct the obstructive effects of fibrosis and scarring rather than removal of infected tissues
  - Drainage of abscesses
- Balanced approach is required between medications and surgery to preserve function and eradicate mycobacteria
- Supervision of therapy is required to ensure compliance and to monitor for complications

MEDICATION

First Line

- Initial treatment requires 6 mo of anti-TB medications
- 1st 2 mo: Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB)
- Following 4 mo: INH and RIF
- Ascorbic acid given with treatment
  - INH – 5 mg/kg (300 mg/d)
    - Pyridoxine supplementation required (peripheral neuropathy)
    - Hepatic toxicity
  - RIF – 10 mg/kg (450–600 mg/d)

- Hepatic toxicity, flu-like syndrome, pruritics
- PZA – 25 mg/kg/d
  - Hepatic toxicity, arthralgias, rash, gastrointestinal upset
- EMB – 15–25 mg/kg/d
  - Irreversible optic neuritis, visual changes
  - Renal excretion (caution in renal failure)

Second Line

- Complicated/resistant TB infections requiring the use of streptomycin, ethionamide, quinolones, and aminoglycosides
  - Streptomycin 15 mg/kg (max 1 g)
    - Vestibular and auditory toxicity, renal damage
  - Ethionamide 15–20 mg/kg (max 500 mg/BID)
    - Gastrointestinal and hepatic toxicity, hypothyroidism
- Multidrug-resistant TB (MDR-TB)
  - Resistant to at least isoniazid and rifampin, and possibly additional agents
- Extensively drug-resistant TB (XDR-TB)
  - Resistant to at least isoniazid and rifampin, and additionally resistant to fluoroquinolones and either aminoglycosides or both

SURGERY/OTHER PROCEDURES

- 55% of patients with GU TB will require surgical intervention
  - Ureteral obstruction
    - Early stent or nephrostomy may decrease loss of renal function and increase opportunity for later reconstruction (2)[C]
    - Some strictures may resolve after medical therapy
  - Nephrectomy
    - Symptomatic (hypertension, obstruction, pyelonephritis)
    - Removal of nonfunctional unit
    - Indicated for coexistent renal malignancies
    - Best delayed 4–6 wk after medical treatment

ADDITIONAL TREATMENT

Additional Therapies

- Steroids
  - Used for treatment of TB-induced ureteral strictures or cystitis
    - Prednisone 20 mg 3 times daily orally
  - Not recommended for routine use
- Latent TB
  - Consider treatment to avoid conversion to active disease

ONGOING CARE

PROGNOSIS

- Prognosis is good in patients who are compliant in therapy
- Better prognosis with early diagnosis of disease

COMPLICATIONS

- Renal TB:
  - Autonephrectomy: Complete nonfunctioning of an affected kidney
  - Perinephric abscess may cause an enlarging flank mass
- Ureteral TB:
  - Stricture formation
  - Hydronephrosis
  - Loss of renal function

FOLLOW-UP

Patient Monitoring

- All TB patients should be screened for HIV/AIDS
- Strictures can evolve after mycobacteria is eradicated
  - Imaging (excretory urography/contrast computed tomography) and urine culture every 3 mo for 1st yr then annual abdominal radiographs
  - Continue long-term imaging if calcifications present

REFERENCES

1. Figueiredo AA, Lucon AM, Junior RF, et al. Epidemiology of urogenital tuberculosis worldwide. *Int J Urol.* 2008;15:827–832.
2. Shin KY, Park HJ, Lee JJ, et al. Role of early endourologic management of tuberculous ureteral strictures. *J Endourol.* 2002;16:755–758.
3. Wise GJ, Shteynshlyuger A. An update on lower urinary tract tuberculosis. *Curr Urol Rep*. 2008;9:305–313.
4. Wang LJ, Wu CF, Wong YC, et al. Imaging findings of urinary tuberculosis on excretory urography and computerized tomography. *J Urol.* 2003;169:524–528.

ADDITIONAL READING

- Blumberg HM, Leonard MK Jr, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. *JAMA*. 2005;293:2776–2284.
- Cek M, Lenk S, Naber KG, et al. EAU guidelines for the management of genitourinary tuberculosis. *Eur Urol.* 2005;48:353–362.

See Also (Topic, Algorithm, Media)

- BCG Sepsis/BCGosis
- Prostatitis, Granulomatous
- Tuberculosis, Bladder and Urethra
- Tuberculosis, Genitourinary, General Considerations
- Tuberculosis, Kidney and Ureter Images
- Tuberculosis, Male External Genitalia

CODES

ICD9

- 016.00 Tuberculosis of kidney, unspecified
- 016.20 Tuberculosis of ureter, unspecified

ICD10
A18.11 Tuberculosis of kidney and ureter

CLINICAL/SURGICAL PEARLS
Compliance to treatment regimen is essential for adequate disease response.

TUNICA ALBUGINEA/PARATESTICULAR TUMORS AND CYSTS

John L. Phillips, MD, FACS
Vladimir A. Valera, MD, PhD

BASICS

DESCRIPTION

- Lesions can arise from the paratesticular regions of the scrotum and testes. These soft tissues include
  - tunica albugenia, tunica vaginalis, spermatic cord structures and mullerian remnants (eg, appendix testis or appendix epididymis)
  - Benign 70%
    - Lipomas (90% of adult PT tumors)
    - Adenomatoid tumors 30%
    - Tunica albugenia cysts
    - Leiomyomas
    - Cystadenomas
    - Adrenal rests
    - Cysts of the appendix testis
    - Hamartomas/pseudotumors (rare)
  - Malignant 30%
    - Leiomyosarcoma
    - Rhabdomyosarcoma (RMS) 24–40%
    - Liposarcoma
    - Malignant mesothelioma (MM)
    - Desmoplastic round cell tumor (DRCT)

EPIDEMIOLOGY

Incidence

- Rare, true incidence unknown
- Europe: 5–7 cases per million
- Adenomatoid tumors typically seen in 4th decade
- Leiomyosarcoma and MM peak in 5th–7th decade
- RMS: Bimodal
  - 2–6 yr & 15–19 yr
    - Most common tumor of lower GU tract in the 1st 2 yr
  - 5–7 cases/10 million children

Prevalence

- Reported in 1 of 20–40 orchiectomy specimens
  - China: 4.7% of pediatric scrotal tumors over 12 yr (1)
  - High in SW Nigeria: 38.5% of adult orchiectomy specimens over 17 yr (2)

RISK FACTORS

- Cryptorchidism not a risk factor for PT tumors

- Asbestos exposure may be risk factor for MM
- Cystadenomas seen in Von Hippel–Lindau (VHL) disease are typically bilateral
- Parental cocaine or THC use seen in pediatric RMS

Genetics

- RMS, embryonal subtype, frequently has monosomy of chromosome 11.
  - Alveolar subtypes express t(2;13)(q35;q14) or t(1;13)(p36;q14) and bodes poorly
- DRCT express t(11;22)(p13;p12) fusions of EWS and WT1.

PATHOPHYSIOLOGY

- Arise from epithelial, mesothelial, or mesenchymal tissues
  - Epididymis
    - Adenomatoid tumor
    - Cystadenoma (1/3 occur in VHL)
  - Spermatic cord
    - Sarcoma (arise from undifferentiated mesoderm)
    - Adrenal rest (found incidentally during hernia repair)
    - Lipoma/leiomyoma/liposarc, etc.
  - Tunica vaginalis (TV)
    - MM

ASSOCIATED CONDITIONS

- Germline conditions
  - Von Hippel–Lindau disease
    - Infertility low even in bilateral cases
  - Li–Fraumeni syndrome confers predisposition
- Somatic (ie, acquired) conditions
  - Ipsilateral hydrocele (eg, reactive)
  - Ipsilateral hernia (ie, cause for exploration)
  - Pulmonary mesothelioma (and asbestos exposure in MM of the TV)
  - Scrotal trauma
  - Epididymitis–orchitis
  - Infertility (ie, cause for workup or exploration)

GENERAL PREVENTION

No known environmental or occupational risk

DIAGNOSIS

HISTORY

- Slowly growing inguinal or scrotal mass
- Often painless
- Found in workup for hernia
- Found in evaluation of scrotal trauma or inflammatory/infectious scrotal conditions

PHYSICAL EXAM

- Inguinal or scrotal mass
- Testis often discrete and normal

  - Adenomatoid tumors may occur more inferiorly on the testis.
  - Superior pole tumors may mimic a spermatocele (SC)
- Evaluate for hernia, hydrocele, SC, and varicocele

ALERT
Fixation to inguinal canal or testis suggests malignancy. Prepare for and rule out sarcoma.

- Fixation or involvement of testis and not the chord suggests primary testicular or MM
  - Rule out germ cell tumor or MM
- Large size >5 cm suggests RMS

ALERT
- Transillumination does not rule out tumor
- Rule out secondary or, more rare, primary lymphoma.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Rule out concurrent infection or inflammation
  - Urinalysis
  - Urine culture
- Rule out concurrent mycobacterial infection (can mimic tumor)
  - PPD history
  - Chest x-ray (rule out granulomas, tumor)
- Assess testicular germ cell tumor (GCT) markers
  - AFP
  - β-hCG
  - LDH
  - PLAP

Imaging

- Scrotal ultrasound critical in evaluation
  - Differentiate testicular from PT process
    - 3D or elastosonography not necessary if tumor distinctly separate from testis
  - Solid masses require exploration
  - Cystic structures such as tunica albuginea cyst may be monitored serially
- CT scan of the chest, abdomen, and pelvis required when malignancy suspected and to rule out metastasis in cases of known malignancy

Diagnostic Procedures/Surgery

- Fine needle aspiration may lead to false negatives or positives
- Solid lesions require inguinal approach
- Benign lesions
  - Observation
  - Testis-sparing surgery
- Malignant or suspicious lesions
  - Radical orchiectomy, inguinal approach
    - High dissection to internal ring
    - Early vascular control

- Resection of adherent structures
  - Skin
  - Fascia
  - Muscle

Pathologic Findings

- Benign lesions usually need low power H&E
  - Adenomatoid tumor
    - Well circumscribed
    - May involve tunica albuginea
    - Benign appearing cords and cystic tubules lined by eosinophilic cells with small nuclei
  - Papillary cystadenoma
    - Well circumscribed
    - Brown fronds within cystic space
    - May have clear cells that resemble renal cell carcinoma (commonly associated with VHL)
- Malignant lesions may need electron microscopy
  - MM
    - Friable, multicystic within hydrocele
    - Epithelioid, papillary, tubulopapillar pattern
    - Fibrovascular core
  - Rhabdomyosarcoma (RMS)
    - Embryonal in 90%
    - Alveolar
    - Mixed pleiomorphic
  - Desmoplastic round cell tumor (DRCT)
    - Firm, white, often near epididymis
    - Small blue cells in nests and cords
    - Mitotically active
  - Leiomyosarcoma
    - Intersecting bundles of smooth muscle cells
    - Atypical and mitotically active
  - Liposarcoma
    - Large, atypical cells, large nuclei
    - Fibrous septae
    - Lipoblasts present

DIFFERENTIAL DIAGNOSIS

- Epididymal tumors (rare)
  - Adenocarcinoma
  - Cystadenoma
- Proliferative folliculitis
  - Resemble nodular fasciitis
  - Incidental at herniorrhaphy
- Hernia, direct or indirect
- Hydrocele

- Lymphadenopathy
- Metastatic tumor
- Squamous cell carcinoma (scrotal skin)
- Sperm granuloma, usually post-vasectomy
- Testis tumor
- Tunica albuginea cyst
- Vasitis nodosa

TREATMENT

GENERAL MEASURES

- Cystic PT structures are treated with observation or rarely conservative excision
- Solid masses usually require excision
  - Benign: use testicle sparing surgery (TSS)
  - Malignant
    - TNM staging
    - Local excision
      - Adjuvant chemotherapy for RMS
      - Adjuvant local radiation for other sarcomas

MEDICATION

First Line

- Malignant rhabsomyosarcoma (RMS)
  - Vincristine
  - Dactinomycin
  - Cyclophosphamide
    - MESNA for bladder protection

Second Line

N/A

ADDITIONAL TREATMENT

Radiation Therapy

Reserved for local adjuvant or salvage control of malignant PT sarcomas

Additional Therapies

- Secondary resection
  - Local recurrence of benign lesions
  - Local recurrence of malignant lesions if localized, no evidence of metastatic disease, and radiotherapy not given

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Benign lesions

  - Resection is usually curative
  - Fertility can be maintained
- Malignant lesions
  - RMS
    - Favorable prognosis in children
    - Stage I in 60–80%
    - Unfavorable prognosis in adults and children >10 yr
  - DCRT unfavorable prognosis with nodal and pulmonary metastasis
  - Mesothelioma. Aggressive; similar to peritoneal mesothelioma
  - Lipo-/leiomyosarcoma
    - Excellent prognosis but may recur locally and require retreatment
    - Metastases exceedingly rare, reportable

COMPLICATIONS

- General as seen for inguinal surgery:
  - Secondary hernia
  - Infection
  - Hematoma
  - Pain
- Loss of testis after testicular sparing surgery (TSS) (rare)
- Infertility (eg, after excision of bilateral cystadenoma or epididymal masses in VHL)

FOLLOW-UP

Patient Monitoring

- Benign lesions
  - Physical exam semiannual and self-exam yearly
- Malignant lesions
  - Liposarcomas rarely metastasize but can recur locally
  - RMS
    - Interdisciplinary oncologic team (3)
    - Serial imaging
    - 40% metastasize to retroperitoneum
    - Role of RPLND in RMS controversial

Patient Resources

- National Cancer Institute
  - Childhood Rhabdomyosarcoma Treatment
    - www.cancer.gov/cancertopics/pdq/treatment/childrhabdomyosarcoma/patient
- Testicular Self-Exam
  - www.nlm.nih.gov/medlineplus/ency/article/003909.htm
- Liddy Schriver Sarcoma Initiative
  - sarcomahelp.org (Accessed August 22, 2014)

REFERENCES

1. Park SB, Lee WC, Kim JK, et al. Imaging features of benign solid testicular and paratesticular lesions. *Eur Radiol.* 2011;21:2226–2234.

2. Salako AA, Onakpoya UU, Osasan SA, et al. Testicular and para-testicular tumors in south western Nigeria. *Afr Health Sci.* 2010;10:14–17.
3. Wiener ES, Anderson JR, Ojimba JI, et al. Controversies in the management of paratesticular rhabdomyosarcoma: Is staging retroperitoneal lymph node dissection necessary for adolescents with resected paratesticular rhabdomyosarcoma? *Semin Pediatr Surg.* 2001;10:146–152.

ADDITIONAL READING

Vagnoni V, Brunocilla E, Schiavina R, et al. Inguinal canal tumors of adulthood. *Anticancer Res.* 2013;33(6):2361–2368.

See Also (Topic, Algorithm, Media)

- Epididymis, Mass (Epididymal Tumor and Cysts)
- Paratesticular Tumors
- Rhabdomyosarcoma, Pediatric (Sarcoma Botryoides)
- Scrotum and Testicle, Mass
- Spermatic Cord Mass and Tumors
- Spermatocele

CODES

ICD9

- 214.8 Lipoma of other specified sites
- 239.5 Neoplasm of unspecified nature of other genitourinary organs
- 608.89 Other specified disorders of male genital organs

ICD10

- D49.5 Neoplasm of unspecified behavior of other genitourinary organs
- N44.1 Cyst of tunica albuginea testis
- N50.8 Other specified disorders of male genital organs

CLINICAL/SURGICAL PEARLS

- Most common adult benign paratesticular tumor: Lipoma.
- Most common adult malignant paratesticular tumor: Liposarcoma.
- Most common pediatric PT tumor is malignant RMS (rhabdomyosarcoma).
- Cure rate of RMS with multimodality therapy: 90%.

UMBILICAL ABNORMALITIES, UROLOGIC CONSIDERATIONS

Evalynn Vasquez, MD, MBA
Derek Matoka, MD

BASICS

DESCRIPTION

- Umbilical abnormalities result from failure of umbilical ring to close or persistence of umbilical structures
- Abnormalities can be classified as:
  - Mass
  - Infection
  - Persistent drainage
- Most likely to present during the neonatal period or early infancy

EPIDEMIOLOGY

Incidence

- Most common mass at the umbilicus in an infant is granulation tissue
- Umbilical hernia: 10–20% of all infants
  - Increased incidence: Premature infants (up to 75% in infants under 1500 g), females, African descent, Down syndrome, Beckwith–Wiedemann syndrome, hypothyroidism, mucopolysaccharidosis
- Omphalitis is currently extremely rare due to adequate hygiene and the use of topical antibiotics on the umbilical cord
- Persistent remnant of the vitelline duct has 2% incidence
- Urachal remnants are common but often asymptomatic (3% of adult autopsy specimens)
- Patent urachus occurs in $<1/1000$ live births
- Urachal carcinoma: 1 in 5 million cases annually

Prevalence

N/A

PATHOPHYSIOLOGY (1)

- The primitive umbilical cord develops with the anterior abdominal wall during weeks 2–3 of gestation
- Early in gestation, the umbilical cord contains the vitelline duct, allantois, two arteries, and one vein
- The vitelline duct is a connection between the midgut and yolk sac. It involutes in weeks 7–9 and becomes the ligament teres of the liver. This ligament attaches to the inferior portion of the umbilical ring (75%) or the superior aspect (25%)
- The bladder forms from the ventral portion of the cloaca. The bladder descends into the pelvis with the urachus connecting the bladder apex to the umbilicus. The urachus involutes to a fibrous cord becoming the median umbilical ligament
- The anterior abdominal wall progressively closes leaving only an umbilical ring
- Failure of normal development or failure of the vitelline duct, urachus, or umbilical ring to

involute results in umbilical abnormalities
- The urachal remnant is represented by the median umbilical ligament in adults. Urachal remnants: Most common; comprise spectrum of anomalies:
  – Patent urachus (rare, 3 in 1 million): Unobliterated urachus draining urine from the bladder to the umbilicus
  – Urachal sinus: Urachus obliterated at the bladder level, but open sinus remains at the umbilicus. Drainage often is the result of episodic infections of the sinus
  – Urachal cyst: Urachus obliterated proximally and distally, but unobliterated fluid-filled cyst remains in between
  – Infected urachal cysts found in all ages
  – Urachal diverticulum of the bladder: May result from drainage of a urachal cyst to the bladder.
- Vitelline duct remnant (omphalomesenteric duct): Connects fet al midgut to yolk sac
  – Umbilical sinus, vitelline cyst, or Meckel (8%–10% of Meckel have umbilical anomaly)
- Arterial umbilical remnants

ASSOCIATED CONDITIONS
- Volvulus or internal hernia with vitelline abnormalities
- GI bleed: Meckel diverticulum
- Bladder outlet obstruction

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Most umbilical disorders are found antenatally or at birth but can have a delayed diagnosis or be found incidentally if asymptomatic
- Discharge suggests vitelline duct remnant, urachal remnant, or umbilical granuloma
- Umbilical infections are often related to hygiene issues.
  – Home births have a slightly increased incidence of omphalitis.
- Painless, intermittent, self-resolving GI bleed in a young child should raise the suspicion of a Meckel diverticulum.
- Acute onset abdominal pain can suggest incarcerated umbilical hernia, volvulus or internal hernia due to fibrous vitelline remnant, or intussusception of a Meckel diverticulum.
- Urachal tumors are typically silent because of their extraperitoneal location; consequently, the majority of patients exhibit local invasion or metastatic disease at presentation.
- UTI or bladder stone can be associated with a urachal diverticulum.

PHYSICAL EXAM
- Granuloma and umbilical polyp: Small bright red remnant of intestinal or gastric mucosa
- Hernia: Non-tender reducible outpouching through umbilical ring
- Omphalitis: Tender, erythematous, bleeding, and discharge at the umbilicus
- Patent urachus: Clear fluid draining in the newborn period often exaggerated with crying or straining
- Urachal cyst: Asymptomatic and incidentally found unless associated with infection. Patient

may then present with fever, voiding symptoms, midline infraumbilical tenderness, mass, or urinary tract infection. Rarely it can rupture into preperitoneal tissues or the peritoneal cavity
- Urachal sinus: May present in infancy or later with clear drainage or nonspecific periumbilical erythema
- Vesicourachal diverticulum: May present with urinary tract infections
- Vitelline umbilical fistula: Found in newborn period with the appearance of an umbilical stoma with pink, circular, intestinal remnant
- Meckel diverticulum: Asymptomatic unless bowel obstruction from intussusception occurs or GI bleed due to mucosal ulceration from acid secretion. Rule of 2's: 2% of the population, 2 feet from the ileocecal valve, 2 inches in length, 2 types of common ectopic tissue (gastric and pancreatic), 2 yr is the most common age at clinical presentation, 2 times more boys are affected

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis: evidence of hematuria or infection
- Check creatinine of draining umbilical fluid to determine if it could be a patent urachus
- Urine cytology may be positive in cases of urachal carcinoma

Imaging

- Ultrasound: Best tool for initial assessment. It accurately determines anatomy of umbilical structures and evaluates for bladder/small bowel communication
- VCUG: Assess for a urachal remnant and can rule out associated bladder outlet obstruction
- Fistulography/Sinogram: Catheterization of tract and injection of contrast may be difficult and unreliable. Can diagnosis vitelline umbilical fistula which will show communication to small bowel.
- Meckel scan: Specific for gastric mucosal cells and accuracy is greater than 90%
- CT or MRI of abdomen and pelvis with IV and PO contrast
  - Gold standard for diagnosis and staging particularly for cancer
  - Midline, calcified, partially cystic mass with local extension is concerning for but not diagnostic of urachal carcinoma.

Diagnostic Procedures/Surgery

Cystoscopy with biopsy or resection

Pathologic Findings

- Umbilical polyp: Excrescence of vitelline duct mucosa retained in the umbilicus
- 10% of bladder adenocarcinomas arise from a urachal remnant.
  - Only type of bladder cancer more common in women than in men
  - Urachal adenocarcinoma tends to present at an earlier age than other forms of bladder adenocarcinoma
  - Histologically, urachal adenocarcinoma tends to be lower grade with improved overall 5-yr survival
  - Mucin production is found in up to 75% of cases; calcification in 50–70%

DIFFERENTIAL DIAGNOSIS

- Umbilical mass
  - Granuloma/umbilical polyp: Infants
  - Umbilical hernia: All ages
  - Urachal neoplasms: Adults
    - Benign (very rare): Adenomas, fibromas, fibroadenomas, fibromyomas, hamartomas
    - Malignant (very rare, less than 0.5% of all bladder cancers): Most adenocarcinoma
  - Sister Mary Joseph nodule (adults): Umbilical metastasis of primary tumors (if primary is known, usually from genital or GI tract)
  - Others: Dermoid cyst, sebum cyst, spontaneous umbilical fistula from Crohn disease/TB/perforated appendix, urachal carcinoma, and skin cancers such as basal-cell and squamous-cell carcinoma
- Infection
  - Omphalitis
  - Infected urachal cyst
- Drainage
  - Urachal remnant:
    - Patent urachus (50%)
    - Urachal cyst (30%)
    - Urachal sinus (15%)
    - Vesicourachal diverticulum (5%)
  - Vitelline remnant: Meckel diverticulum, vitelline umbilical fistula, fibrous vitelline remnant
  - Endometriosis: Pain and hemorrhagic umbilical discharge during menses

TREATMENT

GENERAL MEASURES

Identify the abnormality and manage accordingly

SURGERY/OTHER PROCEDURES (2,3)

- Granuloma and umbilical polyp (infants): Very difficult to differentiate clinically. Treat with silver nitrate. If there is no response after two or three attempts, surgical excision may be necessary. Pedunculated lesions with a narrow stalk may be managed with ligation of the base with absorbable suture
- Hernia (infants): 1 cm or less, spontaneous closure likely in >90%. Hernias >2 cm typically need surgical correction after 3–4 yr of observation
- Omphalitis (infants): Broad spectrum antibiotics. Surgical debridement may be necessary. There is a high mortality rate and risk of polymicrobial necrotizing fasciitis; mortality of up to 15%
- Patent urachus: Resect entire duct via infra-umbilical incision (in newborns), or transverse mid-hypogastric incision in older children; remove cuff of bladder with specimen
- Urachal remnant: Surgical exploration with excision.
  - If urachal cyst is infected, it may be treated initially with broad spectrum antibiotics and drainage.
  - Complete excision can be performed once infection has subsided. Risk of malignant

degeneration has been reported in the literature.
- Patent vitelline duct/ vitelline umbilical fistula (enteric contents per umbilicus): Surgical exploration with excision needs prompt laparotomy and duct excision to avoid intussusception/volvulus
- Meckel diverticulum: Surgical exploration with excision
- Urachal carcinoma
  - Radical cystectomy or partial cystectomy with wide surgical margins and en-bloc resection of urachal remnant extending from bladder to umbilicus, posterior rectus sheath, and all tissue between medial umbilical ligaments is recommended for lower stage, resectable disease.
  - Partial cystectomy may offer a comparable oncologic outcome and less morbidity to radical cystectomy if tumor is completely resected (4)[C]
  - Failure to resect the umbilicus and positive surgical margins are associated with a worse outcome (5)[B]
- Bilateral pelvic lymph node dissection
  - Should follow the standard template for bladder cancer.
  - May be useful for staging but does not provide any survival advantage.
- Surgical resection is particularly well-suited to a laparoscopic or robotic approach with comparable short-term outcomes.

ADDITIONAL TREATMENT

Radiation Therapy

Limited role for unresectable urachal carcinoma

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Minimal long-term sequelae when managed appropriately
- Urachal carcinoma
  - 5-yr overall survival: 27–80%; about 50% for locally advanced disease
  - Less than 20% for metastatic disease
  - 93% for disease confined to the urachus and bladder after surgical resection with bladder preservation
  - 69% for extravesical and periurachal disease after surgical resection with bladder preservation

COMPLICATIONS

Morbidity related to the abnormality and the specific treatment modality that is utilized

Patient Resources

Urology Care Foundation: Urachal Abnormalities
http://www.urologyhealth.org/urology/index.cfm?article=41

REFERENCES
1. Snyder CL. Current management of umbilical abnormalities and related anomalies. *Semin Pediatr Surg.* 2007;16(1):41–49.
2. Frimberger D, Kropp B. Bladder anomalies in children. In: Wein AJ, ed. *Campbell-Walsh Urology*. Philadelphia, PA: Saunders; 2007:3576–3579.
3. Pomeranz A. Anomalies, abnormalities, and care of the umbilicus. *Pediatr Clin North Am.* 2004;51(3):819–827.
4. Siefker-Radtke AO, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: the M.D. Anderson Cancer Center experience. *J Urol.* 2003;169(4):1295–1298.
5. Herr HW, Bochner BH, Sharp D, et al. Urachal carcinoma: Contemporary surgical outcomes. *J Urol.* 2007;178(1):74–78.

ADDITIONAL READING

- Christison-Lagay ER, Kelleher CM, Langer JC. Neonatal abdominal wall defects. *Sem Fet al Neonatal Med.* 2011;16(3):164–172.
- Ledbetter DJ. Congenital abdominal wall defects and reconstruction in pediatric surgery: gastroschisis and omphalocele. *Surg Clin North Am.* 2012;92(3):713–727.
- Yu J-S, Kim KW, Lee HJ, et al. Urachal remnant diseases: spectrum of CT and US findings. *RadioGraphics.* 2001;21:451–461.

See Also (Topic, Algorithm, Media)
- Bladder Cancer, Adenocarcinoma
- Urachal Abnormalities
- Urachal Carcinoma

CODES

ICD9
- 553.1 Umbilical hernia without mention of obstruction or gangrene
- 759.89 Other specified congenital anomalies
- 772.3 Umbilical hemorrhage after birth

ICD10
- K42.9 Umbilical hernia without obstruction or gangrene
- P51.9 Umbilical hemorrhage of newborn, unspecified
- Q89.8 Other specified congenital malformations

CLINICAL/SURGICAL PEARLS

- In the newborn, a granuloma is the most common cause of persistent drainage.
- Ultrasound is an accurate, minimally invasive initial imaging modality.
- Umbilical hernias may be seen in up to 20% of infants, but the majority will resolve by 3 yr of life.
- If surgical excision of a urachal remnant is performed, a bladder cuff should be taken if there is involvement of the dome of the bladder.

UNDERACTIVE BLADDER (DETRUSOR UNDERACTIVITY)

Michael J. Amirian, MD
Leonard G. Gomella, MD, FACS

BASICS

DESCRIPTION

- Detrusor underactivity (DU) often referred to as underactive bladder is a bladder contraction of reduced strength and/or duration
  - Results in prolonged bladder emptying
  - Failure to complete bladder emptying within a normal time span
  - Observed in many neurologic conditions and myogenic failure
- DU is a common cause of lower urinary tract symptoms (LUTS) in both men and women
- A wide range of terminology is currently applied in the literature
  - The only formal definition was from the International Continence Society (ICS) in 2002 was the urodynamic definition of DU along with detrusor acontractility
- Underactive Bladder Syndrome is characterized by urinary symptoms including hesitancy, straining, and incomplete bladder emptying in the absence of anatomic obstruction.

EPIDEMIOLOGY

Incidence

Present in 9–48% of men and 12–45% of older women undergoing urodynamic evaluation for non-neurogenic LUTS (1)

Prevalence

N/A

RISK FACTORS (2)

- Overactive bladder (OAB) may lead to underactive bladder (UAB)
- Diabetes mellitus
- Aging
- Acute Cerebrovascular accident (CVA)
- Multiple sclerosis (MS)
- Parkinson disease
- Injury to spinal cord, cauda equine, and pelvic plexus
  - Pelvic surgery
  - Pelvic and sacral fractures
  - Herniated disc
  - Lesions of pudendal nerve
- Infectious neurologic problems
  - AIDS
  - Neurosyphilis
  - Herpes zoster and herpes simplex
  - Guillain–Barre syndrome
- Medications

- Antimuscarinics, α-receptor antagonists

Genetics

N/A

PATHOPHYSIOLOGY

- Diabetic mellitus leading to diabetic cystopathy
  - Metabolic derangement of Schwann cells
    - Altered metabolism of glucose
    - Ischemia
    - Superoxide-induced, free-radical formation
    - Impaired axonal transport
  - Alteration in physiology of detrusor smooth muscle cell
- Aging
  - Reduction in acetylcholinesterase-positive nerve
    - Reduced parasympathetic innervation
- CVA
  - Cerebellar infarct leading to detrusor areflexia

ASSOCIATED CONDITIONS

OAB syndrome

GENERAL PREVENTION

- Diabetic patients
  - Control blood glucose levels
- Hypertension and hyperlipidemia control
- Smoking cessation

DIAGNOSIS

HISTORY

- History of neurologic injury or medical disorder
- Recurrent episodes of urinary retention
- Lower urinary tract symptoms
  - Straining to urinate
  - Sensation of incomplete bladder emptying
  - Diminished and interrupted urinary stream
  - Urinary hesitancy
  - Rely on abdominal straining to urinate
- Incontinence
  - Overflow, urge, or stress
- Recurrent urinary tract infections

PHYSICAL EXAM

- May reveal a distended bladder
- Suspected or known neurologic injury due to pelvic or sacral injury
  - Testing of sacral dermatomes
    - Assessing perianal sensation

    - Anal sphincter tone
    - Bulbocavernosus reflex
- Neurologic testing
  - Deep tendon reflexes in the lower extremities
  - Clonus
  - Plantar responses

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Beyond routine urinalysis and culture, none specific

Imaging

Upper tract screening if obstruction suspected.

Diagnostic Procedures/Surgery

- Urodynamic evaluation (basis of current ICS definition of UAB)
  - Cystometry
    - Long curve with lack of sensation
    - Low detrusor pressure
  - Electromyography
    - Usually normal
    - May show sphincter denervation and uninhibited sphincter relaxation
- Uroflowmetry
  - Low peak flow
  - Prolonged duration of flow
  - Increased residual urine

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Bladder outlet obstruction
- Detrusor overactivity

TREATMENT

GENERAL MEASURES

- Limited management available (3)
  - No validated, effective oral drugs, no FDA approved medications. All used off label.
- Double void or straining to void
- Avoidance of bladder overdistention
  - Indwelling urinary catheter
  - Intermittent catheterization (preferred)

MEDICATION

First Line

- α-Adrenergic blockers
  - Alfuzosin

  – Doxazosin
  – Terazosin
• Muscarinic receptor agonists
  – Bethanechol, carbachol
• Choline esterase inhibitors
  – Distigmine (Approved outside of US)

Second Line
• Potential therapy
  – Prostaglandin E2
  – Acting on four types of EP receptors
    ◦ Increase detrusor contraction
    ◦ Relax the urethra

SURGERY/OTHER PROCEDURES
• Sacral nerve stimulation and intravesical electrical stimulation
  – Potentially beneficial in select patients
• Invasive surgical reconstruction
  – Latissimus dorsi muscle transposition to restore bladder function

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
• Experimental therapeutics:
  – Stem cell therapy
    ◦ Allow weak detrusor to improve contractility
  – Targeted gene therapy

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Good prognosis with appropriate bladder management

COMPLICATIONS
• Urinary retention
• Urinary tract infections
• Damage to upper urinary tract

FOLLOW-UP
Patient Monitoring
• Post-void residual
• Uroflowmetry
• Urinalysis and urine culture

Patient Resources

- Underactive Bladder Foundation – www.underactivebladder.org

REFERENCES

1. Osman N, Chapple CR, Abrams P, et al. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *Eur Urol.* 2014;65(2):389–398.
2. Miyazato M, Yoshimura N, Chancellor MB. The other bladder syndrome: Underactive bladder. *Rev Urol.* 2013;15(1):11–22.
3. van Koevering GA, Vahabi B, Andersson KE, et al. Detrusor underactivity: A plea for new approaches to a common bladder dysfunction. *Neurol Urodyn.* 2011;30:723–728.

ADDITIONAL READING

Chancellor MB, Blaivas JG. Classification of neurogenic bladder disease. In: Chancellor MB, ed. *Practical Neuro-urology*. Boston, MA: Butterworth Heinemann; 1995.

See Also (Topic, Algorithm, Media)

- Lower Urinary Tract Symptoms (LUTS)
- Neurogenic Bladder, General Considerations
- Overactive Bladder (OAB)

CODES

ICD9

- 596.59 Other functional disorder of bladder
- 788.21 Incomplete bladder emptying
- 788.99 Other symptoms involving urinary system

ICD10

- N31.8 Other neuromuscular dysfunction of bladder
- R33.8 Other retention of urine
- R39.19 Other difficulties with micturition

CLINICAL/SURGICAL PEARLS

The term DU remains surrounded by ambiguity and confusion with a lack of accepted terminology, definition, and diagnostic methods and criteria.

UNDESCENDED TESTES (CRYPTORCHIDISM)

Julia S. Barthold, MD, FACS

BASICS

DESCRIPTION

- Cryptorchidism, or undescended testis (UDT), is failure of one or both testes to descend or remain descended in a dependent scrotal position.
- Position
  - Intra-abdominal (10–20%)
  - Canalicular: Within inguinal canal
  - Distal to external ring, including prepubic, prescrotal/gliding, superficial inguinal pouch
  - True ectopic: Perineal most common
- Subclassifications
  - Congenital: Testis extrascrotal at birth
  - Acquired: Testis intrascrotal at birth but found in an extrascrotal position at a subsequent time (1)
    - Delayed diagnosis of primary UDT
    - After inguinal surgery
    - After spontaneous postnatal descent (recurrent cryptorchidism)
  - Vanishing: Blind-ending spermatic vessels and vas deferens in a boy initially diagnosed with UDT

EPIDEMIOLOGY

Incidence

- 2–4% of full-term boys
- Up to 30% of premature boys (< 37 weeks gestational age)
- Up to half descend spontaneously in the first 3–6 months of life but some will reascend
- Testes of premature boys are more likely to descend and may take a year or longer

Prevalence

- 1% of boys at 1 year of age
- Up to 4% of boys undergo orchidopexy for UDT during childhood, presumably related to risk of acquired UDT
- Up to half of boys present with acquired UDT

RISK FACTORS

- Increased incidence in families (2)
  - Fathers, brothers, dizygotic twins, monozygotic twins
- Low birth weight: Prematurity or SGA
- Maternal environment
- Retractile testis is a risk factor for acquired UDT in some individuals
  - Unilateral > bilateral
  - Risk of ascent 7–32% (3)
  - Normal testes frequently retractile >6 mo up to puberty; peak at 4 yr

- Environmental exposures?—Antiandrogenic and estrogenic compounds in animal models but weak evidence for etiology in human population

Genetics

- Rare variants of *INSL3* or its receptor *RXFP2*
- Possible association with *AR* or *ESR1* variants
- Likely polygenic/multifactorial

PATHOPHYSIOLOGY

- Failure of complete testicular descent
- Requires normal development and function of the gubernaculum
  - Arises from intermediate mesoderm 1st trimester, enlarges 2nd trimester, migrates and then regresses 3rd trimester-birth
  - Requires stimulation by testicular androgens and INSL3
- Acquired UDTs are frequently located in the superficial inguinal pouch and in most cases represent primary undescended testes not clinically identifiable until a later age

ASSOCIATED CONDITIONS

- Inguinal hernia/patent processus vaginalis
  - 50–90%, increased incidence in younger boys
  - Rarely clinically apparent
- Epididymal anomalies
  - Long-looping most common
  - Detachment of caput
  - Atresia rare
  - Association with patent processus vaginalis
  - Clinical relevance unclear
- Hypospadias
- Abdominal wall defects
  - Prune Belly (triad) syndrome; omphalocele; gastroschisis
- Neurologic and musculoskelet al diseases
  - Myelomeningocele, cerebral palsy
- Component of over 300 syndromes
- Abnormal Leydig cell function
  - Subtle reduction in testosterone (T) and/or increased LH/T ratio
  - Low incidence in nonsyndromic UDT
- Disorders of sex differentiation (DSD)
  - Usually associated with abnormal urethral and/or penile development
  - 46XX congenital adrenal hypoplasia (CAH) with complete penile development; very rare; bilateral non-palpable testes; urgent diagnosis in newborn due to risk of salt wasting

GENERAL PREVENTION

Unknown

DIAGNOSIS

HISTORY

- Family history of UDT
- History of inguinal hernia and/or surgery
- Maternal exposures or illness during pregnancy
- Birth history: Gestational age and birth weight

PHYSICAL EXAM

- Document testicular position at birth
- Assess scrotal development: May be hypoplastic
- Assess penile development
  - Hypospadias
  - Micropenis (>2 SD below mean for age)
  - Ambiguous genitalia (DSD)
- Continue periodic exams to assess for spontaneous testicular descent for at least 6 mo
- Assure maintenance of scrotal position
  - After spontaneous descent
  - Older boys with retractile testes
    - Yearly exam, warm room, warm hands, relaxed child if possible
    - Upright cross-legged position or supine with legs abducted
- Evidence that a nonpalpable testis is absent
  - Intrascrotal "nubbin" = vanishing testis
  - Contralateral testicular hypertrophy (length ≥1.8 cm) (4)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Unilateral nonpalpable testis: No testing
- Bilateral nonpalpable testes
  - Rule out CAH in newborn: Karyotype; electrolytes, 17-OH progesterone
  - Hormone levels: T and gonadotropin levels during postnatal surge at 1–3 mo
    - Low anti-Müllerian hormone (AMH)
    - ± abnormal hCG stimulation test

Imaging

- Imaging rarely indicated (5)
  - US inaccurate to determine position
  - MRI/MRA more accurate but rarely used
- *Potentially* useful in selected cases after referral to specialist
  - Obese boys with a history of palpable testes
  - Failure to identify spermatic vessels after laparoscopy or abdominal exploration

Diagnostic Procedures/Surgery

- Laparoscopy
  - Procedure of choice for localization and determination of status of nonpalpable testis
  - Open internal ring: Distal testis likely
  - Closed internal ring: No vessels: look for high abdominal testis (image); small/atretic vessels suggests distal "vanishing" testis.
  - Retroperitoneal exploration to kidney may be required.

Pathologic Findings

- Testicular biopsy
  - Not standard practice at orchidopexy
  - Reduced spermatogonia numbers in UDT
  - Reduced Ad (adult dark) spermatogonia most predictive of spermatogenic function
  - Leydig cell hypoplasia and/or Sertoli cell degeneration—limited data

DIFFERENTIAL DIAGNOSIS

- Retractile testis
- Vanishing testis: Confirmation of blind-ending spermatic vessels; antenatal torsion, or vascular accident
- True agenesis
  - Rare; ipsilateral failure of Wolffian duct development and Müllerian duct regression

TREATMENT

GENERAL MEASURES

- Observe for spontaneous postnatal descent
  - Identify clinical hernia or torsion
  - Ensure permanent, stable scrotal position by 6 mo of age, then yearly observation
  - Observe longer for descent if prematurity
- Plan surgery at 6–18 mo of age if testis fails to descend to improve testicular growth (6)
- Plan surgery at diagnosis in boys with acquired UDT

MEDICATION

- Hormonal treatment not efficacious (7)
  - hCG injections or LHRH nasal spray (not available in the United States)
  - Slight benefit over placebo; efficacy 15–20%
  - Possible adverse effects: Pigmentation, transient pubic hair, behavior changes, adverse testicular effects
  - Inadequate follow-up to rule out recurrence

SURGERY/OTHER PROCEDURES

ALERT
In cases of nonpalpable testis, the surgeon must identify the spermatic vessels and confirm that they are blind-ending or associated with an intact testis.

- Surgery is treatment of choice (3)
- Approach depends on testis palpability
- Inguinal orchidopexy
  - Standard approach for palpable testis
    - Mobilize testis via inguinal incision
    - High ligation of hernia sac if present
    - Transection of lateral retroperitoneal fascial bands to provide additional length
    - Medial translocation behind epigastric vessels (Prentiss maneuver) rarely needed
    - Higher abdominal counterincision possible if further mobilization needed
    - Placement of testis in sub-Dartos pouch without tension

- Success rate ~95%
- Complications: Testicular retraction; testis, cord or nerve injury; bleeding, infection, recurrent hernia (all rare)

• Primary scrotal orchidopexy (Bianchi)
- Increasingly reported as preferred approach for testes distal to external inguinal ring
  - Mobilization of testis and cremasteric muscle/fascia from cord via scrotal incision
  - Standard fixation in subdartos pouch
  - Best for low testes without associated patent processus vaginalis
  - Repair of hernia through scrotum possible although long-term failure rate uncertain and may be higher (8)
  - Similar success and complication rates as compared to inguinal orchiopexy

• Laparoscopic orchidopexy
- Procedure of choice for abdominal or high canalicular testes near internal ring
  - Laparoscopy for testis(es) localization with two additional lower quadrant ports
  - Mobilization of lateral and medial peritoneal attachments to cord
  - Transaction of peritoneum over cord
  - Transfer of mobilized testis through existing or neo-internal ring and standard fixation in subdartos pouch
- Success rates 72–91%

• Open abdominal orchiopexy
- High inguinal incision; Potentially more limited access to proximal cord
- Mobilization similar to laparoscopic approach
- Success rates 77–86%

• **Fowler-Stephens orchiopexy**
- One- or two-stage procedure via open or laparoscopic approach
- Required for high testis and/or short spermatic vessels
- Maintain vascular supply between vas and spermatic vessels
- Transection of spermatic vessels
- Success rates 80–94%

• Orchiectomy of unilateral UDT
- Consider in high abdominal testis, short vas deferens, hypoplastic testis, adolescent/postpubertal male

• Special considerations
- Testicular biopsy in dysmorphic testis; consider in postpubertal males
- Microvascular autotransplant requires specific expertise; solitary testes in low risk patients
- Subcutaneous testis placement as last resort to maintain endocrine function

ADDITIONAL TREATMENT

Additional Therapies

Adjuvant hormonal therapy may improve germ cell number and/or maturation; long-term efficacy uncertain

ONGOING CARE

PROGNOSIS

- Fertility
  - Abnormal semen analysis: Highly variable in unilateral, 20–50%, common bilateral, 75–100%
- Paternity
  - Conception success essentially normal in unilateral, 90%; reduced in bilateral, 30–50%
- Malignancy: Overall relative risk 2.9–6.5
  - Postpubertal presentation; risk may be decreased by prepubertal orchidopexy
  - Testicular position may influence histology
  - Abdominal: Seminoma more common
  - Scrotal: Nonseminomatous germ cell tumor more common

COMPLICATIONS

- Testicular atrophy; increased risk for abdominal testes
- Torsion risk 10× normal

FOLLOW-UP

Patient Monitoring

- Testicular development and position during peripubertal period
- Counseling regarding potential subfertility
- Testicular self-exam

REFERENCES

1. Jensen MS, Olsen LH, Thulstrup AM, et al. Age at cryptorchidism diagnosis and orchiopexy in Denmark: A population based study of 508,964 boys born from 1995 to 2009. *J Urol.* 2011;186:1595.
2. Schnack TH, Zdravkovic S, Myrup C, et al. Familial aggregation of cryptorchidism—A nationwide cohort study. *Am J Epidemiol.* 2008;167:1453.
3. Keys C, Heloury Y. Retractile testes: A review of the current literature. *J Pediatr Urol.* 2012;8:2.
4. Huff DS, Snyder HM III, Hadziselimovic F, et al. An absent testis is associated with contralateral testicular hypertrophy. *J Urol.* 1992;148:627.
5. Tasian GE, Copp HL, Baskin LS. Diagnostic imaging in cryptorchidism: Utility, indications, and effectiveness. *J Pediatr Surg.* 2011;46:2406.
6. Kollin C, Stukenborg JB, Nurmio M, et al. Boys with undescended testes: Endocrine, volumetric and morphometric studies on testicular function before and after orchidopexy at nine months or three years of age. *J Clin Endocrinol Metab*. 2012;97:4588.
7. Penson D, Krishnaswami S, Jules A, et al. Effectiveness of hormonal and surgical therapies for cryptorchidism: A systematic review. *Pediatrics*. 2013;131:e1897.
8. Al-Mandil M, Khoury AE, El-Hout Y, et al. Potential complications with the prescrotal approach for the palpable undescended testis? A comparison of single prescrotal incision to the traditional inguinal approach. *J Urol.* 2008;180:686.

ADDITIONAL READING

Thorup J, Cortes D. Surgical treatment and follow up on undescended testis. *Pediatr Endocrinol Rev.* 2009;7:38.

See Also (Topic, Algorithm, Media)
- Disorders of Sex Development (DSD)
- Groin/inguinal Mass, Male, and Female
- Groin Hernia, Pediatric
- Testis, Normal Size
- Testis, Retractile
- Testis, Tumor and Mass, Adult, General
- Undescended Testes (Cryptorchidism) Algorithm
- Undescended Testes (Cryptorchidism) Images

CODES

ICD9
- 752.51 Undescended testis
- 752.52 Retractile testis
- 752.89 Other specified anomalies of genital organs

ICD10
- Q53.9 Undescended testicle, unspecified
- Q53.11 Abdominal testis, unilateral
- Q55.22 Retractile testis

CLINICAL/SURGICAL PEARLS
- Spontaneous testicular descent is common in the first 6 mo of life but testes may re-ascend.
- Surgery is the standard treatment.
- Testes that appear to be scrotal at birth can be later diagnosed as cryptorchid with potentially increased risk in retractile testes.
- Routine testis exams with well-child visits are indicated.

URACHAL CARCINOMA

Michael O. Koch, MD, FACS
Andrew D. Strine, MD

BASICS

DESCRIPTION

- Urachal carcinoma is a rare non-urothelial malignancy (almost always adenocarcinoma) usually involving the dome of the bladder due to direct extension from the urachal ligament, the structure from which this tumor arises.
- Rare malignancy
  - Less than 1% of all bladder cancers
- Almost exclusively occurs in adults and most commonly in the 4th to 5th decades.
- Adenocarcinoma is the most common histologic subtype.
- Staging is distinct from bladder cancer but not standardized.
  - Sheldon, Mayo (1,2), and Ontario (3) staging systems
- Generally has a poor prognosis due to delayed diagnosis but may be curable with early surgical resection.

EPIDEMIOLOGY

Incidence

1 in 5 million cases annually

Prevalence

Unknown due to its rarity and often asymptomatic nature

RISK FACTORS

None

Genetics

None

PATHOPHYSIOLOGY

- Originates from the urachus.
  - Serves as a communication between the developing bladder and allantois but becomes a fibrous band by 12 weeks of gestation and is recognized as the median umbilical ligament in adults.
  - Composed of urothelium-lined lumen of epithelial origin as well as submucosa and smooth muscle of mesenchymal origin.
    - Any layer may undergo a malignant transformation.
- Locally invades into muscularis propria and perivesical fat with demarcation from urothelium.
- Local extends to space of Retzius, anterior abdominal wall, umbilicus, and peritoneal cavity.
- Metastasizes to pelvic lymph nodes, lungs, liver, and bone.

ASSOCIATED CONDITIONS

Urachal remnants, including patent urachus, urachal sinus, cyst, and diverticulum

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Increasing incidental detection due to routine use of imaging
- Often asymptomatic until more advanced
- Presenting signs and symptoms
  - Hematuria (most common) or mucosuria
  - Abdominal pain
  - Voiding symptoms or urinary tract infection (UTI)
  - Umbilical drainage
  - Omphalitis
  - Umbilical mass

PHYSICAL EXAM
- Palpable urachal mass
  - Large, fixed mass or concurrent ascites may suggest locally advanced, unresectable disease.
- Umbilical drainage or mass that fluctuates in size is more consistent with an infected urachal sinus or cyst.
- Perform a pelvic and rectal examination to evaluate for a gynecologic or rectal malignancy.
- Evaluate for any systemic signs and symptoms of infection and metastatic disease.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Hematologic and chemistry panels
- Urinalysis and urine culture to evaluate for microscopic hematuria and UTI
- Urine cytology to evaluate for a urothelial malignancy
- CA-125 and CA 19-9
  - May be elevated in 40–60% of patients
  - Useful in evaluating the response to systemic therapies

Imaging
- Abdominal ultrasound
  - Often obtained during the initial evaluation and in the pediatric population
  - High specificity for urachal cysts
  - Significant false-positive rate for other urachal lesions
  - Poor characterization of locally advanced disease
- CT or MRI of the abdomen and pelvis with IV and PO contrast
  - Gold standard for diagnosis and staging
  - Midline, calcified, partially cystic mass with local extension is concerning for but not diagnostic of urachal carcinoma.
- Chest x-ray or CT of chest for staging

- Bone scan if advanced disease, bony symptoms, or elevated alkaline phosphatase

Diagnostic Procedures/Surgery

- Cystoscopy with transurethral biopsy or resection
  - Evaluate for intravesical invasion, drop metastases, or metasynchronous bladder cancer
  - Biopsy or resection of tumor and adjacent normal urothelium is recommended but may be difficult due its extravesical location.
  - Any tumor arising from the dome of bladder should be considered urachal in origin until proven otherwise.
- Percutaneous biopsy may be performed but raises a theoretical concern for seeding the biopsy tract.

Pathologic Findings

- A majority (>80%) is adenocarcinoma with glandular features and produces mucin.
  - Similar immunohistochemistry to colonic adenocarcinoma (1)
    - Strong reactivity for 34BE12 and lack of diffuse nuclear reactivity for β-catenin is more suggestive of urachal origin.
  - No immunohistochemical markers to differentiate adenocarcinoma originating from the urachus and bladder
- Other subtypes
  - Sarcoma
  - Squamous-cell carcinoma
  - Urothelial carcinoma
- Pathologic criteria
  - Definitive
    - Tumor located in the dome of bladder or along midline
    - Demarcation between tumor and urothelium
  - Supportive
    - Presence of urachal remnant in tumor
    - Enteric-type pathology
    - Absence of urothelial dysplasia or carcinoma
    - Absence of cystitis glandularis and cystisa
- Favorable (well-differentiated) histology may have a better prognosis than unfavorable (poorly differentiated) histology for similarly staged tumors (3).

DIFFERENTIAL DIAGNOSIS

- Primary bladder lesion
  - Primary bladder cancer of any histologic type at the dome of bladder
  - Secondary malignancy of gynecologic or colorectal origin invading into the bladder
- Periumbilical mass
  - Urachal remnants
    - Patent urachus
    - Urachal cyst
    - Urachal sinus
    - Vesicourachal diverticulum
  - Umbilical hernia

- Urachal neoplasms: Adults
  - Benign (very rare): Adenomas, fibromas, fibroadenomas, fibromyomas, hamartomas
  - Malignant (very rare, less than 0.5% of all bladder cancers): Mostly adenocarcinoma
- Sister Mary Joseph nodule (adults): Umbilical metastasis of primary tumors (if primary is known, usually from genital or GI tract)
- Others: Dermoid cyst, sebum cyst, spontaneous umbilical fistula from Crohn disease/TB/perforated appendix, and skin cancers such as basal-cell or squamous-cell carcinoma

TREATMENT

GENERAL MEASURES

- Typically manifests as locally advanced or metastatic disease.
  - Less than 20% of patients present with stage 1 (no invasion) or 2 (invasion confined to urachus) disease based on Sheldon staging system in most series.
- Management is controversial but typically involves surgical resection.
- Chemotherapy and radiation therapy are generally thought to be less effective and reserved for higher stage disease.

MEDICATION

First Line

- Chemotherapy is typically reserved for unresectable or metastatic disease.
  - No standard regimen established.
  - Regimens using 5-fluorouracil, cisplatin, and either α-interferon or gemcitabine and lucovorin are superior to others.
  - Median overall survival of 20 months reported in patients with at least a partial response or stabilized disease (4)[B].
- No definitive role for neoadjuvant chemotherapy

Second Line

No definitive role but often used as an adjuvant therapy for margin- and node-positive disease as well as recurrences.

SURGERY/OTHER PROCEDURES

- Radical cystectomy or partial cystectomy with wide surgical margins and en-bloc resection of urachal remnant extending from bladder to umbilicus, posterior rectus sheath, and all tissue between medial umbilical ligaments is recommended for lower stage, resectable disease.
  - Partial cystectomy may offer a comparable oncologic outcome and less morbidity to radical cystectomy if tumor is completely resected (3 – 5)[C].
  - Failure to resect the umbilicus and positive surgical margins are associated with a worse outcome (2,4,5)[B].
- Bilateral pelvic lymph node dissection
  - Should follow the standard template for bladder cancer.
  - May be useful for staging but does not provide any survival advantage (1,2)[B].
- Surgical resection is particularly well suited to a laparoscopic or robotic approach with

comparable short-term outcomes.

ADDITIONAL TREATMENT

Radiation Therapy

- Limited evidence
- Occasionally used for unresectable or metastatic disease (with chemotherapy) or as an adjuvant therapy for margin- and node-positive disease as well as recurrences.
- Median overall survival of 19.5 mo and 21 mo reported after radiation therapy alone and radiation therapy with chemotherapy, respectively (1)[B].

Additional Therapies

None

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS

- Clinical and pathologic staging is the most important predictor of survival (1 – 5)[B].
  - Two staging systems (Sheldon and Ashley) (6) (See Section II: Urachal Carcinoma Staging Systems)
- 5-yr overall survival rates range from 27 to 80%, depending on the series.
  - About 50% for locally advanced disease (1 – 5)[B]
  - Less than 20% for metastatic disease (1 – 4)[B]
  - 93% for disease confined to the urachus and bladder after surgical resection with bladder preservation (5)[B]
  - 69% for extravesical and peri-urachal disease after surgical resection with bladder preservation (5)[B]

COMPLICATIONS

- Bleeding
- Infection
- Injury to surrounding organs
- Urinary leak
- Lymphocele
- Postoperative cardiopulmonary complications, including myocardial infarction, deep vein thrombosis, and pulmonary embolism
- Development of recurrent or progressive disease

FOLLOW-UP

Patient Monitoring

- No standard schedule for oncologic surveillance established
- Adaptation from bladder cancer
  - Radical cystectomy
    - History and physical examination, electrolytes, serum creatinine, and urine cytology every 3–6 mo for 2 yr and then as clinically indicated

- Imaging of the chest, abdomen, and pelvis every 3–12 mo for 2 yr based on risk of recurrence and then as clinically indicated
- Partial cystectomy
  - Same as above
  - Cystoscopy every 3–6 mo for 2 yr and then at increasing intervals as clinically indicated

Patient Resources

- Bladder Cancer, National Cancer Institute, National Institutes of Health
  – www.cancer.gov/cancertopics/types/bladder
- Urachal cancer, Offices of Rare Diseases Research, National Institutes of Health
  – rarediseases.info.nih.gov/gard/7836/urachal-cancer/resources/1
- Urachal Anomalies, Urology Care Foundation, American Urologic Association
  – www.urologyhealth.org/urology/index.cfm?index=41

REFERENCES

1. Molina JR, Quevedo JF, Furth AF, et al. Predictors of survival from urachal cancer: A Mayo Clinic study of 49 patients. *Cancer*. 2007;110(11):2434–2440.
2. Ashley RA, Inman BA, Sebo TJ, et al. Urachal carcinoma: Clinicopathologic features and long-term outcomes of an aggressive malignancy. *Cancer*. 2006;107(40):712–720.
3. Pinthus JH, Haddad R, Trachtenberg J, et al. Population based survival data on urachal tumors. *J Urol*. 2006;175(6):2042–2047.
4. Siefker-Radtke AO, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: The M.D. Anderson Cancer Center experience. *J Urol*. 2003;169(4):1295–1298.
5. Herr HW, Bochner BH, Sharp D, et al. Urachal carcinoma: contemporary surgical outcomes. *J Urol*. 2007;178(1):74–78.
6. Mohile SG, Schleicher L, Petrylak DP. Treatment of metastatic urachal carcinoma in an elderly woman. *Nat Clin Pract Oncol*. 2008;5:55–58.

ADDITIONAL READING

- Laboccetta LT, Picard JC. The urachus: A review and update. *AUA Update Series*. 2012;31:89–96.
- Siefker-Radtke A. Urachal Adenocarcinoma: A Clinician's Guide for Treatment. *Semin Oncol*. 2012;39(5):619–624.

See Also (Topic, Algorithm, Media)

- Bladder Cancer, Adenocarcinoma
- Umbilical Abnormalities, Urologic considerations
- Urachal Abnormalities
- Urachal Carcinoma Images ☼
- Urachal Carcinoma Staging Systems

CODES

ICD9

- 188.7 Malignant neoplasm of urachus
- 198.1 Secondary malignant neoplasm of other urinary organs

ICD10

- C67.7 Malignant neoplasm of urachus
- C79.11 Secondary malignant neoplasm of bladder

CLINICAL/SURGICAL PEARLS

- It is difficult to differentiate between an infection and urachal carcinoma for symptomatic urachal lesions.
- There should be a high clinical suspicion for urachal carcinoma in any adult with an urachal lesion.
- Any tumor arising from the dome of bladder should be considered urachal carcinoma until proven otherwise.
- Surgical management of urachal carcinoma should involve a complete resection of the urachus and umbilicus with wide surgical margins.

URETER AND RENAL PELVIC TUMORS, GENERAL CONSIDERATIONS

Julie M. Riley, MD
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BASICS

DESCRIPTION

- Tumors of the ureter and renal pelvis are relatively rare.
- Tumors are most often malignant and account for 5% of all urothelial tumors; most commonly TCC (transitional cell carcinoma), also called urothelial cell carcinoma (UCC).

EPIDEMIOLOGY

Incidence

- 1 in 113,333 or ~2400 cases/yr
- 7% of all kidney tumors
- Ureteric TCC account for 1 in every 25 upper-tract tumors
- Males:female = 2:1
- More common in Caucasian population
  - Asians more often have high-grade tumors

Prevalence

Rare <40 yr, peak incidence 6th–7th decade

RISK FACTORS

- Smoking: Risk from 2.6–8.0
  - Increases with higher dose and duration
- History of bladder cancer: 2–25% of patients with bladder cancer develop upper-tract TCC
- Occupational exposure: Similar to bladder cancer; risk from 4.0 to 5.5
  - ~20% of TCCs
  - Disease latency of 30–50 yr
  - Aromatic amines (aniline dyes [color fabrics]), 2-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, 4,4-diaminobiphenyl, 2-amino-1-naphthol, soot from coal, combustion gas, and aliphatic hydrocarbons
  - High-risk jobs: Autoworkers, leather workers, painters, truck drivers, met al workers, machinists, dry cleaners, dental technicians, beauticians, and physicians
- Coffee: Minor contribution, relative risk of 1.3
- Analgesic abuse: All components implicated; highest risk with phenacetin abuse; latency of 25 yr (dose of 10–15 g over 10 yr); tend to be women who present with high-stage tumors. Relative risk: 2.4 for men and 4.2 for women
- Cyclophosphamide: Hemorrhagic cystitis and carcinoma; 9 times increased risk of carcinoma after exposure; latency of 6–13 yr
- Infectious agents: Chronic bacterial infection with calculi and obstruction; increased risk of SCC (squamous-cell carcinoma)

- Balkan nephropathy: Endemic to Bulgaria, Greece, Romania, and Yugoslavia
  - Carcinogenic potential of *Aristolochia fangchi* and *Aristolochia clematis* (plants endemic to the Balkans).
  - Often multiple, bilateral, and indolent tumors
  - Renal-sparing surgery when possible
- Black Foot disease: Vasculopathy in Taiwan; arsenic contamination of water
- Lynch syndrome

Genetics
- Most have no family history of disease
- Certain familial cancer syndromes show an increased incidence of TCC (Lynch type II)
- Familial clustering exists; difficult to determine if related to environmental factors
- Low-grade superficial TCC: *p15* and *p16* loss (chromosome 9p)
- High-grade TCC: *p53* loss (chromosome 17p)
- Amplification and overexpression of genes that code for growth factors or their receptors
  - EGF-R (chromosome 7): Trisomy 7 associated with TCC
  - Erb-2 mutations associated with TCC

PATHOPHYSIOLOGY
- >90% upper tract urothelial tumors are TCCs
  - ~70% ureteral TCCs occur in distal ureter, 25% mid ureter, and 5% proximal ureter.
  - Tumors of the ureter tend to be less invasive and smaller than those of the renal pelvis.
  - Up to 50% of ureteral TCCs are multicentric.
- SCC: 7%; associated with long-term infection, inflammation, and calculi
- Rare malignant tumors include sarcoma, adenocarcinoma, and carcinosarcoma.
- Rare benign tumors include inverted papilloma and fibroepithelial polyp.

ASSOCIATED CONDITIONS
Urothelial carcinoma of the bladder

GENERAL PREVENTION
- Smoking cessation
- Avoid or limit chronic analgesia use.
- Avoid exposure to implicated toxins

DIAGNOSIS

HISTORY
- Age and sex of patient: Peak incidence in mid-60s, male > female
- Hematuria: Most common presenting symptom (75% of patients)
- Dull flank pain due to the gradual distention of collecting system (30% of patients)
- Tobacco use or occupational exposure (up to 20% of TCCs)
- History of analgesia abuse in past: Dose-related effect; phenacetin is most common
- History of recurrent infections and calculi: SCC
- Asymptomatic: Incidental diagnosis in 10–15%
- Rarely, patients present with signs of advanced disease (abdominal or flank mass, anorexia, weight loss, etc.)

PHYSICAL EXAM

Usually normal; flank or abdominal mass with advanced disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis: Hematuria (gross or microscopic)
- Cytopathology:
  - Voided specimen: Low sensitivity for upper-tract TCC; ureteral catheterization specimens are more sensitive.
  - Accuracy increases with increasing grade of tumor.

Imaging

- Intravenous pyelogram (IVP):
  - 50–75%: Radiolucent filling defect; irregular and continuous with the wall
  - 10–30% show obstruction or non-visualization of the collecting system, which indicates more invasive disease
  - Assess contralateral kidney for lesion and function
- Retrograde pyelography (RGP): Better visualization than IVP (>75% accuracy)
- Antegrade pyelography:
  - Used only if not possible to visualize collecting system via retrograde approach utilizing a percutaneous nephrostomy tube.
- Computed Tomography Urogram (CTU): Primary imaging study, used for diagnosis and staging of tumors (image)
- Magnetic resonance imaging (MRI): For staging

Diagnostic Procedures/Surgery

- Ureteroscopy (URS) and nephroscopy (image):
  - Diagnostic accuracy of 58–83%.
  - Not accurate for staging TCCs due to difficulty in determining the depth of invasion, particularly renal pelvic TCC
- Brush biopsy:
  - High positive predictive value, overall accuracy of 78%
  - significant risk of bleeding and perforation
- Selective cytology barbotage (repeated injection and aspiration of saline): Localize tumor

Pathologic Findings

- Urothelial carcinoma: Papillary (exophytic) predominate:
  - Slender stalks or endophytic (flat)
  - Invasive or noninvasive
  - Almost no tumors of low malignant potential in the upper tract
- SCC is characterized by sheets of cells with well-defined cell borders, deeply eosinophilic cytoplasm, and focal keratin pearl formation.

DIFFERENTIAL DIAGNOSIS

- Malignant filling defect of ureter and renal pelvis:
  - TCC Urothelial cell carcinoma: The most common malignant cause of upper urinary tract filling defects.

  – Squamous cell carcinoma (SCC)
  – Rare malignant tumors: Adenocarcinoma, sarcoma, angiosarcoma, and carcinosarcoma
  – Renal cell carcinoma (RCC)
• Benign filling defect of the ureter and renal pelvis:
  – Air: Iatrogenic, infectious, or due to fistula
  – Blood clot
  – Fibroepithelial polyp
  – Fungus ball
  – Hemangioma
  – Inflammatory lesions: Granuloma, malakoplakia, tuberculosis
  – Inverted papilloma
  – Radiolucent calculus
  – Rare benign tumors: Leiomyoma, neurofibroma, cholesteatoma
  – Renal or sloughed papilla
  – Extrinsic compression on the ureter
  – Mucus: Urinary diversion patients
  – Protein matrix
  – Ureteritis or pyelitis cystica
  – Vascular impression

TREATMENT

GENERAL MEASURES
• If positive cytology is the only sign of upper tract TCC, close follow-up is required.
• Standard treatment is surgical for most benign and malignant lesions.

MEDICATION
First Line
N/A

Second Line
• Instillation therapy with BCG or mitomycin not proven to increase survival:
  – Appears to be safe
  – May be useful in multiple superficial tumors or bilateral disease
  – Difficult to deliver the agent in adequate doses and dwell time

SURGERY/OTHER PROCEDURES
• Standard treatment is nephroureterectomy (NU): Laparoscopic or open
• Renal-sparing surgery indicated: Solitary kidney, bilateral disease, poor function of contralateral kidney, or low grade and stage
• Survival related to stage and grade of tumor rather than to treatment modality
• Radical NU and excision of bladder cuff
  – 80–90% 5-yr survival (low grade and stage)
  – 30–75% recurrence rate in ureteral stump
  – Radical lymphadenectomy not shown to improve survival
  – Endoscopic approach to bladder cuff resection has slightly higher rate of bladder

recurrence (1)
- Endoscopic treatment (ureteroscopy [URS]) or percutaneous):
  - Indications: solitary kidney, poor renal function, bilateral disease, moderate tumor burden, low-grade, poor surgery candidate
  - Risk of perforation is higher than that in bladder (overall complication rate: 7%)
  - Requires close follow-up due to high recurrence rate (recurrence free survival ~ 20% at 10 yr) (2)
  - Laser ablation in low-grade or multiple tumors
  - Seeding of percutaneous tract is low (0.03%) (3)
- Segmental ureteral resection: Solitary low-grade upper and mid-ureteral lesions:
  - Recurrence rate of 6%; higher if multifocal
- Distal ureterectomy and ureteroneocystostomy: Distal, solitary ureteral lesions
- Benign tumors such as fibroepithelial polyp or inverted papilloma: Endoscopic management

ADDITIONAL TREATMENT

Radiation Therapy

Can be used for advanced tumors not amenable to surgery, with decreased efficacy

Additional Therapies

- Neoadjuvant/adjuvant chemotherapy has not been established as in bladder cancer (3)
  - Cisplatin therapies have been successful

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Recurrence rate reduced with more aggressive resection of tumor:
  - 48% recurrence with nephrectomy
  - 32% with nephrectomy plus partial ureterectomy
  - 24% with nephrectomy plus subtotal ureterectomy
  - 12% with NU
- Prognosis largely unchanged in locally advanced disease for last 20 yr
- Better survival for tumors in renal pelvis than ureteral in T3 or higher disease

COMPLICATIONS

- Obstruction of urinary tract
- Development of metastatic disease

FOLLOW-UP

Patient Monitoring

- Cystoscopy with cytology every 3–6 mo for 2–3 yr, then yearly
- 6-mo CT urogram + chest x-ray, then annually
- URS is more sensitive than radiologic techniques for follow-up of upper-tract TCC

Patient Resources

Urology Care Foundation http://www.urologyhealth.org/urology/index.cfm?article=39

REFERENCES
1. Xylinas E, Rink M, Cha EK, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol.* 2012; 65(1):210–217.
2. Cutress ML, Stewart GD, Wells-Cole S, et al. Long-term endoscopic management of upper tract urothelial carcinoma: 20 year single centre experience. *BJU Int.* 2012;110(11):1608–1617.
3. Alva AS, Matin SF, Lerner SP, et al. Perioperative chemotherapy for upper tract urothelial cancer. *Nat Rev Urol.* 2012;9(5):266–273.

ADDITIONAL READING

- Cutress ML, Stewart GD, Zakikhani P, et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma: A systematic review. *BJU Int.* 2012;110(5):614–628.
- Ristau BT, Tomaszewski JJ, Ost MC. Upper tract urothelial carcinoma: Current treatment and outcomes. *Urology*. 2012;79(4):749–756.
- Rouprêt M, Babjuk M, Compérat E, et al. European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol.* 2013;63(6):1059–1071.

See Also (Topic, Algorithm, Media)
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Reference Tables: TNM: Renal Pelvis and Ureter Cancer
- Ureter and Renal Pelvic Tumors, General Considerations Images
- Ureter and Renal Pelvis, Squamous Cell Carcinoma
- Ureter and Renal Pelvis, Urothelial Carcinoma

CODES

ICD9
- 189.1 Malignant neoplasm of renal pelvis
- 189.2 Malignant neoplasm of ureter
- 239.5 Neoplasm of unspecified nature of other genitourinary organs

ICD10
- C65.9 Malignant neoplasm of unspecified renal pelvis
- C66.9 Malignant neoplasm of unspecified ureter
- D49.5 Neoplasm of unspecified behavior of other genitourinary organs

CLINICAL/SURGICAL PEARLS

- Ureteral and renal pelvic tumors are rare.
- Management remains surgical with NU being the gold standard.
- Endoscopic management is becoming more accepted but the risk of under staging and under grading remains.
- Close follow-up is warranted and ureteroscopy remains the most sensitive surveillance test.

URETER AND RENAL PELVIS, SQUAMOUS CELL CARCINOMA

Angela B. Smith, MD
Raj S. Pruthi, MD, FACS

BASICS

DESCRIPTION

- Squamous-cell carcinoma (SCC) of the renal pelvis and ureter is a rare but aggressive tumor characterized by nests of squamous cells with hyperchromatic nuclei and prominent keratin production.
- Most common non-urothelial tumor of the upper urinary tract.

EPIDEMIOLOGY

Incidence

- 0.5–0.8% of all malignant renal tumors (1)[C]
- 6–15% of all upper tract urothelial cancers (4)[C]
- Mean age 61 yr
- Equal incidence male:female (although some series suggest male predominance) (2,3)[C]
- 6× more likely to occur in the renal pelvis than in the ureter

Prevalence

- Prevalence unknown due to rarity of tumor
  - Rare tumor, with case reports in literature

RISK FACTORS

- Chronic inflammation (4)[C]
- Chronic infections associated with (4)[C]
  - Urinary stones
  - Obstruction
- Cyclophosphamide (alkylating agent) shown to increase risk of upper tract SCC

Genetics

- No specific genetic patterns identified
- Possible that DNA ploidy pattern correlates with grade and stage but does not aid prognosis
  - Not definitive; requires further study (3)[C]

PATHOPHYSIOLOGY

- SCC of the renal pelvis and ureter has been shown to be associated with chronic infection and inflammation
  - Presumed that chronic irritation of urothelium leads to squamous metaplasia and subsequent SCC

ASSOCIATED CONDITIONS

- Chronic infections: (4)[C]
  - Genitourinary tuberculosis
  - Struvite stones

  – Chronic pyelonephritis or pyonephrosis
  – Parasitic infection
• Chronic inflammation: (4)[C]
  – Analgesic abuse
  – Prior percutaneous nephrolithotomy
• Horseshoe kidney (3× risk due to stones/infection) (4)[C]
• Renal or ureteral calculi (4)[C]
  – Present in up to 50% of cases
• Bladder cancer history uncommon (3)[C]
  – 5% preceding diagnosis
  – 2% with concomitant bladder cancer

GENERAL PREVENTION

As a rare condition, little evidence exists for prevention of this condition

DIAGNOSIS

HISTORY

• History of chronic renal infections or stones
• Vague abdominal or flank pain
• Gross hematuria
• Local symptoms more common than those with TCC urothelial carcinoma (4)[C]
• Nonspecific symptoms:
  – Anorexia
  – Lethargy
  – Weight loss

PHYSICAL EXAM

• Often no signs on physical exam
• Flank or abdominal mass may be present with advanced disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Urinalysis:
  – Hematuria
  – Pyuria
• Serum chemistries (3)[C]
  – Serum creatinine may be elevated due to tumor infiltration, obstruction, chronic infection, or scarring
  – Paraneoplastic syndrome which may resolve following resection includes:
    ○ Hypercalcemia
    ○ Leukocytosis
    ○ Thrombocytosis

Imaging

• Diagnosis suggested (but not definitive) with radiologic imaging
• Excretory imaging useful (including intravenous pyelogram, CT urogram) and may

demonstrate:
  – Filling defect
  – Solid mass w/ or w/o calcifications
  – Hydronephrosis
• Once pathology confirmed, CT or MRI/MRA necessary for surgical planning
  – Vascular anatomy
  – Presence of metastases
  – Evaluation of contralateral renal unit
  – Size and extent of tumor

Diagnostic Procedures/Surgery

• Cystoscopy to evaluate for lower tract urothelial cancer, selective ureteral cytology
• Retrograde ureteropyelogram and ureteroscopy/pyeloscopy with biopsy essential
  – Often with sessile appearance
  – May have calcifications
• Definitive diagnosis confirmed following nephroureterectomy (see TREATMENT)

Pathologic Findings

• Most moderately or poorly differentiated
• Gross (1)[C]
  – Infiltrating at time of diagnosis
  – Sessile tumor on endoscopy
  – Usually large, necrotic, ulcerated
• Histology (5)[C]
  – Sheets of cells with deeply eosinophilic cytoplasm
  – Large nuclei with prominent nucleoli
  – Focal keratin pearl formation
    ○ Keratin pearls and intercellular bridges may not be apparent in advanced cases

DIFFERENTIAL DIAGNOSIS

• Primary renal neoplasms
  – Renal cell carcinoma
  – Urothelial cancer (TCC) of upper tract
  – Wilms tumor
• Secondary renal neoplasms
  – Lymphoma/leukemia
  – Metastasis to kidney (breast, lung, and others)
• Benign renal masses
  – Xanthogranulomatous pyelonephritis
  – Rare form of chronic pyelonephritis
  – Angiomyolipoma

TREATMENT

GENERAL MEASURES

Surgery (nephroureterectomy) is mainstay of treatment (3)[C]

MEDICATION

First Line

Medical therapy not effective although some patients require broad-spectrum antibiotics in the setting of concurrent infection

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Referent standard treatment is surgical excision (radical nephroureterectomy with excision of bladder cuff) (3)[C]
- Role of retroperitoneal lymph node dissection controversial
- For those patients with infection, pre- and post-operative antibiotics may be required

ADDITIONAL TREATMENT

Radiation Therapy

Occasionally used for adjuvant treatment following surgery; however shown to have little benefit (1)[C]

Additional Therapies

Adjuvant platinum-based chemotherapy appears to have limited benefit (3)[C]

Complementary & Alternative Therapies

No complementary therapies have shown benefit

ONGOING CARE

PROGNOSIS

- Generally poor if found at advanced stage
  - Median survival of 7–14 mo postoperatively (2 – 4)[C]
  - Median 5-yr survival 7.7% (3)[C]
- Tumor stage at diagnosis most important for prognosis (3)[C]
- Grade has been found to add little value (3)[C]

COMPLICATIONS

- Renal insufficiency or failure
- Metastatic disease (3)[C]
  - Regional lymph nodes
  - Lungs
  - Liver
  - Bone

FOLLOW-UP

Patient Monitoring

- Limited data for patient monitoring
- Similar to TCC of upper tract
  - Urine cytology and cystoscopy every 3–4 mo for first 2 yr
  - Value of cystoscopy questionable due to low number of concurrent bladder cancers
- Metastatic workup every 6–12 mo, depending on stage

  – Chest imaging
  – CT abdomen/pelvis
- Monitor renal function periodically

Patient Resources

Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=39

REFERENCES

1. Kayalselcuk F, Bal N, Guvel S, et al. Carcinosarcoma and squamous cell carcinoma of the renal pelvis associated with nephrolithiasis: A case report of each tumor type. *Pathol Res Pract.* 2003;199:489–492.
2. Nativ O, Reiman HM, Lieber MM, et al. Treatment of primary squamous cell carcinoma of the upper urinary tract. *Cancer*. 1991;68:2575–2578.
3. Holmäng S, Lele SM, Johansson SL. Squamous cell carcinoma of the renal pelvis and ureter: Incidence, symptoms, treatment and outcome. *J Urol.* 2007;178(1):51–56.
4. Busby JE, Brown GA, Tamboli P, et al. Upper urinary tract tumors with nontransitional histology: a single-center experience. *Urology*. 2006;67(3):518–523.
5. Perez-Montiel D, Wakely PE, Hes O, et al. High-grade urothelial carcinoma of the renal pelvis: Clinicopathologic study of 108 cases with emphasis on unusual morphologic variants. *Mod Pathol.* 2006;19(4):494–503.

ADDITIONAL READING

- Xylinas E, Rink M, Margulis V, et al. Histologic variants of upper tract urothelial carcinoma do not affect response to adjuvant chemotherapy after radical nephroureterectomy. *Eur Urol.* 2012;62(1):e25–e26.
- Rouprêt M, Babjuk M, Compérat E, et al. ; European Association of Urology. European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol.* 2013;63(6):1059–1071.

See Also (Topic, Algorithm, Media)

- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Reference Tables: TNM: Renal Pelvis and Ureter Cancer
- Ureter and Renal Pelvic Tumors, General Considerations
- Ureter and Renal Pelvis, Squamous Cell Carcinoma Image
- Ureter and Renal Pelvis, Urothelial Carcinoma

CODES

ICD9

- 189.1 Malignant neoplasm of renal pelvis
- 189.2 Malignant neoplasm of ureter

ICD10

- C65.1 Malignant neoplasm of right renal pelvis
- C65.9 Malignant neoplasm of unspecified renal pelvis
- C66.9 Malignant neoplasm of unspecified ureter

CLINICAL/SURGICAL PEARLS

- SCC of upper tract is the most common non-urothelial cancer of the renal pelvis and ureter.
- A few symptoms manifest, but once hematuria and pain present, often advanced stage.
- Usually presents as advanced disease and has poor prognosis at this stage.
- Nephroureterectomy is standard of care with chemotherapy and radiation of limited benefit.

URETER AND RENAL PELVIS, UROTHELIAL CARCINOMA

Emma F.P. Jacobs, MD
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BASICS

DESCRIPTION

Urothelial carcinoma (formerly known as transitional cell carcinoma or TCC) is an epithelial neoplasm of the ureter, renal pelvis, and calyces

EPIDEMIOLOGY

Incidence

- 5–10% of renal tumors are renal pelvis TCC
- 2–5% of urothelial tumors occur in the upper urinary tract (UUT)
- Peak incidence of 10 per 100,000/yr in 75–79 age group
- Mean age at presentation is 65, seldom appear before age 40 yr.
- Incidence is increasing.

Prevalence

Poor data available given rarity of condition

RISK FACTORS

- Bladder cancer (2–4% lifetime risk of UUT TCC)
  - Stage, grade, multiplicity, ureteral reflux, recurrent CIS after BCG, and TCC close to ureteral orifice all increase likelihood of UUT TCC in patient with bladder TCC
- Contralateral UUT TCC (1.6–6% risk)
- Risk factors shared with bladder TCC:
  - Cigarette smoking (≥3 times risk; only partly declines with smoking cessation)
  - Occupational exposure (≥4 times risk):
    - Aniline dyes, β-naphthylamine, benzidine, coal, coke, asphalt, or tar exposure; chemical, petroleum, or plastics industries
  - Cyclophosphamide:
    - Mesna (Uro-protectant) can be coadministered to neutralize acrolein (urotoxic metabolite)
- Other risk factors specific to UUC TCC:
  - Balkan nephropathy (100–200 times risk):
    - Typically bilateral, multifocal, low-grade
    - May be environmental rather than genetic
  - Analgesic abuse (3.6 times risk):
    - Phenacetin, aspirin, acetaminophen, codeine
    - Papillary necrosis (6.9 times risk):
    - Synergistic with analgesic abuse (20 times risk)
  - Chinese weight-loss herb *Aristolochia fangchi*

Genetics

- Male > Female (3:1)
- White > Black (2:1)
- Lynch II syndrome (HNPCC): Familial syndrome predisposing to GI, endometrial, and UUT neoplasms

PATHOPHYSIOLOGY
- Growth patterns include papillary and nodular
- TMN staging (stage is most important predictor of survival)
  - Stage Ta: Papillary, noninvasive
  - Stage Tis: CIS
  - Stage T1: Invades subepithelial connective tissue
  - Stage T2: Invades muscularis
  - Stage T3: Invades periureteral fat (renal pelvis only, and/or invades beyond muscularis into perinephric fat or the renal parenchyma
  - Stage T4: Invades adjacent organ or through kidney into perinephric fat

ASSOCIATED CONDITIONS
- Bladder TCC: 30–50% risk of developing bladder TCC after UUT TCC
- Balkan nephropathy
- Lynch II syndrome

GENERAL PREVENTION
Avoidance of risk factors

DIAGNOSIS
HISTORY
- Gross hematuria, dull flank pain, acute renal colic, weight loss, anorexia, bone pain
- Social history: Tobacco use, occupational exposures
- Medications: Analgesics (i.e., phenacetin, aspirin), cyclophosphamide, exotic herbs
- Family history: Balkan family, colonic malignancy

PHYSICAL EXAM
- Often asymptomatic
- CVA tenderness
- Flank or abdominal mass

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urine analysis: Gross or microscopic hematuria (60–90% present with hematuria)
- Electrolytes, LFTs normal in absence of urinary obstruction, or metastatic disease
- Voided urine cytology: Low sensitivity for low-grade TCC; better for high-grade, CIS

Imaging
- Intravenous urogram (IVU) or intravenous pyelogram (IVP):—traditional diagnsotic study largely replaced by CT Urograms
- Retrograde pyeloureterography
  - Indications: Contrast allergy, renal insufficiency
  - More sensitive than IVU or computerized tomographic urography (CTU)

  - Use dilute contrast (1/2–1/3).
  - Inject through cone-tip or open-ended catheter to fill entire collecting system (10–15 cc).
  - Avoid contrast extravasation due to overfilling.
- Computerized tomographic urography (CTU):
  - 3D reconstruction image quality is equivalent to IVU for UUT TCC.
  - Can differentiate renal parenchymal mass from extrinsic mass, and TCC from calculus
  - Can evaluate for locoregional or distant metastatic disease
- Ultrasound (US):
  - Can help distinguish stone from tumor in the setting of a fillling defect in the upper urinary tract

Diagnostic Procedures/Surgery

- Cystoscopy: Evaluates lower urinary tract for concomitant TCC
- Ureteroscopy: Provides direct visualization of UUT TCC, aspiration for cytology, cup/basket biopsy, and treatment simultaneously
- Catheterized ureteral or RP washing: 65–73% sensitive
- Ureteroscopic cup/basket biopsy: Most sensitive
- Brush biopsy: 91% sensitive, 88% specific

Pathologic Findings

- Pathologic staging of UUT TCC is difficult due to the limited size of biopsy specimens.
- Staging is predicted by biopsy grade.
- Tumor grade may be a more important prognostic factor than pathologic stage in UUT.
- Sending all biopsies for cytopathologic exam can improve the diagnostic yield (cell block).

DIFFERENTIAL DIAGNOSIS

- TCC is the most common malignant cause of UUT filling defects
- Squamous-cell carcinoma—Often associated with stones and recurrent infections
- Rare malignant tumors (adenocarcinoma, sarcoma, angiosarcoma, and carcinosarcoma)
- RCC—Typically found in conjunction with renal mass; has been reported without associated renal mass as a filling defect in the collecting system
- Benign filling defects of the ureter and renal pelvis:
  - Air: Iatrogenic, infectious, fistula
  - Blood clot
  - Fibroepithelial polyp
  - Fungus ball
  - Hemangioma
  - Inflammatory lesions: Granuloma, malakoplakia, TB
  - Inverted papilloma
  - Radiolucent calculus
  - Rare benign tumors: Leiomyoma, neurofibroma, cholesteatoma
  - Renal papilla—Ectopic or end on
  - Sloughed papilla
  - Extrinsic compression of the ureter
  - Mucous (urinary diversion patients)
  - Protein matrix

- Ureteritis or pyelitis cystica
- Vascular impression

TREATMENT

GENERAL MEASURES (2)

- Surgical excision is gold standard.
  - Preservation of renal unit is preferred when possible (low-grade focal disease) or involving the distal ureter (low- or high-grade disease)

MEDICATION

First Line

- Limited role, benefit has not been consistently demonstrated
  - Topical therapy- BCG, mitomycin, thiotepa
    - Instilled via percutaneous nephrostomy, external urethral catheter, or into bladder with indwelling ureteral stent
    - Typically given for large, multifocal, or residual tumor burden

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Open radical nephroureterectomy (RNU) with en-bloc excision of peri-ureteric bladder cuff:
  - Traditional treatment
  - Provides adequate surgical margins, local control, removes need for ipsilateral ureteroscopic surveillance, provides most accurate staging information
  - Role of lymphadenectomy is unclear
- Laparoscopic RNU
  - Equivalent disease-specific and overall survival compared to open RNU
  - Skin incision positioned to allow for distal ureteral dissection and en-bloc specimen removal
- Nephron-sparing surgery—For locally contained low-grade disease or high-grade disease with overwhelming concern for loss of renal function
  - Segmental ureterectomy
  - Used for noninvasive low-grade TCC of proximal or mid ureter too large for endoscopic ablation
  - Distal ureterectomy with reimplantation
    - Used for distal ureteral TCC to large for endoscopic ablation or high-grade TCC
- Endoscopic treatment
  - Indications include solitary kidney, bilateral disease, poor renal function, moderate tumor burden, low-grade disease, high-risk surgical candidates
  - Retrograde or percutaneous antegrade approach
  - Tumor biopsy with cold-cup or basket
  - Treatment techniques include electrosurgical resection, fulguration, laser ablation
  - Recurrence rates: 33% for ureteral TCC, 31% for renal pelvic TCC

ADDITIONAL TREATMENT

Radiation Therapy
Possible role for adjuvant radiation after complete excision. Studies have been small and collectively inconclusive.

Additional Therapies
- Consider systemic chemotherapy for high-stage or node-positive disease in patient with adequate renal function
  - Standard urothelial agents as used for bladder cancer
    - Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)
    - Gemcitabine and cisplatin

Complementary & Alternative Therapies
No accepted therapy

ONGOING CARE

PROGNOSIS
- Overall 5-yr survival based on grade:
  - Grade 1–2: 40–87%
  - Grade 3–4: 0–33%
- 5-yr survival based on stage:
  - Stage Ta, T1, Tis: 60–90%
  - Stage T2: 43–75%
  - Stage T3: 16–33%
  - Stage T4: 0–5%

COMPLICATIONS
Ureteral obstruction, metastatic dissemination

FOLLOW-UP
Patient Monitoring
- If RNU is performed: Cystoscopic surveillance and cytology every 3 mo for 2 yr, then every 6 mo for 2 yr, then yearly thereafter; IVP or CTU yearly
- If nephron-sparing surgery is performed: Ureteroscopic surveillance and cytology every 3 mo until tumor-free, then every 6 mo thereafter; IVP or CTU yearly

Patient Resources
Urology Care Foundation http://www.urologyhealth.org/urology/index.cfm?article=39

REFERENCES

1. Ristau BT, Tomaszewski JJ, Ost MC. Upper tract urothelial carcinoma: Current treatment and outcomes. *Urology*. 2012;79(4):749–756.
2. Rouprêt M, Babjuk M, Compérat E, et al. European guidelines on upper tract urothelial carcinomas: 2013 update. *Eur Urol*. 2013;63(6):1059–1071.

ADDITIONAL READING

- Bagley DH. Treatment of upper urinary tract neoplasms. In: Smith AD, Preminger G, Badlani G, et al., eds. *Smith's Textbook of Endourology*. St. Louis: QMP; 1996:474–487.

- Blute ML. Treatment of upper urinary tract transitional cell carcinoma. In: Smith AD, Preminger G, Badlani G, et al., eds. *Smith's Textbook of Endourology*. St. Louis: QMP; 1996:352–365.
- Chen GL, Bagley DH. Ureteroscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidney. *J Urol*. 2000; 164:1173–1176.
- Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in upper tract urothelial tumors. *Cancer*. 1988;62:2016.
- Keeley FX, Kulp DA, Bibbo M, et al. Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. *J Urol*. 1997;157:33–37.
- Painter DJ, Timoney AG, Denton K, et al. The modern management of upper urinary tract urothelial cancer: Tumour diagnosis, grading and staging. *BJU Int*. 2007;99:973–977.

See Also (Topic, Algorithm, Media)

- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Lynch Syndrome
- Reference Tables: TNM: Renal Pelvis and Ureter Cancer
- Ureter and Renal Pelvic Tumors, General
- Ureter and Renal Pelvis, Squamous-Cell Carcinoma
- Ureter and Renal Pelvis, Urothelial Carcinoma Image

CODES

ICD9

- 189.1 Malignant neoplasm of renal pelvis
- 189.2 Malignant neoplasm of ureter

ICD10

- C65.1 Malignant neoplasm of right renal pelvis
- C65.9 Malignant neoplasm of unspecified renal pelvis
- C66.9 Malignant neoplasm of unspecified ureter

CLINICAL/SURGICAL PEARLS

Due to the high distal recurrence rate (33–55%), it is prudent to ensure that the entire ureteral stump is removed at the time of radical nephroureterectomy (RNU).

URETER, INTRAOPERATIVE INJURY

Daniel D. Dugi III, MD
John M. Barry, MD, FACS

BASICS

DESCRIPTION

- Intra-operative injury to the ureter can ocurr during open, laparoscopic, or endoscopic surgery
- May be direct laceration, suture ligation, crush injury, thermal injury, or devascularization
- Lower 1/3 of ureter (within the pelvis) is most commonly injured
- Injury may cause obstruction of kidney if ureter is ligated or urinary extravasation if lacerated
- Due to the proximity to the vagina, some injuries may result in uretero-vaginal fistula

EPIDEMIOLOGY

Incidence

- Most series report 1–5% of pelvic surgeries; highest rates among radical hysterectomy cases (1)[B]
- 1–5% of ureteroscopic surgeries (1)[A]
- Approximately half of iatrogenic injuries occur during gynecologic surgery (2)[B]

Prevalence

N/A

RISK FACTORS

- Pelvic surgery, especially gynecologic, intestinal, urologic surgery, or aorto-iliac vascular surgery
- Laparoscopic surgery may have a higher incidence than open surgery (3)[B]
- Radiation therapy, cancer, prior pelvic surgery, aorto-iliac aneurysm, and inflammatory processes such as endometriosis, Crohn disease, and diverticulitis

Genetics

N/A

PATHOPHYSIOLOGY

- Ureters are anatomically close to the uterus, uterine and ovarian arteries, sigmoid colon and rectum, and iliac arteries, and they are at risk of injury during operations on these organs
- Although retroperitoneal organs, the ureters may become involved with inflammatory processes within the peritoneum

ASSOCIATED CONDITIONS

Any condition leading to pelvic, abdominal, or retroperitoneal surgery

GENERAL PREVENTION

- Awareness of risk of ureteral injury, especially during pelvic surgery
- Prospective identification of ureter during retroperitoneal or pelvic surgery

- Placement of ureteral catheters prior to complex pelvic surgery to aid in identifying ureters and increasing intraoperative recognition of ureteral injury (4)[C]

DIAGNOSIS

HISTORY

Most ureteral injuries are not recognized intraoperatively (3)[A]

PHYSICAL EXAM

- Intraoperative identification and inspection of ureters in cases where they are at risk for injury may help prevent or recognize an intraoperative injury
- Post-operatively, a patient with an unrecognized ureteral injury may develop fever, abdominal distention, flank or abdominal pain, or peritonitis and ileus from urinary extravasation

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Surgical drain fluid with elevated creatinine level confirms urinary extravasation
- Gross or microscopic hematuria may suggest urinary system injury but is non-specific, and its absence does not exclude injury
- Leukocytosis or elevated serum creatinine from renal obstruction or reabsorption of extravasated urine

Imaging

Contrast studies are critical for postoperative diagnosis. CT scan with IV contrast and excretory phase imaging may show urine extravasation or a urinoma

Diagnostic Procedures/Surgery

- Indigo carmine or methylene blue may help identify ureteral injury if dye is seen in the operative field after intravenous or intravesical administration
- Retrograde pyelography can definitively confirm or exclude ureteral injury. This also allows an attempt at placement of a ureteral stent
- Women with leakage of urine per vagina postoperatively may have ureteral or bladder injury. A tampon dye test may help differentiate between the two:
  - Place a Foley catheter.
  - Give oral phenazopyridine hydrochloride 200 mg orally.
  - When the urine in the Foley catheter drainage is orange, place a tampon into the vagina
  - Fill the bladder gently through the Foley with saline containing indigo carmine or methylene blue.
  - Remove the tampon. If the tampon has only orange dye, there is likely a ureteral fistula and no bladder fistula. If there is also blue dye on the tampon, there is likely a bladder fistula.
  - Further diagnostic imaging studies may still be necessary to guide therapy

Pathologic Findings

Diagnosis usually not made pathologically

DIFFERENTIAL DIAGNOSIS

- Unrecognized bladder injury
- Lymphocele
- Hematoma

TREATMENT

GENERAL MEASURES

Intraoperative recognition ensures best possible outcome and the fewest complications

MEDICATION

First Line

Indigo carmine or methylene blue may help identify ureteral injury if dye is seen in the operative field after intravenous or intravesical administration

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Injuries recognized intraoperatively:
  - Ligation injures: Remove suture and inspect for devascularization
  - Partial-thickness, clean lacerations may be closed with fine interrupted absorbable suture if the surrounding tissue has not be devascularized
  - Injuries within the pelvis are usually best repaired by direct reimplantation into bladder, with psoas hitch, if necessary (3)[C]
  - Injuries above the true pelvis (proximal ureter) may be repaired with direct anastomosis if proximal and distal mobilization allows tension-free repair of healthy, well-vascularized edges (3)[C]
  - More complex repairs, such as Boari flap, trans-uretero-ureterostomy, or ileal ureter should be undertaken cautiously in the acute setting
  - In unstable patients, the ureter may be left ligated and a percutaneous nephrostomy tube placed postoperatively to drain the kidney
  - It is best to leave an indwelling ureteral stent
- Injuries recognized postoperatively:
  - If recognized in the first few days to 1 week after initial injury, operative repair is recommended
  - If recognized later, reoperation after resolution of surgical inflammation 6 weeks or more postoperatively is recommended (2)[C]
  - Retrograde ureteropyelography is helpful in diagnosing ureteral injury and allows for attempt at ureteral stent placement in low-grade injuries (2)[C]
  - Small lacerations or partial ligations may heal after a period of ureteral stenting
  - Percutaneous nephrostomy drainage is recommended if ureteral stenting is not possible. This also allows attempt at antegrade ureteral stent placement
  - Optimal duration of ureteral stenting is not known, but 6 wk is reasonable
  - Percutaneous drainage of urinoma is necessary if the urinoma is infected, symptomatic, or does not decrease in size after reliable renal drainage is established

ADDITIONAL TREATMENT

Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Intraoperative recognition and repair usually prevents complication of urine extravasation or renal obstruction
- Ureteroneocystostomy for distal ureteral injuries has an excellent prognosis. Proximal ureteral repair have a higher risk of long-term complications because of compromised blood supply
- Patients who have delayed recognition of injuries have higher rates of complications and more procedures needed to resolve injury than those with injuries recognized intraoperatively (5)[B]

COMPLICATIONS
- Urine leakage from a ureteral injury may lead to urinoma formation and infection or abscess
- Extravasated urine may cause irritation of the intestines and peritoneum and result in pain and/or ileus
- Ureteral stricture and renal obstruction may cause loss of renal function
- Ureterovaginal fistula
- Complications of ureteral injury and repair may result in nephrectomy

FOLLOW-UP
Patient Monitoring
- Perform follow-up imaging of the kidney to assure no obstruction from ureteral stricture. Renal ultrasound can evaluate for hydronephrosis and urinoma and has no radiation.
  - Excretory imaging (i.e., ExU, CT urography, radioisotope renography with furosemide washout) may be indicated in complex circumstances or when hydronephrosis is found by ultrasound.

Patient Resources
N/A

REFERENCES

1. Al-Awadi K, Kehinde EO, Al-Hunayan A, Al-Khayat A, et al. atrogenic ureteric injuries: incidence, aetiological factors and the effect of early management on subsequent outcome. *Int J Urol Nephrol.* 2005;37:235–241.
2. Brandes S, Coburn M, Armenakas N, et al. Diagnosis and management of ureteric injury: An evidence-based analysis. *BJU Int.* 2004;94:277–289.
3. Parpala-Spaman T, Paananen I, Santala M, et al. Increasing numbers of ureteric injuries after the introduction of laparoscopic surgery. *Scan J Urol Nephrol.* 2008;48:422–427.

4. Da Silva G, Boutros M, Wexner SD, et al. Role of prophylactic ureteric stents in colorectal surgery. *Asian J Endosc Surg.* 2012;5:105–110.
5. Selzman A, Spirnak JP. Iatrogenic ureteral injuries: A 20-year experience in treating 165 injuries. *J Urol.* 1996;155:878–881.

ADDITIONAL READING

Abboudi H, Ahmed K, Royle J, et al. Ureteral injury: A challenging condition to diagnose and manage. *Nat Rev Urol.* 2013;10:108–115.

See Also (Topic, Algorithm, Media)

- Ureter, Stricture
- Ureter, Trauma

CODES

ICD9

- 867.2 Injury to ureter, without mention of open wound into cavity
- 997.5 Urinary complications, not elsewhere classified
- 998.2 Accidental puncture or laceration during a procedure, not elsewhere classified

ICD10

- N99.71 Acc pnctr & lac of a GU sys org during a GU sys procedure
- N99.81 Other intraoperative complications of genitourinary system
- S37.10XA Unspecified injury of ureter, initial encounter

CLINICAL/SURGICAL PEARLS

- During mobilization of the ureter, avoid “skeletonization” and include periureteral tissue to better preserve blood supply.
- Repair ureteral injuries and avoid nephrectomy unless the repair will place the patient at risk.
- A cystostomy allows easy access to the ureteral orifice to aid in stent placement during open surgery.

URETER, OBSTRUCTION

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Stephen Y. Nakada, MD, FACS

BASICS

DESCRIPTION

- Ureteral obstruction can be an anatomic or functional blockage of the ureter and further classified as:
  - Congenital or acquired
  - Acute or chronic
  - Benign or malignant
  - Intrinsic or extrinsic
  - Unilateral or bilateral
- Impact of obstruction dependent on:
  - Degree and duration of obstruction
  - Baseline renal function
  - Potential for reversibility
- Associated definitions:
  - Hydronephrosis
    - Dilation of renal pelvis and calyces
    - Can occur with or without obstruction (obstruction may be anywhere in urinary tract, from urethral meatus to calyces)
  - Hydroureteronephrosis
    - Dilation of renal pelvis, calyces, and ureter
  - Obstructive uropathy
    - Impedance to urinary flow anywhere in urinary tract
  - Obstructive nephropathy
    - Renal parenchymal damage from urinary tract obstruction
- Urinary tract infection and sepsis may be superimposed

EPIDEMIOLOGY

Incidence

- No data available in unselected populations
- Etiology-dependent

Prevalence

- Can occur during fet al development, childhood, or adulthood
  - Occurrence increases with increasing age
- Unilateral > bilateral
- Hydronephrosis may be surrogate marker for obstruction
  - Overall prevalence in autopsy series: 3.1% (1)

RISK FACTORS

- Renal or ureteral calculi

- Malignancy
  - Genitourinary
  - Gynecologic
  - Abdominopelvic
- Trauma
- Radiation

Genetics

- No specific associated familial or hereditary disorders, but cause may be congenital
- 30–50% of children with end-stage renal disease have obstructive uropathy associated with congenital anomalies

PATHOPHYSIOLOGY

- Ureter blockage results in elevated ureteral intraluminal pressure
- With increased pressures in proximal tubule and Bowman capsule, glomerular filtration rate (GFR) decreases
- Persistent obstruction leads to decreased renal blood flow and subsequent ischemia and nephron loss
- Three major points of anatomic ureteral narrowing:
  - Ureteropelvic junction (UPJ)
  - Where ureter crosses iliac vessels
  - Ureterovesical junction (UVJ)

ASSOCIATED CONDITIONS

- Congenital
  - Ureterocele
  - Megaureter
  - UPJ obstruction
  - Stricture
- Inflammatory
  - Abscess
  - Amyloidosis
  - Tuberculosis
  - Fungal bezoars
- Malignancy
  - Ureteral cancer
  - Bladder cancer
  - Metastatic disease
- Vascular
  - Aneurysms
  - Aberrant vessels
- Other
  - Urolithiasis
  - Pregnancy
  - Trauma
  - Retroperitoneal fibrosis

GENERAL PREVENTION
Dependent on underlying etiology

DIAGNOSIS
HISTORY
- Presentation reflects underlying etiology
- May be asymptomatic
- Acute obstruction may cause significant pain
  - Ureteral colic
    - Flank pain (proximal obstruction)
    - Pain radiating to ipsilateral groin (distal obstruction)
- Inquire about history of urinary tract infections, renal failure, urolithiasis, malignancy, radiation therapy

PHYSICAL EXAM
- Pyrexia if associated with infection
- Hypertension possible
- Costovertebral angle tenderness
- Abdominal tenderness

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum studies:
  - Creatinine
    - Often elevated, though may be normal in setting of normal contralateral kidney
  - Electrolytes
- Urine studies:
  - Urinalysis
    - May see hematuria, pyuria, or crystals
    - May see elevated pH secondary to nephron destruction in affected kidney
  - Urine electrolytes

Imaging
- Renal ultrasound
  - Screening test of choice (inexpensive, no radiation or contrast required)
  - Can identify parenchymal thickness, urinary tract dilation
- Intravenous pyelogram/excretory urography
  - Provides anatomic and functional information
  - Low false-positive rate
  - Requires contrast (limit use in renal insufficiency)
- Retrograde pyelogram
  - Delineate collecting system anatomy
- Nuclear renal scan
  - Assess relative renal function and degree of obstruction
    - $T_{1/2}$ >20 minutes consistent with obstruction
  - No contrast required

- Computed tomography (urography)
  - Determine location of obstruction
  - Highly sensitive
  - Requires contrast (limit use in renal insufficiency)

Diagnostic Procedures/Surgery

Perform Whitaker test (pressure flow test) in equivocal cases

Pathologic Findings

- Gross
  - Pelviureteric dilation
  - Papillary blunting
  - Cortical and medullary atrophy
  - Parenchymal edema
  - Enlarged, cystic appearance if total obstruction
- Microscopic
  - Collecting duct, tubular, and lymphatic dilation
  - Interstitial edema and fibrosis
  - Tubular basement membrane thickening

DIFFERENTIAL DIAGNOSIS

- Intrinsic
  - Urolithiasis
  - Sloughed papilla
  - Malignancy
- Extrinsic
  - Abdominopelvic tumors
  - Retroperitoneal fibrosis
  - Pregnancy
  - Vascular anomalies
- Anomalous course of ureter (circumcaval, retrocaval)
- Stricture disease (congenital or acquired)
- Inflammatory disorder
- Neuromuscular dysfunction
- In children:
  - Posterior urethral valves (males)
  - UPJ obstruction
  - UVJ obstruction
  - Ectopic ureter
  - Megaureter
  - Ureterocele

TREATMENT

Ureteral obstruction, if high-grade, bilateral, or associated with renal failure or infection warrants urgent decompression

GENERAL MEASURES

- Early recognition important in preventing irreversible renal functional impairment
- Management of acute obstruction directed at establishing drainage
- After initial stabilization and drainage, determine location and cause of obstruction
- Ureteral obstruction does not always require intervention
  - May observe (e.g., terminally ill patient with normal contralateral kidney, normal serum Cr, and electrolytes)
- Supportive care (pain control, correction of electrolyte abnormalities)

MEDICATION

First Line

- Pain management (oral or parenteral)
  - 1st line: Non-steroidal, anti-inflammatory medications
  - 2nd line: Narcotic medications

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Renal drainage:
  - Retrograde ureteral stent placement
  - Percutaneous nephrostomy tube placement
  - Similar health-related quality of life (2)[C]
  - Preferred technique depends on clinical scenario (e.g., stent preferred if uncorrectable coagulopathy, stent not as effective for extrinsic ureteral obstruction) (3)[C]
- After management of acute obstruction, definitive management directed by cause, renal function, and patient condition
  - Urolithiasis
    - Ureteroscopy with laser lithotripsy/stone extraction, percutaneous nephrolithotomy, or extracorporeal shockwave lithotripsy (location- and calculus-dependent)
  - UPJ obstruction
    - Open or laparoscopic pyeloplasty
  - Vascular lesions (e.g., aortic aneurysm)
    - May require urgent operative intervention
- May consider nephrectomy if affected kidney contributes $<10\%$ to global renal function

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Progressive renal damage may occur
- Poor if untreated bilateral obstruction

COMPLICATIONS

- Acute renal failure
- Chronic renal failure
- Postobstructive dieresis in setting of bilateral ureteral obstruction

FOLLOW-UP

Patient Monitoring

- Serum creatinine
- Serum electrolytes
- Renal ultrasound
- Nuclear renal scan

Patient Resources

MedlinePlus: Unilateral hydronephrosis
http://www.nlm.nih.gov/medlineplus/ency/article/000506.htm

REFERENCES

1. Bell ET. Obstruction of the urinary tract—Hydronephrosis. In: *Renal Diseases*. 2nd ed. Philadelphia, PA: Lea & Febiger; 1950:117–145.
2. Joshi HB, Adams S, Obadeyi OO, et al. Nephrostomy tube or 'JJ' ureteric stent in ureteric obstruction: Assessment of patient perspectives using quality-of-life survey and utility analysis. *Eur Urol.* 2001;39:695–701.
3. Docimo SG, Dewolf WC. High failure rate of indwelling ureteral stents in patients with existing obstruction: Experience at 2 institutions. *J Urol.* 1989;142:277–279.

ADDITIONAL READING

Tseng TY, Stoller ML. Obstructive uropathy. *Clin Geriatr Med.* 2009;25(3):437–443.

See Also (Topic, Algorithm, Media)

- Bladder Tumors, Benign and Malignant, General Considerations
- Filling Defect, Upper Urinary Tract (Renal Pelvis and Ureter)
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric
- Hydronephrosis/hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Prenatal
- Megaureter, Congenital
- Pregnancy, Urinary Tract Obstruction
- Retrocaval/Circumcaval Ureter
- Ureter and Renal Pelvic Tumors, General Considerations
- Ureter, Obstruction Image ☼
- Ureter, Stricture
- Ureteral Stricture Following Urinary Diversion
- Ureter, Stone Passage Statistics
- Ureterocele

- Ureteroenteric Anastamotic Stricture
- Ureteropelvic Junction Obstruction
- Urolithiasis, Adult, General Considerations
- Urolithiasis, Obstructing
- Urolithiasis, Pediatric, General Considerations
- Urolithiasis, Ureteral
- Urosepsis
- Whitaker Test

CODES

ICD9

- 591 Hydronephrosis
- 593.3 Stricture or kinking of ureter
- 753.20 Unspecified obstructive defect of renal pelvis and ureter

ICD10

- N13.1 Hydronephrosis w ureteral stricture, NEC
- N13.5 Crossing vessel and stricture of ureter w/o hydronephrosis
- Q62.39 Other obstructive defects of renal pelvis and ureter

CLINICAL/SURGICAL PEARLS

- Hydronephrosis is an anatomic, not functional, diagnosis.
- Renal scan best study if renal function adequate.
- Bilateral ureteral obstruction, ureteral obstruction in a solitary kidney, and ureteral obstruction associated with renal failure or infection warrant immediate renal drainage.

URETER, TRAUMA

Brad Figler, MD
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BASICS

DESCRIPTION

- Owing to its mobility, narrow diameter, and protected location, ureteral injury from external trauma is rare.
- 75% of ureteral injuries are iatrogenic; 18% form blunt trauma and only 7% from penetrating trauma (1).
- Iatrogenic injury is discussed in detail elsewhere (see Section I: "Ureter, Intraoperative Injury").

EPIDEMIOLOGY

Incidence

- Ureteral injuries represent <1% of all genitourinary injuries caused by violent trauma
- Typically result from gunshot wounds
- Blunt trauma and stab wounds responsible for <20% of ureteral injuries
- Typically occurs concomitant with other injuries (chest, retroperitoneal, intraperitoneal, pelvic)

Prevalence

Unknown

RISK FACTORS

- Penetrating injury to the abdomen and low chest/back
- Flexion/extension injuries (esp. children)
- Diagnosis requires high index of suspicion

Genetics

N/A

PATHOPHYSIOLOGY

- Direct injury from penetrating object
- Stretching of ureter as a result of hyperextension of the body
- Compression against transverse process as a result of rapid deceleration
- American Association for the Surgery of Trauma (AAST) Injury Scoring Scale for ureteral trauma (2)

Grade	Description
1	Hematoma only
2	Laceration <50% of circumference
3	Laceration >50% of circumference
4	Complete tear <2 cm of devascularization
5	Complete tear >2 cm of devascularization

ASSOCIATED CONDITIONS

- Small bowel injury
- Colon injury
- Liver injury
- Iliac vessel injury
- Bladder injury

GENERAL PREVENTION
- Avoid high-risk activity
- Seatbelt use

DIAGNOSIS
HISTORY
- Requires a high index of suspicion
- History of urologic condition or surgery
- Mechanism of injury
  - Hyperextension
  - Deceleration
  - Fall from height
  - Primary location of impact
- Presence of hematuria
  - Onset
  - Duration
- Flank pain
- Fever
- Nausea/vomiting

PHYSICAL EXAM
- Entrance/exit wounds
- Gross hematuria
- Flank or lower abdominal tenderness
- Flank bulge
- Abdominal distention

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Hematuria is unreliable; absent in 26% of cases (3)
- Creatinine may (rarely) be elevated due to extravasation and reabsorption of urine or obstruction.

ALERT
Absence of hematuria does not exclude ureteral injury. Clinical suspicion should guide investigation.

Imaging
- Demonstration of extravasation of contrast is the gold standard for the diagnosis of ureteral trauma.
  - Retrograde pyelography is most reliable for diagnosing ureteral injury; often impractical

in trauma patient.
  – CT with IV contrast and delayed images is an acceptable alternative. Most trauma patients have CT scans before being taken to the OR emergently.
  – On table "one-shot" IVP is sometimes performed in the operating room
    ◦ Administration of 2 mg/kg IV contrast with on table x-ray plain film after 10 min
- Medial extravasation of contrast at the level of the UPJ, suggestive of UPJ or renal pelvis injury
- Ureters should opacify to the level of the bladder on delayed imaging to be diagnostic
- Assess for foreign bodies, fluid collection, and hydronephrosis
- Ultrasound is generally not useful, except in demonstrating a urinoma or hydronephrosis.
- MRI not used acutely in the trauma setting

Diagnostic Procedures/Surgery
- Retrograde pyelogram: Useful to verify presence or absence of suspected injury
- Ureteral exploration is highly sensitive
- Probe wounds to establish trajectory

Pathologic Findings
Microvascular injury from high-velocity missiles or thermal injury can extend up to 2 cm beyond evidence of gross injury

DIFFERENTIAL DIAGNOSIS
- Other urinary tract trauma
  – Kidney
  – Bladder
- Contusion
- Renal pelvis laceration
- Ureteropelvic junction avulsion

ALERT
Delay in diagnosis of ureteral injury is a major contributing factor to morbidity in a trauma patient.

TREATMENT

GENERAL MEASURES (1)
- Initial management of the trauma patient employs primary survey, resuscitation stabilization, and
- Minor ureteral injury:
  – Ureteral stenting or
  – Nephrostomy tube
- Some common options for complete ureteral injury
  – Upper third: Uretero-ureterostomy
  – Middle third: Uretero-ureterostomy or Boari flap and reimplantation; normally a staged procedure and not performed acutely.
  – Lower third: Direct reimplantation or psoas hitch or Blandy cystoplasty.
  – Complete ureteral loss: Ileal interposition or autotransplantation as a delayed procedure

ALERT

- With compete ureteral loss employ “Damage Control” first: tie off ureter, place percutaneous nephrostomy.

- Complete UPJ transections will not heal and need open repair
- Partial UPJ injury (laceration) may be successfully treated by primary repair or stent
- Ureteral contusions or proximity gunshot wounds can be treated successfully by stenting

MEDICATION

First Line

Methylene blue and indigo carmine may help identify the site of a ureteral perforation or transection (see Section I: “Ureter, Intraoperative Injury”).

Second Line

Furosemide (20–40 mg IV) can be administered to speed indigo carmine excretion.

SURGERY/OTHER PROCEDURES

- Principles of ureteral repair include:
  - Careful mobilization
    - Preserve adventitia
    - Avoid electrocautery
  - Debridement of nonviable tissue to bleeding
  - Spatulated
  - Tension-free
  - Watertight
  - Mucosa to mucosa
  - Absorbable suture
  - Ureteral stent
  - Closed suction drain
- Blast effect from high-velocity gunshot wound (GSW) may require more extensive debridement.
- When concomitant injuries (particularly pancreatic) are present, consider omental flap to protect the repair.
- Successful methods for ureteric repair are based on injury location.
  - Upper and middle third: Primary repair
  - Lower third: Reimplantation
- Psoas hitch can reduce tension on repair
  - Divide contralateral inferior pedicle
  - Tack posterior bladder to psoas muscle
  - Use multiple longitudinally placed sutures in psoas fascia to avoid femoral nerve injury
- Advanced techniques typically not appropriate in the acute trauma patient
  - Bowel interposition
  - Transureteroureterostomy
  - Autotransplant
  - Boari flap

ADDITIONAL TREATMENT

Radiation Therapy
N/A

Additional Therapies
- Delayed management ("damage control") if patient unstable:
  - Tie off ureter with long suture and place nephrostomy tubes post-operatively
  - Externalize ureters

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
Long-term outcomes not reported in this population, but long-term results of ureteral surgery are excellent (4)

COMPLICATIONS
- Complication rate after repair of traumatic injuries of the ureter: 25%
  - Prolonged leakage is most common
- Delayed complications include
  - Ureteral stricture
  - Retained ureteral stent
  - Renal loss
  - UTI
  - Hydronephrosis

FOLLOW-UP
Patient Monitoring
- Check JP creatinine at least 2 days after abdominal closure. If consistent with serum, consider removing.
- Stent removal 4–6 wk
- Renal scintigraphy with Lasix 2–4 wk after stent removal to document function/drainage

Patient Resources
MedlinePlus: Injury-kidney and ureter
http://www.nlm.nih.gov/medlineplus/ency/article/001065.htm

REFERENCES

1. Lynch TH, Martínez-Piñeiro L, Plas E, et al. ; European Association of Urology. EAU guidelines on urological trauma. *Eur Urol.* 2005;47(1):1–15. Review.
2. American Association for the Surgery of Trauma (AAST) Injury Scoring Scale. http://www.aast.org/Library/TraumaTools/InjuryScoringScales.aspx. Accessed January 19, 2014.
3. Elliott SP, McAninch JW. Ureteral injuries from external violence: The 25-year experience at San Francisco General Hospital. *J Urol.* 2003;170(4 Pt 1):1213–1216.
4. Ghali AM, El Malik EM, Ibrahim AI, et al. Ureteric injury: Diagnosis, management and outcome. *J Trauma.* 1999;46:150–158.

ADDITIONAL READING

- Brandes S, Coburn M, Armenakas N, et al. Diagnosis and management of ureteric injury: an evidence-based analysis. *BJU Int.* 2004;94(3):277–289. Review.
- Figler BD, Master VA. Urologic trauma. In Chapple CR, Steers WD (eds.). *Practical Urology: Essential Principles and Practicer*. Springer; 2011.
- Morey AF, Brandes S, Dugi DD, et al. Urotrauma: AUA Guideline (https://www.auanet.org/common/pdf/education/clinical-guidance/Urotrauma.pdf Accessed August 21, 2014)

See Also (Topic, Algorithm, Media)

- Bladder Injury, Intraoperative
- Bladder Trauma
- Renal Trauma, Adult
- Ureter, Intraoperative Injury
- Ureter, Obstruction
- Ureter, Stricture
- Ureter Trauma Image

CODES

ICD9

- 867.2 Injury to ureter, without mention of open wound into cavity
- 867.3 Injury to ureter, with open wound into cavity
- 997.5 Urinary complications, not elsewhere classified

ICD10

- N99.81 Other intraoperative complications of genitourinary system
- S37.10XA Unspecified injury of ureter, initial encounter
- S37.19XA Other injury of ureter, initial encounter

CLINICAL/SURGICAL PEARLS

- Diagnosis of ureteral injury requires a high index of suspicion.
- Absence of hematuria does not exclude ureteral injury. Hematuria absent in 25–45% of ureteral trauma.
- Ureteral injury is indicated by extravasation of contrast.
- Primary anastomosis and reimplant with psoas hitch are effective methods for repairing ureteral injuries. More complicated injuries can be managed in a delayed fashion.
- Unstable patients can be managed with temporary drainage followed by delayed management.

URETEROCELE

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BASICS

DESCRIPTION

- Ureterocele is a cystic dilation of the terminal/intravesical ureter.
- May be classified based on anatomic location:
  - Intravesical: Contained entirely within the bladder above the bladder neck; seen frequently in single system ureteroceles.
  - Extravesical (Ectopic): Some portion of ureterocele permanently located at the level of the bladder neck or urethra; seen frequently in duplex system ureteroceles.
- Descriptive classification:
  - Cecoureterocele: Ureterocele extends into urethra, but orifice within the bladder
  - Sphincteric
  - Stenotic
  - Sphinctero-stenotic
  - Blind
  - Nonobstructive
- Most ureteroceles are associated with the upper pole of a duplex collecting system and are usually ectopic
- Today many ureteroceles are detected during routine prenatal screening ultrasounds
- When discovered in adults they are rarely of clinical consequence.

EPIDEMIOLOGY

Incidence

1 in 500 to 1 in 4,000

Prevalence

As high as 1 in 500 (autopsy study)

RISK FACTORS

- More common in girls (5–7:1)
- More common in whites
- Bilateral in 10–15% of cases
- Extravesical ureteroceles associated with upper pole of duplex system often diagnosed in infancy or childhood

Genetics

Likely multifactorial inheritance

PATHOPHYSIOLOGY

- Several hypotheses:
  - During embryogenesis, the mesonephric duct and the distal ureteral bud incorporate into the anterior cloaca/urogenital sinus. Chawalla membrane breaks down allowing the

incorporation of the distal ureter into the developing bladder. Incomplete breakdown of Chwalla membrane is thought to be one cause of the ureterocele.
  – Delay in canalization of lumen of ureteral bud is another theory.

ASSOCIATED CONDITIONS
- Duplicated collecting system: 80%
- Single system: 20%
  – Most common type in boys, but uncommon in girls (5%)
- Vesicoureteral reflux (VUR)
  – Ipsilateral lower pole in duplex system: 50–70%
  – Contralateral kidney: 10–30%

GENERAL PREVENTION
Antibiotic prophylaxis in patients at risk for upper-tract infection (VUR or obstruction)

DIAGNOSIS

HISTORY
- Prenatal hydronephrosis
- UTI/sepsis/failure to thrive
- Hematuria
- Bladder outlet obstruction
  – Most common cause of bladder outlet obstruction in newborn girls
- Intralabial mass (prolapsed ureterocele)

PHYSICAL EXAM
- Abdominal mass (hydronephrosis)
- Intralabial prolapsing cystic mass
  – Often appear congested and dusky
  – Smooth-walled appearance helps differentiate from sarcoma botryoides; other causes can include urethral prolapse and urethral caruncle

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum creatinine
- Urinalysis
- Urine culture

Imaging
- Renal/bladder US:
  – Prenatal hydronephrosis
  – Thin-walled intravesical cystic structure or septations in the bladder
  – Hydroureteronephrosis
  – Duplex collecting system with dilated upper pole
- Voiding cystourethrogram (VCUG)
  – Smooth, broad based filling defect near trigone
  – Critical to image during early filling
    - May efface as bladder fills

- Renal scintigraphy
  - DMSA
    - Evaluate renal parenchyma for scarring, differential function
  - MAG-3
    - Evaluate drainage to determine extent of obstruction, differential function
- IVP:
  - Cobra-head sign in the bladder when contrast fills the ureterocele (not usually performed) (1)

Diagnostic Procedures/Surgery
- Cystoscopy
  - Findings vary, but best seen with partially empty bladder

Pathologic Findings
- Abnormal or absent musculature of distal ureter
- Renal dysplasia
  - Seen in ~40–70% of upper-pole moieties with ureterocele; more common in association with extravesical ureteroceles

DIFFERENTIAL DIAGNOSIS
- Bladder polyps
- Ectopic ureter
- Edema
- Mesonephric duct cyst
- Tumor
- Urethral prolapse

TREATMENT

GENERAL MEASURES
Surgical treatment is needed in most cases

MEDICATION
First Line
- Culture directed antibiotics for treatment of UTI/Sepsis
- Antimicrobial prophylaxis until reflux or obstruction repaired in children:
  - Amoxicillin: 5–7 mg/kg/d as neonate
  - Trimethoprim-sulfamethoxazole: 2 mg/kg/d OR nitrofurantoin 1–2 mg/kg/d beyond 2 mo of age

Second Line
Endoscopic incision if acutely septic

SURGERY/OTHER PROCEDURES
- Endoscopic transurethral incision:
  - Usually effective in relieving obstruction
  - Risk of developing reflux in that system
  - Outpatient procedure

- Effective for intravesical and single-system ureteroceles, less so for extravesical ureteroceles (2)[B]
- Can be a temporizing measure until definitive repair (2)[B]

• Formal surgical repair
- Definitive treatment but higher morbidity
- Goals of surgery: Preserve functional renal parenchyma, relieve obstruction, correct reflux
- Upper-pole heminephrectomy if dilated non-functioning upper pole
- Ureteroureterostomy if upper pole is functional and no lower pole reflux
- Ureterocele excision and common sheath reimplatnation if reflux is present (3)[B]

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Observation if asymptomatic; no or mild reflux or obstruction

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Depends on extent of obstruction, infections, and presence or absence of renal dysplasia

COMPLICATIONS

• The major complication in adults and children is ureteral obstruction (4)
• Sepsis, loss of renal function
• Incontinence (primary or secondary)
• Persistent dilation of ureteral stump
• Persistent VUR

FOLLOW-UP

Patient Monitoring

• Renal and bladder US
• VCUG to diagnose/follow-up VUR
• Monitor renal function if bilateral
• Treat UTI

Patient Resources

• MedlinePlus: Ureterocele. http://www.nlm.nih.gov/medlineplus/ency/article/000462.htm
• Urology Care Foundation: Ureterocele. http://www.urologyhealth.org/urology/index.cfm?article=42

REFERENCES

1. Palmer L. Pediatric urologic imaging. *Urol Clin N Am.* 2006;33(3):209–423.
2. Adorlslo O, Elia A, Landi L, et al. Effectiveness of primary endoscopic incision in treatment of ectopic ureterocele associated with duplex system. *Urology* 2011;77:191–194.

3. Beganovi A, Klijn AJ, Dik P, et al. Ectopic ureterocele: Long-term results of open surgical therapy in 54 patients. *J Urol.* 2007;175:251–254.
4. Coplen DE, Duckett JW. The modern approach to ureteroceles. *J Urol.* 1995;153:166–171.

ADDITIONAL READING

• Byun E, Merguerian PA. A meta-analysis of surgical practice patterns in the endoscopic management of ureteroceles. *J Urol.* 2006;176:1871–1877.
• Husmann D, Strand B, Ewalt D, et al. Management of ectopic ureterocele associated with renal duplication: A comparison of partial nephrectomy and endoscopic decompression. *J Urol.* 1999;162:1406.

See Also (Topic, Algorithm, Media)

• Bladder Mass
• Collecting System, Complete Duplication
• Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Pediatric
• Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Prenatal
• Ureterocele Image
• Vesicoureteral Reflux, Pediatric

CODES

ICD9

• 593.70 Vesicoureteral reflux unspecified or without reflux nephropathy
• 593.89 Other specified disorders of kidney and ureter
• 753.23 Congenital ureterocele

ICD10

• N13.70 Vesicoureteral-reflux, unspecified
• N28.89 Other specified disorders of kidney and ureter
• Q62.31 Congenital ureterocele, orthotopic

CLINICAL/SURGICAL PEARLS

• Early filling x-rays during VCUG mandatory to enhance detection of ureterocele.
• Choice of treatment driven by acuity of illness, degree of obstruction, VUR, and degree of renal dysplasia.
• Definitive endoscopic treatment most successful for single-system ureteroceles.

URETEROENTERIC ANASTOMOTIC STRICTURE

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BASICS

DESCRIPTION

- Ureteroenteric anastomotic stricture (UE) is typically a benign obstruction of the ureter at the level of the sutured anastomosis following an intestinal urinary diversion
  - Typically benign process that develops 7–18 mo postoperatively (1)
    - most often performed in setting of radical cystectomy and ureteral/bowel anastomosis; therefore, recurrent malignancy must be ruled out (malignant stricture)

EPIDEMIOLOGY

Incidence

- Various series report range of 3–10% (1,2)
  - More common on left (1,2)

Prevalence

N/A

RISK FACTORS

- Surgical technique is the main risk factor
  - Aggressive handling of the ureter leads to stricture formation
    - Avoid stretching, grasping, skeletonization, and tension on the ureter
  - A non-refluxing anastomosis may be more prone to stricture formation than a refluxing anastomosis
  - Suture-line gaps lead to urine leak and predispose to stricture

Genetics

N/A

PATHOPHYSIOLOGY

- Aggressive handling, suboptimal technique devascularizes tissue causing poor blood flow and ischemia.
  - Ischemia interferes with healing of ureteral tissue and causes scarring and stricture formation
    - Urine leakage causes inflammation around anastomotic site
    - Lack of mucosa to mucosa apposition impairs healing

ASSOCIATED CONDITIONS

- Any condition where urinary tract surgery requires urinary diversion using a bowel anastomosis
  - Bladder carcinoma
  - Neurogenic bladder
  - Gynecologic malignancies

- Pelvic exenteration for rectal cancer

GENERAL PREVENTION

- Good surgical technique essential
  - No grasping of ureter with instruments, may crush and devascularize tissue
  - Maintain good blood supply—Avoid skeletonization
  - Minimize stretching and tension
  - Ensure mucosa to mucosa apposition
  - Balance watertight anastomosis with excessively close/tightened suture line
  - Ureteral stent may prevent urine leak

DIAGNOSIS

HISTORY

- Complaints of flank pain or fever and UTI suggestive of pyelonephritis
  - Typically presents 6–18 mo after surgery
    - Chronic as opposed to acute process

PHYSICAL EXAM

- Dull achy pain on palpation of flank
  - May be sharp if associated with infection

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- In the case of unilateral stricture with an unaffected contralateral kidney, often no significant abnormal laboratory findings.
  - May have transient rise in serum Cr
  - A urine analysis or dipstick evaluation may demonstrate elevated leukocyte esterase and white blood cells consistent with inflammation. Presence of urinary nitrites and bacteria may occur with concomitant UTI but should be interpreted with caution due to the presence of bowel in the urinary tract.
  - If bilateral strictures are present or patient has poorly functioning or absent contralateral kidney, patient may present with markedly elevated serum creatinine and acute renal failure (hyperkalemia, marked acidosis)

Imaging

- Renal ultrasound or CT imaging are initial diagnostic modalities of choice
  - Ultrasound cost-effective and highly sensitive for demonstrating obstruction
  - CT imaging with pre- and post-IV contrast dye can provide further anatomic and functional information.
    - More costly than US and risk of radiation exposure and contrast-dye allergy in susceptible patients
    - Some patients may have compromised renal function that precludes the use of IV contrast
  - MRI may also be considered if US unavailable and contraindications to CT imaging
  - If kidney appears atrophic consider renal scan to assess function
    - Poorly functioning kidney (<15%) better served with nephrectomy than UE stricture

repair

Diagnostic Procedures/Surgery

- If hydronephrosis found, consider percutaneous antegrade contrast instillation (nephrostogram) of affected side.
- If ileal conduit urinary diversion, instillation of contrast dye directly into the ileal loop (loopogram) may be considered as alternative to nephrostogram
  - Ileal conduit has refluxing anastomosis so loopogram will demonstrate reflux of contrast up the ureter if hydronephrosis not due to obstruction.
    - If no reflux is demonstrated on loopogram, then cause of hydro is likely stricture
    - Loopogram is less costly and noninvasive compared to nephrostogram
    - Nephrostogram can be therapeutic by providing instant drainage via nephrostomy as well as provide access for endoscopic treatment (see "Treatment")
  - Retrograde pyelogram very difficult due to inability to locate and cannulate ureteroenteric orifice during loop endoscopy

Pathologic Findings

Inflammation and scarring identified on pathologic specimen following open surgical revision and excision

DIFFERENTIAL DIAGNOSIS

- Urine reflux
- Ureteral stone
- Extrinsic compression
- Ureteral kinking
- Recurrent malignancy
- Pyelonephritis
  - Differential can be explored with CT or MR imaging which will provide anatomical detail

TREATMENT

GENERAL MEASURES

- Consider pain relief if obstruction causing hyrdonephrosis and flank pain
  - Rule out and treat UTI if suspected
    - UTI, fever, and presence of obstruction is a medical emergency with increased mortality
    - Treat with urgent decompression via nephrostomy tube and systemic antibiotics
- If patient comfortable and no evidence of infection, then consider elective repair

MEDICATION

First Line

- No therapeutic medications
- Consider narcotics and anti-inflammatories for temporary relief of pain
- If infection noted and patient clinically stable, mildly symptomatic, treat with fluoroquinolone or culture specific antibiotics for 7–14 days
- Asymptomatic infection can be treated prior to elective repair

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Nephroureteral or antegrade ureteral stent placement for temporary relief of obstruction or in the setting of palliative care
- Definitive therapy: Open versus endoscopic repair
  - Decision is based on surgeon experience, prior attempts at repair (primary vs. secondary) and length/complexity of stricture
  - Retrospective series suggest higher success rates with open repair (see below)
  - Indwelling stent for 2–3 wk after repair
- Open surgical repair
  - Recommended for strictures >1 cm and failed endoscopic repairs
  - Success rates of up to 71.4–100% reported for primary open revision (2,3)
  - Difficult procedure with mean reported operative time of 240+ (145–450) min, EBL 300+ (150–500) cc (2,4)
- Endoscopic repair
  - Recommended for stricture <1 cm and primary repairs
  - Typically performed antegrade with Ho:Yag laser or Accucise device (2,5). Balloon dilation less commonly used and may be less efficacious.
  - Success rates of 26–50% reported for primary repair (3 – 5).
  - Secondary or redo endoscopic repair has low success rate (35%) (5)
  - Left side strictures and those >1 cm in length appear more prone to failure after repair (2,5)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- If ureteral stricture very long, ureter devascularized or insufficient length and renal unit still functional consider bowel interposition (ileal ureter)
- If renal scan demonstrates poorly functioning kidney (<15%) consider nephrectomy

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Mean time to failure after open and endoscopic repair are 12 and 5 mo, respectively (3)
  - Left sided and redo repairs are at higher risk for failure

COMPLICATIONS

- Uretero enteric stricture
  - Stone formation
  - Hydronephrosis
  - Renal insufficiency
  - Pyelonephritis
- Open repair: complication rate of up to 40% (2,4)

  - Complications include vascular injury, contralateral ureteral injury, urine leak, damage to diversion bowel segment, bowel injury (2,4).
- Endoscopic repair:
  - Complications are rare, most common is infection (UTI/urosepsis) (2,3,5)

FOLLOW-UP

Patient Monitoring

- Consider renal U/S at 6 weeks following repair
  - If hydronephrosis present consider waiting 2 wk (potential post-op anastomotic edema) and perform repeat imaging with contrast based study to rule out obstruction/failure
    - Reflux may occur following repair so should also rule out as possible cause of hydronephrosis

Patient Resources

N/A

REFERENCES

1. Anderson C, Morgan TM, Kappa S, et al. Ureteroenteric anastomotic stricture after radical cystectomy—Does operative approach matter? *J Urol*. 2013;189;541–547.
2. Laven B, O'Connor RC, Gerber GS, et al. Long-term results of endoureterotomy and open surgical revision for the management of ureteroenteric strictures after urinary diversion. *J Urol*. 2003;170:1226–1230.
3. Milhua P, Miller NL, Cookson MS, et al. Primary endoscopic repair versus open revision of ureteroenteric strictures after urinary diversion—single institution contemporary series. *J Endourol*. 2009;23;551–555.
4. Nassar O, Alsafa M. Experience with ureteroenteric strictures after radical cystectomy and diversion: Open surgical revision. *Urology*. 2011;78;459–465.
5. Schöndorf D, Meierhans-Ruf S, Kiss B, et al. Ureteroileal strictures following urinary diversion with an ileal segment: is there a place for endourological treatment at all? *J Urol*. 2013;190(2):585–590.

ADDITIONAL READING

Ureteroenteric Anastomotic Strictures after Radical Cystectomy: Does Operative Approach Matter? Download supplemental table. https://www.mc.vanderbilt.edu/root/vumc.php?site=urologicsurgery&doc=32446

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Ureter, Obstruction

CODES

ICD9

- 593.3 Stricture or kinking of ureter
- 867.2 Injury to ureter, without mention of open wound into cavity
- 997.5 Urinary complications, not elsewhere classified

ICD10

- N13.5 Crossing vessel and stricture of ureter w/o hydronephrosis
- N99.89 Oth postprocedural complications and disorders of GU sys
- S37.10XA Unspecified injury of ureter, initial encounter

CLINICAL/SURGICAL PEARLS

- Avoid aggressive handling of the ureter to prevent devascularization and ischemia during urinary diversion operation.
- Ureteral obstruction, fever, and UTI in a patient with a urinary diversion requires emergent treatment with percutaneous drainage.
- Open primary repair of UE stricture has higher success rate than endoscopic repair.
- Open repair is complex procedure best performed in experienced hands.

URETEROPELVIC JUNCTION OBSTRUCTION

Christopher E. Keel, DO
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BASICS

DESCRIPTION

- Ureteropelvic junction obstruction (UPJO) is a restriction of urine flow from the renal pelvis to ureter
- Most common cause of significant dilation of collecting system in fet al kidney

EPIDEMIOLOGY

Incidence

- 1:500–1000 newborns
  - 25% diagnosed by 1 yr, 50% by 5 yr
- Adult presentation usually in 3rd–4th decade

Prevalence

- Left > right side (67%)
- Male > female (>2:1) (1)

RISK FACTORS

- Familial disposition
- Congenital renal anomalies:
  - Contralateral UPJO: 10–40% risk
  - Vesicoureteral reflux (VUR): 0.5–5% risk
  - Renal duplication: 6% risk
  - Horseshoe kidney: 15% risk
  - Ectopic kidney: 35% risk

PATHOPHYSIOLOGY

- Congenital (most common etiology):
  - Intrinsic etiologies:
    - Adynamic ureteral segment due to ureteral smooth muscle maldevelopment; the most common cause of pediatric UPJO
    - Intrinsic stenosis due to inadequate ureteral recanalization during fet al development
    - Persistent valvular mucosal folds
  - Extrinsic etiologies:
    - Crossing accessory lower-pole vessel; most common cause of adult UPJO
    - High ureteral insertion into renal pelvis
    - Horseshoe, ectopic, or malrotated kidney causing kinking at ureteropelvic junction (UPJ)
- Acquired:
  - Severe VUR can cause ureteral tortuosity and kinking at UPJ
  - Inflammation and scarring from trauma, urolithiasis, instrumentation, infected urinoma, retroperitoneal fibrosis

ASSOCIATED CONDITIONS
- 50% associated with another congenital anomaly:
  - Contralateral renal dysplasia or multicystic dysplastic kidney (MCDK)
  - Contralateral UPJO: Most common
  - Horseshoe or ectopic kidney
  - Incomplete renal duplication
  - Unilateral renal agenesis
  - VACTER/VACTERL syndrome
  - Vesicoureteral reflux (9–18%)

GENERAL PREVENTION
None

DIAGNOSIS
HISTORY
- Prenatal/neonatal presentation:
  - Hydronephrosis seen on antenatal US
  - Typically asymptomatic; but occasionally see feeding difficulties, failure to thrive, sepsis
- Childhood presentation:
  - Episodic abdominal complaints or ipsilateral colicky flank pain
  - Cyclic nausea and vomiting
  - Gross hematuria, classically after minor abdominal or flank trauma
  - UTI
- Adult presentation:
  - Episodic ipsilateral colicky flank pain, classically after diuretic or alcohol intake (aka Dietl crisis)
  - Cyclic nausea and vomiting
  - UTI or pyelonephritis

PHYSICAL EXAM
- Prenatal/neonatal or childhood presentation:
  - Palpable abdominal mass
  - Fever, failure to thrive
- Childhood presentation:
  - Costovertebral (CVA) tenderness
  - Palpable abdominal mass in small children
- Adult presentation:
  - CVA tenderness
- Hypertension (HTN): Due to acute pain or activation of renin–angiotensin–aldosterone system

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Serum BUN and creatinine
- Urine analysis:
  - Microscopic hematuria, rarely gross

  - Trace proteinuria
  - Pyuria and bacteriuria
- Urine culture

Imaging

- Renal US:
  - Most often used as initial screening study in pediatric population
  - Useful to distinguish renal masses and ureterovesical junction obstruction from UPJO
- Defer until 2nd or 3rd day of life to avoid false-negative result secondary to physiologic oliguria
- Computed Tomography (CT):
  - Most commonly employed diagnostic study after neonatal period
  - When IV contrast given, findings include delayed opacification of collecting system, pyelocaliectasis, nonvisualization of ureter, cortical thinning
- Intravenous pyelogram; still occasionally performed
- Diuretic renal scintigraphy (Tc-99mm MAG3):
  - Provides differential renal function
  - $T_{1/2}$ assesses for presence of obstruction:
    - Normal $T_{1/2}$: <10 min
    - Indeterminate $T_{1/2}$: 10–20 min
    - Obstruction $T_{1/2}$: >20 min

Diagnostic Procedures/Surgery

- Cystoscopy with retrograde pyelography:
  - Defines extent of ureteral involvement
  - Allows for placement of temporary ureteral stent to relieve urinary obstruction
  - If available endoluminal ultrasound can define crossing vessels intraoperatively
- Helical CT scan with 3D reconstruction:
  - Allows visualization of collecting system and renal vasculature (crossing vessels)
- Whitaker test (WT): Rarely performed
  - Reserved for equivocal IVP or MAG3
  - Percutaneous catheter with pressure transducer placed in renal pelvis, another placed in bladder via urethra; fluid infused into renal pelvis at 10 cc/min; measure pressure differential:
    - Normal: <15 cm H_2O
    - Equivocal: 15–22 cm H_2O
    - Obstructed: >22 cm H_2O

Pathologic Findings

- Hydronephrosis without hydroureter
- Elevated $T_{1/2}$ >20 min on diuretic MAG3
- Pressure differential >22 cm/H_2O on WT
- Crossing vessel on helical CT scan

DIFFERENTIAL DIAGNOSIS

- Obstructive dilation:
  - Fungal balls
  - Impacted urinary calculus
  - Intraluminal benign or malignant neoplasm
  - Sloughed papilla
- Nonobstructive dilation:
  - Prune belly syndrome
  - Renal or peripelvic cysts
  - VUR
  - Megaureter

TREATMENT

GENERAL MEASURES

- Prevent further deterioration in renal function
- Relieve symptoms of obstruction

MEDICATION

First Line

- Neonatal/newborn presentation:
  - Prophylactic antibiotics to maintain sterile urine:
    - UTI prophylaxis: Ampicillin 25 mg/kg/d as neonates THEN
    - Trimethoprim-sulfamethoxazole 2 mg/kg/d OR nitrofurantoin 1–2 mg/kg/d beyond 2 mo of age
  - Repeat imaging—to monitor for resolution or deterioration of function (2)
- Childhood and adult presentation:
  - No medical therapy appropriate except to treat active infection

SURGERY/OTHER PROCEDURES

- Purpose: Restore renal function
  - Especially in patients with bilateral obstruction, solitary kidney, or poorly functioning contralateral kidney
- Relieve severe symptoms:
  - Percutaneous nephrostomy or ureteral stent
- Treat pyonephrosis if present:
  - Culture-specific antibiotics
  - Percutaneous nephrostomy or ureteral stent may be necessary to ensure adequate drainage of infected urine.
- Expectant treatment:
  - Neonatal hydronephrosis: Obstruction associated with unilateral neonatal hydronephrosis is 15%; a majority of neonates with hydronephrosis can be initially managed nonoperatively.
  - Asymptomatic adults with normal contralateral kidney and significant comorbidities
- Definitive operative treatment:
  - Robotic assisted laparoscopic pyeloplasty
    - Gaining more acceptance and is now becoming the standard approach, even in the

pediatric population, with increasing access to robotic surgical technology (3).
  - Employs the same techniques as those performed both open and laparoscopic
  - Comparative outcomes to open techniques approaching >95%
  - Ease in surgical dissection and suturing techniques, management of associated calculi and crossing vessels, has increased its popularity (4).
  - Offers decreased morbidity, better cosmesis, and quicker return to daily activities
- Laparoscopic pyeloplasty: Success rate >90%; transabdominal or retroperitoneal approach; employs dismembered or Y-V plasty technique;
  - Utilized when robotic technology is not available. Technical demands of laparoscopic suturing techniques is a major drawback.
  - Open pyeloplasty: Procedure of choice in pediatric patients:
    - Dismembered (Anderson-Hynes) pyeloplasty: Most common open technique; success rate >90%; appropriate for high insertion, accessory vessels, massive dilation, long ureteral involvement; excise anatomic and functionally abnormal segment
    - Foley Y-V plasty: Appropriate for high ureteral insertion
    - Spiral or vertical flap: Appropriate for large extrarenal pelvis and long segment of narrowed ureter
    - Ureterocalycostomy: Appropriate for rotational anomalies or reoperation after failed pyeloplasty; partial lower pole nephrectomy is required to prevent anastomotic stenosis.
    - Simple nephrectomy: May be appropriate for ipsilateral poor renal function and normal contralateral renal function, especially if differential renal function <10–15%, extensive stone disease, chronic infection, multiple failed repairs
- Endoscopic procedures: Minimally invasive alternative to open procedures in adults: (5)
  - Antegrade cold-knife incision endopyelotomy: Success rate >60%; requires percutaneous access; nephrostomy tube left indwelling 24–48 hr, ureteral stent left indwelling 6 wk; appropriate for adult patients with stricture <2 cm, UPJO associated with renal calculi, children with secondary UPJO
  - Retrograde ureteroscopic laser incision: Success rate in small series 85–90%; allows direct visualization of incision; requires specialized ureteroscopic equipment and endourologic expertise; ureteral stent left indwelling 6 wk
- Chronic percutaneous nephrostomy or ureteral stent: Reserved for patients who are not candidates for definitive operative treatment

ONGOING CARE

PROGNOSIS

- Prenatal/neonatal presentation:
  - Often does not require definitive operative treatment, due to propensity for self resolution or to remain stable
  - Intervention in severe cases can result in greatly improved renal function
- Childhood and adult presentation:
  - Recent investigations demonstrate excellent long-term success rates with pyeloplasty (>90%) verses 60–70% with endoscopic techniques.

COMPLICATIONS

- Recurrent stricture
  - Usually managed endoscopically or by repeat pyeloplasty
  - Ureterocalycostomy
- Urinary leak/fistula
- Infection
- Rarely sepsis/HTN

FOLLOW-UP

Patient Monitoring

- Expectant management in the neonate:
  - Renal US or MAG3 at 1 mo, followed at 3–6 mo
  - Operative intervention is recommended if >10% difference in renal function, worsening of obstruction or renal function or worsening hydronephrosis
- Postoperative Management
  - Renal US or MAG3 6–12 wk postop
    - 91% of children will have improvement in renal function
    - Adults generally will not improve function but will have improvement in drainage.

REFERENCES

1. Carr MC, Casale P. Anomalies and surgery of the ureter in children. In: Wein AW, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier-Saunders; 2012.
2. Ross SS, Kardos S, Krill A, et al. Observation of infants with SFU grade 304 hydronephrosis: worsening drainage with serial diuresis renography indicates surgical intervention and helps prevent loss of renal function. *J Pediatr Urol.* 2011;7(3):266–271.
3. Barbosa JA, Kowal A, Onal B, et al. Comparative evaluation of the resolution of Hydronephrosis in children who underwent open and robot-assisted laparoscopic pyeloplasty. *J Pediatr Urol.* 2013;9(2):199–205.
4. Boylu U, Oommen M, Lee BR, et al. Ureteropelvic Junction Obstruction Secondary to Crossing Vessels—To Transpose or Not? The Robotic Experience. *J Urol.* 2009;181:1751–1755.
5. Kmi EH, Tanagho YS, Traxel EJ, et al. Endopyelotomy for pediatric ureteropelvic junction obstruction: a review of our 25-year experience. *J Urol.* 2012;188(4 Suppl):1628–1633.

ADDITIONAL READING

None

See Also (Topic, Algorithm, Media)

- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Adult
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Pediatric
- Hydronephrosis/Hydroureteronephrosis, (Dilated Ureter/Renal Pelvis), Prenatal
- Megaureter, Congenital
- Ureter, Obstruction
- Ureteropelvic Junction Obstruction Image

CODES

ICD9

- 592.1 Calculus of ureter
- 593.4 Other ureteric obstruction
- 753.21 Congenital obstruction of ureteropelvic junction

ICD10

- N13.1 Hydronephrosis w ureteral stricture, NEC
- N13.5 Crossing vessel and stricture of ureter w/o hydronephrosis
- Q62.39 Other obstructive defects of renal pelvis and ureter

CLINICAL/SURGICAL PEARLS

- Purpose is to relieve obstruction and preserve kidney function.
- Open or laparoscopic surgical repair remains the best option for treatment.

URETHRA, ABSCESS (PERIURETHRAL ABSCESS)

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BASICS

DESCRIPTION

- Urethral abscess is best defined based on the sex of the patient
  - Men: Infection of the male urethra and periurethral tissues, usually associated with urinary infection and urethra stricture disease.
  - Women: Infection of Skene's glands located on the anterior vaginal wall, usually associated with a chronically infected urethral diverticulum.
    - Diagnosis and management of female urethral abscess are discussed in Section I "Urethra, diverticulum, female (Urethral diverticulum)".

EPIDEMIOLOGY

Incidence

Can occur at any age.

Prevalence

- The exact prevalence is not known.
- More likely in diabetics or those with sexually transmitted diseases.
- Recurrent abscess in up to 19% of patients.

RISK FACTORS

- Diabetes mellitus
- Urethral stricture disease
- Frequent urethral instrumentation
- Periurethral bulking agent injection
- Gonorrhea
- HIV
- Previous periurethral abscess

Genetics

N/A

PATHOPHYSIOLOGY

- Periurethral extravasation of infected urine (1).
- Urine extravasation may be caused by:
  - High-pressure voiding behind a stricture
  - Difficult dilation of a stricture, false passage
  - Traumatic urethral instrumentation
- Often localized to the bulbar urethra or spongiosum.
- Once eroded through Buck's fascia, may cause extensive necrosis of the fascia and adjacent tissues, leading to Fournier gangrene.
- Three potential sources of Fournier gangrene:

  - Periurethral
  - Perirectal
  - Subcutaneous
- Fistula may develop in delayed cases following spontaneous abscess rupture
- Common organisms:
  - *Neisseria gonorrhea*
  - *Chlamydia trachomatis*
  - Gram-negative rods
  - Enterococci
  - Anaerobes

ASSOCIATED CONDITIONS (2)
- Diabetes mellitus
- Immunosuppression (eg, HIV)
- Sexually transmitted disease
- Urethral stricture disease
- Urinary tract infection

GENERAL PREVENTION
- Eradicate and prevent sexually transmitted disease
- Sterilize the urine and defer instrumentation if the urine is infected
- Diversion of urine away from the urethra
- Adequate management of urethral stricture:
  - Dilation
  - Internal urethrotomy
  - Urethroplasty and reconstruction
  - Perineal urethrotomy

DIAGNOSIS

ALERT
Failure to recognize and treat a localized periurethral abscess in a male can result in life-threatening necrotizing fasciitis (fournier gangrene), or septic shock.

HISTORY
- Symptoms may include urethral discharge, dysuria, pain, swelling of penis or scrotum, foul smelling urine, fever, chills, weak urine stream, incomplete emptying, urinary frequency, urgency.
- History of urethral stricture and treatment
- Recent history of urethral instrumentation, dilation, catheterization, bulking agent, sling, or other surgery
- History of sexually transmitted disease, pelvic radiation, trauma (risk factors of stricture)
- History of recurrent UTI
- Diabetes, including glycemic control
- Immunosuppression (eg, HIV)
- Prior periurethral abscess and treatment

– Maintain an index of suspicion for neoplasm for recurrent periurethral abscess and stricture

PHYSICAL EXAM

- Evaluate for urosepsis: fever, tachypnea, tachycardia, hypotension, mental status change.
- Palpate penile shaft and perineum for mass, induration, tenderness, fluctuance, or crepitus.
- Fournier gangrene may involve the penis, scrotum, perineum, extending around the rectum, inner thighs, or up the abdominal wall.
- Palpate for a distended bladder (retention).
- Rectal exam to exclude perirectal abscess.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis of the initial urine stream
- Urine culture and sensitivity
- Wound culture, including anaerobic
- Blood culture (sepsis workup)
- BUN, creatinine (renal function, dehydration)
- WBC with differential
- Coagulation profile (sepsis-induced coagulopathy)

Imaging

- CT (look for subcutaneous air, abscesses)
- Retrograde urethrogram:
  – Not recommended during acute phase
  – Look for extravasation, stricture, fistula
- Transrectal ultrasound imaging of prostate: not recommended during acute phase

Diagnostic Procedures/Surgery

- Post-void residual volume (bladder scanner)
- Aspiration of pus when diagnosis is in doubt

Pathologic Findings

- Tissue inflammation, necrosis, fasciitis
- Biopsy may be used to rule out urethral or perianal cancer in rare cases

DIFFERENTIAL DIAGNOSIS (3,4)

- Anasarca (generalized edema) from liver or renal failure
- Carcinoma of perianal glands
- Fournier gangrene
- Perirectal abscess
- Pneumoscrotum after laparoscopy
- Subcutaneous abscess
- Urethral carcinoma
- Urethral diverticulum (in female)

TREATMENT

GENERAL MEASURES

Supportive treatment of other medical issues: diabetes, hypotension, septic shock, or organ failures

MEDICATION

First Line

- Board spectrum antibiotics coverage
  - Cephalosporin and aminoglycoside
    - Such as ceftriaxone 2g IV q24 plus gentamicin 1.5–2 mg/kg loading dose, followed by 5–7 mg/kg IV q24
  - Consider vancomycin (15–20 mg/kg IV q12)

Second Line

Antibiotics are adjusted based on culture sensitivity

SURGERY/OTHER PROCEDURES

- Incision and drainage of abscess with debridement and excision of necrotic tissue.
- May require repeated exploration and debridement as the margin between necrotic tissue and viable tissue becomes more apparent.
- Needle aspiration or endoscopic transurethral incision may be considered in selected cases.
- Wet to dry dressing change twice a day.
- Wound vac placement after debridement if the wound is clean and if wound location permits.
- Exposed testicle may be placed in the scrotum or thigh pouch.
- Skin grafting may be needed to cover skin loss, alternatively secondary closure of wound.
- Biopsy to exclude urethral or perianal cancer.
- Urinary diversion:
  - Suprapubic tube initially
  - Avoid urethral Foley catheter
  - Perineal urethrotomy as a secondary option in patients with severe bladder spasm or when adequate urine drainage has not been achieved.
- Cystoscopy to evaluate urethral stricture disease after complete resolution of infection.
- Definitive management of stricture should be deferred for 6 mo after resolution of abscess.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Variable based on diagnosis and treatment

- Failure to recognize and treat a periurethral abscess in a male can result in life-threatening necrotizing fasciitis (Fournier gangrene) and septic shock.

COMPLICATIONS

- Sepsis, acute renal failure, death (1%) (5)
- Necrotizing fasciitis: Progression to Fournier gangrene
- Extensive genital skin loss
- Recurrent abscess and urinary infection
- Necrosis of corpora spongiosum
- Urethrocutaneous fistula

FOLLOW-UP

Patient Monitoring

- Frequent wound check until healed.
- Monitoring for recurrent stricture (eg, uroflow)
- Periodic evaluation of urine for infection.
- Testing for sexually transmitted disease.

Patient Resources

Urology Care Foundation: Benign urethral lesions
http://www.urologyhealth.org/urology/index.cfm?article=93

REFERENCES

1. Sanders CJ, Mulder MM. Periurethral gland abscess: Aetiology and treatment. *Sex Transm Infect.* 1998;74(4):276–278.
2. Walther MM, Mann BB, Finnerty DP. Periurethal abscess. *J Urol.* 1987;138:1167–1170.
3. Blaschko SD, et al. Proximal bulbar urethral abscess. *Int Braz J Urol.* 2013;39(1):137–138.
4. Kenfak-Foqoena A, Zarkik Y, Wisard M, et al. Periurethral abscess complicating gonococcal urethritis: Case report and literature review. *Infection.* 2010;38(6):497–500.
5. Malatinsky E. Sepsis caused by periurethral abscess. *Int Urol Nephrol.* 1991;23(5):485–488.

ADDITIONAL READING

Butler JM, Bennetsen D, Dias A. An unusual cause of pelvic pain and fever: Periurethral abscess from an infected urethral diverticulum. *J Emerg Med.* 2011;40(3):287–290.

See Also (Topic, Algorithm, Media)

- Fournier Gangrene
- Urethra, Carcinoma, General Considerations
- Urethra, Discharge
- Urethra, Diverticulum, Female (Urethral Diverticulum)
- Urethra, Mass
- Urethral Stenosis/Stricture, Female
- Urethra, Stricture, Male

CODES

ICD9

- 597.0 Urethral abscess
- 598.9 Urethral stricture, unspecified
- 599.2 Urethral diverticulum

ICD10
- N34.0 Urethral abscess
- N35.9 Urethral stricture, unspecified
- N36.1 Urethral diverticulum

CLINICAL/SURGICAL PEARLS

- In men, urethral abscess is associated with urinary infection, urethral stricture, diabetes, and immunosuppression. In women, it is associated with urethral diverticulum.
- Incision and drainage of abscess may include exploration and debridement of necrotic tissues.
- Board spectrum antibiotics coverage and supportive care.
- Urinary diversion with suprapubic tube are important in the treatment of urethral abscess.
- Early recognition and treatment is key to prevent progression to life-threatening Fournier gangrene and septic shock.

URETHRAL CARCINOMA, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Urethral carcinoma is a tumor arising from the lining of the male or female urethra
- Considered a rare cancer (< 1% of all malignancies)
- Urothelial carcinoma is most common histologic type followed by squamous cell carcinoma and adenocarcinoma.

EPIDEMIOLOGY (1)

Incidence

- Incidence (male): 1.6 per 1,000,000
- Incidence (female): 0.6 per 1,000,000
- Incidence is higher in African American patients
- Incidence increases steadily with age, more steeply in men as compared to women peaks at age 75: 7.6/1,000,000

Prevalence

N/A

RISK FACTORS (1)

- Male
  - Chronic inflammation
    - Intermittent catheterization, urethroplasty
  - History of sexually transmitted infection (STI/STD)
    - HPV (condyloma with HVP 16)
  - Urethritis
  - Urethral stricture disease
  - Prior radiation
    - External beam or seed implant
  - Arsenic exposure (adenocarcinoma of bulbar urethra)
  - Urethral stent
- Female
  - Leukoplakia
  - Chronic inflammation/recurrent UTI
  - STI/STD
    - HPV, condyloma
  - Parturition
  - Urethral diverticula

Genetics

Unknown

PATHOPHYSIOLOGY

- Male
  - Anatomic considerations: The male urethra (averages about 20 cm in length), is divided into distal and proximal portions. The distal urethra, which extends distally to proximally from the tip of the penis to just before the prostate, includes the meatus, the fossa navicularis, the penile or pendulous urethra, and the bulbar urethra. The proximal urethra, which extends from the bulbar urethra to the bladder neck, includes distally to proximally the membranous urethra and the prostatic urethraurethra
  - Squamous-cell carcinoma: Occurs in the membranous urethra, bulbar urethra, and penile urethra
  - Urothelial carcinoma: Typically occurs in the prostatic urethra
- Female
  - Anatomicconsiderations: The female urethra is In adults, it is about 4 cm in length and is mostly contained within the anterior vaginal wall.
  - Squamous-cell carcinoma: Occurs at distal 2/3 of female urethra
  - Urothelial carcinoma: Occurs at the proximal 1/3 of the urethra
  - Adenocarcinoma: Occurs in urethra diverticula

ASSOCIATED CONDITIONS

- STI/STD
- Indwelling catheter
- Urethral stricture disease
- Urethral diverticula
- Bladder cancer

GENERAL PREVENTION

- Prevention of STI
- Prevention of traumatic injury leading to stricture disease
- Smoking cessation

DIAGNOSIS

HISTORY

- Urethral bleeding
- Perineal discomfort
- Decrease force of stream
- Urinary frequency
- Urinary urgency
- Dysuria
- Urinary fistulae
- Urinary tract infection
- STI/STD, condyloma history

PHYSICAL EXAM

- Perineal exam
  - Identifies palpable mass in proximal urethra
- Pelvic exam

  – Identifies visual or palpable mass associated with female urethra
- Examination under anesthesia with bimanual exam
- Inguinal exam to evaluate palpable inguinal adenopathy

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis often demonstrates hematuria
- Urine culture
- Urine cytology
  – Sensitivity 55–59%

Imaging

- Urethrography—Aids in the diagnosis of diverticula and/or stricture disease
  – Voiding cystourethrogram (VCUG)
  – Retrograde urethrogram
- Cross sectional imaging identifies local extension
  – MRI of pelvis
    ○ Preferred imaging modality for urethral carcinoma
  – CT scan of pelvis
  – CT thorax and abdomen in patients with invasive disease (rule out metastasis)

Diagnostic Procedures/Surgery

Cystoscopy with biopsy/transurethral resection

Pathologic Findings (2)

- Urothelial carcinoma 50–60%
- Squamous-cell carcinoma 16–25%
  – More common in women, traditionally considered-more prevalent
- Adenocarcinoma 10–16%
- Primary tumor staging based on TNM classification (See also Reference tables: TNM: Urethra Cancer)
  – T—Primary tumor (men and women)
    ○ Tx Primary tumor cannot be assessed
    ○ Tis Carcinoma in situ
    ○ T0 No evidence of primary tumor
    ○ Ta Non-invasive papillary carcinoma
    ○ T1 Tumor invades subepithelial connective tissue
    ○ T2 Tumor invades any of the following structures: Corpus spongiosum, prostate, periurethral muscle
    ○ T3 Tumor invades any of the following structures: Corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
    ○ T4 Tumor invades other adjacent organs
  – N—Regional lymph nodes
    ○ Nx Regional lymph nodes cannot be assessed
    ○ N0 No regional lymph node metastases
    ○ N1 Metastasis in a single lymph node <2 cm in greatest dimension
    ○ N2 Metastasis in a single lymph node >2 cm in greatest dimension or in multiple nodes

- M—Distant metastasis
  - Mx Distant metastasis cannot be assessed
  - M0 No distant metastasis
  - M1 Distant metastasis
- Primary tumor in prostatic urethra:
  - Tx Primary tumor cannot be assessed
  - Tis pu Carcinoma *in situ* in the prostatic urethra
  - Tis pd Carcinoma *in situ* in the prostatic ducts
  - T0 No evidence of primary tumor
  - T1 Tumor invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
  - T2 Tumor invades any of the following structures: Corpus spongiosum, prostatic stroma, periurethral muscle
  - T3 Tumor invades any of the following structures: Corpus cavernosum, beyond prostatic capsule, bladder neck
  - T4 Tumor invades other adjacent organs
- N (Nodes) and M (metastasis) as above

DIFFERENTIAL DIAGNOSIS

- Adenomatous polyp
- Squamous papilloma
- Transitional cell papilloma
- Leiomyoma
- Nephrogenic adenoma
- Amyloidosis
- Urethral caruncle
- Leukoplakia
- Periurethral abscess
- Skene gland, inflammation/adenitis
- Urethral diverticulum
- Urethral fistula
- Urethral stricture
- Malignant neoplasms
  - Adenocarcinoma
  - Melanoma
  - Metastatic disease
  - Skene (paraurethral) gland, adenocarcinoma
  - Squamous-cell carcinoma
  - Urothelial carcinoma

TREATMENT

GENERAL MEASURES (1,3)

Based on pathology, stage, location of tumor

MEDICATION

First Line

- No medical therapy as first-line treatment
- Preoperative cisplatin-based systemic chemotherapy followed by surgery for locally advanced urothelial cancer has demonstrated a survival advantage
- Preoperative chemoradiation followed by surgery for locally advanced squamous-cell carcinoma has demonstrated a survival advantage

Second Line

Adjuvant systemic chemotherapy based on underlying tumor histopathology

SURGERY/OTHER PROCEDURES

- Male
  - Penile urethra
    - Transurethral resection (TUR)
    - Corpus spongiosum—partial penectomy
    - Proximal penile urethra—total penectomy
  - Prostatic urethra
    - TUR + BCG for Ta or Tis
    - Higher stage-radical cystoprostatectomy
  - Bulbomembranous
    - TUR
    - Primary excision with primary anastomosis
    - Cystoprostatectomy with urethrectomy and total penectomy, with possible bilateral pelvic lymph node dissection
    - Locally advanced disease: Excision of pubic rami
- Female
  - Distal
    - Partial urethrectomy or TUR
  - Proximal—often presents at higher stage
    - Anterior pelvic exenteration
    - Pelvic lymph node dissection

ADDITIONAL TREATMENT

Radiation Therapy

- Used as primary therapy for low-stage distal urethral carcinoma in females
  - Primary brachytherapy or external beam
- Used as adjuvant therapy for advanced cancer

Additional Therapies

Ilioinguinal lymphadenectomy only recommended for palpable disease or for high risk disease in the distal urethra

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS (4)

- Male
  - 5-yr survival: Depends on location, stage, and pathology
- Female
  - 5-yr survival: Depends on location, stage, and pathology
- Complications
  - Associated surgical complications
  - Abscess
  - Cystitis
  - Incontinence
  - Stricture
  - Fistula

FOLLOW-UP

Patient Monitoring

- Q3–6 mo cystoscopy and urine cytology
- Cross sectional imaging to evaluate for local recurrence
- Recurrences often occur early (1–2 yr)

Patient Resources

Urology Care Foundation: Urethral cancer.
http://www.urologyhealth.org/urology/index.cfm?article=65

REFERENCES

1. Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. *Eur Urol.* 2013;64(5):823–830.
2. Eng TY, Naguib M, Galang T, et al. Retrospective study of the treatment of urethral Cancer. *Am J Clin Oncol.* 2003;26(6):558.
3. Gheiler EL, Tefilli MV, Tiguert R, et al. Management of primary urethral cancer. *Urology.* 1998;52(3):487.
4. Dalbagni G, Zhang ZF, Lacombe L, et al. Male urethral carcinoma: Analysis of treatment outcome. *Urology.* 1999;53(6):1126.

ADDITIONAL READING

- Casey RG. The Management of urethral cancer. In: Spiess P, ed. *Essentials and Updates in Urologic Oncology*. NovaScience Publishers; 2013;441–467.
- Trabulsi E, Gomella LG. Penile and urethral cancer. In: DeVita, V et al., eds. *Principles and Practice of Oncology*, 9th ed. Philadelphia, PA: Saunders; 2011.

See Also (Topic, Algorithm, Media)

- Prostate Cancer, Urothelial
- Reference Tables: TNM: Urethra Cancer
- Skene (Paraurethral) Gland, Adenocarcinoma
- Urethra Diverticula
- Urethra, Diverticular Carcinoma
- Urethral Stenosis/Stricture, Female
- Urethra, Squamous Cell Carcinoma

- Urethra Mass

CODES

ICD9

- 189.3 Malignant neoplasm of urethra
- 597.80 Urethritis, unspecified
- 598.9 Urethral stricture, unspecified

ICD10

- C68.0 Malignant neoplasm of urethra
- N34.2 Other urethritis
- N35.9 Urethral stricture, unspecified

CLINICAL/SURGICAL PEARLS

- Urethral cancers appear to be associated with infection with human papillomavirus (HPV), particularly HPV16, a strain of HPV known to be causative for cervical cancer.
- Most urethral cancers are managed surgically.
- Low-grade female distal urethral cancer can be managed with radiotherapy.
- Most locally advanced urethral tumors are best approached by neoadjuvant systemic chemotherapy (±radiotherapy) followed by consolidative surgical resection.
- Outcome strongly correlates with stage

URETHRAL CARUNCLE

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Victor W. Nitti, MD, FACS

BASICS

DESCRIPTION

- Urethral caruncle is a benign tumor consisting of friable mucosa at the posterior edge of the urethral meatus in females.
- Most are asymptomatic.
- Most common in postmenopausal females.

EPIDEMIOLOGY

Incidence

- Most common benign tumor of the female urethra.
- Occurs more frequently in postmenopausal women.
- Uncommon in childbearing years.
- Extremely rare in children.

Prevalence

Common in postmenopausal elderly women

RISK FACTORS

- Postmenopausal vaginal atrophy
- Chronic irritation to the urethral meatus

Genetics

No known genetic association

PATHOPHYSIOLOGY

- Mucosal ectropion of posterior urethral wall secondary to retraction of an atrophic vagina due to decreased estrogens
- Appears unrelated to any viral etiology
- Some cases may be related to the autoimmune phenomena of IgG4-associated disease

ASSOCIATED CONDITIONS

Vaginal atrophy

GENERAL PREVENTION

Prevention of vaginal atrophy

DIAGNOSIS

HISTORY

- Determine menopausal status, as more common in postmenopausal females
- Incidental finding on pelvic exam in asymptomatic women
- Light bleeding or spotting on underwear
- Microscopic hematuria

- Vaginal irritation
- Occasional dyspareunia
- Voiding or obstructive symptoms infrequent
- Tenderness is infrequent

PHYSICAL EXAM
- Erythematous, soft, friable mass seen protruding from a segment of the urethral meatus and palpated on vaginal inspection
- Usually reddish, occasionally may appear blue or black
- Usually located at the ventral (posterior) urethral meatus
- May be tender to palpation
- Usually $<$1–2 cm

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- There are no diagnostic lab tests
- Urine analysis may show RBCs or epithelial cells
- Urine cytology may identify malignancy but it is unrelated to the urethral caruncle

Imaging

Usually not required, may be visualized on MRI

Diagnostic Procedures/Surgery
- Urethroscopy: May help delineate extent of lesion and may be performed in the work up of microscopic hematuria
- Biopsy: Excisional or incisional.
  - Not usually required for diagnosis, but indicated if mass is suspicious for malignancy, it increases in size or fails to respond to topical estrogen cream.

Pathologic Findings
- Papillomatous, granulomatous, and angiomatous varieties
- Histologic:
  - Connective tissue containing many inflammatory cells and blood vessels and covered by an epithelial layer
  - Evidence of necrosis, inflammation, and hemorrhage may be present.
- Transitional or stratified squamous epithelium
- 2% of caruncles have associated malignancy
- Case reports of intestinal heterotopia (1)[C]

DIFFERENTIAL DIAGNOSIS
- Urethral prolapse:
  - Evagination of urethral mucosa
  - Typically circumferential
  - Seen in women of all ages (prepubertal through postmenopausal); caruncle is almost exclusively seen in post-menopausal females
- Malignancy:
  - Urethral carcinoma:
    - Uncommon

- Peak incidence 5th–7th decade
- Usually a firm, nontender, indurated mass
- Irritative and obstructive voiding symptoms may be associated
- Bleeding from urethra or on toilet tissue is more typical.
- Four subtypes of urethral carcinoma: Squamous cell, transitional cell, adenocarcinoma, melanoma (2)[B].

– Lymphoma
– Intestinal metaplasia

• Periurethral glans abscess
• Urethral polyp: Pediatric equivalent of urethral caruncle
• Urethral syndrome
• Urethral condyloma
• Urethral varices
• Thrombosis of urethral vein:
– Bluish, swollen, very tender lesion in similar location to caruncle
• Other causes of postmenopausal bleeding: Cervical, ovarian, uterine pathology

TREATMENT

GENERAL MEASURES

• Most urethral caruncles are asymptomatic and do not require definitive treatment.
• Conservative management with sitz baths, topical estrogen creams, topical anti-inflammatory agents should be used in the majority of patients.
• Excessive or persistent bleeding of obstructive voiding symptoms may prompt treatment.
• If there is any doubt concerning the diagnosis, biopsy should be performed.

MEDICATION

First Line

• Topical estrogen: Apply cream 0.3 mg daily for 2 weeks then decrease to twice a week for maintenance.
– Due to minimal absorption, progesterone is not usually needed.
• Anti-inflammatory medications for mild discomfort, PO, or topical.

Second Line

Systemic estrogen replacement

SURGERY/OTHER PROCEDURES

• Excision:
– Outpatient procedure performed under local anesthesia with or without sedation
– Remove the entire caruncle and approximate the ventral urethral meatal mucosa to the vaginal epithelium
• Ligation (3)[C]:
– Outpatient procedure performed under local anesthesia
• Cryoablation
• Laser fulguration

ADDITIONAL TREATMENT

Radiation Therapy
Applicable only for certain distal urethral malignancies and not for urethral caruncle

Additional Therapies
Sitz baths may alleviate discomfort.

Complementary & Alternative Therapies
None

ONGOING CARE

PROGNOSIS
Excellent

COMPLICATIONS
Urethral stricture or meatal stenosis with surgical excision

FOLLOW-UP
Patient Monitoring
- None specific
- Routine gynecologic follow-up as this is a benign lesion

Patient Resources
Urology Care Foundation: Benign Urethral Lesions.
http://www.urologyhealth.org/urology/index.cfm?article=93

REFERENCES

1. Urakami S, Igawa M, Shiina H, et al. Urethral caruncle with coexistence of intestinal heterotopia. A case report. *Int Urol Nephrol.* 1997;29(3):341–344.
2. Marshall FC, Nishimoto K, Ogata K. Neoplasms and caruncles of the female urethra. *Surg Gynecol Obstst.* 1960;110:723.
3. Park DS, Cho W. Simple solutions for urethral caruncle. *J Urol.* 2004;172(5 Pt 1):1884–1885.

ADDITIONAL READING

- Dmochowski RR, Ganabathi K, Zimmern PE, et al. Benign female periurethral masses. *J Urol.* 1994;152:1943.
- Katz VL. Benign gynecologic lesions: Vulva, vagina, cervix, uterus, oviduct, ovary. In: Katz, ed. *Comprehensive Gynecology*, 5th ed. St. Louis: Mosby, 2007.
- North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. *Menopause*. 2007;14:355.
- Shah SR, Nitti VW: Benign vaginal wall masses and paraurethral lesions. In Nitti WW, Rosenblum R, Brucker BM (eds.) *Vaginal Surgery for the Urologist*. Philadelphia, PA: Elsevier Saunders; 2012;127–136.

See Also (Topic, Algorithm, Media)
- Urethra, Bleeding (Blood at Meatus)
- Urethra, Carcinoma, General Considerations

- Urethra, Diverticulum, Female (Urethral Diverticulum)
- Urethra, Mass
- Urethra, Prolapse (Female)
- Urethral Caruncle Image ☼
- Urethral Discharge

CODES

ICD9

- 599.3 Urethral caruncle
- 627.3 Postmenopausal atrophic vaginitis
- V49.81 Asymptomatic postmenopausal status (age-related) (natural)

ICD10

- N36.2 Urethral caruncle
- N95.2 Postmenopausal atrophic vaginitis
- Z78.0 Asymptomatic menopausal state

CLINICAL/SURGICAL PEARLS

- Urethral caruncles occur most frequently in postmenopausal women.
- Most are asymptomatic and do not need treatment.
- Biopsy is indicated if there is a suspicion for malignancy.
- Topical estrogen is the first-line treatment.
- Surgical intervention should be reserved for patients with larger symptomatic lesions or who fail conservative therapy.

URETHRAL DISCHARGE

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BASICS

DESCRIPTION

- Urethral discharge is abnormal fluid (not urine or semen) released through the urethra most commonly as a result of increased local inflammation.
  - Inflammation secondary to infection, neoplasm, trauma, or local irritation
- Most common symptom of a sexually transmitted infection (STI/STD) in men and most commonly a manifestation of urethritis.
- Appearance of the fluid is commonly characterized as purulent or mucopurulent; scant, watery, or mucoid; or bloody.

EPIDEMIOLOGY

Incidence

Gonorrhea (a common cause of urethral discharge) in men reported to the CDC: 98.7 per 100,000 men

Prevalence

N/A

RISK FACTORS

- Male sex
- Urinary tract infection
- Recent instrumentation or catheterization
- Urothelial carcinoma
- Urethral mass
- Benign prostatic hypertrophy
- Unprotected sexual intercourse

Genetics

N/A

PATHOPHYSIOLOGY (1)

- Urethritis
  - *Neisseria gonorrhea*
    - May present as urethritis, epididymitis, proctitis, or prostatitis
    - Male—Purulent discharge, dysuria
    - Female—Usually asymptomatic, but may have pelvic discomfort, dysuria, dyspareunia
  - Non-gonococcal (*Chlamydia trachomatis, Mycoplasma, Ureaplasma urealyticum*)
    - Chlamydia—Frequently asymptomatic, may present with urethritis, epididymitis, or prostatitis. Gonorrhea may coexist.
    - 25% of women are symptomatic and can have a mucopurulent cervical discharge.
    - 40% of untreated women will develop pelvic inflammatory disease (PID). PID is

associated with infertility and ectopic pregnancy.
  - *Trichomonas vaginalis*
    - Male—Present with urethritis but often asymptomatic.
    - Female—Malodorous, yellow-green vaginal discharge with vulvar irritation.

ASSOCIATED CONDITIONS

With STI coinfection is common (ie, gonorrhea and chlamydia)

GENERAL PREVENTION

- For STI:
  - Abstinence
  - Female and male condoms
  - Education and awareness of risky behavior

DIAGNOSIS

HISTORY

- Age, sex, and duration?
  - Males are more likely to have discharge from a venereal cause
  - STIs are most common in the 15–24–yr-old age group
  - Venereal or traumatic cause is more likely to have acute onset while chronic inflammation or tumor is usually insidious
- Obtain thorough sexual history to discover risk of STI/STD
  - Sex with men, women, or both?
  - Oral, vaginal, or anal intercourse
  - Condom usage
  - How many partners in last month?
  - History of STI/STD
  - Dyspareunia?
- Ask the time since onset, any inciting events, quality or character, quantity, prior treatments, associated symptoms
- History of irritative or obstructive voiding symptoms
  - Hematuria, dysuria, frequency, urgency, incontinence, post void dribbling, straining, incomplete emptying
    - Hematuria noted at beginning, middle or total hematuria, or end of stream helps localize bleeding source to urethra, bladder or upper tracts, or prostate
    - Frequency and urgency can indicate an acute inflammatory response
    - Incontinence can indicate a diverticular source
    - Straining and incomplete emptying indicate obstructive cause
- History of perineal, scrotal, or penile pain
  - Assists in localizing source of discharge
- Any vaginal symptoms?
  - Vaginal mass, discharge, or irritation can indicate presence of urethral diverticulum
- Past medical and surgical history
  - Gonorrhea can have systemic effects
  - Reactive arthritis (arthritis, conjunctivitis, and urethritis) often presents initially with

urethral complaints Prior urethral surgery such as sling for incontinence of artificial urinary sphincter. Erosion of prosthetic material can cause discharge.

- Other symptoms
  - Constitutional symptoms indicate systemic process (fevers, chills, fatigue)
  - In women clearly delineate urethral discharge form vaginal discharge.

PHYSICAL EXAM

- Men
  - Request the patient avoid urination before being examined.
  - Genital skin exam to evaluate for evidence of trauma, ulcers, rashes, abrasions, or masses
  - If no discharge is seen, the urethra should be gently massaged from the ventral part of the penis toward the meatus.
  - Examination of testicles and spermatic cord, scrotum, and inguinal lymph nodes
- Women
  - Genital skin exam to evaluate for evidence of trauma, ulcers, rashes, abrasions, masses, or fissures
  - External genitalia inspection
  - Palpation of urethra for mass, fluctuance, or discharge
  - Bimanual exam to evaluate for tenderness, mobility, and masses

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Positive leukocyte esterase on first void urine is diagnostic of urethritis.
- Gram stain of discharge
  - >5 WBCs/oil immersion field $\rightarrow$ Urethritis
  - Presence of gram $(-)$ intracellular diplococci on gram stain is 99% specific and 95% sensitive for gonococcal urethritis
  - Negative gram stain does not rule out gonococcal urethritis
  - When gonococcal urethritis is suspected and investigatory tests cannot confirm the diagnosis, consider *Neisseria meningitidis* infection (2).
- Repeated nucleic acid amplification testing (NAAT) is the most sensitive test for chlamydia and gonorrhea.
  - Vaginal, endocervical, or urethral swab or first catch urine from men or women
  - Additional PCR-based genotyping is necessary to differentiate lymphogranuloma venereum (LGV) from chlamydia.
    - LGV is caused by specific strains of Chlamydia (L1, L2, L3).
- CBC if evidence of systemic involvement
- BMP if concern for obstruction from prostatic enlargement

Imaging

- If the cause of the discharge is unclear additional imaging
- Men
  - Scrotal ultrasound
  - Renal/bladder ultrasound
  - CT abdomen and/or pelvis

  - MRI pelvis
- Women
  - Pelvic ultrasound (transabdominal or transvaginal)
  - Renal/bladder ultrasound
  - CT abdomen and/or pelvis
  - MRI pelvis

Diagnostic Procedures/Surgery

- Cystourethroscopy
  - Normally needed for more atypical presentations and if discharge persists in spite of adequate medical therapy
  - Evaluate for mass, erythema, false passage, stricture, or diverticulum of urethra
  - Inspect prostate for friability, vascularity, hypertrophy, narrowing, and areas of visual fluctuance

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Inflammatory causes
  - Gonococcal urethritis
  - Non-gonococcal urethritis
    - *Chlamydia trachomatis*
    - *Mycobacterium genitalium*
    - *Trichomonas vaginalis*
    - *Ureaplasma urealyticum*
  - Urethral diverticulum
  - Trichomoniasis
  - TB
  - Periurethral abscess
  - Reactive arthritis (Previously called Reiter syndrome)
- Masses
  - Urethral tumor
  - Urethral caruncle
  - Urethral hemangioma
  - Urethral condyloma
  - Urethral carcinoma
- Trauma/iatrogenic
  - Acute external force
  - Recent instrumentation
  - Recent catheterization
  - Eroded urethral sling or implanted prosthesis
- Mucosal hyperemia
  - Benign Prostatic Hypertrophy often can have initial hematuria due to dilated prostatic vessels (3).

TREATMENT

GENERAL MEASURES

Cause of discharge dictates treatment

MEDICATION

First Line

- Gonococcal and non-gonococcal urethritis
  - Azithromycin 1 g PO × 1 or doxycycline 100 mg PO BID × 7 days plus ceftriaxone 125 mg IM × 1 or cefixime 400 mg PO × 1 is first-line empiric therapy
- Trichomoniasis
  - Metronidazole 2 g PO × 1 or 250 mg TID × 7 days
- Reactive arthritis
  - NSAIDs, methotrexate, cyclosporine, and sometimes corticosteroids
- BPH
  - 5α-reductase inhibitors can be used for refractory prostatic bleeding

Second Line

Please refer to the CDC's published Sexually Transmitted Diseases Treatment Guidelines 2010 for updates and alternatives

SURGERY/OTHER PROCEDURES

- Urethral mass
  - Often surgical excision is preferred approach
  - Urethral carcinoma can be treated effectively with surgical excision—better control with anterior involvement in males (vs. posterior)
  - Diverticulum requires diverticulectomy
- Trauma
  - Radiographic interrogation of anatomy
  - Retrograde urethrogram, cystogram, cystoscopy, CT cystogram
  - Urethral injuries can be repaired surgically after several months of recovery

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

For STI/STD consider screening and treating partner

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

N/A

COMPLICATIONS

- Urethral stricture

- Local spread to other genitourinary organs – cystitis, prostatitis, epididymitis, orchitis
- Abscess formation in urethra, prostate, epididymis, or testicle
- Systemic infection
- Local invasion or metastasis of malignant lesion
- Recurrent pain

FOLLOW-UP

Patient Monitoring

Follow-up is dictated by any associated findings and etiology of discharge

Patient Resources

- Medline Plus: Gram stain of urethral discharge.http://www.nlm.nih.gov/medlineplus/ency/article/003749.htm

REFERENCES

1. Center for Disease Control and Prevention. (2013). Sexually Transmitted Diseases. Retrieved from http://www.cdc.gov/std.
2. Genders RE, Spitaels D, Jansen CL, et al. A misleading urethral smear with polymorphonuclear leucocytes and intracellular diplococci; case report of urethritis caused by *Neisseria meningitidis* . *J Med Microbiol*. 2013;62(Pt 12):1905–1906.
3. Memis A, Ozden C, Ozdal OL, et al. Effect of finasteride treatment on suburethral prostatic microvessel density in patients with hematuria related to benign prostate hyperplasia. *Urol Int*. 2008;80(2):177–180.

ADDITIONAL READING

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010;59 (No. RR-12).

See Also (Topic, Algorithm, Media)

- Gonorrhea Microscopic Image
- Urethra, Bleeding (Blood at Meatus)
- Urethral Carcinoma, General Considerations
- Urethral Condyloma
- Urethral Diverticulum
- Urethral Hemangioma
- Urethritis, Gonococcal and Non-gonococcal

CODES

ICD9

- 098.0 Gonococcal infection (acute) of lower genitourinary tract
- 788.1 Dysuria
- 788.7 Urethral discharge

ICD10

- A54.01 Gonococcal cystitis and urethritis, unspecified
- R30.0 Dysuria

- R36.9 Urethral discharge, unspecified

CLINICAL/SURGICAL PEARLS

- Character, color, and acuity of discharge can usually direct diagnosis.
- Urethral discharge is the most common symptom of an STI/STD in men.
- Carcinoma of the urethra must be ruled out in the presence of bloody urethral discharge.

URETHRAL DIVERTICULA, FEMALE

Alana M. Murphy, MD

BASICS

DESCRIPTION

- A urethral diverticula is an out-pocketing off the urethra between the submucosal layer and the periurethral fascia
- Often contains a collection of urine and/or pus
- Usually connects to the urethra through a neck or ostium
- Classic symptoms are dysuria, dyspareunia, and post-void dribbling

EPIDEMIOLOGY

Incidence (1)

- Depends on avidity with which it is sought
- Mean age at surgery ~48 yr

Prevalence

- *Difficult to determine true prevalence*
- *1–3% asymptomatic women*

RISK FACTORS

Some series have demonstrated a higher prevalence in African American women compared to Caucasian women

Genetics

No known genetic risk factors

PATHOPHYSIOLOGY

- Congenital female urethral diverticula are uncommon
- Most common theory regarding adult female diverticula (2)
  - Infection or obstruction of periurethral glands
  - Obstruction or abscess formation leads to cyst-like cavity
  - Diverticulum is contained within periurethral fascia

ASSOCIATED CONDITIONS

- Urinary incontinence
- Dyspareunia
- Dysuria
- Storage or voiding symptoms
  - Occasional urinary retention

GENERAL PREVENTION

No known method of prevention

DIAGNOSIS

HISTORY

- Classic 3 Ds (rare for all 3 to be present):
  - Dysuria: Pain during voiding
  - Dribbling (incontinence): Typically due to urine leaking from the diverticulum, patient may also have concomitant stress and/or urgency incontinence
  - Dyspareunia: Pain with intercourse
- Nonspecific complaints are common:
  - Frequency/urgency
  - Hematuria
  - Palpable or visible vaginal lump/bulge
  - Periurethral pain
  - Recurrent UTIs
  - Voiding symptoms or urinary retention
- May be an incidental finding

PHYSICAL EXAM

- Inspect the anterior vaginal wall:
  - Some diverticula are visible as a suburethral mass
  - Assess bladder neck mobility
  - Observe for stress incontinence
  - Assess for point tenderness suburethrally, which may be the only sign of a urethral diverticulum.
- If a suburethral mass is noted:
  - Classic sign: Compressing the mass expresses urine or pus from urethral meatus.
  - If the mass does not compress, consider:
    - Vaginal wall cyst
    - Obstructed (noncommunicating) diverticulum
  - Induration suggests stone or cancer
- Evaluate for other pelvic pathology

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis, urine culture
- Preoperative tests appropriate to patient's age and medical condition

Imaging

- Magnetic resonance imaging (MRI) (3)
  - Diverticulum has high signal intensity on T2-weighted imaging
  - Most accurate diagnostic test
  - Does not require the patient to void
  - Shows noncommunicating diverticula
  - Helps surgical planning
  - Shows size, extent, location, and presence of filling defects
- Voiding cystourethrogram (VCUG):
  - Advantage: Less costly than MRI, allows assessment of other causes of voiding symptoms (ie, closed bladder neck)
  - Disadvantages compared to MRI:

    - More invasive
    - Patient must be able to void
    - Less sensitive for diagnosis
    - Less anatomic detail
- Positive-pressure double-balloon urethrogram:
  – Less sensitive than MRI
  – More sensitive than VCUG
  – Requires special radiology expertise
- Ultrasound (US): Highly operator-dependent
  – Intraurethral or transvaginal

Diagnostic Procedures/Surgery

- Cystoscopy:
  – Much less sensitive than VCUG or MRI
  – Ostium usually in mid-urethra at 5–7 o'clock
  – Main value: Rule out other pathology
- Urodynamics (UDS):
  – Not mandatory in straightforward cases
  – Useful if the patient has incontinence or voiding difficulty
  – Fluoroscopic UDS: Combines VCUG with lower-tract functional evaluation

Pathologic Findings

- *Histology of epithelium may be:*
  – *Transitional*
  – *Stratified squamous*
  – *Columnar*
  – *Cuboidal*
  – *Absent (wall just fibrous tissue)*
- *May have carcinoma* (4)
  – *Adenocarcinoma more common than transitional or squamous cell*
- *Diverticulum may contain stones*

DIFFERENTIAL DIAGNOSIS

- Benign neoplasms
  – Leiomyomas:
    - Increased prevalence in females aged 30–50 yr
  – Skene gland cyst or abscess
    - Associated with meatal deviation
  – Gartner duct cyst
  – Ectopic ureterocele
  – Urethral prolapse or caruncle
  – Vaginal wall cyst
- Malignant neoplasms:
  – Primary urethral carcinoma; more common in females:
    - Squamous cell (80%)
    - Transitional cell (15%)

- Adenocarcinoma (4%)
- Melanoma (1%)

– Rarely and adenocarcinoma can arise in a urethral diverticulum or in Skene gland

TREATMENT

GENERAL MEASURES

- No treatment is necessary if the patient is asymptomatic
  – Patient must understand the small risk that the diverticulum may harbor neoplastic cells
- Little is known about the natural history of untreated diverticula
- Antibiotics and analgesics may control symptoms
- With significant symptomatology, surgical excision is best

MEDICATION

First Line

- Antibiotics (eg, trimethoprim/sulfamethoxazole)
- Analgesics (eg, phenazopyridine), and antispasmodics (eg, oxybutynin) may control mild symptoms
- Surgical excision should be considered if medications are required for symptoms

Second Line

If first-line medications do not alleviate symptoms, then surgical excision is appropriate

SURGERY/OTHER PROCEDURES

- Transvaginal excision and reconstruction is the most common operation.
- Key principles of excision include:
  – Well-vascularized anterior vaginal wall flap
  – Preserve periurethral fascia
  – Excise diverticulum completely
  – Watertight, tension-free urethral closure
  – Avoid overlapping suture lines
  – Close dead space
  – Multiple layer closure (consider Martius flap)
  – Adequate bladder drainage with a urethral catheter ± suprapubic catheter
  – Antimuscarinics can be used to prevent bladder spasms
- Perform simultaneous anti-incontinence procedure (fascial sling) for stress urinary incontinence (SUI) if:
  – Stress incontinence is present before surgery
  – Patient desires concomitant treatment

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- If untreated, natural history is not well known
- Reported surgical success rates 70–99%

COMPLICATIONS

- Related to the diverticulum:
  - Stones
  - Carcinoma: Adenocarcinoma, transitional cell, squamous cell
  - Recurrent UTIs
  - Dysuria
  - Dyspareunia
  - Urinary incontinence
  - Storage or voiding symptoms
- Related to the surgery:
  - Infection
  - Bleeding
  - Urinary incontinence
  - Recurrent diverticulum
  - Urethrovaginal fistula
  - Urethral stricture or necrosis
  - Bladder or ureteral injury
  - Vaginal scarring or narrowing

FOLLOW-UP

Patient Monitoring

- VCUG after surgery at the time of catheter removal
- History and genitourinary exam on follow-up visits
- Additional studies if indicated based on history and exam findings

Patient Resources

http://www.urologyhealth.org/urology/index.cfm?article=110

REFERENCES

1. El-Nashar SA, Bacon MM, Kim-Fine S, et al. Incidence of female urethral diverticulum: A population based analysis and literature review. *Int Urogynecol J.* 2013;25(1):73–79.
2. Scarpero HM, Dmochowski RR, Leu PB. Female urethral diverticula. *Urol Clin North Am.* 2011;38(1):65–71.
3. Singla P, Long SS, Long CM, et al. Imaging of the female urethral diverticulum. *Clin Radiol.* 2013;68(7):428–425.
4. Thomas AA, Rackley RR, Lee U, et al. Urethral diverticula in 90 patients: A study with emphasis on neoplastic alterations. *J Urol.* 2008;180(6):2463–2467.

ADDITIONAL READING

Rovner ES. Urethral diverticula: A review and an update. *Neurourol Urodyn*. 2007;26:972–977.

See Also (Topic, Algorithm, Media)
- Dribbling, Post-Void
- Dyspareunia
- Martius Flap
- Müllerian Duct Remnants and Syndrome
- Skene (paraurethral) gland, adenocarcinoma
- Skene (paraurethral) gland, inflammation/adenitis
- Urethra, Abscess (Periurethral Abscess)
- Urethra, Carcinoma
- Urethra, Caruncle
- Urethra, Diverticular Carcinoma
- Urethra, Leiomyoma
- Urethra, Mass
- Urethra, Nephrogenic Metaplasia (Adenoma)
- Urethra, Prolapse (Female)
- Urethral Diverticula Image
- Urinary Tract Infection (UTI), Adult Female
- Vaginal Discharge, Urologic Considerations

CODES

ICD9
- 599.2 Urethral diverticulum
- 625.0 Dyspareunia
- 788.1 Dysuria

ICD10
- N36.1 Urethral diverticulum
- N94.1 Dyspareunia
- R30.0 Dysuria

CLINICAL/SURGICAL PEARLS
- Classic symptoms include dysuria, dyspareunia, and post-void dribbling.
- Definitive management requires transvaginal excision with a multilayer closure.

URETHRAL MASS

Bic N. Cung, MD
Jack H. Mydlo, MD

BASICS

DESCRIPTION

- Urethral masses may be palpable; they are often visualized on cystoscopy or other imaging modalities.
- In females the most common differential includes: urethral caruncle, periurethral/Skene duct cyst, urethral prolapse, ectopic ureterocele, urethral diverticulum, vaginal wall cyst (Müllerian and Gartner duct), and urethral and vaginal malignancy.
- In men inflammatory lesions such as Lichens Sclerosis (LS) or Balanitis Xerotica Obliterans (BXO), periurethral abscess and malignancy can be commonly seen.

EPIDEMIOLOGY

Incidence

- Incidence of urethral mass unknown
- With respect to urethral malignancy:
  - African Americans twice as likely of developing primary urethral cancer as whites
  - Primary urethral cancer at least twice as common in males as in females (1).
  - Most common from 5th to 7th decades of life.

Prevalence

N/A

RISK FACTORS

- Malignancy:
  - Chronic inflammation may increase risk of malignancy.
  - History of bladder cancer may suggest urethral recurrence.
  - HPV-16 infection has been linked to urethral carcinoma in males (2).
- Benign mass
  - Chronic UTIs may suggest anatomic problem such as diverticuli.

Genetics

None

PATHOPHYSIOLOGY

- Anatomic considerations: The male urethra (averages about 20 cm in length), is divided into distal and proximal portions. The distal urethra, which extends distally to proximally from the tip of the penis to just before the prostate, includes the meatus, the fossa navicularis, the penile or pendulous urethra, and the bulbar urethra. The proximal urethra, which extends from the bulbar urethra to the bladder neck, includes distally to proximally the membranous urethra and the prostatic urethra
  - Lymphatic drainage varies according to region:
    - Distal urethra drains to superficial and deep inguinal lymph node (LN).

- Proximal urethra drains to external iliac, obturator, and internal iliac LNs in pelvis.
- Sex accessory glands. These can be the source of infection due to obstruction of their secretory ducts.
  - Prostate
  - Glans Littre
  - Cowper gland

• Anatomicconsiderations: The female urethra is In adults, it is about 4 cm in length and is mostly contained within the anterior vaginal wall.
- Lymphatic drainage varies according to region:
  - Distal 1/3 urethra drains to superficial or deep inguinal LN.
  - Proximal 2/3 urethra drains to external iliac, internal iliac, and obturator (deep pelvic LN).
- Mucus glands
  - Skene gland: Mucus-producing gland that opens into distal urethra; homologous to the prostate glands in males. It can be the site of infection, cysts, or diverticuli.

ASSOCIATED CONDITIONS
None

GENERAL PREVENTION
Safe sexual practices can prevent STDs and decrease risk of inflammatory/infectious conditions.

DIAGNOSIS
HISTORY
• Age and sex of patient
- Malignancy more common >50

• Prior history of bladder cancer may suggest urethral recurrence, particularly in men
• Sexual history:
- Genital warts, gonorrhea may predispose to malignancy.

• Lower urinary tract symptoms:
- Frequency, urgency, hematuria, or dysuria may be associated with stricture or malignancy.
- Obstructive voiding symptoms such as weak stream, straining, and dribbling

• History of UTIs:
- May be associated with urethral diverticulum

PHYSICAL EXAM
• General exam: Assess for lower extremity edema.
• Lymph node assessment:
- Metastatic disease from the distal urethra can involve the superficial inguinal LN.

• External genitalia: Examine for lesions for condyloma acuminatum.
• Urethral exam:
- Carefully palpate full length of lesion.
  - Palpate for abscess or areas of tissue necrosis
- Note location, number, consistency, degree of fixation.

  - Careful bimanual exam to assess for extent of local invasion and involvement of bladder if malignancy is suspected.
  - Inspect meatus for discharge, mass, or stricture.
  - Compression or stripping of a diverticulum in females may express purulent discharge.
- Inspect perineum for fistulous tracts.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis
- Urine culture
- Urine cytology
- Urethral swab: Culture for gonorrhea, Chlamydia, and TB

Imaging

- Ultrasound to evaluate urethral stricture, diverticulum, and foreign body.
- VCUG can help diagnose urethral diverticulum.
- Retrograde urethrogram (RUG) to assess for location and length of urethral stricture.
- Pelvic MRI or CT to assess for urethral diverticulum, metastasis to the pelvic and inguinal LN, evidence of corporal invasion by carcinoma.
  - Pelvic MRI often considered imaging study of choice for urethral neoplasms.

Diagnostic Procedures/Surgery

- Cystoscopy allows direct visualization of the mass and allows for biopsy.
- Percutaneous aspiration of fluctuant mass may provide fluid for cytology and culture.
- Needle biopsy may provide tissue for diagnosis for deep lesions.
- Open surgical biopsy for diagnosis.

Pathologic Findings

Based on specific diagnosis

DIFFERENTIAL DIAGNOSIS

- Depends on clinical presentation and age of patient:
  - Children are more likely to have congenital disease
  - Young adults are more likely due to trauma or STI/STDs
  - Older adults are at greater risk for primary or metastatic malignancy.
- Congenital conditions:
  - Benign fibroepithelial polyp
  - Retention cysts of Cowper gland ducts
  - Ectopic ureterocele
  - Urethral diverticulum
    - The 3 Ds: **d**ysuria, **d**yspareunia, **d**ribbling
- Inflammatory:
  - Stricture disease secondary to gonococcal urethritis
  - Periurethral abscess
  - Accessory gland cysts/abscesses
  - condylomata acuminata
  - TB

- Lichens Sclerosis (LS) or Balanitis Xerotica Obliterans (BXO)
  - Most common cause of meatal stenosis in adults
- Traumatic:
  - Stricture disease secondary to injury; hematoma, foreign body
- Benign neoplasms:
  - Hemangioma
  - Adenomatous polyps
  - Squamous papilloma
  - Transitional cell papilloma
  - Leiomyomas:
    - Increased prevalence in females aged 30–50 yr.
  - Inverted papilloma
    - Type I benign, type 2 higher malignant potential and requires follow-up.
  - Polypoid urethritis
    - Most commonly seen in patients with chronic catheter use.
  - Nephrogenic adenoma
  - Amyloidosis
  - Skene (paraurethral) gland, inflammation/adenoma/abscess
  - Urethral caruncle:
    - More common in postmenopausal women
- Malignant neoplasms:
  - Primary urethral carcinoma, more common in females.
    - Squamous cell (80%)
    - Transitional cell (15%)
    - Adenocarcinoma (4%)
    - Melanoma (1%)
    - Clear cell adenocarcinoma has been associated with urethral diverticulum.
    - Skene (paraurethral) gland adenocarcinoma
    - Metastatic disease
- Miscellaneous conditions
  - Urethral prolapsed:
    - Interlabial, well-circumscribed mass most common in African American females aged 5–7 yr, postmenopausal women is the 2nd most common group.
    - Stone impacted in urethra or dierticulum
    - Foreign body
- Mass in corporal body in male:
  - Metastatic deposit
  - Fibrosis of corporal body from priapism or trauma
  - Peyronie disease plaque
  - Penile prosthesis
- Vaginal wall mass:
  - Leiomyoma
  - Vaginal wall cyst:
    - Gartner duct cysts

TREATMENT

GENERAL MEASURES

- Management is directed by the pathologic findings.
  - Cystoscopic exam with biopsy will usually provide the diagnosis.
  - Imaging and bimanual exam will provide staging information in the case of malignancy.
- In cases with locally advanced disease, multimodality therapy using chemotherapy with radiation is sometimes used.
- Condyloma of the urethra: Intraurethral 5-FU cream, biopsy with fulguration/laser ablation.
- Urethral mucosal prolapsed: Estrogen and anti-inflammatory cream.
- Infectious etiologies: Antibiotic specific to offending organism

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Urethral stricture:
  - Dilation
  - Internal urethrotomy
  - Urethroplasty
- Urethral prolapsed:
  - Excision
- Urethral diverticulum:
  - Excision
- Benign neoplasm:
  - Biopsy for diagnosis
  - Excision, fulguration, laser ablation.
- Malignant neoplasms:
  - Male urethra: Partial or total urethrectomy, possible penectomy with perineal urethrostomy.
  - Female urethra: Total urethrectomy.
  - Cystectomy necessary for high-grade lesions near bladder neck for both males and females.
  - In females, this includes an anterior exenteration (urethrectomy, cystectomy with pelvic lymphadenectomy, hysterectomy with salpingectomy, and anterior vaginal wall).
  - Inguinal and pelvic LN dissections are based on location of lesions.

ADDITIONAL TREATMENT

Radiation Therapy

- May be indicated in some cases of urethral cancer to decrease local recurrence.
- In women, radiation therapy using brachytherapy and external beam radiation combination is a suitable alternative.

Additional Therapies

Cisplatin-based chemo therapy has a role in the adjuvant and neo-adjuvant setting for advance disease (3).

Complementary & Alternative Therapies

Combination of chemotherapy, radiation therapy, and surgery is recommended for advanced female urethral cancer.

ONGOING CARE

PROGNOSIS

- Depends on etiology of mass
- Neoplasms:
  - Males
    - Survival dependent on grade and stage of tumor.
    - Anterior urethral carcinoma of lower grade has best survival and posterior urethral carcinoma of higher grade has worst survival.
  - Distal urethral carcinoma in females of low stage has 70–90% cure rates with surgery.
  - Proximal urethral carcinoma in females are more likely of high stage and has poor prognosis, $<20\%$ 5-yr survival.

COMPLICATIONS

- Dependent on pathology and treatment
- Urethral stricture: Complications secondary to instrumentation and treatment of urethral mass.

FOLLOW-UP

Patient Monitoring

- Cystourethroscopy and urine cytology every 6 mo for urethral carcinoma.
- Urethral condyloma require urethroscopy and retreatment for disease eradication.

Patient Resources

- Urology Care Foundation: Urethral cancer. http://www.urologyhealth.org/urology/index.cfm?article=65
- Urology Care Foundation: Benign urethral lesions. http://www.urologyhealth.org/urology/index.cfm?article=110

REFERENCES

1. Swartz MA, Porter MP, Lin DW, et al. Incidence of primary urethral carcinoma in the United States. *Urology*. 2006;68:1164–1168.
2. Wiener JS, Liu ET, Walther PJ. Oncogenic human papillomavirus type 16 is associated with squamous cell cancer of the male urethra. *Cancer Res*. 1992;52:5018–5023.
3. Dayyani F, Pettaway CA, Kamat AM, et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. *Urol Oncol*. 2013;31(7):1171–1177.

ADDITIONAL READING

Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. *Eur*

Urol. 2013;64(5):823–830.

See Also (Topic, Algorithm, Media)

- Ureterocele
- Urethra, Carcinoma, General Considerations
- Urethra, Caruncle
- Urethra, Diverticulum, Female
- Urethra, Squamous Cell Carcinoma

CODES

ICD9

- 189.3 Malignant neoplasm of urethra
- 223.81 Benign neoplasm of urethra
- 599.84 Other specified disorders of urethra

ICD10

- C68.0 Malignant neoplasm of urethra
- D30.4 Benign neoplasm of urethra
- N36.8 Other specified disorders of urethra

CLINICAL/SURGICAL PEARLS

- Many benign and malignant urethral masses can present with similar constellation of symptoms.
  - Cystoscopic examination and biopsy are often necessary to confirm diagnosis.
- Draining fistulas of the penis and perineum should alert suspicion of malignancy.

URETHRAL SQUAMOUS-CELL CARCINOMA

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BASICS

DESCRIPTION

Squamous-cell carcinoma (SCC) of the urethra is a malignancy arising from the native squamous lining of the male and female urethra.

EPIDEMIOLOGY

Incidence

- Incidence is higher in African American patients as compared to their white counterparts.
  - White males: 0.58 per 1,000,000
  - African American males: 2.3 per 1,000,000
  - White females: 0.43 per 1,000,000
  - African American females: 0.69 per 1,000,000
- Incidence increases steadily with age, more steeply in men as compared to women (1).

Prevalence

N/A

RISK FACTORS

- Male urethral SCC:
  - Chronic irritation after clean intermittent catheterization (CIC)
  - History of sexually transmitted infection (STI): Nearly 25% of patients with urethral carcinoma will give history of STIs.
  - Urethritis
  - Urethral stricture disease ($\geq$50% of patients).
  - HPV
  - History of external beam radiation therapy
- Female urethral SCC:
  - Leukoplakia
  - Chronic irritation
  - Parturition
  - Human papilloma virus
  - Viral infections
  - Recurrent urinary tract infections
  - Possibly urethral diverticula: 4% of female urethral carcinoma is found within the diverticulum.

Genetics

- Possibility raised for aberrations in chromosomes Y, 2, 3, 4, 6, 7, 8, 11, and 20 (2).
- Notably, there have been no abnormalities described in chromosomes 9 and 17, those largely responsible for the development of urothelial carcinoma.

PATHOPHYSIOLOGY

- Male urethral SCC:
  - Occurs in the male membranous urethra (80% SCC), bulbar urethra (80% SCC), and penile urethra (90% SCC).
- Female urethral SCC:
  - Occurs in the distal 2/3 of the female urethra.
- Both male and female urethral carcinoma spread via direct local extension and via lymphatics:
  - Anterior urethra drains to superficial and deep inguinal nodes.
  - Posterior urethra drains to pelvic lymph nodes.

ASSOCIATED CONDITIONS

- Condyloma acuminatum
- History of STIs
- Presence of indwelling catheter
- Urethral diverticula
- Urethral stricture disease

GENERAL PREVENTION

Prevention of STIs with the use of barrier protection such as condoms

DIAGNOSIS

HISTORY

- Particular attention must be made to risk factors and associated GU conditions.
- Male urethral SCC:
  - Urethral bleeding
  - Perineal discomfort
  - Decreased force of stream
  - Urinary urgency or frequency
  - Dysuria
  - Urinary fistulae
  - Chronic irritation (CIC, history of urethroplasty)
- Female urethral SCC:
  - Urethral bleeding
  - Palpable urethral mass
  - Urinary urgency or frequency
  - Induration of urethra or anterior vaginal wall

PHYSICAL EXAM

- Examiner should evaluate for potential mass arising from urethra:
  - Formal pelvic exam for female patients
  - Perineal exam (to evaluate proximal urethra) in male patients
- Particular attention should be given to the inguinal exam, as 20–30% of patients present initially with nodal metastases to the inguinal chain.
- Exam under anesthesia at time of cystoscopy including bimanual palpation of genitalia, urethra, rectum, and perineum helpful to determine extent of disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
- Urine culture
- Urine polymerase chain reaction for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*
- Cytology of 1st voided urine

Imaging

- Retrograde urethrogram/voiding cystourethrogram (RUG/VCUG):
  - Evaluates entire urethra
  - Aids in assessment for stricture disease, urinary fistulae, or urethral diverticula
- Cross-sectional imaging (CT or MRI):
  - Aids in the determination of local involvement, spread to regional lymphatics, or invasion of contiguous structures
  - MRI particularly helpful for assessment of corporal involvement
  - CT urography provides evaluation of upper urinary tract drainage and presence or absence of upper urinary tract neoplasia (more critical in patients with urethral urothelial carcinoma)

Diagnostic Procedures/Surgery

- Cystoscopy with biopsy or transurethral resection:
  - Gold standard in histologic diagnosis of urethral carcinoma
  - Cystoscopic appearance of fungating growth extending into urethral lumen
- Sigmoidoscopy/colonoscopy if concern for involvement of GI tract based upon physical exam or imaging
  - Particularly important in cases of urethral adenocarcinoma to rule out a GI primary source

Pathologic Findings

Fungating tumor with varied cytologic differentiation ranging from well-differentiated lesions producing keratohyaline pearls to anaplastic giant-cell tumors

ALERT

The clinician must have a very high index of suspicion when considering urethral carcinoma, considering the often insidious and nonspecific nature of the patient's complaints.

DIFFERENTIAL DIAGNOSIS

- Condyloma acuminatum
- Benign neoplasms:
  - Hemangioma
  - Adenomatous polyps
  - Squamous papilloma
  - Urothelial cell papilloma
  - Leiomyomas
    - Increased incidence in females aged 30–50 yr
  - Polypoid urethritis
  - Nephrogenic adenoma

  - Amyloidosis
  - Urethral caruncle: More common in postmenopausal women
- Leukoplakia
- Periurethral abscess
- Skene's (periurethral) gland, inflammation/adenitis
- Urethral diverticulum
- Urethral fistula
- Urethral stricture
- Malignant neoplasms:
  - Primary urethral carcinoma:
    - Squamous cell
    - Urothelial cell
    - Adenocarcinoma
    - Melanoma
    - Clear-cell adenocarcinoma has been associated with urethral diverticulum.
    - Skene (periurethral) gland adenocarcinoma
    - Metastases

TREATMENT

GENERAL MEASURES

- Treatment decisions based on sex, stage, and location of tumor
- TNM staging (See Reference tables: TNM: Urethra Cancer)

MEDICATION

First Line

- Localized disease:
  - The precise role for chemotherapy in the treatment of localized urethral SCC is poorly defined; however, chemotherapy not considered 1st-line treatment
- Advanced disease:
  - Preoperative chemotherapy (or chemoradiotherapy) has been shown to be of benefit over surgical resection alone.
    - Cisplatin-based poly-chemotherapeutic regimens should be used.

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Male bulbomembranous urethral SCC (3):
  - Early lesions have been treated successfully with transurethral resection or local excision with end-to-end urethral anastomosis.
  - Radical excision offers best chance at cure, with radical cystoprostatectomy, total penectomy, bilateral pelvic lymphadenectomy recommended.
  - With locally advanced disease, consider en-bloc excision to include the pubic rami and urogenital diaphragm.
- Male penile urethral SCC (3):

- Transurethral resection, fulguration, or local excision may be employed for superficial low-grade tumors.
- For tumors invading the corpus spongiosum, partial penectomy with a 2-cm margin is treatment of choice if localized to the distal half of the penis
- With involvement of the proximal penile urethra, total penectomy is required to obtain an adequate margin of excision.
- Ilioinguinal lymphadenectomy is indicated only in presence of palpable disease, as there has been no documented benefit of prophylactic lymphadenectomy.

• Distal female urethral carcinoma (3):
- Tumors of the distal urethra tend to be low-stage with cure rates of 70–90% with local excision alone.
- External beam radiation therapy is also therapeutic option for distal female urethral carcinoma.

• Proximal female urethral SCC (3):
- Far more likely to extend into the anterior vaginal wall and bladder
- Requires anterior exenteration with wide resection of the vagina; pelvic lymph node dissection is often required to achieve negative surgical margins.

ADDITIONAL TREATMENT

Radiation Therapy

• Localized disease:
- Male urethral SCC:
  - Few series of radiation therapy for patients with early-stage lesions of the anterior urethra who refuse surgery
  - Possible role in palliation, with occasional adjuvant use with extensive resection
- Female urethral SCC:
  - Low-stage distal lesions can be treated with external beam radiation, brachytherapy, or combined therapy with 5-yr survival rates approaching 75%.
  - Although there appears to be some role to adjuvant external beam or brachytherapy in the treatment of locally advanced female proximal urethral carcinoma, the precise role of radiation therapy remains unclear.

• Advanced disease:
- While surgical resection remains standard of care, preoperative radiation therapy combined with cisplatin-based chemotherapy regimens have been shown to give remarkable results in comparison to surgical resection alone.

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

• Male urethral carcinoma (4):
- 5-yr overall survival (OS): 42.3%

  – 5-yr OS (superficial disease): 83.3%
  – 5-yr OS (invasive disease): 35.7%
  – 5-yr OS (anterior urethra): 69.1%
  – 5-yr OS (bulbar urethra): 44.7%
- Female urethral carcinoma (5):
  – 5-yr OS: 32%
  – 5-yr OS (low-stage): 78%
  – 5-yr OS (high-stage): 33%
  – 5-yr OS (anterior urethra): 54%
  – 5-yr OS (posterior urethra): 25%

COMPLICATIONS

- Abscess
- Cystitis
- Incontinence
- Urethral stricture
- Urinary fistula

FOLLOW-UP

Patient Monitoring

- Vast majority of recurrences occur within 1–2 yr following definitive therapy.
- Surveillance is not well established, but routine cystoscopy and urinary cytology for 1–2 yr, with increasing interval between surveillance cystoscopy in the absence of recurrence seems reasonable

Patient Resources

Urology Care Foundation: Urethral cancer.
http://www.urologyhealth.org/urology/index.cfm?article=65

REFERENCES

1. Swartz MA, Porter MP, Lin DW, et al. Incidence of primary urethral carcinoma in the US. *Urology*. 2006;68:1164–1168.
2. Fadl-Elmula I, Gorunova L, Mandahl N, et al. Chromosome abnormalities in squamous cell carcinoma of the urethra. *Genes, Chromosomes, Cancer*. 1998;23:72–73.
3. Sharp DS, Angermeier KW. Surgery of penile and urethral carcinoma. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Elsevier; 2012.
4. Dalbagni G, Zhang ZF, Lacombe L, et al. Male urethral carcinoma: Analysis of treatment outcome. *Urology*. 1999;53:1126–1132.
5. Dalbagni G, Zhang ZF, Lacombe L, et al. Female urethral carcinoma: An analysis of treatment outcome and a plea for a standardized management strategy. *Br J Urol.* 1998;82:835–841.

ADDITIONAL READING

- G. Gakis, Witjes JA, Compérat E, et al. ; members of the EAU Guidelines Panel on Muscle-invasive and *Metastatic Bladder Cancer*. Guidelines on Primary Urethral Carcinoma. *The European Association of Urology (EAU) Guidelines Group on Muscle-invasive and Metastatic*

Bladder Cancer; 2013.
- Trabulsi E, Gomella LG. Penile and Urethral Cancer. In: DeVita V, et al., eds. *Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Saunders; 2011.

See Also (Topic, Algorithm, Media)
- Prostate Cancer, Urothelial
- Reference Tables: TNM: Urethra Cancer
- Skene (Paraurethral) Gland, Adenocarcinoma
- Urethra Diverticula
- Urethra Mass
- Urethra, General Considerations
- Urethral Stenosis/Stricture, Female

CODES

ICD9
- 189.3 Malignant neoplasm of urethra
- 598.9 Urethral stricture, unspecified
- V12.09 Personal history of other infectious and parasitic diseases

ICD10
- C68.0 Malignant neoplasm of urethra
- N35.9 Urethral stricture, unspecified
- Z86.19 Personal history of other infectious and parasitic diseases

CLINICAL/SURGICAL PEARLS
- Primary urethral SCC is a rare entity.
- Surgical excision is the mainstay of treatment.
- Distal tumors tend to be less advanced and more amenable to localized treatment.
- Proximal tumors tend to have a worse prognosis and require more aggressive treatment.
- Preoperative chemoradiotherapy may be used in advanced disease.

URETHRAL STRICTURE, MALE

Brad Figler, MD
Hunter Wessells, MD, FACS

BASICS

DESCRIPTION

- A urethral stricture is a narrowing of the caliber of the anterior or posterior urethra. Progressive scarring can cause voiding symptoms possibly urethral obstruction.
- True stricture of the female urethra is very rare.

EPIDEMIOLOGY

Incidence

Unknown

Prevalence

- Urethral strictures in Medicare: 4.5k/100k men
- Urethral strictures in VA: 274/100k men
- Posterior urethral injury in 6% of pelvic fractures and 15% of severe pelvic fractures

RISK FACTORS

- Sexually transmitted infections (STIs) (sexually transmitted diseases [STDs]), particularly gonorrhea
- Increasing age
- Some data from Medicare suggests black Americans may have higher stricture rates
- Recurrent infection
- Previous TURP or radical prostatectomy
- Catheterization (usually prolonged)
- Urethral instrumentation
- Trauma (straddle injury or pelvic fracture)
- Lichen sclerosis/balanitis xerotica obliterans (BXO)
  - A chronic skin disease that shows a predilection for the anogenital area and may cause anterior urethral stenosis (1)
  - Reported as the most common cause of meatal stenosis.
- Hypospadias, with or without prior repair

Genetics

No known associations

PATHOPHYSIOLOGY

- Anterior urethral strictures
  - Compromised viability of corpus spongiosum secondary to trauma, inflammation or ischemia
- Posterior urethral strictures
  - Pelvic fracture-associated urethral injury and related distraction defects
  - Scarring following TURP or radical prostatectomy

ASSOCIATED CONDITIONS
- Trauma
- STD/STI
- Urethral instrumentation
- BPH
- Prostate cancer
- Lichen sclerosis/BXO

GENERAL PREVENTION
- Limited urethral instrumentation
- Appropriately sized instruments for transurethral procedures
- STD/STI prevention and early treatment (gonorrhea most common)

DIAGNOSIS
HISTORY
- Voiding symptoms
  - Hesitancy
  - Reduced stream
  - Post void dribbling
  - Spraying or split stream
  - Incontinence
  - Retention
- Prior surgery
  - Transurethral surgery or manipulation
  - Hypospadias repair
- Trauma
- STD/STI
  - Urethral discharge
- Recent or remote urinary tract infection
- Prostatitis
- Lichen sclerosis/BXO
- Urinary retention

PHYSICAL EXAM
- Palpable bladder with retention
- Lichen sclerosis/BXO
  - Hyperkeratosis, meatal stenosis
  - Thickened foreskin with glandular adhesion
- Examination of foreskin
- Abundance and quality of penile skin
- Palpable fibrosis of corpus spongiosum
- Evidence of discharge

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis, urinary culture

- Gonorrhea swab
- Uroflowmetry
  - Significant strictures will have flow rates <10 mL/s (normal, >20 mL/s)
- Post void residual urine to evaluate for retention

Imaging
- RUG (anterior urethra)
- VCUG or antegrade urethrography through suprapubic catheter (posterior urethra)
- Sonography

Diagnostic Procedures/Surgery
Urethroscopy with flexible cystoscope or hysteroscope may be helpful

Pathologic Findings
- Fibrotic narrowing composed of dense collagen and fibroblasts.
- Squamous metaplasia is common

DIFFERENTIAL DIAGNOSIS
- Benign or malignant prostatic obstruction
- Urethral carcinoma
- Urethral abscess
- Functional bladder disorder

TREATMENT

GENERAL MEASURES
- Often detected with episodic urinary retention or with the inability to pass a catheter
- Treatment depends on stricture location, length, caliber, and whether previous treatment was attempted
- No role for primary medical management of urethral stricture disease

MEDICATION

First Line
Urinary tract infections should be treated before any intervention

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Dilation and direct vision internal urethrotomy (DVIU)
  - Dilation, cold DVIU, laser DVIU equivalent results
  - Minimally invasive and easy to perform
  - Effective for short (<1 cm), large caliber (>15 Fr) strictures in which dilation or DVIU have not been previously attempted
  - Use sparingly in long, narrow or refractory strictures; these will not be cured with DVIU
  - Techniques
    - Dilation: Balloon, sounds, filiform, and followers
    - DVIU: Incise at 12:00 to limit bleeding
    - For balloon and DVIU, wire helpful

- 18-French Foley catheter for 48–72 h
- Urethroplasty: Anterior
  - Short strictures (≤2 cm) amenable to excision and primary anastomosis
  - Long strictures (>2 cm) require substitution with flap or graft
  - Long strictures with narrow segment may need combination of resection and substitution (augmented anastomosis)
  - Long strictures that are diffusely narrow may need staged urethroplasty with substitution (Johanson urethroplasty)

- Urethroplasty: Posterior
  - Typically, excision and reapproximation required
  - Techniques used to bridge defect:
    - Urethral mobilization
    - Corporal separation
    - Inferior pubectomy
    - Supracrural rerouting
- Grafts
  - Buccal mucosa widely used; favorable outcomes
  - No difference in success rates with ventral/dorsal graft position
- Lichen sclerosis urethral reconstruction
  - One-stage or staged repairs using oral mucosa grafts are the most recommended

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Intermittent catheterization for 3–6 mo in select cases may improve patency rates
- Suprapubic placement is selected cases with inability to pass catheter or postoperatively following open repair
- Urolume™ stent approved for short bulbar urethral strictures; no longer manufactured
- Memokath™ stent may be useful after dilation or DVIU; not currently approved in the United States (2).

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Dilation/DVIU:
  - 75% long-term success rate for short (<1 cm), wide-caliber (>15-French) and non-refractory stricture
  - Minimal long-term efficacy for long, narrow or refractory stricture
- Urethroplasty
  - 90–95% long-term success rate for excision and primary anastomosis
  - 85% long-term success rate for substitution urethroplasty

COMPLICATIONS

- Immediate
  - UTI
  - Bleeding
  - Urinary leak and/or fistula
  - Lower extremity compartment syndrome
- Delayed
  - Postoperative erectile dysfunction may occur, but recovers by 3 mo
  - Stress incontinence is rare, but can occur if internal and external sphincters are damaged —either prior to or at time of urethroplasty
  - Post-void dribbling
  - Bleeding
  - Urethrocutaneous fistula
  - Penile curvature

FOLLOW-UP

Patient Monitoring

- Recurrence most likely within 1 yr
- Uroflowmetry, PVR, and AUA-SS sufficient to monitor for recurrence; cystoscopy optional

Patient Resources

- MedlinePlus: Urethral Stricture.http://www.nlm.nih.gov/medlineplus/ency/article/001271.htm

REFERENCES

1. Palminteri E, Brandes SB, Djordjevic M. Urethral reconstruction in lichen sclerosus. *Curr Opin Urol*. 2012;22(6):478–483.
2. Jordan GH, Wessells H, Secrest C, et al. ; United States Study Group. Effect of a temporary thermo-expandable stent on urethral patency after dilation or internal urethrotomy for recurrent bulbar urethral stricture: results from a 1-year randomized trial. *J Urol*. 2013;190(1):130–136.

ADDITIONAL READING

- Jordan GH, McCammon KA. Surgery of the penis and urethra. In: Wein AJ, ed. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders Elsevier; 2011:chap 36.
- Lumen N, Oosterlinck W, Hoebeke P, et al. Urethral reconstruction using buccal mucosa or penile skin grafts: Systematic review and meta-analysis. *Urol Int*. 2012;89(4):387–394.

See Also (Topic, Algorithm, Media)

- Balanitis Xerotica Obliterans/Lichen Sclerosis et Atrophicus
- Lower Urinary Tract Symptoms (LUTS)
- Sexually Transmitted Infections (STIs) (Sexually Transmitted Diseases [STDs])
- Urethra, Trauma (Anterior and Posterior)
- Urethral Stenosis/Stricture, Female

CODES

ICD9
- 598.00 Urethral structure due to unspecified infection
- 598.1 Traumatic urethral stricture
- 598.9 Urethral stricture, unspecified

ICD10
- N35.9 Urethral stricture, unspecified
- N35.014 Post-traumatic urethral stricture, male, unspecified
- N35.119 Postinfective urethral stricture, NEC, male, unsp

CLINICAL/SURGICAL PEARLS
- Direct vision internal urethrotomy (DVIU) is effective for short, wide-caliber, non-refractory strictures; otherwise non-curative.
- Excision and primary anastomosis for strictures <2 cm.
- Buccal mucosa is excellent graft; success rate similar for dorsal or ventral graft position.
- Recurrences most likely within 1 yr.
- Flow/PVR and AUA-SS sufficient for monitoring postoperatively.

URETHRAL TRAUMA (ANTERIOR AND POSTERIOR)

Lee C. Zhao, MD, MS
Allen F. Morey, MD, FACS

BASICS

DESCRIPTION
- Injury that disrupts the watertight integrity of the urethra, typically in male patients.
- Injury to the urethra in women is less common.

EPIDEMIOLOGY
Incidence
- Occurs in 10% of pelvic fractures
- Estimate 10–20% of anterior urethral stricture from external trauma

Prevalence
N/A

RISK FACTORS
- Pelvic fracture
- Perineal straddle injury
- Urethral instrumentation

PATHOPHYSIOLOGY
- Anterior urethra injuries
  - Less common due to mobility of anterior urethra and protection of the bulbospongiosus
  - Penile fracture (often intercourse related) can cause anterior urethral injury
  - Penile constriction bands
  - Penetrating trauma (gunshot, stabbing)
- Posterior urethra
  - More common due to fixed location of urethra within urogenital diaphragm; the combination of straddle fractures with diastasis of the sacroiliac joint has the highest risk of urethral injury
  - Pelvic fracture
  - Straddle injuries
- Penetrating can injure both anterior and posterior urethra
  - Gunshot wound, stab
- Iatrogenic
  - False passage: instrument or catheter
  - Catheter placement in patient with urethral stricture
  - Chronic indwelling catheters
  - Transurethral surgery using oversized resectoscopes

ASSOCIATED CONDITIONS
- Pelvic fracture
- Pelvic hematoma

- Bladder injury
- Vaginal injury

GENERAL PREVENTION
- Seat belts
- Careful instrumentation of the urethra to prevent iatrogenic injury

ALERT
- The amount of urethral bleeding does not correlate with the degree of injury.
- Pain with urination or inability to void is highly suggestive of urethral disruption in the trauma patient.

DIAGNOSIS

HISTORY
- Description of trauma and mechanism of injury
- Voiding history
  - Retention
  - Hematuria

PHYSICAL EXAM
- Classic clinical triad:
  - Bloody urethral discharge
  - Inability to urinate
  - Palpably full bladder
- Blood at meatus:
  - 37–93% of patients with posterior urethral injury
  - Greater than 75% of patients with anterior urethral (AU) injury.
- Ecchymosis and swelling limited to penile shaft
  - Anterior urethral injury confined by Buck fascia
- Butterfly hematoma
  - Violation of Buck fascia, hematoma confined by Colles fascia
- DRE: High riding prostate may be hard to detect due to associated pelvic hematoma and may not be reliable for urethral disruption
- Vaginal laceration is often associated with urethral injury
- Vaginal introitus blood is present in more than 80% of pelvic fractures and coexisting urethral injury (1).

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC, electrolytes, BUN, creatinine
- Urinalysis

Imaging
- Retrograde urethrography
  - 30-degree oblique position with bottom leg flexed at knee and top leg straight.
  - Place Foley catheter into fossa navicularis, inflate balloon with 2–3 mL
  - Injection of ~25 mL of contrast into urethra

  – Extravasation of contrast indicates the location of the tear
  – Complete injury usually has no contrast flow into the bladder
• CT is inadequate to evaluate urethral trauma
  – Generally obtained for staging of associated injuries

Diagnostic Procedures/Surgery
Flexible cystoscopy

DIFFERENTIAL DIAGNOSIS
• Urethral injury: contusion, complete, partial
• Injury to bladder neck, ureter
• Penile corporal injury
• Labial/vaginal injury

TREATMENT

GENERAL MEASURES
• Perform retrograde urethrogram (RUG) prior to placement of Foley catheter; avoid urethral instrumentation until urethral imaging if the patient is stable.
• If catheter has already been placed, do not remove it. Perform pericatheter RUG with pediatric feeding tube or angiocatheter
• Establish prompt urinary drainage in patients with pelvic fracture associated urethral injury as typically unable to void and undergo aggressive resuscitation
• Urethral injury confirmed by:
  – Extravasation on RUG or VCUG
  – Cystoscopy
• Classification of urethral injury can guide treatment decisions
  – EAU Classification of blunt urethral injury (1)[C]:
    ◦ Grade I: stretch injury
    ◦ Grade II: contusion
    ◦ Grade III: partial disruption
    ◦ Grade IV: complete disruption
    ◦ Grade V: complete or partial disruption of posterior urethra with associated tear of the bladder neck, rectum or vagina

MEDICATION
First Line
• Analgesics as needed
• Antibiotics

Second Line
N/A

SURGERY/OTHER PROCEDURES
• Pelvic fracture and posterior urethral injury
  – Place large bore suprapubic catheter (16-Fr Foley) using percutaneous peel-away sheath
  – We advise against using small pigtail suprapubic catheters
  – For complex injuries with associated bladder trauma, open suprapubic tube placement

with bladder inspection is suggested. Place suprapubic tube (SPT) in patients undergoing ORIF for pelvic fracture (24 Fr, high on bladder and tunneled through skin away from hardware)
  - Open surgical realignment should be avoided due to high risk of erectile dysfunction, incontinence
  - Primary endoscopic realignment may be attempted but has a success rate of 25% (2)[B], but may delay the ultimate curative therapy for this condition. In our experience, traumatic strictures tend to be short and dense, and refractory to endoscopic treatment. Success rates for open anastomotic urethroplasty are greater than 90%.
  - In women, primary open repair is recommended for disruption of the urethra with associated tear of bladder neck and vagina (3)[C] due to risk of incontinence and vesicovaginal fistula
- Penetrating trauma
  - Immediate reconstruction is highly successful
    - High velocity projectile creates blast effect, making immediate reconstruction less reliable
- Iatrogenic urethral injury: Place indwelling Foley for 7 days, followed by voiding cystourethrogram

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Repeated endoscopic treatment of traumatic urethral strictures may lead to longer strictures (4)[B].
- In an unstable trauma patient, a cautious attempt can be made to pass a urethral catheter.
  - If there is any a difficulty a suprapubic catheter can be placed and a retrograde urethrogram performed later (1).

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Posterior urethral injury:
  - Low rate of incontinence in patients with competent bladder neck
- Anterior urethral injury: Good prognosis after primary repair

COMPLICATIONS

- Urethral stricture
- Fistulas
- Incontinence
- Erectile dysfunction

FOLLOW-UP

Patient Monitoring

- Recovery often complicated by other orthopedic and neurologic injuries
- Anterior urethral injury:
  - If primary repair has been performed, catheter should be kept in place for 2–3 wk with follow-up VCUG
- Posterior urethral injury:
  - If endoscopic alignment has been performed, the suprapubic tube should be kept in place for at least one week after removal of urethral Foley. Most endoscopic alignment will fail at 1 wk
  - Perform reconstructive procedures at 4–6 mo

Patient Resources

Urology Care Foundation: Urethral trauma.
http://www.urologyhealth.org/urology/index.cfm?article=44

REFERENCES

1. Martinez-Pineiro L, Djakovic N, Plas E, et al. EAU guidelines on urethral trauma. *Eur Urol.* 2010;57:791–803.
2. Leddy LS, Vanni AJ, Wessells H, et al. Outcomes of endoscopic realignment of pelvic fracture associated urethral injuries at a level 1 trauma center. *J Urol.* 2012;188:174–178.
3. Black PC, Miller EA, Porter JR, et al. Urethral and bladder neck injury associated with pelvic fracture in 25 female patients. *J Urol.* 2006;175:2140–2145.
4. Hudak SJ, Atkinson TH, Morey AF, et al. Repeat transurethral manipulation of bulbar urethral strictures is associated with increased stricture complexity and prolonged disease duration. *J Urol.* 2012;187:1691–1695.

ADDITIONAL READING

- Rosenstein DI, Alsikafi NF. Diagnosis and classification of urethral injuries. *Urol Clin N Am.* 2006;33:73–85.
- Morey AF, Brandes S, Dugi DD, et al. Urotrauma: AUA Guideline (https://www.auanet.org/common/pdf/education/clinical-guidance/Urotrauma.pdf Accessed August 21, 2014)

See Also (Topic, Algorithm, Media)

- Bladder Trauma
- Penis, Trauma
- Urethra, Strictures, Male
- Urethra, Trauma (Anterior and Posterior) Images ☼

CODES

ICD9

- 599.70 Hematuria, unspecified
- 867.0 Injury to bladder and urethra, without mention of open wound into cavity
- 867.1 Injury to bladder and urethra, with open wound into cavity

ICD10

- R31.9 Hematuria, unspecified
- S37.30XA Unspecified injury of urethra, initial encounter
- S37.33XA Laceration of urethra, initial encounter

CLINICAL/SURGICAL PEARLS

- Retrograde urethrography is considered the gold standard for evaluating urethral injury.
- Most pelvic fracture associated injuries occur in the posterior urethra.
- Posterior urethral injury should be managed with suprapubic catheter and delayed definitive repair.
- When placing a suprapubic catheter, should use a large bore Foley catheter placed via a peel away sheath.
- Urethral injury in women associated with bladder neck or vaginal injury should be repaired primarily.
- Anastomotic repair of traumatic strictures has a high success rate.

URETHRITIS, GONOCOCCAL AND NONGONOCOCCAL

Daniel C. Parker, MD
Jack H. Mydlo, MD

BASICS

DESCRIPTION

- Gonococcal urethritis (GU) and nongonococcal urethritis (NGU) are urethral infections characterized by dysuria and urethral discharge
  - Both types are STDs/STI
    - *Neisseria gonorrhoeae* (gram-positive diplococci) on culture/gram stain differentiates GU from NGU
    - *Chlamydia trachomatis* is the most common cause of NGU

EPIDEMIOLOGY

Incidence

- Estimated 820,000 new cases of gonococcal urethritis
  - Most common reportable disease in the United States
- Over 3 million cases of non-gonoccal urethritis annually
- Both GU and NGU are belived to be significantly under repprted

Prevalence

- Gonococcal urethritis: 100.8 per 100,000 population
  - Rate has increased among all gender/racial/ethnic groups since 2009 some data suggests NGU is increasing

RISK FACTORS

- Individuals aged 15–24 yr at highest risk
- African Americans
- Sexual Activity
  - Risk of infection is 10% for men after a single exposure
  - Multiple sexual partners

Genetics

No heritable form of transmission

PATHOPHYSIOLOGY

- GU
  - Caused by *N. gonorrhoeae*
    - Coinfection with Chlamydia 4–35%
    - Incubation is 3–10 days
- NGU
  - *Chlamydia trachomatis* most common (25–60%)
  - Mollicutes*: Ureaplasma urealyticum, Mycoplasma hominis, Mycoplasma genitalium* in up to 40% of cases
  - *Trichomonas vaginalis*, CMV, and HPV have been reported

  – Incubation period is 7–21 days
- Both types acquired during sexual intercourse
- Urethritis is a difficult diagnosis in women because copious discharge may not be present; the hallmark is dysuria and frequency.

ASSOCIATED CONDITIONS
- Other STDs/STI
- Pendulous urethral stricture
- Epididymitis/orchitis

GENERAL PREVENTION
- GU and NGU
  – Proper use of male and female condoms, if multiple sexual partners

DIAGNOSIS

HISTORY
- GU and NGU
  – Systemic symptoms are rare
  – Important information to gather
    - Relationship to sexual activity (when/type)
    - Number of episodes
    - Number of sexual partners
    - Nature of sexual relations
    - Severity of symptoms
    - Characteristics of dysuria and urethral discharge
- NGU
  – Urethral discharge
    - Usually mild to moderate, clear or whitish fluid
  – Dysuria
    - Mild burning with urination or absent
- GU
  – Urethral discharge
    - Usually purulent, green/yellow/white, and copious
  – Dysuria
    - Usually moderate to severe burning with urination
    - May present as urethral itching

PHYSICAL EXAM
- GU and NGU
  – Pendulous urethra may be tender to palpation
  – Abdomen and flanks palpated for tenderness, masses, and bladder distention
  – Scrotal contents examined for testicular/epididymal size, consistency, and tenderness
  – Digital rectal exam (DRE) for prostate size, tenderness, and consistency

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis
  - Obtain 1–4 h after voiding
  - ≥15 PMN leukocytes per HPF of spun sediment in the first-void urine specimen
  - Positive leukocyte esterase on urine dip in the absence of UTI suggests urethritis
  - Up to 30% of patients with urethritis will not have WBC in the urine
- Urethral smear for gram stain and culture
  - Calcium alginate swab inserted 1–2 cm into urethra best to obtain 1–2 hours after voiding
  - Culture plated on Thayer-Martin media for GU
- Sensitivity of DNA targeted assays is improving (1)[A]
  - Nucleic Acid Amplified Test (NAAT) of urine—first 10–30 cc voided
  - NAAT available for: C trachomatis and N gonorrhoeae. Labs can also test for Mycoplasma, Ureaplasma, and Trichomonas vaginalis but these assays are no commonly performed since they are very costly and may not alter the recommended antibiotic regimen

Imaging

Typically not necessary

Diagnostic Procedures/Surgery

Cystourethroscopy with dilation of pendulous urethra may be indicated for chronic cases resulting in urethral stricture.

Pathologic Findings

Urethral inflammation

DIFFERENTIAL DIAGNOSIS

- GU
- NGU
  - *Chlamydia trachomatis*
  - *Mycobacterium genitalium*
  - *Trichomonas vaginalis*
  - *Ureaplasma urealyticum*
- Uncommon infectious causes: TB, adenovirus, uropathogenic *Escherichia coli* (unprotected anal intercourse), herpes simplex, cytomegalovirus
- Urethral diverticulum
- Periurethral abscess
- Reactive urethritis (Formerly Reiter syndrome) associated with conjunctivitis, arthritis, and tenosynovitis
  - No growth on culture
  - Minimal number of leukocytes in urethral smear or urinalysis
- Miscellaneous: Urethral irritation from detergents, body soap, lotions, spermicides, contraceptives, manipulation, and/or foreign body insertion.

TREATMENT

GENERAL MEASURES

- Cases are reportable to health department.
- Sexual intercourse should be avoided until cure.

- Sexual partners within 60 days of diagnosis or symptoms should be evaluated and treated.
- Dual treatment for both *N. gonorrhoeae* and *C. trachomatis* is recommended.

ALERT
The CDC now recommends against the use of quinolones and oral cephalosporins for treatment of gonococcal urethritis in the US due to widespread bacterial resistance (2)[A].

MEDICATION

First Line

- GU
  - CDC recommends dual therapy for GU and NGU
  - Ceftriaxone 250 mg IM once
    - Efficacious in 99% of cases
    - Also treat for NGU (Chlamydia)
- NGU
  - Azithromycin 1 g PO once, or doxycycline 100 mg PO b.i.d. for 10–14 days

Second Line

- GU
  - Cefixime 400 mg PO once
  - Azithromycin 2 g PO once for pregnant women or cephalosporin allergy.
- NGU
  - Erythromycin 500 mg PO q.i.d. for 7 days
  - Ofloxacin 300 mg PO b.i.d. for 10–14 days

SURGERY/OTHER PROCEDURES

Surgery typically not indicated

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Patient education
  - Proper use of condoms and safe sexual practice
  - Reduce number of sexual partners
  - Evaluation and treatment of sexual partners at risk (3)[A]

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Generally good prognosis with treatment for both GU and NGU
  - Systemic manifestations of gonococcal dissemination are rare today:
    - Arthritis
    - Dermatitis

- Meningitis
- Endocarditis

COMPLICATIONS

- GU
  - Periurethritis
    - May lead to abscess
  - Urethral fibrosis
    - May lead to stricture
  - Epididymitis/orchitis
    - May lead to testicular atrophy or infertility
  - Prostatitis
    - May lead to abscess
- NGU
  - Emotional sequelae are common
    - Fear of loss of sexual function or guilt may produce depression
  - Epididymitis and/or nonbacterial prostatitis
  - Usually does not cause severe physical complications in men

FOLLOW-UP

Patient Monitoring

- GU and NGU
  - Post therapy culture and urethral smear to confirm response to therapy

Patient Resources

- CDC. STD fact sheets. http://www.cdc.gov/std
- MedlinePlus: Urethritis. http://www.nlm.nih.gov/medlineplus/ency/article/000439.htm

REFERENCES

1. Whiley DM, Garland SM, Harnett G, et al. Exploring 'best practice' for nucleic acid detection of *Neisseria gonorrhoeae* . *Sex Health.* 2008;5(1):17–23.
2. Del Rio C. Update to CDC's sexually transmitted disease treatment guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR*. 2012;61(31):590–594.
3. Hogben M, Kidd S, Burstein GR, et al. Expedited partner therapy for sexually transmitted infections. *Curr Opin Obstet Gynecol*. 2012;24(5):299–304.

ADDITIONAL READING

- Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010;59 (No. RR-12).
- Nguyen HT. Bacterial infections of the genitourinary tract. In: Tanagho EA, McAninch JW, eds. *Smith's General Urology*. 17th ed. New York, NY: McGraw-Hill; 2008.
- Schaeffer AJ, Schaeffer EM. Infections of the urinary tract. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Elsevier; 2011.
- www.cdc.gov/std/Gonorrhea/STDFact-gonorrhea.htm

See Also (Topic, Algorithm, Media)

- Gonorrhea
- Gonorrhea Microscopic Image
- Sexually Transmitted Diseases (STD), General
- Urethra, Stricture, Male
- Urethral Discharge
- Urethra Discharge Algorithm

CODES

ICD9

- 098.0 Gonococcal infection (acute) of lower genitourinary tract
- 099.40 Unspecified other nongonococcal urethritis [NGU]
- 131.02 Trichomonal urethritis

ICD10

- A54.01 Gonococcal cystitis and urethritis, unspecified
- A59.03 Trichomonal cystitis and urethritis
- N34.1 Nonspecific urethritis

CLINICAL/SURGICAL PEARLS

- GU is caused by the gram-positive diplococci *Neisseria gonorrhoeae*.
- NGU is most commonly caused by *Chlamydia trachomatis*.
- Up to 35% of cases of GU are coinfected with chlamydia.
- The CDC recommends simultaneous treatment for *both* GU and NGU in patients presenting with urethritis.
- Sexual partners within 60 days of diagnosis or symptom onset should be evaluated and treated.

URGENCY, URINARY (FREQUENCY & URGENCY)

Jessica M. DeLong, MD
Kurt A. McCammon, MD, FACS

BASICS

DESCRIPTION

- Urgency is the complaint of a sudden compelling desire to void that is difficult to defer while frequency is the complaint by a patient that he or she voids too often
- Urgency:
  - Urgency is the most common symptom of overactive bladder (OAB).
  - Urge incontinence is involuntary leakage of urine preceded by the above symptom (1).
- Frequency:
  - There is no minimum number of voids.
  - Nocturia is the complaint of waking at night to void one or more times.
- These are classified as storage symptoms.

EPIDEMIOLOGY

Incidence

Not well known; one study showed 9.2%

Prevalence

Estimates vary

RISK FACTORS

- Dependent upon etiology
  - Older age

Genetics

N/A

PATHOPHYSIOLOGY

- Inflammation/irritation
  - Infection, malignancy, urinary lithiasis, etc.
- Neurogenic
- Myogenic (2)
- Polyuria
- Idiopathic

ASSOCIATED CONDITIONS

- Bladder outlet obstruction
- Diverticulosis
- Dysfunctional voiding
- Interstitial cystitis (IC)/painful bladder syndrome (PBS)
- OAB
- Urinary tract infection (UTI)

- Vaginitis

GENERAL PREVENTION

- Treat any underlying condition (eg, UTI)
- Maintain good voiding habits and regular bowel pattern

DIAGNOSIS

HISTORY

- Use validated questionnaires when possible
  - International prostate symptom score (IPSS), IPSS-QOL
  - Urgency sensation scale
- Irritative voiding symptoms:
  - Urgency, frequency, urge incontinence, nocturia
- Obstructive voiding symptoms:
  - Hesitancy, slow stream, post-void dribbling, retention
  - Consider causes of bladder outlet obstruction
- Other medical history
  - Stone disease
  - Malignancy such as bladder cancer
- Symptoms of infection
- Episodes of gross hematuria
- Bowel habits
- Sexual function
- Current medications
  - Diuretics, alpha blockers
- Tobacco use
- Family history
- Pregnancy is normally associated with urinary frequency
- Voiding diary, nature, and volume of fluid intake

PHYSICAL EXAM

- In males:
  - External genital exam to evaluate for phimosis, evidence for lichen sclerosis (LS), urethral discharge or mass
  - Digital rectal exam (DRE) to:
    - Evaluate prostate size, nodularity
    - Assess for rectal mass or fecal impaction
    - Assess perineal sensation, bulbocavernosus reflex, anal sphincter tone
- In females:
  - Pelvic exam to:
    - Assess for mass, pelvic floor support
    - Detect stress urinary incontinence (SUI by employing Valsalva manuever
    - Assess urethral lesions or discharge
- General exam for peripheral edema
- Focused neurologic exam

- Mental status exam
- Motor deficits, gait stability
- Sensory deficits, reflexes

• Abdominal exam
- Palpable mass (retention, fibroids, etc.)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

• Urine analysis (UA): Exclude other pathology
- Specific gravity
- Presence of leukocyte esterase (LE), nitrates, and pyuria suggests UTI
- Microhematuria necessitates further work up
  - Cystoscopy, triphasic CT
- Glucose: Assess for diabetes
- Protein: Assess for medical renal disease
  - Obtain culture if UA suggestive of infection
- Urinary cytology to rule out urothelial carcinoma

Imaging

• Renal/bladder ultrasound (US):
- If bladder outlet obstruction (BOO) suspected (ie, elevated PVR)
- If renal insufficiency

• Dedicated pelvic US (female):
- If adnexal mass or uterine abnormality noted on pelvic exam

• KUB may be appropriate initial study if stones are suspected

• CT:
- If hematuria, triphasic CT is standard of care
- If stones suspected, non-contrast CT

ALERT
If UA suggests infection or hematuria, appropriate evaluation is key.

Diagnostic Procedures/Surgery

• Check post void residual (PVR)

• Cystoscopy:
- If hematuria or persistent problems
  - May detect bladder pathology (tumor, calculus), BOO

• Urodynamics (UDS):
- If conservative therapy fails
- Can help define treatment options and evaluate for neurogenic component

Pathologic Findings

Dependent upon etiology

DIFFERENTIAL DIAGNOSIS

• Inflammation—UTI, urethritis

• Radiation cystitis

• IC/PBS

- Trauma—local or neurologic
- Foreign body
- Neurologic condition (ie, spina bifida, spinal cord injury, neuropathy)
- Neoplasm—urologic or nonurologic by local extension
  - Urothelial carcinoma, especially CIS, often causes urinary frequency
- Urolithiasis
- Polyuria
- Drugs—diuretics, irritants
- Gynecologic-vaginitis, pregnancy

TREATMENT

GENERAL MEASURES

- Based on underlying etiology
  - Treat UTI with appropriate antibiotics
  - Initiate appropriate workup and management of hematuria
- In general, treatment is divided into:
  - Conservative (behavioral)
  - Pharmacotherapy
  - Surgery

MEDICATION

First Line

- Choice based on etiology
- Antimuscarinics are used to inhibit detrusor contractions by competitively inhibiting muscarinic cholinergic receptors. Common side effects: dry mouth and constipation. Maximal effect after 3 mo
  - Oxybutynin
    - 5 mg PO TID; XL 15 mg daily-BID
    - Transdermal patch 3.9 mg/d: may be good option to avoid cognitive side effects
  - Trospium 20 mg PO BID; XR 60 mg PO daily
  - Tolterodine 1–2 mg PO BID
  - Darifenacin 7.5–15 mg PO daily
  - Solifenacin 5–10 mg PO daily
- β-3 adrenergic receptor antagonist: A newer drug; induces detrusor relaxation
  - Mirabegron 25–50 mg PO daily
- α-Blockers are used to decrease outflow obstruction due to prostatic hypertrophy. Common side effects: dizziness, retrograde ejaculation
  - Tamsulosin 0.4 mg PO qhs
  - Alfuzosin 10 mg PO daily
  - Terazosin start 1 mg PO qhs, titrate up to 20 mg
  - Doxazosin start 1 mg PO daily titrate to 8 mg
  - Silodosin 8 mg PO daily
- 5-α-reductase inhibitors are used to lower DHT in men with prostates >40 cc. Are synergistic with α-blockers and take 6–12 mo for maximum effect:

- Finasteride 5 mg PO daily
- Dutasteride 0.5 mg PO daily

Second Line

- PDE5 inhibitors
  - Documented efficacy for men with lower urinary tract symptoms (LUTS)/OAB
    - FDA approved for signs and symptoms of BPH with our without erectile dysfunction
- Imipramine
  - No good quality RCTs
- Estrogens (vaginal superior to systemic) may be beneficial for post-menopausal women
  - Contraindicated if history of venous thromboembolism (VTE), breast cancer

SURGERY/OTHER PROCEDURES

- Intravesical botulinum toxin A (onabotulinumtoxinA) injection
  - If refractory to pharmacologic therapy
  - Decreases bladder contraction
  - Clean intermittent catheterization (CIC) may be necessary postoperatively
- Sacral neuromodulation: Interstim® implantation
  - Stimulation of S3 afferent nerve
  - 2-stage procedure; revision rates 7–33%
  - Not recommended in neurogenic voiding dysfunction, elderly
- Correction of BOO
  - Transurethral resection of prostate (TURP); transurethral incision of prostate (TUIP)
- Correction of pelvic floor prolapse in females
- If fails all other therapy and associated with incontinence can consider bladder augmentation or urinary diversion

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Behavioral therapy is first-line
  - Bladder training may include biofeedback and pelvic floor physical therapy
  - Timed voiding
  - Kegel exercises may be of benefit

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

Generally a long-term problem; dependent on etiology

COMPLICATIONS

Common side effects of pharmacotherapy include dry mouth and constipation

FOLLOW-UP

Patient Monitoring

- Depends upon etiology, treatment, response
  - Often periodic visit with voiding diary, uroflow, PVR

Patient Resources

MedlinePlus: Frequent or urgent urination.
http://www.nlm.nih.gov/medlineplus/ency/article/003140.htm

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: Report from the standardization sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21:167–178.
2. Michel MC, Chapple CR. Basic mechanisms of urgency; preclinical and clinical evidence. *Eur Urol.* 2009;56:298–308.
3. Xin Z, Huang Y, Lu J, et al. Addition of antimuscarinics to alpha-blockers for treatment of lower urinary tract symptoms in men: A meta-analysis. *Urology*. 2013;82:270–277.

ADDITIONAL READING

N/A

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Incontinence, Urinary, Adult Female
- Lower Urinary Tract Symptoms (LUTS)
- Neurogenic Bladder
- Overactive Bladder (OAB)
- Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC)
- Prostate, Benign Hyperplasia/Hypertrophy (BPH)
- Prostatitis, General

CODES

ICD9

- 596.51 Hypertonicity of bladder
- 788.41 Urinary frequency
- 788.63 Urgency of urination

ICD10

- N32.81 Overactive bladder
- R35.0 Frequency of micturition
- R39.15 Urgency of urination

CLINICAL/SURGICAL PEARLS

- Hematuria warrants appropriate workup. May be a presentation of genitourinary malignancy.
- Anticholinergics are contraindicated in patients with untreated narrow-angle glaucoma.

- Combination of antimuscarinics plus alpha blockers may be better than either alone for men with LUTS (3).
- Use anticholinergics with caution in elderly patients, as cognitive effects may be pronounced.
- Use of intravaginal estrogen for postmenopausal women may worsen incontinence.

URINARY RETENTION AFTER STRESS URINARY INCONTINENCE SURGERY IN FEMALES

Bradley C. Gill, MD, MS
Sandip P. Vasavada, MD, FACS

BASICS

DESCRIPTION
- Inability to void spontaneously following surgery for stress urinary incontinence
- Voiding with Valsalva or straining following surgery for stress urinary incontinence
- Procedure performed may be either midurethral sling or retropubic urethropexy

EPIDEMIOLOGY
Incidence
- Estimated 3–11% for midurethral sling
- Estimated 3–7% for retropubic urethropexy

Prevalence
- More common with retropubic or transvaginal slings than transobturator slings
- Likely more common with synthetic than biologic sling materials
- Episodes are generally transient and last days to weeks but resolution up to 3 mo can occur

RISK FACTORS (1)
- Weak detrusor contraction or incomplete voiding preoperatively
- Procedure done with “tension” rather than “tension free” placement
- Inability to urinate or elevated post-void residual postoperatively

PATHOPHYSIOLOGY
- Iatrogenic urethral obstruction by extrinsic compression
- Retropubic suspension can cause urethral “kinking”
- Tension-free vaginal tape has lowest rate of retention
- Retention is frequently self-limited and will resolve within 6–12 wk following anti-incontinence surgery

ASSOCIATED CONDITIONS
- Bladder diverticulum
- Cystocele
- Cystolithiasis
- Detrusor hypocontractility
- Recurrent urinary tract infections
- Urethral stricture

DIAGNOSIS

HISTORY
- Details of retention

  - Timing of symptom onset with regard to surgery
  - Duration of symptoms and consistency with voiding
  - Associated with discomfort, distention, or incontinence
- Urologic conditions
  - Detrusor hypocontractility on urodynamic studies
  - Episodes of cystolithiasis
  - Recurrent urinary tract infections
  - Cystocele
- Urologic interventions
  - Intra-detrusor botulinum toxin injections
  - Previous midurethral sling or urethropexy
- Other interventions
  - Abdominopelvic surgery, radiation, or injury
  - Spine surgery or injury
- Current medications
  - Antimuscarinics or anticholinergics
  - Alpha adrenergic agonists
- Diabetes mellitus

PHYSICAL EXAM

- Visual inspection of the abdomen and suprapubic area
- Abdominal palpation with attention to the suprapubic area
- Visual inspection of external genitalia for discharge or bleeding
- Speculum examination
  - Swelling or bulging anterior vaginal wall
  - Incisional discharge or bleeding
  - Cystocele
- Palpation of external genitalia, vaginal sidewalls, and pelvic floor muscles
  - Urethral or anterior vaginal wall bulging or tension
  - Tension and mobility of surgically placed sling or sutures
  - Pelvic floor muscle tension, spasm, or tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Renal function panel
- Serum electrolytes
- Blood counts

Imaging

- Bladder volume ultrasound
- Residual bladder volume after decompression

Diagnostic Procedures/Surgery

- Catheterization only if easily passable with indwelling left temporarily
- Cystoscopy if catheterization not possible with guide wire placement

DIFFERENTIAL DIAGNOSIS

- Bladder diverticulum
- Detrusor hypocontractility
- Occult urinary retention or incomplete emptying
- Sling placed under too much tension
- Neurogenic bladder
- Diabetic cystopathy
- Cystocele
- Medication

TREATMENT

GENERAL MEASURES (2,3)

- Catheterization and observation of iatrogenic obstruction
  - Trial of intermittent self-catheterization to observe for resolution
  - Temporary indwelling catheter with office visits for trails of voiding
  - Cystoscopy and guidewire placement if catheterization not possible
  - Consider operative intervention if no resolution within 3 mo
- Emergent bladder drainage for an impassable urethra
  - Operative sling incision pending anticipated delay for arranging surgery
  - Suprapubic aspiration and drainage at bedside
  - Percutaneous nephrostomy tubes if no other options are possible
- Careful urethral dilation may be considered soon after surgery
- Evacuation of hematoma if suspected as etiology of urethral compression

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Elective bladder diverticulectomy as indicated
- Transvaginal retropubic urethrolysis if more conservative measures fail

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Excellent considering multiple options

- Major risk is incontinence recurrence
  – 15–20% recurrence of stress urinary incontinence symptoms

COMPLICATIONS
- Infection
- Urethral/bladder injury
- Recurrent incontinence

FOLLOW-UP

Patient Monitoring
- Office follow-up every 7–14 days for trials of voiding if an indwelling catheter placed
- Standard postoperative follow-up if a surgical intervention is pursued

Patient Resources

N/A

REFERENCES

1. Tse V, Chan L. Outlet obstruction after sling surgery. *Br J Urol Int.* 2011;108(S2):24–28.
2. Ingber MS, Vasavada SP, Moore CK, et al. Force of stream after sling therapy: Safety and efficacy of rapid discharge care pathway based on subjective patient report. *J Urol.* 2011;185(3):993–997.
3. Song PH, Yoo ES. Five-year outcomes of the transection of synthetic suburethral sling tape for treating obstructive voiding symptoms after transobturator sling surgery. *Urology*. 2012;80(3):551–555.

ADDITIONAL READING

- Chapple CR. Retropubic suspension surgery for incontinence in women. In: *Campbell-Walsh Urology*. 2012; Edition 10, Chapter 71:2047–2068.
- Dmochowski RR, et al. Slings: Autologus, biologic, synthetic, and midurethral. In: *Campbell-Walsh Urology*. 10th ed. 2012; Chapter 73:2115–2167.

See Also (Topic, Algorithm, Media)
- Urethral Sling, Indications, and Anatomic Positions
- Urethral Sling, Materials
- Urethra, Obstruction
- Urinary Retention, Adult Female

CODES

ICD9
- 599.60 Urinary obstruction, unspecified
- 788.29 Other specified retention of urine
- 997.5 Urinary complications, not elsewhere classified

ICD10
- N36.8 Other specified disorders of urethra
- N99.89 Oth postprocedural complications and disorders of GU sys
- R33.8 Other retention of urine

CLINICAL/SURGICAL PEARLS

- Think about how sling vectors impact function.
- Many cases will resolve themselves with time.
- If consistently occurring change the technique.

URINARY RETENTION, ADULT FEMALE

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BASICS

DESCRIPTION

- Urinary retention is the inability to properly empty the urinary bladder. It can be further classified as acute and chronic.
  - *Acute retention of urine* is defined by the International Continence Society (ICS) as a painful, palpable or percussable bladder, when the patient is unable to pass any urine (1).
  - *Chronic retention of urine* is defined by the ICS as a non-painful bladder, which remains palpable or percussable after the patient has passed urine. Such patients may be incontinent (1).
- Females can void with low detrusor pressures and valsalva, making diagnosis more complicated than the old adage "high pressure, low flow"

EPIDEMIOLOGY

Incidence

Occurs in 2.7–23% of women, most commonly after anti-incontinence surgery

Prevalence

Usually self-limited

RISK FACTORS

- Anti-incontinence surgery (eg, urethral slings)
- Diabetes
- Neurologic conditions
- Psychological conditions

Genetics

N/A

PATHOPHYSIOLOGY (2)

- Kinking or stricture of the urethra depending on procedure performed or anatomy
- Cases of neurologic complications include detrusor acontractility versus detrusor sphincter dyssynergia
- Diabetes mellitus, causing low detrusor tone

ASSOCIATED CONDITIONS

- Chronic constipation
- Multiple sclerosis (MS)
- Pelvic organ prolapse (POP)
- Spinal cord injury
- Stress urinary incontinence

GENERAL PREVENTION

- Avoidance of anti-incontinence surgery or optimization of patient selection and/or surgical technique
- Quick detection of neurologic conditions

DIAGNOSIS

HISTORY

- Complaints of frequency, decreased force of stream, urgency or urge incontinence, or UTI are indicative of bladder outlet obstruction (BOO)
- Feeling of vaginal bulge
- History of stroke, diabetes, MS, Parkinson's disease, "back problems," neurologic conditions, depression
- Chronic narcotic medication use
- Chronic constipation
- Use of psychotropic medication

PHYSICAL EXAM

- Examine abdomen to evaluate any prior surgeries
- Bladder distension
- Pelvic examination:
  - Urethral hypermobility, cystocele, pelvic organ prolapse, diverticulum, vaginal/pelvic mass, rectal prolapse, or rectocele
- Motor/sensory tone to rule out neurologic disorder
- Stress urinary incontinence (or overflow incontinence)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
- Urine culture
- Complete metabolic panel

Imaging

- Ultrasound:
  - Measure post-void residual urine
  - Look for hydronephrosis
- MRI of brain/spinal cord in young females with new onset voiding symptoms (MS, occult spinal dysraphism)

Diagnostic Procedures/Surgery

- Videourodynamics show high pressure, low flow state with closed bladder neck in primary BOO, "spinning top"
  - Flow rate less than 12 mL/s with maximum detrusor pressure of 20 cm H_2O
  - Uroflow—"saw tooth" pattern. Does not distinguish between BOO and decreased detrusor function
  - EMG of sphincter to assess for sphincter/detrusor coordination
- Cystoscopy to assess for stones, eroded material, diverticulum, extrinsic mass, stricture, or kinking

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Iatrogenic (26%)—most commonly following anti-incontinence surgery.
  - 2–8% of women require reintervention.
  - Retropubic suspension can cause urethral "kinking"
  - Tension-free vaginal tape has lowest rage of retention
  - Retention is frequently self-limited and will resolve within 6–12 wk following anti-incontinence surgery
    - Manage with catheterization or clean intermittent catheterization
- Anatomic:
  - Urethral stricture (13%)
  - Ectopic ureterocele
  - Urethral diverticulum (3%)
  - Urethral malignancy
  - Bladder neck obstruction
  - Pelvic organ prolapse (24%)
- Dysfunctional Voiding (5%)
  - Pseudomyotonia—severe spasticity of sphincter without nerve stimulation (rare)
  - Fowler syndrome—young women without neurologic disease. Highly responsive to neuromodulation.
    - Higher incidence of depression and polycystic ovarian syndrome
- Neurologic
  - Detrusor sphincter dyssynergia (5%)
- Pharmacologic
  - Anticholinergic, opioid, and other narcotic medications
    - Antihistamines
    - Anticholinergics: Atropine, belladonna, benztropine, mesylate, cyclic antidepressants, phenothiazines, ipratropium bromide
    - Antispasmodics
    - Tricyclic antidepressants
    - α-Agonists: Cold preparations, ephedrine derivatives, amphetamines
    - Narcotics
    - Detrusor muscle relaxants: Tolterodine, trospium, oxybutynin, solifenacin, hyoscyamine
    - NSAIDS
- Psychogenic
- Myogenic (eg, detrusor acontractility)

TREATMENT

GENERAL MEASURES (3)
- Treatment based on underlying cause
- Stop medications predisposing to retention
- Evaluation and management of chronic constipation/bowel dysfunction

- Foley catheterization vs. clean intermittent catheterization (preferred) to manage acute retention

MEDICATION

First Line

- Alpha-adrenergic blockade can be useful in patients with dysfunctional voiding
  - Tamsulosin: 0.4 mg daily
  - Doxazosin: 1–4 mg daily
  - Terazosin: 1–5 mg daily
  - Prazosin: 1–5 mg daily

Second Line

- Baclofen for patients with neurologic causes of dysfunctional voiding
  - 5 mg TID, increase 15 mg/d q3 days, max. 80 mg/d divided TID/QID

SURGERY/OTHER PROCEDURES

- For iatrogenic causes, intervention should be postponed for a period of 12 wk to allow for stabilization of symptoms
  - Urethrolysis is the gold standard, circumferentially free the urethra
    - Recurrence or development of stress incontinence high as 30%
  - Bladder neck incision/resection has mixed result in primary bladder neck obstruction, caution not to cut too deep and develop fistulas
  - Refractory strictures can undergo reconstruction with vaginal flap

ADDITIONAL TREATMENT

Radiation Therapy

NA

Additional Therapies

- Urethral dilation for urethral strictures. Caution because this can lead to fibrosis and is falling out of favor.
- Clean intermittent catheterization may be best choice for patients with acontractile bladder
- Constipation management
  - Colace 100 mg 1 tab by mouth BID
  - Magnesium citrate 250 mL PO

Complementary & Alternative Therapies

Concurrent evaluation and management by gastroenterology

ONGOING CARE

PROGNOSIS

- Depends on the etiology
  - Iatrogenic retention following slings has a good success rate with urethrolysis up to 92%
  - α-Blockade shows 50% improvement in PVR, symptoms, and flow rate

COMPLICATIONS

- Urethrolysis can lead to development of stress incontinence
- Bladder neck incision can lead to incontinence, vesicovaginal fistula, or need for repeat

procedures
- Urethral dilation can cause recurrent stricture and fibrosis

FOLLOW-UP

Patient Monitoring

- Repeat urodynamic studies are recommended if problem persists
- Videourodynamics should be done if concern for bladder neck obstruction
- Neurologic evaluation if new diagnosis of MS, Parkinson's disease

Patient Resources

National Kidney and urologic diseases information clearinghouse.
http://kidney.niddk.nih.gov/kudiseases/pubs/UrinaryRetention/

REFERENCES

1. Abrams P. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61(1):37.
2. Buchko BL, Robinson LE. An evidence-based approach to decrease early post-operative urinary retention following urogynecologic surgery. *Urol Nurs*. 2012;32(5):260–264.
3. Kuznetsov D, Kobashi K. Bladder outlet obstruction in females. *AUA Update Series*. 2005;7(24):53–60.

ADDITIONAL READING

- Adelowo AO, Hacker MR, Merport Modest A, et al. Do symptoms of voiding dysfunction predict urinary retention? *Female Pelvic Med Reconstr Surg*. 2012;8(6):344–347.
- Kim JW, Moon du G, Shin JH, et al. Predictors of voiding dysfunction after mid-urethral sling surgery for stress urinary incontinence. *Int Neurolurol J*. 2012;16(1):30–36.
- Yande S, Joshi M. Bladder outlet obstruction in women. *J Midlife Health*. 2011;2(1):11–17.

See Also (Topic, Algorithm, Media)

- Bladder Outlet Obstruction (BOO)
- Multiple Sclerosis, Urologic Considerations
- Pelvic Organ Prolapse (Cystocele and Enterocoele)
- Urinary Retention after Stress Urinary Incontinence Surgery in Females
- Urinary Retention, Adult Male
- Urinary Retention, Adult Male Algorithm
- Urinary Retention, Pediatric
- Urinary Retention, Postoperative

CODES

ICD9

- 598.9 Urethral stricture, unspecified
- 788.20 Retention of urine, unspecified
- 788.29 Other specified retention of urine

ICD10

- N35.9 Urethral stricture, unspecified
- R33.8 Other retention of urine
- R33.9 Retention of urine, unspecified

CLINICAL/SURGICAL PEARLS

- There are multiple causes of urinary retention in females; urodynamics can help distinguish causes.
- In young females with new onset voiding complaints must rule out diabetes or neurologic diagnosis such as MS.
- Pelvic organ prolapse is a major cause of retention.

URINARY RETENTION, ADULT MALE

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BASICS

DESCRIPTION

- Urinary retention is the inability to properly empty the urinary bladder. It can be further classified as acute and chronic.
  - ***Acute retention of urine*** is defined by the International Continence Society (ICS) as a painful, palpable, or percussable bladder, when the patient is unable to pass any urine (1).
  - ***Chronic retention of urine*** is defined by the ICS as a non-painful bladder, which remains palpable or percussable after the patient has passed urine. Such patients may be incontinent (1).

EPIDEMIOLOGY

Incidence

Incidence increases with age in males (~10% in men aged 70 yr)

Prevalence

Exact prevalence is difficult to estimate

RISK FACTORS

- General: Diabetes, herpes zoster, drugs, psychogenic, neurologic disease, bladder calculus, recent surgery (especially with epidural or spinal anesthesia), groin surgery such as hernia repair, prostate brachytherapy, stroke, pelvic trauma
- Elderly men: BPH, prostate cancer, history of retention, urologic procedures or instrumentation, medications, prostatitis, urothelial carcinoma (rare cause)
- Recent inguinal/pelvic surgery (ie, hernia)
- Medications:
  - Antihistamines
  - Anticholinergics: Atropine, belladonna, benztropine, mesylate, phenothiazines, ipratropium bromide
  - Antispasmodics
  - Tricyclic antidepressants
  - α-Agonists: Cold preparations, ephedrine derivatives, amphetamines
  - Narcotics
  - Detrusor muscle relaxants: Tolterodine, trospium, oxybutynin, solifenacin, hyoscyamine
  - NSAIDS

Genetics

- Increased risk of moderate-to-severe symptoms in men with positive family history
  - Some BPH thought to be inherited in pattern consistent with autosomal dominant pattern

PATHOPHYSIOLOGY

- Most commonly occurs in patients with preexisting bladder outlet obstruction or with a

known history of neurologic voiding dysfunction.
- Infection, bleeding, or over distension is the usual precipitating event.
- Drainage of bladder results in prompt symptomatic relief.
- Although acute retention is usually thought of as painful, in certain circumstances pain may not be a presenting feature.
  - When due to prolapsed intervertebral disc, post partum, or after regional anaesthesia such as an epidural anesthetic.
  - The retention volume should be significantly greater than the expected normal bladder capacity.
  - In patients after surgery, due to bandaging of the lower abdomen or abdominal wall pain, it may be difficult to detect a painful, palpable, or percussible bladder (1).

ASSOCIATED CONDITIONS
- Diabetes
- Disease of prostate
  - BPH
  - Prostate cancer
  - Prostatitis
- Neurologic conditions
  - Neurogenic bladder
  - Multiple sclerosis
  - Cerebrovascular accident
  - Parkinson disease
  - Spinal cord injury
  - Demyelinating disorders
- UTI
- Recent hernia or other surgery

DIAGNOSIS
HISTORY
- Acute retention: Sudden onset of the inability to void more than small volumes of urine
  - Associated with an uncomfortable sensation and a distended bladder
- Chronic retention: Longstanding inability to completely void, with occasionally large PVRs, but not usually associated with discomfort.
  - Common symptoms include frequency, urgency, overflow incontinence, and weak urinary stream
- Retention may suggest infection or BPH:
  - Symptoms of bladder outlet obstruction: Weak stream, hesitancy, incomplete voiding, dribbling.
  - Symptoms of irritative voiding: Frequency, urgency, dysuria, nocturia
- Previous urinary retention
- Urologic procedure/instrumentation resulting in scarring, stricture, or clot retention.
- STDs
- Strictures
- Medication use

- Recent gross hematuria, resulting in clot retention.
- Pain: Bone pain and weight loss suggest prostate cancer.
- Spinal cord injury or pelvic trauma.
- Recent surgery, especially in those with spinal or epidural anesthesia.
- Diabetes mellitus

PHYSICAL EXAM

- Palpable abdominal mass
  - Assess for severe urgency and/or pain on suprapubic palpation
- DRE
  - Symmetrically enlarged prostate suggests BPH
  - Nodularity suggests cancer
  - Boggy, tender prostate suggests prostatitis
- Complete neurologic exam if suspicion for a neurologic etiology exists
  - Anal (S2) and levator muscle tone (S3–S4)
  - Check sensation over the penis (S2), perianal area (S2–S3), outside of the foot (S2), sole (S2–S3), and large toe (S3)
  - Suspect spina bifida or meningomyelocele when extremity findings do not parallel perineum findings, ie, absent sensation and tone in feet but partial tone or sensation in perineum
- Examine genitalia for rashes or lesions, ie, herpes zoster flare

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Chemistry: BUN and creatinine may be abnormal in retention especially if hydronephrosis is present
  - Increased post obstructive diuresis risk with post renal obstructive renal failure
- Urinalysis and culture
  - Leukocyte esterase or nitrite positivity with pyuria suggests infection
  - Hematuria suggestive of infection, tumor, or calculi
- PSA usually not checked acutely due to false positive with prostatitis, recent prostate surgery, etc.

Imaging

- Bedside bladder scan
  - Post void residual (PVR) can be obtained and useful for diagnosis of acute and chronic urinary retention
- Renal/bladder US
  - Can be obtained if diagnosis uncertain
  - Can delineate hydronephrosis and/or bladder wall thickening
- CT of abdomen/pelvis
  - Can delineate bladder calculi, prostate size, hydronephrosis, bladder wall thickening, obstructing masses, and foreign bodies
- Retrograde urethrogram
  - Obtained if history of pelvic trauma with new onset urinary retention to rule out urethral injury

Diagnostic Procedures/Surgery

- Foley catheter placement for bladder drainage is diagnostic and curative
- Cystoscopy for definitive diagnosis or acutely to place catheter
- Urodynamic studies
  - Uroflowmetry, cystometrogram, electromyography, urethral pressure profile, pressure flow studies

DIFFERENTIAL DIAGNOSIS

- Generally either bladder outlet obstruction or bladder dysfunction:
  - Anatomic:
    - Penis: Phimosis, paraphimosis, meatal stenosis, foreign-body constriction
    - Urethra: Tumor, foreign body, calculus, urethritis, stricture, clot retention, hematoma
    - Prostate: BPH, prostate cancer, bladder neck contracture, prostatitis, prostatic infarction
  - Trauma
    - Urethral disruption
  - Neurologic
    - Motor paralytic: Spinal shock, spinal cord syndromes, ie, spina bifida, meningomyelocele
    - Sensory paralytic: Tabes dorsalis, diabetes, multiple sclerosis, and pernicious anemia
    - Syringomyelia, myasthenia gravis
    - Herpes zoster, poliovirus
    - Herniated disks
  - Drugs: see “Risk Factors”

TREATMENT

GENERAL MEASURES

- Acute retention: Catheterization for decompression
  - In men with BPH, consider immediate α-blocker therapy to improve likelihood of successful catheter removal
  - Some consider suprapubic tube (SPT) superior in the management of short-term retention
- Chronic retention: Clean intermittent catheterization preferred over long-term indwelling catheter
- Definitive management may involve medications, surgical intervention, or chronic catheterization strategies
- Urodynamic studies may be required to establish diagnosis
- Treatment should be directed toward cause, with goal of preventing future episodes
- Antibiotics as indicated for infection
- Decrease or stop medications that can contribute to voiding dysfunction

MEDICATION

First Line

- Most medications are used for BPH; may also help with transient postoperative retention (2).
- α-Adrenergic blockers: Relax prostatic/bladder neck smooth muscle tone, most useful for acute retention
  - Alfuzosin 10 mg/d

  - Doxazosin start 1 mg/d to max. 8 mg
  - Silodosin 8 mg/d
  - Tamsulosin start 0.4 mg to max. 0.8 mg
  - Terazosin start 1 mg/d to max. 20 mg
- Side-effects: syncope, orthostasis, retrograde ejaculation, asthenia, and nasal congestion
- 5α-reductase inhibitors: Reduce prostatic volume, longer-term effects
  - Finasteride or dutasteride
  - Side-effects: Decreased libido and sexual dysfunction
  - Reduce PSA by ~50% and correction should be used when evaluating risk for cancer
- Combination therapy (α-adrenergic blocker + 5α-reductase inhibitor)
- Tadafil 2.5–5 mg/d FDA approved to treat both lower urinary tract symptoms (LUTS) and erectile dysfunction (ED)

Second Line

- Bethanechol (10–50 mg PO tid–qid)
  - Direct cholinergic stimulant; increases detrusor tone
  - Indicated for the treatment of acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention
  - Side effects: Diarrhea, nausea, bronchospasm, hypotension, tachycardia, seizure

SURGERY/OTHER PROCEDURES

- If catheter placement fails, bedside or intraoperative cystoscopy can be performed:
  - Cystoscopy is usually diagnostic and can delineate urethral stricture, a false passage, bladder neck contracture, and obstructing prostatic tissue.
  - Once bladder is entered under direct vision, a wire can be placed and dilations sequentially performed. The wire can then be used to allow passage of a Council tip catheter.
- If cystoscopy is unsuccessful, consider SPT placement
  - Open SPT preferable in patients with history of multiple abdominal surgeries
  - If no prior surgery, place SPT via percutaneous approach

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- >30% of patients with an episode of urinary retention will recur if untreated
- Prevention of recurrence underscores management decisions

COMPLICATIONS

- Bladder rupture in acute urinary retention; usually associated with trauma.
- Relief of chronic prolonged obstruction may result in post-obstructive diuresis or major hemorrhage secondary to bladder mucosal disruption or tearing of bladder vessels, hematuria may require evacuation of clots.
- Significant hypotension may occur secondary to vaso-vagal response.
- Longstanding, untreated urinary retention can lead to reflux nephropathy and permanent voiding dysfunction.

FOLLOW-UP

Patient Monitoring

- Monitoring of electrolyte imbalance and fluid resuscitation for post obstructive diuresis (>200 mL/h).
- Patient with signs of infection or impaired renal function should be admitted and observed.

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
http://kidney.niddk.nih.gov/kudiseases/pubs/UrinaryRetention/

REFERENCES

1. Curtis LA, Dolan TS, Cespedes RD, et al. Acute urinary retention and urinary incontinence. *Emerg Med Clin N Am.* 2001;19(3):591–620.
2. Edwards JL. Diagnosis and management of benign prostatic hyperplasia. *Am Fam Physician*. 2008;77(10):1403–1410.

ADDITIONAL READING

- Groves HK, Chang D, Palazzi K, et al. The incidence of acute urinary retention secondary to BPH is increasing among California men. *Prostate Cancer Prostatic Dis*. 2013;16(3):260–265.
- Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and post-void residual urine in men: Separating truth from tradition. *J Urol.* 2008;180(1):47–54.

See Also (Topic, Algorithm, Media)

- Bladder Neck Contracture
- Bladder Outlet Obstruction
- Foley Catheter Problems
- Lower Urinary Tract Symptoms
- Post Obstructive Diuresis
- Prostate Cancer, General
- Prostatitis
- Suprapubic Pain
- Urethra, Stricture
- Urinary Retention, Adult Female
- Urinary Retention, Male Algorithm ‡
- Urinary Retention, Pediatric
- Urinary Retention, Postoperative

CODES

ICD9

- 596.0 Bladder neck obstruction
- 600.91 Hyperplasia of prostate, unspecified, with urinary obstruction and other lower urinary symptoms (LUTS)
- 788.20 Retention of urine, unspecified

ICD10

- N32.0 Bladder-neck obstruction
- N40.1 Enlarged prostate with lower urinary tract symptoms
- R33.9 Retention of urine, unspecified

CLINICAL/SURGICAL PEARLS

In chronic retention clean intermittent catheterization (CIC) is preferred over long-term indwelling catheter.

URINARY RETENTION, PEDIATRIC

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BASICS

DESCRIPTION

- Urinary retention is the inability to properly empty the urinary bladder. Can be acute or chronic partial or complete.
  - Acute
    - Uncommon in children
    - Acute onset of inability to void for over 12 h
    - Associated with uncomfortable often painful sensation and distended bladder.
  - Chronic
    - Inability to void over long period of time
    - Usually asymptomatic

EPIDEMIOLOGY

Incidence

Not reported

Prevalence

2:1 boys:girls

RISK FACTORS

- Acute onset
  - Surgery, narcotic use, immobility, urinary tract infection (bacterial or viral), local inflammation (balanitis, meatal stenosis, labial adhesions, cellulitis), constipation, incarcerated inguinal hernia, acute neurologic inflammatory processes, invasive mass, drug related
- Chronic
  - Dysfunctional voiding, Hinman syndrome (non-neurogenic neurogenic bladder), lazy bladder syndrome, spina bifida, reduced mental status, benign obstructing mass, locally invasive mass, posterior urethral valves, prune belly syndrome

Genetics

Genes related to underlying etiology

PATHOPHYSIOLOGY

- Obstruction
  - External compression, intrinsic obstruction by valve, stone, stricture, etc.
- Neurogenic bladder
- Inflammation/infection
  - Effect on brain/meninges (encephalitis, meningitis), spinal cord (transverse myelitis), nerve roots (radiculitis), peripheral nerves (neuritis)
- Constipation (1)

  - Distended rectum displaces bladder and trigone anteriorly, impairing bladder outflow. Impairment of urethrovesical and sacral reflexes from rectal distension.
- Drug related
  - Disruption of autonomic balance between bladder and proximal urethra

ASSOCIATED CONDITIONS
- Dysfunctional elimination syndrome
- Neurologic inflammatory disorders: Transverse myelitis, Guillain–Barré syndrome, encephalitis
- Neurologic neoplasms: neuroblastoma, ependymoma, Ewing sarcoma
- Benign neurologic abnormalities: Tethered cord
- Inflammatory conditions
- Obstructive processes
  - Posterior urethral valves, prune belly syndrome, urethral strictures, foreign body, or stones

GENERAL PREVENTION
Early education of proper voiding habits (drinking water, voiding 6–8 times per day, avoiding constipation).

DIAGNOSIS

HISTORY
- Recent events, including surgery
- Subtle neurologic changes
- History of constipation
- History of hematuria, dysuria
- Recent medications

PHYSICAL EXAM
- Palpable mass (bladder)
- External genitalia exam
  - Meatal stenosis, phimosis, balanoposthitis; labial adhesions, prolapsed urethra
- Spine and lower back
  - Sacral dimple, sacral tuft
- Motor and sensory exam
- Digital Rectal exam
  - Tone
  - Mass

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
- Urine culture
- Electrolytes
  - Creatinine, potassium, magnesium

Imaging

- Renal bladder ultrasound (RBUS), pelvic ultrasound
- MRI spine (if no other etiology identified)
- Voiding cystourethrogram (VCUG) if concern for PUV, stricture (wait until urine culture negative prior to study)
- Retrograde urethrogram

Diagnostic Procedures/Surgery
- Urodynamic evaluation
- Cystoscopy

Pathologic Findings
Based on etiology

DIFFERENTIAL DIAGNOSIS
- Obstruction
  - Tumor
  - Benign mass (fibroepithelial polyp)
  - Urethral valves (posterior or anterior)
  - Urethral stone
  - Prolapsing ureterocele
  - Urethral stricture
  - Paraurethral cyst
  - Hydrometrocolpos
- Inflammation
  - Cystitis (bacterial or viral) (2)
  - Bacterial
    - Gram positive
    - Gram negative
  - Viral
    - Herpes simplex virus (HSV)
    - Varicella Zoster virus (VZV)
    - Cytomegalovirus (CMV)
    - Epstein Barr Virus (EBV)
  - Eosinophilic cystitis
  - Prostatic abscess
- Neurogenic dysfunction
  - Neuropathic bladder
    - Myelomeningocele
    - Sacrococcygeal teratoma
    - Prune belly syndrome
    - Tethered spinal cord
  - Detrusor sphincter dyssynergia
- Other
  - Constipation
  - Adverse drug effect
  - Trauma

– Electrolyte abnormalities (hypermagnesemia) (1)

TREATMENT

GENERAL MEASURES

- Empty bladder with catheter
- Initiate clean intermittent catheterization until resolution.
- Complete workup based upon findings on history and physical exam
- For chronic retention, after complete workup to rule out pathologic cause, begin behavioral modification (increase water intake, increasing voiding attempts to every 3 h, treat constipation)

MEDICATION

First Line

- Polyethylene Glycol 3350 for constipation/dysfunctional elimination syndrome
  - 0.5–1.5 g/kg daily, max. dose 17 g/d.
    - Use only in children older than 6 mo

Second Line

- α-Blockers (3,4)
  - Smooth muscle relaxation and decreased bladder outlet resistance:
    - Doxazosin <6 yr 0.5 mg daily
    - Doxazosin >6 yr 1 mg daily
- Steroids for inflammatory processes (2)
  - Very seldom used. Stress dose steroids.

SURGERY/OTHER PROCEDURES

- In acute setting, place urethral catheter
- If unable to place catheter, place suprapubic cystostomy tube.
- For posterior urethral valves, perform cystoscopy, transurethral incision of valves.
- For urethral stones, cystoscopy and laser lithotripsy or basket extraction (may require antegrade and retrograde approach).
- For obstructing fibroepithelial polyp, transurethral resection possible, vs. open cystotomy and excision.
- For obstructing prolapsing ureterocele, incision of ureterocele may leave obstructing tissue. May require excision of ureterocele and bladder neck reconstruction.
- Urethral stricture—based on length
- For significant detrusor sphincter dyssynergia, may benefit from botulinum toxin injection into urethral sphincter vs. urethral dilation

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Behavioral modification
  - Timed voiding
  - Increased water intake

– Pelvic floor relaxation

Complementary & Alternative Therapies
Biofeedback program for dysfunctional elimination syndrome

ONGOING CARE

PROGNOSIS
Based upon etiology.

COMPLICATIONS
- Bladder rupture in acute urinary retention; usually associated with trauma
- Postobstructive diuresis after relief of acute retention
- Urinary tract infection from stasis of chronic retention
- Chronic retention with high detrusor pressure can lead to renal impairment
- Missed diagnosis of malignant cause of urinary retention

FOLLOW-UP
Patient Monitoring
- Monitor for post-obstructive diuresis after drainage. May require fluid replacement in neonates
- Follow uroflow and post-void residual after treatment

Patient Resources
National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
http://kidney.niddk.nih.gov/kudiseases/pubs/UrinaryRetention/

REFERENCES

1. Gatti JM, Perez-Brayfield M, Kirsch AJ, et al. Acute urinary retention in children. *J Urol.* 2001;165:918–921.
2. Chu SD, Singer JS. Acute urinary retention secondary to Epstein-Barr Virus infection in a pediatric patient: A case report and review of causes of acute urinary retention. *Urology*. 2013;81(5):1064–1066.
3. Thom M, Campigotto M, Vemulakonda V, et al. Management of lower urinary tract dysfunction: A stepwise approach. *J Ped Urol.* 2012;8:20–24.
4. Austin PF, Homsy YL, Masel JL, et al. α-Adrenergic blockade in children with neuropathic and non-neuropathic voiding dysfunction. *J Urol.* 1999;162:1064–1067.

ADDITIONAL READING
N/A

See Also (Topic, Algorithm, Media)
- Posterior Urethral Valves
- Prune Belly Syndrome
- Sacral agenesis, urologic considerations
- Ureterocele
- Urinary Retention, Adult Female
- Urinary Retention, Adult Male

- Urinary Retention, Adult Male Algorithm
- Urinary Tract Infection, Complicated Pediatric

CODES

ICD9

- 596.0 Bladder neck obstruction
- 599.0 Urinary tract infection, site not specified
- 788.20 Retention of urine, unspecified

ICD10

- N32.0 Bladder-neck obstruction
- N39.0 Urinary tract infection, site not specified
- R33.9 Retention of urine, unspecified

CLINICAL/SURGICAL PEARLS

- Urinary retention in a newborn must be closely evaluated with RBUS and VCUG to rule out posterior urethral valves, ureterocele, and urethral atresia.
- Young boys presenting with acute urinary retention should undergo DRE to rule out prostatic or bladder rhabdomyosarcoma.

URINARY TRACT INFECTION (UTI), ADULT FEMALE

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BASICS

DESCRIPTION

- Urinary tract infection (UTI) in a female is defined as a symptomatic urothelial inflammation secondary to bacterial adhesion and internalization within the urinary tract.
- Most common human bacterial infection.
- Tremendous economic impact
  - ~ $3.5 billion annually in the United States.
- Possibility of progression to urosepsis
- Anatomical: Lower (confined to bladder and/or urethra) vs. upper (involving the ureters and/or kidneys)
- Complicated: Structural or functional abnormality, or if immunosuppressed (See Section I in "Urinary tract infection (UTI), complicated, adult")
- Recurrence (rUTI): 3 or more culture positive infections within 12 mo
  - Reinfection: Different infecting uropathogen, negative culture between infections or infection occurs >2 wk after successful treatment
  - Persistence: Recurrence within 2 wk of treatment and identical uropathogen
- Asymptomatic bacteriuria: 2 consecutive midstream urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ in the absence of symptoms

EPIDEMIOLOGY

Incidence

- 13,320 cases per 100, 000 adult women/yr (1)
- 44% have at least 1 rUTI in 12 mo
- 5% more than 3 rUTIs in 12 mo
- Bacteriology of female UTI (2):
  - Ambulatory: *Escherichia coli* (74.2%), *Klebsiella pneumonia* (6.2%), *Enterococcus species* (5.3%), *Streptococcus agalactiae* (2.8%), *Proteus mirablis* (2.0%), and *Staphylococcus saprophyticus* (1.4%)
  - Nosocomial: *E. coli* (65.5%), *Enterococcus* species (8.0%), *K. pneumonia* (8.0%), *Klebsiella oxytoca* (8.9%), *P. mirablis* (2.2%), *Pseudomonas aeruginosa* (1.8%)
  - Nursing home: *E. coli* (46.6%), *Enterococcus* species (11.4%), *Proteus mirabilis* (10.1%), *K. pneumonia* (9.7%), *Pseudomonas aeruginosa* (3.2%)

Prevalence

53,067 cases per 100,000 adult women (1)

RISK FACTORS

- Behavioral factors
  - Sexual intercourse, spermicide use, barrier contraceptives, recent antibiotic use, dysfunctional voiding

- Anatomic Variations
  - Perineal and urethral anatomy is thought to be important only in absence of other risk factors
  - Urinary tract obstruction: Medullary sponge kidney, calyceal diverticula, ureteral obstruction, ureteropelvic junction obstruction, vesicoureteric reflux, primary bladder neck, urethral stricture, or benign prostatic hyperplasia
- Physiologic Factors
  - Diabetes mellitus
    - 1.2–2.2-fold increased risk
    - Theories: Hyperglycosuria, increased glycosylation of uroplakin Ia, less effective urinary glycoproteins, and impaired bladder contractility and emptying (diabetic cystopathy)
  - Pregnancy
    - Prevalence of bacteriuria is similar to non-gravid females
    - However, 22–35% progression to pyelonephritis. Secondary to hydronephrosis of pregnancy
  - Neurologic diseases
    - Detrusor-external sphincter dyssynergia
  - Other: Alternations in toll-like receptors, anti-microbial peptides (defensins and cathelicidin), anti-bacterial adherence factors (eg, Tamm–Horsfall protein) and growth factors (eg., TGF-β1 and VEGF
  - Postmenopausal female
    - Atrophic vaginitis, decreased levels of lactobacilli, incontinence, cystocele, elevated post-void residual

Genetics

- Positive female family history strongly predictive of UTI
- Greater binding of uropathogenic coliforms
  - ABH blood group non-secretor status
  - P1 status
- Alterations in HSPA1B, CXCR1&2, TLR2&4, and TGF-β1 genes

PATHOPHYSIOLOGY

- Routes of infection:
  - Ascending (majority)
    - From extra urinary sources such as the distal gut or vaginal epithelium (majority)
  - Hematogenous (rare)
    - Increased with ureteral obstruction
    - Staphylococcus bacteremia or Candidal fungemia
  - Quiescent intracellular reservoirs
    - Dormant uropathogenic bacteria residing within urothelial cells
    - Evade host immune responses and can emerge at any given time to reinfect host
- Adherence and internalization
  - Mediated via bacterial FimH and terminal mannose units of host uroplakin Ia

ASSOCIATED CONDITIONS

- Postmenopausal

- Diabetes mellitus
- Urolithiasis
- Anatomic or function abnormalities of the urinary tract

GENERAL PREVENTION
- Avoidance of spermicidal products and barrier contraceptives
- Although hygiene, pericoital voiding, hydration has not been shown to be uniformly effective in UTI prevention women are encouraged to clean perineum wiping front to back and should empty bladder before, and after intercourse

DIAGNOSIS
HISTORY
- UTI signs/symptoms: General malaise, frequency, urgency, urge incontinence, dysuria, suprapubic pain pressure, cloudy urine, foul smelling urine, hematuria
- Pyelonephritis: Fever, chills, flank pain
- Negatively predictive: Vaginal discharge, foul vaginal odor, pruritus, urethral discharge
  - Suggestive of vaginitis or urethritis
- Review previous UTI episodes: Number, frequency, temporal associations (eg, sexual activity), results of documented urine cultures, treatment, and treatment efficacy
- Medical/surgical history: Childhood UTIs, structural/functional abnormalities, immunocompromise, recent hospitalization, genitourinary manipulation/surgery
- Gynecologic history: Menstrual cycle, birth control, menopausal status, STI/STD's, pelvic organ prolapse

PHYSICAL EXAM
- Vital signs: Hemodynamic instability can be associated with pyelonephritis/urosepsis
- Abdominal exam: Suprapubic tenderness, bladder distension suggestive of urinary retention
- Costovertebral angle tenderness with pyelonephritis
- Pelvic exam:
  - Assessment of vaginal epithelium
  - Vaginal discharge
  - Pelvic organ prolapse
  - Urethral abnormalities:
    - Diverticulum: Suburethral tenderness, cystic mass, and/or expression of urethral discharge
    - Skene's gland infection: Expression of discharge from Skene's gland duct

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis
  - Leukocyte esterase
    - Sensitivity 68–98%
    - Specificity 59–96%
    - Positive predictive value 19–86%
    - Negative predictive value 91–97%
  - Nitrite

    - Sensitivity 19–45%
    - Specificity 95–98%
    - Positive predictive value 50–78%
    - Negative predictive value 82–89%
  - Leukocyte esterase and nitrite
    - Sensitivity 35–84%
    - Specificity 98–100%
    - Positive predictive value 84%
    - Negative predictive value 98%
- Microscopy
  - Bacterial counts $>30{,}000$ cfu/mL for detection
  - ≥ 1 bacteria per hpf (uncentrifuged urine) correlates to $\geq 10^5$ cfu/ml via culture
  - Pyuria: ≥ 10 WBCs/hpf
- One study has suggested that midstream urine generally is not indicated in the treatment of healthy premenopausal women with presumptive cystitis.
  - Cultures can be complicated by the potential for contamination of the voided urine specimen by periurethral organisms (enterococci and group B streptococci), which cannot be distinguished from bladder organisms.

Imaging

- Generally unnecessary; obtain if suspect complicated UTI
  - Indications: persistent fever (72 h after initiation of treatment), suspected urolithiasis (urine pH ≥ 8.0, history of calculi, very severe flank pain), unexplained/persistent hematuria, bacterial persistence, analgesic abuse, urinary retention
  - First line: renal ultrasound
  - CT $\pm$ intravenous contrast: alternative for further evaluation or renal abscess, renal mass, or urolithiasis

Diagnostic Procedures/Surgery

- Cystoscopy not necessary unless hematuria, bacterial persistence, recurrent UTIs
- Urodynamic testing: urinary retention, voiding dysfunction, neurologic disease

Pathologic Findings

Cystoscopy: generalized erythema and edema of urothelium

DIFFERENTIAL DIAGNOSIS

- Urothelial malignancy: Persistent microscopic or gross hematuria, lower urinary tract symptoms recommendation is for cystoscopy and CT urogram
- Urolithiasis
- Vaginitis: Vaginal discharge, odor, pruritus, dyspareunia
- Urethritis: Urethral discharge, dysuria, pruritus, STI history
- Painful bladder syndrome: Characterized by bladder pain with filling that is alleviated with voiding, chronic frequency, and urgency

TREATMENT

GENERAL MEASURES

- Empiric antimicrobials ideally started after urine specimen collected
  - Adjust to urine C + S if necessary
- NSAIDs for discomfort

MEDICATION

First Line

- Acute UTI
  - Algorithm outlines an approach to choosing an optimal empiric antimicrobial for uncomplicated cystitis (3,4)
  - If complicated UTI, urine specimen should be collected prior to treatment and treatment duration should be adjusted to 10–14 days
  - If patient is systemically unwell/urosepsis consider broad spectrum IV antimicrobials such as 2nd- or 3rd-generation cephalosporins ± urinary tract imaging

Second Line

- Prevention:
  - Intravaginal estrogen in post-menopausal women: Creams, suppositories, vaginal ring
  - Methenamine salts: Hydrolyzed to ammonia and formaldehyde in urine (bacteriostatic)
    - Cochrane review: Only short-term efficacy
    - Improved efficacy with vitamin C
  - D-mannose: Fim H inhibitor; no clinical studies
  - Antimicrobials for recurrent UTI
    - Self-start therapy: Start 3-day course after onset of symptoms; contact provider if symptoms persist beyond 48 h
    - Postcoital prophylaxis (See Section II)
    - Continuous prophylaxis

SURGERY/OTHER PROCEDURES

- Rarely indicated unless the following present:
  - Obstruction and urosepsis: Stent or percutaneous nephrostomy tube (PCNT)
  - Renal abscess drainage: Percutaneous drainage
  - Urethral diverticulum
  - Emphysematous pyelonephritis: Drainage or nephrectomy

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Cranberry supplements
  - Some data to suggest cranberry supplements are effective at preventing rUTI (relative risk 0.62; 95% CI 0.49–0.8) (4)
  - Twice daily dosing more effective

ONGOING CARE

PROGNOSIS

- Typically will have prompt symptomatic response to antimicrobial therapy
- Recurrence can occur

COMPLICATIONS

Urosepsis, pyonephritis, renal abscess, emphysematous cystitis or pyelonephritis (diabetic or immunocompromised patients)

FOLLOW-UP

Patient Monitoring

- Routine follow-up urine cultures not recommended
- Annual chest x-ray when using nitrofurantoin prophylaxis long-term

Patient Resources

Urology Care Foundation: Urinary Tract Infections in adults.
http://www.urologyhealth.org/urology/index.cfm?article=47

REFERENCES

1. Griebling TL. Urinary tract infections in women. Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. NIH Publication No. 07-5512. Litwin MS, Saigal CS, eds. Washington, DC: US Government Publishing Office; 2007; chapter 18, pp. 587–619.
2. Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol.* Nature Publishing Group; 20101;7(12):653–660.
3. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Diseases*. 2011;52(5):e103–e120.
4. Wang C-H, Fang CC, Chen NC, et al. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: A systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med.* 2012;172(13):988.

ADDITIONAL READING

Hooton TM, Roberts PL, Cox ME, et al. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med.* 2013; doi:10.1056/NEJMoa1302186.

See Also (Topic, Algorithm, Media)

- Bacteruria and Pyuria
- Cystitis, General Considerations
- Pregnancy, Bacteruria, Pyuria, and UTI
- Pyelonephritis
- Urinary Tract Infection (UTI), Adult Female Algorithm
- Urinary Tract Infection (UTI), Complicated, Adult

CODES

ICD9
- 595.9 Cystitis, unspecified
- 597.80 Urethritis, unspecified
- 599.0 Urinary tract infection, site not specified

ICD10
- N30.90 Cystitis, unspecified without hematuria
- N34.2 Other urethritis
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

Always consider urolithiasis with UTI when flank pain is severe.

URINARY TRACT INFECTION (UTI), ADULT MALE

Patricia Lewandoski, MD
Akhil Das, MD, FACS

BASICS

DESCRIPTION

- A urinary tract infection (UTI) is a male is an inflammatory response of urothelium to bacterial invasion with associated bacteriuria and pyuria (1)
- Defined by source of infection:
  - Cystitis: Infection of bladder; dysuria, frequency, urgency, suprapubic pain, hematuria.
  - Isolated cystitis in men rare, usually associated with prostatitis or pyelonephritis
  - Pyelonephritis: Infection of kidney; chills, fever, flank pain ± symptoms of cystitis
  - Prostatitis infection or inflammation of prostate; acute or chronic; either bacterial or nonbacterial based on NIH classification (see Section I: "Prostatitis, General")
  - Urethritis: Infection of urethra
- Defined as uncomplicated or complicated
  - Uncomplicated: Isolated infection or reinfection in a healthy young male with normal urinary tract; urethritis or prostatitis
  - Complicated: Infection associated with:
    - Structurally abnormal urinary tract (eg, bladder outlet obstruction/BPH), or
    - Functionally abnormal urinary tract (eg, neurogenic bladder)
    - Impaired host defense (eg, immunosuppression/diabetes)
    - Increased bacterial virulence
- Most UTIs in men are complicated.
- Defined based on chronicity:
  - Unresolved: UTI that has not responded to antimicrobial treatment
  - Recurrent: UTI that occurs after complete resolution (proven by negative culture after complete antimicrobial course) of previous UTI
- Reinfection: A recurrent UTI from reintroduction of bacteria into previously sterilized urine
- Bacterial persistence: A recurrent UTI due to a source of bacterial colonization (eg, infected stone, prostate, or foreign body)
- Other definitions (and suggested therapies):
  - Emphysematous cystitis/emphysematous pyelonephritis: Complicated UTIs associated with gas in bladder wall or renal parenchyma; typically found in diabetes; gas-forming organisms and obstruction (in pyelonephritis); treated with parenteral antimicrobials; pyelonephritis may require nephrectomy
  - Xanthogranulomatous pyelonephritis:
    - Chronic renal infection associated with obstruction, nephrolithiasis; massively enlarged, nonfunctioning kidney; presenting signs of flank pain, fever, and persistent bacteriuria
- Asymptomatic bacteriuria in men:
  - 10^2 CFU/mL of single organism from cath specimen or 10^5 CFU/mL from single clean catch in men without symptoms of UTI

– Treatment recommended only prior to urologic procedures (2)[C]
- Prophylaxis in those at risk (ie, spinal cord injury or other cause for indwelling catheter) is not recommended; treat only when symptomatic.

EPIDEMIOLOGY

Incidence

12.6/1000 person years (if prostatitis included as UTI) (3)[C]

Prevalence

- Increases with age to >10% in men aged >65 yr
- Asymptomatic bacteriuria in elderly men approaches 60–80%.

RISK FACTORS

- Risk factors for complicated UTI:
  – Male gender
  – Elderly
  – Diseases: Diabetes mellitus; recent UTI, immunosupressive disease or diseases requiring the use of immunospsuppression such as steroids
  – Recent antimicrobial use
  – Indwelling urinary catheter
  – Recent urologic intervention or hospital infection
  – Urinary tract obstruction (eg, BPH, urethral stricture disease); urinary stasis
  – Urinary calculi
  – Uncircumcised
  – Spinal cord injury
  – Unprotected anal intercourse
  – History of childhood UTI

Genetics

Certain individuals (including those with HLA-A3) prone to recurrent UTIs have increased epithelial cell receptivity for uropathogenic *Escherichia coli*.

PATHOPHYSIOLOGY

- UTI occurs via 1 of 3 routes (1):
  – Ascending: Via inoculation of urethra/urethral catheter with bowel flora: Most common
  – Hematogenous seeding of kidney
  – Lymphatic spread
- Males are more resistant to UTI than females due to longer urethra, antibacterial nature of prostatic fluid, drier periurethral environment.
- UTIs occur as a result of interaction between host defense mechanisms and bacterial virulence:
  – Inherent host defense mechanisms:
  – Urinary flow helps decrease retrograde infection; conversely, residual urine/obstruction increases risk of infection
  – Urine: Urea, pH, organic acids help prevent growth; glucose provides environment conducive for bacterial growth and increases risk of infection
  – Bladder: Host recognition of bacteria, with innate immune response against infection;

exfoliation of infected urothelial cells
  – Infection of urinary tract involves attachment of bacterium to the host's epithelium.
  – Adherence of bacteria to urothelial cells necessary for infection; some virulent bacteria have type 1 pili (mediate attachment to cells); pyelonephritis bacteria contain P pili
- Common community-acquired uropathogens: *E. coli* (most common), *Proteus*, *Klebsiella pneumonia*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*
- Common nosocomial uropathogens: *E. coli*, *Klebsiella*, Enterobacter, Citrobacter, *Serratia*, *Pseudomonas*, *Enterococcus faecalis*, *Providencia*, *S. epidermidis*

ASSOCIATED CONDITIONS
See "Risk Factors."

GENERAL PREVENTION
Maintenance of low residual urine clearing any foreign bodies (catheters, stones)

DIAGNOSIS
HISTORY
- Assess for any of risk factors listed above.
- Workup of recurrent UTI, inquire about risk factors and obtain a complete and thorough culture history of involved bacteria, treatment course, and documented evidence of clearance of bacteria.

PHYSICAL EXAM
- Obtain vital signs to assess severity of infection, presence of systemic disease.
- Assess for suprapubic pain, flank pain, and urethral discharge and rectal exam for tenderness and fluctuance.
- Uncircumcised: May increase risk of infection

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urine analysis: Quality of specimen grossly assessed by presence (poor) or absence (good) of squamous cells
- Microscopic analysis for bacteria: False-positive from foreskin contamination if poor-quality specimen; false-negative if 10^2–10^4 bacteria/mL (too few to be seen under slide)
- Dipstick: WBC must be present for infection but WBC without bacteriuria may be present with stones, indwelling stent, tuberculous infection
  – Nitrite: Bacterial reduction of nitrate in urine
  – Leukocyte esterase: Presence of WBC
  – Sensitivity of nitrite and leukocyte esterase positivity varies greatly; does not replace microscopic analysis for bacteria
- Culture: Midstream clean catch: Reduce bacterial contamination of culture in uncircumcised men by retracting foreskin and cleansing
  – 10^2–10^3 CFU/mL in dysuric male with pyuria is indicative of infection (clean catch).
- For lower UTI, consider localization studies (see Section I: "Prostatitis, General").

Imaging
- Recommended in most men to rule out complicated infection, if not responding to therapy,

in patients with rapid recurrent infection and found to have bacteria susceptible to antimicrobial used (i.e., persistence), when obstruction suspected
- CT urogram or MRI: Provide excellent detail, evidence of urinary tract abnormalities, stones, or foreign bodies, among others

Diagnostic Procedures/Surgery
- Cystoscopy: Same indications as listed under "Imaging"; allows direct visualization of bladder to assess for foreign body, ectopic ureters, diverticula, stones, or other abnormalities
- PVR: Should be considered in men with BPH, voiding dysfunction; high residual with stasis increases risk of infection
- Localization studies: Selective cultures from each kidney via ureteral catheterization and prostatic cultures are helpful in identifying source of bacterial persistence.

Pathologic Findings
N/A

DIFFERENTIAL DIAGNOSIS
- Urgency, frequency, dribbling, and dysuria can be symptoms of prostatitis.
- Prostatitis:
  – NIH Class I: Acute bacterial prostatitis, sudden onset
  – NIH Class II: Chronic bacterial prostatitis; Insidious onset, relapsing, recurrent UTI
- For cystitis: Interstitial cystitis vs. urethritis
- For pyelonephritis: Pancreatitis vs. appendicitis vs. diverticulitis vs. acute focal/multifocal nephritis

TREATMENT

GENERAL MEASURES
- Maintain adequate hydration/good hygiene.
- Remove urinary catheters as soon as possible to prevent catheter associated UTI

MEDICATION
First Line
- Antimicrobial therapy for UTI in men is extrapolated from data for treatment of women. (see Section I: "Prostatitis, General")
- If severe infection or toxicity is present, CT should be obtained to rule out obstructive pyelonephritis; if found, decompression is critical.
- Common oral antimicrobials (1):
  – Trimethoprim-sulfamethoxazole: Inexpensive, covers staphylococci, streptococci, and most gram-negatives except *Pseudomonas*
  – Fluoroquinolones: More expensive (levofloxacin > ciprofloxacin), cover staphylococci and most gram-negatives including *Pseudomonas*
- Common parenteral antimicrobials:
  – Ampicillin: Covers streptococci, enterococci, *E. coli, Proteus*; addition of β-lactamase inhibitor covers *Klebsiella and Haemophilus*; no pseudomonal coverage; good 1st-line IV drug

  - Gentamicin: Staphylococci, most gram-negatives including *Pseudomonas*; augments ampicillin for coverage in pyelonephritis
- For cystitis (1)[C]:
  - Take into account local resistance profiles
  - No controlled trials; antimicrobials based on local resistance patterns, previous culture
  - Further tailored to culture sensitivities
  - Duration: For most men with complicated infections, treat for at least 10 days
- In complicated UTI, obtain culture during therapy and 1–2 wk after therapy is complete to document clearance.
  - For uncomplicated UTI, longer-duration treatment (>7 days) has no association with a reduced risk for early or late recurrence compared to shorter treatment (≤7 days)
- For pyelonephritis (1)[C]:
  - For men, pyelonephritis is a complicated UTI and outpatient therapy is initiated only after treatment of complicating factors is initiated.
  - Renal/perirenal abscess: Suspected if indolent/recurrent fever >72 h and/or persistently positive culture despite therapy; CT when suspect; if small abscess antimicrobial treatment; if large (>3 cm) abscess or perinephric abscess: percutaneous drainage
- Outpatient therapy:
  - Fluoroquinolone (7 days) is more effective than trimethoprim-sulfamethoxazole (14 days)
  - Tailor antimicrobial to culture sensitivities.
  - If no improvement, use IV therapy
- Inpatient therapy:
  - IV fluoroquinolone or ampicillin + gentamicin or 3rd-generation cephalosporin
  - Duration without bacteremia: 2–3 days IV then 10–14 days PO antimicrobial
  - Duration with bacteremia: 7 days IV, then 10–14 days appropriate PO antimicrobial
- Repeat cultures on therapy and 10–14 days after completion of course should be negative; if positive, continue a 14-day specific regimen

Second Line

Abscesses in the upper urinary tract or prostate often require percutaneous drainage.

SURGERY/OTHER PROCEDURES

- As needed for cause of recurrent UTI, such as stone, foreign body, or enlarged prostate.
- Transurethral resection (TUR) (unroofing procedure) or percutaneous drain may be required for prostatic abscess.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Cranberry juice: No male evidence (4)[B]

ONGOING CARE

PROGNOSIS

When appropriate antimicrobial therapy is chosen, complicating factors are identified and treated, and close follow-up is achieved with documentation of clearance of infection, a good prognosis is expected.

COMPLICATIONS

- Sepsis
- Upper urinary tract infections with abscess formation can cause loss of renal function.

FOLLOW-UP

Patient Monitoring

Follow-up culture, post void resideual urine (PVR) and adassessment of lower urinary tract symptoms (LUTS)

Patient Resources

Urology Care Foundation: Urinary Tract Infection in Adults.
http://www.urologyhealth.org/urology/index.cfm?article=47

REFERENCES

1. Schaeffer AJ, Schaeffer EM. Infections of the urinary tract. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders; 2011.
2. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005;40:643.
3. Ruben FL, Dearwater SR, Norden CW, et al. Clinical infections in the noninstitutionalized geriatric age group: Methods utilized and incidence of infections. The Pittsburgh Good Health Study. *Am J Epidemiol.* 1995;141(2):145.
4. Drekonja DM, Rector TS, Cutting A, et al. Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes. *JAMA Intern Med.* 2013;173(1):62–68.

ADDITIONAL READING

EAU Guidelines on Urological Infections.
http://www.uroweb.org/gls/pdf/18_Urological%20infections_LR.pdf

See Also (Topic, Algorithm, Media)

- Prostatitis, Acute, Bacterial (NIH 1)
- Prostatitis, Chronic, Nonbacterial, Noninflammatory (NIH CP/CPPS III B)
- Prostatitis, Chronic, Bacterial, (NIH II)
- Prostatitis, Chronic, Nonbacterial, Inflammatory (NIH CP/CPPS III A)
- Prostatitis, General
- Pyelonephritis
- Urethritis, Acute Male
- Urinary Tract Infection (UTI), Complicated, Adult
- Urinary Tract Infection (UTI), Pediatric

CODES

ICD9
- 590.80 Pyelonephritis, unspecified
- 595.9 Cystitis, unspecified
- 599.0 Urinary tract infection, site not specified

ICD10
- N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
- N30.90 Cystitis, unspecified without hematuria
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS
- Most UTIs in men are considered complicated and require a longer course of antibiotics.
- UTI-related prostatitis requires a minimal of 7 days of treatment.

URINARY TRACT INFECTION (UTI), CATHETER-ASSOCIATED (CAUTI, CA-UTI)

Jeremy N. Reese, MD, MPH
Timothy D. Averch, MD, FACS

BASICS

DESCRIPTION

- Catheter-associated urinary tract infection (CAUTI/CA-UTI) is defined as an infection occurring in a person whose urinary tract is currently catheterized or has been catheterized within the previously 48 h.
- May refer to indwelling urethral or suprapubic catheters as well as routine intermittent catheter use.

- Catheter-associated asymptomatic bacteriuria (CA-ASB) is the presence of bacteria in the urinary tract without signs or symptoms of infection.
- CA-UTI and CA-ASB are often not distinguished from each other in reported cases of catheter associated bacteriuria and may result in inappropriate antibiotic use contributing to antimicrobial resistance and adverse event reporting to governmental agencies.
  - UTIs are the most common type of healthcare-associated infection reported to the National Healthcare Safety Network (NHSN).

EPIDEMIOLOGY

Incidence

- CA-UTI is the most common nosocomial infection in the United States, accounting for 40% of hospital-acquired infections and over 80% of the 900,000 cases of bacteriuria annually.
- 15–25% of hospitalized patients have a urethral catheter inserted during their stay
- Incidence of CA-bacteriuria is thought to be 3–8% per catheter-day, with 3.1–7.4 CA-UTIs per 1000 urinary catheter days reported in US intensive care units
- Cost: $1006 per episode of CA-UTI

Prevalence

5–10% of long-term care facility patients are managed with indwelling or intermittent catheterization, accounting for >100,00 patients in the United States at any given time

RISK FACTORS

Duration of catheter use, placement outside operating room, open drainage system, female sex, diabetes mellitus, renal insufficiency, and inappropriate use (discussed below)

Genetics

N/A

PATHOPHYSIOLOGY

- Urethral catheterization is most important predisposing factor for nosocomial UTI
  - Disrupted mucosa exposes new binding sites for bacteria allowing for growth of less virulent organisms

- Indwelling catheter may introduce bacteria at time of insertion, allowing ascension of uropathogens into bladder at time of insertion and then later via intra- and extra-luminal spread
  - 2/3rd of identified pathogens are extraluminally acquired vs. 1/3rd intraluminally acquired
- Bacterial adhesions and production of exopolysaccharides allow for replication on the catheter surface and formation of biofilms
  - Short-term catheter use tends to be associated with a single organism, whereas longer catheter use is associated with polymicrobial growth
  - Biofilms protect bacteria from antimicrobials and host immune response, facilitating spread of antimicrobial resistance genes
- *Escherichia coli* is most common isolate, as well as *Klebsiella*, *Serratia*, Citrobacter, Enterobacter, *Pseudomonas*, *Staphylococcus*, and *Enterococcus*.
  - *Providencia*, *Morganella*, and *Proteus* species more commonly isolated from long-term catheters

ASSOCIATED CONDITIONS

Spinal cord injury, neurogenic bladder, urinary incontinence, sacral or perineal wounds, prolonged immobilization

GENERAL PREVENTION

- Limiting use of urinary catheters, aseptic insertion, early discontinuation of catheter use, use of pre-sealed closed drainage systems, maintaining drainage bag below level of bladder (1) [A]
  - Absolute indications include: urinary retention, accurate measurement of urine output in critically ill patients, prolonged general or spinal anesthetic, following selected urologic or gynecologic procedures, comfort care
- Application of institutional reminders such as nurse or electronic-based reminders, automatic stop-orders, use of reminder stickers or dated collection bags, requirement of physician order to place and maintain catheters
- No trials support use of: antimicrobial or chemical prophylaxis, routine catheter irrigation, antimicrobial use in drainage bag, antibiotic use at time of routine catheter exchange or removal
  - Routine screening for CA-ASB should be avoided (1)[A]
- Alternatives to indwelling urethral catheters
  - Condom catheters provide alternative to short-term catheter use in men with low-post void residuals
  - Urethral and suprapubic catheters have similar rates of CA-UTI, although suprapubic catheters are often more comfortable, spare urethral catheterization, and are easier to exchange
  - Intermittent catheterization significantly reduces rates of CA-ASB and is associated with higher patient satisfaction
- Healthcare providers should clean their hands with soap and water or use an alcohol-based hand rub before and after touching catheters.
- Avoid disconnecting the catheter and drain tube.

- The catheter is secured to the leg to prevent pulling on the catheter.
- Avoid twisting or kinking the catheter.
- Keep the bag lower than the bladder to prevent urine from backflowing to the bladder.
- Empty the bag regularly. The drainage spout should not touch anything while emptying the bag.

DIAGNOSIS

HISTORY

- CA-UTI: Patients with signs and symptoms of UTI with current or recent (<48 h) indwelling urinary catheter or routine intermittent catheter use
  - Symptoms may include chills, rigors, altered mental status, malaise, flank pain, and pelvic discomfort
  - Patients with a recently removed catheter may report dysuria, urinary urgency and/or frequency
  - Spinal cord injury patients may report increased spasticity, autonomic dysreflexia and/or sense of uneasiness

PHYSICAL EXAM

- A few physical exam findings are reliable to diagnose CA-UTI but may include suprapubic and/or costovertebral angle tenderness, hematuria, or fever
- Foul-smelling and/or cloudy urine have not been shown to be significant clinical predictors of CA-UTI
  - Encourage hydration if no other clinical indicators of infection and reassess thereafter

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CA-UTI: Patients with signs and symptoms of UTI with current or recent (<48 h) indwelling urinary catheter or routine intermittent catheter use with cultures growing >103 cfu/mL (1)[A]
- CA-ASB is defined as cultures growing >105 cfu/mL WITHOUT signs or symptoms or UTI (1)[A]
- Urine specimen should be sent for culture prior to initiation of antimicrobials (1)[A]
- Catheters should be replaced, if still indicated, and a culture should obtained from newly placed catheter (1)[A]
- If catheter can be discontinued, a midstream voided specimen should be used for culture (1)[A]
- Pyuria on urinalysis is not sufficient to diagnose CA-UTI or CA-ASB, but its absence can exclude infection (1)[A]

Imaging

- Not routinely indicated
- May be necessary in cases of suspected complicated UTI such as concern for urolithiasis, foreign body, abscess, emphysematous infection, or vesicoureteral reflux

Diagnostic Procedures/Surgery

- Not routinely indicated

- Urodynamic studies may be useful to determine necessity of routine catheterization, particularly in spinal cord injury (SCI) population
- For patients with long-term catheter use (eg, SCI, neurogenic bladder population), routine cystoscopy has been suggested for cancer detection due to increased risk of both transitional cell and squamous-cell carcinomas
  - Lifetime bladder malignancy incidence ranges from 0.39% to 2.4% in published retrospective reviews of SCI patients

Pathologic Findings

Pathology is not routinely performed

DIFFERENTIAL DIAGNOSIS

- In patients presenting with fever, rigors, altered mental status, and other non-specific symptoms, all other sources of infection must be ruled out as CA-ASB is diagnosed in >85% of patients with long-term catheter use
- Bladder tumor: Hematuria must be worked up, given increased risk of malignancy from long-term catheter use
- Bladder calculus: Associated with chronic urinary stasis
- Local inflammation: Vaginitis, urethritis, interstitial cystitis

TREATMENT

GENERAL MEASURES

- Prevention through early removal of urinary catheters is best preventative treatment
- Routine screening for and treatment of CA-ASB should be avoided (1)[A]
- Optimal duration of therapy is unknown, but typically ranges from 3 to 21 days depending on severity of symptoms (eg, cystitis, pyelonephritis, associated abscess, or bacteremia)
  - Most literature suggests 7–14 days of therapy for CA-UTI (1)[A]
  - 3-day regimen suggested in younger woman (<65 yr) in whom a catheter was recently removed (1)[B]
- Catheters placed >2 wk prior should be exchanged at time of diagnosis (prior to cultures being sent) to improve antimicrobial penetration and reduce bacterial concentrations (1)[A]
- When possible, antibiotic therapy should be culture driven to avoid exposure to additional antimicrobial agents

MEDICATION

First Line (2,3)

- Given incidence of polymicrobial colonization as well as involvement of both gram-positive and -negative organisms, no 1st-line agent can be recommended.
- Serious infections must be covered with broad-spectrum antibiotics and narrowed based on culture sensitivity patterns.
- Treatment of minor infections should be delayed until culture sensitivities are available to guide antimicrobial selection

Second Line

N/A

SURGERY/OTHER PROCEDURES

Rarely indicated, but may be necessary in cases of encrusted catheters, emphysematous, or abscess forming infections (see Section I: UTI, complex, adult)

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Antimicrobial coated catheters may delay detection of CA-ASB in short-term catheter use (<1 wk) (1)[B].
- Methenamine salts may reduce CA-ASB and CA-UTI in short-term catheter use (<1 wk) (1) [C].
- Cranberry products have not been shown to be effective in the prevention or treatment of infection in CA-UTI population (1)[A].
- Catheter irrigation has not been shown to prevent or treat CA-ASB or CA-UTI (1)[A].

ONGOING CARE

PROGNOSIS

- Generally good (4)
- Patient hospitalization lengths and costs are elevated when diagnosed with CA-ASB or CA-UTI
- Mortality rate among hospitalized patients with bacteremic UTI is ~13%; however, <1% of CA-ASB results in bacteremia.

COMPLICATIONS

Patients with indwelling catheter experience increased rates of bacteremia, upper tract inflammation and infection, catheter obstruction, urinary stone formation, fistula formation, urethral erosion, incontinence, and bladder cancer

FOLLOW-UP

Patient Monitoring

- Institutional education on indications for catheter use and reminder systems for early catheter removal such as nursing protocols, electronic reminders, chart and collection bag stickers
- Attention to and staff education to urologically essential catheters (eg, radical prostatectomy, etc)

Patient Resources

Medline Plus: Catheter Related UTI.
http://www.nlm.nih.gov/medlineplus/ency/article/000483.htm

REFERENCES

1. Hooten TM, Bradley SF, Cardenas DD, et al. Diagnosis, Prevention, and Treatment of

Catheter-Associated Urinary Tract Infections in Adults: 2009 International Clinical Practice Guidelines from the Infectious Disease Society of America. *Clin Infect Dis.* 2010;50:625–663.
2. Tambyah PA, Oon J. Catheter-associated urinary tract infection. *Curr Opin Infect Dis.* 2012;25:365–370.
3. Conway LJ, Larson EL. Guidelines to prevent catheter-associated urinary tract infectiorn: 1980 to 2010. *Heart & Lung.* 2011;41:271–283.
4. Gould CV, Umscheid CA, Agarwal RK, et al. ; Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol.* 2010;31:319–326.

ADDITIONAL READING

- CDC Health Care Associated Infections (HAIs) website: http://www.cdc.gov/HAI/ca_uti/uti.html
- Niel-Weise BS, van den Broek PJ, da Silva EM, et al. Urinary catheter policies for long-term bladder drainage. *Cochrane Database Syst Rev.* 2012;8:CD004201.
- Siddiq DM, Darouiche RO. New strategies to prevent catheter-associated urinary tract infections. *Nat Rev Urol.* 2012;9:305–314.

See Also (Topic, Algorithm, Media)

- Cystitis, General Considerations
- Pyelonephritis
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Complicated, Adult
- Urinary Tract Infection (UTI), Pediatric

CODES

ICD9

- 041.49 Other and unspecified Escherichia coli [E. coli]
- 599.0 Urinary tract infection, site not specified
- 996.64 Infection and inflammatory reaction due to indwelling urinary catheter

ICD10

- B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
- N39.0 Urinary tract infection, site not specified
- T83.51XA Infect/inflm reaction due to indwell urinary catheter, init

CLINICAL/SURGICAL PEARLS

- Advise against routine screening for CA-ASB due to increasing antimicrobial resistance and inappropriate use.
- Most important prevention is adherence to indications for catheter use and prompt removal when no longer indicated.
- When catheter use is unavoidable, it should be aseptically inserted, maintained with closed drainage system and removed as early as possible.

- When infection is suspected, culture specimen should be sent from a newly placed catheter or midstream voided specimen.
- Treatment should be driven by culture sensitivities and typically last 7–14 days.

URINARY TRACT INFECTION (UTI), COMPLICATED, ADULT

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BASICS

DESCRIPTION

- Complicated urinary tract infection (UTI) occurs in adults with functional or structural abnormalities of the genitourinary system who develop an infection. Associated abnormalities can include:
  - Structurally abnormal urinary tract (eg, BPH, kidney stones)
  - Functionally abnormal urinary tract (eg, neurogenic bladder, vesicoureteric reflux)
  - Impaired host defense (eg, immunosuppression/diabetes)
  - Increased bacterial virulence, multidrug-resistant organism
  - Children and pregnant women
  - Hospital-acquired infection (1)
- Patients with complicated UTI are more likely to harbor multiresistant pathogens, and whose infections are more difficult to eradicate (2).

EPIDEMIOLOGY

Incidence

- UTI accounts for 7 million physician visits annually and 100,000 hospital admissions.
- Complicated UTI is a wide spectrum; its incidence depends on age, sex, host, and environmental factors.

Prevalence

- For men, the lifetime prevalence of UTI is 14 per 100. Compared to women which is 53 per 100.
- The prevalence of asymptomatic bacteriuria, which makes host at risk for symptomatic episodes of complicated UTI
  - Patients with indwelling catheter: Approaches 100% based on timing.
  - Elderly nursing home residents: 50%
  - Patients with neurogenic bladder managed by clean intermittent catheterization: 30–40% (Table 1).

RISK FACTORS

- Male gender
- Elderly
- Hospital associated infection
- Pregnancy
- Diseases: Diabetes mellitus; history of recent UTI; diseases that cause immunosuppression or require treatment with immunosuppressive agents such as steroids
- Recent antimicrobial use
- Indwelling urinary catheter
- Recent urologic intervention

- Urinary tract obstruction (eg, kidney stones, benign prostatic hypertrophy [BPH], urethral stricture disease)
- Spinal cord injury with neurogenic bladder
- Azotemia caused by intrinsic renal disease

Genetics

- Six genes in humans have found to be associated with host response to infection predispose them to UTI
  – HSPA1B, CXCR1 & 2, TLR2, TLR4, TGF-β1

PATHOPHYSIOLOGY

- Primary UTI occurs via 1 of 3 routes (1):
  – Ascending by inoculation of urethra/urethral catheter with bowel flora: Most common
  – Hematogenous seeding of kidney
  – Lymphatic spread
- Structural, functional, or metabolic abnormalities allow infection of more uncommon pathogens, and increase the rate of therapy failure
- *Escherichia coli*, accounts for only approximately half of infections with complicated UTI, compared to uncomplicated (75–95%)
- A broader range of organisms can seen in complicated UTI, include *Proteus mirabilis* and *Klebsiella pneumoniae* as well as *Pseudomonas*, *Serratia*, *Providencia,* enterococci, staphylococci, and fungi (3)

ASSOCIATED CONDITIONS

- Diabetes mellitus (10%)
- Renal failure
- Multiple sclerosis
- Spinal cord injury

GENERAL PREVENTION

- Proper infection control practice in health care facilities to avoid contact transfer of resistant organisms between patients.
- Avoid over-treatment of asymptomatic bacteruria
- For patients with spinal cord injury, maintain a low bladder pressure to prevent reflux, ascending infections, and progression to renal failure. Monitoring of bladder pressure and function can be done with urodynamics testing
- Prevention of complicated UTI with long-term prophylaxis in at risk adult population is not recommended due to the emergence of resistant organisms (4)

DIAGNOSIS

HISTORY

- Assess for any of risk factors listed above.
  Clinical presentation may or may not be associated with clinical symptoms (eg, dysuria, urgency, flank pain, fever)
- Clinical presentation may vary from severe obstructive pyelonephritis with imminent urosepsis to catheter associated UTI, which disappears once the catheter is removed.

- Patients with spinal cord injuries can present with bladder, leg spasms, or autonomic dysreflexia.
- Patients with multiple sclerosis may present with fatigue or worsening neurologic function.
- Fever without localizing findings is a common presentation of UTI in patients with chronic indwelling catheters.

PHYSICAL EXAM

- Check vital signs to assess severity of infection, presence of systemic disease.
- Assess for suprapubic pain, flank pain, urethral discharge rectal exam for tenderness
- Evaluate for anatomical abnormalities, such as the presence of a nephrostomy tube, or an ileal conduit

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urinalysis
  - Pyuria is almost always present
  - Unless the collecting system is obstructed
  - White cell casts suggest a renal origin
- Urine culture is positive for a UTI with the following:
  - $\geq 10^5$ cfu/mL in mid-stream sample
  - $\geq 10^4$ cfu/mL in a straight catheter urine sample

Imaging

- Is recommended in patients suspected of complicated infection, especially in those not responding to therapy for 48–72 h, in patients with rapid recurrent infection and found to have bacteria susceptible to antimicrobial used (ie, persistence), when obstruction suspected, as well as history of kidney stones or has symptoms of renal colic
- Renal Ultrasound
  - For patients who could not be exposed to radiation
  - Cheap and readily available
  - Best to evaluate for hydronephrosis
  - Lack details and sensitivities of other imaging modalities
- Computed tomography (CT) urogram
  - The study of choice
  - Most sensitive in detecting abnormalities and able to delineate the extent of disease. Has 3 phases
    - No contrast—evaluate for renal or ureteral calculi, gas-forming infections, hemorrhage
    - Contrast—detect areas lacking perfusion due to infection induced ischemia
    - Delayed phase—detect for any filling defects such as fungus ball
- Magnetic resonance imaging (MRI)
  - Has no advantage over CT except in patients who wants to avoid contrast and radiation (3)

Diagnostic Procedures/Surgery

- Urologic evaluation is often necessary in the setting of a complex UTI
- Urinary obstruction associated with UTI must be relived emergently. e.g. placing a ureteral stent or nephrostomy tube for a obstructing ureteral calculus, or placing a Foley catheter for

urethral stricture.
- Cystoscopy allows direct visualization of bladder to assess for foreign body, ectopic ureters, diverticula, stones, or other abnormalities that could be a nidus for infection
- Post-void residual (PVR): Should be considered in men with baseline voiding symptoms; high residual with stasis increases risk of infection
- Localization studies: Selective cultures from each kidney via ureteral catheterization and prostatic cultures are helpful in identifying source of bacterial persistence.

Pathologic Findings
- In acute pyelonephritis—polynuclear leukocytes are seen throughout renal tubules, may form casts that can be seen in an urinalysis
- In chronic pyelonephritis, both lymphocytes and plasma cells are the predominant cells.

DIFFERENTIAL DIAGNOSIS
- For cystitis: Interstitial cystitis vs. urethritis
- For pyelonephritis:
  - Pancreatitis vs. appendicitis vs. diverticulitis vs. acute focal/multifocal nephritis
  - Urolithiasis

TREATMENT

GENERAL MEASURES

If severe infection or toxicity is present, CT should be obtained to rule out obstructive pyelonephritis; if found, decompression is critical.

MEDICATION

First Line
- Common oral antimicrobials:
  - Fluoroquinolones: More expensive (levofloxacin > ciprofloxacin), cover staphylococci and most gram-negatives including *Pseudomonas*
  - Trimethoprim-sulfamethoxazole: Resistance is often seen, therefore not recommended for empiric therapy (3)
- Commonly parenteral antimicrobials:
  - For those who have hemodynamic instability, or cannot tolerate oral therapy, or for patients with suspected resistant organisms
  - Gentamicin: Can cover Staphylococci, most gram-negatives including *Pseudomonas*; augments ampicillin for coverage in pyelonephritis
  - Cephalosporin
  - Carbapenem
  - Aminopenicillin PLUS a β-lactam inhibitor. Aminopenicillin by itself (eg, ampicillin) is not recommended for empiric therapy (3)
- For complicated pyelonephritis (1,5)
  - Renal/perirenal abscess is suspected if indolent/recurrent fever >72 h and/or persistently positive culture despite antimicrobial treatment; CT when suspect; if small renal abscess, then antimicrobial treatment; if large (>3 cm) renal abscess or perinephric abscess, then percutaneous drainage

– Inpatient therapy is recommended:
  - IV fluoroquinolone or ampicillin + gentamicin or 3rd-generation cephalosporin (3)
  - Duration without bacteremia: 2–3 days IV then 10–14 days PO antimicrobial
  - Duration with bacteremia: 7 days IV, then 10–14 days appropriate PO antimicrobial

Second Line

- Colistin: Reserved for extended-spectrum β-lactamase (ESBL)-producing bacteria that are resistant to gentamycin and carbapenems.
- Tigecycline: Has activity against ESBL-bacteria, but is unstable in urinary tract.

SURGERY/OTHER PROCEDURES

As needed for cause of complicated UTI, such as stone, foreign body, or enlarged prostate

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Cranberry juice and products have not been shown to reduce the risk of complicated UTI.

ONGOING CARE

PROGNOSIS

When appropriate antimicrobial therapy is chosen, complicating factors are identified and treated, and close follow-up is achieved with documentation of clearance of infection, a good prognosis is expected.

COMPLICATIONS

- More likely to occur in patients with comorbidities
- Acute complicated pyelonephritis can progress to emphysematous pyelonephritis, renal abscess, perinephric abscess, or papillary necrosis.
- Infections can spread to cause bone and joint infection, or endocarditis
- Renal failure in patients with spinal cord injury with recurrent sepsis

FOLLOW-UP

Patient Monitoring

Repeat urine cultures must be obtained because patients with complicated UTI are more at risk for recurrent infection

REFERENCES

1. Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders; 2012.
2. Neal DE. Complicated Urinary Tract Infections. *Urol Clin N Am*. 2008;35:13–22.
3. Hooton TM, Calderwood SB, Bloom A. Acute Complicated cystitis and pyelonephritis. UptoDate.com. Accessed January 2014.
4. Nicolle LE; AMMI Canada Guidelines Committee. Complicated urinary tract infection in

adults. *Can J Infect Dis Med Microbiol*. 2005:16(6):349–360.
5. Pallett A, Hand K. Complicated urinary tract infections: Practical solutions for the treatment of multiresistant Gram-negative bacteria. *J Antimicrob Chemother*. 2010;65(Suppl):iii25–33.

See Also (Topic, Algorithm, Media)
- Pyelonephritis
- Urethritis, Acute Male
- Urinary Tract Infection (UTI), Adult Female
- Urinary Tract Infection (UTI), Adult Male
- Urinary Tract Infection (UTI), Complicated, Adult Image ☼
- Urinary Tract Infection (UTI), Complicated, Pediatric

CODES

ICD9
- 592.0 Calculus of kidney
- 599.0 Urinary tract infection, site not specified
- 600.01 Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)

ICD10
- N20.0 Calculus of kidney
- N39.0 Urinary tract infection, site not specified
- N40.1 Enlarged prostate with lower urinary tract symptoms

CLINICAL/SURGICAL PEARLS

- Complicated UTI can have a wide range of atypical presentations, eg, MS patients with neurologic decompensation, spinal cord injury patients with spams or autonomic dysreflexia, or nursing home patient who has indwelling Foley with fever should be suspected of UTI.
- CT should be considered the imaging of choice, and with a low threshold with any history of stone, flank pain, or pyelonephritis not improving or persistent positive culture.
- Presence of obstruction on imaging requires urgent decompression.

URINARY TRACT INFECTION (UTI) COMPLICATED, PEDIATRIC

Christopher J. Long, MD
Douglas A. Canning, MD, FACS

BASICS

DESCRIPTION

- A complicated urinary tract infection (UTI) is an infection in the presence of abnormalities of metabolism, GU structure, or function
- There is an increased risk of therapy failure and patient morbidity and mortality.
- For recurrent UTI:
  - Unresolved: Incompletely treated infection
  - Reinfection: Infection by another organism
  - Persistent infection: Seeding from another site (ie, abscess)

EPIDEMIOLOGY

Incidence

- Highest incidence < 2-yr-olds
- Males/females < 1-yr-olds: 3–4%/2% develop UTI
- Males more likely to develop UTI in the first year of life then shifts to female predominance

Prevalence

Has not been delineated for each particular subpopulation/risk factor in the pediatric population

RISK FACTORS

- Previous UTI: 26% recur within 3 mo
- Metabolic abnormalities: Diabetes, pregnancy
- Impaired host response: Transplant, chemotherapy, HIV
  - Neonates < 90 days: Impaired immunity
- Structural anomalies
  - Calculi, renal cysts, abscess, pyelonephritis, bladder diverticulum
  - Urinary diversion, bladder augmentation
  - Posterior urethral valves, reflux, prune belly, bladder exstrophy, urogenital sinus
- Uncircumcised males 10× risk of UTI
- Neurogenic bladder
- Intermittent catheterization: Increases rate of bacteriuria
  - Single use, sterile catheters show no benefit

Genetics

- Polymorphisms of the interleukin-8 (IL-8) cytokine and decreased receptor expression increase risk for developing pyelonephritis
- Blood group antigen phenotype has been shown to play a role in UTI resistance
- Familial susceptibility to UTI
- Autosomal dominant inheritance of vesicoureteral reflux

- African Americans less likely to develop UTI when compared to whites, Hispanics

PATHOPHYSIOLOGY
- Fecal seeding of the perineum allows ascending infection of the GU tract
- Biofilm formation on stents or catheters
- Increased bladder pressure
  - Decreased bladder capacity
  - Compromised Foley catheter drainage
  - Dysfunctional voiding
- Bacteriology of *E. coli* increase affinity for GU tract: P fimbriae and MRHA (mannose-resistant hemagglutination)

ASSOCIATED CONDITIONS
- Urinary stasis increases risk of UTI
- Stents or catheters located within the GU tract act as a nidus for bacterial colonization
- Surgically correctable conditions of the GU tract
- Spina bifida (1)

GENERAL PREVENTION
- Antibiotic prophylaxis
  - Low-dose daily antibiotic
  - Healthy children have no proven benefit
  - Benefit for anatomic abnormality such as severe VUR
- Consider circumcision in boys <12 mo of age with GU tract anomalies
- Consider correction of vesicoureteral reflux (VUR) in females approaching puberty for increased risk of pyelonephritis during pregnancy
- Treatment of constipation and dysfunctional voiding

DIAGNOSIS

HISTORY
- Vague in infants and nonverbal children: Fever, irritability, poor feeding, vomiting, diarrhea, abdominal distention, new onset incontinence, jaundice.
- Older children: Dysuria, incontinence, voiding dysfunction, lower abdominal pain, enuresis
- Neurogenic bladder: Adominal pain, new onset back pain, new or worsening incontinence, pain with catheterization or urination, malodorous or cloudy urine
- Presence and severity of fever
- Previous UTIs and how documented (urine analysis, culture, how culture was obtained).
- Urinary stream, voiding history
- Previous GU/GI surgery
- Family history of infections and/or GU anomalies
- Prenatal history including ultrasounds

PHYSICAL EXAM
- Clinical signs of urosepsis
- Palpable bladder or kidneys, bladder or flank tenderness
- Foul smelling urine

- External genital anomalies: Labial adhesions, evidence of previous genital surgery
- Circumcision status

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Blood work: CBC, BMP, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin
  - Procalcitonin, CRP, ESR correlate with systemic illness and suggest pyelonephritis/sepsis
- Diagnosis: 2 or more symptoms, >100,000 CFU/mL of a single organism, and >10 WBC/HPF on urine microscopy
- Urinalysis (UA)
  - Leukocyte esterase, nitrite
  - Microscopy: WBC, bacteria
- Urine culture: obtained with UA
  - Consider lower threshold (>50,000 CFUs per mL) PLUS pyuria ± bacteriuria in some cases

Imaging

- Renal and bladder ultrasound: Assess hydronephrosis or incomplete bladder emptying
- Voiding cystourethrogram if not already performed
  - Document test of cure prior to study
- Renal cortical scan: Rule out scarring or pyelonephritis
  - Consider Gallium scan for complicated cases

Diagnostic Procedures/Surgery

- Catheterized or midstream specimen is preferred depending upon patient age
  - Suprapubic aspiration has highest accuracy but increases morbidity for patients
  - Bagged specimen not recommended
- Cystoscopy is rarely indicated
  - Can document bladder diverticulum, stones, etc., as source of UTI
- Specific intervention for GU anomalies (ie, treatment of reflux) once therapy is completed

Pathologic Findings

- *Escherichia coli* is the most common isolated organism although less so compared to uncomplicated UTI (45–51%)
- *Proteus, Pseudomonas,* and *Candida* are more commonly identified in complicated UTI
- Infants <90 days; *Enterococcus* and *Listeria* are most common organisms

DIFFERENTIAL DIAGNOSIS

- Younger children (<24 mo) presenting with fever: otitis media, gastroenteritis, upper respiratory tract infection
- Stone disease
- Urethritis
- Dysfunction voiding/elimination syndrome
- Pregnancy
- Appendicitis
- Bladder outlet obstruction

- Epididymitis
- Abuse

TREATMENT

GENERAL MEASURES (2,3)

- Antibiotic therapy after urine culture obtained
- Oral antibiotic therapy vs. IV antibiotics dependent upon severity of infection
  - Stratify by presence or absence of fever, concern for urosepsis, elevated WBC, etc.
- Duration of therapy 7–14 days
- Increased rate of resistant organisms

MEDICATION

First Line

- 3rd-generation cephalosporin ± aminoglycoside
  - Cefotaxime: 50–180 mg/kg/d (q4–6h)
  - Ceftriaxone: 50–75 mg/kg/d (q12–24h)
  - Ceftazidime: 90–150 mg/kg/d (q8–12h)
  - Aminoglycoside (gentamicin, tobramycin): 7.5 mg/kd/d (q8h)
    - *Enterococcus* resistance to 3rd-generation cephalosporins

Second Line

- Fluoroquinolones
  - Ciprofloxacin: 20–40 mg/kg/d (q8h)
    - Concern for cartilage damage limits its use in pediatric populations
- Carbapenem
- Combination therapy:
  - Aminoglycoside plus β-lactam inhibitor
  - Aminoglycoside plus fluoroquinolone

SURGERY/OTHER PROCEDURES

- Circumcision in boys with GU anomaly
- Correction of urologic anomaly if possible
- Removal of urinary stents or catheters if possible
- Video urodynamics to assess bladder emptying in particular if history of neurogenic bladder

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies (5)

- Targeted therapy for voiding dysfunction
  - Timed voiding, biofeedback
  - Anticholinergic medications for small, overactive bladder
- Pelvic floor therapy for detrusor sphincter dyssynergia
- Consider supressive antibiotics in selected cases: Nitrofurantoin 1–2 mg/kg PO daily, Sulfamethoxazole/trimethoprim (SMZ-TMP) 5–10 mg/kg SMZ,1–2 mg/kg TMP PO daily (Do not use nitrofurantoin or sulfa in children <6 weeks); Trimethoprim 1–2 mg/kg PO daily.

Ampicillin or amoxicillin not recommended due to resistance

Complementary & Alternative Therapies (4)

- Ensure adequate hydration
- At home urine tests for families for early detection of UTI
- Breast feeding has been shown to confer protection during immune compromised neonatal period
- Cranberry juice/supplements show little, if any, benefit in the adult population; no data in children
- Probiotics have not been shown to prevent UTI

ONGOING CARE

PROGNOSIS

- Dependent upon severity of infection (febrile vs. afebrile, pyelonephritis, degree of subsequent renal scarring)
- While a single UTI rarely has long term sequelae, recurrent infections place the kidney at increased risk for damage

COMPLICATIONS

- Urosepsis
- Pyelonephritis
- Hypertension (HTN)
- Loss of renal function, progression of renal scarring
- Compromise of renal transplant

FOLLOW-UP

Patient Monitoring

- Document test of cure with repeat urine culture
- Yearly blood pressure assessment
- Consider nephrology referral

Patient Resources

American Association of Pediatrics. http://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Detecting-Urinary-Tract-Infections.aspx

REFERENCES

1. Madden-Fuentes RJ, McNamara ER, Lloyd JC, et al. Variation in definitions of urinary tract infections in spina bifida patients: A systematic review. *Pediatrics*. 2013;132:132–139.
2. Younis N, Quol K, Al-Momani T, et al. Antibiotic resistance in children with recurrent or complicated urinary tract infection. *JNMA*. 2009;48(173):14–19.
3. Siomou E, Papadopoulou F, Kollios KD, et al. Duplex collecting system diagnosed during the first 6 years of life after a first urinary tract infection: A study of 63 children. *J Urol.* 2006;175(2):678–681.
4. Shortliffe LMD. Infection and Inflammation of the pediatric genitourinary tract. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders; 2012.

5. Nickavar A, Sotoudeh K. Treatment and prophylaxis in pediatric urinary tract infection. *Int J Prev Med.* 2011;2(1):4–9.

ADDITIONAL READING

Subcommittee on urinary tract infection, steering committee on quality improvement and management. Urinary tract infection: Clinical guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2013;128(3):595–610.

See Also (Topic, Algorithm, Media)

- Urinary Tract Infection, Pediatric
- Urinary Tract Infection (UTI), Complicated, Pediatric Image
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

- 590.80 Pyelonephritis, unspecified
- 599.0 Urinary tract infection, site not specified
- 771.82 Urinary tract infection of newborn

ICD10

- N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
- N39.0 Urinary tract infection, site not specified
- P39.3 Neonatal urinary tract infection

CLINICAL/SURGICAL PEARLS

- Complicated UTIs can lead to increased patient morbidity and mortality.
- Treatment plan should be tailored to the specific underlying contributing factors leading to UTI development.
- Prompt initiation of broad spectrum antibiotics after urine culture is obtained with subsequent tailoring of antibiotic therapy based on bacteria sensitivities is recommended in cases suspicious for urosepsis.
- Maintain a high degree of suspicion for potentially surgically correctable causes. Corrrection will likely decrease UTI risk.

URINARY TRACT INFECTION (UTI), PEDIATRIC

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BASICS

DESCRIPTION

- A urinary tract infection (UTI) represents inflammatory changes in the urinary tract caused by the presence of an infectious agent
- Spectrum of severity, from local infection to systemic changes/urosepsis

EPIDEMIOLOGY

Incidence

- 180,000 children annually will develop UTI in the United States
- 0.7% of all pediatric office visits each year (3.5–5% of emergency department visits)
- Overall 2% of febrile infants, 5% of all infants:
  - 21% of uncircumcised male infants
  - 5% of female infants
  - 2.3% of circumcised male infants

Prevalence

Prevalence is variable and closer to an adult level as age groups increase

RISK FACTORS

- Previous UTI:
  - ~25% of infants with a symptomatic UTI will have a recurrence
  - Older females may have a 40–60% risk of recurrent infection
- Immunosuppressive states, including diabetes, chemotherapy, and steroid use
- Anatomic and functional abnormalities of the urinary tract which predispose to urinary stasis:
  - Vesicoureteral reflux, ureterocele, ureteropelvic junction obstruction, bladder diverticula, posterior urethral valves
  - Neurogenic bladder, dysfunctional voiding/elimination behaviors (eg, constipation)
- Urologic instrumentation (catheters)
- Older children: Sexual activity
- Circumcision (1):
  - Uncircumcised males <1 yr of age have the highest rate of UTI of all gender and age groups (10 times higher than circumcised males)
  - AAP has stopped short of endorsing routine circumcision, but acknowledges apparent protective effect against UTIs and penile cancer
  - Consider circumcision in infant males with UTI

Genetics

- Incompletely understood
- Multifactorial, including altered carbohydrate secretion antigens on cell surface molecules

which may increase bacterial adherence

PATHOPHYSIOLOGY

- Usually ascending infections, although hematogenous spread can be seen in infants or immunocompromised populations
- Colonization of female introitus or male preputial epithelium with intestinal flora
- The most common pathogen *is Escherichia coli* (~85%)
- Other uropathogens include *Klebsiella, Proteus, Enterobacter, Citrobacter*, *Staphylococcus saprophyticus*, and *Enterococcus*
- Viral (eg, adenovirus, BK virus) and fungal *(Candida*) infections may be seen in immunocompromised patients
- Both humoral and cellular responses result in inflammation of the urinary tract
- Bacterial virulence factors include O antigen (part of lipopolysaccharide), K antigen (part of capsule), and P fimbriae contributes to bacterial ascent to the upper tracts, even in the absence of reflux

ASSOCIATED CONDITIONS

- Dysfunctional elimination including incontinence, holding or retention of urine, and constipation increase risk of UTI
- Immunocompromise
- Structural abnormalities of the GU tract

GENERAL PREVENTION

- Good voiding/elimination habits
- Treatment of constipation
- Identification and treatment of underlying urologic conditions which may predispose to urinary stasis

DIAGNOSIS

HISTORY

- Vague in infants:
  - Symptoms: Fever, irritability, poor feeding, vomiting, diarrhea, abdominal distention, foul-smelling urine
  - Older children may complain of dysuria, incontinence, changes in voiding habits, flank or abdominal pain, enuresis
- Presence, severity, and duration of fever
- Previous UTIs and how documented (eg, culture, urinalysis, symptoms)
- Prenatal history including prenatal ultrasounds
- Previous GU/GI surgery
- Family history of infections and/or GU anomalies

PHYSICAL EXAM

- Specific findings in infants are rare; may see fever, failure to thrive, jaundice, or lethargy
- Older children may have suprapubic, flank, abdominal and/or upper quadrant tenderness
- CVA tenderness suggests pyelonephritis
- A scrotal exam will help rule out epididymitis

- Careful external genital exam to rule out trauma, local irritation, urethral discharge, phimosis, and anatomic abnormalities
- Circumcision status
- Palpable abdominal or flank mass (eg, severe hydronephrosis or distended bladder)

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis (2):
  - Microscopic exam after dipstick urine analysis increases the test's sensitivity and specificity. It can also yield clues to contamination (epithelial cells)
  - Positive leukocyte esterase (indicates WBCs in the urine) is up to 95% sensitive in children with symptoms
  - Positive nitrite (many gram-negative bacteria produce this substance) has a sensitivity of 30–45%, but a specificity that nears 100%
  - Combined positive nitrite-leukocyte esterase 80–90% sensitive and 60–98% specific
  - >10 WBCs per HPF on an unspun specimen or >5 WBCs on a spun sediment is usually indicative of infection
  - Identification of bacteria on Gram stain has a sensitivity and specificity better than that of a dipstick evaluation for nitrite and leukocyte esterase
- Urine culture is the gold standard to diagnose UTI (2):
  - >100,000 CFU/mL on a voided or catheterized specimen, and any bacteria on a suprapubic aspirate is generally considered a positive culture
  - Lower colony counts in symptomatic children, or growth of pathogenic bacteria (eg, *Klebsiella, Pseudomonas*) should also be treated
  - In non-toilet trained children, >50,000 CFU/mL of a single pathogen is also consistent with UTI
- Blood tests are unreliable in diagnosing UTI
- Asymptomatic bacteriuria (no symptoms, <5 WBC/hpf, but positive culture) should prompt treatment if a pathogenic organism is present

Imaging

- The need for and timing of imaging following UTI remains controversial; it is not required in the acute setting, but may be indicated at follow-up
  - Consider evaluating all children <5 yr after their 1st documented UTI; and all girls, regardless of age, with febrile or recurrent infections, particularly with voiding dysfunction
  - Renal/bladder US should be considered following a febrile UTI
  - Need for and timing of VCUG is controversial: The American Academy of Pediatrics (AAP) recommends VCUG after second febrile UTI unless there is a suspicion of underlying anatomic abnormality (3), while most pediatric urologists recommend VCUG following first febrile UTI
- 40% of children with a single febrile UTI have VUR
- Absence of clinical improvement after 48 h of appropriate treatment should raise concern for structural or functional abnormalities
- DMSA scan may reveal renal inflammation in acute pyelonephritis and/or scarring from previous infections

- Older girls with recurrent cystitis in the absence of voiding dysfunction should be evaluated with pre- and post-void renal and bladder sonography (4)
- In toilet-trained children in whom voiding dysfunction may be a factor, assessment of voiding patterns (eg, uroflow) may be helpful

Diagnostic Procedures/Surgery

None specific, though cystoscopy may be performed for associated conditions or chronic infections as indicated

Pathologic Findings

- Cystitis and pyelonephritis are generally associated with inflammatory response
- Renal scarring may be manifested by architectural changes including collagen deposition and glomerular loss

DIFFERENTIAL DIAGNOSIS

- UTIs present similarly to other infections:
  - Bacteremia and sepsis
  - Epididymitis
  - Gastroenteritis
  - Sexual abuse
  - STD/STI in a sexually active child
  - Vaginitis
- Also consider: Appendicitis, diabetes, dysfunctional voiding/elimination, pregnancy in postpubertal females, urolithiasis, urinary obstruction

ALERT

Findings suggestive of an STI/STD infection should raise concern for sexual abuse

TREATMENT

GENERAL MEASURES

- Initial, empiric treatment should be based on clinical suspicion of UTI as well as reliability of patient and family
- As the symptoms are often vague, a high index of suspicion must be maintained to ensure early detection of pyelonephritis
- Hospitalization might be required based on patient age and clinical status, although infants >2 mo and nontoxic children with suspected pyelonephritis can be treated as outpatients as long as compliance is not an issue
- Children with asymptomatic bacteriuria may not require treatment with antibiotics if the urinary system is otherwise normal

MEDICATION

ALERT

- In children, use 7–14 day treatment course (<7 days has been shown to be inferior).
- Fluoroquinolones should not be a 1st-line choice and are limited to resistant organisms.
- Nitrofurantoin has poor tissue penetration and should not be used for suspected pyelonephritis.

- Age of child and comorbid conditions should be considered when selecting antibiotics.

First Line

- Infants <2 mo (IV therapy preferred)
  - Ampicillin Neonates <7 d. 50–100 mg/kg/24 h IV ÷ q8h Term infants.75–150 mg/kg/24 h ÷ q6–8h IV Children >1 mo. 200 mg/kg/24 h ÷ q6h IM or IV
  - Gentamicin Infants <7 d <1200 g. 2.5 mg/kg/dose q18–24h.Infants >1200 g: 2.5 mg/kg/dose q12–18h. Infants >7 d: 2.5 mg/kg/dose IV q8–12h. Children: 2.5 mg/kg/d IV q8h; ↓ w/ renal Insufficiency
  - 3rd-generation cephalosporin
- Cefixime: 8 mg/ kg/d PO ÷ daily-bid; ↓ w/ renal impairment
- Cefdinir: 7 mg/kg PO bid or 14 mg/kg/d PO; ↓ in renal impairment
- Ceftibuten: 9 mg/kg/d PO; ↓ in renal impairment; take on empty stomach (susp)
- Children >2 mo
  3rd-generation cephalosporin: Cefixime, Cefdinir, Ceftibuten
- Children <2 yr of age should be treated with therapeutic doses (IM, IV, PO, or combination)
- School-aged children without systemic signs may be treated with an oral broad-spectrum antibiotic such as SMZ-TMP, nitrofurantoin
- Appropriate to start broad-spectrum antibiotics while awaiting culture results (5)

Second Line

Antibiotic course should be tailored by comorbidities, age, and local bacterial resistance patterns

SURGERY/OTHER PROCEDURES

- May be indicated following resolution of infection if child has specific urinary abnormalities predisposing to or exacerbating effects of urinary tract infection (eg, obstruction, VUR)
- Surgical correction of reflux is aimed at protecting upper tracts and is associated with a decrease in the number of febrile UTIs

ADDITIONAL TREATMENT

- In children with UTI and dysfunctional voiding/elimination behaviors, improvement in the latter will often result in fewer recurrent UTIs
- Regular (eg every 2 h) voiding
- Avoidance of constipation

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

- Cranberries may be effective in decreasing bacterial adherence, but there are no specific recommendations for children at present
- Probiotics may favorably alter gastrointestinal flora, but again there are no specific recommendations for use

ONGOING CARE

PROGNOSIS

- Most children do not have any long-term sequelae from a single UTI
- Prompt, efficacious treatment can prevent systemic sequelae
- Recurrence is common, especially in those with anatomic/functional abnormalities
- Identification of predisposing and comorbid factors may help prevent recurrent UTI

COMPLICATIONS

- Renal insufficiency/failure: Renal scarring in ~8% of children overall
- Urosepsis

FOLLOW-UP

Patient Monitoring

- If scarring is present, consider a nephrology consult to monitor for evaluation of HTN, proteinuria, and renal insufficiency
- Patients with a history of UTI may be more likely to develop UTIs and toxemia during pregnancy (CITE)

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
http://kidney.niddk.nih.gov

REFERENCES

1. American Academy of Pediatrics Task Force on Circumcision. Male circumcision. *Pediatrics*. 2012;130:e756.
2. Shaikh N, Morone NE, Lopez J, et al. Does this child have a urinary tract infection? *JAMA*. 2007;298:2895.
3. Newman TB. The new American Academy of Pediatrics urinary tract infection guideline. *Pediatrics*. 2011;128:572.
4. Bauer R, Kogan B. New developments in the diagnosis and management of pediatric UTIs. *Urol Clin N Am*. 2008;35:47–58.
5. Sedberry-Ross S, Pohl H. Urinary tract infections in children. *Curr Urol Rep*. 2008;9:165.

ADDITIONAL READING

Urinary Tract Infection: Clinical Practice Guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595–610.

See Also (Topic, Algorithm, Media)

- Urinary Tract Infection (UTI), Complicated, Pediatric
- Urinary Tract Infection, Pediatric Algorithm
- Vesicoureteral Reflux, Pediatric

CODES

ICD9

- 041.49 Other and unspecified Escherichia coli [E. coli]
- 599.0 Urinary tract infection, site not specified

- 771.82 Urinary tract infection of newborn

ICD10

- B96.20 Unsp Escherichia coli as the cause of diseases classd elswhr
- N39.0 Urinary tract infection, site not specified
- P39.3 Neonatal urinary tract infection

CLINICAL/SURGICAL PEARLS

- A high index of suspicion is often required for an accurate diagnosis of UTI, especially in nonverbal children.
- Treatment of the acute infection should be tailored to the child's age, comorbidities, and clinical condition, as well as local antibiotic resistance patterns and culture results.
- Surgical intervention is undertaken when conservative management is unlikely to prevent further UTIs and/or protect the kidneys.
- Patients with recurrent febrile infections, VUR, and/or kidney scarring should be followed carefully for development of renal disease.

UROLITHIASIS, ADULT, GENERAL

Margaret S. Pearle, MD, PhD, FACS
Jodi A. Antonelli, MD

BASICS

DESCRIPTION

- Concretion that occurs in the urinary tract
- May be asymptomatic but can also be associated with mild to severe symptoms

EPIDEMIOLOGY

Incidence

- Peak incidence: 4th–6th decades of life
- More common in Caucasians than in Hispanics, Asians, or African Americans
- More common in men; increasing in women

Prevalence

- Prevalence in US adults is 8.8% (10.6% for men, 7.1% for women) (1)[A]
- Prevalence gradient increases from North to South and West to East

RISK FACTORS

- Personal or family history
- Hot, arid, or dry climate
- Obesity and weight gain
- Low fluid intake, dehydration
- Diets high in sodium, animal protein, oxalate
- Comorbidities: chronic diarrheal states, GI surgery, gout, diabetes, recurrent UTIs hyperparathyroidism, cystinuria, type 1 renal tubular acidosis, sarcoidosis
- Anatomic anomalies: Ureteropelvic junction obstruction, horseshoe kidney, caliceal diverticula, medullary sponge kidney

Genetics

- Multiple genetic polymorphisms may contribute to calcium stone formation
- Heritable disorders: Primary hyperoxaluria, cystinuria, Lesch–Nyhan syndrome, xanthinuria, type I renal tubular acidosis

PATHOPHYSIOLOGY

- Most common stone—calcium oxalate (60%)
- Calcium (Ca) stones—occur in settings of hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitrituria
- Hypercalciuria—urine Ca >200 mg/d
  - Absorptive hypercalciuria—Increased intestinal absorption of Ca
  - Renal hypercalciuria—Impaired renal reabsorption of Ca
  - Resorptive hypercalciuria—Primary hyperparathyroidism, rare cause is sarcoidosis
- Hyperoxaluria—Urine oxalate >40 mg/d
  - Primary hyperoxaluria—Excess endogenous oxalate production

  - Enteric hyperoxaluria—Increased intestinal absorption of oxalate
  - Dietary hyperoxaluria—Overindulgence in oxalate-rich foods, Ca restriction, excess vitamin C supplementation, reduced *Oxalobacter formingenes* (oxalate-degrading intestinal flora)
- Hyperuricosuria—Uric acid (UA) >600 mg/d
  - Causes: excess animal protein intake, gout, myelproliferative disorders
  - Urine pH <5.5—Uric acid or calcium stones
  - Urine pH >5.5—Ca oxalate stones
- Hypocitriuria—Urine citrate <320 mg/d
  - Citrate inhibits Ca stone formation
  - Low urine citrate occurs in states of acidosis—Renal tubular acidosis, chronic diarrhea
- Uric acid stones—Radiolucent
  - Congenital causes—Disorders of renal tubular urate transport, disorders of UA metabolism
  - Acquired causes—Obesity, high animal protein intake, volume depletion
- Cystine stones
  - Cystinuria—Inherited disorder of impaired renal absorption of cystine
- Infection stones—Composed primarily of magnesium, ammonium, and phosphate
  - Alkaline urine produced by urease-splitting bacteria—*Proteus* (most common), *Klebsiella*, *Pseudomonas*, *Staphalococcus*
- Miscellaneous stones
  - Xanthine—Radiolucent, inherited disorder of the enzyme (XDH) that catalyzes xanthine to UA, another cause—high-dose Allopurinol use
  - Ammonium acid urate—Associated with laxative abuse, inflammatory bowel disease (IBD), ileostomies
  - Matrix—Typically radiolucent, associated with infection, may contain protein
  - Medication-related—Indinavir (not visible on x-ray or CT), triamterene (radiolucent), topiramate, and carbonic anhydrase inhibitors (calcium phosphate stones)
- Stones in pregnancy
  - Overall risk similar to non-gravid women
  - Majority occur in 2nd–3rd trimester
  - Physiologic hydronephrosis may promote crystallization through urinary stasis
  - Hypercalciuria is enhanced by placental production of vitamin D

ASSOCIATED CONDITIONS

- Chronic diarrheal states: GI surgery: gastric bypass/banding, small bowel resection
- Hyperparathyroidism
- Gout
- Sarcoidosis
- Primary hyperoxaluria
- Cystinuria
- Type I renal tubular acidosis
- Medullary sponge kidney

GENERAL PREVENTION

- Hydration
- Dietary limitation of animal protein (all types), sodium, and oxalate (chocolate, nuts,

brewed tea, spinach, rhubarb, potatoes, beets); maintenance of recommended daily allowance of calcium (~1 g)
- Keep vitamin C intake low

DIAGNOSIS

HISTORY
- Can be asymptomatic
- Personal/family history of kidney stones
- Gross hematuria
- Pain—Flank, abdomen, ipsilateral groin
  - Renal colic—Pain in flank/abdomen that occurs in waves
  - Acute colic may suggest obstruction
- Nausea/vomiting—may suggest obstruction

PHYSICAL EXAM
- Can be unremarkable
- Elevated heart rate and blood pressure—pain
- Febrile, tachycardic, hypotensive
- Abdominal/CVA tenderness
- Costovertebral angle tenderness

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Urinalysis—Microhematuria, pyuria
- Crystalluria—Hexagonal (cystine), coffin-lid (MAP), dumbell (Ca oxalate monohydrate)
- Leukocytosis/leukopenia—Inflammation and/or infection
- Elevated serum creatinine—Bilateral obstruction or solitary kidney

Imaging
- Non-contrast CT of abdomen and pelvis—Gold standard to identify urinary stones
  - Low-dose protocol limits radiation exposure
  - Provides additional anatomic information: Hydronephrosis, kidneys and other viscera
- Plain radiography: Not as sensitive or specific as CT for stones, useful for follow-up
- Ultrasound—Often difficult to visualize adult ureters, first-line for pregnant women, consider transvaginal ultrasound for pregnant women
- Intravenous pyelogram (IVP)—Assesses anatomy of collecting system, renal function, obstruction; limited availability, must give IV contrast; CT urography generally replaces this
- MRI—Poor for stones of all types; some value in pregnant women but data are limited

Diagnostic Procedures/Surgery
Endoscopic procedures are both diagnostic and therapuetic

Pathologic Findings
Stone analysis—Ca oxalate monohydrate or dihydrate, Ca phosphate, uric acid, cystine, struvite, matrix, mixed

DIFFERENTIAL DIAGNOSIS
- Any of the following causes may be confused with pain related to urolithiasis:

- Vascular: Abdominal aortic aneurysm, mesenteric ischemia
- Gastrointestinal: Appendicitis, bowel obstruction, cholecystitis/biliary colic, constipation, diverticulosis/diverticulitis, gastritis, pancreatitis, peptic ulcer
- Gynecologic: Ectopic pregnancy, tubo-ovarian abscess, ovarian torsion/cyst rupture
- Musculoskelet al—Back pain
- Urologic: Pyelonephritis, urinary tract infection, sloughed renal papilla, ureteropelvic junction obstruction

TREATMENT

GENERAL MEASURES

ALERT
Fever, leukocytosis/leukopenia, tachycardia, hypotension, tachypnea, bacteriuria, and/or pyuria with upper tract stone is life-threatening; treat with renal decompression (ureteral stent or nephrostomy tube)

- Conservative therapy
  - Hydration, analgesia, medical expulsive therapy (best evidence for alpha-blockers)
  - % passage with conservative measures
    - 80%—Stone 2–3 mm
    - 50%—Stone 4–5 mm
    - 20%—Stone 7–8 mm
  - Strict instructions to return for fevers, worsening pain, unable to tolerate oral fluids
- Relative indications for intervention
  - Large stone burden—Staghorn or partial staghorn or large ureteral stone
  - Stone location—Renal pelvis, ureter
  - Concern for infection; severe pain
  - Unable to tolerate oral fluids
  - Renal deterioration, solitary kidney
  - Repeated presentations to emergency room

MEDICATION

First Line

- Analgesia—anti-inflammatory (ibuprofen, ketorolac), acetaminophen, narcotic
- Antibiotics
  - Infection or positive urine culture (Empiric ciprofloxin, adjust based on culture results)
  - Prophylactic
    - Lower tract: Cysto stone manipulation
      - *Fluoroquinolone or Trimethoprim sulfamethoxazole
    - Upper tract: Percutaneous renal surgery:
      - *1st/2nd-generation cephalosporin, aminoglycoside + metronidazole or clindamycin
    - Upper tract: Ureteroscopy (all patients) or ESWL with risk factors
      - * Fluoroquinolone or trimethoprim sulfamethoxazole
- Medical expulsive therapy
  - α-Blockers: Increase stone passage, reduce time to stone passage, reduce pain

- Tamsulosin 0.4 mg PO QD (2)[A]

- Directed at metabolic abnormality
  - Hypercalciuria: Thiazide or thiazide-like diuretic with potassium citrate/chloride (avoids hypokalemia)
    - Hydrochlorothiazide: 50 mg/d or 25 mg BID
    - Chlorthalidone: 25–50 mg/d
    - Indapamide: 1.25–2.5 mg/d
  - Low urine pH, low citrate
    - Potassium citrate: 20–60 mEq/d in 2–3 divided doses with meals to desired level of urinary citrate
  - Cystinuria: Tiopronin 200 mg BID and titrate to 200–300 BID or TID with potassium citrate or sodium bicarbonate (goal urine pH of 7.5).
  - Uric acid: Allopurinol 100–300 mg/d if dietary measures fail to reduce elevated serum UA
  - Dissolution therapy
    - Alkalinize urine with potassium citrate 40–60 mEq individed doses or sodium bicarbonate 1300 mg BID
      *Uric acid: Goal urine pH of 6.5
      *Cystine: Maintain urine pH >7.0–7.5

Second Line

Antiemetics if colic is associated with nausea

SURGERY/OTHER PROCEDURES

- Preoperative urine culture should be negative or appropriately treated prior to surgery
- Excorporeal shockwave lithotripsy (ESWL)—70% successful with 1 treatment, best when stones <2 cm in the kidney (not lower pole) and proximal ureter
- Ureteroscopy with laser lithotripsy (URS)—80–90% successful for ureteral stones and kidney stones <1.0 cm
- Percutaneous nephrolithotomy (PCNL)—large (≥2 cm) renal or proximal ureteral stones
- Ureteral calculi (3)[A]
  - <10 mm—surveillance, URS, or SWL
  - ≥10 mm—URS or SWL
- Renal calculi
  - <2 cm—SWL (not lower pole), URS, PCNL
  - ≥2cm—PCNL is treatment of choice

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Avoid future episodes: Hydration (≥2 L/24 h)

Complementary & Alternative Therapies

None

ONGOING CARE

PROGNOSIS

- First-time stone-formers have a 50% chance of recurrent calculi within 5 yr
- Dietary modifications and medical therapy tailored to metabolic abnormality can prevent recurrence in 75% of patients and reduce new stone formation in 98% of patients

COMPLICATIONS

- Potential renal function deterioration after 4–6 wk of untreated urinary tract obstruction
- Surgical treatment of urinary stones carries risks of bleeding, infection, injury to urinary tract (ie, ureteral strictures, ureteral perforation)
- Pneumothorax and/or hydrothorax can occur with percutaneous renal access (especially above the 12th rib)

FOLLOW-UP

Patient Monitoring

- Low risk—Inactive stones, first-time formers without risks (family history, GI/bone disease, gout, obesity, diabetes)
  - – Screening evaluation—Diet/medical history, serum studies (Cr, K, CO_2, Ca, P, UA, iPTH), stone analysis, urine culture or
  - – Conservative therapy
- High risk—Recurrent/active formers, children/adolescents, solitary kidney, first-time former with risks listed above
  - – Screening evaluation as above
  - – Two 24-h urine collections

Patient Resources

AUA Urology Care Foundation. http://www.urologyhealth.org/urology/index.cfm?article=148

REFERENCES

1. Scales CD Jr, Maalouf NM, Pearle MS, et al. Prevalence of kidney stones in the US. *Eur Urol.* 2012;62(1):160–165.
2. Hollingsworth JM, Rogers MA, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: A meta-analysis. *Lancet.* 2006;368:1171.
3. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. *J Urol.* 2007;178(6):2418–2434.

ADDITIONAL READING

- Bagga HS, Chi T, Miller J, et al. New insights into the pathogenesis of renal calculi. *Urol Clin North Am.* 2013;40(1):1–12.
- Goldfarb DS, Arowojolu O. Metabolic evaluation of first-time and recurrent stone formers. *Urol Clin North Am.* 2013;40(1):13.
- Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: Diagnosis and treatment recommendations. *J Urol.* 2005;173(6):1991.

See Also (Topic, Algorithm, Media)

- Metabolic Stone Evaluation (24 Hour Urine Studies)
- Urolithiasis, Adult, General Considerations Images
- Urolithiasis, Renal
- Urolithiasis, Ureteral
- Urolithiasis, Calcium Oxalate/Phosphate
- Urolithiasis, Cysteine and Cystinuria (Hypercystinuria)
- Urolithiasis, Staghorn
- Urolithiasis individual topics (Section II)

CODES

ICD9

- 592.0 Calculus of kidney
- 592.1 Calculus of ureter
- 592.9 Urinary calculus, unspecified

ICD10

- N20.0 Calculus of kidney
- N20.1 Calculus of ureter
- N20.9 Urinary calculus, unspecified

CLINICAL/SURGICAL PEARLS

- The most important measure to avoid future stones is adequate hydration ($\geq$2 L/d).
- Upper urinary tract stone with UTI requires decompression with stent or nephrostomy tube.
- Preoperative urine culture should be negative or treated prior to definitive surgical treatment.
- Medical management can significantly reduce risk of future stones.
- Urinary stones in a solitary kidney should be treated aggressively.

UROLITHIASIS, CALCIUM OXALATE/PHOSPHATE

John J. Pahira, MD

BASICS

DESCRIPTION

- Deposition of calcium salts in the urinary tract may result in a urinary calculus.
- Ca oxalate in its pure form or mixed with Ca phosphate (hydroxyapatite) is the most common type of calculus in industrialized countries.

EPIDEMIOLOGY

Incidence

- US annual stone incidence: 16.4/10,000
- Male > Female (3:1–2.0)
- Age of peak incidence: 20–40 yr
- 1 in 8 men, 1 in 20 women lifetime risk
- Stone incidence by composition: Ca oxalate 30–56%; mixed Ca oxalate and Ca phosphate: 11–31%

Prevalence

- 10–15% US prevalence of stones
- Lifetime prevalence of kidney stone disease is estimated at 1–15%, with the probability of having a stone varying according to age, gender, race, and geographic location.

RISK FACTORS

- See also Section II: "Urolithiasis, Risk Factors"
- Intrinsic: Polygenic defect; hypercalciuria inherited as autosomal dominant trait; white males; other illnesses: (IBD, etc.), elevated PTH, medullary sponge kidney, recurrent UTI
- Anatomic: UPJ obstruction, horseshoe kidneys
- Extrinsic risk factors: Geography/climate
- Diet: Elevated dietary protein, oxalates, refined sugars, and Ca, and low fiber intake; high salt intake increases Urinary Calcium (UCa)
- Water intake: Low consumption increases risk
- Occupation: Sedentary occupations

Genetics

- Ca oxalate: Multifactorial; hypercalciuria an autosomal dominant trait
- Idiopathic hypercalciuria: 5–10% of normals and 30–60% with Ca nephrolithiasis
- Familial tendency to form stones

PATHOPHYSIOLOGY

Hypercalciuria may be heterogeneous.

- Normocalcemic hypercalciuria (idiopathic hypercalciuria): 30–60% of Ca oxalate stones
- AH: Intestinal hyperabsorption of Ca:
  - Hypercalciuria: Increased filtered load and decreased renal tubular reabsorption due to decreased PTH

- Renal loss of Ca compensates for absorption, maintains normal (SCa)
  - Hypercalciuria: >4 mg/kg weight/24 hr on random diet (>250 mg/24 hr), *OR* >200 mg/24 hr after 1 wk diet to 400 mg Ca and 100 mEq Na/d (1)
  - AH type I: Uncommon, most severe form; persistent hypercalciuria >250 mg/24 hr on random diet or restricted diet with normal SCa and normal or slightly decreased PTH level; 2-hr fasting UCa normal.
  - AH type II: Most common, mild form; hypercalciuria >250 mg/24 hr on random diet but normo-calciuria on Ca/Na-restricted diet, normal SCa and PTH
  - AH type III: Vitamin D–dependent hypercalciuria, renal phosphate "leak"; low serum phosphate, elevated urinary phosphate, and Ca-enhanced Vitamin D_3 synthesis by the kidney leads to increased intestinal Ca absorption
- Renal hypercalciuria (renal leak):
  - Impaired renal tubular reabsorption of Ca; decreased in SCa; elevated PTH; elevated vitamin D_3, and increased intestinal hyperabsorption
  - SCa normal, mild secondary elevated PTH
  - UCa elevated on both random and restricted diets; 2-hr fasting UCa elevated
- Resorptive hypercalciuria:
  - Primary elevated PTH; elevated SCa and UCa secondary to increased PTH secretion, causing excessive resorption of bone and an increased intestinal absorption of Ca due to increased PTH and increased renal synthesis of vitamin D3
  - 2-hr fasting UCa is elevated
- Unclassified hypercalciuria:
  - Hypercalciuria with normal SCa, normal PTH, and elevated 2-hr fasting UCa
  - Na cellulose phosphate may help distinguish AH by eliminating problem of inadequate dietary preparation prior to fast and load Ca studies; renal hypercalciuria by reducing the suppressive effect of absorbed Ca on parathyroid stimulation
- Other causes Ca oxalate stones:
  - Hyperuricosuria (urinary uric acid >600 mg/24 hr); only abnormality in 10% of Ca stones; up to 40% of Ca stone-formers with other physiochemical abnormalities
  - May initiate Ca oxalate stones by direct induction of heterogeneous nucleation of Ca oxalate crystals, or by absorption of certain macromolecular inhibitors
- Hyperoxaluria:
  - Urinary oxalate >45 mg/24 hr
  - Mild hyperoxaluria (45–80 mg/24 hr) is as important a risk factor for idiopathic Ca oxalate stones as hypercalciuria and is found in 37% of patients with Ca oxalate stones
  - Activity of stone disease correlates better with level of urinary oxalate than Ca.
  - Most common: Intestinal hyperabsorption of oxalate: Intestinal resection (enteric hyperoxaluria), IBD, celiac, gastric/small bowel resection; JI bypass
  - Bile salts and fatty acids increases large-bowel oxalate absorption.
  - Fat malabsorption causes Ca to complex with bile acids and form Ca soap, which decreases free Ca in the intestinal lumen, which can complex with oxalate, and decrease oxalate for absorption.
  - Stone formation due to hyperoxaluria but also contributed to by low-volume urinary output, low citrate secondary to hypokalemia, chronic metabolic acidosis

  - Low magnesium levels may be secondary to intestinal malabsorption.
  - Primary hyperoxaluria type I:
    - Autosomal recessive, defect of AGT
    - Elevated urinary oxalic, glycolic, glyoxylic acids
    - Clinically, nephrocalcinosis, tissue deposition of oxalate, and renal failure, with death by age 20 yr if untreated
    - 2/3 have undetectable AGT on liver biopsy; glyoxylate oxidized to oxalate
  - Primary hyperoxaluria type II:
    - Rare (21 cases) deficiency of d-glycerate dehydrogenase and glyoxylate reductase
    - Elevated urinary oxalate and glycerate; nephrocalcinosis and renal failure
  - Dietary hyperoxaluria:
    - Excess oxalate-rich foods (dark green vegetables, tea, nuts, concentrated fruit juices, chocolate); vitamin C >1000 mg/d
  - Pyridoxine (vitamin B_6) deficiency, ethylene glycol toxicity, hepatic conversion to glycoaldehyde and glycolic acid, methoxyflurane anesthesia, converted in liver to oxalate
  - Hypocitraturia:
    - Citrate <220 mg/24 hr; sole abnormality in 10%; 15–60% with other Ca stones causes
    - Acidosis most important factor in hypocitraturia; decreases urinary citrate secondary to increased renal tubular reabsorption and decreased synthesis
    - Causes of metabolic acidosis: IBD, chronic diarrhea; thiazide-induced hypokalemia, and intracellular acidosis; purine-rich diet (high acid-ash); strenuous exercise (lactic acid); RTA (type I, distal); increased Na intake. UTI with bacteria-degrading citrate decreases urinary Ca salts by forming soluble complexes with Ca.
- Hypomagnesuria:
  - Urinary Mg <50 mg/24 hr; coexists with hypocitraturia in 2/3 and with low urine volume (<1 L/24 hr) in 40%
  - Pathogenesis is not known; may be dietary (IBD and malabsorption)

ASSOCIATED CONDITIONS
IBD, chronic pancreatitis, chronic diarrhea, elevated PTH, medullary sponge kidney, UTIs

GENERAL PREVENTION
See “General Measures” below

DIAGNOSIS
HISTORY
- See “Flank Pain” and “Urolithiasis, General.”
- Review stone history, family history, and the intrinsic and extrinsic risk factors noted earlier

PHYSICAL EXAM
See “Flank Pain” and “Urolithiasis, General.”

DIAGNOSTIC TESTS & INTERPRETATION
Lab (1)
- Abbreviated protocol for low-risk single-stone formers (history, dietary habits, basic metabolic panel including Ca, PTH, and uric acid, urinalysis/pH, radiologic imaging, stone

analysis)
- A comprehensive metabolic evaluation (with Ca fast/ load test) in recurrent stones and increased stone risk can be replaced by a simple evaluation (metabolic panel and 1–2 24-hr urines):
  – 24-hr urine (volume, Ca, Cr, oxalate, citrate, Na, phosphate, magnesium, pH, uric acid, sulfate)
  – Data best on a diet at least 1 month after stone passage or 1 wk after IVP studies
  – D/C drugs that may affect the tests (vitamins, antacids, diuretics, allopurinol, etc.)

Imaging
- CT: Most sensitive
- US, KUB, Excretory Urography (ExU)
- MRI not useful for calcifications/urinary calculi

Diagnostic Procedures/Surgery (2)
- In deciding which stone-formers require a metabolic evaluation consider the following:
  – 80–90% have predisposing urinary abnormality or underlying disease identified.
  – Treatment program is to be maintained for life.
  – 50–60% patients pass only 1 stone/lifetime.
  – Involve your patient in the decision to perform a workup; explain risk and benefits.
- Criteria for metabolic evaluation:
  – Anatomic abnormality; family history of stones; history of gout or major stone complications; history of metabolic stone (uric acid or cystine), infection stone (struvite), pure Ca phosphate stone (RTA or elevated PTH)
  – Metabolically active (x-ray evidence of new stone or stone growth in the past year or the documented passage of a new stone or gravel)
    - Osteoporosis or pathologic skelet al fracture
    - Recurrent stone formation
    - Renal insufficiency
    - Significant number of risk factors
    - Solitary kidney; age at onset <20 yr

Pathologic Findings
- Stone analysis: Varying percent composition from Ca oxalate and/or Ca phosphate
- Crystals: Ca oxalate monohydrate (dumbbell/hourglass), Ca oxalate dehydrate (envelope/bipyramidal), Ca phosphate-apatite (amorphous)

DIFFERENTIAL DIAGNOSIS
- Hypercalcemia: Primary elevated PTH, RTA, vitamin D excess, immobilization, sarcoidosis, metastatic malignancies, milk-alkali syndrome, hyperthyroidism, myxedema, adrenal insufficiency, furosemide administration
- See: “Section I Filling Defect-Upper Urinary Tract.”
- See: Section I “Flank Pain”

TREATMENT

GENERAL MEASURES

- Treat active UTI.
- Medical expulsion therapy for a symptomatic ureteral stone (1)[C] (See "Urolithiasis, General")
- Prevention tailored to patient need.
- 1st-time stone-formers at low risk for recurrence should follow a conservative approach.
- Conservative treatment is appropriate for all stone-forming patients, regardless of cause.
- High fluid intake, daily urine output of 2 L; Na and oxylate restriction
- Restrict protein (8 oz meat/chicken/fish/day)
- Vitamin C <2 g/d
- Avoid excess Ca intake. 1 serving with each meal acceptable; avoid late at night
- Ca citrate: "Stone-friendly" supplement
- Avoid stone-provoking drugs: Vitamin D, antacids, furosemide, uricosurics, triamterene

MEDICATION (3)

First Line

- Absorptive hypercalciuria type I:Thiazide (not a selective therapy for AH as does not decrease intestinal Ca; limited long-term effect):
  – Hydrochlorothiazide 25–50 mg b.i.d.
  – Consider K citrate (20 mEq b.i.d.)
  – Alternates: Indapamide 1.25–2.5 mg/d or chlorthalidone (25–50 mg/d):
  – Restrict dietary oxalate, Na to 2000 mg/d
  – Magnesium supplementation
- AH type II: Moderate Ca restriction (600 mg/d or 1–2 servings dairy/d); Na restriction; thiazide if not effective; K citrate supplementation
- AH type III: orthophosphate (Neutra-Phos-K) 250–500 mg tid/qid
- Renal hypercalciuria: Thiazide to increase tubular Ca reabsorption; hydrochlorothiazide 25–50 mg b.i.d.; Indapamide 1.25–2.5 mg/d, Chlorthalidone 25–50 mg/d, K citrate supplementation (Polycitra K syrup 15–30 mL b.i.d.; Polycitra K crystals 1 packet b.i.d.; Urocit K 10–20 mEq b.i.d.); Na restriction (2 g Na diet; keep urinary Na <100 mg/d)
- Hyperuricosuric Ca nephrolithiasis: Increase fluid intake; reduce dietary purine (eg, red meat); urinary alkalization (pH 6.5–7.0), K citrate; reduce endogenous uric acid production (allopurinol 300 mg/d); if serum uric acid >8 mg/dL, or if urinary uric acid >800 mg/24 hr
- Hypocitraturic Ca nephrolithiasis: K citrate, increases intracellular pH, which increases citrate production
- Hyperoxaluria: High fluid intake; low-oxalate diet; (see http://ohf/diet.html) K citrate (60–120 mEq/d), Ca supplementation (Ca citrate, TUMS); therapy to control diarrhea. Fish oil and probiotics may help reduce oxalate excretion.
- Type I RTA: K citrate

Second Line

Absorptive hypercalciuria type I: Na cellulose phosphate out of favor (GI effects); use if UCa >500 mg/d; 2nd line only

SURGERY/OTHER PROCEDURES

See "Urolithiasis, Adult, General."

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Untreated recurrence for Ca oxalate stones: 10% at 1 yr, 35% at 5 yr, 50% at 10 yr
- Medical therapy: Decreases new stone formation; remission >80%, and >90% recurrence reduction

COMPLICATIONS

- Obstructing calculus: sepsis and/or progressive renal damage.
- Un-obstructing calculus: May sometimes grow and cause obstruction, deterioration of renal function.

FOLLOW-UP

Patient Monitoring

- Provide patients with appropriate written dietary hand-outs
- Patients with recurrent stones on medical therapy require periodic monitoring:
  - Urine analysis, urine pH
  - Serum chemistry if warranted
  - 24-hr urine collection
  - KUB, US, or CT

Patient Resources

Urology Care Foundation: http://www.urologyhealth.org/urology/index.cfm?article=148

REFERENCES

1. Pak CYC, Kaplan R, Bone H, et al. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. *N Engl J Med*. 1975;292:497.
2. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 AUA guidelines for the management of ureteral calculi. *J Urol*. 2007;178(6):2418–2434.
3. Preminger GM. Medical management of urinary calculus disease. Part I and II AUA Update, Volume XIV, Lesson 5 & 6, 1995.

ADDITIONAL READING

Lange JN, et al. Metabolic Evaluation and Medical Management of the Calcium Stone Former. AUA Update, Vol. 31, Lesson 22, 2012.

See Also (Topic, Algorithm, Media)

- Hypercalcuria
- Metabolic Stone Evaluation (24 Hour Urine Studies)

- Oxalate, Dietary
- Urolithiasis, Adult, General
- Urolithiasis, Calcium Oxalate/Phosphate Image ☼

CODES

ICD9

- 275.40 Unspecified disorder of calcium metabolism
- 592.0 Calculus of kidney
- 592.9 Urinary calculus, unspecified

ICD10

- E83.52 Hypercalcemia
- N20.0 Calculus of kidney
- N20.9 Urinary calculus, unspecified

CLINICAL/SURGICAL PEARLS

- A family history of nephrolithiasis is important risk when deciding on a metabolic work-up.
- A slight increased PTH is best indication of renal leak hypercalciuria with normal SCa and persistent hypercalciuria on a restricted diet.
- When starting on a thiazide for hypercalciuria, it is important to check serum calcium in 2–4 wk to rule out an occult hyperparathyroidism.
- Accurate 24 hr urinary uric acid cannot be done until the patient is placed on urinary alkalization as acidic urine can cause uric acid to precipitate out of solution causing underestimation.

UROLITHIASIS, CYSTINE, AND CYSTINURIA (HYPERCYSTINURIA)

Anthony J. Tracey, MD, MPH
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BASICS

DESCRIPTION

- Cystinuria is caused by an autosomal recessive error of transepithelial transport involving the intestine and the kidneys. Cystine lithiasis is the clinical result of crystallization and stone formation in the urinary tract.
  - Excessive urinary excretion secondary to reduced tubular absorption of cystine disulfate (1).
  - There is a transport defect of dibasic amino acids including cystine, ornithine, lysine, and arginine (COLA). (See also Section I: "Urolithiasis, Pediatric.") (1)
- Cystine stones form when concentrations rise above the saturation point (roughly 250 mg cystine per liter of urine)
- Cystinuria accounts for about 1–2% of adult and 6–8% of pediatric nephrolithiasis (1)
- Historically, three types of cystinuria have been recognized in humans—type I, type II, and type III—on the basis of levels of urinary cystine in obligate heterozygotes; however, this classification correlates poorly with molecular findings; newer genetic classification is available (see below).
- Cystinuria is distinct from cystinosis, which is intracellular cystine accumulation leading to the Fanconi syndrome and progressive renal failure

EPIDEMIOLOGY

Incidence

- For patients with cystinuria:
  - One new stone formation per patient per year
  - An average of one surgical procedure every 3 yr
  - 7 surgical procedures for nephrolithiasis by middle age (2)
  - Average age at first stone diagnosis was 12.2 yr
  - Mean number of stone episodes of 0.42 and 0.21 per year occurring in men and women, respectively.

Prevalence

- Homozygous: 1 in 15,0000 in the United States
- Heterozygous: 1 in 20–200 in the United States
- Libyan Jews: 1 in 2,500 (3)
- Cystinuria is more common in Caucasians
- Cystine stones are common in the second or third decade of life
- 20% of these patients develop calculi in childhood

RISK FACTORS

Family history (See genetics)

Genetics

- Identification of genetic mutations that cause cystinuria have led to a new classification system based on genotype that is more accurate than the prior phenotypic one.
- Mutations in 2 genes, *SLC3A1* and *SLC7A9* (3)
- Recent classification by International Cystinuria Consortium (ICC) to account for the chromosomal localization of the mutation:
  - Type A (SLC3A1 gene is located on chromosome 2p16.3-p21)
  - Type B (SLC7A9 gene is located on chromosome 19q12-13.1)
  - Type AB (both chromosomes)
- Homozygotes exhibit urinary cysteine levels as high as 2000 µmol/g of creatinine
- Heterozygotes do not form stones; urinary excretion <100 mg/d
- Autosomal recessive complete; urinary excretion 250–1,400 mg/d
- Autosomal recessive incomplete; urinary excretion 100–300 mg/d (1)

PATHOPHYSIOLOGY

- Cystine is a homodimer of the amino acid cysteine.
  - Cystinurics have impaired renal cystine transport, with decreased proximal tubular reabsorption of filtered cystine resulting in increased urinary cystine excretion with the consequence of cystine urolithiasis.
- Clinical consequences present only when crystals precipitate (low cystine solubility at normal urinary pH values).
- Cystine stone formers have slightly lower creatinine clearance than other types of stone formers.

ASSOCIATED CONDITIONS

- Defective renal acidification
- Hypercalciuria 19%
- Hypertension
- Hyperuricosuria 22%
- Hypocitraturia 44%
- Urolithiasis

GENERAL PREVENTION

- Create high urine volume (>1.5 L/m^2/d) to reduce the urinary concentration of cystine to below its solubility limit (200–300 mg/L)
- Alkalize urine to pH of >7.5 (3–4 mEq/kg/d potassium citrate/bicarbonate, in 3–4 divided doses. Alkaline urine increases solubility of cysteine) (1)
- Restrict sodium and protein.

DIAGNOSIS

HISTORY

- Stones in childhood (3)
- Family history of stones (3)
- The presentation of a large branched calculi

PHYSICAL EXAM

CVA tenderness may be present with active stone disease

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine is screened for cystine using the cyanide-nitroprusside test (positive = purple hue) with cystine >75 mg/L)
  - Cyanide converts cystine to cysteine; this binds nitroprusside then binds resulting in a purple color usually in <10 min.
- If positive, a 24-hr urine quantitative test is performed.
  - Normal cystine excretion is 30 mg/d (0.13 mmol/d),
  - Cystinurics >400 mg/d (1.7 mmol/d) (1).
- Heterozygotes for cystinuria and with the Fanconi syndrome, excrete <250 mg/d (1 mmol) and usually do not form stones.
- Urine microscopy: Hexagonal or benzene crystals, which are pathognomonic of cystinuria.
  - Microscopic crystalluria is present in 26–83% of patients.
  - Can also be seen in cystinosis
- Cystine capacity: A highly specialized assay that measures the ability of urine to take up additional cystine from a preformed solid phase reaction (under saturation, or "positive cystine capacity") or to give it up to the solid phase (supersaturation, or "negative cystine capacity")
  - May help guide drug dosing and treatment

Imaging

- CT scan of abdomen without contrast
  - Preferred imaging modality
- KUB may show stones with a fuzzy gray appearance (1)
  - Stones are less radiopaque than calcium stones but usually well seen
- Renal ultrasonography
  - More economical than CT scan for monitoring the growth of renal calculi
  - Indicated for children and frequent stone formers to reduce radiation (2)

Diagnostic Procedures/Surgery

N/A

Pathologic Findings

Renal biopsy is not usually performed. However, renal pathology may include plugging of the Ducts of Bellini with cystine crystals, tubular dilation, and focal fibrosis.

DIFFERENTIAL DIAGNOSIS

- Other forms of urolithiasis (calcium oxylate, uric acid, etc.)
- Any of the following may be confused with pain related to urolithiasis:
  - Vascular: Abdominal aortic aneurysm, mesenteric ischemia
  - Gastrointestinal: Appendicitis, bowel obstruction, cholecystitis/biliary colic, constipation, diverticulosis/diverticulitis, gastritis, pancreatitis, peptic ulcer
  - Gynecologic: Ectopic pregnancy, tubo-ovarian abscess, ovarian torsion/cyst rupture
  - Musculoskelet al: Back pain

- Urologic: Pyelonephritis, urinary tract infection, sloughed renal papilla, ureteropelvic junction obstruction

TREATMENT

GENERAL MEASURES

- For existing calculi treatment is similar to other stones based on clinical indication
- Extracorporeal shockwave lithotripsy has been discouraged for stones >1 cm by some authors (2)
  - Cysteine stones are often not well fragmented by ESWL (extracorporeal shock wave lithotripsy)
  - Multiple treatments are usually required
- Algorithm for Patients with Renal cystine stones:
  - Percutaneous nephrolithotripsy (PNL) for cystine renal calculi larger than 15 mm in diameter
  - Ureteroscopy effective for cysteine ureteral stones and for select renal cystine calculi
  - Laparoscopic pyelolithotomy may also be possible for stones in favorable locations of the ureter or renal pelvis.
  - ESWL monotherapy for cystine renal calculi 15 mm or smaller (High failure rate)

MEDICATION

First Line

See general prevention

Second Line

- Use chelating agents (bind cystine) only if the conservative methods do not work
- These increase cystine solubility in urine via formation of a more soluble mixed-disulfide bond
- These medications have potentially serious side effects and must be monitored.
  - α-Mercaptopropionylglycine (Thiola, Tiopronin)
    - Most frequently used cystine-binding agent
    - Dosage start at 100 mg, orally two times per day, doses titrated to achieve urinary concentrations of cystine less than 250 mg/L urine.
    - Side effects include asthenia, GI distress, rash, joint aches, and mental status changes
    - Better tolerated than d-penicillamine
  - d-penicillamine (Cuprimine)
    - binds with cystine to yield a disulfide more soluble than cystine
    - Typically start therapy at 250 mg per day and titrate to effect
    - Significant side effects: nephrotic syndrome, dermatitis, and pancytopenia.
  - Captopril: Potential alternative
    - More favorable side effect profile: Fatigue, hypotension, and chronic cough
    - No long-term clinical trials demonstrate the effectiveness of captopril in preventing recurrent cystine stone formation

SURGERY/OTHER PROCEDURES

See General Measures above

ADDITIONAL TREATMENT

Radiation Therapy

NA

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- One study reported 1.22 stone episodes per year (2)
- The medical compliance of patients with cystinuria can be poor.
- A few patients are able to achieve and maintain targeted goals of medical intervention
  - 15% achieved and maintained therapeutic success, as defined by urine cystine concentration less than 300 mg/L.
  - 42% achieved therapeutic success but subsequently had failure at an average of 16 mo
- Rare Kidney Stone Consortium has developed a registry and will lead further efforts in managing cystinuria

COMPLICATIONS

- Studies report 1.22 stone episodes per year
- Chronic pyelonephritis—19%
- Renal impairment—Approximately 70%
- Risk for nephrectomy—10–20%
- End-stage renal failure—5%
- Hypertension—10%
- Mental illness and mental retardation (2)

FOLLOW-UP

Patient Monitoring

- Patients should have frequent clinical, radiologic, and laboratory surveillance
  - Patients should follow a diet low in protein and sodium chloride
  - Urinary pH level, and check first-morning urine for cystine crystals (2)
  - Regularly check renal function
  - RBC counts, WBC counts, and platelet counts should be monitored for patients on d-penicillamine and tiopronin (2).
  - KUB and renal ultrasound should be routine
- Surveillance:
  - Annually perform 24-hr urine testing and imaging for patients with stable disease (2)
  - Multidisciplinary approach early in disease
    - Nephrologists
    - Renal dietitians

Patient Resources

- http://www.cystinuria.com/

- http://www.cystinuria.org/index.php
- Urology Care Foundation
  http://www.urologyhealth.org/content/moreinfo/kidneystone05.pdf

REFERENCES

1. Vella M, Karydi M, Coraci G, et al. Pathophysiology and clinical aspects of urinary lithiasis. *Urol Int.* 2007;79(Suppl I):26–31.
2. Biyani CS, Cartledge J. "Cystinuria" Medscape Article 2012; emedicine.medscape.com/article/435678
3. Eggermann T, Venghaus A, Zerres K. et al. Cystinuria: an inborn cause of urolithiasis. *Orphanet J Rare Dis.* 2012;7:19–29.

ADDITIONAL READING

Sumorok N, Goldfarb DS. Update on cystinuria. *Curr Opin Nephrol Hypertens.* 2013;22(4):427–431.

See Also (Topic, Algorithm, Media)

- Cystinosis
- Metabolic Stone Evaluation (24 Hour Urine Studies)
- Sodium Cyanide-Nitroprusside Test
- Urolithiasis, Adult, General
- Urolithiasis, Calcium Oxalate/Phosphate
- Urolithiasis, Cystine and Cystinuria (Hypercystinuria) Image
- Urolithiasis, Pediatric, General
- Urolithiasis, Staghorn
- Urolithiasis, Ureteral Calculi Algorithm

CODES

ICD9

- 270.0 Disturbances of amino-acid transport
- 592.9 Urinary calculus, unspecified

ICD10

- E72.01 Cystinuria
- N20.9 Urinary calculus, unspecified

CLINICAL/SURGICAL PEARLS

- Cystine stones are often not well fragmented by ESWL and may be considered for cystine renal calculi < 15 mm.
- Consider PCNL for cystine renal calculi larger than 15 mm in diameter.
- Ureteroscopy effective for cystine ureteral stones and for select renal cystine calculi.

UROLITHIASIS, PEDIATRIC, GENERAL CONSIDERATIONS

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BASICS

DESCRIPTION

- Urolithiasis can be found anywhere in the urinary tract of a child.
- Urolithiasis is much less common in children than adults
  - Urolithiasis is an increasingly common disease of childhood.
- The most commmon stones in children are calcium (calcium oxalate and calcium phosphate), uric acid, Struvite and cysteine.

EPIDEMIOLOGY

Incidence

- In adolescents, the incidence of nephrolithiasis has increased 6–10% per year over the last 20 yr (1,2).
- White > African American
- Male = Female
- Increased incidence in the Southwest United States.

Prevalence

The prevalence is unclear.

RISK FACTORS

- When a metabolic evaluation is performed, an abnormality can be identified in 40–50% of children.
  - Most common metabolic abnormalities are hypercalciuria and hypocitraturia.

PATHOPHYSIOLOGY

- Urine contains inhibitors of crystallization and thus can sustain large concentrations of solute (eg, Ca, uric acid) in a metastable state; however, perturbations of the equilibrium between inhibitors and promoters of stone formation may destabilize the urine to a point where solute cannot be held in solution and spontaneous nucleation occurs.
- Infection:
  - Urea-splitting organisms produce urease, which catalyzes the hydrolysis of urea.
  - Magnesium ammonium phosphate (struvite) and calcium phosphate stones
  - Urine is alkaline due to urease.
  - Most often present in patients with an anatomic abnormality that leads to chronic infection (neurogenic bladder, reflux, obstruction, etc.)
- Anatomic:
  - Ureteropelvic/vesical obstruction
  - Neurogenic bladder
  - Previous bladder neck surgery
- Hypercalciuria:

- Renal: Impaired tubular reabsorption of calcium causes increased parathyroid hormone release, which normalizes serum calcium.
- Absorptive: Increased absorption from intestines causes decreased parathyroid hormone and therefore decreased calcium tubular reabsorption:
  - Type 1: Severe
  - Type 2: Mild
- Resorptive (exceedingly rare):
  - Results from primary hyperparathyroidism
  - Elevated PTH and serum calcium, low serum phosphorous, high urine calcium
- Iatrogenic (medications): Loop diuretics (furosemide), corticosteroids, methylxanthines (theophylline, aminophylline)
- RTA: Inability to acidify urine in response to an acid load:
  - Metabolic acidosis; high urine pH
  - Type I (distal) most common: Disorder of hydrogen ion excretion that leads to bone demineralization and thus hypercalciuria
  - Most common stone is calcium phosphate, which results from hypercalciuria, hypocitraturia, and elevated urine pH

- Uric acid stones/hyperuricosuria:
  - Rare in children; high purine intake, uricosuric drugs (probenecid, sulfinpyrazone, allopurinol), renal tubular disorders, cyanotic congenital heart disease, hemolysis, and myeloproliferative disorders
  - Lesch–Nyhan syndrome and type I glycogen storage disease: Increased uric acid
- Cystinuria: Autosomal recessive disorder of amino acid transport; impaired reabsorption of cystine
- Hyperoxaluria:
  - Primary types I and II are rare autosomal recessive disorders with hepatic enzyme defects
  - Secondary: Excessive intake of ethylene glycol, ascorbic acid, methoxyflurane, or increased intestinal absorption due to bowel disease/resection, gastric bypass

ASSOCIATED CONDITIONS

- Bartter syndrome
- Cystinuria
- Diabetes, obesity, and sugary drinks are associated with an increased risk of nephrolithiasis in adults. These risk factors have not been well studied in children.
- Distal RTA
- Gout (Hypoxanthine-guanine phosphoribosyl transferase deficiency and phosphoribosyl pyrophosphate synthetase superactivity) is rare in children unless associated with a genetic disorder
- Hyperparathyroidism
- Hypervitaminosis D
- Intestinal malabsorption (Crohn disease, bowel resection, cystic fibrosis)
- Ketogenic diet (high-fat, low-carbohydrate)
- Medications (furosemide, acetazolamide, protease inhibitors, and anticonvulsants such as topiramate and zonisamide).
- Primary hyperoxaluria

- Prolonged immobility
- Recurrent UTIs
- Rickets (associated with Dent disease and hereditary hypophosphatemic rickets with hypercalciuria)
- Tetany (familial hypomagnesemia with hypercalciuria and nephrocalcinosis and autosomal dominant hypocalcemic hypercalciuria)
- Urinary tract abnormalities (spina bifida, horseshoe kidney, UPJ obstruction, VUR)
- William syndrome

GENERAL PREVENTION
- Maintain adequate hydration and fluid volume
- Treat underlying disorders (anatomic or metabolic)

DIAGNOSIS
HISTORY
- Patient: Prematurity, medications, dietary habits, fluid consumption, malignancies, previous intestinal disorder/surgery, hematuria
- Family: Cystinuria, primary hyperoxaluria, RTA, uric acid lithiasis
- Abdominal/flank pain ± nausea/vomiting

PHYSICAL EXAM
- Hypertension associated with acute pain or obstruction
- Occasional abdominal or flank tenderness
- Growth charts may identify decreased growth patterns associated with certain childhood diseases associated with stones(cystic fibrosis, distal RTA, hyperoxaluria, etc.).

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- Acute Episode: Urinalysis
  - Macroscopic or microscopic hematuria is found in 85% of children with nephrolithiasis (3).
- Metabolic evaluation
  - Following the resolution of the acute stone episode, obtain at least one 24-hr urine collection in children who are toilet-trained
  - Analyze for calcium, oxalate, uric acid, sodium, citrate, creatinine levels, volume, pH, and cystine. It is essential to evaluate the results with respect to weight and creatinine level to accurately interpret the results.
  - Hypercalciuria is defined by a urinary calcium excretion of greater than 4 mg/kg over 24 hr while ingesting a routine diet.
  - Urine creatinine excretion (normal 15–25 mg/kg/d) is useful in assessing the adequacy of the urine collection.
  - Urine calcium—creatinine ratios (UCa/Cr) from a spot urine sample should be obtained in children who have not been toilet-trained.
    - Except for neonates, there is an inverse relationship between age and UCa/Cr.
    - At approximately 5 years of age, UCa/Cr approaches 0.21, the upper limit of normal for adults (4).

Imaging
- Ultrasound: Reliable when it identifies a kidney stone, but it has only moderate sensitivity particularly for stones in the mid-ureter.
- CT: Accurate but delivers ionizing radiation, concerns for increased cancer risk, particularly with exposure at young ages
- A reasonable approach is to use US as the initial study. A non-contrast CT is indicated in children with persistent symptoms of nephrolithiasis and a non-diagnostic US.

Diagnostic Procedures/Surgery
N/A

Pathologic Findings
- Stone analysis to determine composition
- Calcium oxalate stones are most common, followed by calcium phosphate.
- The prevalence of struvite, cystine, and uric acid stones is each $<10\%$.

DIFFERENTIAL DIAGNOSIS
See Section I: “Urolithiasis, Adult, General.”

TREATMENT
GENERAL MEASURES
- Indications for surgery: fever in the presence of an obstructing stone, pain refractory to oral analgesics, acute kidney injury, and an obstructing stone in a solitary kidney.
- Evaluate all children for underlying metabolic disorder.
- Goal is to decrease stone-promoting risk factors (urinary calcium, sodium, oxalate, uric acid, and low urine volume), and increase protective factors (urine pH, citrate, magnesium)
- Hydration:
  - Water preferred; avoid caffeine, sodium, and sugary drinks (sports drinks)
- Dietary modifications when applicable

MEDICATION
First Line
- Should a trial of spontaneous passage be indicated, appropriate oral analgesics are important (ie, narcotics).
- Tamsulosin may increase passage of distal ureteral stones in children (5).

Second Line
- Hypercalciuria:
  - Hydrochlorothiazide:
    - 1–2 mg/kg/d in children
    - 25–100 mg/d in adults
- Hypocitraturia
  - Potassium citrate
    - 2–4 mEq/kg/d
    - adults 30–90 mEq/d
- Uric acid stones:
  - Limit dietary sodium

- Alkalinization of urine to pH >6.5:
- Allopurinol (decrease uric acid production) 200 mg/d

• Cystinuria:
- Create high urine volume (>1.5 L/m^2/d)
- Chelating agents (bind cystine):
  - Thiola
  - D-penicillamine

• Hyperoxaluria:
- Limit sodium and oxalate-rich foods (eg, spinach, rhubarb, nuts, tea, bran, strawberries)
- Supplemental citrate, magnesium, phosphorous (stone inhibitors)

SURGERY/OTHER PROCEDURES

• The optimal management based on the size, location, and presumptive stone composition, as well as the age, size, and health of the patient.

• Extracorporeal Shock Wave Lithotripsy (ESWL)
- Renal/proximal ureteral stones, <1 cm, all ages
- Use for distal stones not well defined
- Success rate depends upon many variables:
  - Stone size and location, energy utilized, density of stone, anatomic abnormalities
- Complications
  - Subcapsular hematoma: Self-limiting
  - Interstitial fibrosis: Insignificant unless multiple procedures
  - Injury to surrounding organs:

• Ureteropyeloscopy:
- Rigid and flexible endoscopes permit access to almost all areas of the collecting system in nearly all children:
- Pre-placement of stent is sometimes necessary to passively dilate the ureter.
- Access sheaths (with/without pre-stenting) facilitate procedures requiring multiple endoscope passes.
- All forms of lithotripsy are safe; holmium laser most effective

• Percutaneous nephrolithotomy (PCNL):
- Appropriate for large intrarenal/proximal ureteral stones:
- Also failed primary procedures (SWL, ureteroscopy), and with associated anatomic abnormalities (congenital, acquired, etc.)
- Access at same time as or prior to surgery:
- Sheath size as small as possible to allow for success of procedure and to accommodate flow of irrigant around scope
- Renal access: best access to stone burden.
  - Multiple tracts are safe.
  - Irrigation (saline): Warmed for children
- Postoperative management: Appropriate drainage; chest x-ray in recovery room (upper pole access)
- Complications:
  - Bleeding: Place tube (traction if necessary); embolize if significant
  - Perforation/extravasation: If significant, stop procedure and place nephrostomy tube

- Infection: Appropriate antibiotics; confirm patency of tube/stent
- Pleural effusion/pneumothorax: Chest tube, needle drainage
- Intestinal injury: Expectant management; colostomy tube

• Open/laparoscopic pyelolithotomy (rare): Large pelvic/staghorn stones

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

Adequate hydration to dilute urine

ONGOING CARE

PROGNOSIS

• Up to 50% of children will develop recurrent stones within 10 yr of initial occurrence, which is similar to rates in the adult population.
• The odds of recurrence is up to 5× higher in children with an identifiable metabolic abnormality.

COMPLICATIONS

Obstruction, infection, lost productivity, impaired renal function

FOLLOW-UP

Patient Monitoring

• Repeat 24-hr urine 3–4 mo after instituting therapy and if stone recurs after initial stabilization.
• Assess periodically for stone growth or new stone disease with US.

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC).
http://kidney.niddk.nih.gov/kudiseases/pubs/stoneschildren/

REFERENCES

1. Dwyer ME, Krambeck AE, Bergstralh EJ, et al. Temporal trends in incidence of kidney stones among children: A 25-year population based study. *J Urol.* 2012;188:247.
2. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. *J Urol.* 2010;184:1100–1104.
3. Persaud AC, Stevenson MD, McMahon DR, et al. Pediatric urolithiasis: Clinical predictors in the emergency department. *Pediatrics*. 2009;124(3):888–894.
4. Sargent JD, Stukel TA, Kresel J, et al. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr.* 1993;123:393–397.
5. Mokhless I, Zahran AR, Youssif M, et al. Tamsulosin for the management of distal ureteral stones in children: A prospective randomized study. *J Pediatr Urol.* 2011:1–5.

See Also (Topic, Algorithm, Media)

- Cystinuria
- Hypercalcuria (Absorptive, Renal, and Resorptive)
- Renal Tubular Acidosis
- Urolithiasis, Adult, General
- Urolithiasis, Cystine and Cystinuria
- Urolithiasis, Pediatric, General Considerations Images ☼

CODES

ICD9

- 275.49 Other disorders of calcium metabolism
- 592.0 Calculus of kidney
- 592.9 Urinary calculus, unspecified

ICD10

- E83.52 Hypercalcemia
- N20.0 Calculus of kidney
- N20.9 Urinary calculus, unspecified

CLINICAL/SURGICAL PEARLS

- Kidney stones can occur at any age, even in premature infants.
- Most occur in teens, with teen girls having the highest incidence in adolescents.

UROLITHIASIS, RENAL

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BASICS

DESCRIPTION

- Renal urolithiasis refers to kidney stones within the kidney itself (parenchyma, calyces or renal pelvis. The majority of stones inthe urinary tract have their origin in the kidney.
- Renal urolithiasis is a significant cause of patient renal morbidity and a major source of medical costs in the UnitedStates.
- Calcium oxalate stones most common; also uric acid, struvite (magnesium ammonium phosphate), calcium phosphate, cystine, etc.

EPIDEMIOLOGY

Incidence

- Estimated to be 10–15% in the United States
- Males are affected 2–3× more than females
- Peak incidence: 4th–6th decades
- More common in Southeast, Southwest, and Northwest United States.
- Increasing incidence with increased obesity
- Accounts for 7–10 of every 1000 hospital visits

Prevalence

Highest prevalence in Caucasians

RISK FACTORS

- Calcium stone formation
  - Dietary excess
  - Hyperparathyroidism
  - inappropriate loss of calcium in urine through renal tubules
  - Excessive intestinal absorption
  - Inadequate levels of stone inhibitors in urine
  - Sarcoidosis
  - Multiple myeloma
  - Leukemia
- Uric acid stone formation
  - Purine excess
  - Gout
  - Myeloproliferative disorders
  - Chronic dehydration
  - Lesch–Nyhan syndrome
  - Ingestion of uricosuric drugs
- Struvite stones
  - UTI with urease-splitting organisms (*Proteus*, *Klebsiella*, etc.)

- Alkalinizes urine and magnesium ammonium phosphate crystallization
- Cystine stones
  – Inherited disorder of renal tubular reabsorption of cysteine (See Urolithiasis, Cystine)

Genetics

- In general, urolithiasis associated with polygenic defect and partial penetrance
  – Cystinuria: Homozygous recessive
- Renal tubular acidosis (RTA): Inherited

PATHOPHYSIOLOGY

- Supersaturation: Urine oversaturated with certain types of crystal, which then is precipitated out of solution.
  – Saturation level is variably pH dependent based on crystal type
- Inhibitor deficiency: Inhibitors may limit crystal growth and aggregation
  – Urinary citrate and magnesium are inhibitors
- Non-infection stones: Calcium oxalate, calcium phosphate (brushite, carbonate apatite), uric acid
- Infection stones: Magnesium ammonium phosphate (struvite), carbonate apatite, ammonium urate
- Genetic defects: Cystine, xanthine, 2,8-dihydroxyadenine (DHA)
- Drug stones: Indivavir, triamterene, others

ASSOCIATED CONDITIONS

- Congenital malformations or anatomic variations of kidney, collecting system, ureter, or bladder may predispose patient to urolithiasis due to stasis and/or impaired urine drainage
- Crohn disease
- Dehydration
- Gout
- Inflammatory bowel disease
- Intestinal bypass
- Medullary sponge kidney
- Renal tubular acidosis

GENERAL PREVENTION

- Decreased sodium intake
- Diuretics
- Encourage fluid intake; avoid dehydration
- Increase urinary citrate
- Reduce dietary protein (purine) if at-risk
- Restrict oxalate consumption

DIAGNOSIS

HISTORY

- Acute onset of severe pain
  – Partially obstructive stones have more chronic, mild to moderate pain
  – Pain radiates to groin or lower abdomen

- Gross hematuria
- Previous history of kidney stones or UTIs
- Family history of urolithiasis
- Changes in urination patterns

PHYSICAL EXAM
- CVA tenderness
  - Moderate, deep tenderness in flank radiating to groin
  - Great tenderness suggests pyelonephritis
- Fever present if associated infection

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Urinalysis
  - Microscopic hematuria
    - Unless complete obstruction
    - Crystalluria may provide important information regarding the type of calculus.
  - Pyuria
    - May suggest concomitant UTI
- Urine gram-stain and culture
  - Authors opinion: Catheterized urine specimen should be collected for urinalysis, gram-stain, and culture in all female patients under consideration for surgical intervention
- CBC
  - Leukocytosis: Suggests secondary infection
- Basic metabolic profile
  - Elevated creatinine
    - May be present if bilateral obstruction present
  - Calcium level
  - Glucose: Impaired glycemic control in patients with diabetes especially in setting of infection

Imaging
- Non-contrast low-dose helical computed tomography (CT)
  - Rapid study
  - 1st-line test with acute renal colic
  - Can determine degree of hydronephrosis, size, and location of stones
- Intravenous pyelogram (IVP)
  - Requires IV contrast
  - Delayed x-rays needed if high-grade obstruction present
  - Some stones radiolucent—not visible on IVP
  - Can provide some assessment of renal function
- Ultrasound
  - Non-invasive, 1st-line evaluation for in patients at risk for X-ray exposure
    - Children, pregnant females
    - Operator-dependent
  - Difficult to visualize ureter in adult

- Resistive index (>0.7) suggestive of obstruction in the setting of acute obstruction
- Ureteral Jets—Presence does not rule out partial obstruction

Diagnostic Procedures/Surgery

- Retrograde pyelography
  - Invasive
  - Can assist concomitant surgical management

Pathologic Findings

- Hydronephrosis
  - Note degree and anatomic location of obstruction
  - Perinephric stranding on CT

DIFFERENTIAL DIAGNOSIS

- Abdominal aortic aneurysm
- Appendicitis
- Bowel obstruction
- Gastritis, pancreatitis, peptic ulcer
- Mesenteric ischemia
- Musculoskelet al back pain
- Pyelonephritis, urinary tract infection
- Cholecystitis or biliary colic
- UPJ obstruction
- Sloughed renal papilla

TREATMENT

ALERT

The presence of pyuria, fever, leukocytosis, or bacteriuria suggests the possibility of a urinary infection and the potential for an infected obstructed renal unit or pyonephrosis. Such a condition is potentially life-threatening and should be treated as a surgical emergency.

GENERAL MEASURES

- Hydration and adequate pain control
- Patients with likelihood of spontaneously passing a stone (<4–5 mm in size) in the absence of indication for surgical intervention may be sent home with analgesics and a trial of medical expulsive therapy (MET); (hydration, analgesia, symptomatic relief)
  - Should be instructed to return if pain worsens, or severe vomiting or fever
  - Likelihood of spontaneous stone passage is related to location and size of stone
  - Stones 2–3 mm: 80% probability of passing
  - Stones 4–5 mm: 50% probability of passing
  - Stones 7–8 mm: 20% probability of passing
  - Stones >1 cm: unlikely to pass spontaneously
- Controversy exists regarding maximum period of observation for partially obstructing stone without development of significant irreversible renal dysfunction; generally, within 4–6 wk.

- Indications for intervention:
  - Fever and/or infection
  - Intractable pain
  - Unable to tolerate oral fluid and at risk for dehydration
  - Progressive renal deterioration; obstruction of solitary functioning kidney
- All urinary tract infections should be treated with culture-sensitive antibiotics prior to surgical treatment

MEDICATION

First Line (1,2)

- Patients with evidence of active UTI should be treated with broad-spectrum antibiotics (eg, ampicillin and gentamicin, 3rd-generation cephalosporin).
- Antiemetic if acute colic is associated with nausea and vomiting.
- Medical expulsive therapy (MET):
  - α-Blockers (ie, terazosin, tamsulosin) or calcium-channel blockers (eg, nifedipine) can relax musculature of the ureter and lower urinary tract and can reduce pain associated with stone passage (tamsulosin 0.4 mg PO QD).
- Uric acid stones and cystine stones can be dissolved with medical therapy; calcium stones and struvite stones cannot be dissolved:
- Uric acid stones: Alkalinize urine with potassium citrate or bicarbonate, to maintain urinary pH between 6.5 and 7.0:
  - Urinary pH >7.5 can precipitate calcium phosphate with resulting stone formation.
  - May dissolve up to 1 cm per month
- Cystine stones: see Urolithiasis, Cystine

Second Line

N/A

SURGERY/OTHER PROCEDURES (3)

- Primary goal is to achieve maximal stone clearance with minimal morbidity.
- Patients with active UTI/sepsis: Obstructed kidney is drained by placement of ureteral stent or percutaneous nephrostomy tube.
- Preoperative urine culture should document no infection before stone removal:
- Calculi in kidney: Ureteroscopy vs. ESWL with or without stent placement (>1 cm)
- >2 cm: Percutaneous nephrolithotomy or if >1.5 cm in lower pole.
- Shock-wave lithotripsy (SWL)
  - Intrarenal calculus <2 cm
  - Relative contraindications
    - Stone > 2 cm
    - Within dependent or obstructed portions of collecting system
    - Body habitus/obesity that inhibits imaging and targeting of the stone
    - Lower pole stone
    - Uncorrected coagulopathy or recent anticoagulant use
- Ureteroscopy
  - Used for lower pole stones or stones resistant to SWL
  - Effective for treatment of cystine, calcium oxalate monohydrate, and brushite stones

- Percutaneous nephrolithotomy (PCNL)
  - Stones >2 cm; no bleeding diathesis or obesity
  - Staghorn calculi
- Laparoscopic and robotic stone surgery for large non-branching calculi
- "Sandwich technique"
  - SWL in combination with other modality

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

NA

Complementary & Alternative Therapies

NA

ONGOING CARE

PROGNOSIS

- The most important measure to avoid future stone episodes is increased fluid intake.
- Once patient has initial incident, 50% chance that in 5 yr will have recurrent calculus.
- Produce >2 L of urine/day
- 24-hr urine collection for metabolic analysis
- Stone fragment chemical analysis should be performed when possible
- Metabolic workup after 2nd episode

COMPLICATIONS

- Pyelonephritis
- Renal deterioration
- renal abscess formation
- Surgery carries standard risks of bleeding, infection, ureteral stricture.
- Pneumothorax with nephrostomy access

FOLLOW-UP

Patient Monitoring

- Oral hydration to make 2–2.5 L of urine/day
- Diet low in protein and sodium intake
- Dietary modification and medical intervention tailored to underlying metabolic abnormality can prevent recurrence of stones in 75% patients and significantly reduce new stone formation in up to 98% of patients.
- Restriction of oxalate-rich foods such as chocolate, nuts, soybeans, rhubarb, spinach, sweet potatoes, beets.
- Maintenance of adequate intake of dietary calcium

Patient Resources

Urology care foundation: http://www.urologyhealth.org/urology/index.cfm?article=148

REFERENCES

1. Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: Asystematic review for an American College of Physicians Clinical Guideline. *Ann InternMed*. 2013;158:535.
2. Sarkissian C, Noble M, Li J, et al. Decision making for asymptomatic renal calculi: Balancing benefit and risk. *Urology*. 2013;81:236.
3. Bandi G, Best SL, Nakada SY. Current practice patterns in the management of upper urinary tract calculi in the north central US. *J Endourol*. 2008;22(4):631–636.

ADDITIONAL READING

EAU Guidelines on Urolithiasis. http://www.uroweb.org/gls/pdf/21_Urolithiasis_LR.pdf

See Also (Topic, Algorithm, Media)

- Metabolic Stone Evaluation (24 Hour Urine Studies)
- Ureter, Stone Passage Statistics
- Urolithiasis, Adult, General
- Urolithiasis, Calcium Oxalate/Phosphate
- Urolithiasis, Cystine and Cystinuria (Hypercystinuria)
- Urolithiasis Image
- Urolithiasis, Pediatric, General
- Urolithiasis, Staghorn
- Urolithiasis, Ureteral Calculi Algorithm
- Urolithiasis, Uric Acid

CODES

ICD9

- 274.11 Uric acid nephrolithiasis
- 275.49 Other disorders of calcium metabolism
- 592.0 Calculus of kidney

ICD10

- E79.8 Other disorders of purine and pyrimidine metabolism
- E83.52 Hypercalcemia
- N20.0 Calculus of kidney

CLINICAL/SURGICAL PEARLS

Renal stones >1 cm are unlikely to pass spontaneously.

UROLITHIASIS, STAGHORN

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BASICS

DESCRIPTION

- Staghorn calculi are branched stones that occupy a large portion of the collecting system. Typically, they fill the renal pelvis and branch into several or all of the calices.
- Partial staghorn: Fills some but not all of the collecting system
- Complete staghorn: Fills nearly the entire collecting system
- Can be comprised of any of the following stone types, with struvite and calcium carbonate apatite the most commonly seen:
  - Struvite (magnesium ammonium phosphate)
  - Calcium carbonate apatite
  - Cystine
  - Uric acid
  - Calcium oxalate
  - Calcium phosphate
- Some literature refers to staghorn calculi as "coral calculi" or "coral nephrolithiasis" based on its characteristic shape.

EPIDEMIOLOGY

Incidence

- Not well-defined, with conflicting studies
- More common in women than in men

Prevalence

N/A

RISK FACTORS

- Chronic indwelling catheter
- Chronic infection
- Dehydration
- Metabolic disorders (hypercalciuria, cystinuria, hyperoxaluria)
- Neurogenic bladder
- Ureteral obstruction or reflux
- Urinary diversion

Genetics

N/A

PATHOPHYSIOLOGY

- Staghorn calculi are most frequently composed of mixtures of magnesium ammonium phosphate (struvite) and/or calcium carbonate apatite
  - These are also commonly referred to as "infection stones"

- Strong association with urinary tract infection caused by specific organisms that produce the enzyme urease that promotes the generation of ammonia and hydroxide from urea.

- Cystine or uric acid (pure form or mixed) can sometimes grow in a “staghorn” or branched configuration, but calcium oxalate or phosphate stones only rarely grow in this configuration.
- Urinary stasis due to obstruction or smooth muscle paralysis due to endotoxins
- Infection with urea-splitting organisms
  – Often harbored inside stones
  – Produce urease—hydrolyzes urea into ammonia, bicarbonate, and carbonate
    - *Proteus*
    - *Pseudomonas*
    - *Klebsiella*
    - *Staphylococcus*
    - *E. coli*
    - *Mycoplasma*
    - *Yeast*

ASSOCIATED CONDITIONS
- Chronic urinary tract infections
- Urinary tract obstruction
- Urinary diversion
- Neurogenic bladder

GENERAL PREVENTION
- Hydration
- Treatment of urinary tract infections
- Elimination of stones prior to evolution into staghorn calculus

DIAGNOSIS
HISTORY
- Often asymptomatic
- Discovered incidentally on imaging
- Recurrent or persistent urinary tract infection
- Fever, malaise, weight loss
- Renal insufficiency
- Flank pain
- Hematuria
- Neurogenic bladder
- Urinary diversion
- Metabolic disorders

PHYSICAL EXAM
- Costovertebral angle tenderness
- Rarely, palpable mass

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- CBC
- Basic metabolic panel
- PTT/INR
- Urinalysis and culture
  - pH >7.0 may indicate urea-splitting infection
  - Culture may demonstrate commonly associated bacteria
  - Persistence of a species may indicate a stone harboring infection

Imaging
- May be seen on KUB or ultrasound
- CT is gold-standard
  - Provides clear information on stone location and configuration
  - Evaluates cortical thickness
  - Can identify excluded calyces and calyceal diverticula
  - Provides information on location of surrounding structures
  - Aids selection of access site(s)

Diagnostic Procedures/Surgery
Diagnosis is made based on imaging studies

Pathologic Findings
- Gross pathology—calculus material
- Microscopic evaluation of crystals aids in determination of stone composition

DIFFERENTIAL DIAGNOSIS
- Blood clot
- Fibroepithelial polyp
- Fungus ball
- Granuloma
- Hemangioma
- Malakoplakia
- Renal cell carcinoma and other renal malignancy
- Tuberculosis
- Upper tract carcinoma (urothelial, other)
- Xanthogranulomatous pyelonephritis (XGP)

TREATMENT

GENERAL MEASURES
- Culture-specific antibiotic therapy
- Relief of obstruction in anticipation of later intervention (stent, percutaneous nephrostomy tube)
- Observation is associated with significant morbidity, including renal deterioration and septic events. Only appropriate for patients who would not tolerate definitive intervention

MEDICATION
First Line

Culture-specific antibiotics

Second Line

- Acetohydroxamic acid
  - May reduce recurrence of struvite stones
  - Inhibits bacterial urease, decreasing urinary ammonia production
  - Adult dose: 12 mg/kg/d PO, 3–4 times a day on empty stomach. 1.5 g/d maximum.
  - Pediatric dose: 10 mg/kg/day titrated
  - May have severe side effects including deep venous thrombosis, myelosuppression, hepatotoxicity, palpitations, edema, nausea, vomiting, diarrhea, headache, loss of taste sensation, hallucinations, rash, abdominal discomfort
  - Must follow CBC and liver functions
  - Contraindicated in patients with severe renal insufficiency (serum creatinine >2.5 mg/dL)

SURGERY/OTHER PROCEDURES

- Goal is complete elimination of stone burden
- Percutaneous nephrolithotomy (PCNL) is gold-standard (1)
- Shockwave lithotripsy (SWL) is not recommended as monotherapy for most staghorn calculi
- If combination SWL and PCNL or "sandwich" therapy is performed, PCNL should be the last intervention
- SWL monotherapy can be considered for small stones (<500 mm^2), provided a ureteral stent or nephrostomy tube is placed. May also be used in pediatric patients.
- Open surgery is not commonly performed. May be used in extraordinary cases where clearance is not expected within a reasonable number of less-invasive procedures
- Nephrectomy for kidneys with negligible function or Xanthogranulomatous pyelonephritis (XGP)
- Dissolution may be effective in carefully selected patients, but has the potential for significant side effects. It is not presently included in the guidelines for staghorn management.

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Prophylactic antibiotics to suppress UTI

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Observation associated with significant risk of renal deterioration (28–48%) (2,3)
- Good prognosis for patients who are rendered stone-free

COMPLICATIONS

- Observation

  - Death
  - Functional renal loss
  - Pyelonephritis
  - Sepsis
- Intervention
  - Anesthesia complications
  - Death
  - Hematoma
  - Hemorrhage
  - Injury to colon, liver, spleen
  - Pneumothorax/hydrothorax
  - Upper tract injury
  - Urinary fistula
  - Urinoma

FOLLOW-UP

Patient Monitoring

- KUB and ultrasound at regular intervals
- Urinalysis and culture
- Consider metabolic evaluation (serum studies, 24-hr urine study)

Patient Resources

N/A

REFERENCES

1. Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol*. 2005;173:1991–2000.
2. Koga S, Arakaki Y, Matsuoka M, et al. Staghorn calculi—long-term results of management. *Br J Urol*. 1991;68:122–124.
3. Teichman JM, Long RD, Hulbert JC, et al. Long-term renal fate and prognosis after staghorn calculus management. *J Urol*. 1995;153:1403–1407.

ADDITIONAL READING

- Healy KA, Ogan K. Pathophysiology and management of infectious staghorn calculi. *Urol Clin N Am*. 2007;34:363–374.
- (AUA) Report on the Management of Staghorn Calculi (2005). https://www.auanet.org/education/guidelines/staghorn-calculi.cfm. Accessed January 25, 2014.
- Segura, JW. Staghorn calculi. *Urol Clin N Am*. 1997;24:71–80.

See Also (Topic, Algorithm, Media)

- Pyelonephritis, Xanthogranulomatous
- Urinary Tract Infection (UTI), Complicated, Adult
- Urinary Tract Infection (UTI), Complicated, Pediatric
- Urolithiasis, Adult, General

- Urolithiasis, Pediatric, General
- Urolithiasis, Staghorn Image ☼

CODES

ICD9

- 274.11 Uric acid nephrolithiasis
- 592.0 Calculus of kidney
- 599.0 Urinary tract infection, site not specified

ICD10

- N12 Tubulo-interstitial nephritis, not spcf as acute or chronic
- N20.0 Calculus of kidney
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- Staghorn calculi are large branching renal calculi most often associated with urinary tract infections.
- Observation carries a high risk of morbidity, including renal deterioration and sepsis.
- Percutaneous nephrolithotomy is the gold-standard for treatment.

UROLITHIASIS URETERAL

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BASICS

DESCRIPTION

- Ureteral urolithiasis refers to a stone present in the ureter.
- Ureteral stones usually pressent with severe colicky pain that radiates from the loin (flank) to the groin as the stone passes to the lower ureter. Ureteral stone can cause obstructive uropathy as well as urosepsis which are a clinical emergency.
- Stone composition:
  - Calcium oxalate 85%
  - Uric acid 5–10%
  - Calcium phosphate and oxalate 10%
  - Struvite (infection stones) 2–20%
  - Cystine 1%

EPIDEMIOLOGY

Incidence

- The incidence of ureteral stones is increasing worldwide
- 116 affected individuals per 100,000 in the United States
- Peak incidence reported age ranging from 40 to 49 yr
- Prevalence rates decrease in women over age 59 yr and men over age 69 yr
- 2.3% for women and 7% for men
- White > Hispanics > Asian > Blacks

Prevalence

The prevalence of stone disease in the United States is 5.2% which has doubled since the 1960s.

RISK FACTORS

- Genetic and environmental factors
- Diet and climate have the most significant impact on the prevalence
- Males are 3 times more affected than females
- Diet: Dehydration, high animal protein, high salt diet, vitamin D (too much?), vitamin C and (low?) calcium consumption
- Obesity, metabolic syndrome
- Previous history of stone formation
- Urinary tract infection: urease producing bacteria such as Proteus
- Family history: 3 times normal risk
- Drugs: Chemotherapy, corticosteroids
- Hot climate

Genetics

- Stone formation is common in Caucasian and Asians.
- 25% of kidney stone patients report a family history of stone disease
- Familial renal tubular acidosis and cystinuria predispose for stone formation

PATHOPHYSIOLOGY

- Supersaturation: The urine is supersaturated with salts when the concentration of the salt exceeds its solubility product (K_{sp}). Beyond this point crystallization start to form. The concentration at which crystallization occurs is called formation product (K_f).
- Supersaturation depends on urinary PH, ionic strength, solute concentration, and complexation.
- Inhibitors of crystallization: The presence of inhibitors allows urine to hold more solute in solution, inhibiting stone formation
  - Calcium oxalate: Absorptive hypercalciuria, resorptive hypercalciuria, renal hypercalciuria, hypercalcemia, hyperuricosuria, hyperoxaluria, hypocitraturia, enteric hyperoxaluria
  - Uric acid stones: Gout, myeloproliferative disorders, idiopathic uric acid stones, chemotherapy
  - Calcium phosphate and oxalate stones: Distal renal tubular acidosis
  - Struvite stones: Occur as a result of infection with urease-producing bacteria that breakdown urea into ammonia
  - Cystine stones: Occur in patients with cystinuria an autosomal recessive disorder resulting in reduced absorption of cystine from the proximal tubules
  - Medication stones (rare): Triamterene, indinavir.

ASSOCIATED CONDITIONS

- Primary hyperparathyroidism
- Medullary sponge kidney/nephrocalcinosis
- Distal (type 1) renal tubular acidosis
- Chronic diarrheal states: GI surgery: gastric bypass/banding, small bowel resection
- Gout
- Sarcoidosis
- Primary hyperoxaluria
- Cystinuria

GENERAL PREVENTION

- Adequate hydration
- Low protein diet
- Reduce dietary salt
- Allopurinol for uric acid stones
- Alkalinization of urine using potassium citrate
- Restrict oxalate consumption

DIAGNOSIS

HISTORY

- Acute onset colicky pain that radiates from the loin to the groin

- Patient moves around trying to find a comfortable position
- Lower ureteral stone pain may radiate to the tip of the penis
- Microscopic haematuria and very rarely macroscopic haematuria
- Previous history of renal stones
- Urinary frequency, urgency, and urinary incontinence are associated with lower ureteral stones

ALERT
Obstructed infected kidney is a clinical emergency.

PHYSICAL EXAM
- The most important aspect of examination of patient with ureteral stone is core body temperature.
- Abdominal examination may reveal tenderness.
- Urosepsis is associated with high temperature, low blood pressure, and tachycardia.

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC to test for underlying infection (See General Measures).
- Serum creatinine to detect renal impairment.
- Urine analysis: To check for hematuria, nitrite, and leukocytes.
  – Up to 30% of patients with ureteral stones have no blood in their urine.

Imaging
- Computed tomography: Non-contrast spiral CT is the imaging of choice for patient with suspected ureteral stone.
- Intravenous urography: Can document renal anatomy.
- X-ray KUB: Only in radio opaque stones. Most practical for conservative management.
- Ultrasound:
  – Operator dependent. Very useful in pregnancy, patients with contrast allergy and children. Can miss small kidney stones. Normal examination does not rule out ureteral stone since hydronephrosis is a relatively late finding.
- MR urography: May be used to diagnose Ureteral stones due to ureteral dilatation, but stones usually not well seen. Cost and availability also limit its routine use.

Diagnostic Procedures/Surgery
Retrograde pyelography: Occasionally used in the diagnosis. Is used in conjunction with ureteroscopy.

Pathologic Findings
Depend on stone composition

DIFFERENTIAL DIAGNOSIS
- Abdominal aortic aneurysm
- Acute appendicitis
- Acute cholecystitis
- Pancreatitis
- Peritonitis

- Pyelonephritis
- Renal cell carcinoma
- Upper-tract TCC
- Ureteropelvic junction obstruction

TREATMENT

GENERAL MEASURES

- Ureteral calculi which are associated with renal impairment and/or signs of infection are indication for emergency treatment with broad-spectrum antibiotics and decompression of the renal tract.
- Infected stones warrant close observation to limit morbidity and mortality. Systemic inflammatory response syndrome (SIRS) is the earliest manifestations of the continuum leading to sepsis and shock and these patients require intensive monitoring. These criterion for SIRS include 2 or more of the following (1):
  - Temperature $>38^{\circ}C$ or $<36^{\circ}C$
  - Heart rate >90 BPM
  - Respiratory rate >20 breaths/min
  - WBC $>$ 12,000/mm^3 or $<4000/mm^3$ or $>10\%$ bands
- Mortality is improved with decompression of an infected system (ureteral or percutaneous nephrsotomy tube [PCNT]) (2).
- Watchful waiting: Small ureteral stones will pass spontaneously and do not require any intervention (see rate of spontaneous stone passage).
- Indication of conservative management:
  - Stone size less than 10 mm
  - Well-controlled pain
  - No clinical evidence of infection
  - Adequate renal function reserve
- Spontaneous passage of stone depends on the stone size, shape, location, and associated ureteral edema
  - 68% of stones 5 mm or less pass spontaneously
  - 47% of stones 6–10 mm in diameter
  - $>$ 10 mm unlikely will pass
- Average stone passage time is 3 wk, stone has not passed within 2 mo is unlikely to pass.

MEDICATION

First Line

- Pain control: Nonsteroidal anti-inflammatory drugs, or opiate analgesia.
- Antiemetics: If the acute pain is associated with nausea and vomiting.
- Treat dehydration and avoid excessive fluid intake as it may increase discomfort.
- Broad-spectrum empiric antibiotic in the presence of infection, modified based on culture
  - 3rd-generation cephalosporin, or a fluoroquinolone (ciprofloxacin, levofloxacin)
  - Aminoglycoside or a carbapenem with high rate of fluoroquinolone resistance.
  - For hospital-acquired urosepsis following urologic interventions, an antipseudomonal 3rd-generation cephalosporin or piperacillin/β-lactamase inhibitor in combination with an

aminoglycoside or a carbapenem.
- Ureteroscopy: Fluoroquinolone, trimethoprim sulfamethoxazole, or aminoglycoside ± ampicillin or 1st/2nd-generation cephalosporin or amoxicillin/clavulanate (3).
- Percutaneous nephrolithotomy (PCNL): 1st/2nd-generation cephalosporin, or aminoglycoside + metronidazole or clindamycin or aminoglycoside/sulbactam or fluoroquinolone (3)

Second Line
- Medical expulsive therapy: α1-adrenergic adrenoceptor blockers (such as tamsulosin) cause smooth muscle relaxation and increase spontaneous stone passage rate by 1/3. However, it is not licensed yet for this purpose. It is contraindicated in the presence of infection.
- Oral chemolysis: High fluid intake and alkalinization of urine with potassium citrate is indicated in uric acid and cystine stones.

SURGERY/OTHER PROCEDURES
- Extracorporeal shock wave lithotripsy (ESWL): Using ultrasound shock wave to fragment the stone. The efficacy is related to the stone size and location. The clearance rate for stone <10 mm in the upper ureter is >80%
- Ureteroscopy and endoscopic lithotripsy: Has a higher clearance rate for upper ureteral stones >10 mm and all mid Ureteral and distal ureteral stones compared to ESWL.
- There are no significant differences between ESWL and ureteroscopy and the use of either treatment depend on local resources.
- Other treatment modalities such as percutaneous nephrolithotomy, open ureterolithotomy, laparoscopic ureterolithotomy are rarely used.
- The presence of infection requires emergency management Antibiotics with urinary diversion (stent or PCNT).

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

Prevention of further stone formation (see general prevention)

Complementary & Alternative Therapies

No alternative or complementary medications have been shown to be beneficial

ONGOING CARE

PROGNOSIS
- The prognosis of ureteral calculi is excellent.
- Patient with recurrent stone formation needs metabolic workup.

COMPLICATIONS
- Infection, bleeding, and pneumothorax are the complications of the treatment
- Multiorgan failure
- Renal impairment
- Urosepsis

FOLLOW-UP

Patient Monitoring

- Patient is followed to detect any further stone formation
- Prevention measures to avoid further stone formation (see general prevention)
- Patients with septic stone picture require at least 14 days of culture appropriate antibiotics

Patient Resources

Urology Care Foundation: Kidney and Ureteral Stones.
http://www.urologyhealth.org/urology/index.cfm?article=148

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. ; ACCP/SCCM Consensus Conference Committee Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. *Chest*. 1992;101:1644.
2. Borofsky MS, Walter D, Shah O, et al. Surgical decompression is associated with decreased mortality in patients with sepsis and ureteral calculi. *J Urol*. 2013;189(3):946.
3. Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (2008). http://www.auanet.org/education/guidelines/antimicrobial-prophylaxis.cfm

ADDITIONAL READING

- Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol*. 2003;170:2202–2205.
- Goldsmith ZG, et al. Cooling off Hot Stones AUA News, Volume 18; Issue 10; October, 2013.
- Preminger GM, Tiselius HG, Assimos DG, et al. ; EAU/AUA Nephrolithiasis Guideline Panel. 2007 guideline for the management of ureteral calculi. *J Urol*. 2007;178:2418–2434.
- Romero V, Akpinar H, Assimos DG, et al. Kidney stones: A global picture of prevalence, incidence, and associated risk factors. *Rev Urol*. 2010;12(2–3):e86–e96.

See Also (Topic, Algorithm, Media)

- Urolithiasis, Adult, General Considerations
- Urolithiasis, Pediatric, General Considerations
- Urolithiasis, Renal
- Urolithiasis, Ureteral Algorithm
- Urolithiasis, Ureteral Image
- Urosepsis

CODES

ICD9

- 592.1 Calculus of ureter
- 599.0 Urinary tract infection, site not specified
- 599.60 Urinary obstruction, unspecified

ICD10

- N13.9 Obstructive and reflux uropathy, unspecified

- N20.1 Calculus of ureter
- N39.0 Urinary tract infection, site not specified

CLINICAL/SURGICAL PEARLS

- In the setting of an infected obstructing ureteral calculus, there is no significant difference in outcome whether stented or treated by percutaneous drainage.
- Recent studies suggest that in unstable patients with very large stone burdens percutaneous drainage may be preferred.

UROLITHIASIS, URIC ACID

Aaron G. Boonjindasup, MD, MPH
Raju Thomas, MD, MHA, FACS

BASICS

DESCRIPTION
- Urinary stones that are composed primarily of uric acid and can be found anywhere in the urinary tract.
- Uric acid usually precipitates in acidic urine.

EPIDEMIOLOGY
Incidence
Account for 5–10% of all urinary tract stones

Prevalence
1/1000 adults

RISK FACTORS
- Persistent acidic urine is most important pathogenic factor.
- Strenuous exercise, dehydration
- Bowel related:
  - Crohn disease, regional ileitis
  - Ulcerative colitis, ileostomy, short bowel syndrome
- Hyperuricosuria, gout
  - Uric acid nephrolithiasis occurs in 10–25% of patients with gout
- Purine gluttony
- Inborn errors of metabolism
  - Lesch–Nyhan syndrome
    - Hypoxanthine guanine phosphoribosyl transferase deficiency (HGPRT)
  - Phosphoribosylpyrophosphate synthetase overactivity
  - Glucose-6-phosophate deficiency
- Myeloproliferative states
  - Neoplasia
  - Leukemia
  - Hemolytic anemia
  - Chemotherapy
- Decreased urinary volume
- Diabetes associated with metabolic syndrome

Genetics
Autosomal dominant for familial variant

PATHOPHYSIOLOGY (1)
- Uric acid crystallization caused by the supersaturation of urine with respect to undissociated uric acid.

- Free uric acid is 20× LESS soluble in urine than urate salt.
- At a pH of 5.35, ½ of the uric acid is a urate salt and ½ is free uric acid.
- At pH of 6.5, 90% of the uric acid is soluble.
- Uric acid may serve as a nidus.
  - Calcium oxalate stone formation
- Acute and chronic nephropathy due to uric acid crystals in renal tubules
  - May be related to hyperuricemia or gout
- Uricase—enzyme that converts uric acid to allantoin
  - Allantoin—10 to 100× more soluble in urine than uric acid
- Relationship between obesity, diabetes, and the metabolic syndrome
  - Causes of low urinary pH.
  - Low urinary pH in turn is the major urinary risk factor for uric acid stones
- High plasma uric acid (UA) is a precipitating factor for gout and renal calculi as well as a strong risk factor for metabolic syndrome and cardiovascular disease.

ASSOCIATED CONDITIONS

- Obesity with insulin resistance (metabolic syndrome)
  - High waist circumference and BMI are associated with higher insulin resistance and leptin production; both reduce uric acid excretion.
- Myeloproliferative disorders
- Congenital disorders
  - Lesch–Nyhan syndrome
- Gout
- Inflammatory bowel disease

GENERAL PREVENTION

- Low purine diet in at-risk population
- Encourage fluid intake

DIAGNOSIS

HISTORY

- Acute presentation of urolithiasis
  - Pain, fever, chills, nausea, vomiting
- Purine gluttony
  - Diet high in red meats, fish, poultry
- Dehydration
  - Poor urine output
  - Poor urine volume
- Gout
  - Up to 20% of patients will have uric acid calculi
- Family history of uric acid stones
- Short bowel syndrome, inflammatory bowel disease, ileostomy
- History of myeloproliferative disorders

PHYSICAL EXAM

Costovertebral angle (CVA) tenderness

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Serum uric acid level may be normal or elevated
  - >380 μmol/L or 6.4 mg/100 mL
  - Latent hyperuricemia may require purine loading test
- Urinalysis
  - pH: Acidic. Generally <5.8
  - Crystals: Coffin-lid crystals
- 24-h urine collection for uric acid
  - Volume <2 L/d
  - pH <6.0
  - Uric acid >4.0 mmol/d
  - Can often underestimate the total amount of uric acid of pH drops lower than 5.5

Imaging

- Non-contrast abdominal spiral computed tomography (CT): Gold standard
- Plain x-ray Kidneys, ureters, bladder (KUB)
  - Uric acid stones are often RADIOLUCENT (noncalcified); plain film often not useful
- Renal ultrasound
- Intravenous (IV) urogram

Diagnostic Procedures/Surgery

- Stone analysis
- 24-hr urine collection for uric acid

Pathologic Findings

- Long-term deposition of crystals in the renal parenchyma can cause chronic urate nephropathy.
- Microtophi cause giant-cell inflammatory reaction
  - Proteinuria
  - Inability of the kidney to concentrate urine
- May have orange appearance when viewed endoscopically

DIFFERENTIAL DIAGNOSIS

- Other renal calculi
  - Calcium oxalate monohydrate
  - Calcium oxalate dehydrate
  - Cysteine
  - Struvite
- Filling defect if IV urogram is obtained
  - Urothelial neoplasm
  - Blood clot
  - Fungus ball
  - Sloughed renal papilla
  - Stricture
- Bladder calculi
  - 50% consist of uric acid

TREATMENT

GENERAL MEASURES (2)

ALERT
- During alkalinization, do not allow urinary pH to chronically rise above 7.0.
- This may cause precipitation of other urinary calcium salts (heterogenous nucleation/epitaxy).

- Acute renal colic should be treated accordingly (see Section I "Urolithiasis, adult, general considerations")
- Uric acid stones are often amenable to medical therapy
  - Low-protein/low purine diet
  - >2 L fluid intake/day
  - Alkalinization of urine
- Medical therapy should only be initiated in moderately symptomatic or asymptomatic patients

MEDICATION

First Line (3)

- Potassium citrate 30–60 mEq/d
  - Urine alkalinization
  - Goal is pH between 6.0 and 7.0
    - Do not exceed 7.0, may precipitate other stones
  - May require 3–4 mo to dissolve stone
  - Requires patient to monitor urine pH daily with Nitrazine paper or pH paper
- Sodium bicarbonate 650 mg q6–8h
  - May cause high sodium load

Second Line

- Allopurinol 100–600 mg/d
  - Hyperuricemia or urinary uric acid secretion >100 mg/d
  - Inhibits conversion of hypoxanthine and xanthine to uric acid
  - Use if failed urine alkalinization
  - Add to PO alkalinization
  - SE: Skin rash, fever, acute attack of gout

SURGERY/OTHER PROCEDURES

- Dependent on size and position of stone
  - Extracorporeal shock wave lithotripsy (ESWL)
  - Ureteroscopy with lithotripsy
  - Percutaneous nephrolithotomy
- Rarely
  - Open/laparoscopic nephrolithotomy
  - Alkaline irrigation via nephrostomy tube

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Treat underlying illness
- Evaluate for and treat gout if elevated serum uric acid
- Correct metabolic syndrome though diet and weight reduction
- Febuxostat a relatively new xanthine oxidase inhibitor (80 mg daily) has been used in the management of hyperuricemia in patients with gout with limited information on uric acid stones. It can reduce uric acid excretion.

Complementary & Alternative Therapies

- Foods rich in urate should be restricted in patients with uric acid stone disease.
- The intake of urate should not exceed 500 mg/d.

ONGOING CARE

PROGNOSIS

Dependent on etiology and stone characteristics

COMPLICATIONS

- Sepsis
- Obstructive nephropathy

FOLLOW-UP

Patient Monitoring

- Urinalysis
  – pH, crystals, red blood cells (RBCs)/white blood cells (WBCs)
- Follow stone size with US or low-dose CT every 3–6 mo on medical therapy

Patient Resources

- Urology Care Foundation: Kidney and Ureteral Stones. http://www.urologyhealth.org/urology/index.cfm?article=148
- National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). http://kidney.niddk.nih.gov/Kudiseases/pubs/kidneystonediet/index.aspx

REFERENCES

1. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis.*Curr Opin Nephrol Hypertens.* 2004;13:1981–1989.
2. Kraft K, Pattaras J. Medical management of urolithiasis. *AUA Update Series*. 2007. Vol 26: Lesson 36.
3. Kenny JE, Goldfarb DS. Update on the pathophysiology and management of uric acid renal stones. *Curr Rhematol Rep.* 2010;12(2):125–129.

ADDITIONAL READING

- Mehta TH, Goldfarb DS. Uric acid stones and hyperuricosuria. *Adv Chronic Kidney Dis.* 2012;19(6):413–418.
- Tiselius HG, Alken P, Buck C, et al. EAU Guidelines on Urolithiasis. http://www.uroweb.org/fileadmin/user_upload/Guidelines/Urolithiasis.pdf. Accessed April

6, 2014.

See Also (Topic, Algorithm, Media)

- Bladder Calculi
- Metabolic Stone Evaluation (24 Hour Urine Studies)
- Pregnancy, Urolithiasis
- Urate, Dietary
- Urolithiasis, Adult, General
- Urolithiasis, Calcium Oxalate/Phosphate
- Urolithiasis, Pediatric, General
- Urolithiasis, Uric Acid Image ☼

CODES

ICD9

- 274.11 Uric acid nephrolithiasis
- 592.0 Calculus of kidney
- 790.6 Other abnormal blood chemistry

ICD10

- E79.0 Hyperuricemia w/o signs of inflam arthrit and tophaceous dis
- N20.0 Calculus of kidney
- N20.9 Urinary calculus, unspecified

CLINICAL/SURGICAL PEARLS

- Common conditions that increase the risk of uric acid stone formation: gout, chronic diarrhea, diabetes, and metabolic syndrome.
- Uric acid stones are often radiolucent (noncalcified); therefore, plain film often not useful.
- Non-contrast abdominal spiral computed tomography (CT) is considered the gold standard for imaging urolithiasis including uric acid stones.
- The metabolic syndrome causes low urinary pH which in turn is a major urinary risk factor for uric acid stones.
- Alkalinization can dissolve uric acid calculi.

UROSEPSIS

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Nick Cowan, MD

BASICS

DESCRIPTION

- Sepsis is the systemic inflammatory response syndrome (SIRS) with associated infection, and urosepsis identifies the source of the infection as originating somewhere in the urinary tract.
- International Sepsis Definitions Conference definitions:
  - SIRS: 2 or more of the following:
    - Temperature >38°C or <36°C
    - Heart rate >90 beats/min
    - RR >20 breaths/min or $PaCO_2$ <32 mmHg
    - WBC >12,000 cells/mL or <4,000 cells/mL or >10% bands
  - Sepsis:
    - SIRS in response to a suspected or proven infection
  - Severe sepsis: Sepsis-induced tissue hypo-perfusion or organ dysfunction (any of the following thought to be due to infection):
    - Sepsis induced hypotension
    - UOP <0.5 mL/kg/hr for more than 2 hr despite adequate resuscitation
    - Lactate above upper limits normal
    - Acute mental status changes
    - Platelets <100,000 cells/mL
    - Acute lung injury/ARDS
  - Septic shock: Sepsis-induced hypotension despite adequate fluid resuscitation, along with signs of hypoperfusion
- Differentiate SIRS and sepsis
  - Noninfectious processes (such as acute pancreatitis) may also be complicated by tissue injury secondary to the inflammatory system.
  - SIRS refers to the dysregulated host inflammatory response in the absence of infection.
  - It is essential to distinguish an underlying disease (infection or non-infection) and the host response (sepsis or SIRS).
- It is estimated that UTIs account for 5% of severe sepsis cases.

EPIDEMIOLOGY

Incidence

- Sepsis occurs in >1.6 million patients in the United States annually, with an estimated incidence of 240 cases per 100,000 population.
- Patients aged ≥65 yr account for nearly 60% of all episodes of severe sepsis.

Prevalence

N/A

RISK FACTORS

- Advanced age (≥65 yr)
- Diabetes, malignancy, immunosuppression, cachexia, immunodeficiency, alcoholism
- Obstructive uropathy: BPH, prostate cancer, stricture, urolithiasis, neurogenic bladder disorders, retroperitoneal masses and fibrosis, sloughed papilla, endometriosis
- Abnormal/congenital anatomy: ureteropelvic junction obstruction, polycystic kidneys, ureterocele, vesicoureteral reflux, phimosis
- Inflammatory/infectious diseases:
  - Pyelonephritis, acute bacterial prostatitis, renal abscess, perinephric abscess, epididymo-orchitis, Fournier gangrene
- Precipitating interventional/nosocomial events resulting in bacteremia and subsequent urosepsis:
  - Indwelling catheters, urologic instrumentation/surgery such as prostate biopsy, transurethral surgery

Genetics

Genetic factors are known to be major determinants of susceptibility to death from infectious disease.

PATHOPHYSIOLOGY

- Sepsis is a systemic, deleterious host response to infection leading to severe sepsis and septic shock.
- The most common etiology of urosepsis is secondary to a bacterial infection with *Escherichia coli, Proteus* sp., *Enterobacter* and *Klebsiella* sp., *and Pseudomonas aeruginosa*
- Obstruction in an infected urinary tract further contributes to the development of sepsis.
- Primary initiator of gram-negative bacteria septic shock is endotoxin, a lipopolysaccharide component of the bacterial cell membrane.
- Exotoxins released by some bacteria can initiate septic shock:
  - However, the bacteria themselves and cell wall components are primarily responsible for the development of septic shock.
- The intravascular activation of inflammatory systems results in overproduction of cytokines such as tumor necrosis factor (TNF) and IL-1.

ASSOCIATED CONDITIONS

- Acute pyelonephritis
- Lower UTI
- Urolithiasis
- Urologic procedure/instrumentation

GENERAL PREVENTION

- Urine culture and appropriate antibiotic coverage prior to urologic procedure
- To further reduce incidence of nosocomial UTI: remove Foley as soon as it is no longer needed, use aseptic insertion technique, maintain unobstructed flow, use closed urinary drainage systems (1)[B].

DIAGNOSIS

HISTORY

- A thorough history should be obtained, with emphasis on identifying the primary etiology:
  - Classic presentation of fevers, chills, followed by hypotension seen in only ~30% of patients.
- A history of hydronephrosis, urolithiasis, flank pain, UTIs, immunocompromised status, urinary retention, and recent urologic instrumentation/procedure is common.
- Evaluate for mental status changes.

PHYSICAL EXAM

- Emphasis on identifying the primary source of the infection
- Most common findings: Hyper thermia, hypothermia, tachycardia, tachypnea, and hypotension
- Earliest signs of sepsis may be increased respiratory rate with respiratory alkalosis.
- Examine for all urologic and non-urologic sources of bacteremia:
  - Purulent subcutaneous fluid collections; chest exam; costovertebral angle tenderness; abdominal or suprapubic tenderness; examine of the scrotum, testis, perineum; prostatic fluctuance; extremities for tenderness or swelling.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- CBC with differential: Usually shows elevated WBC count with elevated neutrophil count.
  - Patients may also have neutropenia
- Basic metabolic panel (BMP), liver finction tests (LFT's), lactate: May show evidence of end-organ dysfunction
- Blood, urine, and wound culture with a Gram stain for preliminary identification:
  - If possible obtain 2 sets of blood cultures before starting empiric antibiotics
  - Specific organisms causing sepsis are identified in about half of patients

Imaging

- Obtain based on presumptive initiating event and clinical symptoms
  - US can quickly evaluate for hydronephrosis
  - CT scan can evaluate for stones, fluid collections and gas within tissues

Diagnostic Procedures/Surgery

Diagnostic procedures should be tailored to identifying the initiating event.

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Upper urinary tract source:
  - Emphysematous pyelonephritis
  - Pyelonephritis, pyonephrosis
  - Renal and perirenal abscess
  - Xanthogranulomatous pyelonephritis
- Lower urinary tract source:
  - Acute bacterial prostatitis
- External genitalia:

- Epididymitis/orchitis
- Fournier gangrene
- Pyoderma gangrenosum
- Testicular abscess

• Common non-urologic causes of sepsis:
- Central lines
- Empyema, pneumonia
- Endocarditis, mediastinitis
- Prosthetic device infection
- Intra-abdominal processes: Pancreatic infection, cholecystitis, cholangitis, peritonitis, diverticular/appendiceal/tubo-ovarian abscess
- Septic arthritis
- Soft-tissue infection

• Noninfectious conditions that mimic sepsis:
- Acute adrenal insufficiency
- GI bleed
- Myocardial infarction
- Pancreatitis
- Pulmonary embolus
- Transfusion reactions

TREATMENT

GENERAL MEASURES

• Early goal-directed therapy, "Rivers protocol":
- Goal MAP ≥65 mmHg, CVP 8–12 mmHg, UOP ≥0.5 mL/kg/hr
- Start empiric IV antibiotics (ABX) within 1 hr. of recognition of severe sepsis or septic shock
- Volume expansion with isotonic fluids
- Supplemental oxygen with or without intubation and assisted ventilation if indicated
- Vasoactive drugs to achieve hemodynamic goals (norepinephrine preferred to dopamine)
- Maintain glycemic control
  - Keep glucose <180 mg/dL as intensive glycemic control (80–110 mg/dL) has shown either no change or increased mortality, and increased rates of hypoglycemia (2)[A]

ALERT
Autopsy studies in persons who died in the ICU show that the failure to diagnose and treat infections with antibiotics or surgical drainage is the most common avoidable error.

MEDICATION

First Line (3)

• Broad-spectrum antibiotic coverage (against both gram-positive and gram-negative bacteria) should be instituted immediately.

• Nosocomial urosepsis monotherapy:
- Piperacillin/tazobactam, imipenem, or meropenem

  – Add vancomycin if MRSA a concern
• Monotherapy for urosepsis due to aerobic gram-negative bacilli:
  – Aztreonam: 2 g IV q6–8h; max 8 g/d
  – Levofloxacin: 500 mg IV q24h
  – 3rd-generation cephalosporins:
    ◦ Ceftriaxone: 1–2 g IV q12–24h
    ◦ Cefotaxime: 2 g IV q6–8h
    ◦ Ceftazidime: 500 mg IV q8–12h
  – 4th-generation cephalosporin:
    ◦ Cefepime: 2 g IV q12h
• Monotherapy for suspected enterococci (*E. faecalis*) urosepsis: Ampicillin or vancomycin (penicillin-allergic).
• Community-acquired urosepsis infection:
  – Levofloxacin, aztreonam, or an aminoglycoside plus ampicillin
• Fournier gangrene:
  – Piperacillin/tazobactam 3.375 IV q6h, add vancomycin 1 g IV q12h if MRSA suspected
  – Imipenem: 500–1,000 mg IV q6h for polymicrobial coverage.
  – Clindamycin: 600–900mg IV q8hr for anaerobic coverage if *Clostridia* are suspected (to block toxin production)

Second Line
• Reassess antimicrobial regimen daily and deescalate when sensitivity results are available.
• Switch to PO ABX when clinically stable for at least 48 hr and usually complete a 7–10 day course based on the cause of the infection.

SURGERY/OTHER PROCEDURES
• Patients should undergo surgical drainage of purulent collections, debridement of necrotic tissue, and relief of urinary tract obstruction.
• Retrograde ureteral catheterization and percutaneous nephrostomy effectively relieve obstruction and infection due to ureteral calculi
  – Neither modality has demonstrated superiority in promoting a more rapid recovery

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
• Definitive correction of any correctible factors when patient stabilized
• Corticosteroid use in sepsis is complex and current data do not show improved survival in severe sepsis

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
• Mortality rates associated with severe sepsis and septic shock are 25–30% and 40–70%,

respectively.
- Factors associated with a higher risk of mortality from sepsis: Fever, WBC count, serum creatinine, diabetes mellitus, lactate, and albumin.

ALERT
Mortality rate decreased by 42% when early goal-directed therapy achieved within the first six hours for severe sepsis and septic shock.

COMPLICATIONS
Renal insufficiency, hepatic dysfunction, end organ failure, cardiac events, death

FOLLOW-UP
Patient Monitoring
- Patient should be continued on appropriate ABX coverage for 7–10 days, longer if needed.
- Repeat cultures can be obtained to ensure treatment is adequate.

Patient Resources
International Sepsis Forum: Understanding Sepsis.
http://internationalsepsisforum.com/sepsis-booklet

REFERENCES

1. Russell J. Management of sepsis. *N Engl J Med*. 2006;355(16):1699–1713.
2. Dellinger R, Levy MM, Rhodes A, et al. ; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580.
3. Grabe M, Bjerklund-Johansen TE, Botto H. Guidelines on Urological Infections. Arnhem, The Netherlands: European Association of Urology (EAU); 2011:33–39.

ADDITIONAL READING

- Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet*. 2005;365:63.
- Bugano DD, Camargo LF, Bastos JF, et al. Antibiotic management of sepsis: Current concepts. *Expert Opin Pharmacother*. 2008;9(16):2817–2288.
- Hotchkiss R, Karl I. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138–150.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368–1377.
- Wagenlehner FM, Weidner W, Naber KG, et al. Optimal management of urosepsis from the urological perspective. *Int J Antimicrob Agents*. 2007;30(5):390–397.

See Also (Topic, Algorithm, Media)
- Epididymitis
- Fournier Gangrene
- Prostatitis, Acute, Bacterial (NIH I)
- Pyelonephritis, Acute
- Pyelonephritis, Emphysematous
- Pyelonephritis, Xanthogranulomatous
- Renal and Perirenal Abscess

CODES

ICD9

- 599.0 Urinary tract infection, site not specified
- 785.52 Septic shock
- 995.92 Severe sepsis

ICD10

- N39.0 Urinary tract infection, site not specified
- R65.20 Severe sepsis without septic shock
- R65.21 Severe sepsis with septic shock

CLINICAL/SURGICAL PEARLS

- Early goal-directed therapy guided by invasive monitoring (mean arterial pressure [MAP], central venous pressure [CVP] and urine output [UOP]) within the first 6 hours after recognition or sepsis.
- Blood culture x2 prior to antibiotics if possible.
- Start empiric ABX within 1 hour of recognition of severe sepsis or shock.
- Initial fluid resuscitation with crystalloid.

UROSTOMY PROBLEMS

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BASICS

DESCRIPTION

- Urostomy is an incontinent urinary diversion and relies on an external appliance (pouching system) for the collection of urine.
- Urostomy can be made of either small or large intestine, with the distal ileum being the most common bowel segment used:
  - Also called ileal conduit, cutaneous ureteroileostomy if made up of ileum
  - Colon conduit, if made up of segment of large bowel.
  - Very rarely, a urostomy can consist of the ureters being directly anastomosed to the skin (cutaneous ureterostomies). These are uncommon in adults but are sometimes performed in children.
- Complications of the abdominal urinary stoma (urostomy) are the most common problem encountered in the postoperative period in patients undergoing urinary diversion.

EPIDEMIOLOGY

Incidence

- 2.8–19% of patients develop stomal stenosis with ileal conduits.
- 10–20% of patients with colon conduits develop stenosis.
- Parastomal hernia:
  - Occurs in 2–6.6% of patients with loop ileostomies
  - Rare with end stomas (1–4%)
  - More commonly occur with loop stomas (4–20%)
- Nearly all patients will have a stomal-related complication at some point.

Prevalence

N/A

RISK FACTORS

- Obesity
- Chronic cough
- Wound infection
- Abdominal distension
- Malnutrition
- Immunosuppression/steroid use
- Poor surgical technique
- Lack of proper stomal care
- Warm weather, excessive sweating, oily skin may cause the skin barrier adhesive to loosen
- Weight gain or loss can alter the topography of the stoma itself and the surrounding skin that may affect the security of the face plate adherence

Genetics

N/A

PATHOPHYSIOLOGY

- A pouching system (also called an appliance) collects the urine that exits from the stoma:
  - 2 styles of pouching systems are available:
    - Both include an adhesive faceplate, flange, skin barrier, or wafer (the part that sticks to the skin), and a urine collection pouch.
    - 1-piece pouches fused to skin barrier.
    - 2-piece systems have a face plate and a pouch that can be removed from the barrier.
- Patients should be encouraged to empty the pouch as needed but at least every 2–4 hr.
- The faceplate and system should be changed if there is leakage or every 4–7 days depending on individual patient characteristics.
- A properly constructed stoma usually protrudes ~1.5 cm from the abdominal wall:
  - Initially, a properly constructed stoma will be somewhat edematous. It will reduce slightly in size over several weeks following surgery. This means that the initial hole in the faceplate may change as the edema resolves.
  - The stoma is ideally not placed near a skin fold and is sufficiently far from the incision that the appliance will adhere and not leak.
- Early complications usually relate to impaired vascular supply (1):
  - Stomal necrosis can result in retraction, with a flush ostomy that is difficult to apply an appliance to.
- Early stomal retraction can be caused by an insufficient length of bowel segment or improper technique in securing and eversion of the stoma.
- Stomas stenosis: with or without obstruction:
  - Reported in 2.8–19%
  - May be asymptomatic, painful, or cause appliance fit problems
  - Stomal stenosis is less for loop stoma than end stomas.
  - Multifactorial causes: Fascial or muscular constriction, ischemia, and retraction allowing skin edges to overgrow opening (hyperkeratosis)
- Parastomal Hernia:
  - Gap between the intestinal segment forming the stoma and the surrounding fascia
  - Factors include obesity, malnutrition, chronic cough, wound infection.
  - Placement of the intestinal segment through the rectus fascia minimizes the risk of herniation.
  - Stomas placed lateral to the rectus fascia are more likely to develop a parastomal hernia (2.8% in rectus fascia vs. 21% lateral to rectus fascia).
  - Most parastomal hernias worsen with time.
- Poorly fitting appliances can cause social embarrassment and skin irritation and breakdown:
  - Urine contact (alkaline) with the skin can cause stomal encrustation, stomal epithelization, and eventual stenosis due to hyperkeratosis.
  - Unless contraindicated, maintaining the urine in an acid state is more protective of the skin (see below).
  - Peristomal skin problems can occur frequently and early after surgery.
- Irritative adhesives
- Fungal infections: redness and pruritus.

- Bleeding from portal HTN
- Urine pH:
  - Most fruits and vegetables: alkalinized urine.
  - Meats and cereals: acidic urine.
  - Unless contraindicated, keep urine in acidic pH range; protects skin, limits the deposition of urine crystals in and around the stoma.
- Calcifications and small stones due to exposed staples usually pass spontaneously

ASSOCIATED CONDITIONS
- Congenital anomalies such as exstrophy or myelodysplasia
- Urothelial carcinoma
- Urethral carcinoma

GENERAL PREVENTION
- Parastomal skin care can reduce bleeding, stomal stenosis, and dermatitis.
- Surgical technique ensuring a properly formed stoma in an appropriate location based on the abdominal wall contours
- Proper site location by an experienced stoma nurse preoperatively takes into account many variables, including the contour of the abdomen in the sitting and standing positions and the type of belts and garments worn by the patient.
- Proper selection of pouching system:
  - Compatibility with abdominal contours
  - Proper sizing of the pouch opening to minimize urine exposure on the skin
  - The opening on the adhesive skin barrier should be no more than 1/8-inch larger than the stoma to help keep urine off the skin.
- Emptying pouch appropriately such that excessive weight of the pouch will not disrupt the skin adhesion (usually when about 1/3 full)
- When changing the faceplate, the patient should learn to gently push the skin away from the sticky barrier rather than pulling the barrier off the skin.
- An acidic urine will be more protective of the peristomal skin than alkaline urine.

DIAGNOSIS

HISTORY
- Timing of diversion
- Weight change; may alter the fit of the faceplate
- Review the care of the stoma and appliance:
  - Frequency of face plate change
  - Frequency of emptying the collection pouch
- Complaints of parastomal skin lesions, bleeding, or dermatitis
- Problems with the adhesives, paste, tape, or pouch material

PHYSICAL EXAM
- Peristomal skin lesions:
  - Irritative parastomal lesions that are manifested by hypopigmentation, hyperpigmentation, and skin atrophy
  - Erythematous erosive lesions that are macular, scaling with loss of epidermis

– Pseudo-verrucous appear wartlike
- Minor bleeding from the exposed mucosa is common. Significant bleeding can be seen in cases of ileal conduit varices.
- Examine for evidence of parastomal herniation: Defect along fascial region of urostomy usually redicible
- Stomal stenosis or hyperkeratosis:
  – Calibrate ostomy with a sterile catheter if stomal stenosis present.
- Note presence of urinary crystals on the skin.

DIAGNOSTIC TESTS & INTERPRETATION

Lab

Usually not necessary

Imaging

- Not usually necessary. However, in the setting of severe stomal stenosis or prolapse, CT or US may identify dilation of the intestinal segment or evidence of hydronephrosis.
- Loopogram to identify if there is reflux or obstruction of the ureters with prolapse or parastomal herniation.

Diagnostic Procedures/Surgery

Calibration of the stoma with a red rubber catheter and determination if there is retained urine may be useful.

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Cutaneous allergic reaction or fungal infection
- Parastomal hernia
- Peristomal skin breakdown
- Stomal bleeding, prolapse, retraction, stenosis

TREATMENT

GENERAL MEASURES

- Proper initial surgical technique will minimize short- and long-term stomal problems.
- Proper stomal care and problem-solving is often accomplished by consultation with a certified ostomy care health provider:
  – Wound, Ostomy and Continence Nursing Certification Board (WOCNCB) provides certification in ostomy nursing
- A proper pouching system should have the following characteristics:
  – Secure, leak-proof seal that lasts 3–7 days
  – Protective of the skin around the stoma
  – Nearly invisible when covered with clothing
  – Easy to put on and take off
- Convex-style appliances can sometimes compensate for a retracted or flush stoma:
  – Many styles and adhesive types may offer options to correct many fit problems.
- A 1-piece urostomy system tends to be more flexible that a 2-piece unit; may help with

stomas that are near a deep abdominal fold or crease.
- Ostomy belts can sometimes help with securing the appliance in place and minimize mechanical disruption of the system.
- Gently trimming peristomal hair may help with face plate adherence.
- Allergic reaction to adhesive or other components can be addressed by switching to another product.
- Urine crystals on the skin or stoma (whitish gritty particles) are caused by alkaline urine:
  – Cranberry juice in place of citrus juices (citrus juices make the urine more alkaline)
  – Consider vitamin C daily
  – Some acid ash foods (make urine acidic) include: Most meats, breads and cereals, cheese, corn, cranberries, eggs, macaroni, nuts, pasta, prunes, fish, and poultry.
  – A 1:1 dilution of water and white vinegar applied with a cloth moistened with the mixture will dissolve the crystals.
- A pouch cover can help keep the skin beyond the skin barrier dry and reduce the incidence of superficial fungal infections where the pouch hangs down and contacts the skin.

MEDICATION

First Line
- Antifungal agents: Nystatin or miconazole powder lightly applied twice a day in cases of superficial fungal infection
- Severe allergic reactions to adhesive or appliance may require topical steroids short-term.

Second Line

N/A

SURGERY/OTHER PROCEDURES
- Surgical repair for parastomal hernias:
  – High likelihood of recurrence with or without relocation of the fascial opening. Suprafascial synthetic mesh wrap may decrease recurrence.
  – Period of conservative management appropriate; Laparoscopic repair reported
- Surgical revision for stomal stenosis
- Surgical revision of retracted stoma
- Liposuction reported to correct inverted stoma in obese patients
- Looposcopy to remove calculi

ADDITIONAL TREATMENT

Radiation Therapy

Some limited reports of radiation to treat stomal stenosis–related hyperkeratosis

Additional Therapies

Formally trained wound and ostomy care nurses or a nure with extensive experience can often help resolve many issues.

Complementary & Alternative Therapies

Asparagus and seafood may cause increased odor. Hydration helps limit odors in general.

ONGOING CARE

PROGNOSIS

Very good when intervention is applied in a timely fashion to prevent irreversible upper tract deterioration from stomal stenosis.

COMPLICATIONS

- Recurrent stomal stenosis
- Recurrent parastomal hernia
- Recurrent skin irritation from poor ostomy care
- Appliance leakage

FOLLOW-UP

Patient Monitoring

- Stomal wound care
- Cancer surveillance as per protocol

Patient Resources

- Wound, Ostomy and Continence Nursing Society. http://www.wocn.org/?page=patients
- Urostomy And Continent Urinary Diversion. http://kidney.niddk.nih.gov/kudiseases/pubs/urostomy/

REFERENCE

1. Salvadalena GD. The incidence of stoma and peristomal complications during the first 3 months after ostomy creation. *J Wound Ostomy Continence Nurs*. 2013;40(4):400–406.

ADDITIONAL READING

- American Cancer Society Urostomy Guide: http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/ostomies/ur Accessed August 2013.
- Gitlin J, Taneja SS. Complications of conduit urinary diversion. In: Taneja SS, et al., eds. *Complications of Urologic Surgery*, 4th ed. Philadelphia, PA: Saunders, 2010.
- Khalil el-SA. Long term complications following ileal conduit urinary diversion after radical cystectomy. *J Egypt Natl Canc Inst.* 2010;22(1):13–18.

See Also (Topic, Algorithm, Media)

- Catheterizable Stoma Problems
- Ureteroenteric Anastomotic Stricture
- Urostomy Problems Image

CODES

ICD9

- 553.29 Other ventral hernia without mention of obstruction or gangrene
- 997.5 Urinary complications, not elsewhere classified

ICD10

- K43.5 Parastomal hernia without obstruction or gangrene
- N99.531 Infection of other stoma of urinary tract
- N99.538 Other complication of other stoma of urinary tract

CLINICAL/SURGICAL PEARLS

- Urostomy difficulties are common.
- A urostomy that is flush with the skin causes significant skin excoriation and complications, so attempt to have the stoma protrude at least 1–2 cm above the skin when creating it in the OR.
- A convex stoma appliance can be helpful for stoma issues.

VAGINAL MESH EROSION

Jessica M. DeLong, MD
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BASICS

DESCRIPTION

- Mesh erosion is 1 of the major complications of prolapse surgery conducted by transvaginal approach.
- Currently, most common mesh used for pubovaginal sling (PVS) and pelvic organ prolapse (POP) repair is polypropylene mesh
- Most sling erosions diagnosed 1–18 mo postoperatively (mean 9 mo)
- Most common and consistently reported mesh-related complication for POP (1)
- May occur in isolation or in combination with urethral or bladder erosion
- Note: More specific term may be "vaginal extrusion"

EPIDEMIOLOGY

Incidence

- 0.012–23% for midurethral slings; varies widely in literature (2)
- Wide variation with POP repair as well
  - Attributed to type of synthetic material used
  - Older synthetic materials had higher risk of extrusion due to intrinsic properties

Prevalence

- Unknown; increasing over time with increasing use of mesh
- Likely underreported

RISK FACTORS

- Patient factors
  - Estrogen deficiency
  - History of local radiation
  - Early resumption of intercourse
- Operative factors
  - Use of tightly woven, large-diameter mesh
  - Excessive sling tension or mesh too loose
  - Perforation of urethra or bladder
  - Inadequate vaginal closure
  - Superficial mesh placement

Genetics

N/A

PATHOPHYSIOLOGY

- Not completely understood. Theories:
  - Subclinical infection
  - Poor wound healing

– Iatrogenic injury/technical error (3)

ASSOCIATED CONDITIONS
- Stress incontinence
- POP
- Cystocele

GENERAL PREVENTION
- Perform intraoperative cystoscopy to minimize risk of urinary tract erosion
- Appropriate patient selection
- Rigorous surgical technique

ALERT
Be familiar with FDA warnings regarding risks of intravaginal mesh & counsel patients appropriately.

DIAGNOSIS

HISTORY
- Determine timing, details of initial surgical procedure and type of mesh used
- Patients often present with storage symptoms, vaginal discharge, pelvic pain/dyspareunia, UTI
- May complain of de novo lower urinary tract symptoms (LUTS)
- Delay in presentation is common
- Sexual activity/sexual function

PHYSICAL EXAM
- Pelvic exam
  – Localize sites of pain
  – Palpate for exposed mesh
  – Note discharge, if present
- Abdominal exam
  – Assess for tenderness, suprapubic pain if retropubic sling placed

DIAGNOSTIC TESTS & INTERPRETATION
Lab
Urine analysis

Imaging
Usually not indicated

Diagnostic Procedures/Surgery
- Cystoscopy
  – Perform if concern for urethral or bladder involvement
- Urodynamics may be of value to assess lower urinary tract function
- Check PVR if concern for retention

Pathologic Findings
Inflammation, fibrosis

DIFFERENTIAL DIAGNOSIS
- Urethral mesh erosion
- Bladder mesh erosion
- UTI

TREATMENT

GENERAL MEASURES
- In general treatment is divided into:
  - Conservative
  - Surgical
- Some patients may be observed with reasonable success

MEDICATION
First Line
- Culture specific antibiotic course if UTI present
- Vaginal estrogen cream
  - May be effective for small erosions
  - Apply small amount to tip of index finger, apply vaginally 2–3 times/wk
    - Contraindicated if history of deep venous thrombosis (DVT), estrogen-responsive cancer

Second Line
N/A

SURGERY/OTHER PROCEDURES
- Transvaginal excision
  - Only exposed mesh vs. entire mesh
- Primary reapproximation of tissue over exposed mesh (4)
- Martius flap interposition at the discretion of the surgeon

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
- Unclear in literature
  - Recurrent SUI is common and may be alleviated by repeat PVS placement
    - Generally autologous material preferred
  - Pain may not be corrected with mesh removal
- Expectant management may be successful in up to 42% of patients
- However, a recent multicenter review of the topic indicated that the majority of women who

present for management of synthetic mesh complication after POP or SUI surgery have severe complications that require surgical intervention, with a significant proportion requiring >1 surgical procedure (5).

COMPLICATIONS

- Voiding dysfunction after surgical management of synthetic sling erosion is common (3)
- Sexual dysfunction, male and female dyspareunia
- Persistent pain
- Vesicovaginal fistula formation
- Recurrent stress urinary incontinence (SUI)
  - Can place 2nd pubo vaginal sling (PVS)

FOLLOW-UP

Patient Monitoring

- Depends upon treatment
  - If patient observed, will need follow-up exams
  - If mesh excised, patient should return if bothersome symptoms

Patient Resources

www.fda.gov—health notification regarding use of surgical mesh for POP and SUI

REFERENCES

1. U.S. Food and Drug Administration. FDA safety communication:UPDATE on serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse. Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm (Accessed July 12, 2014)
2. AUA guidelines: Guideline for the surgical management of female stress urinary incontinence: Update(2009). Available at: http://www.auanet.org/education/guidelines/incontinence.cfm (Accessed July 12, 2014)
3. Starkman JS, Wolter C, Gomelsky A, et al. Voiding dysfunction following removal of eroded synthetic mid urethral slings. *J Urol*. 2006;176:1040–1044.
4. Giri SK, Narasimhulu G, Flood HD, et al. Management of vaginal extrusion after tension-free vaginal tape procedure for urodynamic stress incontinence. *Urology*. 2007;69:1077–1080.
5. Abbott S, Unger CA, Evans JM, etal. Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: A multi-center study. *Am J Obstet Gynecol.* 2013 Oct 11. pii: S0002-9378(13)01065-X. doi: 10.1016/j.ajog.2013.10.012. [Epub ahead of print]

ADDITIONAL READING

- Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol.* 2010;183(5):1906–1914.
- Dmochowski RR, Padmanabhan P, Scarpero HM. Slings: Autologous, biologic, synthetic and midurethral. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds.*Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011.

• Mohr S, Kuhn P, Mueller MD, et al. Painful love-"hispareunia" after sling erosion of the female partner. *J Sex Med*. 2011;8(6):1740–1746.

See Also (Topic, Algorithm, Media)

• Hispareunia
• Pelvic Organ Prolapse (Cystocele and Enterocele)
• Stress Urinary Incontinence, Female
• Urethral Discharge
• Urethral Sling, Indications and Anatomic Positions
• Urethral Sling, Materials
• Vaginal Mesh Erosion Image ☼

CODES

ICD9

• 599.84 Other specified disorders of urethra
• 629.31 Erosion of implanted vaginal mesh and other prosthetic materials to surrounding organ or tissue
• 996.39 Other mechanical complication of genitourinary device, implant, and graft

ICD10

• N36.8 Other specified disorders of urethra
• T83.711A Erosion of implnt vag prstht mtrl to surrnd org/tiss, init
• T85.628A Displacement of other specified internal prosthetic devices, implants and grafts, initial encounter

CLINICAL/SURGICAL PEARLS

• Erosion commonly presents with vaginal discharge, discomfort; urgency, urge urinary incontinence, and irritative voiding symptoms.
• Preoperative counseling is key; inform patients about risks and benefits of mesh use.
• Good physical exam is key to early detection.

VAGINITIS/VULVOVAGINITIS

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BASICS

DESCRIPTION

- Vaginitis is infection or inflammation of only the vagina. Vulvovaginitis involves both the vagina and vulvar areas
- The spectrum of conditions that cause vulvovaginal symptoms such as itching, burning, irritation, and abnormal discharge (1)
- Can be infectious, noninfectious (chemical or irritants), or hormonal
- Bacterial vaginitis (BV) is the most common cause of vaginal discharge in women of childbearing age

EPIDEMIOLOGY

Incidence

7.4 million cases of BV annually in USA

Prevalence

- Among women with vulvovaginitis symptoms, prevalences are (1):
  - BV: 22–50%
  - Candidiasis: 17–39%
  - Trichomoniasis: 4–35%

RISK FACTORS

- Depends on etiology
- Risk factors for BV include new sex partner, multiple partners, and douching (2)
- Risk factors for vulvovaginitis candidiasis (VVC) (3):
  - Recent use of antibiotics
  - Corticosteroids
  - Diabetes mellitus
  - Immunosuppression
  - Pregnancy
- Risk for any STD is increased with:
  - Number of partners
  - Number of partners' partners
  - Unprotected sexual contact

Genetics

Evolving data supporting potential genetic predisposition

PATHOPHYSIOLOGY

- Depends on etiology
  - BV: Normal vaginal *Lactobacillus* are replaced with anaerobic bacteria, *Gardnerella vaginalis* and *Mycoplasma hominis* (some of these are normal vaginal flora; their

overgrowth leads to BV)
  – VVC: Overgrowth of *Candida*
  – Trichomonas and other STIs: Infection with organism
  – Atrophic vaginitis: Lack of estrogen

ASSOCIATED CONDITIONS

STI/STD's are often associated with other STI/STD's

GENERAL PREVENTION

- Avoid local irritants such as perfumed soaps and shower gels, wipes, powders, and sprays
- Wash external skin with water alone or mild soap
- Avoid tight clothing
- For STIs, treat partners as applicable
- Avoid douching, a risk factor for BV
- For trichomoniasis and other STIs:
  – Latex male condoms
  – Abstain from sexual contact, or be in a long-term mutually monogamous relationship with an uninfected partner

DIAGNOSIS

HISTORY

- Potential predisposing factors:
  – Prior vaginitis
  – Antibiotic use
  – Pregnancy
  – Diabetes
  – Sexual intercourse
  – Method of contraception
  – STI history
  – Response to prior treatment
  – Any current treatments that have been self-administered (OTC products)
- Symptoms of current condition:
  – Duration
  – Itching, burning
  – Color, consistency, and odor of discharge

PHYSICAL EXAM

- Inspect the vulva, vagina, and cervix for:
  – Erythema or skin lesions
  – Degree of estrogenization
  – Discharge
  – Foreign body (eg, forgotten tampon)
  – Friable cervix: Consider *Chlamydia* or gonorrhea
- Inspect the vulva, vagina, and cervix for:
  – BV: White or gray, homogeneous, thin, coats the vaginal walls, can have fishy odor
  – *Candida*: White, thick, curdy, not malodorous

  - Trichomonas: Yellow or yellow-green, malodorous, can be profuse and frothy
  - Cervicitis: Purulent, comes from cervix
  - Extensive condyloma can cause discharge
- Palpate for tenderness:
  - Vulvar tenderness without discharge suggests atrophic vaginitis, vulvodynia, or dermatologic condition

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Urine analysis and culture if dysuria is present
- Evaluate discharge by wet mount and KOH:
  - Put a drop of discharge on a glass slide
  - Add a drop of saline to the discharge, add cover slip, and look under microscope for *Trichomonas* and clue cells (BV)
  - Repeat with another slide, using a drop of 10% KOH instead of saline.
  - "Whiff test": Fishy smell (amine odor) immediately after KOH application suggests BV.
    - Wait 2 min for KOH to dissolve most of the cells. Yeast cells or hyphae remain undissolved.
- Clinical diagnosis of BV (Amsel criteria) requires the presence of ≥ 3 of the following:
  - Homogeneous, thin, white discharge that smoothly coats the vaginal walls
  - Vaginal pH $>$ 4.5 (sample from midvagina)
  - Positive amine test (aka whiff test) (fishy odor before or after addition of 10% KOH)
  - Presence of clue cells on microscopic exam
- Diagnosis of candidiasis:
  - Hyphae or yeast cells on KOH or wet mount
  - If *Candida* suspected but not seen on KOH or wet mount, send discharge for yeast culture
- Diagnosis of trichomoniasis:
  - See organisms on wet mount about 60% sensitive (1,2)
  - FDA-approved point-of-care tests have sensitivity $>83\%$ and specificity $>97\%$ (2)
    - Affirm VP III (45 min for result)
    - OSOM Trichomonas Rapid Test (10 min)
  - Culture is most accurate test for trichomonas ($\sim 98\%$)
- Indications for *Chlamydia*/Gonorrhea testing (1):
  - Purulent discharge
  - Discharge has leukocytes (>10 WBC on microscopy) without trichomonads
  - Friable cervix; symptoms of PID (pelvic pain, fever)
  - Patient in high-risk group for STIs
  - NAAT (nucleic acid amplification testing) should be used for diagnosing *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with cervicitis

Imaging

Rarely indicated

Diagnostic Procedures/Surgery

- Vaginal sidewall pH can help with diagnosis:
  - Premenopausal: normal pH 4–4.5

- BV: pH >4.5
- Trichomoniasis: pH 5–6
- Candidiasis: pH 4–4.5

– Postmenopausal: normal pH >4.7

• Biopsy may be indicated for vulvar dermatologic disorders or to rule out cancer. Not needed in most cases

Pathologic Findings

Based on organism

DIFFERENTIAL DIAGNOSIS

• The most common vaginal infections that cause discharge are:
  – Bacterial vaginosis (BV)
  – Vulvovaginitis Candidiasis (VVC)
  – Trichomoniasis
  – Cervicitis due to *Chlamydia* or gonorrhea can present with discharge
  – Group A *Streptococcus* (very rare)
• Noninfectious etiologies:
  – Atrophic vaginitis
  – Ectropion
    - May normalize vaginal discharge volume
    - Normalize physiologic presence of endocervical glandular tissue on the cervix.
    - More common with estrogen–progestin contraceptives and with pregnancy.
  – Foreign body (ie, retained tampon)
  – Allergies and irritants: Contraceptives, douches, perfumes, soaps, laundry detergents, panty liners, etc.
  – Vulvar dermatologic conditions
  – Vulvodynia

TREATMENT

GENERAL MEASURES

• See “General Prevention.”
• Attempt to identify specific cause based on history, lab testing to target treatment
• Correct underlying conditions if possible

MEDICATION

First Line

• Bacterial vaginosis (2,5):
  – Metronidazole 500 mg PO BID for 7 days
  – Metronidazole gel 0.75%; 1 applicator (5 g) per vagina every day for 5 days
  – Clindamycin cream 2% 1 applicator (5 g) per vagina at bedtime for 7 days
• Uncomplicated VVC:
  – Multiple topical azole regimens, or single PO dose 150 mg fluconazole
    - All have similar results
    - Fluconazole has many drug interactions.

- Complicated VVC (2): (< 5% of women)
  - Defined as severe disease (extensive erythema, edema, excoriation, fissures), recurrent disease, not *Candida albicans*, uncontrolled diabetes, debilitation, immunosuppression, or pregnancy, > 4 per year
  - Start with same drugs but give longer courses (7–14 days).
  - If azoles fail, use 600 mg of boric acid in a gelatin capsule, per vagina daily for 2 wk
- Trichomonas (2):
  - Metronidazole or tinidazole 2 g single dose PO (tinidazole is equivalent or superior) (2)
  - Gel is much less effective than PO dose.
- Cervicitis: Azithromycin 1 g PO single dose OR Doxycycline 100 mg PO BID for 7 days
  - Consider concurrent treatment for gonococcal infection if prevalence of gonorrhea is high in the patient population (Ceftriaxone 250 mg IM 1 dose)
- Atrophic vaginitis: Topical estrogen is effective; several forms can be used

Second Line

- BV (2):
  - Clindamycin ovules 100 mg per vagina at bedtime for 3 days
  - Clindamycin 300 mg PO BID. for 7 days
- VVC: No 2nd-line treatments described (2)
- Trichomoniasis: Metronidazole 500 PO BID for 7 days (2)

Pregnancy Considerations

- Bacterial vaginosis (1,2)
  - BV in pregnancy is associated with preterm birth and postpartum endometriosis
  - However only proven benefit of treating symptomatic BV in pregnancy is reduction in symptoms
  - Trial results inconsistent for screening/treating asymptomatic high-risk patients
  - USPSTF recommends not screening for BV in low or average risk for preterm birth
  - BV treatment in pregnancy (2):
    - Metronidazole 500 mg PO BID for 7 days
    - Metronidazole 250 mg PO TID for 7 days
    - Clindamycin 300 mg BID for 7 days
    - Topical clindamycin should not be used in the 2nd half of pregnancy
- VVC: If pregnant, the only recommended treatment is topical azole for 7 days (2)
- Trichomoniasis in pregnancy is associated with adverse outcomes, but no strong evidence that treatment improves outcomes, therefore(1, 2):
  - No need to screen
  - Do treat women who have symptoms
  - Metronidazole is pregnancy category B and OK for 2 g single PO dose
  - Tinidazole is pregnancy category C
  - With both drugs, stop breast-feeding.

SURGERY/OTHER PROCEDURES

N/A

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Partners should be notified and examined if chlamydia, gonorrhea, or trichomoniasis found
- For atrophic vaginitis, if estrogen cannot be used, moisturizers and lubricants may help

Complementary & Alternative Therapies

For *Candida*, no evidence for lactobacilli, yogurt, garlic, tea tree oil, a low-carbohydrate diet, or desensitization to *Candida* species antigen (1); but minimal evidence for atrophic vaginitis.

ONGOING CARE

PROGNOSIS

Depends on etiology

COMPLICATIONS

Inflammation from trichomonas, gonococcal urethritis, chlamydial urethritis, and nongonococcal, nonchlamydial urethritis might facilitate HIV transmission to her partner (3)

FOLLOW-UP

Patient Monitoring

- BV is not thought to be a STD (4):
  - No follow-up needed if symptoms resolve (2)
  - Partner notification not needed/partner treatment does not improve the outcome
- Candidiasis (2):
  - No follow-up needed unless symptoms persist or recur within 2 mo
  - No partner treatment, unless he has balanitis or if she has frequent recurrences
- Trichomoniasis (2):
  - Treat partners and avoid sexual contact until both partners have completed treatment and are asymptomatic
  - Consider follow-up screening as >17% relapse within 3 mo

Patient Resources

Medline Plus: Vaginitis
http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000566.htm

REFERENCES

1. ACOG Committee on Practice Bulletins–Gynecology. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis. *Obstet Gynecol.* 2006;107:1195–1206.
2. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. Online at http://www.cdc.gov/std/treatment/2010/vaginal-discharge.htm (Accessed July 21, 2014)
3. Kagan R, Williams RS, Pan K, et al. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. *Menopause*. 2010;17(2):281–289.
4. Sherrard J, Donders G, White D, et al. European (IUSTI/WHO) guideline on the management of vaginal discharge, 2011. *Int J STD AIDS*. 2011;22:421–429.

ADDITIONAL READING

Muzny CA, Schwebke JR. The clinical spectrum of Trichomonas vaginalis infection and challenges to management. *Sex Transm Infect.* 2013;89(6):423–425.

See Also (Topic, Algorithm, Media)

- Sexually Transmitted Infections (STI) (Sexually Transmitted Diseases [STD]), General
- Vaginitis/Vulvovaginitis Image
- Vaginal Discharge Algorithm
- Vaginal Discharge, Urologic Considerations
- Vaginosis

CODES

ICD9

- 112.1 Candidiasis of vulva and vagina
- 131.01 Trichomonal vulvovaginitis
- 616.10 Vaginitis and vulvovaginitis, unspecified

ICD10

- A59.01 Trichomonal vulvovaginitis
- B37.3 Candidiasis of vulva and vagina
- N76.0 Acute vaginitis

CLINICAL/SURGICAL PEARLS

- Pelvic pain and fever are red flags for pelvic inflammatory disease.
- Avoid alcohol with metronidazole until 24 hr after last dose (72 hr for tinidazole) as it can cause nausea.
- Clindamycin cream may weaken latex condoms and diaphragms for 5 days after use.
- Consider delaying breast-feeding 12–24 hr after metronidazole and 72 hr for tinidazole.

VARICOCELE, ADULT

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BASICS

DESCRIPTION

- Varicocele is an abnormal dilation of the pampiniform plexus of veins situated within the spermatic cord
- Can be asymptomatic, cause discomfort and may impact spermatogenesis.
- Clinical grading of varicoceles:
  - Subclinical: Nonpalpable
  - Grade I: Small, not grossly visible, palpated only during Valsalva
  - Grade II: Moderate size, not grossly visible, easily palpated in standing position without Valsalva
  - Grade III: Large and grossly visible while standing
- Only palpable are clinically relevant
- If prior to puberty or unilateral right varicocele, suggests underlying pathology (See Varicocele, Pediatric)

EPIDEMIOLOGY

Incidence

- Decrease in incidence with increasing body mass index (BMI)
- Increased (3–8x) among 1st-degree relatives with varicocele (1)

Prevalence

- 15% of males
- Majority left sided (75–90%), 33% bilateral
- Seen in 35–40% of men presenting with primary infertility vs. 70–80% with secondary infertility (infertility after previously conceiving a child)
  - Not causative of infertility in the majority of men

RISK FACTORS

- Congenital absence of valves in spermatic vein
- Acquired incompetence of valves, extrinsic compression increasing intravascular pressure (eg, retroperitoneal pathologic process)

Genetics

Ongoing area of research

PATHOPHYSIOLOGY

- Varices
  - Due to absent or incompetent venous valves in spermatic veins allowing retrograde flow
  - May be congenital or acquired
  - Thought to be due to right-angle insertion of left spermatic vein into left renal vein resulting in turbulent flow and increased intravascular back pressure

  - Extrinsic compression
    - Mass
    - "Nutcracker effect": Left renal vein compressed between superior mesenteric artery and the aorta producing elevated left gonadal vein pressures
- Infertility due to varicoceles:
  - Poorly defined, many theories
    - Increased intratesticular temperature compared to controls (0.6–0.8 C)
    - Loss of countercurrent testicular cooling mechanism
    - Elevated temperature reduces testosterone synthesis by Leydig cells, injures germinal cell membranes, alters protein metabolism, and reduces Sertoli cell function
    - Increased testicular hypoxia and oxidative stress due to impaired venous drainage (possibly affecting Leydig cells, DNA fragmentation)
    - Reflux of gonadotoxic renal and adrenal metabolites
  - Can alter spermatogenesis
  - Decreased sperm quality (concentration, motility, morphology, DNA integrity)

ASSOCIATED CONDITIONS
- Infertility
- Testicular atrophy
- Rarely, tumor, renal vein thrombus

GENERAL PREVENTION
None

DIAGNOSIS

ALERT
Acute onset suggests obstruction of renal or gonadal vein (possibly secondary to tumor).

HISTORY
- Infertility
- Pain
  - Most asymptomatic
  - Dull ache, heavy sensation, sensation of increased heat
  - Increases with activity (including intercourse), standing, and with Valsalva
  - Relieved by recumbency

PHYSICAL EXAM
- Gold standard for diagnosis
  - Examine in a warm room after patient has been standing for 10 min
  - Examine with patient supine and standing upright, with performing Valsalva while in upright position
  - Palpation described as "bag of worms"
  - See subheading "Basics, description" for grading

DIAGNOSTIC TESTS & INTERPRETATION
Lab

- Semen analysis (SA)
  - 2–3 days of sexual abstinence prior to collection
  - "Stress pattern" on SA
  - Concentration <20 million/mL; motility $<60\%$; morphology $<14\%$ strict normal forms (oligoasthenoteratospermia or OAT)
- FSH >4.5 & OAT indicates varicocele may be impacting sperm production

Imaging

- Radiographic testing should only be used when presence is uncertain on physical exam (eg, obesity), recurrence is suspected, or varicocele is present after treatment. (2)[C]
- Ultrasound:
  - Helps exclude other intrascrotal pathology
  - Varicocele defined as dilation of pampiniform plexus veins with Valsalva to caliber of >3 mm with and/or reversal of flow with Valsalva during color Doppler
- Internal spermatic venography:
  - Potentially diagnostic and therapeutic
  - Only used for recurrent varicoceles
  - Invasive
- Abdominal imaging if renal or other retroperitoneal mass suspected of causing varicocele

Diagnostic Procedures/Surgery

Venography, as described above

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Spermatic cord mass:
  - Adenomatoid tumor of the cord
  - Epidermoid cyst
  - Epididymitis/epididymo-orchitis
  - Fibrous pseudotumor
  - Hernia
  - Hemangioma
  - Hydrocele/hydrocele of the cord
  - Inguinal lymphadenopathy
  - Leiomyoma
  - Malignant tumor (liposarcoma, rhabdomyosarcoma, leiomyosarcoma, malignant histiocytoma)
  - Metastasis
  - Polyorchidism
  - Sarcoid
  - Sperm granuloma
  - Spermatocele
  - Testis tumor
  - Undescended/retractile testicle
  - Vasitis and vasitis nodosa (typically associated with epididymitis)

ALERT
Suspect renal or retroperitoneal tumor if varicocele is exclusively right sided or remains engorged when the patient is placed in the supine position.

TREATMENT

GENERAL MEASURES

- Subclinical varicoceles have questionable impact on fertility, and repair may not improve fertility rates (3)[B]
- NSAIDs and ice may provide symptomatic relief
- Indications for treatment of infertile male (should meet all criteria):
  - Varicocele palpable on exam
  - Man with abnormal semen parameters or abnormal sperm function tests
  - Couple with known infertility
  - Female has normal or potentially treatable cause of infertility
  - Treatment will enable natural pregnancy or less invasive assisted reproductive techniques (ART) eg, intrauterine insemination (IUI)
- Surgical varicocelectomy significantly improves semen parameters in infertile men with palpable varicocele and abnormal semen parameters (4)[A].
- Pain from symptomatic varicocele or testicular atrophy (>15–20%) are also indications for repair

MEDICATION

First Line

Pain: Analgesics (eg, NSAIDs) usually not durable therapy

Second Line

None

SURGERY/OTHER PROCEDURES

- Surgical treatment successfully eliminates over 90% of varicoceles
- Bilateral repair warranted when varicoceles are noted on both sides in presence of elevated FSH and testicular hypotrophy
- Operative intervention classified by anatomic site of varix ligation and surgical technique
- Anatomic site of ligation:
  - Subinguinal microsurgical: The standard in recent years, incision over the cord below the external ring
    - Number of veins requiring ligation is greater
    - Microscope and Doppler to protect spermatic artery and lymphatics
    - Recurrence rates ~1%
    - Hydrocele rates <1%
  - Inguinal: Inguinal incision, ligation of spermatic veins within inguinal canal
    - Allows for concurrent hernia repair
    - Recurrence rates up to 16%
    - Hydrocele rate up to 30% if nonmicrosurgical
  - Scrotal: The transcrotal approach is considered obsolete

- Retroperitoneal (Palomo or high ligation): Muscle splitting incision, exposure of spermatic vessels with or without preservation of spermatic artery
  - Mass ligation permitted due to presence of collateral arterial circulation (vasal, cremasteric artery)
  - Recurrence rates 15–25%
  - Hydrocele rate ~7%
- Surgical technique:
- Open with or without magnification:
  - Magnification preferred to spare arteries and lymphatics, and allow ligation of small venous tributaries
  - Subinguinal or inguinal microscopic varicocelectomy offers the best overall outcome (5) [A]
- Laparoscopic:
  - High ligation
  - Recurrence rates <2%
  - Hydrocele rate 5–8%
  - 5% of patients experience transient anterior thigh numbness

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Interventional radiology:
- Used as a 2nd-line therapy for those who fail surgery
- Venography with access through the femoral or internal jugular vein
- Occlusion therapy (sclerotherapy, embolization)
- Quicker recovery (3–4 days) but higher recurrence rate (up to 27%)

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- See “Surgery/Other Procedures” for recurrence rates of individual techniques
- Pain or relief of pain typically immediate after recovery from surgery

COMPLICATIONS

- See “Surgery/Other Procedures” for treatment specific complication rates
- Hydrocele
- Recurrence
- Testicular artery injury
- Nerve injury
- Testicular atrophy

FOLLOW-UP

Patient Monitoring

- Varicocele recurrence:
  - Typically evident within 6–13 mo
- Infertility:
  - Semen analysis (SA) at 3-mo intervals; semen should be monitored for at least 1 yr or until pregnancy has been achieved
  - Young men with varicocele and normal SA should be followed with testis size SA and FSH every 1–2 yr

Patient Resources

- www.maledoc.com Urologist maintained male infertility, potency, and health blog
- Urology Care Foundation: Varicoceles http://www.urologyhealth.org/urology/index.cfm?article=116

REFERENCES

1. Raman, JD, Walmsley K, Goldstein M. Inheritance of varicoceles. *Urology*, 2005;65(6):1186–1189.
2. American Urological, Inc. and American Society for Reproductive Medicine. Report on varicocele and infertility: AUA best practice statement . Linthicum (MD): American Urological Association Education and Research, Inc.; 2011.
3. Jarow JP, Ogle SR, Eskew LA. Seminal improvement following repair of ultrasound detected subclinical varicoceles. *J Urol.* 1996;155(4):1287–1290.
4. Agarwal A, Deepinder F, Cocuzza M, et al. Efficacy of varicocelectomy in improving semen parameters: New meta-analytical approach. *Urology*. 2007;70(3):532–538.
5. Cayan S, Shavakhabov S, Kadioglu A. Treatment of palpable varicocele review in infertile men: A meta-analysis to define the best technique. *J Androl.* 2009;30:33–40.

ADDITIONAL READING

- Lee J, Binsaleh S, Lo K, et al. Varicoceles: The diagnostic dilemma. *J Androl.* 2008;29(2):143–146.
- Practice Committee of American Society for Reproductive Medicine. Report on varicocele and infertility. *Fertil Steril.* 2008;90(5 Suppl):S247–S249.
- Ross AE, Burnett AL. Varicocele-adult. In: Gomella LG, ed. *The 5-Minute Urology Consult.* 2nd ed. Philadelphia, PA: Lippincott; 2009.
- Sabanegh E, Agarwal A. Male Infertility. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012.
- Will MA, Swain J, Fode M, et al. The great debate: Varicocele treatment and impact on fertility. *Fertil Steril.* 2011;95(3):841–852.

See Also (Topic, Algorithm, Media)

- Infertility, Urologic Considerations
- Spermatic Cord Mass and Tumors
- Varicocele, Adult Image ☼
- Varicocele, Pediatric

CODES

ICD9

- 456.4 Scrotal varices
- 752.89 Other specified anomalies of genital organs

ICD10

- I86.1 Scrotal varices
- Q64.8 Other specified congenital malformations of urinary system

CLINICAL/SURGICAL PEARLS

- Majority of varicoceles are left sided (75–90%) with diagnosis by physical exam.
- Subclinical (nonpalpable) varicoceles have questionable impact on fertility, and repair may not improve fertility rates.
- Suspect renal or retroperitoneal tumor if varicocele is acute in onset, exclusively right sided or remains engorged when the patient is placed in the supine position.
- Subinguinal microscopic varicocelectomy offers the best overall outcome, though approach should depend on surgeon comfort.

VARICOCELE, PEDIATRIC

Hyeyoung Lee, MD, MS
Harry P. Koo, MD, FAAP, FACS

BASICS

DESCRIPTION

A pediatric varicocele is defined as an abnormal dilatation of the internal spermatic veins in the pampiniform plexus of the spermatic cord in a male generally <18 yr of age. Usually asymptomatic; may cause testicular hypotrophy

EPIDEMIOLOGY

Incidence

- Reported frequency of varicoceles in adolescent boys is ~16%, developing as a result of testicular enlargement and concomitant increased blood flow in puberty
- Actual incidence may be underestimated and detected later during evaluation of infertility in adulthood

Prevalence

- 8–16% of adolescent males but unusual in prepuberty
- 90% left sided
- 1–7% right sided
- 2% bilateral
- No racial, cultural, or geographic predilection
- More common in tall, thin males

RISK FACTORS

- Increased height, and relatively low weight and body mass index
- Congenital incompetence or absence of valves of internal spermatic vein
- Acquired incompetence of valves, extrinsic compression increasing intravascular pressure (eg, inguinal hernia repair, retroperitoneal pathologic process)
- May be associated with generalized venous abnormality

Genetics

- Varicocele prevalence as high as 67% has been reported in sons of fathers with varicocele
- Risk of varicocele in 1st-degree relatives is 4–8 times higher, suggesting genetic susceptibility (1)

PATHOPHYSIOLOGY

- Unique angle of left spermatic vein entering the left renal vein compared to right spermatic vein entering IVC
- Left spermatic vein is 8–10 cm longer than the right
- "Nutcracker" phenomenon of left renal vein passing between aorta and superior mesenteric artery
- Erect posture (no varicocele in four-legged animals)
- Different mechanisms are hypothesized to cause testicular insult

- Hyperthermia:
  - Increased testicular arterial blood flow interferes with countercurrent heat exchange
  - Increased testicular temperature affects enzymatic reactions
  - Decreased proliferation and increased apoptosis of germ cells
  - Heat shock protein A2, oxidative stress patterns, calcium channels, and DNA fragmentation affected
- Testicular hypotrophy: Significant testicular volume loss in 30–70% of adolescents with a varicocele:
  - Most rapid growth of testis between ages 11 and 16 yr
  - Testicular hypotrophy reversible in 90% of patients after varicocelectomy
- Venous stasis:
  - Possible oxygen depletion in testis
  - Human studies do not support theory
- Adrenal/renal reflux:
  - Theory of toxic exposure to testis from reflux of adrenal and renal metabolites
  - Data inconclusive
- Endocrine imbalance:
  - Abnormal response in patients with varicocele to GnRH stimulation
  - Unclear how it affects future fertility or hypotrophy

ASSOCIATED CONDITIONS

Secondary causes can include retroperitoneal tumor, renal mass with renal vein extension, renal vein thrombosis, retroperitoneal fibrosis

GENERAL PREVENTION

None

DIAGNOSIS

HISTORY

- Usually asymptomatic, associated pain reported in 2–11%
- Symptomatic dull ache or fullness in scrotum, worsened with activity
- Occasional testicular pain due to venous congestion
- Change in size with position or Valsalva
- Found after routine pediatric physical exam

PHYSICAL EXAM

- Examine patient upright and supine, with and without Valsalva
- Grading criteria:
  - Grade 0: Subclinical, not visible or palpable, only detected by ultrasound (US)
  - Grade I: Palpable only with Valsalva
  - Grade II: Palpable but not readily visible
  - Grade III: Visible through scrotal skin
- Check patient in supine position—idiopathic varicoceles may disappear, while secondary varicoceles persist if caused by tumor, especially on right side
- “Bag of worms” superior to testicle
- Negative transillumination

- Examine for bilateral varicocele and lymphedema
  - If present, rule out secondary varicocele
- Testicular exam:
  - Visual inspection
  - Orchidometer—Prader vs. disk to determine testicular volume of each testicle and the comparison between the two testes
    - Prader orchidometer: Consists of 12 solid ellipsoid testis-shaped models ranging in volume from 1 to 25 mL (1–6, 8, 10, 12, 15, 20, and 25 mL), against which the testis is compared
    - Disk or Takihara orchidometer: Series of 15 punched-out elliptical rings; volumes ranging from 1 to 30 mL (1–6, 8, 10, 12, 14, 16, 19, 22, 26, and 30 mL)
  - 2 cc or 20% size discrepancy suggests testicular hypotrophy
  - Testicular hypotrophy is correlated with poor semen quality

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Semen analysis: Can be performed if Tanner stage 5 or >18 yr old
- Response to GnRH stimulation: Not useful for surgical decision making

Imaging

- Scrotal US
- Color Doppler US can detect subclinical varicoceles that are not palpable
  - Decrease in volume of 2 cc or 20% size warrants intervention
  - Spermatic vein diameter >2 mm in standing position with Valsalva is noted in up to 96% of boys with grade III varicocele
  - Lambert formula: 0.71 (length × width × depth on US measurement)

Diagnostic Procedures/Surgery

Diagnosis confirmed by physical exam ± US

Pathologic Findings

- Leydig cell atrophy is known to be associated with high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and low testosterone levels
- Endothelial proliferation and basement membrane thickening in venules and capillaries
- Germ cell maturation arrest and sloughing, ultrastructural changes in Sertoli cells, Leydig cell atrophy to hyperplasia have been described in testicular biopsy specimens (2)

DIFFERENTIAL DIAGNOSIS

- Epididymal cyst (spermatocele)
- Hydrocele:
  - Communicating
  - Scrotal
  - Spermatic cord
- Inguinal hernia
- Lipoma of cord
- Paratesticular rhabdomyosarcoma

TREATMENT

GENERAL MEASURES

- Management is either observation or surgical intervention
- Nonoperative treatment can be proposed when the patient or guardian fully understands the need for lifelong follow-up and the potential for progressive subfertility
- Surgical indications in the pediatric population:
  - 2 cc or 20% size discrepancy between testicles based on US or orchidometer measurements
  - Symptomatic
  - Bilateral varicoceles
  - Abnormal semen analysis
  - Solitary testis with varicocele

MEDICATION

First Line

N/A

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Surgical technique based on comfort and experience of surgeon
- Techniques described in more detail in Section I: "Varicocele, Adult"
- 50–75% of patients demonstrate catch-up growth, not necessarily meaning improved semen quality
- Testicular artery sparing:
  - Doppler can help identify
  - Preferred in adults because of concerns with infertility
  - Should be considered in adolescents
- Laparoscopic:
  - Retroperitoneal or transperitoneal
  - High ligation of vessels (Palomo)
  - Closer to left renal vein; usually fewer veins to ligate
  - Laparoscopy offers magnification, facilitating artery/lymphatic sparing
  - Single port laparoscopic approach provides excellent cosmesis
- Subinguinal/inguinal microsurgical:
  - Provides facilitated artery and lymphatic sparing
  - Low risk of hydrocele
  - Time consuming
- Radiographic embolization:
  - Limited data in children and adolescents, less successful than open or laparoscopic approach
  - Significant radiation exposure
  - Generally reserved for recurrent/persistent varicocele

ADDITIONAL TREATMENT

Radiation Therapy
N/A

Additional Therapies
N/A

Complementary & Alternative Therapies
N/A

ONGOING CARE

PROGNOSIS
No definitive evidence that adolescents with varicocele will have impaired fertility in future or that surgical correction will improve/prevent infertility

COMPLICATIONS
- Recurrence or persistence of varicocele:
  – 1–35% depending on technique (3)
- Postoperative hydrocele (1–9%)
- Testicular atrophy
- Failure of catch-up growth
- Possible decreased fertility

FOLLOW-UP
Patient Monitoring
- If asymptomatic and no testicular size discrepancies, observe with biannual or annual exams
- If postsurgical, assess for testicular catch-up growth and hydrocele formation after 3 mo with US. Then monitor biannually or annually

Patient Resources
- Urology Care Foundation: Varicoceles
  http://www.urologyhealth.org/urology/index.cfm?article=116

REFERENCES

1. Mokhtari G, Pourreza F, Falahatkar S, et al. Comparison of prevalence of varicocele in first-degree relatives of patients with varicocele and male kidney donors. *Urology*. 2008;71:666–668.
2. Heinz HA, Voggenthaler J, Weissbach L. Histopathological findings in testes with varicocele during childhood and their therapeutic consequences. *Eur J Pediatr*. 1980;133:139–146.
3. Barthold JS. Abnormalities of the testis and scrotum and their surgical management. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2011.

ADDITIONAL READING

- Ayan S, Woodhouse CRJ. The treatment of adolescents presenting with a varicocele. *BJU*. 2007;100:744–747.
- Diamond DA. Adolescent varicocele. *Curr Opin Urol*. 2007;17:163–267.

• Kass EJ. Adolescent varicocele. *Pediatr Clin N Am.* 2001;48:1559–1569.
• Robinson S, Hampton L, Koo HP. Adolescent varicocele. *Urol Clin N Am.* 2010;37:269–278.

See Also (Topic, Algorithm, Media)
• Infertility, Urologic Considerations
• Spermatic Cord Mass and Tumors
• Varicocele, Adult

CODES

ICD9
• 456.4 Scrotal varices
• 459.81 Venous (peripheral) insufficiency, unspecified
• 752.89 Other specified anomalies of genital organs

ICD10
• I86.1 Scrotal varices
• I87.8 Other specified disorders of veins
• Q64.8 Other specified congenital malformations of urinary system

CLINICAL/SURGICAL PEARLS

• Varicocele is found in 8–16% of adolescents.
• Genetic susceptibility, thin and tall body habitus, and venous abnormalities increase the risk of varicocele.
• Surgical treatment is indicated if testicular hypotrophy, bilateral varicocele, abnormal semen analysis or symptoms.
• Laparoscopic and open suprainguinal varicocelectomy are almost equally effective.
• Microsurgical approach minimizes risk of hydrocele development.

VAS DEFERENS, CONGENITAL ABSENCE

Pravin K. Rao, MD

BASICS

DESCRIPTION

- Congenital absence of the vas deferens in males can be bilateral (CBAVD) or unilateral (CUAVD)
- Primarily relevant to infertility evaluation
- Absence of the vas deferens interrupts transport of sperm beyond testis/epididymis
- Often accompanied by poor development of epididymides and seminal vesicles (SVs), causing low-volume ejaculate.
- Diagnosis is made by physical exam
- CBAVD present in >98% of cystic fibrosis (CF) patients
- CBAVD
  - Always azoospermic (bilateral obstruction)
- CUAVD
  - Can be azoospermic due to unidentified contralateral defects or testis failure
  - More often (-) CFTR mutations (vs. CBAVD)
  - Higher incidence renal anomalies (vs. CBAVD)

EPIDEMIOLOGY

Incidence

- 65–98% of men with CF
- 1.3% of all infertile men

RISK FACTORS

- CF
- Family history of CF or CBAVD
- See associated conditions

Genetics

- Most common: Mutations of cystic fibrosis transmembrane conductance regulator (CFTR)
- CFTR:
  - Chromosome 7
  - Causes spectrum of conditions ranging from AVD to clinical CF
  - Mutations of both chromosomes necessary for clinical CF or CBAVD
  - Mutations appear to have incomplete penetrance (1)[B]
  - Single chromosome mutations = carrier
  - "Severe" vs. "Mild" mutations
- CF patients
  - ~88% have severe mutation of both chromosomes
  - ~11% have severe mutation on 1 CFTR gene and mild on the 2nd (2)[B]
- CBAVD without clinical CF

- ~88% carry 1 severe mutation and 1 mild mutation
- ~12% carry mild mutations on both (Claustres 2000)

- Genetics of CUAVD less understood
  - Most CUAVD thought to be due to embryologic defect (non-CFTR)
  - Some men with CUAVD do have CFTR mutations (3)[B]
  - Some may be due to unidentified CFTR mutation or other genetic factor(s)

PATHOPHYSIOLOGY

- CFTR
  - Glycosylated transmembrane protein
  - Function: Chloride channel
  - Sites:
    - Lungs, liver, pancreas, intestines
    - Vasa deferentia/GU tract
- CFTR mutation
  - Point mutations most common in CF
  - Altered chloride transport
  - Thick, viscous secretions
    - Multisystem disease in CF
    - Obstruction/degeneration of vasa vs. agenesis.
- Vas deferens is a derivative of mesonephric (Wolffian) duct.
  - Wolffian abnormalities often seen with AVD
    - Seminal vesicle (SV) hypoplasia or absence
    - Causes low-volume ejaculate.
    - See: Associated Conditions

ASSOCIATED CONDITIONS

- CF
  - CBAVD is considered the mildest manifestation of CFTR disease spectrum
  - CF is most severe
  - Nearly all CF patients have CBAVD
- Genitourinary abnormalities
  - Renal agenesis
  - Abnormalities of mesonephric structures
    - Ejaculatory ducts
    - SVs
- Low testicular volume
  - Seen more commonly when CFTR mutations not detected (4)[B]
  - May indicate primary testicular cause

GENERAL PREVENTION

CFTR screening of both partners can help assess and manage risk of CF and CBAVD for offspring

DIAGNOSIS

HISTORY

- Medical history
  - Presence of associated conditions
- Patients usually asymptomatic except for infertility
- Screen for other causes of infertility/azoospermia
  - Developmental/puberty history
    - Testicular descent
  - Sexual function, libido
    - Hypogonadism, testis failure
- Screen for CF manifestations
  - Sinopulmonary symptoms
  - GI/digestive problems

PHYSICAL EXAM

- Findings in AVD
  - Absent vas deferens (bilateral/unilateral)
  - Absent or hypoplastic body/tail of epididymis
  - Present caput epididymis, often dilated
- Considerations:
  - Evaluate for skip lesions
  - Check for other causes of infertility
    - Varicocele
    - Atrophic testis
- Normal in CBAVD:
  - Testis size (>3.5 cm length, 2–3 cm diameter)
  - Digital rectal exam
    - Prostate usually normal
    - SVs usually nonpalpable/hypoplastic; may be cystic

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Potential semen analysis findings:
  - Low volume (<1.5 cc)
  - Azoospermia if bilateral obstruction
  - Acidic pH (decreased basic SV fluid)
  - Seminal fructose might be negative
  - Presence of sperm rules out bilateral obstruction
- Postejaculatory urinalysis
  - Evaluates for retrograde ejaculation
  - Part of evaluation for low-volume azoospermia
- CFTR genetic mutation screen
  - Assesses for mild vs. severe mutations
  - Can prove, but not exclude, a congenital form of CF
  - Risk is difficult to predict with some rare CFTR mutations
  - Negative CFTR screen reduces, but does not eliminate, risk of being a carrier
    - Thus, suggest screening in female partner

- CFTR screening for partner
  - Helps guide genetic counseling regarding CF risk for offspring

Imaging

- Renal ultrasound
  - For all men with vasal agenesis
  - Evaluates for renal anomalies/agenesis
  - Optional if CFTR mutation detected
    - Renal anomalies rare
- Transrectal ultrasound (TRUS)
  - Part of evaluation for low-volume azoospermia
  - Not necessary with CBAVD
  - Evaluates for ejaculatory duct obstruction
  - Normal findings:
    - Vasal diameter: 0.3–0.5 cm
    - SV width: 0.3–1.5 cm
    - SV length: 1.4–4.6 cm
    - Ejaculatory duct diameter: <0.1 cm
  - Optional: Aspiration of dilated SVs
    - Ejaculatory Disturbances
- Vasography (see below)

Diagnostic Procedures/Surgery

- Vasography
  - Fluoroscopic injection of contrast material
  - Assesses patency of vas/vasa
  - Only done at time of planned microsurgical reconstruction of ejaculatory duct(s), due to risk of damage/obstruction at vassal entry point
  - Of limited utility in CBAVD since reconstruction usually not an option

Pathologic Findings

N/A

DIFFERENTIAL DIAGNOSIS

- Spermatogenic failure causing azoospermia
  - Congenital/genetic causes
    - Y chromosome microdeletions
    - Sex chromosome abnormalities (XXY male)
    - Undescended testes
  - Gonadotoxin exposure
    - Chemotherapy
    - Radiation
    - Environmental
  - Varicocele
- Obstruction causing azoospermia
  - Inflammatory or infectious causes
    - Sexually transmitted infections

    - Tuberculosis
  - Vasal obstruction/vasectomy
  - Epididymal obstruction
  - Ejaculatory duct obstruction
- Poor development of accessory sex organs causing low-volume ejaculate
  - Hypogonadotropic hypogonadism
  - Pituitary tumor
  - Disorders of sexual differentiation
- Respiratory infections and male infertility can also be due to primary ciliary dyskinesis
  - This condition is characterized by immotile sperm and situs inversus

TREATMENT

GENERAL MEASURES

- Infertility treatment requires assisted reproductive techniques (ART)
- Sperm retrieval techniques
  - See Surgery, below
- Donor semen
  - Intrauterine insemination
  - IVF/ICSI
- Consider referral for genetic counseling regarding CF risk for offspring

MEDICATION

First Line

- Medications used only to treat other conditions found on evaluation (eg, hypogonadism)
  - Clomiphene citrate
  - Avoid exogenous testosterone if patient is planning to use his own sperm for ART
    - Suppresses endogenous gonadotropins and testosterone/sperm production

Second Line

N/A

SURGERY/OTHER PROCEDURES

- Sperm retrieval for ART
  - Testicular sperm extraction (TESE)
  - Testicular sperm aspiration (TESA)
  - Microsurgical epididymal sperm aspiration (MESA)
  - Sperm can be used for IVF or ICSI

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

N/A

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Besides association with CF/CFTR disease spectrum, no other known detriment to health
- Fertilization and pregnancy rates with ART in obstructive azoospermia are most closely tied to female factors.

COMPLICATIONS

CF or CBAVD in offspring

FOLLOW-UP

Patient Monitoring

N/A

Patient Resources

N/A

REFERENCES

1. Shin D, Gilbert F, Goldstein M, et al. Congenital absence of the vas deferens: Incomplete penetrance of cystic fibrosis gene mutations. *J Urol.* 1997;158(5):1794–1798.
2. Claustres M, Guittard C, Bozon D, et al. Spectrum of CFTR mutations in cystic fibrosis and in congenital absence of the vas deferens in France. *Hum Mutat.* 2000;16(2):143–156.
3. Kolettis PN, Sandlow JI. Clinical and genetic features of patients with congenital unilateral absence of the vas deferens. *Urology*. 2002;60(6):1073–1076.
4. Robert F, Bey-Omar F, Rollet J, et al. Relation between the anatomical genital phenotype and cystic fibrosis transmembrane conductance regulator gene mutations in the absence of the vas deferens. *Fertil Steril.* 2002;77(5):889–896.

ADDITIONAL READING

Ratjen F, Doring G. Cystic Fibrosis. *Lancet.* 2003;361(9358):681–689.

See Also (Topic, Algorithm, Media)

- Assisted Reproductive Techniques (ART)
- Cystic Fibrosis, Urologic Considerations
- Ejaculatory Disturbances (Delayed, Decreased, or Absent)
- Infertility, Urologic Considerations
- Retrograde Ejaculation
- Vasography

CODES

ICD9

- 606.0 Azoospermia
- 606.9 Male infertility, unspecified
- 752.89 Other specified anomalies of genital organs

ICD10

- N46.01 Organic azoospermia

- N46.8 Other male infertility
- Q55.4 Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate

CLINICAL/SURGICAL PEARLS

Low-volume ejaculate in CBAVD and CUAVD is usually due to poor development of accessory sex organs (SVs).

VASECTOMY AND POSTVASECTOMY PAIN SYNDROME

Christopher L. Starks, MD
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BASICS

DESCRIPTION

- Vasectomy is a surgical procedure that creates a disruption of the vas deferens leading to permanent male sterilization
  - Vasectomy is the safest, least expensive, and most reliable form of sterilization (1,2)
- Postvasectomy pain syndrome: Poorly understood and largely unpredictable chronic testicular pain >3 mo duration after vasectomy
  - Variable constellation of symptoms including but not limited to orchalgia, pain with daily activities, and pain with intercourse/ejaculation

EPIDEMIOLOGY

Incidence

- Vasectomy
  - Number of vasectomies performed each year is ~175,000–500,000
- Postvasectomy pain syndrome
  - 15–33% of men may experience persistent mild or troublesome testicular discomfort following vasectomy with 4% experiencing significant long-term testicular pain (orchalgia)
  - Long-term pain requiring some kind of intervention or surgical therapy occurs in up to 1 in 1,000 vasectomized men

Prevalence

~5% of couples of reproductive ages rely on vasectomy for contraception

RISK FACTORS

N/A

Genetics

N/A

PATHOPHYSIOLOGY

- Vasectomy
  - Vasectomy involves disrupting the vas deferens via suture ligation, electrocautery, clips, and/or fascial interposition
  - Vasectomy disrupts the blood–testis barrier
    - Antisperm antibodies in 60–80% of men
    - Does not appear to result in cell-mediated immunity
- Postvasectomy pain syndrome
  - Proposed mechanisms:
    - Increased pressure on the testicle and epididymis
    - High pressure may cause blowouts of sperm resulting in tender sperm granulomas and

epididymal regions
- Nerve entrapment
- Fibrosis

ASSOCIATED CONDITIONS
N/A

GENERAL PREVENTION
No preoperative factors have been identified in the postvasectomy pain syndrome

DIAGNOSIS

HISTORY
- Vasectomy
  - A careful history ensuring that the patient understands that this is a permanent method of sterilization should occur
  - A directed history including previous scrotal and inguinal surgery
- Postvasectomy pain syndrome
  - Mean time to onset of pain reported as 2 yr
  - Symptoms associated with postvasectomy pain syndrome include:
    - Persistent pain in the groin, testicle, or epididymis
    - Pain with an erection and/or engaging in sexual activity
    - Pain with ejaculation
    - Decreased libido and/or erections

PHYSICAL EXAM
- Prevasectomy
  - Ideally a preprocedure consultation should occur in person
  - Detailed physical exam performed to ensure the vas deferens are easily palpable
  - Patients with unusual scrotal sensitivity or anatomy may be identified, and may be recommended for procedure with sedation
- Postvasectomy pain syndrome
  - Physical exam commonly reveals fullness/tenderness at the proximal vas, epididymis, or at a granuloma site
  - Evidence of sperm granuloma
  - Epididymal tenderness or other masses
  - Examine for evidence for groin hernia

DIAGNOSTIC TESTS & INTERPRETATION
Lab
N/A

Imaging
- Postvasectomy pain syndrome
  - Usually not necessary
  - Ultrasound imaging can confirm epididymal engorgement, thickening, or nodularity

Diagnostic Procedures/Surgery
N/A

Pathologic Findings

- Vasectomy
  - Routine histologic exam of excised vas segment is not required
  - Analysis of testicular histology after vasectomy demonstrates dilatation of the seminiferous tubules, interstitial fibrosis, and reductions in the seminiferous cell population

DIFFERENTIAL DIAGNOSIS

- Postvasectomy pain syndrome
  - Hydrocele
  - Infection (eg, epididymitis)
  - Inguinal hernia
  - Intermittent testicular torsion
  - Nerve injury or entrapment
  - Psychogenic causes
  - Referred pain
  - Testicular or paratesticular neoplasm
  - Varicocele

TREATMENT

ALERT
Patients must be fully informed that an alternative form of birth control must be used immediately after vasectomy and until a semen analysis is clear.

GENERAL MEASURES

- Vasectomy
  - A minimally invasive or “no-scalpel vasectomy” technique should be used
  - Methods of performing vasectomy are based upon surgeon preference. These include:
    - Excision of a portion of the vas
    - Clips vs. suture ligation of vas ends
    - Cautery of mucosa
    - Interposition of the vas ends between fascia (may reduce recanalization)
- Postvasectomy pain syndrome
  - Conservative therapies are the mainstay: Scrotal support, activity limitation, sitz baths, ice-packs

MEDICATION

First Line

- Postvasectomy pain syndrome
  - Antibiotics
    - Empirically often used with no documented benefit in the absence of obvious infection
  - Nonsteroidal anti-inflammatory medication
    - Prolonged course (>3 mo) suggested before employing more aggressive approaches (see below)

Second Line
Tricyclic antidepressants and neuroleptic medication (eg, gabapentin) can be considered

SURGERY/OTHER PROCEDURES
- Postvasectomy pain syndrome
  - With the failure of long-term conservative management, more invasive treatments: Sperm granuloma excision, denervation of the cord, open-ended vasectomy, epididymectomy, and orchiectomy may be considered
  - With pain localized to a sperm granuloma on physical exam, granuloma excision with occlusion of vas with intraluminal cautery usually relieves the pain and reduces the risk of recurrence
    - In 1 study up to 50% were pain free following epididymectomy
    - Epididymectomy renders the vasectomy completely irreversible and may jeopardize the blood supply to the testes, which can result in ischemic atrophy
    - Vasectomy reversal: There are no controlled trials, but reversal may offer best chances of significant improvement (50% pain free in 1 series). The drawback is that fertility is restored (3)

ADDITIONAL TREATMENT
Radiation Therapy
N/A

Additional Therapies
- Postvasectomy pain syndrome
  - Men with intractable symptoms might benefit from a multidisciplinary team approach involving a urologist and a pain-clinic specialist, including a psychologist
  - Many men with chronic orchalgia also had signs of major depression or chemical dependencies (4)
  - Spermatic cord blocks
  - Local intralesional steroids
  - Transrectal injections into the region of pelvic plexus (5 mL bupivacaine and methyl prednisolone) have been used to manage cases of chronic orchalgia and may be considered as salvage therapy in refractory cases (5)
  - Neuromodulation and the use of testosterone have also been reported in this setting (6)

Complementary & Alternative Therapies
- Vasectomy
  - Patients should continue other means of contraception if they do not desire permanent sterilization

ONGOING CARE
PROGNOSIS
- Vasectomy
  - Patients are instructed that vasectomy does not work immediately
  - They should use contraception and consider themselves fertile until a postvasectomy semen analysis (PVSA) is negative

  - Even once vas occlusion is confirmed, the risk of preventing pregnancy is not 100% reliable. Risk of pregnancy is 1 in 2,000 for men who have PVSA showing azoospermia or rare nonmotile sperm
  - Repeat vasectomy is needed in $<1\%$
- Despite counseling, up to 5% of men will change their mind postvasectomy and request a vasectomy reversal

COMPLICATIONS

- Bleeding/hematoma: $\sim$1–2%
- Infection: $<1\%$
- Symptomatic sperm granuloma: $<1\%$
- Postvasectomy pain syndrome: 15–33%

FOLLOW-UP

Patient Monitoring

- PVSA should be a fresh uncentrifuged semen sample and should be examined within 1–2 hr of ejaculation
- PVSA can be made by the patient between 8–16 wk after vasectomy
- Acceptable PVSA show azoospermia or only rare nonmotile sperm
- Vasectomy should be considered a failure if motile sperms are present at 6 mo

Patient Resources

Urology Care Foundation: Vasectomy http://www.urologyhealth.org/urology/index.cfm?article=53&display=1

REFERENCES

1. Sharlip ID, Belker AM, Honig S, et al. Vasectomy: AUA guidelines. *J Urol.* 2012;188:2482–2491.
2. Dohle G, Diemer T, Kopa Z, et al. European Association of Urology guidelines on vasectomy. *Eur Urol.* 2012;61:159–163.
3. Horovitz D, Tjong V, Domes T, et al. Vasectomy reversal provides long-term pain relief for men with the post vasectomy pain syndrome. *J Urol.* 2012;187:613–617.
4. Granitsiotis P, Kirk D. Chronic testicular pain: An overview. *Eur Urol.* 2004;45:430–436.
5. Yamamoto M, Hibi H, Katsuno S, et al. Management of chronic orchialgia of unknown etiology. *Int J Urol.* 1995;2:47–49
6. Morley C, Rogers A, Zaslau S. Post-vasectomy pain syndrome: Clinical features and treatment options. *Can J Urol.* 2012;19(2):6160–6164.

ADDITIONAL READING

Tandon S, Sabanegh E. Chronic pain after asectomy: A diagnostic and treatment dilemma. *BJU Int.* 2008;102:166–169.

See Also (Topic, Algorithm, Media)

- Sperm Granuloma
- Spermatocele
- Testis, Pain (Orchalgia)
- Vas Deferens, Obstruction

- Vasectomy Reversal

CODES

ICD9

- 338.18 Other acute postoperative pain
- 608.89 Other specified disorders of male genital organs
- V26.52 Vasectomy status

ICD10

- G89.18 Other acute postprocedural pain
- N50.8 Other specified disorders of male genital organs
- Z98.52 Vasectomy status

CLINICAL/SURGICAL PEARLS

- A minimally invasive approach to accessing the vas (ie, no scalpel vasectomy) should be used.
- There are a variety of methods and techniques that can be used to disrupt the vas bilaterally including excision, clips, suture ligation, cautery, and fascial interposition.
- There are rare complications from vasectomy including hematoma and postvasectomy pain syndrome.

VESICOURETERAL REFLUX, ADULT

Sanjay S. Kasturi, MD

BASICS

DESCRIPTION

- Vesicoureteral reflux (VUR) is defined as retrograde passage of urine from the bladder into the ureter and/or renal pelvis and calyces
- VUR in the presence of bacteria is a risk factor for pyelonephritis and may lead to upper-tract pathology. It may be unilateral or bilateral, primary or secondary
- A more common problem in children, it can be associated with significant morbidity in adults and may be an uncommonly unrecognized cause of hypertension (HTN) in this population

EPIDEMIOLOGY

Incidence

- 5% of adults have VUR
- Female > male

RISK FACTORS

- 85% of childhood reflux occurs in girls; likely to be similar in adults
- Family history of VUR
- Conditions that predispose to secondary VUR (eg, neuropathic bladder)

Genetics

Having a parent or sibling with VUR increases the risk of childhood VUR

PATHOPHYSIOLOGY

- Primary VUR (1)
  - Failure of development or breakdown of the distal ureteral antireflux mechanism
  - Normally, the distal 4–5 cm of the ureter courses through the muscular wall of the bladder before reaching the bladder trigone
  - This tunnel prevents reflux of urine
  - Congenital deficiency of the intravesical tunnel is the most common etiology
- Secondary VUR
  - Disorders that cause elevated intravesical pressure: BPH, spinal cord injury, MS, and other neurologic diseases
  - Patients who have undergone urinary diversion (ileal conduit) or bladder replacement (orthotopic neobladder, catheterizable diversions) commonly have VUR
  - Bacterial cystitis can often cause transient ureteral reflux due to inflammation
  - Genitourinary TB can cause the ureteral orifices to become fixed and relatively patulous
- International Reflux Study Committee classifies VUR into 5 grades:
  - Grade I: Reflux partly up to the ureter
  - Grade II: Reflux up to the pelvis and calyces without dilatation; normal calyceal fornices
  - Grade III: Same as grade II, but with mild dilatation and tortuosity of the ureter and

minimal blunting of the fornices
  – Grade IV: Moderate dilatation and tortuosity of the ureter, pelvis, and calyces; complete blunting of fornices
  – Grade V: Gross dilatation and tortuosity of the ureter, pelvis, and calyces; absent papillary impressions in the calyces
- Mild reflux: Grades I and II
- Moderate reflux: Grade III
- Severe reflux: Grades IV and V
- Reflux associated with diversions such as ileal conduit is considered to be low pressure with minimal long-term damage to upper tracts.

ASSOCIATED CONDITIONS
- See causes of high bladder storage pressure mentioned above
- Typically seen in refluxing anastomosis: Neobladders, ileal conduits, renal transplantations

GENERAL PREVENTION
None; Long-term renal damage can be limited by appropriate prevention of infection and management of secondary cause of VUR

DIAGNOSIS

HISTORY
- History of VUR in childhood
- Family history of VUR
- Recurrent UTIs
- Simple cystitis leading to fever and flank pain suggestive of pyelonephritis
- Lower urinary tract voiding symptoms, suggesting outlet obstruction or neuropathic bladder

PHYSICAL EXAM
- CVA tenderness with pyelonephritis
- Digital rectal exam for BPH
- Palpable bladder
- Neurologic impairment
- HTN (if renal compromise)

DIAGNOSTIC TESTS & INTERPRETATION

Lab
- Blood testing is not necessary, except for severe cases in which renal function should be evaluated
- Proteinuria (if renal compromise)
- Urine analysis and culture should demonstrate the presence of infection if the patient is symptomatic:
  – Between infections, the urine will often be normal

Imaging
- US can show hydroureteronephrosis dependent on severity of VUR
- VCUG: Definitive test for identifying and grading the severity of reflux. It may also point toward the cause of VUR

- A nuclear medicine cystogram (indirect VCUG):
  – Can be performed with MAG3
  – Provides less anatomic information than the VCUG but does not require catheterization

Diagnostic Procedures/Surgery

Video urodynamic studies combine the information provided by the VCUG with physiologic information on bladder filling and voiding

Pathologic Findings

- Renal lesions (scarring) can be associated with higher grades of reflux
- Chronic scarring may, over time, cause HTN

DIFFERENTIAL DIAGNOSIS

- Other causes of flank (loin) pain and infection (eg, renal colic, ureteropelvic junction obstruction) (see Section I: "Flank Pain")
- Other causes of hydroureteronephrosis or ureteral obstruction (See Section I: "Hydronephrosis/Hydroureteronephrosis [Dilated Ureter/Renal Pelvis], Adult")

TREATMENT

GENERAL MEASURES

- Treatment of secondary VUR is directed at the primary cause (management of BPH, treatment of UTI, etc.)
- Early treatment of cystitis can prevent progression to pyelonephritis

MEDICATION

First Line

- Patients with recurrent UTI may benefit from prophylactic antibiotics
- Primary asymptomatic adult VUR does not otherwise require ongoing medical therapy as risk of progressive renal impairment is low
- Pregnant women with known VUR should be given antibiotic prophylaxis until delivery (eg, amoxicillin 250 mg/d PO) (2)

Second Line

- Secondary VUR may benefit from medical treatment of underlying cause:
  – Anticholinergic preparations in detrusor overactivity
  – α-Blockade or 5α-reductase inhibition in bladder outlet obstruction

SURGERY/OTHER PROCEDURES

- Primary VUR rarely requires surgical intervention in adults; however, where indicated procedures include:
  – Endoscopic treatment: Injection of bulking agents below the ureteral orifice:
    ◦ Initial results are good; however, long-term follow-up is scant
  – Several agents have been used for endoscopic correction of VUR:
    ◦ Polytetrafluoroethylene (Teflon)
    ◦ Cross-linked bovine collagen, dextranomer/hyaluronic copolymer (Deflux)
    ◦ Since the FDA approval of Deflux in 2001, this has been the most commonly used injectable agent for VUR

– Ureteric reimplantation can be undertaken transvesically, extravisually, or by a combination of both:
  ◦ Some common techniques include: Cohen cross-trigonal, Politano–Leadbetter, Lich–Gregoir (extravesical) reimplantations

ADDITIONAL TREATMENT

Additional Therapies

Additional therapeutic options in the treatment of the underlying condition for secondary VUR include intradetrusor botulinum toxin and sacral neuromodulation

Complementary & Alternative Therapies

Some data suggest cranberry juice and live-culture yogurt can be effective in preventing UTI

ONGOING CARE

PROGNOSIS

Depends on underlying etiology and severity of VUR

COMPLICATIONS (3,4)

- Chronic pyelonephritis
- Reflux nephropathy
- Renal impairment rare in primary VUR unless pre-existing from childhood, but can be encountered in secondary VUR
- UTI
- Urolithiasis

FOLLOW-UP

Patient Monitoring

- Medical follow-up is unnecessary in patients without HTN or proteinuria, unless the patient develops recurring infections, at which point repeat workup is needed
- Patients with intrinsic renal disease due to prior reflux (in childhood) require follow-up of BP, creatinine, and urine protein

Patient Resources

http://kidney.niddk.nih.gov/kudiseases/pubs/vesicoureteralreflux/

REFERENCES

1. Bailey RR, Lynn KL, Robson RA. End-stage reflux nephropathy. *Ren Fail*. 1994;16(1):27–35.
2. El-Khatib M, Packham DK, Becker GJ, et al. Pregnancy-related complications in women with reflux nephropathy. *Clin Nephrol.* 1994;41(1):50–55.
3. Hall MK, Hackler RH, Zampieri TA, et al. Renal calculi in spinal cord-injured patient: Association with reflux, bladder stones, and Foley catheter drainage. *Urology*. 1989;34(3):126–128.
4. Zhang Y, Bailey RR. A long-term follow up of adults with reflux nephropathy. *N Z Med J*. 1995;108(998):142–144.

ADDITIONAL READING

- Buckley O, Geoghegan T, O'Brien J, et al. Vesicoureteric reflux in the adult. *Br J Radiol.*

2007;80(954):392–400.
• Murphy AM, Ritch CR, Reiley EA, et al. Endoscopic management of vesicoureteral reflux in adult women. *BJU Int.* 2011;108(2):252–254.

See Also (Topic, Algorithm, Media)
• Heikel–Parkkulainen Reflux Classification System
• Hydronephrosis/Hydroureteronephrosis (Dilated Ureter/Renal Pelvis), Adult
• Reflux Nephropathy
• Pyelonephritis, Chronic
• Urinary Tract Infection (UTI), Adult Female
• Urinary Tract Infection (UTI), Adult Male
• Urinary Tract Infection (UTI), Complicated, Adult
• Vesicoureteral Reflux, Adult Image ☼
• Vesicoureteral Reflux, Pediatric

CODES

ICD9
• 593.70 Vesicoureteral reflux unspecified or without reflux nephropathy
• 593.71 Vesicoureteral reflux with reflux nephropathy, unilateral
• 593.73 Other vesicoureteral reflux with reflux nephropathy NOS

ICD10
• N13.70 Vesicoureteral-reflux, unspecified
• N13.721 Vesicoureter-reflux w reflux neuropath w/o hydrourt, unil
• N13.729 Vesicoureter-reflux w reflux nephropathy w/o hydrourt, unsp

CLINICAL/SURGICAL PEARLS

Women with VUR tend to present with infections, while men tend to present with HTN and proteinuria.

VESICOURETERAL REFLUX, PEDIATRIC

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BASICS

DESCRIPTION

- Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the ureter and/or kidney
- Primary VUR occurs in the absence of underlying lower urinary tract dysfunction
- Secondary VUR is associated with abnormally increased pressures or anatomy in the bladder or urethra

EPIDEMIOLOGY

Incidence

- Incidence is ~1% (1)[C]
- 30% in those with a febrile UTI
- 16.2% in those with prenatal hydronephrosis
- VUR detection varies with indication for radiographic evaluation, eg, 31% of children with UTIs and 17.2% of those without sonographic renal abnormalities had VUR (1)[C]

Prevalence

N/A

RISK FACTORS

- Caucasian race
- Younger age
- Female
- Family history
- Conditions associated with VUR secondary to anatomic anomalies: Bladder exstrophy, prune belly syndrome, ureteral duplication
- Obstructing bladder pathologies can create hostile and excessive storage and emptying pressures that eventually overwhelm a normal antirefluxing intramural flap–valve mechanism: Posterior urethral valves, myelodysplasia
- Severe voiding dysfunction

Genetics

- Likely autosomal dominant with incomplete penetrance
- Seen in 27–51% of siblings of children with VUR; up to 100% in identical twins
- Seen in 50–66% of children of parents with VUR

PATHOPHYSIOLOGY

- The normal ureter enters the bladder at an oblique angle through the bladder wall; with bladder filling on contraction, the ureter is compressed and retrograde flow of urine (reflux) is prevented

- Primary VUR is associated with a functionally shortened submucosal tunnel
- Secondary VUR occurs in the setting of abnormal lower urinary tract function with resulting increase in bladder pressures
- VUR is graded on a scale of I–V:
  - I: Ureter only
  - II: Renal pelvis and calyces without dilatation
  - III: Renal pelvis and calyces with calyceal blunting
  - IV: Renal pelvis and calyces with ureteral tortuosity
  - V: Severe ureteral tortuosity

ASSOCIATED CONDITIONS

- Primary VUR: Hydronephrosis, UTI, bladder/bowel dysfunction
  - Also ipsilateral or contralateral renal anomalies: Ureteral duplication, ureteral ectopia, ureterocele, lulticystic dysplastic kidney (MCDK) or ureteropelvic junction (UPJ) obstruction
- Secondary VUR: All of the above, as well as neurogenic bladder, posterior urethral valves, prune belly syndrome, bladder exstrophy

GENERAL PREVENTION

- Primary VUR: None
- Secondary VUR: Optimizing lower urinary tract function to prevent elevated pressure and decreased bladder compliance

DIAGNOSIS

HISTORY

- Typically asymptomatic
- Frequently found on evaluation of patients with history of hydronephrosis, pyelonephritis, or UTIs
- Obtain careful history of UTI and other infections, fevers, abdominal or flank pain, dysuria, elimination habits
- Review antenatal imaging, gestational course, postnatal growth and development

PHYSICAL EXAM

- Complete physical exam for baseline functional information
- Neurologic exam for spina bifida
- Abdominal and pelvic exam:
  - Palpable kidneys secondary to hydronephrosis
  - Palpable bladder secondary to incomplete emptying
  - CVA tenderness
  - Suprapubic tenderness
  - Circumcision status in males
- Poor somatic growth seen in some patients with renal insufficiency
- Blood pressure should be compared with age-adjusted normative values
- Identify or exclude causes of secondary VUR, eg, neurogenic bladder

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Voided specimen urine for assessment of proteinuria, evidence of infection
  - Catheterized urine samples are more accurate for diagnosis of infection but are more costly and invasive; collect in patients with high index of suspicion based on voided sample or in patients with history of VUR
- Cultures sent only when urinalysis or clinical presentation is suspicious for infection
- Serum creatinine and electrolytes are not routinely checked unless significant sonographic anomalies in renal units, history of multiple febrile UTIs, or significant renal scarring on radionuclide imaging; evaluate at initial diagnosis and again only when substantial change in clinical condition
- Annual CBC appropriate in patients taking daily sulfamethoxazole or nitrofurantoin

Imaging

- Voiding cystourethrogram (VCUG) or radionuclide cystogram
- Renal ultrasound and nuclear medicine scan may suggest presence of VUR but are not sensitive or specific enough for definitive diagnosis
- Renal ultrasound utilized to help define upper tract anatomy, eg, hydronephrosis or duplicated systems, assess quality of renal parenchyma, ensure adequate renal growth
- Renal scintigraphy (DMSA scan) is the gold standard for detection of renal scarring
  - Differential renal function
  - Diagnosis of acute pyelonephritis/scarring

Diagnostic Procedures/Surgery

- Uroflowmetry to screen for abnormal voiding pattern in toilet-trained children may be useful
- Urodynamics to evaluate bladder compliance and function in children with secondary VUR
- Routine cystoscopy is avoided, but can be considered preoperatively to further evaluate duplication, diverticula, or ureteral ectopia

Pathologic Findings

Patients with reflux nephropathy and renal scarring may have increased deposition of collagen and scar tissue in the renal parenchyma

DIFFERENTIAL DIAGNOSIS

- Should be based on the abnormal symptom or clinical finding that prompted the evaluation
  - UTI: Dysuria, lower tract infection vs. pyelonephritis
  - Hydronephrosis: Physiologic hydronephrosis, ureterovesical junction obstruction, ureteropelvic junction obstruction, congenital megaureter
  - Always consider secondary causes when evaluating for VUR

TREATMENT

GENERAL MEASURES

- Counsel parents on pathophysiology and natural history of VUR: Causes, comorbid conditions, potential sequelae, likelihood of resolution, risks and benefits of alternative treatment plans
- Spontaneous resolution of primary reflux is common and depends on initial grade of reflux,

gender, age, voiding dysfunction, presence of renal scarring, and timing of VUR on VCUG
- Goal of intervention is to prevent renal scarring, recurrent febrile UTI, and long-term complications such as hypertension and renal insufficiency

MEDICATION

First Line

- Prophylactic daily antibiotics to keep urine sterile, preferentially given at bedtime to maximize urinary retention
  - <2 mo age: Amoxicillin 20 mg/kg/d
  - ≥ 2 mo of age: Trimethoprim–sulfamethoxazole 2 mg/kg/d (concentrates in urine); nitrofurantoin is an alternative, but liquid is expensive and bad tasting

ALERT
American Academy of Pediatrics (2011): meta-analysis of 6 randomized controlled studies demonstrated no difference in rates of UTI between patients taking prophylactic antibiotics and those not taking prophylactic antibiotics (2)[A].

- Findings met strenuous objection from pediatric urology community based on multiple methodologic flaws
- Majority of urologists continue to endorse prophylactic antibiotics in patients being followed conservatively, and consider exceptions case by case

Second Line

- Management of elimination habits:
  - Constipation: Encourage daily soft bowel movement, consider polyethylene glycol, probiotics
  - Urinary urgency and/or urge incontinence refractory to behavioral modification: Addition of an anticholinergic (eg, oxybutynin)

SURGERY/OTHER PROCEDURES

- Surgical intervention recommended for persistent VUR, worsening renal function, recurrent UTIs (3)[A]
- May be performed endoscopically or via open approach
  - Tailor approach to clinical presentation, medical history, anatomy, shared goals of clinician and patient
- Endoscopic intervention:
  - Benefit of using natural orifice, avoiding incision/scar; typically same-day surgery
  - Success rate dependent on surgeon, reflux grade, and bulking agent; typically 70–85%
  - Injection of bulking agent in and around ureteral orifice
  - Only 1 currently in use in US: Deflux, Salix (dextranomer–hyaluronic acid copolymer)
- Ureteral reimplantation:
  - Higher success rate (95–99%)
  - Can be performed via intra- or extravesical approach
  - Laparoscopic/robotic approaches have success rates comparable to open
- If VUR persists after either approach, surgery may be repeated
  - These patients must be vigorously evaluated for secondary cause of VUR, such as dysfunctional elimination

ADDITIONAL TREATMENT

Radiation Therapy

N/A

Additional Therapies

- Treatment of constipation and voiding dysfunction, including adherence to a bowel regimen, increased hydration and a timed voiding schedule is mandatory in children with VUR and elimination dysfunction
- Selective use of anticholinergic medications

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Overall resolution rate according to grade:
  - Grade I: Over 90%
  - Grade II: 70–80%
  - Grade III: 50–60%
  - Grade IV: 10–30%
  - Grade V: <10%
- Likelihood of resolution depends on many factors: Age, gender, laterality, reflux grade, volume of bladder at onset of reflux, presence/absence of voiding dysfunction (4)[B]
- Online neural network available: http://godot.urol.uic.edu/urocomp/svm_vur.html (5)[B]
- Bladder and bowel dysfunction shown to decrease and delay resolution
- Ureteral duplication associated with delay in time to resolution, but not significantly with changes in overall resolution rate

COMPLICATIONS

- Renal insufficiency
  - Reflux nephropathy most common cause of renal failure in children, often associated with renal scarring
    - Scarring occurs from infection in renal parenchyma; prophylactic antibiotics keep urine sterile
    - May manifest as hypertension, proteinuria, elevated serum creatinine, decreased GFR
    - Severe cases may progress to chronic renal insufficiency and end-stage renal disease
  - Dysplastic renal parenchyma
    - Increased risk with high-grade VUR
    - Sonography, serial creatinine, proteinuria, blood pressure checks may help identify these patients

FOLLOW-UP

Patient Monitoring

- Patients with VUR:
  - Annual complete physical exam with blood pressure check and urinalysis (proteinuria, infection)

  – Serial imaging: No consensus on interval, but general agreement of renal ultrasound and cystography every 1–2 yr
- After surgical correction or spontaneous resolution:
  – Annual blood pressure check and urinalysis (proteinuria, infection)
  – Use of routine sonography is debated
  – VCUG or nuclear cystography should be considered with symptoms of pyelonephritis or new sonographic abnormalities
- Siblings of children with VUR should undergo renal ultrasonography; VCUG reserved for cases of symptoms or ultrasound abnormalities (6)[A]

Patient Resources

National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC): http://kidney.niddk.nih.gov/kudiseases/pubs/vesicoureteralreflux/

REFERENCES

1. Elder JS. Vesicoureteral reflux. In: Kliegman R, Nelson WE, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier /Saunders; 2011:1834–1838.
2. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Clinical Practice Guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595–610.
3. Cooper CS, Austin JC. Vesicoureteral reflux: Who benefits from surgery? *Urol Clin N Am.* 2004;31:535–541.
4. Knudson MJ, Austin JC, McMillan ZM, et al. Predictive factors of early spontaneous resolution in children with primary vesicoureteral reflux. *J Urol.* 2007;178:1684–1688.
5. Shiraishi K, Matsuyama H, Nepple KG, et al. Validation of a prognostic calculator for prediction of early vesicoureteral reflux resolution in children. *J Urol.* 2009;182:687–690.
6. Skoog SJ, Peters CA, Arant BS Jr, et al. Pediatric VUR guidelines panel summary report: Clinical practice guidelines for screening siblings of children with VUR and neonates/infants with prenatal hydronephrosis. *J Urol.* 2010;184:1145–1151.

ADDITIONAL READING

None

See Also (Topic, Algorithm, Media)

- Urinary Tract Infection (UTI), Complicated, Pediatric
- Urinary Tract Infection (UTI), Pediatric
- Vesicoureteral Reflux, Adult
- Vesicoureteral Reflux, Pediatric Image ☼

CODES

ICD9

- 593.70 Vesicoureteral reflux unspecified or without reflux nephropathy
- 753.5 Exstrophy of urinary bladder
- 756.71 Prune belly syndrome

ICD10

- N13.70 Vesicoureteral-reflux, unspecified
- Q64.10 Exstrophy of urinary bladder, unspecified
- Q79.4 Prune belly syndrome

CLINICAL/SURGICAL PEARLS

- VCUG should be performed in children with febrile UTI and non–toilet-trained infants with UTI, and in other children as clinically indicated.
- All children with VUR should be assessed for dysfunctional elimination to reduce the likelihood of UTI.

VON HIPPEL–LINDAU DISEASE/SYNDROME

Jed-Sian Cheng, MD, MPH
Gennady Bratslavsky, MD

BASICS

DESCRIPTION

- Von Hippel–Lindau (VHL) disease is a multisystem autosomal dominant neoplastic syndrome with a predisposition to develop:
  - Clear cell renal cell carcinoma (ccRCC) and cystic lesions
  - Pancreatic neuroendocrine tumors (NET) and cystic lesions
  - Pheochromocytomas
  - Central nervous system (CNS) hemangioblastomas
  - Retinal angiomas
  - Endolymphatic sac tumors (ELST)
  - Cystadenomas of the epididymis (males) or broad ligament (females)

EPIDEMIOLOGY

Incidence

Rare: 1 in 35,000 live births

Prevalence

Prevalence in USA: About 7,000 people

RISK FACTORS

- Inheritance of a mutated VHL allele
- No gender or racial predilection

Genetics

- Autosomal dominant inheritance pattern
- *VHL* is a tumor suppression gene on chromosome 3p25–26 (3)
- Affected individuals inherit 1 copy of a mutated VHL from the affected parent
- The loss or mutation of the 2nd (initially normal) allele in the cell leads to tumor formation (mechanism known as a 2-hit model)
- Present technology identifies the mutated gene in 100%

PATHOPHYSIOLOGY

- Mutated VHL leads to aberrant VHL protein (pVHL)
- Abnormal pVHL is unable to target hypoxia inducible factor (HIF) for degradation
- Accumulation of HIF protein upregulates downstream genes such as *VEGF, GLUT-1, PDGF, TGF-α, Epo,* and many others, leading to tumor formation

ASSOCIATED CONDITIONS

- Multifocal and bilateral ccRCC in 50%
- Renal cysts seen in up to 70%
- Pheochromocytomas in about 20%

  - Extra-adrenal pheochromocytomas in $<5\%$
- CNS hemangioblastomas in 75%
- Retinal angiomas in 50–55%
- Pancreatic NET in 15–20%
- Pancreatic cysts are seen in up to 60%
- ELST in 5–10%
- Papillary cystadenomas of the epididymis or broad ligament in $<5\%$
- VHL-associated lung cysts/tumors in $<1\%$
- VHL-associated ovarian tumors in $<1\%$

GENERAL PREVENTION
- Close surveillance of affected individuals and timely intervention
- Genetic screening of family to initiate early surveillance

DIAGNOSIS

HISTORY
- Family history of RCC or pheochromocytoma, CNS or pancreatic surgeries, hearing or vision problems is often elicited
- Patients may present with ≥ 1 symptoms related to the organ involved
- Renal tumors and cysts:
  - Usually detected incidentally or during screening by imaging in VHL patients
  - May present with hematuria, flank pain, abdominal fullness, weight loss, cachexia in advanced disease
- Pheochromocytoma:
  - Headaches, palpitations, episodic sweating, anxiety attacks, personality changes
  - Severe hypertension (HTN) leading to hemorrhagic stroke
  - Rarely may present with weight loss, cachexia, bone pain, or cough in setting of metastatic disease
  - May be asymptomatic
- CNS hemangioblastomas:
  - Often asymptomatic
  - Headaches, vertigo, ataxia, vomiting, wide-based gait, sensory loss, seizures
  - Size and location of the lesion(s) often determine symptoms
- Retinal angiomas:
  - Blurred or decreased vision, eye pain
  - If undetected, may present with blindness
- Pancreatic NET and cysts:
  - Most are asymptomatic
  - Diarrhea, steatorrhea, and diabetes may occur if pancreas is replaced by cysts
  - Early satiety if pancreatic cysts are large and compressing the stomach
  - Bone pain and painless jaundice in rare cases of extrinsic compression of the biliary system or metastatic disease
- ELST:
  - Hearing decrease or loss, tinnitus, vertigo
- Cystadenomas of epididymis:

– Scrotal or testicular tenderness or mass

PHYSICAL EXAM

- Careful urologic, neurologic, and ophthalmologic exam can often help with diagnosis of VHL
- ccRCCs:
  – Undetected unless large in size
  – May cause marked varicocele
  – Occasionally, skin lesions or jaundice may be appreciated in metastatic RCC
- Pheochromocytoma:
  – HTN, tachycardia, arrhythmias
- CNS hemangioblastomas:
  – Nystagmus, papilledema, loss of proprioception, and sensory deficits
- Retinal angiomas:
  – Decreased visual acuity, characteristic retinal hemangiomas, and retinal detachment
- Pancreatic NET:
  – Undetected on exam unless large in size, metastatic, or causing obstruction
- ELST:
  – Decrease or loss of hearing
- Papillary cystadenomas of the epididymis:
  – Paratesticular tenderness and palpable epididymal masses

DIAGNOSTIC TESTS & INTERPRETATION

Lab

- Elevated plasma and urine catecholamines are seen in patients with pheochromocytoma:
  – Norepinephrine or normetanephrine are most commonly elevated in VHL patients
  – Other catecholamines may also be elevated
- Similar to sporadic ccRCC:
  – Hypercalcemia, erythrocytosis, anemia, or elevated liver function tests (LFTs) may be seen as paraneoplastic lab abnormalities
- Elevated erythropoietin levels or erythrocytosis may be seen with CNS involvement

Imaging

- Brain and spine magnetic resonance imaging (MRI) for detection of CNS hemangioblastomas and ELSTs
- Abdominal imaging: Ultrasound (US) in children, and computed tomography (CT) or MRI in adults for detection of renal or pancreatic masses, as well as adrenal and extra-adrenal pheochromocytomas
- Metaiodobenzylguanidine scan (MIBG) scan is helpful in localizing active pheochromocytoma
- Chest CT or MIBG may be helpful for extra-abdominal pheochromocytomas

Diagnostic Procedures/Surgery

- Genetic testing
- Occasionally, the glucagon stimulation test or clonidine suppression for pheochromocytoma

Pathologic Findings

- ccRCCs:

  – Usually multifocal and bilateral
  – May be several hundreds of gross and microscopic lesions in a single kidney
  – Most commonly Fuhrman nuclear grade II
  – Cysts commonly lined by clear cells
- Pheochromocytoma:
  – Encapsulated and vascular
  – Frequently multifocal and bilateral
  – Microscopic: Nests of cells in round clusters
- CNS hemangioblastomas:
  – Solitary or multiple lesions in cerebellum, spinal cord, brainstem, or cerebrum
  – Benign vascular lesions
- Pancreatic NET:
  – Usually multifocal intermixed with cysts
  – May metastasize to liver or bones unless resected in timely manner
  – Well-demarcated, unencapsulated nodules
  – Microscopic: Nests of polygonal cells with vesicular nuclei
- ELST:
  – Locally aggressive; usually slow growing
  – Microscopic: Low-grade papillary adenocarcinomas
- Papillary cystadenomas of the epididymis or the broad ligament:
  – Benign lesions
  – Well circumscribed but unencapsulated
  – Microscopic: Papillary and tubular architecture with a fibrous stroma

DIFFERENTIAL DIAGNOSIS
- Metastatic RCC or other primary
- Multiple endocrine neoplasia type 2 (MEN-2)
- Non-VHL familial bilateral multifocal RCC
- Other familial types of hereditary renal carcinoma syndromes
- Polycystic kidney disease
- Sporadic form of bilateral RCC
- Succinate dehydrogenase B (SDHB) deficiency syndrome in the presence of pheochromocytoma and renal masses

TREATMENT

GENERAL MEASURES
- Vigilant surveillance of kidneys, adrenals, pancreas, retina, brain, and spinal cord are the most important measures for timely intervention
- Surgery is still the mainstay of VHL treatment
- Nephron-sparing surgery is recommended when the largest solid tumor reaches 3 cm in the largest dimension

MEDICATION
First Line
- No VHL-specific medical treatment

- Treatment directed to address immediate presenting symptoms (eg, antihypertensives in patients presenting with pheochromocytoma)
- Other agents may be necessary for the management of related diseases such as RCC
- Preoperative blockade in a patient with a known pheochromocytoma
  - National Cancer Institute (NCI) regimen: Phenoxybenzamine 10 mg BID and metyrosine 250 mg TID for 2 wk preop

Second Line

N/A

SURGERY/OTHER PROCEDURES

- ccRCC:
  - Dozens of tumors may be resected in a single setting with adequate renal preservation
  - To minimize renal ischemia, most of the surgery is performed without hilar clamping
  - Select patients may benefit from laparoscopic or robotic surgery
  - Prior renal surgery or ablation makes surgery more challenging and increases morbidity
  - Bilateral nephrectomies and renal transplantation may be a valid option for occasional patients
- Pheochromocytoma:
  - Laparoscopic, robot-assisted, or open partial adrenalectomies are performed to preserve maximal adrenal function and avoid steroid dependence (1)
- Pancreatic NET:
  - Resection is the most definitive treatment
  - The type of surgical resection and procedure is determined by tumor size and location
- ELSTs or hemangiomas: Surgical resection
- Retinal angiomas: Laser ablation or cryotherapy

ADDITIONAL TREATMENT

Radiation Therapy

Occasional stereotactic irradiation of the metastatic disease or CNS hemangioblastomas not amendable to surgical resection

Additional Therapies

- A few clinical trials are presently in progress for treatment of VHL-associated tumors
- Genetic counseling, ophthalmology, neurosurgery, and otolaryngology support as needed

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- Much depends on the stage of the renal lesions at presentation
- Growth rate similar to sporadic counterpart of about 3 mm on average per year
- No metastasis with solid RCC lesions <3 cm (2)
- Metastatic potential of RCC lesions increases with increase in the size of the lesion, with up to 50% metastasis in those with tumors >6 cm
- Pancreatic NET also increase metastatic potential with increase in size

COMPLICATIONS

- Hypertensive crisis resulting in hemorrhagic stroke
- Severe neurologic deficit or paralysis
- Blindness
- Metastatic disease from either RCC, pheochromocytoma, or pancreatic NET

FOLLOW-UP

Patient Monitoring

- Radiographic surveillance is performed every 1–2 yr with CT or MRI for kidneys, adrenal, pancreas; and MRI for brain or spinal cord
  - More frequent for faster-growing lesions
- Ophthalmology exams yearly
- Otology exams every 5 yr
- Pediatric considerations
  - Yearly ophthalmologic exam from birth
  - Yearly urinary catecholamines from age 2 yr
  - Yearly abdominal US from age 10 yr
- Pregnancy considerations
  - Higher risk of miscarriage with active pheochromocytoma
  - Treatment of pheochromocytoma is preferred before pregnancy or early in the pregnancy

Patient Resources

www.vhl.org

REFERENCES

1. Benhammou JN, Boris RS, Pacak K, et al. Functional and oncologicoutcomes of partial adrenalectomy for pheochromocytoma in patients with von Hippel-Lindau syndrome after at least 5 yearsof follow up. *Urology*. 2005;66(1):19–23.
2. Duffey BG, Choyke PL, Glenn G, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. *J Urol.* 2005;72(1):63–65.
3. Linehan WM, Vasselli J, Srinivasan R, et al. Genetic basis of cancer of the kidney: Disease-specific approaches to therapy. *Clin Cancer Res.* 2004;15(10 Pt 2):6282S–6289S.

ADDITIONAL READING

- Shuch B, Linehan WM, Bratslavsky G. Repeat partialnephrectomy: Surgical, functional and oncologicaloutcomes. *Curr Opin Urol.* 2011;21(5):368–375.
- Singer EA, Vourganti S, Lin KY, et al. Outcomes ofpatients with surgically treated bilateral renalmasses and a minimum of 10 years of follow up. *J Urol.* 2012;188(6):2084–2088.
- Zbar B, Glenn G, Merino M, et al. Familial renal carcinoma: Clinical evaluation, clinical subtypes and risk of renal carcinoma development. *J Urol.*2007;177(2):461–465.

See Also (Topic, Algorithm, Media)

- Adrenal Mass
- Epididymis, Mass (Epididymal Tumor and Cysts)
- Pheochromocytoma
- Renal Cell Carcinoma, General

- Renal Cell Carcinoma, Localized (T1–T2)
- Renal Cysts (Intrarenal, Peripelvic, and Parapelvic)
- Renal Mass
- Von Hippel-Lindau Disease/Syndrome Image ☼

CODES

ICD9

- 189.0 Malignant neoplasm of kidney, except pelvis
- 209.60 Benign carcinoid tumor of unknown primary site
- 759.6 Other hamartoses, not elsewhere classified

ICD10

- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- D3A.8 Other benign neuroendocrine tumors
- Q85.8 Other phakomatoses, not elsewhere classified

CLINICAL/SURGICAL PEARLS

Suspect VHL in a patient with strong family history of RCC or pheochromocytoma, CNS or pancreatic surgeries, hearing or vision problems.

WILMS TUMOR (NEPHROBLASTOMA)

Jonathan S. Karpelowsky, MD, PhD
Grahame H.H. Smith, MBBS

BASICS

DESCRIPTION

- Wilms tumor (nephroblastoma) is the most common primary malignant renal tumor in childhood
- Represents 6% of all childhood cancers
- Most present in children with abdominal mass
- Symptoms may include pain, hypertension, or hematuria
- Wilms tumor is considered a pediatric renal tumor, but does rarely occur in adults

EPIDEMIOLOGY

Incidence

- 6% of all childhood tumors
- 80% of cases occur in age <5
- 7% bilateral (present at mean age 2.5)
- 12% multifocal within a single kidney
- Rare >10 yr and <6 mo
- Median age 3.5 yr

Prevalence

8 per million children every year

RISK FACTORS

- Increased frequency in children with:
  - Beckwith–Wiedemann syndrome: 1 in 10 children develop a tumor of the liver, adrenal cortex, or kidney
  - Hemihypertrophy (2% risk)
  - Denys–Drash syndrome
  - WAGR syndrome (Wilms tumor/aniridia/genitourinary anomalies/mental retardation syndrome), (30% risk)
  - Perlman syndrome
  - Sotos syndrome (2–3% risk)
- Presence of nephrogenic rests:
  - 1% of kidneys on infant postmortems
  - 35% of unilateral Wilms
  - Almost 100% of bilateral Wilms
- Higher risk in African American compared to Caucasians for Wilms tumor
- Lower risk in Asians compared to Caucasians

Genetics

- WT1 (11p13): Denys–Drash and WAGR syndromes

- WT2 (11p15): Beckwith–Wiedemann syndrome
- FWT1 (17q), FWT2 (19q): Familial; 1–2% of cases
- 16q, loss of long arm in 20% of cases
- 1p, loss of short arm in 10% of cases

PATHOPHYSIOLOGY
- An embryonal tumor marked by proliferation of metanephric blastema composed of 3 cell types: Blastemal, stromal, epithelial
- Histology: Favorable vs. unfavorable (ie, anaplasia pre- or postchemotherapy and blastemal predominant histology postchemotherapy)
- Anaplasia seen in 5%

ASSOCIATED CONDITIONS
- Congenital anomalies in 15% of Wilms tumors
- GU anomalies: Renal anomalies, cryptorchidism, hypospadias, ureteral duplication, ambiguous genitalia (4%)
- Hemihypertrophy (3%)
- Aniridia (1%)
- Denys–Drash syndrome (male pseudohermaphroditism, renal mesangial sclerosis, renal failure)
- WAGR syndrome
- Beckwith–Wiedemann syndrome (macroglossia, organomegaly, hemihypertrophy)
- Other: Perlman syndrome, Sotos syndrome, Simpson–Golabi–Behmel syndrome

GENERAL PREVENTION
N/A

DIAGNOSIS
HISTORY
- Abdominal mass
- Fever, anorexia, weight loss
- Hematuria

PHYSICAL EXAM
- Most common presentation is abdominal mass
- HTN: 20–25% from activation of RAAS (renin-angiotensin-aldosterone system)
- Occasionally present as acute abdomen or with hypotension from tumor rupture

DIAGNOSTIC TESTS & INTERPRETATION
Lab
- CBC: Anemia, polycythemia
- Liver function tests
- BUN, creatinine
- Serum calcium
- Urine analysis: 25% with microhematuria
- Coagulation studies to assess for an acquired von Willebrand disease

Imaging

- Abdominal US: Initial study and if there is any concern about intravascular extension
- CT of abdomen and chest: To detect smaller lesions in either renal unit not detected by US; chest imaging to evaluate for pulmonary metastasis
- Bone scan: If history of bone pain or elevated alkaline phosphatase or serum Ca

Diagnostic Procedures/Surgery

- National Wilms Tumor Study Group (*NWTSG*)/Children's Oncology Group (COG), recommends surgical excision or biopsy, followed by adjuvant treatment
- SIOP (International Society of Pediatric Oncology) treatment involves preoperative chemotherapy followed by surgery. Histology and staging are potentially altered but the tumor response to chemotherapy is noted and aids in risk stratification
- Percutaneous biopsy is not recommended

Pathologic Findings

- Gross: Tan or grayish, fleshy tumor with a pseudocapsule
- Microscopic (3 features): Stromal (immature spindle cells and can have muscle cartilage or fat), epithelial (recapitulates kidney with glomeruli and tubules), and blastemal (undifferentiated cells)
- Venous invasion in up to 20%; usually single tumor; 7% bilateral and 12% multifocal
- Histology relates to final outcome:
  - Favorable (95%)
  - Unfavorable (Anaplasia) (5%): Nuclear enlargement (>3-fold), hyperchromasia, abnormal mitoses. Unfavorable marker of chemoresistance

DIFFERENTIAL DIAGNOSIS

- Clear cell sarcoma
- Rhabdoid tumor
- Neuroblastoma
- Multilocular cystic nephroma
- Mesoblastic nephroma
- Multicystic dysplastic kidney
- Renal cell carcinoma
- Renal medullary carcinoma

TREATMENT

GENERAL MEASURES

- Multimodality therapy combining surgery, chemotherapy, and radiation
- Treatment decisions based on staging
- Staging relies on anatomic extent of tumor (no genetic, histologic, or biomarkers); higher stages have worse prognosis and require more aggressive therapy
- 2 systems currently used, the NWTSG/COG and SIOP; they are difficult to compare directly due to the fact that NWTSG/COG is a prechemotherapy staging and SIOP post-neoadjuvant therapy:
  - NWTSG/COG: Commonly used in USA and Canada; based on surgical evaluation prior to chemotherapy

– SIOP: Commonly used in Europe, based on surgical findings following chemotherapy

MEDICATION

First Line

- SIOP studies favor preoperative chemotherapy for 6 wk with dactinomycin plus vincristine following which surgery is undertaken and the tumor response to chemotherapy and the residual histology, ie, if is blastemal predominant will risk stratify further therapy
- Chemotherapy recommendations based on NWTSG/COG, which is given adjuvantly postoperatively
- Children <24 mo and with a specimen weight of <550 g and favorable histology are being considered under study for surgery only and no chemotherapy
- Pulse-intensive dactinomycin plus vincristine (18 wk) for:
  – Stage I: Favorable histology, age >2 yr, or tumor <550 g
  – Stage I: Anaplasia
  – Stage II: Favorable histology
- Pulse-intensive dactinomycin, vincristine, and doxorubicin (24 wk) for:
  – Stages III–IV: Favorable histology
  – Stages II–IV: Focal anaplasia
  – Stage V: Doxorubicin, vincristine, cyclophosphamide, etoposide
  – Stages II–IV: Diffuse anaplasia (1)

Second Line

The optimal salvage chemotherapy regimen is unknown. Recurrent/persistent tumors have been treated with cyclophosphamide, ifosfamide, carboplatin, etoposide, and cisplatin combinations

SURGERY/OTHER PROCEDURES

- Choose incision that provides adequate exposure: Transabdominal, thoracoabdominal, chevron
- Unilateral tumor:
  – Radical nephrectomy
  – Contralateral exploration not needed if not seen on adequate preoperative imaging
  – Lymph node: Sample perihilar, pericaval, and para-aortic nodes; excise suspicious nodes minimum of 3–5 nodes
- Bilateral tumor:
  – Biopsy not initially required
  – Reimage 6 wk after chemotherapy; if <50% response consider open bilateral biopsy, if >50% response then continue therapy to 12 wk and then aim for nephron sparing surgery
  – Renal preservation is key to avoid renal failure; important for patient with syndromes at high risk for metachronous disease
- Tumor spillage:
  – Local: Percutaneous anterior/posterior percutaneous biopsy; open incisional biopsy (stage III)
  – Peritoneal spillage or tumor thrombus spillage is more extensive (stage III)
- Local invasion: Usually can be resected en masse; if not, biopsy and treat with chemotherapy

ADDITIONAL TREATMENT

Radiation Therapy

- Stage III favorable histology and stages II–III focal or diffuse anaplasia:
  - Abdominal/flank irradiation 10.8 Gy
- Stage IV favorable histology and stage IV focal or diffuse anaplasia:
  - Abdominal/flank irradiation 10.8 Gy
  - Lung radiation 12 Gy with lung metastasis on chest x-ray or CT only metastasis not responding to therapy (CT only metastasis that respond to chemotherapy and have no loss of heterozygosity can have pulmonary radiotherapy omitted)

Additional Therapies

Ongoing studies of NWTSG/COG to assess modifying treatment based on risk stratification

Complementary & Alternative Therapies

N/A

ONGOING CARE

PROGNOSIS

- 5-yr overall survival: 90%
- 4-yr postnephrectomy overall survival:
  - Favorable histology:
    - Stage I: 98%
    - Stage II: 96%
    - Stage III: 95%
    - Stage IV: 90%
  - Unfavorable histology:
    - Stage I: 83%
    - Stage II: 81%
    - Stage III: 72%
    - Stage IV: 37%
    - Stage V: 55%
- Unfavorable histology: 12% of patients, but 50% of deaths
- Prognostic factors: Histology, stage, patient age (younger better prognosis, but less significant today due to improved treatments)
- Future treatment will include 1p and 16q loss of heterozygosity in the risk and treatment stratification

COMPLICATIONS

- Surgical:
  - Bowel obstruction (5.1%)
  - Hemorrhage (1.9%)
  - Wound infection (1.9%)
  - Vascular injuries (1.4%)
  - Injuries to other visceral organs (1%)
- Medical:
  - Renal impairment

    - 1% chance from surgical, chemotherapy, and/or radiation
    - Increased in bilateral disease with radiation
    - Unilateral disease risk in Denys–Drash
  - Cardiotoxicity
    - Congestive heart failure in patients treated with doxorubicin; dose dependent
  - Hepatotoxicity
    - Vincristine and dactinomycin; dose related
  - Secondary malignancies
    - Highest risk in patients treated with both doxorubicin and radiation; occur in radiation field; mean 16.1-yr post therapy
- Radiation:
  - Short stature, muscle atrophy, scoliosis
  - Highest risk in age <1
  - Thyroid disease and mammary tissue damage in chest radiation
  - Pregnancy complications increased in females receiving high-dose abdominal radiation

FOLLOW-UP

Patient Monitoring

- Screen patients with aniridia, hemihypertrophy, and Beckmann–Wiedemann syndrome with abdominal US every 3–4 mo to age 7
- 1% of children develop contralateral Wilms within 6 yr of 1st diagnosis
- Majority of Wilms tumor recurrence occurs within 2 yr of nephrectomy
- Favorable histology, <24 mo, and tumor weight <550 g
  - Chest x-ray, abdominal US every 3 mo for 1st 2 yr after diagnosis, then every 6 mo for 1 yr, then yearly for 2 yr
- All others:
  - Chest x-ray 6 wk and 3 mo after surgery; then every 3 mo for 15 mo, every 6 mo for 18 mo, and yearly for 2 yr
  - Abdominal US every 3 mo for 2 yr, then every 6 mo for 3 yr

Patient Resources

National Wilms Tumor Study. www.nwtsg.org

REFERENCE

1. Dome JS, Cotton CA, Perlman EJ, et al. Treatment of anaplastic histology Wilms' tumor: Results from the fifth Wilms' tumor study. *J Clin Oncol*. 2008;24:2352–2358.

ADDITIONAL READING

- Ahmed HU, Arya M, Tsiouris A, et al. An update on the management of Wilms' tumour. *Eur J Surg Oncol*. 2007;33:824–831.
- Dome JS, Fernandez CV, Mullen EA, et al. Children's oncology group's 2013 blueprint for research: Renal tumors. *Pediatr Blood Cancer*. 2013;60:994–1000.
- Ehrlich PF. Wilms tumor: Progress and considerations for the surgeon. *Surg Oncol*. 2007;16(3):157–171.
- Hamilton TE, Shamberger RC. Wilms tumor: Recent advances in clinical care and biology. *Semin Pediatr Surg*. 2012;21(1):15–20.

See Also (Topic, Algorithm, Media)
- Abdominal Mass, Newborn/Child, Urologic Considerations
- Renal Mass
- Wilms Tumor (Nephroblastoma) Image ☼
- Wilms Tumor Staging System National Wilms Tumor Study Group (NWTSG Now COG)
- Wilms Tumor Staging System: International Society of Pediatric Oncology (SIOP)

CODES

ICD9
- 189.0 Malignant neoplasm of kidney, except pelvis
- 253.0 Acromegaly and gigantism
- 759.89 Other specified congenital anomalies

ICD10
- C64.9 Malignant neoplasm of unsp kidney, except renal pelvis
- E22.0 Acromegaly and pituitary gigantism
- Q87.3 Congenital malformation syndromes involving early overgrowth

CLINICAL/SURGICAL PEARLS

An asymptomatic abdominal mass is the most common manifestation of Wilms tumor.

SECTION II

Short Topics: A to Z

Section Editors: Deborah T. Glassman, MD
Alana M. Murphy, MD

11β-HYDROXYLASE (CYP11B1) DEFICIENCY

DESCRIPTION Comprises 5–8% of congenital adrenal hyperplasia (CAH) cases. Autosomal recessive disorder that manifests as childhood hypertension, hypokalemia, and muscle weakness. Low plasma renin activity is a hallmark. A deficiency in 11β-hydroxylase leads to low cortisol levels, high adrenocorticotropic hormone levels, and adrenal hyperplasia. Afflicted females are virilized and may have male-appearing genitalia. Males may be hyperdeveloped. Diagnosed by high levels of deoxycorticosterone and/or 11-deoxycortisol in serum or their tetrahydro-metabolites in a 24-hr urine. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Congenital Adrenal Hyperplasia.")

TREATMENT

- Oral hydrocortisone (10–20 mg/m^2/d)
- Refractory hypertension treated with spironolactone, amiloride, and/or calcium channel blockers
- Surgical correction of ambiguous genitalia in females
- Prenatally treated with steroid administration to mother

REFERENCE

White PC. Steroid 11 beta-hydroxylase deficiency and related disorders. *Endocrinol Metab Clin North Am.* 2001;30(1):61–79.

2,8-DIHYDROXYADENINE (2,8-DHA) UROLITHIASIS

DESCRIPTION Adenine phosphoribosyltransferase (APRT) deficiency is a defect of purine metabolism and is inherited as an autosomal recessive trait. APRT is a salvage enzyme that catalyzes the conversion of adenine to adenosine monophosphate. The APRT deficiency results in adenine accumulation with oxidation by xanthine dehydrogenase (XDH) to 2,8-dihydroxyadenine (2,8-dihydroxyadenine or 2,8-DHA) then excreted in urine. This compound is extremely insoluble and its crystallization can lead to stone formation and renal failure. The diagnosis is based on stone analysis by infrared spectroscopy or exam of urine, which may reveal typical 2,8-DHA crystals.

TREATMENT

The crystallization of 2,8-DHA and subsequent renal damages may be prevented with allopurinol therapy, a xanthine oxidase inhibitor.

REFERENCE

Bouzidi H, Lacour B, Daudon M. 2,8-dihydroxyadenine nephrolithiasis: From diagnosis to therapy. *Ann Biol Clin (Paris)*. 2007;65(6):585–592.

21-HYDROXYLASE (CYP21A2) DEFICIENCY

DESCRIPTION Responsible for >90% of CAH cases. This enzyme deficiency leads to low cortisol levels and high ACTH level, leading to adrenal hyperplasia. It is the most common cause of female pseudohermaphrodism. Most have aldosterone deficiency, which can lead to fatal salt wasting. Untreated patients are tall as children but short as adults. Untreated

females may have secondary amenorrhea or polycystic ovarian syndrome. Males may have small testes with precocious secondary sexual characteristics. Diagnosed by elevated 17α-hydroxyprogesterone levels in serum with ACTH stimulation test. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Congenital Adrenal Hyperplasia.")

TREATMENT

- Oral hydrocortisone (10–20 mg/m^2/d)
- 9α-fluorohydrocortisone for salt wasters
- Surgical correction of ambiguous genitalia in females
- Prenatally treated with steroid administration to mother

REFERENCE

White PC, Bachega TA. Congenital adrenal hypoplasia due to 21 hydroxylase deficiency: From birth to adulthood. *Semin Reprod Med.* 2012;30(5):400–409.

5α-REDUCTASE DEFICIENCY

DESCRIPTION An autosomal recessive disorder characterized by a 46XY male with external female phenotype at birth, normally developed wolffian structures, and bilateral testes residing outside the abdominal cavity. The primary etiology is the loss of dihydrotestosterone (DHT) during fet al development. Hypoplasia or absence of the prostate and a blind-ending vagina are common. Virilization occurs at puberty. Diagnosed by normal-to-high male plasma testosterone levels, abnormal ratios of serum testosterone to DHT, or abnormal ratios of urinary 5α- to 5β-steroid metabolites. (See also Section I: "Disorders of Sexual Development [DSD].")

TREATMENT

- Male gender assignment: Genital reconstruction and supplemental androgen
- Female gender assignment: Orchiectomy, estrogen/progesterone therapy, and vaginoplasty

REFERENCE

Cheon CK. Practical approach to steroid 5-alpha-reductase type 2 deficiency. *Eur J Pediatr.* 2011;170(1):1–8.

AARSKOG SYNDROME (FACIODIGITOGENITAL SYNDROME)

DESCRIPTION A malformation syndrome carried by both an X-linked and an autosomal dominant form. Primary diagnostic criteria include short stature, hypertelorism, short nose with anteverted nares, maxillary hypoplasia, a crease below the lower lip, mild interdigital webbing, clinodactyly, and shawl scrotum. Cardiac abnormalities are also reported. There is no specific treatment.

REFERENCE

Teebi AS, Rucquoi JK, Meyn MS. Aarskog syndrome: Report of a family with review and discussion of nosology. *Am J Med Genet.* 1993;46(5):501–509.

ABDOMINOPERINEAL RESECTION (APR), UROLOGIC CONSIDERATIONS

DESCRIPTION Commonly performed for rectal cancers in which the rectum, anus, and a portion of the sigmoid colon are removed (also known as Miles resection or abdominal perineal proctosigmoidectomy). The extensive pelvic dissection can lead to a number of urologic problems. Urinary retention and urinary incontinence represent 2 distinct urologic complications after abdominoperineal resection (APR). Injury to detrusor branches of the pelvic nerve can cause detrusor denervation and urinary retention. In addition, injury to intrapelvic branches of the pelvic and pudendal nerves to the urinary sphincter can result in intrinsic sphincter deficiency (ISD) and urinary incontinence. Impotence and urinary retention can occur in males; urinary incontinence and altered sexual function may occur in females, secondary to removal of the anterior vaginal wall. Damage to the ureters is not uncommon during the procedure.

TREATMENT

- Stent placement preoperatively may help in identifying the ureters.
- Intermittent catheterization for retention; TURP or other bladder outlet procedure may be considered preoperatively in men with BPH.
- Impotence managed with penile prosthesis, vacuum device, or intracorporal therapy.

REFERENCE

Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. *Nat Rev Urol.* 2011;8(1):51–57.

ABRAMS–GRIFFITHS NOMOGRAM

DESCRIPTION Bladder outlet obstruction can be defined only by pressure–flow measurement. The Abrams–Griffiths nomogram is an easy method of classifying these data to distinguish between the presence or absence of obstruction. Using the values for maximal flow and the corresponding voiding detrusor pressure, a point can be plotted on the nomogram that determines whether the bladder outlet is obstructed, unobstructed, or equivocally obstructed. For those that fall in the equivocal zone, further criteria for the mean slope of the pressure–flow plot and the minimal voiding detrusor pressure are used to determine whether obstruction is present. The nomogram has shown excellent prognostic value in multiple studies in predicting the outcome of outlet reduction procedures. Although the Abrams–Griffiths nomogram is somewhat simplistic, none of the more complex methods of pressure–flow analysis has been shown to be a better predictor of treatment outcome to date. (See also Section II: “Pressure–Flow Studies” and “Urodynamics, Indications, and Normal Values.”)

REFERENCE

Lim CS, Abrams P. The Abrams-Griffith nomogram. *World J Urol.* 1995;13:34.

ACETAMINOPHEN ABUSE, UROLOGIC CONSIDERATIONS

DESCRIPTION 1–2% of patients with acetaminophen overdose present with renal

insufficiency. Proposed mechanisms for etiology are uncertain, but may involve increased cytochrome P-450, prostaglandin synthetase, and N-deacetylase enzymes. Although clinical management rarely leads to renal biopsy, histopathologic specimens would most likely show proximal tubule epithelial cell necrosis. A urinalysis can differentiate acetaminophen nephrotoxicity from hepatorenal syndrome (HRS) or prerenal azotemia. If acetaminophen nephrotoxicity is the etiology of renal insufficiency, a urine sediment would have granular casts with variable hematuria or pyuria. Urine sodium would typically be >20 mmol/L, compared to <10 mmol/L with HRS. Onset of renal insufficiency ranges from 1–8 days (peak 3–16 days). The return to baseline renal function may take approximately 1 mo with a 1% chance of requiring dialysis. There is no clear relationship between acetaminophen dose and nephrotoxicity.

TREATMENT

- N-acetylcysteine has a clear role in preventing liver necrosis but not in the treatment of acetaminophen nephrotoxicity.
- Treatment focuses on supportive care, including management of volume status, blood pressure, and electrolyte balance.

REFERENCE

Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: Pathophysiology, clinical manifestations, and management. *J Med Toxicol.* 2008;4:2–6.

ACQUIRED RENAL CYSTIC DISEASE

DESCRIPTION The development of renal cysts in patients with long-standing ESRD or severe chronic renal insufficiency. The cause is not known, but an accumulation of toxins unfiltered by dialysis is theorized. Usually asymptomatic, it can present with abdominal pain or hematuria. It is more common in males, and there is a 3–6 times greater incidence of renal cell carcinoma (RCC) compared to the general population (individual risk 4–7%). In dialysis-related RCC, neoplastic cells of acquired cystic disease-associated RCC are positive for alpha-methylacyl-CoA racemase (AMACR), but negative for cytokeratin (CK) 7. Tumors tend to be very aggressive, with a high incidence of metastasis. Risk increases with increased time on dialysis. (See also Section I: “Renal Cysts [Intrarenal, Peripelvic and Parapelvic].”)

TREATMENT

- Close follow-up for early detection of malignancy (periodic imaging)
- Renal transplantation can reverse growth of cysts, but malignancy can still occur

REFERENCE

Farivar-Mohseni H, Perlmutter AE, Wilson S, et al. Renal cell carcinoma and end stage renal disease. *J Urol.* 2006;175(6):2018–2020.

ACROSOME REACTION ASSAY

DESCRIPTION The acrosome is a membrane-bound organelle covering the anterior 2/3 of the sperm head. This organelle contains numerous enzymes whose release, termed the acrosome reaction, is required for penetration of the hard zona pellucida of the ovum. It is

hypothesized that human sperm bind to the ovum, after which the acrosome reaction is induced by 1 or more of the zona pellucida glycoproteins. Abnormalities of any aspect of this reaction may be a source of male-factor infertility. Transmission electron microscopy, although the procedure of choice to detect acrosome reaction defects, is labor-intensive and expensive. This test may be recommended in cases of profound abnormalities of head morphology or in the setting of unexplained infertility in patients with poor IVF pregnancy rates. (See also Section II: "Semen Analysis, Technique, and Normal Values.")

REFERENCE

Agarwal A. Assessing sperm function. *Urol Clin North Am.* 2008;35(2);157–171.

ACTINOMYCOSIS, RENAL

DESCRIPTION Actinomycosis is a chronic granulomatous infection caused by a gram-positive anaerobic *Actinomyces* bacteria, usually *A. israelii.* No pathognomonic findings are common; it can reach the kidney by hematogenous spread or instrumentation. Fibrosis and fistulas are common. The infection can present as sepsis with negative urine culture. Imaging can reveal renal abscesses and hydronephrosis, and the condition has been typically diagnosed postoperatively due to a renal mass prompting nephrectomy; it is diagnosed by gram-positive organisms on stain and prolonged incubation of bacteria. Microscopic exam of the organism can appear as yellow bodies called sulfur granules.

TREATMENT

- Nephrectomy of involved renal unit is usually necessary
- Aggressive antibiotic therapy with long-term penicillin followed by doxycycline and ciprofloxacin

REFERENCE

Dhanani NN, Jones DM, Grossman HB. Medical management of renal actinomycosis. *J Urol.* 2004;171(6 Part 1):2373–2374.

ACUTE KIDNEY INJURY (AKI), DEFINITIONS

DESCRIPTION Acute renal failure (ARF) has been defined as the abrupt loss of kidney function resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. While this loss in kidney function is detected by elevated serum creatinine, several problems are associated with the use of this measure to quantitatively define ARF, particularly the lack of consensus in the quantitative definition. The Acute Dialysis Quality Initiative (ADQI) has proposed a graded definition of ARF called the RIFLE criteria. The Acute Kidney Injury Network modified the RIFLE criteria to include less severe ARF, a time constraint of 48 hr, and to allow for correction of volume status and obstructive causes of ARF prior to classification. The Acute Kidney Injury Network uses the term acute kidney injury (AKI) to represent the spectrum of ARF. The proposed diagnostic criteria for AKI are: An abrupt (<48 hr) increase in creatinine concentration of ≥ 0.3 mg/dL (26.4 mmol/L) from baseline, a percentage increase in the serum creatinine $\geq 50\%$, or oliguria of <0.5 mL/kg/h for >6 hr. (See also Section I: "Acute kidney Injury,

Adult (Renal Failure, Acute), Acute Kidney Injury, Pediatric (Renal Failure, Acute); Section II "Rifle Criterion for Acute Renal Injury.")

REFERENCE

Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: Report of an initiative. *Am J Kidney Dis.* 2007;50:1–4.

ADENOFIBROMA, METANEPHRIC, PEDIATRIC

DESCRIPTION Metanephric adenofibroma is a very rare benign tumor 1st described as nephrogenic adenofibroma by Hennigar and Beckwith in 1992. This tumor appears to affect predominantly young people (mean, 14 yo; range, 20 mo–35 yo). The most common symptom is hematuria, but a significant proportion of patients are asymptomatic. Polycythemia is a peculiar incidental finding that resolves after resection of the tumor. The radiologic appearances are nondiagnostic and indistinguishable from other solid pediatric renal tumors, particularly Wilms tumor. Histologically, this tumor is characterized by proliferation of benign-appearing mesenchymal cells surrounding multifocal nodules of immature epithelial cells. The latter cells show differentiation toward glandular and papillary structures. The mesenchymal component of metanephric adenofibroma closely resembles congenital mesoblastic nephroma in cytologic appearance. At present, all metanephric adenofibroma lesions should be excised to establish diagnosis, but no further adjuvant therapy is required.

REFERENCES

Hennigar RA, Beckwith JB. Nephrogenic adenofibroma. A novel kidney tumor of young people. *Am J Surg Pathol.* 1992;16:325–334.

Palese MA. Metanephric stromal tumor: A rare benign pediatric renal mass. *Urology.* 2001;58:462.

ADRENAL ANGIOMYOLIPOMA

DESCRIPTION Angiomyolipoma arising the adrenal is very rare with only a few reported in the literature. They are usually asymptomatic, diagnosed incidentally, and much more common in the kidney. Histologically it consists of mature fat cells, smooth muscle fibers, and thin-walled blood vessels. Management is identical to any adrenal mass: Assessment of functional status of the tumor with surgery if the patient is symptomatic or lesion is >5 cm (risk of malignancy and possibly bleeding). (See also Section I: "Adrenal Mass" and Section II: "Adrenal; Myelolipoma [Adrenal Myolipoma].")

REFERENCE

Yener O, Özçelik A. Angiomyolipoma of the right adrenal gland. *ISRN Surg.* 2011;2011:102743.

ADRENAL CALCIFICATIONS

DESCRIPTION Adrenal calcifications may be the result of hemorrhage (secondary to trauma, venous thrombosis, stress, or bleeding diatheses), infection (usually granulomatous

diseases), or may be associated with different tumors. Necrosis and calcification are more common in association with adrenal carcinoma but are not diagnostic. Bilateral calcified adrenal glands may be seen in adrenal insufficiency or secondary Addison disease. Calcifications may be detected on MRI because of their susceptibility artifact but are much better appreciated on CT images.

REFERENCE

Kenney PJ, Stanley RJ. Calcified adrenal masses. *Urol Radiol.* 1987;9:9–15.

ADRENAL CYSTS AND PSEUDOCYSTS

DESCRIPTION A rare (0.064–0.18% on autopsy studies) condition, more often detected on imaging. Most are asymptomatic. These cysts can cause GI discomfort, pain if large, and even an acute abdomen with rupture or infection. Four major types are recognized: Endothelial, pseudocyst, epithelial, and parasitic, in order of decreasing incidence. Parasitic cysts arise primarily from *Equinococcus granulosus* infection. Adrenal pseudocysts are thought to result from infarction or hemorrhage of a cyst or tumor.

TREATMENT

- >3.5 cm: Aspiration for fluid analysis and cytology to rule out malignancy
- <3.5 cm: Observe with serial imaging (US or CT or MRI).

REFERENCE

Sebastiano C, Zhao X, Deng FM, et al. Cystic lesions of the adrenal gland: Our experience over the last 20 years. *Hum Pathol.* 2013;44(9):1797–1803.

ADRENAL CYTOMEGALY

DESCRIPTION Found infrequently in children and adults and considered a benign mass lesion, the condition is seen often in Beckwith–Wiedemann syndrome. Other possible associations include hemolytic disease of the newborn, erythroblastosis fet alis, and congenital rubella. It is characterized by the presence of large polyhedral cells with eosinophilic granular cytoplasm and enlarged nuclei in the adrenal cortex. Adrenal cytomegaly rarely forms cysts. This condition is thought to be a degenerative process but not a malignancy, possibly caused by a physiologic condition that demands increased functional capacity and proliferation of adenocytes.

REFERENCE

Noguchi S, Masumoto K, Taguchi T, et al. Adrenal cytomegaly: Two cases detected by prenatal diagnosis. *Asian J Surg.* 2003;26(4):234–236.

ADRENAL HEMORRHAGE

DESCRIPTION Adrenal hemorrhage (AH) is a collection of blood producing a mass effect in 1 or both adrenal glands, with or without adrenal necrosis and insufficiency. It occurs in up to 30% of selected neonatal intensive care patients, 14–22% of newborns at autopsy, and up to 15% at autopsy of adult patients dying in shock. Signs and symptoms include fever, flank

or abdominal pain, tachycardia, nausea, vomiting, respiratory distress, and weakness. Unilateral AH may be an incidental finding during imaging. AH may result from multiple mechanisms: Stress, sepsis (Waterhouse–Friderichsen syndrome), anticoagulation-related hypotension, vascular spasm, adrenal venous thrombosis, or heparin-associated thrombocytopenia.

Workup may show dropping hemoglobin and electrolyte abnormalities (hyponatremia, hyperkalemia in 56% of bilateral AH).

TREATMENT

Includes replacement of fluids, electrolytes, and blood if anemia is significant. Patients should be started on steroid replacement if adrenal insufficiency is suspected. Surgical exploration may be necessary for uncontrollable hemorrhage, uncertain diagnosis, or if abscess formation is suspected.

REFERENCE

Simon DR, Palese MA. Clinical update on the management of adrenal hemorrhage. *Curr Urol Rep.* 2009;10(1):78–83.

ADRENAL HYPOPLASIA

DESCRIPTION Reduced ACTH production can result in hypoplasia of the adrenal gland (secondary adrenal hypoplasia); this can occur as a result of lack of pituitary trophic signaling, such as in pituitary agenesis. Congenital adrenal hypoplasia (primary) is an inherited disorder, with several forms identified. The major form of adrenal hypoplasia is X-chromosome linked and traced to the DAX-1 (AHCH) gene. This gene is in close proximity to other genes encoding for glycerol kinase and Duchenne muscular dystrophy (both associated with adrenal hypoplasia). Hypogonadotrophic hypogonadism is also a common finding. It typically presents in the neonatal period or with adrenal crisis (dehydration, hyponatremia, hyperkalemia, hypotension, hypoglycemia). Disorders of the external genitalia may include micropenis, undescended testes, or hypospadias. It can be detected by biochemical testing (serum cortisol, corticotropin-releasing hormone (CRH) stimulation test, etc.). Antenatal maternal estriol screening can also detect adrenal hypoplasia. Treatment is replacement of adrenal hormones.

Diagnosis must be made early, or it can be fatal secondary to salt wasting.

REFERENCE

Ferraz-de-Souza B, Achermann JC. Disorders of adrenal development. *Endocr Dev.* 2008;13:19–32.

ADRENAL INCIDENTALOMAS

DESCRIPTION Incidentally discovered adrenal lesions – called “adrenal incidentalomas” – are by-products of increased availability and use of advanced imaging. Adrenal masses are found in approximately 4% of patients undergoing abdominal CT scans, and the prevalence increases with age. Most are nonfunctional, benign adenomas. It is important to consider 2 questions in the evaluation of an adrenal incidentaloma: Whether it is functioning and

whether it is malignant. Differential diagnosis includes benign nonfunctioning adenoma; cyst/pseudocyst; hormonally active tumors such as pheochromocytoma, primary hyperaldosteronism, and Cushing disease (nodular hyperplasia); myelolipoma and malignancies including adrenocortical carcinoma; or metastasis from lungs, breast, colon, kidney, melanoma, or lymphoma. Incidentaloma <4 cm are likely benign. A 1-mg dexamethasone suppression test and measurement of plasma-free metanephrines is recommended for all patients with an adrenal incidentaloma, as well as a serum potassium and plasma aldosterone concentration-plasma rennin activity ratio for patients with hypertension. (See also Section I: "Adrenal Mass.") (Image ☼)

TREATMENT

- Surgical removal is indicated with hormonally active tumors, as well as any tumors >6 cm.
- Observation is warranted for any mass <4 cm and nonfunctioning. A repeat CT 6–12 mo after the initial study is reasonable for follow-up.

REFERENCE

Grumbach MM, Biller BM, Braunstein GD, et al. Management of the clinically inapparent adrenal mass (incidentaloma). *Ann Intern Med.* 2003;138(5):424–429.

ADRENAL METASTASES

DESCRIPTION The 4th most common site of metastatic tumor spread. Common metastases include breast (most common), lung, kidney, stomach, pancreas, and melanoma. (See also Section I: "Adrenal Mass.")

REFERENCE

Gittens PR Jr, Solish AF, Trabulsi EJ. Surgical management of metastatic disease to the adrenal gland. *Semin Oncol.* 2008;35(2):172–176.

ADRENAL MYELOLIPOMA (ADRENAL MYOLIPOMA)

DESCRIPTION Referred to as *myolipoma* and *myelolipoma* in the literature, this rare, usually nonfunctioning lesions are composed of adipose and hematopoietic cells may represent extramedullary hematopoiesis. It is rarely metabolically active (Cushing or Conn syndrome) and usually asymptomatic, except when very large or if hemorrhage occurs. They mostly occur in the adrenal glands, but extra-adrenal myelolipomas have been reported (presacral, retroperitoneum). It can be diagnosed radiographically and is more typically incidentally discovered at imaging or autopsy. Ultrasound shows a highly echogenic mass. CT demonstrates focal densities near that of fat (Hounsfield units of –30 to –115). MRI T1-weighted images demonstrate high signal intensity, whereas T2-weighted images are moderately intense. The main diagnostic similarity is well-differentiated liposarcoma. (See also Section I: "Adrenal Mass.")

TREATMENT

Excision if symptomatic or if diagnosis cannot be confirmed radiographically or on needle biopsy.

REFERENCE

Nabi J, Rafiq D, Authoy FN, et al. Incidental detection of adrenal myelolipoma: a case report and review of the literature. *Case Rep Urol.* 2013;2013:789481. doi: 10.1155/2013/789481.

ADRENAL ONCOCYTOMA

DESCRIPTION Oncocytic neoplasms of the adrenal gland, unlike that of the kidney, are rare with only 147 cases described. 80–90% of lesions are nonfunctional and only 10–20% of lesions show malignant elements. Typically occurs from 27–72 yr of age. More common in women (2.5:1 compared to men) and the left adrenal gland (3.5:1 compared to the right). Histologically, lesions are highly granular and eosinophilic due to an abundance of mitochondria. Grossly, they are large, well-rounded, and encapsulated with an average diameter of 8 cm (2–20 cm). When cross sectioned, they have a brown, yellow, or mahogany appearance. All tumors >6 cm should be excised. Percutaneous biopsy of an indeterminate mass has 73% sensitivity. Resection of the adrenal lesion can be performed either laparoscopically or using an open technique. If benign, the prognosis is excellent; if malignant, there is a 20–35% 5-yr survival rate. (See also Section I: "Adrenal Mass.")

REFERENCE

Mearini L, Del Sordo R, Costantini E, et al. Adrenal oncocytic neoplasm: A systematic review. *Urol Int.* 2012;1–9.

ADRENALITIS

DESCRIPTION An inflammation of the adrenal gland that can lead to primary adrenal insufficiency (Addison disease), which accounts for 80% of cases. Tuberculosis is the 2nd leading cause, with the balance made up by fungal infections, hemorrhage, metastatic neoplasms, sarcoidosis, amyloidosis, and adrenal leukodystrophy. Autoimmune adrenalitis can be associated with thyroiditis, diabetes mellitus, pernicious anemia, vitiligo, hypoparathyroidism, and mucocutaneous candidiasis (autoimmune polyendocrine syndrome type 1, also known as candidiasis-hypoparathyroidism-Addison disease-syndrome), or with autoimmune polyendocrine syndrome type 2 (also known as Schmidt syndrome). HIV with opportunistic CMV adrenalitis accounts for an increasing number of cases. (See also Section I: "Adrenal insufficiency, acute (adrenal crisis) and "Addison Disease.")

TREATMENT

- Replacement of adrenal and other hormones, as necessary
- Treatment of underlying cause

REFERENCE

Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: Twenty years experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005;90(6):3243.

ADRENOCORTICAL DISEASE, PRIMARY PIGMENTED NODULAR

DESCRIPTION Primary pigmented nodular adrenocortical disease (PPNAD) is a rare ACTH independent form of Cushing syndrome, accounting for <1% of Cushing syndrome patients. Hypercortisolism is resistant to a dexamethasone suppression test. Typically, bilateral adrenal glands are involved with gross appearance of multiple nodules of varying sizes and pigmented colors. Histologically, the nodules are circumscribed, unencapsulated, and comprised of polygonal cells with an eosinophilic appearance. 25% of patients manifest Carney complex, which includes spotty skin pigmentation, endocrine tumors, and neuroendocrine tumors. Treatment requires bilateral adrenalectomy as unilateral and partial adrenalectomy has resulted in recurrence. (See Section I: "Cushing Disease and Syndrome.")

REFERENCE

Manipadam M, Abraham R, Sen S, et al. Primary pigmented nodular adrenocortical disease. *J Indian Assoc Pediatr Surg.* 2011;16(4):160–162.

ADRENOGENITAL SYNDROME

DESCRIPTION This is the most common cause of disorders of sexual development (DSD) (formerly ambiguous genitalia), caused by an inborn error of metabolism involving cortisol synthesis. At fault is a defect in any 1 of 5 enzymes involved in the cortisol biosynthetic pathway (21-hydroxylase, 11-hydroxylase, 3-hydroxysteroid dehydrogenase, 20.22-desmolase, or 17-hydroxylase), which may result in CAH. Usually presents with an autosomal recessive inheritance. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Congenital Adrenal Hyperplasia.")

SYNONYMS

- CAH
- Female pseudohermaphrodite
- Male pseudohermaphrodite

COMPLICATIONS

- For untreated females:
  - Premature pubic and axillary hair development
  - Rapid somatic maturation, premature epiphyseal closure, short adult stature
  - No breast development or menstruation until excessive androgen production is suppressed
- For untreated males:
  - Sexual and somatic precocity within 1st 2 yr of life
  - Premature epiphyseal closure, short adult stature
- Untreated males and females with salt-losing variant:
  - Progressive weight loss, dehydration within 1st few weeks of life

TREATMENT

- Early diagnosis with ascertainment of correct sex and prevention of salt wasting and metabolic consequences
- Steroid replacement with cortisone, fluorohydrocortisone as needed
- Surgical genital reconstruction may be necessary early in life, based on specific findings

REFERENCES

Newman K, Randolph J, Anderson K. The surgical management of infants and children with ambiguous genitalia. Lessons learned from 25 years. *Ann Surg.* 1992;215:644–653.
New MI, Abraham M, Yuen T, et al. An update on prenatal diagnosis and treatment of congenital adrenal hyperplasia. *Semin Reprod Med.* 2012;30(5):396–399.

ADRENOLEUKODYSTROPHY

DESCRIPTION Rare, X-linked recessive metabolic disorder occurring in boys, and characterized by adrenal atrophy and widespread, diffuse cerebral demyelination. It produces mental deterioration, corticospinal tract dysfunction, and cortical blindness. There is lab evidence of adrenal cortical dysfunction. 2 phenotypes, with onset in childhood or young adulthood, exhibit hypogonadism. Death inevitably occurs within months of onset. A defect is theorized in peroxisomes, which handle long-chain fatty acids. *Lorenzo's oil* (a mixture of glyceryl trioleate and glyceryl trierucate oil) has been tried in this disease, with some delay in neurologic symptoms. Bone marrow transplantation is under study.

SYNONYM
Formerly Schilder disease

REFERENCE
Moser HW, Moser AB, Hollandsworth K, et al. "Lorenzo's oil" therapy for X-linked adrenoleukodystrophy: Rationale and current assessment of efficacy. *J Mol Neurosci.* 2007;33(1):105–113.

AGING MALE SURVEY

DESCRIPTION The Aging Male Survey (AMS) is a questionnaire developed to detect hypogonadism in adult men. It has 3 domains: Psychological, Somato-vegetative, and sexual. The minimum and maximum scores are 5 and 25, respectively, for the Psychological and Sexual domains and 7 and 35 for the Somato-vegetative domain. The higher the score, the more severe the symptoms. The AMS has been shown to have a sensitivity (83%) and specificity (39%) similar to those of the shorter ADAM Survey. (See also Section I: "Andropause [Late Onset Male Hypogonadism]" and Testosterone, Decreased [Hypogonadism; Section II: "Androgen Deficiency in the Aging Male [ADAM] and ADAM Survey.")

REFERENCE
Moore C, Huebler D, Zimmermann T, et al. The Aging Males Symptom Scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol.* 2004;46:80–87.

AL GHORAB CORPORAL SHUNT

DESCRIPTION A surgical treatment for the management of priapism refractory to penile irrigation. A small transverse incision is made on the dorsum of the glans. A section of septum between the glans spongiosa and the corpora cavernosa is removed to create a shunt. (See also Section I: "Priapism" and Section II "Al Ghorab Corporal Shunt With Burnett "Snake" Maneuver.)

REFERENCE

Benjelloun S, el Mrini M, Aboutaieb R, et al. [Priapism. Apropos of 10 cases]. *J Urol (Paris)*. 1993;99(2):91–93.

AL GHORAB CORPORAL SHUNT WITH BURNETT "SNAKE" MANEUVER

DESCRIPTION A modification of the Al Ghorab distal corporal-glanular shunt for priapism. The Burnett "snake" modification involves passing a 7/8 Hegar dilator through the amputated distal tips of the corpora cavernosa bilaterally. The dilator is passed to the proximal limit of the corpora cavernosum laterally on each side to avoid urethral injury. Milking of ischemic blood and clot is performed until bright red blood is visualized. A study of 10 patients with a mean follow-up of 7 mo reported that 8 men had no recurrence of priapism. Of the 6 men who had normal erectile function preoperatively, 2 had partial erectile function postoperatively.

REFERENCE

Segal R, Readal N, Pierorazio PM, et al. Corporal Burnett "snake" surgical maneuver for the treatment of ischemic priapism: Long-term followup. *J Urol.* 2013;189:1025–1029.

ALAGILLE SYNDROME

DESCRIPTION An autosomal dominant disorder associated with abnormalities of the liver, heart, eye, skeleton, and kidneys. A characteristic facial appearance is also seen. Renal abnormalities are not specific but include dysplasia and renal failure. This autosomal dominant disorder is mapped to chromosome 20; it is treated by renal replacement therapy as needed.

SYNONYM

Alagille–Watson syndrome

REFERENCE

Hartley JL, Gissen P, Kelly DA. Alagille syndrome and other hereditary causes of cholestasis. *Clin Liver Dis.* 2013;17(2):279–300.

ALKALINE PHOSPHATASE, UROLOGIC CONSIDERATIONS

DESCRIPTION As an enzyme produced in many tissues, such as bone, liver, placenta, and intestine, alkaline phosphatase can monitor the progression of metastatic cancer to bone (such as prostate cancer). (Bone source can be distinguished from other sources by its heat lability compared with other forms.) This test has also been recommended by some authors as a useful tool for monitoring seminoma.

REFERENCE

Stoop H, Kirkels W, Dohle GR, et al. Diagnosis of testicular carcinoma in situ (intratubular and microinvasive) seminoma and embryonal carcinoma using direct enzymatic alkaline phosphatase reactivity on frozen histological sections. *Histopathology.* 2011;58(3):440–446.

ALKAPTONURIA

DESCRIPTION An inherited inborn error of metabolism of phenylalanine and tyrosine metabolism wherein homogentisic acid (HGA) accumulates in the body and is excreted in a large amount in the urine. If allowed to stand, the urine gradually turns dark (black urine disease). Alkali can accelerate this process. Ochronosis (deposition of a bluish-black pigment noted in the connective tissue) may lead to arthropathy. Of urologic interest, renal failure occurs, rarely, with long-standing disease. Even more rarely, HGA stones can occur. It is caused by a single gene defect, causing absence of HGA oxidase. It is treated by dietary restriction of phenylalanine and tyrosine and large doses of ascorbic acid; otherwise, treatment is symptomatic.

SYNONYM

Black urine disease

REFERENCE

Kazancioglu R, Taylan I, Aksak F, et al. Alkaptonuria and renal failure: a case report. *J Nephrol.* 2004;17(3):441–445.

ALLOPURINOL HYPERSENSITIVITY SYNDROME (AHS)

DESCRIPTION 2% of patients treated with allopurinol will develop minor adverse reactions, including drug eruption, pruritic maculopapular exanthema or minor vasculitis, which often disappear after cessation of treatment. In contrast, AHS is life threatening and includes at least 2 of the following major criteria:

- Deteriorating renal function
- Acute hepatocellular injury
- Cutaneous rash including erythema multiforme (EM), generalized maculopapular exanthema, generalized exfoliative dermatitis (GED), or Steven–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

Diagnostic criteria may also include 1 of the above and at least 1 of the following minor criteria:

- Fever
- Eosinophilia
- Leukocytosis

TREATMENT

Febuxostat alternative for patients with AHS

REFERENCE

Calogiuri G, Nettis E, Di Leo E, et al. Allopurinol hypersensitivity reactions: Desensitization strategies and new therapeutic alternative molecules. *Inflam Allergy-Drug Targets.* 2013;12:19–28.

ALOPECIA GENITALIUM

DESCRIPTION A poorly understood and clinically insignificant condition marked by the loss

and subsequent regrowth of pubic hair, possibly due to tight fitting undergarments.

REFERENCE

Pavona, NA. Alopecia genitalium: Personal observation. *Tech Derm Urol.* 1981;10:24.

α-(ALPHA) FETOPROTEIN

DESCRIPTION A single-chain glycoprotein (MW 70,000) that primarily aids in the management of testicular cancer. It is normally produced by the liver, yolk sac, and GI tract of the fetus; its half-life is 5 (3.5–6) days. Serum *α*-fetoprotein (AFP) levels are normally elevated in the 1st 8 mo of life. The normal adult level is <8 ng/mL; this can be elevated in 38% of cases of embryonal cell carcinoma, 64% of teratocarcinoma, and in yolk sac tumors. Other reasons for elevation include neuroblastoma, hepatoblastoma (hepatoma), hepatocellular, neural tube defects, fet al death, ataxia-telangiectasia, and some cases of benign hepatic disease.

REFERENCE

Ritchey ML, Andrassy RJ, Kelalis PP. Pediatric urologic oncology. In: Gillenwater JY, Grayhack JT, Howards SS, et al., eds. *Adult and Pediatric Urology.* 3rd ed. St Louis, MO: Mosby; 1996.

ALPORT DISEASE/SYNDROME

DESCRIPTION Alport disease/syndrome consists of hereditary nephritis, high-frequency neural hearing loss, and ocular abnormalities. It can present as hematuria, proteinuria, or uremia. Family history is crucial in diagnosis. The nephritis is progressive, usually resulting in renal failure by the 3rd decade. Males are more severely affected. It is caused by a genetic mutation on a single locus on the X chromosome, with altered type IV collagen production. Treat with renal replacement therapy, as needed.

REFERENCE

Gregory MC, Terreros DA, Barker DF, et al. Alport syndrome—clinical phenotypes, incidence, and pathology. *Contrib Nephrol.* 1996;117:1–28.

ALSTRÖM–EDWARDS SYNDROME

DESCRIPTION A progressive autosomal recessive genetic disorder affecting multiple organ systems. It may be detected at birth or in early childhood. Clinically, patients with Alström syndrome develop cone–rod dystrophy leading to eventual blindness, have sensorineural deafness, and normal intelligence. Patients develop obesity, endocrine disturbances such as type 2 diabetes mellitus, dilated cardiomyopathy, and progressive renal and hepatic failure. Alström syndrome is caused by specific mutations in the *ALMS1* gene, located at chromosome 2p13. No specific treatment is available for infertility; renal replacement therapy is indicated as needed.

SYNONYM

Alström syndrome

REFERENCE

Mendioroz J, Bermejo E, Marshall JD, et al. Alström syndrome: Clinical and genetic features, and a diagnostic guide to foresee complications. *Med Clin (Barc).* 2008;131(19):741–746.

ALZHEIMER DISEASE, UROLOGIC CONSIDERATIONS

DESCRIPTION Alzheimer disease is the principal cause of dementia in the elderly patient population. The urologic manifestations include urinary incontinence, overactive bladder, and erectile dysfunction (ED). Patients may be difficult to treat due to limited cooperation with the treatment plan; toileting schedules can help with early incontinence episodes. Often considered a cuae of "functional" urinary and fecal incontinence. Current theories regarding the etiology of Alzheimer disease revolve around cortical cholinergic loss. This may also make the treatment of urologic manifestations even more difficult by limiting the use of anticholinergic agents. Rule out other correctable causes before ascribing urinary tract problems to this disease specifically. (See Section I: "Incontinence, Urinary, Adult Male"; Section I: "Incontinence, Urinary, Adult Female.")

REFERENCE

Resnick NM, Yalla SV, Laurino E. The pathophysiology and clinical correlates of established urinary incontinence in frail elderly. *N Engl J Med.* 1989;320:1–7.

AMBIGUOUS GENITALIA

DESCRIPTION DSD (Disorders of sexual development) refers to a child born with a congenital discrepancy between external genitalia, gonadal, and chromosomal sex. In 2006, consensus conference stated that the potentially pejorative terms "pseudohermaphrodite," "hermaphrodite," and "intersex" be replaced by the more appropriate diagnostic category "DSD." It is recognized that some DSDs present with abnormalities of the external genitalia (ambiguous genitalia). These abnormalities that prompt evaluation occur in approximately 1 in 4,500 live births. These findings may include may include micropenis, clitoromegaly, bilateral cryptorchidism, perineal hypospadias with bifid scrotum, posterior labial fusion, phenotypic female appearance with a palpable gonad (with or without inguinal hernia) hypospadias and unilateral nonpalpable gonad as a few examples. (See also Section I: "Disorders of Sexual Development [DSD]" and Section II: "Androgen Insensitivity Syndrome [AIS]"; or "Androgen Resistance Syndrome, Complete [CAIS] and Partial [PAIS].")

REFERENCES

Houk CP, Levitsky L. Evaluation of the infant with ambiguous genitalia. In: UpToDate.com, Accessed March 9, 2014.

Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *International Consensus Conference on Intersex; Pediatrics*. 2006;118(2):e488.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA (AAST) ORGAN SEVERITY SCALES: GENITOURINARY INJURIES

DESCRIPTION Numerous classifications of traumatic injuries exist, but the most widely

used and accepted classification was developed by the American Association for the Surgery of Trauma's Organ Injury Scaling Committee. (See also Section I: "Bladder Trauma; Penis, Trauma; Renal Trauma, adult; Ureter, Trauma; Urethra, Trauma.")

REFERENCE

Santucci RA, et al. Validation of the American Association for the Surgery of Trauma organ injury severity scale for the kidney. *J Trauma.* 2001;50(2):195–200.

AMINOACIDURIA

DESCRIPTION Excretion of an overabundance of amino acids in the urine, most often due to an inborn error of metabolism. Aminoaciduria is found in association with renal tubular acidosis, Fanconi syndrome, and other primary renal tubular disturbances. It may also occur secondary to other diseases that affect the kidney, such as diabetes mellitus (DM) and diabetes insipidus (DI).

REFERENCE

Neithercut WD, Spooner RJ, Hendry A, et al. Persistent nephrogenic diabetes insipidus, tubular proteinuria, aminoaciduria, and parathyroid hormone resistance following long term lithium administration. *Postgrad Med J.* 1990;66(776):479–482.

AMMONIUM CHLORIDE LOADING TEST

DESCRIPTION An acid loading test to rule out distal renal tubular acidosis. Performed by giving 0.1 g/kg ammonium chloride oral solution over 45 min after a 6-hr fast. 100 mL of water are given every hour during the test. Urine pH is measured hourly for 4 hr. Serum bicarbonate values are taken at hours 2 and 4 to ensure adequate acidification (<16 mmol/L). The normal result is urine pH <5.4; distal RTA exists if pH >5.4. (See also Section II: "Renal Tubular Acidosis.")

REFERENCE

Weger W, Kotanko P, Weger M, et al. Prevalence and characterization of renal tubular acidosis in patients with osteopenia and osteoporosis and in nonporofic controls. *Neprhol Dial Transplant.* 2000;15(7):975–980.

AMMONIUM URATE UROLITHIASIS

DESCRIPTION Extremely rare form of stone disease ($<0.5\%$), endemic in countries with poor nutrition and in patients with Crohn disease. In contrast to uric acid stones, these grow only in urine with pH <6.5. Caused mostly by infection, usually mixed with struvite stones.

TREATMENT

- Clear infection and increasing urine output to >2.5 L/d.
- Chemolitholysis is not possible, and surgical intervention may be necessary. Encourage a balanced diet.

REFERENCE

Hossain RZ, Ogawa Y, Hokama S, et al. Urolithiasis in Okinawa, Japan: A relatively high prevalence of uric acid stones. *Int J Urology.* 2003;10(8):411–415.

AMSTERDAM AND BETHESDA CRITERIA FOR LYNCH SYNDROME

DESCRIPTION Criteria have been developed to aid in the diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome). Lynch syndrome caused by a germline mutation in a mismatch repair gene and associated with tumors exhibiting microsatellite instability (MSI), is characterized by an increased risk of colon cancer and cancers of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract (upper tract urothelial carcinoma), brain, and skin. Originally developed in 1991, they have been modified several times with the most current version referred to as Bethesda Criteria.

- **Amsterdam II Criteria (Revised International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer [HNPCC] Criteria 1998)** 3 or more relatives with HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis) plus all of the following:
  - 1 affected patient should be a 1st-degree relative of the other 2;
  - 2 or more successive generations should be affected;
  - Cancer in 1 or more affected relatives should be diagnosed before the age of 50 yr;
  - Familial adenomatous polyposis should be excluded in any cases of colorectal cancer;
  - Tumors should be verified by pathologic exam.
- **Revised Bethesda Criteria (2003)** Just 1 these criteria need to be met:
  - Diagnosed with colorectal cancer before the age of 50 yr;
  - Synchronous or metachronous colorectal or other HNPCC-related tumors (which include stomach, bladder, ureter, renal pelvis, biliary tract, brain [glioblastoma], sebaceous gland adenomas, keratoacanthomas and carcinoma of the small bowel), regardless of age;
  - Colorectal cancer with a high-microsatellite instability morphology that was diagnosed before the age of 60 yr;
  - Colorectal cancer with 1 or more 1st-degree relatives with colorectal cancer or other HNPCC-related tumors. 1 of the cancers must have been diagnosed before the age of 50 yr (this includes adenoma, which must have been diagnosed before the age of 40 yr);
  - Colorectal cancer with 2 or more relatives with colorectal cancer or other HNPCC-related tumors, regardless of age

REFERENCES

Hubosky SG, Boman BM, Charles S, et al. Ureteroscopic management of upper tract urothelial carcinoma (UTUC) in patients with Lynch Syndrome (hereditary nonpolyposis colorectal cancer syndrome). *BJU Int.* 2013;112(6):813–819.

Piñol V, Castells A, Andreu M, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. *JAMA.* 2005;293(16):1986–1994.

ANAL SPHINCTER TONE AND SENSATION, UROLOGIC CONSIDERATIONS

DESCRIPTION Anal sphincter tone is a vital part of the GU evaluation, especially in a

person with new-onset urinary incontinence. Normal anal sphincter tone is a function of somatic fibers traveling over S2–S4 in the pudendal nerve. A hypoactive sphincter suggests a lower motor neuron lesion, whereas a hyperactive sphincter may be an upper motor neuron lesion. The loss of voluntary contraction of the sphincter suggests interruption of centrally directed fibers somewhere between the motor strip of frontal cortex and the pudendal nerve. The bulbocavernosus reflex (BCR), which is widely used in evaluating urinary incontinence and ED, requires anal sphincter contraction in response to squeezing the glans of penis.

REFERENCE

Magee MC. *Basic Science for the Practicing Urologist.* New York, NY: Cambridge University Press, 1983.

ANDERSON-HYNES PYELOPLASTY

DESCRIPTION Used to treat ureteropelvic junction (UPJ) obstruction. The UPJ is excised, and excess renal pelvis is removed. The widely spatulated ureter is reanastomosed to the renal pelvis with interrupted chromic sutures, and the excess renal pelvis is closed with simple or running suture. After nephrostomy, a ureteral stent is placed. (See also Section I: "Ureteropelvic Junction Obstruction.")

REFERENCE

Szydelko T, Kasprzak J, Lewandowski J, et al. Dismembered laparoscopic Anderson-Hynes pyeloplasty versus non-dismembered laparoscopic Y-V pyeloplasty in the treatment of patients with primary ureteropelvic junction obstruction: A prospective study. *J Endourol.* 2012;26(9):1165–1170.

ANDREWS PROCEDURE (HYDROCELE)

DESCRIPTION A technique described in 1907 where the hydrocele sac at the superior portion of the tunica vaginalis is incised 2–3 cm. This step is followed by eversion of the edges of the tunica vaginalis, which is wrapped around the cord structure.

SYNONYM

Bottle Operation

REFERENCE

Andrews EW. The "Bottle Operation" method for radical cure of hydrocele. *Annals of Surgery.* 1907;46(6):915–918.

ANDROGEN DEFICIENCY IN THE AGING MALE (ADAM) AND ADAM QUESTIONNAIRE

DESCRIPTION Previously referred to as andropause, this has more recently been described as ADAM. The onset of ADAM is unpredictable, and its manifestations are subtle and variable. It is associated with a decrease in testosterone, but also with decreased growth hormone, melatonin, and dehydroepiandrosterone (DHEA). Clinical manifestations include fatigue, depression, decreased libido, and erectile dysfunction (ED), as well as changes in cognition

and mood. The ADAM questionnaire is a screening tool to detect late-onset hypogonadism, with a sensitivity and specificity of 88% and 60%, respectively, compared with serum-bioavailable testosterone levels. A positive answer represents yes to questions 1 or 7 or to any 3 other questions.

The Androgen Deficiency in Aging Male (ADAM) Questionnaire		
Yes	No	1. Do you have a decrease in libido (sex drive)?
Yes	No	2. Do you have a lack of energy?
Yes	No	3. Do you have a decrease in strength and/or endurance?
Yes	No	4. Have you lost height?
Yes	No	5. Have you noticed a decreased enjoyment of life?
Yes	No	6. Are you sad and/or grumpy?
Yes	No	7. Are your erections less strong?
Yes	No	8. Have you noticed a recent deterioration in your ability to play sports?
Yes	No	9. Are you falling asleep after dinner?
Yes	No	10. Has there been a recent deterioration in your work performance?

REFERENCES

Morales A, Heaton JP, Carson CC 3rd. Andropause: A misnomer for a true clinical entity. *J Urol.* 2000;163(3):705–712.

Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* 2000;49:1239–1242.

ANDROGEN DEPRIVATION SYNDROME (ADS)/METABOLIC SYNDROME

DESCRIPTION Long-term androgen deprivation therapy (ADT), for the treatment of prostate cancer, results in hypogonadism and increased risk of type 2 diabetes mellitus. Furthermore, death from cardiovascular disease (CVD) is the most common cause of prostate cancer–related death in these men. ADS is a spectrum of adverse effects: Hot flushes, impotence, loss of libido, emotional lability, anemia, hyperglycemia, increased triglycerides and cholesterol, muscle atrophy, decreased muscle strength, testicular atrophy, osteoporosis, depression, anxiety, malaise, fatigue, and memory difficulties. *Metabolic syndrome* defined by the NIH Adult Treatment Panel III criteria is also part of this spectrum and may include abdominal obesity, hyperglycemia, hypertriglyceridemia, elevated HDL cholesterol, and hypertension. Treatment of the metabolic syndrome includes:

- Management of underlying causes (overweight/obesity and physical inactivity): Weight management, increased physical activity
- Treat lipid and nonlipid risk factors if they persist despite these lifestyle therapies: Treat hypertension; use aspirin for coronary heart disease (CHD) patients to reduce prothrombotic state; treat elevated triglycerides and/or low HDL; monitor blood sugars.

REFERENCES

Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol.* 2006;24(24):3979–3983.

National Cholesterol Education Program. Available at http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm. (Accessed August 28, 2014)

ANDROGEN INSENSITIVITY SYNDROME (AIS; OR ANDROGEN RESISTANCE SYNDROME), COMPLETE (CAIS) AND PARTIAL (PAIS)

DESCRIPTION Androgen insensitivity is a disorder of androgen action and a common form of 46,XY DSD. Mutations in the androgen receptor lead to variable defects in virilization or infertility in 46,XY males with testes and normal testosterone formation. Clinical presentation ranges from phenotypic women with decreased or absent axillary and pubic hair (complete androgen insensitivity syndrome [CAIS]) through individuals with partial androgen insensitivity (PAIS), including women with partial virilization, to phenotypic men with variable defects in virilization to men with isolated infertility An X-linked recessive disorder with a prevalence range from 1 in 20,400 genetic males to 1 in 99,000 genetic males. The typical mode of presentation is in an adolescent female who has breast development with a pubertal growth spurt but has not had her menarche with little or no axillary and pubic hair. Insensitivity can be complete insensitivity or partial. (See also Section I: "Disorders of Sexual Development [DSD]" and Section II: "Ambiguous Genitalia.")

Clinical Features of Complete Androgen Insensitivity Syndrome

Karyotype	46, XY
Inheritance	X-linked recessive; mutations in AR gene
Genitalia	Female with blind vaginal pouch
Wolffian duct derivatives	Often present, depending on mutation type
Müllerian duct derivatives	Absent or vestigial
Gonads	Testes
Habitus	Scant or absent pubic and axillary hair; breast development and female habitus at puberty; primary amenorrhea
Hormone and metabolic profile	Increased LH and testosterone levels; increased estradiol (for male reference range); FSH levels often normal or slightly increased. Resistance to androgenic and metabolic effects of testosterone

Management of complete (severe) androgen insensitivity relates primarily to the optimal timing of gonadectomy. Because the testes produce estradiol, which results in appropriate changes for the female phenotype, it is considered by many preferable to leave the testes in situ until puberty is complete. In partial androgen insensitivity, the external genitalia may be ambiguous at birth, but the prototypic phenotype is characterized by perineoscrotal hypospadias, micropenis, and a bifid scrotum. The testes may also be undescended.

Clinical Features of Partial Androgen Insensitivity Syndrome	
Karyotype	46, XY
Inheritance	X-linked recessive; mutations in AR gene
External genitalia	Ambiguous with blind vaginal pouch, undermasculinized, isolated hypospadias, normal male with infertility (mild AIS)
Wolffian duct derivatives	Often normal
Müllerian duct derivatives	Absent
Gonads	Testes (usually undescended)
Habitus	Decreased to normal axillary and pubic hair, beard growth, and body hair; gynecomastia common at puberty
Hormone and metabolic profile	Increased LH and testosterone concentrations; increased estradiol (for men); FSH levels may be normal or slightly increased
	Partial resistance to androgenic and metabolic effects of testosterone

REFERENCE

Hughes IA, Deeb A. Androgen resistance. *Best Pract Res Clin Endocrinol Metab.* 2006;20(4):577–598.

ANDROGEN/ANABOLIC STEROID ABUSE

DESCRIPTION Androgens are steroid hormones that include testosterone and its derivatives, including androstenedione, DHT, and dromostanolone. In the medical realm, androgens at physiologic doses treat androgen deficiency due to hypothalamus, pituitary, or testis disorder of genetic or acquired etiology. The use of androgens at supra-physiologic doses greatly enhances muscle strength, size, and performance, thus promoting its abuse most notably in power sports and body building. While banned by all major sports organizations, androgen abuse is rampant and has been linked to several high-profile athletes. Androgen abuse is a frequent cause of male infertility by suppression of Leydig cell production of testosterone, which results in deficient spermatogenesis. Abnormalities in sperm motility and morphology are commonly seen, and usually recover spontaneously within 4 mo after cessation of abuse.

REFERENCE

Dohle GR, Smit M, Weber RF. Androgens and male fertility. *World J Urol.* 2003;21(5):341–345.

ANGIOKERATOMA OF FORDYCE (PENILE AND SCROTAL ANGIOKERATOMAS)

DESCRIPTION Vascular malformation of subepidermal blood vessels with an overlying epidermal proliferative reaction. Capillary ectasia is present in the papillary dermis. Typically, numerous dark red to blue dome–shaped papules are linearly arranged on the scrotum and, less commonly, on the penis. In women, 1 larger vulvar papule is typical.

Usually asymptomatic, but can cause annoying bleeding either spontaneously or with scratching or intercourse. The etiology is not known but possibly related to increased regional venous pressure; some believe an association with varicocele exists. Typically seen in older patients; these are distinct from congenital scrotal hemangiomas (see Section II: "Scrotum, Hemangioma.")

TREATMENT
Electrosurgery and lasers are effective, but rarely necessary.

REFERENCE
Schiller PI, Itin PH. Angiokeratomas: An update. *Dermatology.* 1996;193(4):275–282.

ANGIOLYMPHOID HYPERPLASIA, PENILE

DESCRIPTION A subtype of a broad class of histiocytoid hemangiomas in which 4 features are found: (1) Vacuolated histiocytoid cells, (2) tumor vessels that are thick-walled or capillaries consisting only of histiocytoid endothelial cells, (3) interstitial eosinophils, and (4) lymphoid infiltrates. These are usually confined to the skin of 1 area of the body.

SYNONYMS
- Pseudopyogenic (or atypical pyogenic) granuloma
- Inflammatory angiomatous nodule
- Subcutaneous angioblastic hyperplasia with eosinophilia
- Epithelioid hemangioma
- Intravenous atypical vascular proliferation

TREATMENT
Local surgical excision or laser (CO_2) ablation.

REFERENCE
Allen PW, Ramakrishna B, MacCormac LB. The histiocytoid hemangiomas and other controversies. *Pathol Ann.* 1992;27(Pt 2):51–87.

ANGIOMYXOMA, PERINEAL

DESCRIPTION Benign lesion of the pelvic soft tissue, but may very rarely metastasize. Characterized by slow, infiltrative growth. May present as mass in the pelvis. Histologically, demonstrates wavy collagen fibrils related to the myxoid change. Multiple prominent blood vessels are also seen. It occurs mainly in females and can be quite locally aggressive, with frequent local recurrence. Treatment is through wide local excision with close postoperative monitoring.

REFERENCE
Hong RD, Outwater E, Gomella LG. Aggressive angiomyxoma of the perineum in a man. *J Urol.* 1997;157(3):959–960.

ANGIOSARCOMA, GENITOURINARY

DESCRIPTION A very rare malignancy that grossly appears as a well-circumscribed mass or diffusely fungating tumor that may involve any organ. Microscopically, angiosarcoma shows numerous vascular channels. It stains positively for factor VIII immunohistochemically. These sarcomas can be widely metastatic and have persistent local recurrence. Bladder angiosarcoma has been reported postradiation for treatment of other malignancies; chronic lymphedema, foreign bodies, and other toxins have been implicated.

TREATMENT

- Radical resection of affected area (penectomy, cystectomy with diversion)
- Lymph node dissection for presence of lymphadenopathy
- Adjuvant radiation may be useful; chemotherapy for adjuvant or metastatic disease is not usually effective

REFERENCE

Wu X, Chen Z, Ji H, et al. Angiosarcoma of the penis: A case report and literature review. *Int Urol Nephrol.* 2012;44(5):1341–1343.

ANOGENITAL INTRAEPITHELIAL NEOPLASIA

DESCRIPTION Genital warts are caused by human papilloma virus (HPV), a DNA-containing virus that is spread by direct skin-to-skin contact; 100 different types of HPV exist, and over 30 types can infect the genital area. Risk factors for acquiring HPV include multiple sexual partners, early age at onset of sexual intercourse, and having a sexual partner with HPV. Most infections are subclinical and asymptomatic. Anogenital HPV infection is common in HIV-infected men who have sex with men. These patients have a strongly increased risk of HPV-induced anal cancer and its precursor lesion, anal intraepithelial neoplasia (AIN), and a moderately increased risk for penile cancer. Many of these men also have penile intraepithelial neoplasia (PIN), a penile cancer risk factor. Some authors recommend that all HIV positive men who have sex with men be screened for PIN. (See also Section I: "HIV/AIDS, Urologic Considerations" and Section II "HPV (Human Papilloma Virus), Urologic Considerations.")

REFERENCE

Kreuter A, Brockmeyer NH, Weissenborn SJ, et al. Penile intraepithelial neoplasia is frequent in HIV-positive men with anal dysplasia. *J Invest Derm.* 2008;128, 2316–2324.

ANORGASMIA, FEMALE

DESCRIPTION Part of female orgasmic disorder, anorgasmia describes the absence of orgasm following a normal sexual excitement phase. A DSM-IV diagnosis, patients can have marked distress and difficulty in interpersonal situations. Treatment includes behavioral therapy and reduction in anxiety, such as directed masturbation, desensitization, sex education, education regarding communication skills, and Kegel exercises. Pharmaceutical therapies have not currently proven uniformly beneficial (See Section I: "Dyspareunia, Female" and "Sexual Dysfunction, Female.")

REFERENCE

Meston C, Hull E, Levin RJ, et al. Disorders of orgasm in women. *J Sexual Med.* 2004;1:66–68.

ANTERIOR URETHRAL VALVES

DESCRIPTION Much less common than posterior urethral valves, this condition is characterized by obstruction of the anterior urethra, usually associated with a urethral diverticulum. It is caused by a diverticulum acting as valves, although cusps without diverticulum have been reported. It usually presents with voiding symptoms or bulging diverticulum on the ventral shaft with voiding. Diagnosed by VCUG and renal ultrasound. Retrograde urethrogram may miss the valve. It may be associated with reflux, but less so than with PUV. Renal deterioration is less common than with PUV.

TREATMENT

- Foley catheter if azotemia occurs
- Endoscopic valve fulguration or single-stage urethroplasty if urethra is adequate
- Staged urethroplasty for large diverticulum
- Vesicostomy for reflux or persistent azotemia

REFERENCE

Routh JC, McGee SM, Ashley RA, et al. Predicting renal outcomes in children with anterior urethral valves: A systematic review. *J Urol.* 2010;184(4 Suppl):1615–1619.

ANTIANDROGEN WITHDRAWAL SYNDROME (FLUTAMIDE WITHDRAWAL SYNDROME)

DESCRIPTION A decrease of PSA levels occurs in 15–40% of patients upon withdrawal of nonsteroidal antiandrogen in those treated for advanced prostate cancer with total androgen blockade that is rarely durable. This is possibly caused by a mutation in the androgen receptor, which then acts to stimulate growth of tumor when bound by the agent. Initially reported for flutamide, but bicalutamide and nilutamide have also shown this effect. This effect should be sought before adding other more cytotoxic agents to patients with castrate resistant prostate cancer, and could partially explain the activity of some salvage therapies.

REFERENCE

Miyamoto H, Rahman MM, Chang C. Molecular basis for the anti-androgen withdrawal syndrome. *J Cell Biochem.* 2004;91(1):3–12.

ANTISPERM ANTIBODIES

DESCRIPTION Antisperm antibodies develop when a disruption occurs in the blood–testis barrier; they may be a cause of infertility. Causes can include ductal obstruction (ie, vasectomy), infection, cryptorchidism, and varicocele, but are often idiopathic. Serum antisperm antibody levels are not as useful as antibodies in the semen, which can be measured by immunobead testing. The higher the percentage of sperm binding to the bead, the lower the probability of pregnancy. Scoring varies by lab, but normal is generally considered to be $<10\%$ of sample binding to the bead. Condoms, antibiotics, steroids, and sperm washing have all been utilized, with variable results. Presently, assisted reproductive

techniques (ARTs) such as in vitro insemination are most effective. (See also Section I: "Infertility"; Section II: "Semen Analysis, Abnormal Findings and Terminology"; "Semen Analysis, Technique and Normal Values.")

REFERENCE

Zini A, Fahmy N, Belzile E, et al. Antisperm antibodies are not associated with pregnancy rates after IVF and ICSI: Systematic review and meta-analysis. *Hum Reprod.* 2011;26(6):1288–1295.

APHTHOUS ULCER, EXTERNAL GENITALIA

DESCRIPTION Aphthae are localized, painful, shallow, round to oval ulcers often covered by a gray fibromembranous slough and surrounded by an erythematous halo. Complex aphthosis involves almost constant, multiple, oral or oral and genital aphthae. Those involving both oral and genital aphthae are termed *bipolar aphthosis* (BA) of Neumann. Most specialists consider bipolar aphthosis to be a forme fruste of Behçet disease (BD). The prevalence of genital aphthae in BD varies from 60–90% in various reports. Genital aphthae are most commonly seen in male patients on the scrotum and in female patients on the vulva. In females, genital aphthae tend to be larger and deeper, sometimes even leading to perforations. Genital aphthae, especially those that are larger, may be confused with STDs; a common misdiagnosis is genital herpes or Donovanosis. (See also Section I: "Penis, Cutaneous Lesion" and Section II: "Behçet Disease" and "Genital Ulcers.")

REFERENCE

Somesh G, Ajith C, Malhotra S, et al. Bipolar aphthosis presenting as mutilating genital ulcers in women. *Indian J Dermatol Venereol Leprol.* 2004;70(6):357–360.

APPENDIX TESTIS AND APPENDIX EPIDIDYMIS, TORSION

DESCRIPTION The appendix testis, historically known as the hydatid of Morgani, is a vestigial remnant of the müllerian duct in the paratesticular region. It is present in >90% of testes at autopsy. It is usually located on the superior aspect of the testis and attached to the tunica vaginalis. Grossly it appears polypoid or a sessile nodule, typically 2–4 mm in length. It can undergo torsion and cause acute scrotum. In children, this torsion is the most common cause of an acute scrotum. This condition is characterized by the "blue dot sign." It is difficult to clinically distinguish between testicular torsion and torsion of the appendix testis or epididymitis. Diagnosis is made by scrotal ultrasound.

The appendix epididymis is also referred to as the "vestigial caudal mesonephric collecting tubule." It is present in 35% of autopsy cases and on ultrasound is seen in 18% of cases. Grossly it appears as a pedunculated spherical or elongated structure arising from the antero-superior head of the epididymis. It may also undergo torsion and cause an acute scrotum that must be differentiated from testicular torsion.

Torsion of these testicular and epididymal appendages are benign conditions but must be differentiated form testicular torsion which can lead to ischemia and infarction of the testicle if not recognized and treated promptly. Epididymitis is very rare in this age group and the urinalysis is negative. Most cases occur in children between the ages of 7 and 14 yr. Pain

onset is usually acute and unlike cases of testicular torsion, nausea, and vomiting may not be present.

3 elements serve to predict testicular torsion: Pain <6 hr, absent cremasteric reflex, and diffuse testicular tenderness. In the absence of any of these elements, none of the subjects had testicular torsion; when all 3 elements present, 87% had testicular torsion. A paratesticular nodule at the superior aspect of the testicle, with or without the characteristic "blue-dot appearance" seen with the scrotal skin pulled over the lesion, is pathognomonic. The blue-dot is present in only 21% of cases and may not be easily seen in children with pigmented skin.

Color Doppler transscrotal ultrasound is the imaging modality of choice for evaluation of the acute scrotum. With torsion of an appendage, testicular blood flow is usually normal. Ultrasonography can distinguish torsion of a testicle and torsion of an appendix testis or appendix epididymis. Nuclear scanning has limited utility.

If the likelihood of a torsed appendage is high, it can be managed conservatively. If these is any doubt as to the diagnosis surgical exploration is indicated to limit the risk of testicular loss with a missed testicular torsion. The necrotic tissue of the testicular or epididymal appendix causes no significant damage to the surrounding structures other than the inflammation and discomfort. Most cases are managed conservatively. Scrotal discomfort gradually resolves over the next 1–2 wk. Limit activity initially and the use of scrotal support and ice can help initially. Nonsteroidal anti-inflammatory medications usually provide symptomatic relief. (See also Section I: "Torsion, Testis or Testicular/Epididymal Appendages" and "Torsion, Testis or Testicular/Epididymal Appendages Images.")

REFERENCES

Bostwick DG. In: Bostwick DG, Cheng L, eds. *Spermatic cord and testicular adnexae in Urologic Surgical Pathology*, 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008; Chapter 14.

Karmazyn B, Steinberg R, Kornreich L, et al. Clinical and sonographic criteria of acute scrotum in children: A retrospective study of 172 boys. *Pediatr Radiol*. 2005;35(3):302–310.

ARISTOLOCHIC ACID (FANG CHI)

DESCRIPTION Aristolochic acid is a toxin found in plants of the genus *Aristolochia*, a vine widely known as birthwort and contained in herbal remedies used to treat a variety of ailments such as arthritis, gout, and inflammation. Certain Chinese herbal medicines contain this toxin. In 2001, the US Food and Drug Administration warned consumers of the dangers of aristolochic acid-containing herbs, and regulations established in the Europe Union in 2004 effectively banned the substance. However, Internet sites still sell the processed drug or source plant, which remains legal in China and several other countries. Associated with end-stage renal disease (ESRD) and upper tract urothelial carcinoma. Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* (plants endemic to the Balkans). Balkan Endemic Nephropathy has been linked to consumption of bread grain with seeds from the weed *Aristolochia clematitis*. Moreover, the vine has been found to be an environmental carcinogen through the contamination of food supplies of farming villages in the Balkans, where *Aristolochia* grows wildly in the local wheat fields. A meta-analysis of eight studies reported a pooled odds ratio of 5.97 (95% CI: 2.78–12.84) for aristolochic acid related UTUC. The lower dose confidence

limit for aristolochic acid related ESRD is 0.42 g cumulative aristolochic acid exposure. The plant contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the nonexposed population and is predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with upper tract urothelial carcinoma. Genome-wide sequencing has allowed a link between aristolochic acid exposure directly to an individual getting cancer. (See also Section II: “Balkan Nephropathy.”)

REFERENCES

Chen CH, Dickman KG, Moriya M, et al. Aristolochic acid-associated urothelial cancer in Taiwan. *Proc Natl Acad Sci USA.* 2012;109(21):8241–8246.

Wu F, Wang T. Risk assessment of upper tract urothelial carcinoma related to aristolochic acid. *Cancer Epidemiol Biomarkers Prev.* 2013:25(5):812–820.

ARTERIOVENOUS FISTULA (AVF), RENAL (OR ARTERIOVENOUS MALFORMATION [AVM])

DESCRIPTION Renal AVF or AVM are uncommon lesions. They can be congenital, acquired, or idiopathic. Most (70%) are iatrogenic and occur as a result of renal biopsy, blunt or penetrating trauma, inflammation, malignancy, or renal surgery. Congenital fistulas account for ~20% and are often found under the mucosa, accounting for the bleeding presentation. The right kidney is more often involved than the left, and women twice as often as men. May rarely present as a renal mass. The peak incidence occurs in patients 30–40 yo. Acquired or idiopathic lesions are usually aneurysmal. Congenital renal AVF frequently causes hematuria. Symptoms can include abdominal bruit, hypertension, headache, and palpitation. Indications for treatment include progressive increase in the size of the fistula, recurrent or persistent hematuria, and hemodynamic effects (cardiac decompensation, hypertension, high-output heart failure). Arteriography is the gold standard for evaluating renal AVF (demonstrating simultaneous visualization of major arteries and veins). Doppler US is a good screening tool. CT or MRI angiography can usually demonstrate the lesion adequately. Endovascular techniques are used even for giant aneurysms with AVFs. For small renal AVFs, macroparticules or methyl cyanoacrylate glue should be used. For larger fistulas, coils or detachable balloons are used. With any concerns for the possibility of systemic and pulmonary embolism, high-flow AVF should be managed by open resection or ligation.

REFERENCE

Dönmez FY, Coşkun M, Uyuşur A, et al. Noninvasive imaging findings of idiopathic renal arteriovenous fistula. *Diagn Interv Radiol.* 2008;14:103–105.

ARTIFICIAL INSEMINATION (AI)

DESCRIPTION The process by which semen is introduced into the female reproductive tract by artificial means, for the purpose of improving the chance for conception in fertile couples with patent tubes. Variations include controlled ovarian hyperstimulation, intrauterine insemination (IUI), direct interperitoneal insemination (DIPI), a combination of IUI and DIPI,

fallopian tube sperminfusion (FSI), and peritoneal oocyte and sperm transfer. Other related means of improving fertility include in vitro fertilizations (IVFs), such as zygote intrafallopian transfer (ZIFT) and tubal embryo stage transfer (TEST) techniques.

REFERENCE

Veltman-Verhulst SM, Cohlen BJ, Hughes E, et al. Intra-uterine insemination for unexplained subfertility. *Cochrane Database Syst Rev.* 2012;9.

ASK-UPMARK KIDNEY

DESCRIPTION These are small kidneys with areas of normal architecture separated by grooves overlying dilated calices without pyramids. The parenchyma of the grooved areas contain thyroid-like tubules and lack glomeruli. Cause is unknown, but vesicoureteral reflux and ascending infection have been implicated. They are typically unilateral and associated with vesicoureteral reflux, and commonly present as malignant hypertension, but cases of nonmalignant hypertension and recurrent UTIs occur. Nephrectomy of the affected side for refractory hypertension is the treatment.

SYNONYM

Segmental renal hypoplasia

REFERENCE

Zezulka AV, Arkell DG, Beevers DG, et al. The association of hypertension, the Ask-Upmark kidney and other congenital abnormalities. *J Urol.* 1986;135(5):1000–1001.

ASOPA HYPOSPADIAS REPAIR

DESCRIPTION The dorsal preputial foreskin's inner rectangular graft is tubularized to form the neourethra, and the outer opposing skin, which shares the same blood supply, serves as the outer penile shaft skin cover.

REFERENCE

Wacksman J. Use of the Hodgson XX (modified Asopa) procedure to correct hypospadias with chordee: Surgical technique and results. *J Urol.* 1986;136(6):1264–1265.

ASPERGILLOSIS, GENITOURINARY

DESCRIPTION Only *Candida* infections are more common opportunistic infections in the urologic population than aspergillosis. It affects patients with diabetes and malignancy, and immunosuppressed patients (HIV, renal transplant). It can cause renal parenchymal disease or obstructive uropathy. The prostate has been a rare site of infection. Renal aspergilloma or pseudotumor has been reported in patients with AIDS. Urine cultures can be negative, but aspiration and cytology can demonstrate typical septated hyphae. Therapy is systemic amphotericin B and at least 3 mo of itraconazole, or voriconazole. Amphotericin B irrigations into the involved renal unit have been used to supplement systemic therapy. Direct instillation of amphotericin B into the urinary pelvis through a ureteral catheter or nephrostomy tube has been the most successful approach to therapy. Through a retrograde

ureteral catheter instillation of a solution of amphotericin (50 mg/L in sterile water) is infused at 40 mL/h. Shade the solution to limit degradation. Monitor pressure with a pop-off mechanism at 20-cm water. (See also Section I: "Fungal Infections, Genitourinary.")

REFERENCE

Wise GJ, Freyle J. Changing patterns in genitourinary fungal infections. *AUA Update Series* . Volume XVI, Lesson 1, 1997.

ASPERMIA

DESCRIPTION A condition of no ejaculate, which should be differentiated from *azoospermia,* where an ejaculate is present but the sperm are absent from the fluid. (See also Section I: "Infertility, Urologic Conside-rations" and "Ejaculatory Disturbances (Delayed, Decreased, or Absent)"; Section II: "Semen Analysis, Technique, and Normal Values"; Section II: "Semen Analysis, Abnormal Findings, and Terminology.")

CAUSES

- Complete bilateral obstruction of ejaculatory duct
- Congenital anorchidism, imperforate anus, and other congenital anomalies
- Medication (chlorpromazine, α-blockers, methyldopa, imipramine)
- Radical prostatectomy (RP)
- Retrograde ejaculation; failure of seminal emission
- Surgical (bladder neck dysfunction secondary to TURP, TUIP, retroperitoneal lymph node dissection)

REFERENCE

Zorn B, Virant-Klun I, Stanovnik M, et al. Intracyto-plasmic sperm injection by testicular sperm in patients with aspermia or azoospermia after cancer treatment. *Int J Androl.* 2006;29(5):521–527.

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

DESCRIPTION ART includes all fertility treatments in which both eggs and sperm are handled. Although the Centers for Disease Control and Prevention does not include treatments in which only sperm are handled, there are various methods of sperm retrieval as defined below:

- Percutaneous epididymal sperm aspiration (PESA): Aspiration of sperm from epididymis percutaneously
- Microsurgical epididymal sperm aspiration (MESA): Done by open surgery
- Testicular sperm aspiration (TESA): Done percutaneously
- Testicular sperm extraction (TESE): Done through open biopsy of testicular tissue
- Intrauterine insemination (IUI) or Artificial insemination (AI): Also not ART by strict definition; however these are methods for fertility performed during ovulation by inserting a catheter into the cervical os and injecting concentrated sperm into the uterus, thereby bypassing the cervical mucous barrier.

The following are classical methods of ARF:

- Gamete intrafallopian transfer (GIFT): Oocytes and semen are retrieved, the semen is concentrated, then both are placed into the fallopian tube by laparoscopy.
- In vitro fertilization (IVF): Fertilization by either incubating sperms with oocytes or by injecting a single live sperm into an oocyte with a micropipette (called intracytoplasmic sperm injection [ICSI]). The resultant embryo is transplanted to the uterus or fallopian tube with a catheter through the cervix.
- ZIFT: After IVF of an egg, the resultant embryo is placed into the fallopian tube laparoscopically, instead of through the cervix.

REFERENCE

Carbone Jr DJ. Male reproductive physiology and assisted reproductive technology. *AUA Update Series.* Vol. XVIII, Lesson 21:162, 1999.

ASTHENOSPERMIA

DESCRIPTION A general term for defects in sperm movement, usually a decrease in sperm motility to <50–60% of normal. It can be detected on semen analysis and can be a cause of male factor infertility. (See also Section I: "Infertility, Urologic Considerations"; Section II: "Semen Analysis, Abnormal Findings, and Terminology.")

CAUSES

- Antisperm antibodies
- Hypoandrogenic state
- Idiopathic
- Immotile cilia (Kartagener syndrome and immotile cilia syndrome)
- Infection
- Partial ejaculatory duct obstruction (EDO)
- Varicocele (most common surgically correctable abnormality)

TREATMENT

- Aimed at offending agent (ie, antibiotics for infection, sperm washing for antibodies, varicocelectomy)
- Interest has been noted in vitamins C and E and other free-radical scavengers
- ARTs

REFERENCE

Meacham RB, et al. Male infertility. In: Gillenwater JY, Grayhack JT, Howards SS, Duckett JW, eds. *Adult and Pediatric Urology*. 3rd ed. St. Louis, MO: Mosby, 1996.

ATHLETIC HEMATURIA

DESCRIPTION Hematuria, microscopic, or gross, can be noted in athletes engaged in high-intensity or long-duration exercise. Usually benign in course. Repeated episodes of hematuria may cause anemia in some athletes. Theorized causes include foot-strike hemolysis, renal ischemia, release of a hemolyzing factor, direct trauma to bladder or kidney, dehydration, myoglobinuria, increased circulation, and NSAIDs. Treatment includes adherence to sensible training guidelines and hydration.

SYNONYMS
- Sport-related hematuria
- Exercise-induced hematuria

REFERENCE
Jones GR, Newhouse I. Sport-related hematuria: A review. *Clin J Sport Med.* 1997;7(2):119–125.

ATOPIC DERMATITIS (ECZEMA), UROLOGIC CONSIDERATIONS

DESCRIPTION Also called eczema, disseminated neurodermatitis, atopic eczema, and Besnier prurigo, this chronic pruritic eczematous condition affects characteristic sites. In adults, the genitalia is a common site. Patients present with itching, excoriation, edema, erythema, and scaling. As the disease progresses, the skin undergoes lichenification (thickening). The cause is unknown, but there is a familial association with this and other atopic diseases (allergic rhinitis, asthma).

TREATMENT
Topical corticosteroids such as triamcinolone 0.1% BID; nighttime sedation with antihistamines or other agent. Treat stress and remove irritants (soaps, solvents, fabrics made of wool or nylon).

REFERENCE
Edwards L, Lynch PJ. In: Sams WM, et al., eds. *Principles and Practice of Dermatology*. New York, NY: Elsevier, 1998:960–961.

ATTENTIVE DIGITAL RECTAL EXAM

DESCRIPTION Utilized to obtain prostatic secretions in urine to identify DNA, RNA, protein, and metabolite based biomarkers for the detection of prostate cancer. Clinical studies have identified PCA3 and TMPRSS2:ERG fusion transcripts as promising RNA markers for cancer detection and possibly prognosis. A “light prostatic massage” should be performed, including firm pressure to depress the gland by 1 cm. A total of 3 strokes per lobe should be performed from base to apex and from lateral to median line. (See Attentive digital rectal exam [DRE] Image ☼)

REFERENCE
Truong M, Yang B. Toward the detection of prostate cancer in urine: A critical analysis. *J Urol.* 2013;189:422–429.

ATYPICAL ADENOMATOUS HYPERPLASIA OF THE PROSTATE (ADENOSIS)

DESCRIPTION Some lesions can be confused with low-grade prostate cancer on small-needle biopsy samples. The differential diagnosis of these confusing pseudoneoplastic lesions includes atypical adenomatous hyperplasia of the prostate (AAH), sclerosing adenosis, postatrophic hyperplasia, basal cell hyperplasia, and others that must be differentiated from

low-grade prostatic carcinoma. Histologically, AAH is a crowded focus of small glands. It has not yet been definitively associated with an increased risk of prostate cancer. AAH is no longer considered a premalignant lesion but rather a benign small glandular process of the transition zone that simulates acinar adenocarcinoma. It is recommended to stain for 34βE12, which detects basal cell–specific CK. If basal cell staining is present, this helps to rule out carcinoma. Although the biologic significance of AAH is uncertain, its light microscopic appearance and immunophenotype allow it to be distinguished from carcinoma in most cases. The lesion appears to be distinct from atypical small acinar proliferation prostate (ASAP), which appears to be more associated with prostate cancer. In AAH, rebiopsy is not usually indicated. (See also Section II: "Atypical Small Acinar Hyperplasia, Prostate (ASAP)"; Section II: "Postatrophic Hyperplasia of the Prostate Gland.")

SYNONYMS

- Small gland hyperplasia
- Atypical adenosis
- Atypical small acinar hyperplasia

REFERENCE

Armah HB, Parwani AV. Atypical adenomatous hyperplasia (adenosis) of the prostate: A case report with review of the literature. *Diagn Pathol.* 2008;3:34.

ATYPICAL SMALL ACINAR PROLIFERATION, PROSTATE (ASAP)

DESCRIPTION Prostate needle biopsies occasionally contain cells identified as ASAP that are suspicious for but not diagnostic of malignancy. About 2% of contemporary prostate needle biopsy specimens contain collections of small acini that are suspicious for cancer but that fall below the diagnostic threshold and are often reported as "ASAP suspicious for but not diagnostic of malignancy." Prostate cancer has been identified in specimens from subsequent biopsies in up to 60% of cases of ASAP, indicating this finding is a significant predictor of cancer. Identification of ASAP (with or without high-grade PIN) warrants repeat biopsy for concurrent or subsequent invasive prostate carcinoma. (See also Section I: "Prostatic Intraepithelial Neoplasia"; Section II: "Atypical Adenomatous Hyperplasia and Postatrophic Hyperplasia of the Prostate.")

REFERENCE

Bostwick DG, Meiers I. Atypical small acinar proliferation in the prostate: Clinical significance. *Arch Pathol Lab Med.* 2006;130(7):952–957.

AUA (AMERICAN UROLOGIC ASSOCIATION) SYMPTOM INDEX FOR BPH

DESCRIPTION Also called the *BPH symptom index*, and the AUA symptom score or AUA-SS this standardized instrument assesses the degree of lower urinary tract symptoms (LUTS) due to BPH in men, as well as guides response to treatment. Originally developed by the AUA, it is now used widely used. (See Section VII: Reference tables: AUA Symptom Index/International Prostate Symptom Score [I-PSS].) The AUA Index consists of 7 questions that assess emptying, frequency, intermittency, urgency, weak stream, and straining, with

each graded on a score of 0–5. Scores can range from 0–35. The index currently categorizes symptoms as:

- Mild (score ≤7)
- Moderate (score 8–19)
- Severe (score 20–35)

The International Prostate Symptom Score (I-PSS) is identical to the AUA index, except that it adds a single question to assess the quality of life based on the patient's perception of the problem. This is scored from 0 (or "delighted") to 6 (or "terrible").

It is suggested that patients with mild symptoms (AUA-SS ≤7) and patients with moderate or severe symptoms (AUA-SS ≥8) who are not bothered by their symptoms (ie, symptoms do not interfere with daily activities) should be managed by watchful waiting, although a wide range of patients with bothersome moderate to severe symptoms prefer this strategy as well. Today, most patients undergo medical management (α-blockers with or without 5α-reductase inhibitors or 5α-reductase alone prior to any surgical intervention). Surgical options include TURP, transurethral incision of the prostate, open prostatectomy, or minimally invasive therapies (such as transurethral microwave thermotherapy, transurethral needle ablation, and water-induced thermotherapy). (See also Section II: "International Prostate Symptom Score [I-PSS]"; Section VII: "AUA Symptom Index for BPH/I-PSS.")

REFERENCE

McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol.* 2011;185(5):1793–1803.

AZOOSPERMIA

DESCRIPTION The absence of viable sperm on semen analysis and a documented cause of male factor infertility. Azoospermia can be obstructive or nonobstructive. When 1st noted, the sample should be centrifuged and the pellet examined for the presence of sperm. If present, a workup for oligospermia should be performed. A postejaculate urine analysis should be obtained to rule out retrograde ejaculation (ie, the urine contains significant numbers of sperm, 10–15/HPF). If absent, a physical exam for the presence of vas deferens and hormone studies are indicated. Treatment is based on the underlying cause. (See also Section I: "Infertility, Urologic considerations"; Section II: "Semen Analysis, Abnormal Findings, and Terminology.")

CAUSES

- Congenital absence of vas deferens
- Ductal obstruction
- Germ cell failure
- Gonadotoxins
- Hypogonadotropic hypogonadism
- Idiopathic
- Testicular failure (Klinefelter syndrome)

REFERENCE

Practice Committee of American Society for Reproductive Medicine in collaboration with

Society for Male Reproduction and Urology. Evaluation of the azoospermic male. *Fertil Steril.* 2008;90(5 Suppl):S74–S77.

BACK PAIN, UROLOGIC CONSIDERATIONS

DESCRIPTION The differential diagnosis of back pain includes several potential urologic etiologies:

- Cauda equina syndrome is a surgical emergency. Common findings are bladder dysfunction (especially urinary retention) and saddle anesthesia, in addition to sciatica and weakness
- Endocrine: Adrenal hyperplasia or infarction
- Gynecologic: Neoplasm of uterus or ovary, dysmenorrhea, salpingitis, uterine prolapse
- Infectious: Osteomyelitis, subarachnoid or spinal abscess, tuberculosis, meningitis, basilar pneumonia
- Mechanical: Pregnancy, obesity, fatigue, scoliosis
- Medication: Tadalafil-incidence of back pain and/or myalgia in 9.4% in patients receiving tadalafil 10 mg; 8.3% in patients receiving tadalafil 20 mg, and 3.7% in placebo-treated patients.
- Neoplastic: Myeloma, Hodgkin disease, carcinoma of pancreas or adrenal, metastatic neoplasm from breast, prostate, lung
- Renal: Hydronephrosis, calculus, neoplasm, renal infarction, pyelonephritis
- Trauma: Injury to bone, joint, internal organs, or ligament

REFERENCES

Gerber GS, Brendler CB. Evaluation of the urologic patient: history, physical examination, and urinalysis. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012:73–98.

Seftel AD, Farber J, Fletcher J, et al. A three-part study to investigate the incidence and potential etiologies of tadalafil-associated back pain or myalgia. *Int J Impot Res.* 2005;17(5):455–461.

BALANITIS XEROTICA OBLITERANS/LICHEN SCLEROSIS ET ATROPHICUS

DESCRIPTION BXO (Balanitis Xerotica Obliterans) is an inflammatory lesion of the glans and foreskin, now considered to be synonymous with lichen sclerosis et atrophicus (LSA). The term BXO is used when the skin of the genitalia is affected. BXO can cause itching and decreased sensitivity in the head of penis, but the hallmark is urethral meatal stenosis or distal urethral stricture. Differential diagnosis includes leukoplakia, Bowen disease (BD), erythroplasia of Queyrat, or squamous cell carcinoma (SCC) of the glans or preputial skin; biopsy is necessary to confirm the absence of malignancy. (See also Section I: “Penis, Cancer, General Considera-tions” and “Penis, Cutaneous Lesion.”)

TREATMENT

- Local therapy with steroid, estrogen, or testosterone cream
- Surgical therapy with circumcision (when appropriate) and flap reconstruction of fossa navicularis for severe cases; meatal or urethral dilation rarely gives durable response

REFERENCE

Clouston D, Hall A, Lawrentschuk N. Penile lichen sclerosis (balanitis xerotica obliterans).

BJU Int. 2011;108(Suppl 2):14–19.

BALANITIS, ZOON (PLASMA CELL BALANITIS)

DESCRIPTION Also called *balanoposthitis chronica circumscripta plasma cellularis* and *plasma cell balanitis*. Can be confused clinically with erythroplasia of Queyrat. Grossly, it appears as a shiny, glazed-red macular erythematous lesion with multiple, pinpoint, bright red "cayenne pepper" spots. Histologically, a subepidermal inflammatory infiltrate of plasma cells and dermal red cell extravasation is present. No malignant transformation is reported. Proposed etiologies include *Mycobacterium smegmatis*, heat, poor hygiene, or constant friction. Treated by circumcision.

REFERENCE

Weyers W, Ende Y, Schalla W, et al. Balanitis of Zoon: A clinicopathologic study of 45 cases. *Am J Dermatopathol.* 2002;24(6):459–467.

BALKAN NEPHROPATHY

DESCRIPTION An interstitial nephropathy endemic to the Balkan Republics of Yugoslavia, Bulgaria, and Romania, and that afflicts mainly the middle-aged rural populations. It is slowly progressive, and may eventually end in ESRD. Anemia, proteinuria, and hypertension can be severe. Renal biopsy has no specific markers for the disease. Balkan endemic nephropathy is caused by eating bread that is contaminated with a toxin called aristolochic acid, which comes from a plant called Aristolochia. Balkan endemic nephropathy can occur in multiple family members, but it is not an inherited condition. A strong association with increased incidence of upper tract transitional cell carcinoma (TCC) has been documented, although bladder TCC incidence is normal. Treatment involves aggressive surveillance for TCC and renal replacement therapy, as necessary. (See also Section II: "Aristolochic acid [fang chi].")

REFERENCE

Stefanovic V, Polenakovic M. Fifty years of research in Balkan endemic nephropathy: Where are we now? *Nephron Clin Pract.* 2009;112(2):51–56.

BANFF CLASSIFICATION, TRANSPLANT REJECTION

DESCRIPTION A classification method developed in 1993 for standardization of criteria in the histologic diagnosis of renal allograft rejection. The Banff classification characterizes renal biopsy findings into a scheme that outlines possible clinical approaches to manage the rejection. (See also Section I: "Transplant Rejection, Renal.")

REFERENCE

Solez K, Racusen LC. The Banff classification revisited. *Kidney Int.* 2013;83(2):201–206.

BARCAT-REDMAN HYPOSPADIAS REPAIR

DESCRIPTION In a modification of the Mathieu procedure, this repair mobilizes the posterior urethral plate and splits the glans in addition to the parameatal flap. The full-

thickness parameatal and urethral plate grafts are tubularized together and laid to rest in the new urethral groove.

REFERENCE

Snodgrass WT. Hypospadias. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012:3503–3536.

BARIATRIC SURGERY, UROLOGIC CONSIDERATIONS

DESCRIPTION Jejunoileal bypass, the 1st bariatric procedure, produced severe hyperoxaluria secondary to steatorrhea. Modern bariatric surgery utilizes gastric restrictive procedures and sometimes bypass of variable amounts of small intestine, such as a Roux-en-Y gastric bypass and biliopancreatic diversion. Modern bariatric surgery is associated with less malabsorption compared to jejunoileal bypass; however, contemporary bariatric bypass patients continue to have hyperoxaluria, hypocitruria, and lower urine volumes, which result in an increased risk of calculus formation.

REFERENCE

Tasca A. Metabolic syndrome and bariatric surgery in stone disease etiology. *Curr Opin Urol.* 2011;21:129–133.

BARTTER SYNDROME

DESCRIPTION Congenital abnormality that usually presents in childhood with metabolic acidosis, hyperreninemic hyperaldosteronism, and hypokalemia. Presenting symptoms are muscle weakness, polyuria, and sometimes growth retardation. Patients are normotensive. Renal biopsy reveals juxtaglomerular hyperplasia. Defective platelet aggregation and decreased vascular responsiveness to pressors are also noted. Pathophysiology includes decreased sodium transport in the thick ascending loop of Henle; decreased vascular responsiveness and increased prostaglandin secretion may also play a role. This condition is incurable; potassium supplementation, prostaglandin synthesis inhibitors, aldosterone antagonists, and ACE inhibitors can help greatly to ameliorate symptoms.

REFERENCE

Fremont OT, Chan JC. Understanding Bartter syndrome and Gitelman syndrome. *World J Pediatr.* 2012;8(1):25–30.

BASHFUL BLADDER (PARURESIS, SHY BLADDER SYNDROME, "PEE-SHY")

DESCRIPTION This is the inability to urinate with others present, such as in a public restroom. It is a relatively common disorder but little is understood about the phobia. According to DSM-IV TR, this disorder is classified as social phobia.

REFERENCE

Hammelstein P, Soifer S. Is "shy bladder syndrome" (paruresis) correctly classified as social phobia? *Anxiety Disord.* 2006;20(3):296–311.

BCG REFRACTORY TRANSITIONAL CELL CARCINOMA (TCC)

DESCRIPTION TCC that recurs after treatment with intravesical BCG treatment. Failure of initial intravesical therapy may be managed by further intravesical therapy or cystectomy, with more aggressive therapy indicated for high-risk patients having superficial invasion (T1), high-grade lesions or concomitant carcinoma in situ (CIS). Patients with high-risk features who fail a 2nd course of BCG have a very high risk of progression to muscle-invasive TCC. In addition, relapses after ≥ 2 courses of BCG appear to be associated with poor outcomes, despite subsequent aggressive therapy. Several different salvage therapies, including intravesical interferon alone or in combination with BCG, valrubicin, mitomycin C, gemcitabine, and other chemotherapeutic agents, as well as photodynamic therapy, have been described for BCG failures. Salvage therapies have poor response rates, however, and radical cystectomy remains the "gold standard" for the salvage of failed intravesical therapy in high-risk patients. (See Also Section I: "Bladder Cancer, General.")

REFERENCE

Sengupta S, Blute ML. The management of superficial transitional cell carcinoma of the bladder. *Urology.* 2006;67(3 Suppl 1):48–54.

BCL-2, UROLOGIC CONSIDERATIONS

DESCRIPTION The protein product of the gene bcl-2 acts as an apoptosis-blocking agent. It appears to be required for normal morphogenesis of the kidney, and may be unimportant as a prognostic factor in RCC. It is seen in higher levels in prostatic intraepithelial hyperplasia but is variable in prostate cancer. Levels increase during XRT. Expression is increased in high-grade bladder tumors.

REFERENCE

King ED, Matteson J, Jacobs SC, et al. Incidence of apoptosis, cell proliferation and bcl-2 expression in transitional cell carcinoma of the bladder: Association with tumor progression. *J Urol.* 1996;155(1):316–320.

BECKWITH–WIEDEMANN SYNDROME

DESCRIPTION This condition is characterized by macroglossia, abdominal wall defects, adrenal cytomegaly, and neonatal hypoglycemia. Other characteristic features include gigantism, earlobe creases and pits, facial nevus flammeus, and prominent eyes with infraorbital creases. Neonatal hypoglycemia is frequent, of which Wilms tumor, adrenal cortical carcinoma, and hepatoblastoma are most common. Mental retardation is not associated. Most cases are sporadic, but a genetic cause related to mutation or deletion of imprinted genes within the chromosome 11p15.5 region. The mode of inheritance of BWS is complex. Possible patterns include autosomal dominant inheritance with variable expressivity, contiguous gene duplication at 11p15, and genomic imprinting resulting from a defective or absent copy of the maternally derived gene. Several lines of evidence suggest that BWS may be caused by relative overexpression of the maternally imprinted IGF2 gene. Some suggest a slightly increased risk in babies born by assisted reproduction. Close follow-up early

in life is recommended for tumor surveillance as 1 of the most ominous findings is the increased risk of neoplasia. In 1 series the majority of tumors were Wilms tumors (67%), followed by hepatoblastomas (11%), rhabdomyosarcomas (5%), and neuroblastomas (4%).

SYNONYM
EMG syndrome (exomphalos, macroglossia, and gigantinism)

REFERENCES
Online Mendelian Inheritance in Man; http://www.omim.org/entry/130650. Accessed March 1, 2014.
Weng EY, Mortier GR, Graham JM Jr. Beckwith-Wiedemann syndrome. An update and review for the primary pediatrician. *Clin Pediatr.* 1995;34(6):317–326.

BEER NEPHROURETERECTOMY

DESCRIPTION Refers to a retroperitoneal 2-incision approach to a nephroureterectomy through a flank and a separate Gibson or a midline Czerny incision.

REFERENCE
Bergman H, Lockhart J. Surgery of the ureteral stump. In: Kaufman JJ, eds. *Current Urologic Therapy*. Philadelphia, PA: Saunders, 1986:212–214.

BEER POTOMANIA

DESCRIPTION A hypo-osmolality syndrome of beer drinkers, usually with hyponatremia. Patients with beer potomania have a history of significant beer drinking, often long term, in conjunction with a poor diet. This may occur because beer has very little sodium and no protein, and the condition is potentially augmented by the possibility of inappropriate antidiuretic hormone (ADH) secretion.

TREATMENT
Fluid restriction, ICU monitoring, and serial serum sodium levels, with slow correction of hyponatremia.

REFERENCE
Sanghvi SR, Kellerman PS, Nanovic L. Beer potomania: An unusual cause of hyponatremia at high risk of complications from rapid correction. *Am J Kidney Dis.* 2007;50:673–680.

BEHÇET DISEASE

DESCRIPTION This is a multisystem vasculitis that is most active during young adulthood syndrome characterized by oral and genital ulcers (vulvar and penile), uveitis, vascular involvement (venous thrombosis, vasculitis), and nonmucous membrane skin lesions of unknown etiology. Lesions on the genitalia are herpetiform and can be painful. Other genital ulcers, such as syphilis, herpes, and chancroid, must be ruled out 1st. Genital ulcers are treated with local moisture-retaining dressings, topical anesthetics, and steroids. Rebamipide is used to treat aphthous ulcers. For severe mucocutaneous lesions, immunosuppressive systemic agents (corticosteroids, azathioprine, pentoxifylline, dapsone, interferon-alfa,

colchicine, and thalidomide) have demonstrated benefit.

REFERENCE

Emmi G, Silvestri E, Squatrito D, et al. Behçet's syndrome pathophysiology and potential therapeutic targets. *Intern Emerg Med.* 2014;9(3):257–265.

BELLINI DUCT CARCINOMA (COLLECTING DUCT CARCINOMA)

DESCRIPTION A variant of RCC in which the cell of origin is the collecting duct. Very few cases are reported in literature. Immunohistochemically, the lesion stains with high–molecular-weight keratin and lectin. Histologically, cells demonstrate intracyto-plasmic mucicarminophilic material, which is not seen in RCC. Radical nephrectomy for localized disease is the treatment of choice. Chemotherapy is used (interferon-α–based) for metastatic disease. (See also Section I: "Renal Mass.") (Image ☼)

REFERENCE

Kassouf W, Binsaleh S, Cohen DD, et al. Bellini duct carcinoma with ovarian metastasis. *Can J Urol.* 2004;11(6):2461–2462.

BELT PROCEDURE

DESCRIPTION Named for Dr. Elmer Belt, who described his technique for performing radical perineal prostatectomy in 1939. Dr. Belt described a new approach to the prostate through the perineum, between the longitudinal fibers of the rectum and the circular fibers of the external anal sphincter. This approach dramatically decreased blood loss. However, Dr. Belt also recommended leaving behind the apex of the prostate to achieve better urinary control, and opening the anterior layer of the Denonvillier fascia during the dissection.

REFERENCE

Belt E, Albert CE, Surber AC Jr. A new anatomic approach in perineal prostatectomy. *J Urol.* 1939;41:482–497.

BENCHEKROUN ILEAL VALVE

DESCRIPTION A hydraulic ileal valve is used as the continence mechanism in ileal or ileocecal reservoirs. As the reservoir fills, increased pressure occurs in the valve, which is created by invaginating an ileal segment that then serves as the efferent continent limb.

REFERENCE

McKiernan JM, et al. Continent urinary diversion. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012:2450–2478.

BERGER DISEASE (IgA NEPHROPATHY)

DESCRIPTION Sometimes referred to as "idiopathic immunoglobulin A nephropathy," this condition was 1st described by Berger and Hinglas in 1968. As the most common primary glomerulonephritis, it exhibits a wide variation in manifestation, ranging from a benign,

indolent course to rapidly progressive renal failure. Commonly presents with hematuria, proteinuria, and abnormal urine sediment. Diagnosed by renal biopsy demonstrating IgA deposits in the mesangium on immunofluorescence staining.

TREATMENT

- Recent promise seen in corticosteroids, fish oil, and ACE inhibitors
- Renal transplant for cases of renal failure

REFERENCE

Cheng J, Zhang X, Tian J, et al. Combination therapy of ACE inhibitor and an angiotensin receptor blocker for IgA nephropathy: A meta-analysis. *Int J Clin Pract.* 2012;66(10):917–923.

BERGMAN SIGN

DESCRIPTION In urologic radiography, the Bergman sign occurs when the ureter is dilated immediately below a neoplasm, rather than collapsed, as below an obstructing stone, thus showing a chalice shape. Retrograde pyelography demonstrates an irregular ureteral filling defect with complete obstruction and distal ureteral dilation, producing the chalice appearance; a ureteral catheter tends to curl in this segment. The Bergman sign is pathognomonic for neoplasm.

REFERENCE

Bergman H, ed. *The Ureter.* 2nd ed. New York, NY: Springer-Verlag; 1981.

β-hCG (HUMAN CHORIONIC GONADOTROPIN)

DESCRIPTION Glycoprotein with a molecular weight of 38,000 and a half-life of 2 days. It is produced normally by the syncytiotrophoblast cells in pregnancy. hCG is composed of 2 subunits, α and β. The β-subunit is identical to a subunit of LH. Urologic uses include staging and follow-up of testicular cancer (elevated in 100% of choriocarcinoma, 7% of seminoma, 60% of embryonal carcinomas). Has been produced by urothelial tumors and secreting polyembryoma. Therapeutically can be given exogenously to stimulate Leydig cells in secondary hypogonadism and facilitate descent of undescended testicles when administered over several weeks. Typical regimen is 500–2,500 U IM 2 times a week for 4 wk. The hCG test is used to diagnose anorchia in underscended testicles; a failure to increase testosterone after administration suggests anorchia. (See also Section I: “Testis, Cancer, General”; Section I: “Testis, Nonseminomatous Germ Cell Tumors, General.”)

REFERENCE

Bower M, Rustin GJ. Serum tumor markers and their role in monitoring germ cell cancers of the testis. In: Vogelzang NJ, et al., eds. *Comprehensive Textbook of Genitourinary Oncology.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

BETHANECHOL SUPERSENSITIVITY TEST

DESCRIPTION A historical variation of urodynamic testing wherein bethanechol was

administered subcutaneously 20 min before testing. Usually considered when normal bladder contraction is weak or absent. If positive, a rise in filling pressure of >20 cm of water and a shift in the filling curve to the left are noted. A positive test represents bladder denervation. No change during the test represents myogenic damage.

REFERENCE

Snyder JA, Lipsitz DU. Evaluation of female urinary incontinence. *Urol Clin North Am.* 1991;18(2):197–209.

BEZOARS (FUNGUS BALLS)

DESCRIPTION Fungal infections of the kidney occur most commonly in the setting of diabetes, immunosuppression, urinary obstruction, or indwelling urinary catheters or stents. Most commonly *Candida* species such as *C. albicans* and *tropicalis* are involved. Other fungi such as *Torulopsis glabrata* and *Aspergillus* may cause renal infections, although less commonly. These infections can cause the formation of fungal balls or bezoars, which can be seen on imaging as a renal pelvic mass or filling defect and may cause obstruction; in the bladder, they may cause irritative voiding symptoms. Urinary tract imaging in the setting of candiduria (funguria) is needed in patients who have persistent candiduria and are at increased risk of bezoars (diabetics or other urologic abnormalities). Urinary tract fungal bezoars are managed with a combination of surgical and medical therapy. (See also Section I: "Fungal Infections, Genitourinary"; Section II: "Funguria.")

TREATMENT

- Treat medically until endoscopic procedure to remove the bezoar has been accomplished, symptoms have resolved, and cultures are negative
- Candida bezoars: Fluconazole (200–400 mg/d [3–6 mg/kg/d] PO)
- Alternative regimen: Amphotericin B (0.5–0.7 mg/kg/d IV) with or without flucytosine (100 mg/d PO divided into 4 doses)
- Aspergillosis bezoars: Use voriconazole load: 6 mg/kg q12h for 2 doses; then maintenance of 4 mg/kg q12h
- With upper tract involvement, amphotericin B mixed 50 mg/L of sterile water by ureteral catheter, or nephrostomy can be considered

REFERENCE

Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503.

BIFID RENAL PELVIS

DESCRIPTION A term for incomplete ureteral duplication. Bifid renal pelvis indicates that the confluence of 2 separate pyelocalyceal systems is located at the UPJ. If the confluence is inferior to the UPJ but superior to the entry into the bladder, then this would be termed bifid ureters (Image ☼).

REFERENCE

Decter R. Renal duplication and fusion anomalies. *Pediatric Urol.* 1997;44;1323–1341.

BIFID SCROTUM

DESCRIPTION A congenital anomaly in which the scrotal folds are completely separate. This is generally seen in conjunction with other anomalies, and may be present in CAH and 5α-reductase deficiency, almost always associated with hypospadias.

REFERENCE

Palmer JS. Genitourinary manifestations in boys and girls associated with genetic diseases. *J Men's Health Gend.* 2006;3(1):71–79.

BIOFEEDBACK, UROLOGIC CONSIDERATIONS

DESCRIPTION Any method of training the body while receiving feedback on the specific function being trained. Biofeedback ranges from "low tech" (eg, vaginal cones for incontinence) to expensive electronic systems (utilizing EMG or pressure probes). Biofeedback is applied in urology for improvement of urinary incontinence, generally by strengthening pelvic floor muscles, and for treatment of dysfunctional voiding. Biofeedback has also been used to teach patients to stop uninhibited detrusor contractions, teach relaxation of the pelvic floor and promote normal voiding in children.

REFERENCE

Bø K, Kvarstein B, Nygaard I. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. *Obstet Gynecol.* 2005;105:999–1005.

BIOFILM, UROLOGIC CONSIDERATIONS

DESCRIPTION When microorganisms adhere to the surface of a urologic device (catheter, ureteral stent, implant) and create a matrix of extracellular polymeric substance. Biofilms provide resistance to antimicrobial agents by preventing penetration through the film and thereby limiting access to bacteria. Bacteria protected by a biofilm can also have poor expression of antimicrobial binding proteins and activation of intrinsic resistance genes. Biofilm bacteria can typically withstand 1,000–1,500× the concentration of antimicrobial agents utilized to kill nonfilm bacteria. Numerous strategies to avoid biofilm formation are currently being researched. Options include modifying biomaterial surface properties, antibiotic-impregnated material and frequent changes of foreign bodies when suitable.

REFERENCE

Tenke P, Köves B, Nagy K, et al. Update on biofilm and infections of the urinary tract. *World J Urol.* 2012;30:51–57.

BIOTHESIOMETRY, PENILE

DESCRIPTION A simple, inexpensive method of testing the vibratory sensitivity threshold when evaluating neurogenic causes of impotence. It is performed by measuring vibratory thresholds, usually in at least 3 different areas of the body, such as the medial malleolus,

fingertips, and glans penis. Probably not as accurate and reproducible as other forms of neurologic testing, such as tibial-evoked potentials, pudendal-evoked potentials, and BCR latency. (See also Section I: "Erectile Dysfunction/Impotence, General.")

REFERENCE

Bemelmans BL, Hendrikx LB, Koldewijn EL, et al. Comparison of biothesiometry and neuro-urophysiological investigations for the clinical evaluation of patients with erectile dysfunction. *J Urol.* 1995;153(5):1483–1486.

BIRT–HOGG–DUBé SYNDROME

DESCRIPTION Birt–Hogg–Dubé (BHD) syndrome is a rare, autosomal dominant disorder 1st described in 1977. It is caused by germline mutations in the BHD (FLCN) gene that lies within the chromosomal band 17p11.2 and encodes for a tumor-suppressor protein, folliculin. Folliculin is highly expressed in a variety of tissues, including the skin, kidney, and lung (stromal cells and type I pneumocytes). BHD syndrome is the cutaneous triad of fibrofolliculomas (hamartoma of the hair follicle), trichodiscomas, skin tags, and a propensity for renal tumors. The renal tumors are often chromophobe RCC, oncocytoma, or hybrids of these tumors. However, many will develop clear cell tumors as well. These tumors are more likely to be multiple and bilateral. (See also Section I: "Renal Cell Carcinoma, General.")

REFERENCE

Adley BP, Smith ND, Nayar R, et al. Birt-Hogg-Dubé syndrome: Clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med.* 2006;130(12):1865–1870.

BITES TO PENIS, ANIMAL, AND HUMAN

DESCRIPTION Bites to the penis can result in significant morbidity. Of animal bites, the most common is the dog bite. These can be potentially severe, with deep tissue destruction. In the cases of animal bites, patients tend to present early, and usually the wound can be closed after copious irrigation and any necessary debridement is performed. Broad-spectrum antibiotics should be administered for polymicrobial contamination and, in the case of dog bites, penicillin-VK may be given to treat *Pasteurella multocida,* which may be present in 20–25% of bites. Human bites tend to present later and pose a significant risk for infection. These should be copiously irrigated, broad-spectrum antibiotics should be administered, and wound closure is generally avoided. (See also Section I: "Penis, Trauma.")

REFERENCES

Cummings JM, Boullier JA. Scrotal dog bites. *J Urol.* 2000;164:57–58.
Wessells H. Penile and genital injuries. *Urol Clin North Am.* 2006;33(1):117–126.

BK VIRUS, UROLOGIC CONSIDERATIONS

DESCRIPTION A common member of the human polyoma DNA virus, with a seropositivity rate of 60–100% of the general population; it rarely presents any symptoms in immunocompetent hosts, and is not known to cause malignancy. During states of immunosuppression (eg, chemotherapy, AIDS, transplantation), this virus can reactivate and

become a significant pathogen. BK virus often affects the urinary tract, with infections of the kidney and bladder being most common due to affinity to urothelial cells. In kidney transplant recipients, it can cause tubulointerstitial nephritis and ureteral stenosis. It has been shown to cause nephropathy in AIDS patients. BK virus has been found in the urine of immunosuppressed patients (viruria) having hemorrhagic cystitis (0.5–5 mo after bone marrow transplantation), causing both life-threatening hematuria and dysuria, as well as asymptomatic infections. Other causes of hemorrhagic cystitis in the differential include cyclophosphamide toxicity and adenovirus infection. The urine cytology–detectable abnormality of polyomavirus-infected cells is an enlarged nucleus with a single large basophilic intranuclear inclusion known as a "decoy cell"; this appears to be the best diagnostic test. Viral urine cultures and PCR are not useful in the diagnosis. It is named after the 1st patient (B.K.) in whom the virus was identified. (See also Section I: "Cystitis, Hemorrhagic [Infectious, Noninfectious, Radiation]" and "Immunocompromised Patients, Urologic Considerations.")

REFERENCE

Sukov WR, Lewin M, Sethi S, et al. BK virus-associated nephropathy in a patient with AIDS. *Am J of Kidney Dis.* 2008;51(4):15–18.

BLACK-WATER FEVER

DESCRIPTION Black-water fever is a clinical entity characterized by acute intravascular hemolysis, classically occurring after the introduction of quinine for treatment of malaria. It is a rare but serious condition, in which hemolysis and anemia produce characteristically dark-colored urine. The condition has become rare since 1950, when quinine was replaced by chloroquine. Currently, it has reemerged from increased reutilization of quinine because of the development of resistance to chloroquine. Treatment of black-water fever is supportive, including stopping the offending drug, blood transfusion for severe anemia, and a short course of steroids. (See Section II: "Malaria, Urologic Considerations.")

REFERENCE

Tombe M. Images in clinical medicine. Hemoglobinuria with malaria. *N Engl J Med.* 2008;358(17):1837.

BLADDER AGENESIS

DESCRIPTION Rare and usually lethal congenital abnormality that has been reported in <20 living patients. Associated abnormalities include renal agenesis, retroiliac ureters, crossed fused renal ectopia, malrotation of the gut, colonic duplication, anal atresia, intraperitoneal iliac arteries, and bicornuate uterus. It is caused by a urogenital sinus abnormality during wk 5–7 of development.

TREATMENT

- Separation of urinary and fecal stream
- Other reconstructive surgeries as appropriate

REFERENCE

Kaefer M, Adams MC. Penis and bladder agenesis in a living male neonate. *J Urol.* 1997;157(4):1439–1440.

BLADDER AUGMENTATION

DESCRIPTION Bowel segments are most commonly used to improve bladder capacity and manage poorly compliant bladders. The goal is to protect upper urinary tract drainage and maintain renal function. Augmentation cystoplasty is utilized mainly in patients with disorders of the neurologic system (eg, spinal cord injury [SCI], multiple sclerosis [MS], myelodysplasia). Modifications with bladder neck reconstruction and/or addition of continent channels (Mitrofanoff or Monti channels) can be utilized to facilitate both continence and ease in drainage. Complications associated with bladder augmentation include failure to adequately improve bladder capacity, metabolic disturbances, mucous plugging, urinary tract infections, bladder calculi, vesicoureteral reflux, bladder perforation, and malignancy (usually adenocarcinoma most commonly located at the region of the anastomosis).

REFERENCE

Biers S, Venn SN, Greenwell TJ. The past, present, and future of augmentation cystoplasty. *BJU Int.* 2011;109:1280–1293.

BLADDER CANCER, INTRAVESICAL AGENTS

DESCRIPTION Either immunotherapy agents, such as BCG, or chemotherapy agents, such as mitomycin C, are instilled directly into the bladder for the treatment of either carcinoma in situ or high-grade superficial urothelial carcinoma. Adjuvant intravesical chemotherapy regimens have been shown to decrease recurrence rates but no clear improvement in overall progression has been documented. Patients who fail intravesical therapy should be evaluated for extirpative treatment. (See also Section I: “Bladder Cancer, General,” “Bladder Cancer, Nonmuscle-Invasive Bladder Cancer [Ta, T1],” and “Bladder Cancer, Urothelial, Superficial Carcinoma In Situ (CIS) (NMIBC).”)

Agent	Description	Dose	Use	Efficacy	Considerations
Chemotherapy					
Mitomycin c	Alkylating agent-prevention of tumor cell implantation, adjunct therpy post TUR	40 mg/20 mL saline	Adjuvant within 6 hr of TUR resection ideal as single dose, maintenance dose not reduce risk	Recurrence 36.7–48.4%	Avoid dermal exposure and avoid if perforation is suspected
Anthracyclines (doxorubacin, epirubicin, valrubicin, adriamycin)	Alkylating agent-prevention of tumor cell implantation, adjunct therpy post TUR	Epirubicin 80 mg/50 mL saline	Similar to mitomycin but epirubicin has superior shelf life in comparison to mitomycin c		
Thiotepa	Alkylating agent-prevention of tumor cell implantation, adjunct therpy post TUR	30 mg/50 mL saline	Single adjuvant dose and then single dose every 3 mo up to 1 yr	No difference in comparison to no adjuvant therapy	Low–molecular-weight increases risk of absorption and bone marrow dyscrasia. Largely abandoned
Immunotherapy					
BCG**	Live attenuated of *Mycobacterium bovis*	Induction 6-wk course plus maintence for 3 yr (3-wk course at 3, 6, 12, 18, 24, 30, 36 mo)	Utilized in high-risk nonmuscle invasive bladder cancer after TUR has healed (CIS, high-grade Ta, T1)	Recurrence 16–40% and progression 4.4–40%	Only 16% of people will complete full 3-yr maintenance course secondary to toxicity
Interferon alpha	Glycoprotein	10 million–100 million units	Best reported use in BCG failure in combination with BCG	CIS 37% at 12 mo and 47% at 24 mo	Majority of failures within 4 mo of initial treatmemt
Salvage therapies					
Valrubicin	Analog of doxarubacin		Utiliztion in BCG refractory or patients refusing radical cystectomy	BCG refractory patients 21% complete response	
Gemcitabine	Deoxycytidine analog	1,000–2,000 mg	BCG failure	20–75% recurrence free survival	

**FDA Approved for bladder cancer.

REFERENCE

Logan C, Brown M, Hayne D. Intravesical therapies for bladder cancer-indications and limitations. *BJU Int.* 2012;110 (Suppl 4):12–21.

BLADDER CANCER, UROTHELIAL, MICROPAPILLARY

DESCRIPTION Micropapillary (MP) bladder cancer is a uncommon variant of urothelial carcinoma, accounting for 0.7–12% of all bladder cancers. This variant has an aggressive profile and is largely resistant to intravesical BCG. The majority of patients, approximately 2/3, have advanced T3/4 staging upon radical cystectomy and 50% have pN+ disease. Median 10-yr survival is 31%, in contrast to 53% for patients with non-MP urothelial carcinoma. Treatment should include early radical cystectomy (Image ☼).

REFERENCE

Wang J, Boorjian SA, Cheville JC, et al. Outcomes following radical cystectomy for micropapillary bladder cancer versus pure urothelial carcinoma: A matched cohort analysis. *World J Urol.* 2012;30:801–806.

BLADDER CHORIOCARCINOMA

DESCRIPTION Primary choriocarcinoma of the bladder is exceedingly rare. Only 7 cases are described in the literature. Most cases present with hematuria and may also have gynecomastia. Metastases and β-hCG elevation were seen in the majority of reported cases. A full metastatic workup including scrotal exam and ultrasound are mandatory. 3 of the 7 cases were treated with resection and then chemotherapy, and all 3 showed good response (1 patient died of pulmonary embolus during therapy), the other 4 patients died of the disease.

(See also Section I: “Bladder Cancer, General.”)

REFERENCE

Hanna NH, Ulbright TM, Einhorn LH. Primary choriocarcinoma of the bladder with the detection of isochromosome 12p. *J Urol.* 2002;167(4):1781.

BLADDER CONTRACTILITY INDEX (BCI)

DESCRIPTION A urodynamic variable. BCI = $PdetQ_{max}$ + $5Q_{max}$ (Q_{max} is the maximum flow rate and $PdetQ_{max}$ is the detrusor pressure at maximum flow). Poor detrusor contractility is defined as BCI <100, normal contractility is BCI between 100 and 150, and strong bladder contractility is BCI >150.

REFERENCE

Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. *BJU Int.* 1999:84(1):14–15.

BLADDER DIVERTICULUM

DESCRIPTION A bladder diverticulum is a herniation of the vesical mucosa through the detrusor muscle. Bladder diverticula may be congenital or acquired. Most acquired diverticula are associated with long-standing bladder outlet obstruction (high intravesical pressures) and are most commonly seen in older men with benign prostatic hypertrophy or other forms of bladder outlet resistance; it is rare in women. The condition usually evolves from bladder wall trabeculation, to cellule, and finally a diverticulum, typically located on the lateral wall and rarely at the dome. Since the acquired diverticuli have no muscle wall components, they do not empty well and cause urinary stasis with increased risk of infection, stones, and urothelial carcinoma (intradiverticular tumors have a prevalence of 1–10%). The lack of a muscular wall makes urothelial carcinoma more likely to extend outside the bladder early. Congenital bladder diverticula are uncommon and occur almost exclusively in boys. When next to the ureteral orifice (Hutch diverticula), this can result in vesicoureteric reflux on that side. Treatment usually involves correction of the outlet obstruction to reduce high-pressure voiding. Diverticulectomy (open or laparoscopic) can be performed for recurrent infection or bladder calculi. Treatment for cancers within diverticula may include transurethral resection (can be complicated by narrow ostia and thin diverticular wall), laser ablation, diverticulectomy, partial cystectomy, and radical cystectomy with or without intravesical therapy (Image ☼).

REFERENCE

Zeman PA, et al. Lower urinary tract symptoms. In: Siroksy MB, et al., eds. *Handbook of Urology*. 3rd ed. Philadelphia, PA: Lippincott; 2004.

BLADDER EARS

DESCRIPTION Transient bladder outpouchings into the inguinal ring of male infants <6 mo

old. This close association of the bladder with the internal ring resolves spontaneously. Inguinal herniorrhaphy in male infants can result in significant bladder damage if bladder ears are present. The condition is differentiated from bladder diverticula by absence of a definable neck.

REFERENCE

Redman JF, Jacks DW, O'Donnell PD. Cystectomy: A catastrophic complication of herniorrhaphy. *J Urol.* 1985;133(1):97–98.

BLADDER FILLING DEFECTS

DESCRIPTION Filling defect on a contrast study of the urinary bladder (cystography) may be the result of:

- Air: Artifactual, postinstrumentation, vesicoenteric fistula
- Benign tumor: Prostatic enlargement, inverted papilloma, endometriosis
- Blood clot
- Calculus
- Congenital: Ureterocele
- Extrinsic compression by pelvic organ or mass, pelvic lipomatosis
- Fungus ball (bezoar)
- Infective, inflammatory: Inflammatory edema
- Instruments (catheters), foreign body
- Malignant tumor: Bladder and prostate malignancy, tumors invading urinary bladder from contiguous organs (eg, uterus, colon)
- Radiologic artifact: Fold in nondistended bladder

See also Section I: "Bladder calculi (vesical calculi)" and Section II: "Bladder Mass, Differential Diagnosis." (Image ☼)

BLADDER HEMANGIOMA

DESCRIPTION A bladder anomaly most often associated with Klippel–Trenaunay syndrome (extensive port wine stains on extremities), bladder hemangioma is a rare, benign tumor. It presents with gross hematuria, at times severe. Bladder hemangiomas may be solitary or multiple.

TREATMENT

- Endoscopic treatment with Nd:YAG laser ablation
- Partial cystectomy can be required for large lesions or uncertainty in diagnosis

REFERENCE

Kato M, Chiba Y, Sakai K, et al. Endoscopic neodymium:yttrium aluminium garnet (Nd:YAG) laser irradiation of a bladder hemangioma associated with Klippel-Weber syndrome. *Int J Urol.* 2000;7(4):145–148.

BLADDER HERNIA

DESCRIPTION Most are found in the inguinal or femoral region and are often associated

with bladder outlet obstruction in men. It is estimated that up to 4% of all inguinal hernias can contain some degree of bladder herniation. Rarely, massive herniation may be found, with significant portions on the bladder and distal ureter descending into the scrotum; bladder infarction and obstruction has been reported. In women, herniation of the bladder into the anterior vaginal wall is technically a cystocele. Treatment is repair of inguinal hernia, with reduction of bladder herniation. Bladder outlet obstruction should be identified and treated in males as this may contribute to the original herniation and subsequent recurrences.

SYNONYM
Scrotal cystocele

REFERENCE
Bisharat M, O'Donnell ME, Thompson T, et al. Complications of inguinoscrotal bladder hernias: A case series. *Hernia.* 2009;13(1):81–84.

BLADDER HYPOPLASIA

DESCRIPTION Lack of urinary bladder development, leading to inadequate function and storage capacity. Hypoplasia is caused either the failure of production or storage of urine, or from complete bypass of the bladder. Causes include urogenital sinus abnormalities, severe epispadias, bilateral renal agenesis, severe renal dysplasia, and bilateral ureteral ectopia. Bladder reconstruction with bowel segments can be attempted.

REFERENCE
Frimberger DC, Kropp BP. Bladder Anomalies in Children. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012:3381.

BLADDER, INFLAMMATORY PSEUDOTUMOR

DESCRIPTION A benign spindle cell lesion in patients who have not had surgery (as opposed to postoperative spindle cell nodule). Most patients are from 20–50 yo and present with gross hematuria. The lesion is nodular or pedunculated, but some may be sessile and invade the muscularis propria. This is a benign lesion, but it must be differentiated from myxoid sarcomatoid carcinoma and myxoid leiomyosarcoma. Resection is the treatment.

REFERENCE
Young RH, Eble JN. Non-neoplastic disorders of the urinary bladder. In: Bostwick DG, Eble JN, eds. *Urologic Surgical Pathology*. 1st ed. St. Louis, MO: Mosby; 1997.

BLADDER LEIOMYOMA

DESCRIPTION Though very rare, it is the most common mesodermal tumor of the bladder, constituting 0.5% of all bladder neoplasms. Usually incidentally discovered, though if large or pedunculated may present with bladder outlet obstruction. Seen more commonly in females. Generally homogeneous and smoothly marginated on ultrasound and CT. MRI better and shows the submucosal origin, usually has low T2 and intermediate T1 signal.

TREATMENT

- Pedunculated lesions are amenable to transurethral resection
- Sessile or large tumors may require partial cystectomy

REFERENCE

Goel R, Thupili CR. Bladder leiomyoma. *J Urol.* 2013; Epub ahead of print.

BLADDER, LYMPHOMA

DESCRIPTION In lymphoma, involvement of the bladder is usually secondary to systemic disease. Primary lymphoma of the bladder is rare, and carries an excellent prognosis. Most patients are female in the 7th–8th decades. Patients typically present with gross hematuria. The tumors can be single or multiple, sessile or papillary. Most common types are large-cell and small cell lymphocytic lymphoma and further classified as MALT (extranodal marginal zone B-cell lymphoma) lymphomas thought to result from chronic inflammation. Many patients in recent series have chronic cystitis. Radiotherapy has been the treatment of choice for localized lymphoma; otherwise, systemic therapy is undertaken if the bladder is not the primary site.

REFERENCE

Kempton CL, Kurtin PJ, Inwards DJ, et al. Malignant lymphoma of the bladder: Evidence from 36 cases that low-grade lymphoma of the MALT-type is the most common primary bladder lymphoma. *Am J Surg Pathol.* 1997;21(11):1324–1333.

BLADDER MASS, DIFFERENTIAL DIAGNOSIS

Malignant	Benign
Urothelial carcinoma (TCC)	Inverted papilloma
Squamous cell carcinoma	Nephrogenic adenoma
Adenocarcinoma	Leiomyoma
Small cell (neuroendocrine) tumor	Hemangioma
Sarcoma	Granulomas
Sarcomatoid tumors	Abscess
Melanoma	Bladder diverticulum
Metastatic disease	Inflammatory pseudotumor
	Filling defect due to: calculi, air, clot, foreign body, fungus ball

(See also Section II: "Bladder Filling Defect" and "Bladder Wall Thickening.") (Image ☼)

REFERENCE

Abol-Enein H. Nonurothelial cancer of the bladder. *Urology.* 2007;69(1 Suppl):93–104.

BLADDER, METASTASIS TO

DESCRIPTION The bladder may become involved by tumors by direct extension (most commonly) or metastatic spread. The most common locally invasive are colon, prostate, rectum, and cervix. Distant metastasis to the bladder include stomach, skin, lung, breast, and rarely melanoma. These metastasis are almost always solitary and are often located in the bladder neck or trigone. Lymphoma can be metastatic or primary and secondary involvement by leukemia has been reported.

REFERENCE

Cheng L, et al. Chapter 6. In: Bostwick DG, Cheng L, eds. *Neoplasms of the urinary bladder in Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008.

BLADDER NECK CONTRACTURE

DESCRIPTION Scarring and stenosis of the bladder neck occur most commonly as a postoperative complication of transurethral resection of the prostate or radical prostatectomy at the site of vesicourethral anastomosis. Bladder neck contracture may lead to decreased urinary flow, high-pressure voiding, urinary retention, urinary tract infections, and incontinence. Factors associated with this complication include urinary leak at the anastomosis, poor mucosal approximation, suture retraction, ischemia, or foreign bodies such as surgical clips. Postoperative radiation may contribute. Radiation monotherapy can cause contracture with the presentation from 12–36 mo after completion. Management consists of dilation, endoscopic incision (laser, cold cut, electrosurgical) or resection, and, in severe cases, open repair utilizing a Y–V plasty. Occasionally, intermittent self catheterization may be needed to maintain patency.

REFERENCE

Blumenthal KB, Sutherland DE, Wagner KR, et al. Bladder neck contractures related to the use of Hem-o-lok clips in robot assisted laparoscopic radical prostatectomy. *Urology*. 2008;72(1):158–161.

BLADDER NECK HYPERTROPHY

DESCRIPTION Hypertrophy of the bladder neck is often seen in conjunction with BPH and may lead to obstructive symptoms and dysfunctional high-pressure voiding. Pure bladder neck hypertrophy has also been implicated in chronic pelvic pain syndrome (CPPS) and may respond best to α-adrenergic blockade. (See also Section I: “Bladder Outlet Obstruction [BOO].”)

REFERENCE

Hruz P, Danuser H, Studer UE, et al. Non-inflammatory chronic pelvic pain syndrome can be caused by bladder neck hypertrophy. *Eur Urol.* 2003;4:106–110.

BLADDER, NEUROFIBROMA

DESCRIPTION A rare benign tumor of the nerve sheath from overgrowth of Schwann cells, these lesions originate in the bladder from ganglia in the wall. They can present in childhood as obstruction or voiding symptoms. Malignant degeneration is rare. The condition is sporadic or related to neurofibromatosis. Conservative resection, as needed, is the usual treatment. With severe obstruction or intolerable symptoms, cystectomy may be needed.

REFERENCE

Salvitti M, Celestino F, Gerocarni Nappo S, et al. Diffuse ganglioneuromatosis and plexiform neurofibroma of the urinary bladder: An uncommon cause of severe urological disease in an infant. *J Pediatr Urol.* 2013;9(3):e131–e133.

BLADDER OUTLET OBSTRUCTION INDEX (BOOI)

DESCRIPTION Based on the International Continence Society (ICS) nomogram for identifying bladder outlet obstruction during urodymamic evaluation. The ICS nomogram categorizes patients with LUTS into obstructed, equivocal (or slightly obstructed) or unobstructed based on the maximum detrusor pressure during voiding versus the maximum flow rate.

$$BOOI = PdetQ_{max} - 2Q_{max}$$

$PdetQ_{max}$ is the maximum detrusor pressure at peak flow and Q_{max} is the maximum flow rate.

Patients are obstructed if the BOOI is >40, equivocal if the BOOI is 20–40, and unobstructed if the BOOI is <20.

REFERENCES

Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: Three simple indices to define bladder voiding fuction. *BJU Intl.* 1999;84(1):14–15.

Rom M, Waldert M, Klingler HC, et al. Bladder outlet obstruction in men with acute urinary retention: an urodynamic study. *World J Urol.* 2013;31(5):1045–1050.

BLADDER PAIN/INTERSTITIAL CYSTITIS SYMPTOM SCORE (BPIC-SS)

DESCRIPTION BPIC-SS is a questionnaire to select bladder pain syndrome/interstitial cystitis patients for clinical trials. It may have a role in clinical practice in the future. It consists of 8 questions divided into broad areas: Urge to urinate, urinary frequency, and bladder pain and pressure. For the scoring, a single score is created by summing all 8 items to create a total score ranging from 0–38.

Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

Concept	Item
Urge to urinate	In the past 7 days, how often did you still feel the need to urinate just after you urinated?
	In the past 7 days when you urinated, how often was it because of pain in your bladder?
	In the past 7 days, how often did you urinate to avoid pain in your bladder from getting worse?
Urinary frequency	In the past 7 days, how bothered were you by frequent urination during the daytime?
	In the past 7 days, how bothered were you by having to get up during the night to urinate?
Bladder pain and pressure	In the past 7 days, how often did you have a feeling of pressure in your bladder?
	In the past 7 days, how often did you have pain in your bladder?
	Select the number that describes your worst bladder pain in the past 7 days.

Modified from Humphrey L, et al. *European Urology.* 2012;61(2):271–279.

REFERENCE

Humphrey L, Arbuckle R, Moldwin R. et al. The Bladder Pain/Interstitial Cystitis Symptom Score: Development, Validation, and Identification of a Cut Score European Urology, Volume 61, Issue 2, 2012; Pages 271–279.

BLADDER, PARAGANGLIOMA

DESCRIPTION Exceedingly rare tumor, with 15% being malignant. Accounts for 10% of extra-adrenal pheochromocytomas. Catecholamine release is sometimes triggered by voiding, bladder distention, defecation, or intercourse. Typical symptoms are those of a pheochromocytoma (diaphoresis, paroxysmal hypertension, palpitations, headaches, syncope). The lesion may arise from embryonic nests of chromaffin cells in the sympathetic plexus of the detrusor muscle. Cystoscopy should be accompanied by adrenergic blockade; routine biopsy should be avoided. Transurethral resection is considered inadequate, since most lesions involve the entire thickness of the bladder wall. Treatment for smaller lesions consists of partial cystectomy with pelvic lymph node dissection. Radical cystectomy is recommended with large tumors or if lymphatic involvement is present.

REFERENCE

Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: A review. *Eur Urol.* 2003;44(6):672.

BLADDER, PHEOCHROMOCYTOMA

DESCRIPTION Similar to pheochromocytomas in other areas of body; 10% are malignant. They are thought to arise from paraganglionic cells in bladder, usually around the trigone. Most are hormonally active and can present with hypertension during bladder emptying and filling. Can appear as a submucosal tumor on cystoscopy. Late metastasis can occur, so long-term follow-up is warranted.

TREATMENT

- Partial cystectomy is the treatment of choice
- TUR may cause a hypertensive crisis

REFERENCE

Beilan J, Lawton A, Hajdenberg J, et al. Pheochromocytoma of the urinary bladder: A systematic review of the contemporary literature. *BMC Urol.* 2013;13(1):22.

BLADDER SARCOMA (LEIOMYOSARCOMA/RHABDOMYOSARCOMA)

DESCRIPTION Types of sarcoma that have been described in the bladder include angiosarcoma, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, chondrosarcoma, and osteosarcoma. These, combined, account for <1% of all malignant tumors of the bladder. They usually present with hematuria or voiding symptoms. Sarcomas of the bladder are rare aggressive malignancies. Leiomyosarcoma is the most common malignant mesenchymal tumor that arises in the bladder of adults. It occurs more frequently in men. On histology, parallel bundles of spindle cells are seen. The mainstay of treatment is aggressive excision (4–

5 cm margins), but even with such treatment the 5-yr disease-specific survival is 62%. Rhabdomyosarcomas are most common in young children. Embryonal rhabdomyosarcomas in children characteristically produce polypoid lesions in the base of the bladder, and is known as *sarcoma botryoides*. For pediatric rhabdomyosarcoma, a multimodal approach utilizing surgery, radiation, and chemotherapy is employed, with improving rates of bladder preservation and improving prognosis. Metastatic disease treatment consists of resection, radiation, and chemotherapy with single-agent (doxorubicin or ifosfamide). (See also Section I: "Bladder Cancer, General"; Section I: "Rhabdomyosarcoma, Pediatric [Sarcoma Botryoides].")

REFERENCES

Rosser CT, Slaton JW, Izawa JI, et al. Clinical presentation and outcome of high-grade urinary bladder leiomyosarcoma in adults. *Urology*. 2003;61:1151–1155.

Stevens MC. Treatment for childhood rhabdomyosarcoma: The cost of cure. *Lancet Oncol*. 2005;6(2):77–84.

BLADDER SMALL CELL CARCINOMA (OAT CELL, SIGNET RING)

DESCRIPTION Neuroendocrine or small cell carcinoma is an aggressive malignancy derived from either neuroendocrine or pluripotent cells. This tumor most commonly arises in the lung, but may occur in multiple locations including the bladder and less frequently the prostate. Neuroendocrine tumor of the bladder is rare, with ~286 cases reported in the English literature. It can be seen alone or in combination with other tumor types, most frequently TCC. Small cell carcinoma of the bladder presents as any other bladder tumor, most frequently with hematuria. The diagnosis is made pathologically. The tumor usually presents as muscle-invasive disease (94% in 1 series), and often with metastatic disease (67% in same series). Most common sites of metastases are to lymph nodes, liver, bone, lung, and brain. Due to the high rate of early dissemination, chemotherapy is the mainstay of treatment, with radical cystectomy often performed afterward. The tumor also appears responsive to combined chemotherapy and radiation. Prognosis is generally worse than for urothelial carcinoma. (See also Section I: "Bladder Cancer, General.") (Image ☼)

SYNONYMS

- Small cell carcinoma
- Neuroendocrine tumor
- Oat cell carcinoma

TREATMENT

- Partial or radical cystectomy
- Platinum-based chemotherapy has achieved partial regression

REFERENCE

Koga F, Yokoyama M, Fukushima H. Small cell carcinoma of the urinary bladder: A contemporary review with a special focus on bladder-sparing treatments. *Expert Rev Anticancer Ther*. 2013;13(11):1269–1279.

BLADDER, TEARDROP

DESCRIPTION Diffuse pelvic pathology can compress the bladder into a teardrop configuration on various imaging studies, such as excretory urography or cystogram. Causes include pelvic lipomatosis, pelvic hematoma, pelvic adenopathy, and enlarged pelvic vasculature (usually caused by vena cava obstruction). Occasionally, a muscular patient with a hypertrophied iliopsoas muscle can exhibit this finding.

REFERENCE

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston: Little, Brown; 1991:287–288.

BLADDER TRABECULATION AND CELLULES

DESCRIPTION Trabeculation is a cystoscopic description of hypertrophy of smooth muscle bundles in the muscularis propria layer of the bladder wall, which occurs over time due to high-pressure voiding in the setting of bladder outlet obstruction. The obstruction may be due to anatomic obstruction such as benign prostatic hyperplasia (BPH) in the adult or posterior urethral valves in the child, or to neurogenic dysfunction such as detrusor sphincter dyssynergia. It is a manifestation of increased collagen deposition in the bladder wall. More extreme degrees of trabeculation are termed “cellules.” These small pockets are caused when the bladder mucosa is pushed between the collagen and muscle fibers of the bladder wall. Cellules may progress to form an acquired bladder diverticulum. (See also Section II: “Bladder Diverticulum.”) (Image ☼)

REFERENCES

Bai SW, Park SH, Chung DJ, et al. The significance of bladder trabeculation in the female lower urinary system: An objective evaluation by urodynamic studies. *Yonsei Med J*. 2005;46(5):673–678.

Sirosky MB, Babyan RK. Lower urinary tract symptoms. In: Siroksy MB, et al., eds. *Handbook of Urology*. 3rd ed. Philadelphia, PA: Lippincott; 2004.

BLADDER, VILLOUS ADENOMA

DESCRIPTION This tumor has a histologic appearance identical to villous adenoma of the colon. It can also be seen in the urachus. Cystoscopically, it appears exophytic and papillary. Histologically, a mucous-secreting epithelium with goblet cells is seen. It is treated by transurethral resection with possible cystectomy, if invasion is suspected.

REFERENCE

Channer JL, Williams JL, Henry L. Villous adenoma of the bladder. *J Clin Pathol*. 1993;46(5):450–452.

BLADDER WALL CALCIFICATION, DIFFERENTIAL DIAGNOSIS

DESCRIPTION Bladder wall calcification is a relatively uncommon finding. The differential includes:

- Amyloidosis
- Bilharzia (urinary schistosomiasis)
- Cyclophosphamide-induced cystitis
- Encrusted cystitis
- Mitomycin C intravesical treatment
- Tuberculosis
- Urothelial carcinoma

REFERENCE

Pollack HM, Banner MP, Martinez LO, et al. Diagnostic considerations in urinary bladder wall calcification. *AJR Am J Roentgenol.* 1981;136(4):791–797.

BLADDER WALL THICKENING, DIFFERENTIAL DIAGNOSIS

DESCRIPTION Bladder wall thickening can be seen on US, CT, or MRI. The differential includes:

- Bacterial/viral cystitis
- Bilharzial infection (urinary schistosomiasis)
- Bladder cancer (urothelial carcinoma, nonurothelial carcinoma)
- Bladder fistula (Crohn disease, diverticulitis)
- Hemorrhagic cystitis
- High-pressure storage/voiding (eg, bladder outlet obstruction, neurogenic bladder)
- Systemic lupus erythematosus
- Tuberculosis (Image ☼)

REFERENCE

Wong-You-Cheong JJ, Woodward PJ, Manning MA, et al. Inflammatory and nonneoplastic bladder masses: Radiologic-pathologic correlation. *Radiographics*. 2006;26(6):1847–1868.

BLASTOMYCOSIS, GENITOURINARY

DESCRIPTION *Blastomyces dermatitidis* is endemic in the Ohio, Mississippi, and Missouri river basins. It is an opportunistic infection in immunocompromised patients, particularly associated with prolonged steroid use (>2 mo), HIV, solid tumors treated with radiation or chemotherapy, and end-stage renal and hepatic disease. GU blastomycosis tends to involve the prostate and epididymis, and produces voiding complaints. Genitourinary disease may be seen in 20–30% of disseminated infections. Prostatic abscess can be seen. Up to 30% can have epididymal involvement. GU blastomycosis is a manifestation of systemic disease; it has been reported to be transmitted by sexual relations to the GU system of the partner. Diagnosis may be made by isolation of fungus from the urine, semen, or tissue. Detection of blastomyces A antigen by immunodiffusion may be helpful in diagnosis. Other serologic testing with enzymeimmnoassay and radioimmunoassay have high sensitivity (85–88%) and specificity (100%).

TREATMENT

- Standard therapy for disseminated infection is long-term amphotericin B

- Long-term ketoconazole (12 mo) at 400 mg/d may be effective for prostatitis/epididymitis
- Itraconazole may be effective in focal uncomplicated infections

REFERENCES

Wise GJ, Freyle J. Changing patterns in genitourinary fungal infections. *AUA Update*, Vol. XVI, Lesson 1, 1997.

Wise GJ, Talluri GS, Marella VK. Fungal infections of the genitourinary system: Manifestations, diagnosis, and treatment. *Urol Clin North Am*. 1999;26(4):701–718.

BLEOMYCIN TOXICITY

DESCRIPTION Used in combination chemotherapy for testicular cancer as well as cervical, ovarian, SCC, and lymphoma, induces single- and double-strand breaks in DNA called *scission*. Pulmonary fibrosis (fibrosing alveolitis) is a potentially lethal toxicity; it can develop 1–6 mo after treatment and has been reported to occur beyond 6 mo. Bleomycin may also cause hypersensitivity pneumonitis and nodular pulmonary densities. Skin changes, alopecia, and stomatitis are common. Vascular toxicity, anaphylaxis, and Raynaud phenomenon have been reported. Clinical indications of pulmonary toxicity may include any of the following: Cough (nonproductive), dyspnea, pleuritic chest pain, fever, tachypnea, rales, lung restriction, and hypoxemia. Renal insufficiency is a risk factor for bleomycin toxicity (80% eliminated by the kidney).

TREATMENT

- Discontinue drug with suspected bleomycin-induced injury; steroids may help some cases.
- Attention to minimizing oxygen concentration and hydration status during surgery is essential.

REFERENCE

Fyfe AJ, McKay P. Toxicities associated with bleomycin. *J R Coll Physicians Edinb*. 2010;40(3):213–215.

BLUE DIAPER SYNDROME

DESCRIPTION Defect in tryptophan absorption in which the urine contains indoles, giving it a blue color. Similar to Hartnup disease, a chronic course is usual. Hypoplasia of the optic disc and abnormal eye movements have also been reported.

SYNONYMS

- Familial hypercalcemia with nephrocalcinosis and indicanuria
- Tryptophan malabsorption

TREATMENT

Low-tryptophan diet; no treatment known for underlying defect

REFERENCE

Chen Y, Wu L, Xiong Q. The ocular abnormalities of blue diaper syndrome. *Metab Pediatr Systemic Ophthalmol*. 1991;14(3–4):73–75.

BLUE DOT SIGN

DESCRIPTION A blue discoloration seen through the scrotal wall when the testes are tented against the skin. Indicates the presence of torsion of appendix testes or appendix epididymis. Should be assessed during the evaluation of scrotal pain or swelling. The torsed appendix may swell to the size of the testicle itself. If torsion of the cord can be ruled out by palpation of the unequivocally normal testicle, appendiceal torsion can be observed. (See also Section I: "Torsion, Testis or Testicular/Epididymal Appendages.")

REFERENCE

Dresner ML. Torsed appendage. Diagnosis and management: Blue dot sign. *Urology*. 1973;1(1):63–66.

BLUE NEVUS (MELANOSIS), UROLOGIC CONSIDERATIONS

DESCRIPTION Benign melanotic lesion of the prostate that must be differentiated from malignant melanoma. It is usually an incidental finding after TURP. In prostate, the term *blue nevus* has been used when melanin is confined to ovoid or elongated melanocytes in the stroma, whereas the term melanosis has been used for those prostatic lesions that have melanin in both the stromal melanocytes and glandular epithelium. It has been reported in lesions with adenocarcinoma.

REFERENCE

Muzaffar S, Aijaz F, Pervez S, et al. Melanosis of the prostate: A rare benign morphological entity. *Br J Urol*. 1995;76(2):265–266.

BOARI-OCKERBLAD FLAP

DESCRIPTION After appropriate bladder mobilization, a tonguelike flap of bladder based on the ipsilateral superior vesicle artery is incised. The base of the flap should be at least 4 cm, while the tip should be at least 3 cm. The tubularized flap is then anchored to the psoas minor tendon, and either direct or tunneled anastomosis with the ureter is then performed. Useful to reimplant the ureter when there is loss of the distal ureter.

REFERENCE

Nakada SY, Hsu T. Management of Upper Urinary Tract Obstruction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:1122–1168.

BODY MASS INDEX (BMI), UROLOGIC CONSIDERATIONS

DESCRIPTION The BMI is defined as the weight (in kilograms) divided by the height (in meters^2). BMI is used to categorize obesity (see table). Higher BMI carries many increased health risks, including diabetes and coronary artery disease. Obesity and elevated BMI have many detrimental effects and associations in urology. Elevated BMI has been shown to be an independent risk factor for incontinence in females and for adverse outcomes in prostate cancer. BMI has been clearly correlated with incidence and risk of formation of renal calculi in both men and women. It has been implicated in ED, with reduction of BMI correlating with

increased IIEF score. Increased BMI as a marker of obesity implies increased difficulty in many open, laparoscopic, and percutaneous procedures. A BMI calculator from the NIH is available online at: http://www.nhlbisupport.com/bmi/. (See also Section II: "Obesity, Urologic Considerations.")

Classification of Overweight and Obesity by BMI

	Obesity Class	BMI (kg/m^2)
Underweight		<18.5
Normal		18.5–24.9
Overweight		25.0–29.9
Obesity	I	30.0–34.9
Obesity	II	35.0–39.9
Extreme obesity	III	≥40

REFERENCES

Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: A randomized controlled trial. *JAMA*. 2004;291:2978–2984.

Taylor EN, Stampfer MJ, Curhan GC, et al. Obesity, weight gain, and the risk of kidney stones. *JAMA*. 2005;293:455–462.

BONE MARROW/STEM CELL TRANSPLANTATION, UROLOGIC CONSIDERATIONS

DESCRIPTION High-dose chemotherapy regimens used for bone marrow transplantation and stem cell transplantation are accompanied by multiple toxic side effects. The most common urologic complication is hemorrhagic cystitic (HC), with an incidence ranging from 7–68%. HC is commonly seen in a dose dependent manner after the administration of cyclophosphamide and ifosfamide. Both medications have the same metabolite, acrolein. HC can further be caused by busulfan, pelvic irradiation, thrombocytopenia, and the presence of a urinary viral infection (adenovirus, BK virus, cytomegalovirus [CMV], polyoma virus). Early onset HC tends to be due to acrolein exposure, late HC is associated with viral etiologies. Other possible urologic sequelae of high-dose chemotherapy exposures include bladder fibrosis, fistula, bladder contracture, chronic urinary tract infections, pyuria, and secondary malignancies. A preventative measure for HC is premedication with 2-mercaptoethane sodium sulfonate (Mesna) and hydration. Catheter drainage and continuous bladder irrigation may limit acrolein exposure to bladder urothelium. Tumor lysis syndrome and uric acid stone development are also possible.

REFERENCE

Monarch PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: A data-driven review. *Arthritis Rheum*. 2010;62(8):9–21.

BONE METASTASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Bone metastasis is a common problem in urologic malignancies. Prostate cancer has a predilection to metastasize to bone but bone metastasis from renal cell

carcinoma, urothelial carcinoma, and adrenocortical carcinoma is also seen. An elevated alkaline phosphatase suggests bone lesions. The diagnosis often involves a radionucleotide bone scan with confirmatory imaging study and possibly a biopsy. Bone metastases are associated with pain (which may be severe), pathologic fractures, and possible spinal compression (often referred to as skelet al-related events or SRE). These lesions often require treatment independently from the primary tumor. Options for treatment include chemotherapy, surgery, and external beam radiation. Radiation therapy is often highly successful at controlling local bony symptoms and radioisotopes such as strontium-89 are useful for palliation of more extensive bone metastasis. Radium 223 (Xofigo) an α-emitter has been approved for bony metastatic prostate cancer and can improve quality of life and extend survival in metastatic castrate resistant prostate cancer. In prostate cancer in particular, bisphosphonate therapy such as zolendronic acid, and osteoclast targeting agents such as denosumab are used to prevent progression and skelet al-related complications and may be effective at preventing occurrence of bone metastases (Image ☼).

REFERENCES

Bishr M, Saad F. Preventing bone complications in prostate cancer. *Curr Opin Support Palliat Care.* 2012:6(3):299–303.

Coleman RE. Clinical features of metastatic bone disease and risk of skelet al morbidity. *Clin Cancer Res.* 2006;15;12(20 Pt 2):6243s–6249s.

BONE MINERAL DENSITY, UROLOGIC CONSIDERATIONS

DESCRIPTION Prolonged ADT for prostate cancer is associated with decreased bone mineral density (BMD) and osteoporosis, leading to disabling skelet al fractures. Bisphosphonate therapy (zoledronic acid, alendronate, others), smoking cessation, weight-bearing exercise, and vitamin D and calcium supplementation can help improve BMD during androgen ablation therapy. (See also Section II: “Osteoporosis and Osteopenia, Urologic Considerations.”) Some recommend that BMD should be monitored during androgen-deprivation therapy using BMD scans (dual-energy x-ray absorptiometry or DEXA):

- T-score: The number of standard deviations (SDs) by which the patient’s bone mass falls above or below the mean peak bone mass for a 30-yr-old healthy adult. For every 1 SD decrease in T-score, relative risk of fracture increases ~1.5–2.5-fold
- WHO interpretation of T-scores: Normal: ≥–1; Osteopenia: –1 to –2.5; Osteoporosis ≤–2.5; Severe osteoporosis: ≤–2.5 and ≥1 fracture

REFERENCE

Ryan CW, Huo D, Stallings JW, et al. Lifestyle factors and duration of androgen deprivation affect bone mineral density of patients with prostate cancer during 1st year of therapy. *Urology*. 2007;70(1):122–126.

BONE SCAN, UROLOGIC CONSIDERATIONS

DESCRIPTION The radionucleotide bone scan is a sensitive test for bone metastases and is obtained during the initial staging or in the setting of recurrent or metastatic disease in urologic malignancies (prostate, urothelial, renal, and adrenocortical carcinomas). A standard

bone scan is generally performed by acquiring multiple images of the skeleton 3–4 hr after IV injection of ^{99m}technetium-labeled methylene-diphosphonate (MDA). Due to low specificity, if a lesion is identified, particularly when solitary, further investigation is necessary using confirmatory testing. This may be done with plain radiographs, CT, or MRI. Bone scans are extensively used in prostate cancer to detect and follow bone metastases. In prostate cancer patients with extensive bony metastasis, the bone scan may have a "super scan" appearance, in which the focal lesions coalesce to produce diffusely increased uptake. An increase in the contrast between bone and background soft tissue and faint or absent renal images are the typical appearances seen on a "super scan." (Image ☼)

REFERENCE

Coleman R, Rubens R. Radionucleotide bone scan. In: Abeloff, ed. *Clinical Oncology*. 3rd ed. New York, NY: Churchill Livingstone; 2004.

BONNEY TEST (MARSHALL TEST)

DESCRIPTION A clinical test used for >50 yr for the diagnosis of stress incontinence and for the selection of patients for incontinence surgery. As originally described, the test consists of 2 parts:

- The patient coughs with a full bladder, and simultaneous urine loss from the urethra is visually confirmed.
- The examiner elevates the bladder neck with a finger on either side of the urethra while the patient coughs again.
- If the patient is then continent, the test is considered positive and the patient is thought to have an anatomic defect correctable by surgical elevation of the bladder neck. Bonney cautioned that the fingers must be carefully placed to avoid compressing the urethra in the midline.

The contemporary clinical utility of the test has been questioned by many clinicians.

REFERENCE

Miyazaki FS. The Bonney test: A reassessment. *Am J Obstet Gynecol*. 1997;177(6):1322–1328; discussion 1328–1329.

BORS-COMARR CLASSIFICATION OF VOIDING DYSFUNCTION

DESCRIPTION Based on observations noted with spinal cord injury patients. The system takes into account 3 main factors:

- Anatomic location of the lesion (upper motor neuron, lower motor neuron)
- Completeness of the lesion (partial vs. complete SCI)
- Presence of residual urine, which would mean "unbalanced," according to the definition
- Best applied to patients with a complete neurologic lesion after spinal shock has resolved

REFERENCE

Pryse-Phillips W, Pryse-Phillips W. *Companion to Clinical Neurology*. 2nd ed. New York, NY: Oxford; 2003.

BOSNIAK CLASSIFICATION OF RENAL CYSTS

DESCRIPTION Classification system to differentiate renal cystic masses visualized on CT as benign or malignant. Cysts are graded on scale from I–IV, with grade I having typical appearance of benign simple cyst, and grade IV having appearance of RCC. Classification is based on homogeneity and complexity of cystic fluid, presence or absence of septations, calcifications, or solid components; and the density of cystic fluid as determined by Hounsfield units. (See also Section II: "Renal Cysts," Section II: "Renal Mass.")

- Category I: Benign simple cysts; thin walls without septa, calcifications, or solid components; water density and no contrast enhancement. No further imaging needed.
- Category II: Benign cysts with a few thin septa; the wall or septa may contain fine calcification and sharp margins, are nonenhancing, and usually measure <3 cm.
- Category IIF: Well-marginated and may have thin septa or minimal smooth thickening of the septa or wall, which may contain calcification that may also be thick and nodular; no contrast enhancement. Includes totally intrarenal nonenhancing lesions >3 cm. These require follow-up (designated by the "F" designation).
- Category III: Indeterminate cysts with thickened irregular or smooth walls or septa; enhancement present. 40–60% are malignant (cystic RCC and multiloculated cystic RCC). Other class III lesions are benign and include hemorrhagic cysts, infected cysts, and multiloculated cystic nephroma. Surgery is recommended, although additional imaging by MRI or with biopsy is supported by some clinicians.
- Category IV: Risk of malignancy is 85–100%. Characteristics of category III cysts plus they contain contrast-enhancing soft tissue components that are adjacent to and independent of the wall or septum. Surgery is recommended (Image ☼).

REFERENCE

Israel GM, Bosniak MA. *Urology*. 2005;66(3):484–488.

BOURNE TEST

DESCRIPTION A diagnostic test for the detection of enterovesical or colovesical fistulas. Radiographs are taken of centrifuged urine samples, which are obtained immediately after a barium enema. In 1 series of 10 patients, in 7 of the 10, the Bourne test was the only positive evidence of an otherwise occult colovesical fistula later proven at surgery.

REFERENCE

Lawrence C, Shaffer HA Jr, Bickston SJ. Image of the month. Bourne test, enterovesical fistulas. *Gastroenterology*. 2003;125(2):291, 641.

BOWENOID PAPULOSIS

DESCRIPTION Bowenoid papulosis is an uncommon skin lesion affecting the genitals, groin, and perianal areas of young, sexually active adult men and women. The histology appearance resembles Bowen disease. BP is rarely invasive and may even regress spontaneously, thus conservative treatments are often adequate. The natural history of the disease is unknown, but the lesions usually follow a benign clinical course, and spontaneous regression is

observed. Evolution of the lesions to invasive carcinoma is rare. The papules are asymptomatic, discrete, small (averaging 4 mm in diameter), flat, reddish violaceous or brown, often coalescent, and usually have a smooth, velvety surface. Many patients have a history of genital infection with viral warts or herpes simplex. Genital warts are primarily caused by HPV types 6 and 11. Treatment should be conservative. Individual lesions can be adequately treated by excision, cautery, cryoablation, or laser surgery, much as ordinary warts, without the need for wide surgical margins. Alternatively, lesions may be treated for 3–5 wk with 5% 5-fluorouracil cream or imiquimod cream QOD.

REFERENCE

Campione, E, Centonze C, Diluvio L, et al. Bowenoid Papulosis and Invasive Bowen's Disease: A multidisciplinary approach. *Acta Derm Venereol.* 2013;93(2):228–229.

BOYARSKY GUIDELINES FOR BPH

DESCRIPTION To provide reproducible guidelines for the severity of symptoms of prostatism, BPH, and LUTS, scored questionnaire formats have been developed. Traditional assessment tools include the Madsen–Iversen Point System and the Boyarsky Guidelines. These have been generally replaced by the AUA or I-PSS questionnaires, but are used in several ongoing follow-up studies of BPH therapies.

REFERENCE

Boyarsky S, Jones G, Paulson DF, et al. A new look at bladder neck obstruction by the Food and Drug Administration regulators: Guidelines for investigation of benign prostatic hypertrophy. *Trans Am Assoc Genitourinary Surg.* 1976;68:29–32.

BOYCE NEPHROTOMY (ANATROPHIC NEPHROLITHOTOMY)

DESCRIPTION The longitudinal anatrophic nephrotomy takes advantage of a nearly avascular plane in the kidney (Brödel white line), which can be used to remove staghorn calculi (Boyce anatrophic nephrolithotomy). The incision site in the lateral posterior surface of the kidney can be accurately identified by injecting indigo carmine in the posterior renal artery branch. Once the capsule is incised, the parenchyma is divided with the blunt end of the knife in the proper plain. Traditionally used for staghorn calculi.

REFERENCE

Straffon RA. Anatrophic nephrolithotomy. In: Novick AC, Streem BS, Pontes JE, et al., eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:191–197.

BRACHYTHERAPY SEED EMBOLUS

DESCRIPTION Brachytherapy is used to treat prostate cancer via image-guided implantation of radioactive seeds of iodine^{125} or palladium^{103}. These seeds, when placed into periprostatic tissue, have been noted to migrate, at times entering the prominent periprostatic veins and traveling centrally. Multiple investigations have yielded varying rates of seed displacement and embolization ranging from 0.7–55% of all cases. The most common target organ is the

lung, but reports of coronary artery and hepatic emboli exist through a patent foramen ovale. The iodine^{125} seed measures 4.5 mm in length and 0.8 mm in diameter and, due to its small size, is more frequently involved in embolization. Because of their size, these emboli are often asymptomatic and are diagnosed incidentally on imaging studies. 2 concerns regarding this process are possible injury to the end organ, especially in cases of patent foramen ovale, and diminution of the radiation dose to the prostate.

REFERENCE

Nguyen BD. Cardiac and hepatic seed implant embolization after prostate brachytherapy. *Urology*. 2006;68(3):673.

BRAIN METASTASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Brain metastatic disease can be seen with several urologic malignancies, most commonly with renal cell carcinoma and germ cell tumors (GCT). They generally are poor prognostic indicators. Patients may be asymptomatic with occult disease or display neurologic symptoms such as headache, nausea, and vomiting, mental status changes, seizures, or focal signs. Patients presenting with urologic tumors and neurologic signs should be worked up for brain metastases. CT scan is generally quick and readily available, but MRI has higher sensitivity and is better at distinguishing metastases from other intracranial processes. Due to their high impact on quality of life, these often require prompt treatment usually via radiation therapy or surgical removal.

REFERENCE

Nguyen TD. Brain metastasis. *Neurol Clin*. 2007;25(4):1173–1192.

BRENNER TUMORS

DESCRIPTION These are tumors of variable malignant potential of the ovary. Extraovarian and testicular origins have been reported, and they usually present as an ovarian mass. Light microscopy demonstrates distinctive nests of transitional cells indistinguishable from urothelium. Classified as typical, metaplastic, proliferating, or malignant, these lesions usually stain for carcinoembryonic antigen (CEA). Theorized origin is from a metaplastic process of coelomic epithelium. Usually, surgical removal is used to assess malignant potential.

REFERENCE

Caccamo D, Socias M, Truchet C. Malignant Brenner tumor of the testes and epididymis. *Arch Pathol Lab Med*. 1991;115(5):524–527.

BRICKER URETERAL ANASTOMOSIS

DESCRIPTION A direct ureteral-to-small bowel end-to-side refluxing anastomosis incorporating full-thickness ureteral and intestinal wall. It is used in ileal conduit construction.

REFERENCE

Dahl DM, McDougal WS. Use of intestinal segments in urinary diversion. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:2411–2449.

BRIGHAM SLING (URETHROPEXY)

DESCRIPTION Used to treat stress incontinence in women. A combined endoscopic needle sling procedure that utilizes a rectus fascial strip placed at the bladder neck through a vaginal incision. The fascial sling is held in place with needles placed through the anterior abdominal wall, similar to the Stamey and Raz suspension needle procedures. (See also Section I: "Incontinence, Urinary, Adult Female.")

REFERENCE

Loughlin KR. The Brigham sling. *Contemp Urol*. 1998;10:69–75.

BRINK SCORE

DESCRIPTION A digital test of pelvic muscle strength for evaluation of a pelvic muscle exercise program. Factors of perceived pressure, alteration of the vertical plane, and time were combined to form a 7-point scale. Currently used in pelvic floor physical therapy regimens.

REFERENCE

Brink CA, Wells TJ, Sampselle CM, et al. A digital test for pelvic muscle strength in women with urinary incontinence. *Nurs Res*. 1994;43:352–356.

BRITISH TESTICULAR TUMOR CLASSIFICATION

DESCRIPTION Used mainly in Great Britain, and based on the concept that all nonseminomatous tumors represent displaced, nonorganized embryonic blastomeres and are therefore teratomas. Disparate lesions are classified under a common category. The World Health Organization classification is used in most of the rest of the world.

REFERENCE

Ulbright TM. Neoplasms of the testes. In: Bostwick D, ed. *Urologic Surgical Pathology*. 1st ed. St. Louis, MO: Mosby; 1997.

BRONCHOGENIC CYST, RETROPERITONEAL

DESCRIPTION Bronchogenic cysts are congenital abnormalities arising from remnants of the primitive foregut, which gives rise to the respiratory diverticulum. Generally asymptomatic and benign, these lesions are often incidentally discovered. The true prevalence is unknown due to their asymptomatic nature. Retroperitoneal location is exceedingly rare with only approximately 60 cases reported in the literature. Most retroperitoneal bronchogenic cysts are located near the left adrenal gland or peripancreatic. Anatomopathologic criteria include pseudostratified, ciliated columnar epithelium with cartilage, smooth muscle or seromucous glands. May become larger over time due to continued epithelial secretion. Infection, perforation, hemorrhage, and malignant

degeneration are possible and surgical extirpation is recommended. Definitive diagnosis can only be made histopathologically. (See also Section I: “Retroperitoneal Masses, Fluid, and Cysts.”)

REFERENCE

Govaerts K, Van Eyken P, Verswijvel G, et al. A bronochognic cyst, presenting as a retroperitoneal cystic mass. *Rare Tumors*. 2012;4(1):e13.

BRUNN BUDS AND NESTS (VON BRUNN NESTS)

DESCRIPTION Variant of bladder epithelium, noted in 80–90% of normal bladders. Brunn buds are an invagination of surface epithelium into the lamina propria. Brunn nests represent a further invagination within the lamina propria and are a more progressed form of a Brunn bud. Cystitis cystica is thought to result from a Brunn nest that closes over on itself, forming a cyst. May become involved with urothelial carcinoma; controversy exists as to whether radical or conservative therapy is indicated if these lesions are involved by TCC.

REFERENCE

Dinney CP, Ramirez EI, Swanson DA, et al. Management of transitional cell carcinoma involving von Brunn’s nests. *J Urol*. 1995;153:944–949.

BRUSHITE (CALCIUM MONOHYDROGEN PHOSPHATE)

DESCRIPTION A type of calcium phosphate calculus of the kidney. Brushite stones are particularly dense and are 2nd only to cysteine stones in their resistance to fragmentation. Calcium phosphate is the most common type of stone seen in distal renal tubular acidosis (type 1). On metabolic evaluation, primary calcium phosphate stone formers tend to have higher urine volumes, and higher calcium and lower citrate excretion than do idiopathic calcium oxalate formers. (See also Section I: “Urolithiasis, Adult, General”; Section II: “Urolithiasis, Calcium Oxylate/Phosphate.”)

REFERENCE

Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. *Kidney Int*. 2005;67(2):576–591.

BTA TESTING (BTA AND BTA STAT URINE TEST)

DESCRIPTION The BTA test (Bard; Redmond, Washington) is a latex agglutination assay. It qualitatively detects high–molecular-weight basement membrane complexes, present when tumor cells become invasive and undergo proteolytic degradation. A comparison of BTA with bladder wash cytology reported a higher sensitivity of BTA (54% vs. 23%); however, BTA was associated with a high false-positive rate (specificity 9%). A multicenter trial demonstrated sensitivities of 40% and 16% for BTA and urine cytology, respectively.

The initial BTA test had 2 limitations: It was a latex agglutination test, and it yielded high false-positive rates. Consequently, the new BTA stat test was developed; it is a monoclonal antibody immunoassay that detects the presence of newly identified human complement factor H-related protein (hCFhrp). A study of BTA stat reported higher sensitivity compared

with cytology. BTA stat has also had higher sensitivity compared with the BTA test (58% vs. 44%). The specificity of BTA stat was reported as 72% for benign genitourinary disease and 95% in healthy volunteers. The main advantage of the BTA test is that it can simply be performed in an office setting and provides rapid results.

REFERENCE

Leyh H, Hall R, Mazeman E, et al. Comparison of the Bard BTA test with voided urine and bladder wash cytology in the diagnosis and management of cancer of the bladder. *Urology*. 1997;50:49–53.

BULBOCAVERNOSUS REFLEX

DESCRIPTION Used as a means of evaluating sacral neurologic integrity. The reflex is commonly elicited by touching the labium minus lateral to the clitoris or squeezing the glans penis and observing for anal contraction. Afferent limb of reflex arc is the pudendal nerve, efferent limb is via the inferior hemorrhoidal branch of the pudendal nerve. Reflex is integrated at the S2–S4 cord level. Relevant urologically for its innervation of the bladder outlet and in erectile function and ejaculation.

REFERENCE

Wester C, Fitzgerald MP, Brubaker L, et al. Validation of the clinical bulbocavernosus reflex. *Neurourol Urodyn*. 2003;22(6):589–591.

BULKING AGENTS, INJECTABLE

DESCRIPTION Injections of various agents (synthetic and natural) have been used in urology to treat conditions such as vesicoureteral reflux, intrinsic sphincter deficiency (ISD), and stress urinary incontinence (SUI). Some products that have been used in the United States are listed here. Collagen is no longer available but is included in the table due to its widespread use in the past. A recent study in elderly patients with SUI noted improvement in incontinence after bulking therapy. In contrast to earlier reports, side effects due to injections were few and mild. Coaptite, macroplastique, and durasphere are actively used for SUI in the United States. Only Deflux is still used for VUR in the United States. (See also Section I: “Incontinence, Urinary, Adult Male”; Section I: “Incontinence, Urinary, Adult Female”; Section I: “Vesicoureteral Reflux, Pediatric”; and Section II: “STING Procedure.”)

Table: Bulking Agents, Injectable

Material	Brand Name	Description
Combination of calcium hydroxylapatite (CaHA) particles and a sodium carboxymethylcellulose carrier gel	Coaptite	CaHA is a principle component of human bone and tooth and has been used in multiple orthopedic and dental applications. It is demonstrated biocompatible and safe. Causes fibroblast infiltration rather than heterotopic ossification. The carrier gel suspends the CaHA particles and degrades over several months.
Polytetrafluoroethylene	PTFE (Teflon)	The small size of particles (90% $<40\ \mu m$) allows them to be phagocytosed, which can result in distant migration and granuloma formation. Not FDA approved for incontinence (migration risk).
Glutaraldehyde cross-linked bovine collagen	GAX-Collagen	Highly purified 35% suspension of bovine collagen (95% type I collagen and 1–5% type III collagen). Does not cause granuloma formation or migration to distant body sites. Begins to degrade in 12 wk; completely degraded in 19 mo, but the injected material transforms into living connective tissue.
Pyrolytic carbon-coated zirconium beads	Durasphere	Nonresorbable pyrolytic carbon-coated zirconium beads are much larger (212–500 μm) than either PTFE or silicone polymers and are transferred in a 2.8% β-glucan water-based gel. Durasphere is more viscous than collagen, and its injection was more technically demanding.
Ethylene vinyl alcohol (EVOH)	Tegress	Permanently implanted nonpyrogenic, injectable bulking agent (EVOH dissolved in DMSO). The resulting mixture is 8% EVOH in DMSO. After injection into tissue, the DMSO diffuses away, resulting in the EVOH precipitating into a complex cohesive. Spongiform mass. This phase transformation takes place rapidly (within 60s), and this effect creates increased tissue bulk.
Silicone polymers	Macroplastique	Textured polydimethylsiloxane macro particles ($>100\ \mu m$) suspended in a bioexcretable carrier hydrogel of polyvinylpyrrolidone (povidone) in which the solid particle content is 33% of the total volume.
Dextranomer microspheres	Deflux	Viscous gel of dextranomer microspheres (50 mg/mL) in a carrier gel of nonanimal stabilized hyaluronic acid, constituting a biocompatible and biodegradable implant. The dextranomer microspheres range from 80–250 μm (average 130 μm). The hyaluronic acid acts mainly as a carrier, leaving the dextranomer microspheres at the implant site.

REFERENCES

Mayer RD, Dmochowski RR, Appell RA, et al. Multicenter prospective randomized 52-week trial of calcium hydroxylapatite versus bovine dermal collagen for treatment of stress urinary incontinence. *Urology*. 2007;69(5):876–880.

Mohr S, Siegenthaler M, Mueller MD, et al. Bulking agents: an analysis of 500 cases and review of the literature. *Int Urogynecol J*. 2013;24(2):241–247.

Wilson TS, Lemack GE, Zimmern PE. Management of intrinsic sphincteric deficiency in women. *J Urol*. 2003;169(5):1662–1669.

BULLOUS PEMPHIGOID

DESCRIPTION A dermatologic condition thought to be autoimmune related. The condition is more common in men and in patients >60 yr of age. Although variable in clinical presentation, a preliminary nonbullous phase is usually characterized by severe pruritus and nonspecific skin changes, followed by formation of confluencing vesicles and marked erythema of the skin. Immunohistochemical evaluation of the skin biopsy shows IgG deposition along the skin basement membrane. Commonly used medications are anti-inflammatory agents (eg, corticosteroids, tetracyclines, dapsone) and immunosuppressants (eg, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide). Most patients require therapy for 6–60 mo.

REFERENCE

Gual A, Iranzo P, Mascaró JM Jr. Treatment of bullous pemphigoid with low-dose oral cyclophosphamide: A case series of 20 patients. *J Eur Acad Dermatol Venereol.* 2014;28(6):814–818.

BUN (BLOOD UREA NITROGEN), INCREASED/DECREASED

DESCRIPTION Blood urea nitrogen (BUN) is a product of dietary protein metabolism. It is produced in the liver and cleared by the kidneys. The serum BUN level depends on both the rate of production and the rate of renal clearance. In renal failure, BUN and creatinine levels generally increase. Factors that might increase BUN include drugs (lithium, diuretics, aminoglycosides, corticosteroids), GI bleeding, prerenal azotemia, renal disease (diabetic nephropathy, pyelonephritis, glomerulonephritis), and obstructive nephropathy. Factors that lower BUN include liver disease, malnutrition and low-protein diets, 3rd-trimester pregnancy, celiac disease, and acromegaly. BUN along with sodium is thought to be responsible for the solute diuresis (postobstructive diuresis) that results after relief of renal obstruction.

REFERENCE

Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med.* 2004;116(7):466–473.

BURCH COLPOSUSPENSION

DESCRIPTION The pubocervical fascia at the level of the bladder neck is fixed to Cooper's ligament bilaterally, usually through a Pfannenstiel incision and a retropubic exposure. It is used in treatment of stress incontinence in women.

REFERENCE

Burch JC. Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse. *Am J Obstet Gynecol.* 1961;81281–81290.

BUSCHKE-LOWENSTEIN TUMOR

DESCRIPTION Nonmalignant penile or perineal lesion, which may be large and exophytic. May cause urethral erosion and fistulas. Can be very locally invasive and mistaken grossly for SCC. Microscopically, broad rete pegs, filled with benign squamous cells and surrounded by a layer of inflammatory cells, are noted. A possible role of HPV 6 and 11 in the development is theorized. Treatment is by local excision after proven diagnosis. (See also Section I: "Condylomata Acuminata (Venereal Warts)"and "Penis, Lesion.")

SYNONYMS

- Verrucous carcinoma
- Giant condyloma acuminata

REFERENCE

Chu QD, Vezeridis MP, Libbey NP, et al. Giant condyloma acuminata (Buschke-Lowenstein tumor) of the anorectal and perianal regions. Analysis of 42 cases. *Dis Colon Rectum.*

1994;37(9):950–957.

BYAR FLAPS

DESCRIPTION The penile prepuce is split dorsally and transferred ventrally, yielding redundant ventral skin (Byars flaps) to be used in 2nd-stage hypospadias repair.

REFERENCE

Snodgrass WT. Hypospadias. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3503–3536.

CALCIFICATIONS, ABDOMINAL AND PELVIC

DESCRIPTION Abdominal and pelvic calcifications are a common finding on plain radiographs and CT. The differential is very broad and includes renal, ureteral and bladder calculi, vascular calcifications (arthrosclerosis and phleboliths), calcified tumors, lymph nodes, seminal vesicles, vas deferens, and infectious processes (TB) (Image ☼).

REFERENCE

O'Connor OJ. Imaging of hematuria. *Radiol Clin North Am.* 2008;46(1):113–132.

CALCIFICATIONS, BLADDER

DESCRIPTION Bladder calcifications on CT or plain radiograph:

- Intraluminal: Bladder calculi, 7% of bladder urothelial carcinomas may be calcified and appear as small stones, encrusted cystitis, foreign body, iatrogenic (postop sutures, retained prostate chips, catheter fragments, hair [due to chronic self-catheterization], following intravesical BCG or mitomycin)
- Bladder wall: Infections (tuberculosis, schistosomiasis), squamous cell carcinoma, cyclophosphamide-induced cystitis, prior radiation treatment, amyloidosis

REFERENCE

O'Connor OJ. Imaging of hematuria: *Radiol Clin North Am.* 2008;46(1):113–132.

CALCIFICATIONS, PROSTATE

DESCRIPTION Calcifications within the prostate are fairly common and can be detected in over 50% of older men. In 1 series of normal men calcifications were found in 23.1% of men aged 20–29 yr compared with 83% for men aged 60–69 yr. Prostatic calculi in childhood are rare. On Doppler imaging they create a prominent "twinkle" artifact. Prostatic calculi usually coexist with prostatitis or BPH in elderly men. It is unclear whether prostatic calculi independently cause LUTS. The prostatic stones are usually located between adenoma and the compressed prostatic tissue sometime referred to as the "surgical capsule" of the gland. Many prostatic stones appear to be calcified proteinaceous bodies called corpora amylacea. Corpora amylacea have no clinical significance, and even if dense or clumped, they are usually not palpable. Primary or endogenous calculi are said to be formed in acini from corpora amylacea. Secondary or exogenous calculi are formed in the prostatic and ejaculatory ducts. Prostatic utricle cysts can also calcify or contain multiple stones.

Prostatic calculi quite often are asymptomatic. Prostatic calcifications are not found more frequently in men with prostatitis but larger calcifications are more likely to be associated with LUTS. However, these calcifications can be a nidus for chronic bacterial infections in some men as many are surrounded by biofilm.

Radiation oncologists have explored the use of prostate calcifications as naturally occurring fiducial markers. The relationship between prostate cancer and calcifications has not been confirmed. Extensive calcifications can be seen after some cases of cryotherapy of the prostate and with tuberculous involvement of the prostate. (See also "Prostate Utricle Calcification.")

REFERENCES
Kim WB, Doo SW, Yang WJ, et al. Influence of prostatic calculi on lower urinary tract symptoms in middle-aged men. *Urology*. 2011;78(2):447–449.
Zackrisson B, Hugosson J, Aus G. Transrectal ultrasound anatomy of the prostate and seminal vesicles in healthy men. *Scand J Urol Nephrol.* 2000;34(3):175–180.

CALCIFICATIONS, RENAL

DESCRIPTION May represent calcified renal calculi or calcified cystic or solid renal neoplasms. RCC is detectable on plain radiography and calcified ~8–18% of the time. Other possible etiologies for renal calcifications include papillary tip calcifications, calcified renal pelvis TCC, nephrocalcinosis, calcified renal artery, and tuberculosis (Image ☼).

REFERENCE
O'Connor OJ. Imaging of hematuria. *Radiol Clin North Am.* 2008;46(1):113–132.

CALCINOSIS, IDIOPATHIC SCROTAL

DESCRIPTION Occurs in pre-existing epidermal cysts or in the dermis without cysts. Usually affects young men. Multiple cysts (>50) are not uncommon. Calcifications range in size from a few millimeters to 3 cm. They may represent epidermal cysts that have, over time, lost their normal wall and calcified. Surgical excision is curative if symptomatic.

REFERENCE
Ro JY, et al. Chapter 15: Penis and scrotum. in urologic surgical pathology. In: Bostwick DG, Cheng L eds. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008.

CALCIPHYLAXIS

DESCRIPTION Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare cutaneous-systemic disease seen with advanced chronic kidney disease. The classical clinical picture is a necrotic and progressive skin ulcer (reticular pattern), primarily in the lower legs and susceptible to local infection. It is a product of mural calcification and occlusion of cutaneous and subcutaneous arteries and arterioles. Calciphylaxis has been reported to occur in 1–4.5% of patients in dialysis, mostly in hemodialysis, with preponderance in patients who are obese, diabetic, present liver disease, are using systemic corticosteroids or have a calcium-phosphate product of >70 mg^2/dL. Calciphylaxis is reported to be a lethal complication with an estimated 1-yr survival rate of .8%. Mortality is usually reported as a result of local and systemic infections and sepsis. Sodium thiosulfate has been proposed as therapy for calciphylaxis with improvements with reduction of pain, inflammation, and healing of lesions (Image ☼).

REFERENCE
Marques SA, Kakuda AC2, Mendaçolli TJ2, et al. Calciphylaxis: A rare but potentially fatal event of chronic kidney disease. Case report. *An Bras Dermatol.* 2013;88(6 Suppl 1):44–47.

CALCIUM LOAD AND FAST STUDIES

DESCRIPTION Tests performed to evaluate hypercalciuria in stone-formers. 1 method is to place patients on a low-calcium, low sodium diet for 1 wk. A fast is performed from 9 PM–9 AM. At 7 AM, the patient empties his bladder. This urine is discarded. 600 mL of distilled water is then consumed. Urine is collected from 7 AM–9 AM. At 9 AM, 1 g of calcium is consumed, and urine is collected from that point until 1 PM. Urine samples are analyzed for calcium, creatinine, and cAMP. Results can then differentiate between absorptive hypercalciuria, renal hypercalciuria, and hyperparathyroidism. On a normal diet, 24-hr urinary calcium levels are considered <300 mg/d (7.5 mmol/d) in men and <250 mg/d (6.25 mmol/d) in women. (See also Section I: "Urolithiasis, Adult, General"; Section I: "Urolithiasis, Calcium Oxylate/Phosphate"; Section II: "Hypercalciuria [Absorptive, Renal and Resorptive].")

REFERENCE

Rivers K, Shetty S, Menon M. When and how to evaluate a patient with nephrolithiasis. *Urol Clin North Am*. 2000;27(2):203–213.

CALCIUM SUPPLEMENTATION AND UROLITHIASIS

DESCRIPTION Oral calcium supplementation may be used for a variety of conditions, including osteoporosis. Because calcium carbonate and calcium phosphate are widely used but poorly absorbed from the intestinal tract, these can increase urinary calcium excretion and promote calcium oxalate/phosphate stone disease. Calcium citrate (Citracal) has 950 mg of calcium citrate and 200 mg of elemental calcium in each tablet and increases urinary calcium excretion. However, this formulation also increases urinary citrate excretion, which potentially offsets the lithogenic potential of the calcium supplement–induced hypercalciuria. If calcium supplementation is to be considered to prevent osteoporosis, calcium citrate preparations should be used. In women with a history of stone disease, consider a 24-hr urine collection to identify those who will become or remain hypercalciuric while on calcium supplementation. In patients who are normocalciuric while receiving calcium citrate, no further intervention is necessary. In those patients found to be hypercalciuric, treatment with thiazide diuretics or slow-release potassium phosphate can be used.

REFERENCE

Heaney RP. Calcium supplementation and incident kidney stone risk: A systematic review. *J Am Coll Nutr*. 2008;27(5):519–527.

CAMEY I AND II ORTHOTOPIC URINARY DIVERSION

DESCRIPTION In the Camey I procedure, a 40-cm segment of the midportion of the ileum is chosen for an orthotopic urinary diversion that can reach the urethra. A LeDuc antireflux ureteral ileal anastomosis is carried out on each end of the ileal segment. In the Camey II version, the initial Camey I diversion is modified by using 65 cm of ileum, which is detubularized along its antimesenteric border. It is folded into a U-shape configuration, the adjoining sides of the U are sutured, and the resulting bowel is then folded again to create a pouch anastomosed to the urethra with a LeDuc ureteral anastomosis.

REFERENCE

Lilien OM, Camey M. 25-year experience with replacement of the human bladder (Camey procedure). *J Urol.* 2002;167(2 Pt 2):1161–1167.

CANAL OF NUCK HYDROCELE AND CYST (FEMALE HYDROCELE)

DESCRIPTION In the female, the labia majora are homologous to the scrotum in the male. The labia majora contain the terminal portion of the round ligaments of the uterus and an obliterated remnant of peritoneum similar to the tunica vaginalis, which may persist as the canal of Nuck. A hydrocele (fluid collection) may rarely form in the canal of Nuck.

REFERENCE

Dietrich CS 3rd, Gehrich A, Bakaya S. Surgical exposure and anatomy of the female pelvis. *Surg Clin N Am.* 2008;88(2):223–243.

CANDIDIASIS—CUTANEOUS, EXTERNAL GENITALIA

DESCRIPTION *Candida albicans,* the most common *Candida* fungus; rarely colonizes normal skin. Risk factors include the elderly, damaged skin, diabetes, broad-spectrum antibiotic use, steroids, pregnancy, and immunosuppression. Can involve warm, moist areas such as distal urethra, scrotum, inguinal region, glans penis of uncircumcised male and cause itching, burning, discharge, dryness, and dysuria in females (vulvovaginitis). Vesicopustules that enlarge and rupture can progresses to maceration and erythema. There are distinct red borders, often with satellite lesions with vaginal discharge being white and thick. Microscopic exam of scrapings or discharge with potassium hydroxide or Gram stain reveals hyphae/pseudohyphae. (For systemic candida, see Section I: “Fungal Infections, Genitourinary.”)

TREATMENT

- Keep affected areas dry and exposed to air
- Men: Topical Nystatin 100,000 U/d, miconazole cream QID
- Women vulvovaginitis: Oral fluconazole (single 150-mg dose) or topicals such as Nystatin 100,000–200,000 U/d for 1–2 wk

Clotrimazole troches or cream 100 mg/d for
3–7 days, others
More severe infections may require long-term
ketoconazole

REFERENCE

Margesson LJ. Vulvar disease pearls. *Dermatol Clin.* 2006;24(2):145–155.

CAPTOPRIL TEST

DESCRIPTION As a functional test for renovascular hypertension, plasma renin activity (PRA) is measured before and 1 hr after the administration of 25 mg of captopril. The test is considered positive if all of the following occur: Postcaptopril PRA >12 ng/mL/h, an absolute increase in PRA >10 ng/mL/h, and a 400% increase in baseline PRA (150%

increase if the baseline PRA was >3 ng/mL/h). A positive captopril test points to renovascular hypertension. The test has a sensitivity of ~74% and a specificity of 89%. All diuretics and ACE inhibitors must be discontinued 1 wk prior to the test, and a normal or light-sodium diet is necessary.

REFERENCE

Pickering TG, Blumenfeld JD, Laragh JH. Renovascular hypertension and ischemic nephropathy. In: Brenner BM, ed. *The Kidney*. 5th ed. Philadelphia, PA: Saunders; 1996:2106–2125.

CARCINOID TUMORS, GENITOURINARY

DESCRIPTION Very rare in the GU tract, carcinoid tumors have been described in the kidneys, ovaries, uterine cervix, urethra, testes, and bladder, and may have associated carcinoid syndrome. They are usually 5-hydroxyindoleacetic acid and argentaffin positive on special staining. Electron microscopy demonstrates granules similar to Kulchitsky cells. Primary treatment is surgical excision.

REFERENCE

Kaplan AL, Margolis DJ, Said J, et al. Primary carcinoid tumor of urinary bladder discovered on pelvic magnetic resonance imaging. *Urology*. 2012;80(5):55–57.

CARCINOSARCOMA, BLADDER

DESCRIPTION Rare tumor exhibiting elements of epithelial and mesenchymal origin. These usually are bulky, fast growing, invasive tumors. Epithelial elements are typically TCC, but they can be any of the other tumor types. Mesenchymal elements are usually spindle cells with evidence of chondroid, osteoid, smooth muscle, or rhabdomyoblastic differentiation. Usually presents with painless, gross hematuria.

TREATMENT

- Transurethral resection or radical cystectomy, as appropriate
- Chemotherapy and radiotherapy for metastatic disease, but outcomes are poor (Image ☼)

REFERENCE

Orsatti G, Corgan FJ, Goldberg SA. Carcinosarcoma of urothelial organs: Sequential involvement of urinary bladder, ureter, and renal pelvis. *Urology*. 1993;41(3):289–291.

CARCINOSARCOMA, PROSTATE

DESCRIPTION Very rare tumor, similar to the carcinosarcoma of the bladder. These tumors are mixtures of epithelial and sarcomatous elements. The epithelial element in the prostate, however, is adenocarcinoma. Most differentiate from collision tumors, which are separate coexisting tumors of differing cell types. True carcinosarcomas have an intermixture of cells in the same tumor. Has been described following radiation therapy. Treatment is RP, if organ-confined.

REFERENCES
Nazzeer T, Barada JH, Fisher HA, et al. Prostatic carcinosarcoma: Case report and review of literature. *J Urol*. 1991;146(5):1370–1373.
Tseng TY, Sevilla DW, Moul JW, et al. Prostatic carcinosarcoma 15 years after combined external beam radiation and brachytherapy for prostatic adenocarcinoma: A case report. *Prostate Cancer Prostatic Dis*. 2006;9:195–197.

CARNEY SYNDROME (CARNEY COMPLEX)

DESCRIPTION Also called familial myxoma, the syndrome is characterized by skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, and schwannomas. Primary pigmented nodular adrenocortical disease or PPNAD, which causes Cushing syndrome, is the most frequently observed endocrine tumor in Carney Complex or CNC, occurring in approximately 25%. Pale brown to black lentigines are the most common presenting feature of CNC and typically increase in number at puberty. Cardiac myxomas occur at a young age. Large-cell calcifying Sertoli cell tumors (LCCSCTs) are observed in 1/3 of affected males within the 1st decade and in almost all adult males. It is an autosomal dominant disorder. Carney complex gene 1 is the regulatory subunit 1A of protein kinase A (PRKAR1A) located at 17q22–24 and is present in about 60%. Prognosis depends on malignant spread of tumors.

TREATMENT
Open-heart surgery for cardiac myxomas; surgical excision of cutaneous and mammary myxoma; bilateral adrenalectomy for Cushing syndrome; transsphenoidal surgery for pituitary adenoma; surgery for cancerous thyroid adenomas; orchiectomy for boys with LCCSCT and gynecomastia to avoid premature epiphyseal fusion and induction of central precocious puberty; surgery to remove primary and/or metastatic psammo-matous melanotic schwannomas (*PMS*) of the spine

REFERENCE
Pagon RA, et al., eds. GeneReviews. http://www.ncbi.nlm.nih.gov/books/NBK1286/, Accessed March 2, 2014.

CARNEY TRIAD

DESCRIPTION Syndrome of tumors affecting at least 5 organs, the stomach, the lung, the paraganglionic system, the adrenal and the esophagus. Generally seen in young females; 80% of patients present before age 30 and 85% are females. Gastrointestinal stromal tumors (GISTs) of the stomach, lung chondroma, paraganglioma, adrenal adenoma, pheochromocytoma, and esophageal leiomyoma are syndrome-defining tumors. Of the classic triad, GIST is the most common presenting lesion (75%), followed by lung chondroma (15%) and paraganglionic tumor (10%). 1/5 of patients had a clinically nonfunctioning adrenal tumor. Generally accepted as a genetic disorder, it is not familial and the genetic etiology is unknown.

REFERENCE

Carney JA. Carney triad. *Front Horm Res*. 2013;41:92–110.

CARUNCLE, URETHRAL

DESCRIPTION An inflammatory lesion of the distal female urethra that usually presents as an asymptomatic urethral mass in the postmenopausal woman. Usually reddish in appearance and covered by mucosa, the lesion protrudes from the urethral meatus. The lesion may thrombose or necrose and may present with spotting of the underwear or even pain. Treatment may involve local estrogen replacement or simple excision. Excision should be considered for any atypical-appearing lesions as pathologically significant lesions such as melanoma have been known to mimic this lesion. (See also Section I: “Urethra, Mass.”)

REFERENCE

Park DS, Cho TW. Simple solution for urethral caruncle. *J Urol*. 2004;172(5 Pt 1):1884.

CASALE PROCEDURE

DESCRIPTION A variation of the Yang–Monti ileal tube, which is often too short to reach from the bladder to the skin surface. This procedure produces a long (12 cm) catheterizable tube (12–16 Fr) from a short (3.5 cm) segment of bowel, usually ileum. It was designed to take the place of the appendix as a continent channel for intermittent catheterization of the bladder utilizing the Mitrofanoff principle. To increase the canal length, as may be necessary in obese children, Casale used an initial segment that is twice as long, partially split in the middle, and then opened the segment in a spiral fashion on opposite sides to make a longer strip that can be tubularized in continuity. The long-term results of the Casale tube are comparable to those of the appendix and Yang–Monti tube in terms of durability, continence, and complication rate (Image ☼).

REFERENCE

Casale AJ. A long continent ileovesicostomy using a single piece of bowel. *J Urol*. 1999;162(5):1743–1745.

CAT-EYE SYNDROME

DESCRIPTION Also called *Schmid–Fraccaro syndrome*, a rare, congenital syndrome with features of coloboma of the iris and anal atresia with fistula, downslanting palpebral fissures, preauricular tags and/or pits, frequent occurrence of heart and renal malformations, and normal or near-normal mental development. The urologic abnormalities reported include various renal malformations, eg, absence of 1 or both kidneys, hydronephrosis, supernumerary kidneys or renal hypoplasia, chronic pyelonephritis, horseshoe kidney, hydronephrosis, and vesicoureteral reflux, and an associated additional chromosome 22. Close monitoring for possible pyelonephritis is warranted.

REFERENCE

Cat Eye Syndrome. Online Mendelian Inheritance in Man. http://omim.org/entry/115470, Accessed March 1, 2014.

CAUDA EQUINA SYNDROME

DESCRIPTION A term applied to the clinical picture resulting from compression of the cauda equina (or "horse tail") formed by nerve roots caudal to the level of spinal cord termination. This includes perineal sensory loss, loss of anal and urethral sphincter control, and loss of erections. The most common causes include posterior, central lumbar disc herniation, spinal stenosis, tumor, and trauma. Cauda equina syndrome is present in 1–5% of all prolapsed lumbar disks. Characteristically, the affected patient has an acontractile detrusor with no bladder sensation, and often an inactive sphincter EMG. Treatment consists of surgical relief of pressure, although the neurologic deficit can be permanent. On follow-up urodynamics, an acontractile detrusor and variable EMG activity may persist.

REFERENCE

Mauffrey C, Randhawa K, Lewis C, et al. Cauda equina syndrome: An anatomically driven review. *Br J Hosp Med (Lond)*. 2008;69(6):344–347.

CAUDAL REGRESSION SYNDROME

DESCRIPTION First described by Duhamel in 1961, this syndrome is caused by disordered embryogenesis during the 4th–5th wk of gestation. It features a wide array of abnormalities centering on the anorectal, urogenital, and lower spine areas. Severe cases demonstrate fusion of the lower limbs, sacral agenesis, imperforate anus, and absent GU tract (except gonads). In less severe cases, imperforate anus and/or sacral agenesis is seen. These, in turn, are associated with voiding dysfunction. Vesicoureteral reflux is also quite common. Managing the myriad problems requires a multidisciplinary approach.

SYNONYMS

- Caudal dysplasia sequence
- VACTER/VACTERL syndrome

REFERENCE

Boemers TM, van Gool JD, de Jong TP, et al. Urodynamic evaluation of children with the caudal regression syndrome (caudal dysplasia sequence). *J Urol*. 1994;151:1038–1040.

CAVERNOSOGRAPHY

DESCRIPTION A test used to evaluate veno-occlusive leak in erectile dysfunction. It is performed by the injection of contrast material into the corpora cavernosa after the injection of a pharmacologic agent, such as papaverine, to stimulate erection. Any visualized leakage of contrast material outside the corpora could be a defect in the veno-occlusive mechanism. Typical leak points include the glans, corpus spongiosum, superficial or deep dorsal veins, and cavernous and crural veins.

REFERENCE

Hsu GL, Hsieh CH, Wen HS, et al. Penile venous anatomy: An additional description and its clinical implication. *J Androl*. 2003;24(6):921–927.

CAVERNOSOMETRY

DESCRIPTION A test used to evaluate veno-occlusive leak in ED. Performed by 1st stimulating erection, either by saline infusion into the corpora or injection of a pharmacologic agent. Intracorporeal pressure measurements are then recorded. The inability to raise intracorporeal pressure to levels equal to systolic blood pressure or a rapid drop of pressure after cessation of infusion is indicative of veno-occlusive dysfunction.

REFERENCE

Vardi Y, Glina S, Mulhall JP, et al. Cavernosometry: Is it a dinosaur? *J Sex Med.* 2008;5(4):760–764.

CECIL URETHRAL STRICTURE REPAIR

DESCRIPTION The stricture is 1st excised, and the defect is closed with urethral skin. In the 2nd stage, a neourethra is created by tabularizing the ventral penile skin, as described by Thiersch. The penis is then buried in a mid-line scrotal incision. In the 3rd stage, the penis is freed from the scrotum, using scrotal skin to cover the ventrum of the penis, and the scrotum is primarily closed.

REFERENCE

Devine CJ, Devine PC. Operations for urethral stricture. In: Novick AC, et al., eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:650–680.

CECOURETEROCELE

DESCRIPTION A ureterocele is a congenital saccular dilatation of the terminal portion of the ureter. Cecoureteroceles are elongated beyond the ureterocele orifice by tunneling under the trigone and the urethra and represent a subtype of ureterocele.

REFERENCE

Smith EA, Parrott TS. The unsuspected cecoureterocele. *J Urol.* 1994;152(1):182–184.

CELLO SCROTUM

DESCRIPTION A published factitious medical condition in which a cello player irritates the scrotum. Admitted as a "hoax" condition in 2009.

REFERENCE

Murphy E, Murphy JM. Cello scrotum confession. Murphy's lore. *BMJ*. 2009;338:b288.

CEREBRAL PALSY, UROLOGIC CONSIDERATIONS

DESCRIPTION Cerebral palsy is a broad term describing a generally nonprogressive brain dysfunction occurring perinatally (up to age 3 yo by some definitions) with the consequence of long-term cerebral dysfunction. The etiology is thought to involve injury, infection, or a period of anoxia. The range of symptoms is broad, from mild mental retardation to severe developmental and motor delay. Surprisingly little is written on the exact urologic

manifestation of cerebral palsy, and even the incidence of urologic dysfunction is unclear. In some series, up to 36% of patients with cerebral palsy had lower urinary tract dysfunction. In another series, the most common symptoms included incontinence (74%), frequency (56%), and urgency (37%). The most common urodynamic findings were detrusor overactivity (DO) (87% of those undergoing urodynamics), with 25% of these exhibiting apparent striated sphincter dyssynergia. (See also Section I: "Neurogenic Bladder, General Considerations.")

REFERENCE

Ozturk M, Oktem F, Kisioglu N, et al. Bladder and bowel control in children with cerebral palsy: Case-control study. *Croat Med J*. 2006;47(2):264–270.

CERVICAL CANCER, UROLOGIC CONSIDERATIONS

DESCRIPTION Iatrogenic complications regarding cervical cancer treatment are well documented. If pelvic exenteration is performed, urinary diversion is obligatory. Radical hysterectomy has risks of ureteral and bladder damage, which may result in a fistula. Radiation therapy also can be morbid, with radiation cystitis, ureteral stricture, and fistula possibly resulting. The increased risk of bladder cancer after radiation therapy is controversial. (See also Section VII: "TNM Staging.")

REFERENCE

Magerina JF. Complication of irradiation and radical surgery for gynecologic malignancies. *Obstet Gynecol Surv*. 1993;48(8):571–575.

CHANCROID

DESCRIPTION An STD/STI caused by *Haemophilus ducreyi* and relatively uncommon in the United States but a common STD/STI in developing countries. The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid. *H. ducreyi* is a gram-negative coccobacilli and resembles a "school of fish" on Gram stain (clumping in long parallel strands). Incubation is 4–10 days and the ulcer is 1–2 cm, nonindurated, purulent, and ragged with painful adenopathy in over 50%. Sites include the distal penis in men and labia and vagina in women. Diagnosis is based on clinical findings. No FDA-cleared PCR test for *H. ducreyi* is available in the United States, but such testing can be performed by clinical labs that have developed their own PCR test and have conducted a CLIA verification study. A probable diagnosis of chancroid, for both clinical and surveillance purposes, can be made if all of the following criteria are met: (1) the patient has 1 or more painful genital ulcers; (2) the patient has no evidence of *Treponema pallidum* infection by darkfield exam of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; (3) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and 4) a test for HSV performed on the ulcer exudate is negative.

TREATMENT

Recommended treatment is a single dose of azithromycin 1 g PO or ceftriaxone 250 mg IM or ciprofloxacin 500 mg PO BID × 3 days (contraindicated if pregnant or lactating) or

erythromycin base 500 mg PO TID for 7 days. (See also Section I: "Sexually Transmitted Infections [STIs] and Sexually Transmitted Diseases [STDs], General.")

REFERENCE

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR Recomm Rep*. 2010;59 (No. RR-12):1–110.

CHARCOT-BOETTCHER CRYSTALS AND FILAMENTS

DESCRIPTION A normal ultrastructural component of human Sertoli cells observable with electron microscopy. Can be used to establish Sertoli origin in atypical sex cord-stromal tumors.

REFERENCE

Jarzembowski JA, Lieberman RW. Pediatric sex cord-stromal tumor with composite morphology: A case report. *Pediatr Dev Pathol*. 2005;8(6):680–684.

CHARGE ASSOCIATION

DESCRIPTION CHARGE refers to the association of coloboma, congenital heart disease, choanal atresia, retarded growth and development, structural brain abnormalities, and ear anomalies. Of urologic interest is the association with genital hypoplasia secondary to low androgen levels. Mostly sporadic, but a familial form has been reported. It is theorized to originate during a developmental error of neural crest elements at about the 6th wk.

Early management of sensory defects is important. Androgen replacement is used for genital hypoplasia.

REFERENCE

Harvey AS, Leaper PM, Bankier A. CHARGE association: Clinical manifestations and developmental outcome. *Am J Med Genet*. 1991;39:48–55.

CHEMOTHERAPY TOXICITY, UROLOGIC CONSIDERATIONS

DESCRIPTION All chemotherapeutic agents have potentially significant toxicities and side effects. For the urologic surgeon, certain toxicities may be more commonly encountered. Both commonly used chemotherapeutic regimens for urothelial carcinoma, methotrexate/vinblastine/adriamycin/cisplatinum and gemcitabine/cisplatinum have significant nephrotoxicity, which can be problematic for older patients or patients with renal insufficiency or malignant ureteral obstruction. Bleomycin, used for nonseminomatous germ cell tumors as part of the bleomycin, etoposide, cisplatinum (BEP) regimen causes pulmonary toxicity. If postchemotherapy retroperitoneal lymphadenectomy is necessary, the anesthetist should be counseled to avoid high inspired oxygen concentrations and minimize crystalloid fluid resuscitation, as these factors may exacerbate bleomycin-related pulmonary toxicity. Cyclophosphamide may cause hemorrhagic cystitis because of its toxic downstream metabolite, acrolein, which is excreted into the urine. Administering the agent Mesna decreases this toxicity. Cyclophosphamide also increases the risk of subsequent bladder cancer up to 9-fold. (See also Section II: "Bleomycin Toxicity.")

REFERENCES
Baniel J, Foster RS, Rowland RG, et al. Complications of postchemotherapy retroperitoneal lymph node dissection. *J Urol.* 1995;153:976–980.
Vlaovic R, Jewett AS. Cyclophosphamide induced bladder cancer. *Can J Urol.* 1999;6:745–748.

CHLAMYDIA SEXUALLY TRANSMITTED DISEASE

DESCRIPTION Chlamydia is the most common bacterial STD in the world. Although often asymptomatic (up to 70% in women), it may cause urethritis, cervicitis, pelvic inflammatory disease (PID) in women, and prostatitis and epididymitis in men. In young sexually active males, it is the most common cause of epididymitis. *Chlamydia trachomatis* is an intracellular bacterium and does not grow in standard urine culture preparations. Nucleic acid amplification test by PCR of urine specimen is an effective diagnostic and screening tool. Alternatively, specialized cultures of urethral or cervical swabs can be performed. Treatment with azithromycin 1 g PO as a single dose or doxycycline 100 mg BID for 7 days is standard treatment. In pregnancy, erythromycin base 500 mg QID for 7 days is a safe alternative. Screening of sexual partners is recommended. (See also Section I: “Sexually Transmitted Diseases [STDs], General.”)

REFERENCE
Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR Recomm Rep.* 2010;59 (No. RR-12):1–110.

CHRISTMAS TREE BLADDER

DESCRIPTION A radiologic change in the bladder wall caused by detrusor muscle hypotrophy and fibrosis as a result of detrusor-sphincter dyssynergia. Also called *pinecone appearance.*

REFERENCE
Genitourinary system and retroperitoneum. In: Mettler FA, ed. *Essentials of Radiology*. 2nd ed. Philadelphia, PA: Saunders; 2005.

CHRONIC KIDNEY DISEASE (CKD)

DESCRIPTION The Kidney Disease Improving Global Outcomes (KDIGO) organization developed updated clinical practice guidelines in 2012 to provide guidance on the evaluation, management, and treatment of chronic kidney disease (CKD) in adults and children who are not receiving renal replacement therapy (see table). CKD is defined as the presence of kidney damage (usually detected as urinary albumin excretion of ≥ 30 mg/day, or equivalent) or decreased kidney function (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/ 1.73 m^2) for 3 or more months, irrespective of the cause. The persistence of the damage or decreased function for at least 3 mo is necessary to distinguish CKD from acute kidney disease (AKI). The term “end-stage renal disease” (ESRD) generally refers to CKD treated with either dialysis or transplantation. Identifying the cause of kidney disease (eg,

diabetes, drug toxicity, auto-immune diseases, urinary tract obstruction, kidney transplantation) enables specific therapy directed at preventing further injury. In addition, the cause of kidney disease has implications for the rate of progression and the risk of complications. The purpose of CKD staging is to guide management (risk for progression and complications of CKD). (See also Section I: "Chronic Kidney Disease, Adult [Renal Failure, Chronic]."")

Revised Chronic Kidney Disease (CKD) Classification Based Upon Glomerular Filtration Rate and Albuminuria

GFR Stages	GFR (mL/min/1.73 m^2)	Terms
G1	>90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)
Albuminuria Stages	**AER (mg/d)**	**Terms**
A1	<30	Normal to mildly increased (may be subdivided for risk prediction)
A2	30–300	Moderately increased
A3	>300	Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)

The cause of CKD is also included in the KDIGO revised classification but is not included in this table. GFR: glomerular filtration rate; AER: albumin excretion rate; CKD: chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcomes. (Reproduced with permission from Wolters Kluwer: Levey, AS and Inker LA. Definition and staging of chronic kidney disease in adults in UpToDate.com. Accessed March 2, 2014.)

REFERENCES

KDIGO. Summary of recommendation statements. *Kidney Int.* 2013;3(Suppl):5.
National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39 (Suppl 1):S1.

CHRONIC PELVIC PAIN SYNDROME/CHRONIC PROSTATITIS (CPPS/CP) IN MALES

DESCRIPTION Chronic pelvic pain syndrome (CPPS) is a diagnosis that can be made in either a man or a woman. Guidelines define CPPS/CP in males as CPP for at least 3 of the preceding 6 mo in the absence of other identifiable causes. Older terms used include prostatodynia and abacterial prostatitis.

- Males: Guidelines define CPPS as CPP for at least 3 of the preceding 6 mo in the absence of other identifiable causes. Sometimes referred to as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical syndrome. The symptomatology is based on urologic symptoms and/or pelvic pain or discomfort. While the term "prostatitis" is often used it is unclear to what degree the prostate is the cause of symptoms. Nonbacterial prostatitis occurs in men with no history of urinary tract infection and negative bacterial cultures of urine and prostatic fluid. The inflammatory type (NIH III A. Chronic prostatitis/pelvic pain syndrome, inflammatory) presents with GU or rectal pain or voiding symptoms; the prostatic fluid contains inflammatory cells. Men with the noninflammatory type (NIH IIIB. Chronic prostatitis/pelvic pain syndrome, noninflammatory), whose prostatic fluid has no leukocytes, have similar symptoms, but pelvic pain is usually the predominant complaint. (See Section I: "Prostatitis, Chronic, Nonbacterial, Inflammatory [NIH CP/CPPS III A]";

Section I: “Prostatitis, Chronic Nonbacterial, Noninflammatory [NIH CP/CPPS III B]”; Section II: “Pelvic Pain, Male.”)

TREATMENT

- Empiric 8–12 wk course of antibiotics
- Consider prostatic massage, if no response
- High-dose α-blockers (Flomax, Cardura, Hytrin)
- Anti-inflammatory agents, lifestyle changes, stress reduction, holistic therapies

REFERENCE

Nickel JC, Shoskes DA, Wagenlehner FM. Management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): The studies, the evidence, and the impact. *World J Urol.* 2013;31(4):747–753.

CHRONIC PELVIC PAIN SYNDROME (CPPS) IN FEMALES

DESCRIPTION CPPS is a diagnosis that can be made in either a man or a woman. In women it is pain of at least 6-mo duration. The pain location is below the umbilicus and is usually severe enough to result in functional disability or need treatment. See table for causes. The best treatment plan for CPP is based upon shared decision making by the clinician and patient. A combination of treatments may be the optimal approach. (See also “Section I: Pelvic Pain, Female.”)

Conditions Associated with Chronic Pelvic Pain in Women
Gynecologic
Endometriosis
Chronic pelvic inflammatory disease
Pelvic adhesions
Pelvic congestion (pelvic varicosities)
Adenomyosis
Ovarian remnant syndrome
Residual ovary syndrome
Leiomyoma
Endosalpingiosis
Neoplasia
Fallopian tubal prolapse (posthysterectomy)
Tuberculous salpingitis
Benign cystic mesothelioma
Postoperative peritoneal cysts
Mental health issues
Somatization
Substance abuse
Physical and sexual abuse
Depression
Sleep disorders
Urinary tract
Interstitial cystitis/painful bladder syndrome
Recurrent urinary tract infection
Urethral diverticulum
Chronic urethral syndrome
Neoplasia
Radiation cystitis
Gastrointestinal tract
Irritable bowel syndrome
Inflammatory bowel disease and other causes of colitis
Diverticular colitis
Chronic intermittent bowel obstruction
Neoplasia
Chronic constipation
Celiac disease (Celiac sprue)
Musculoskeletal
Pelvic floor myalgia
Myofascial pain (trigger points)
Coccygodynia
Piriformis syndrome
Hernia
Abnormal posture
Fibromyalgia
Peripartum pelvic pain syndrome
Neurologic disorders
Neuralgia, especially of the iliohypogastric, ilioinguinal, genitofemoral, or pudendal nerves
Herniated nucleus pulposus
Neoplasia
Neuropathic pain
Abdominal epilepsy
Abdominal migraine

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REFERENCE

Howard F. Causes of chronic pelvic pain in women. in UpToDate.com Wolters Kluwer, Accessed March 2, 2014.

CHRONIC PROSTATITIS SYMPTOM INDEX (CPSI)/NIH-CPSI (NATIONAL INSTITUTES OF HEALTH CPSI)

DESCRIPTION The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), a reliable validated instrument developed by the NIH Chronic Prostatitis Collaborative Research Network to aid in the quantification of chronic prostatitis symptoms. The NIH-CPSI

is intended for clinical practice as well as research protocols. The instrument contains 9 questions. The major domains relate to pain (location, severity, frequency), the nature of voiding (irritative and obstructive symptoms), and the impact of prostatitis on quality of life. The goal of this multi-institutional collaborative effort was to define and measure the symptoms of chronic prostatitis and their impact on the daily lives of patients. The test is self-administered and can be completed in 5 min. Higher scores indicate worse outcomes in all domains, with a possible maximum score of 43. (See also Section I: "Prostatitis, Chronic Nonbacterial, Inflammatory & Noninflammatory (NIH CP/CPPS III A and B)," "Prostatitis, General" and "Section VII: Reference Tables: National Institutes of Health (NIH) Chronic Prostatitis Symptom Index [CPSI].").

REFERENCES

Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol.* 1999;162:369–375.

CHURG-STRAUSS SYNDROME

DESCRIPTION Also called *allergic angiitis and granulomatosis*, this is a vasculitis characterized by extravascular microscopic granulomas in the lungs, heart, GI tract, and skin. Histologically, necrosis and intense eosinophilic infiltration accompanied by histiocytes are seen. Both necrotizing and eosinophilic granulomatous vasculitis usually involve small arteries and veins, often with a history of atopy. Patients present with fever and weight loss. Eosinophilia, anemia, and an elevated ESR are found. The prostate may be involved by the granulomatous process. Treatment involving corticosteroids with cytotoxic drugs is being investigated.

REFERENCE

Langford CA, Sneller MC. New developments in the treatment of Wegener's granulomatosis, polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. *Curr Opin Rheumatol.* 1997;9(1):26–39.

CHYLOCELE

DESCRIPTION Also called *filarial hydrocele*, chylocele is a cyst-like collection of lymphatic fluid/drainage into the tunica vaginalis around the testis. The fluid is usually described as milky and contains leukocytes. This may result from lymphatic disruption secondary to diseases such as filariasis. Filariasis affects 120 million people in >80 countries and is caused by *Wuchereria bancrofti,* which is transmitted by mosquitoes. Chyloceles usually do not resolve after needle aspiration and require the underlying cause to be surgically or medically addressed. Freedom from infection at the time of surgery is critical for a favorable outcome. (See also "Section I: Scrotum and Testicle, Mass.")

TREATMENT

- Vertical scrotal incision with complete excision of tunica vaginalis sac
- Orchiectomy and chordectomy for severe cases

- Medical treatment of filariasis (diethylcarbamazine, ivermectin, albendazole)

REFERENCE

DeVries CR. The role of the urologist in the treatment and elimination of lymphatic filariasis worldwide. *BJU Int.* 2002;89(S1):37–43.

CIRCUMCISION, FEMALE

DESCRIPTION Female genital cutting, also known as female circumcision or genital mutilation, is a culturally determined practice, predominantly performed in parts of Africa and Asia. The World Health Organization classified female genital cutting into 4 types of procedures.

- Type I consists of excision of the prepuce, with or without excision of part or all of the clitoris.
- Type II involves clitoridectomy and partial or total excision of the labia minora.
- Type III, or infibulation, includes removing part or all of the external genitalia and reapproximation of the remnant labia majora, leaving a small neointroitus.
- Type IV involves other forms of injuries to the genital region including pricking, piercing, stretching, burning, scraping, or any other manipulation of external genitalia.

Short-term urologic problems with the procedure include urethral edema and urinary retention potential. Long-term problems include dysmenorrhea, dyspareunia, fibrosis, keloids, sebaceous cysts, vulvar abscesses, infertility, and difficulty with pelvic exams, coitus, and vaginal delivery. Urologic issues include chronic UTI, voiding difficulties, urethral strictures, meatal obstruction meatitis, and urinary crystals.

REFERENCE

Nour NM. Female genital cutting (circumcision). In UpToDate.com, Accessed March 8, 2014.

CISPLATIN TOXICITY

DESCRIPTION Cisplatin is a very commonly used antitumor agent with significant adverse effects. Administered in urology for urothelial carcinoma and testicular cancer, its nephrotoxicity is cumulative and dose-dependent, and commonly limits use. Other significant effects include myelosuppression, ototoxicity, GI disturbances, and neurotoxicity. (See also Section II: “Chemotherapy Toxicity, Urologic Considerations.”)

TREATMENT

- Amifostine has been used to limit toxicity.
- Use of other platinum-based compounds may decrease toxicity while maintaining efficacy.

REFERENCE

Schellens JH, Pronk LC, Verweij J. Emerging drug treatments for solid tumors. *Drugs*. 1996;51(1):45–72.

CLITORAL LENGTH

DESCRIPTION Anatomically the clitoris is composed of the glans clitoris and the crura, its

dimensions are generally independent of BMI, age, and height. Average length of the glans clitoris is 5.1 +/– 1.4 mm. Total average clitoral length from the tip of the glans to the insertion of the crura on the pubis is 16.0 +/– 4.3 mm. Multiparous women have slightly larger clitoral dimensions than nulliparous women with a total length on average 0.9 mm greater and a glans length 0.5 mm greater. (See also Section II: "Clitoromegaly.")

REFERENCE

Verkauf BS, Von Thron J, O'Brien WF, et al. Clitoral size in normal women. *Obstet Gynecol.* 1992;80(1):41–44.

CLITORAL PRIAPISM

DESCRIPTION A rare condition that is associated with an extended duration of clitoral erection due to local engorgement of clitoral tissue causing clitoral or vulvar pain. The prolonged erection is not associated with sexual stimulation, and can last from minutes to days. It has been associated with medications: α-blockers, inhibitors of serotonin reuptake (SSRI antidepressants), and non-SSRI antidepressants and with TCC obstructing venous and lymphatic outflow. Stopping the offending agent can result in resolution within 24–72 hr. Other treatments reported: Imipramine, NSAIDs, ice packs, opiates, and, rarely, intracavernous injection of adrenaline. (See also Section II: "Clitoromegaly.")

REFERENCE

Gharahbaghian L. Clitoral Priapism with No Known Risk Factors. *West J Emerg Med.* 2008;9(4):235–237.

CLITOROMEGALY

DESCRIPTION Enlargement of the clitoris is most commonly see in newborns. When noted, the practitioner must consider the possibility of intersex issues. The condition may be so severe as to appear as a normal male penis, although chordee is also usually present. Virilization is most commonly secondary to CAH. The underlying cause must be addressed. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Congenital Adrenal Hyperplasia.")

REFERENCE

Rink RC, Kaefer M. Surgical management of disorders of sexual differentiation, cloacal malformation, and other abnormalities of the genitalia in girls. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3629–3666.

CLONIDINE SUPPRESSION TEST

DESCRIPTION A test sometimes used to rule out pheochromocytoma. Clonidine (0.3 mg) is administered and plasma norepinephrine levels are then measured. Those patients with essential hypertension with an elevation of norepinephrine levels will experience a 50% decrease in this catecholamine level. Patients with pheochromocytoma will not be suppressed. Patients should not be taking diuretics, β-blockers, or tricyclic antidepressants; α-blockers do not interfere with the test.

REFERENCE

Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: How to distinguish true- from false-positive test results. *J Clin Endocrinol Metab*. 2003;88(6):2656–2666.

CLOSTRIDIUM DIFFICILE COLITIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Also known as *pseudomembranous enterocolitis*, this is a potentially life-threatening infection of the colon due to overgrowth of *C. difficile*. It can be precipitated by antibiotic therapy – most commonly fluoroquinolones, clindamycin, cephalosporins, and penicillins – but any antibiotic can be implicated. This suppression of normal bowel flora by antibiotics and overgrowth of *C. difficile* has been reported in association with bowel preparation prior to elective surgery, as well as in addition to the use of antibiotics for any indication. Watery diarrhea and abdominal pain are the main symptoms of *C. difficile* infection, but it can range from the asymptomatic carrier state, diarrhea with colitis, or pseudomembranous colitis (endoscopic evidence of "pseudomembranes"), to severe life-threatening disease with toxic megacolon. Low-grade fever and leucocytosis are common. It is diagnosed by classic endoscopic findings, culture of organism, or detection of toxin in stool. Enzyme immunoassay (EIA) allows the direct detection of *C. difficile* toxin and is the test of choice.

TREATMENT

- Removal of antibiotic therapy. If antibiotic therapy is essential, attempt to use an agent with lesser likelihood of causing *C. difficile* overgrowth (aminoglycosides, macrolides, sulfonamides, tetracycline, or vancomycin).
- Metronidazole (500 mg TID or 250 mg QID) is recommended as initial treatment of less severe cases. If needed, IV metronidazole 500 mg q8h; treat for 10–14 days with follow-up toxin assay.
- Alternatively, oral vancomycin 125 mg QID.

REFERENCE

Kelly CP, LaMont JT. *Clostridium difficile*: More difficult than ever. *N Engl J Med*. 2008;59:1932–1940.

CLOT RETENTION

DESCRIPTION The culmination of visible blood in the urine that has formed clots within the bladder. The presence of blood clots impede the outflow of urine via the urethra and result in urinary obstruction. If not addressed emergently, clot retention can lead to pain, abdominal distension, hydroureteronephrosis, and bladder rupture.

TREATMENT

- Bedside insertion of urinary catheter for drainage and evacuation of blood clots
- May require operative cystoscopy and treatment of underlying cause of hematuria
- Correction of blood coagulation disorders

REFERENCE

Hicks D, Li C. Management of macroscopic hematuria in the emergency department. *EMJ*. 2007;24:385–390.

COBB COLLAR

DESCRIPTION Congenital narrowing of the bulbar urethra that can present with hematuria, UTI, or weak stream. Endoscopy and retrograde urethrogram reveal a bulbar urethral narrowing. The obstructing membrane is located just distal to the external sphincter and is reinforced by a fold extending from the verumontanum. Treatment is endoscopic resection.

SYNONYMS
- Moerman rings
- Congenital obstructive posterior urethral membrane

TREATMENT
Endoscopic resection

REFERENCE
Dewan PA, Keenan RJ, Morris LL, et al. Congenital urethral obstruction: Cobb's collar or prolapsed congenital obstructive posterior urethral membrane (COPUM). *Br J Urol*. 1994;73(1):91–96.

COBRA HEAD SIGN

DESCRIPTION The radiologic appearance on an intravenous urogram (IVU) of an intravesical ureterocele of a single ureter in an adult, also called *spring onion sign*. The dilated ureterocele, filled with contrast material, protrudes into the bladder, which is also filled with contrast material, but is separated from it by a thin radiolucent halo. The ureterocele might be congenital or acquired, as in cases of trauma or inflammation.

REFERENCE
Nussbaum AR, Dorst JP, Jeffs RD, et al. Ectopic ureter and ureterocele: Their varied radiographic manifestations. *Radiology*. 1986;159:227–235.

COCCIDIOMYCOSIS, GENITOURINARY

DESCRIPTION Outbreaks of *Coccidioides immitis* infection are common when people are exposed to dust that contains the spore. An opportunistic infection more common in patients <5 and >50 yo, it is associated with AIDS, steroid use, and chemotherapy for malignancy. After pulmonary inoculation, the patient can develop erythema nodosum (valley bumps or valley fever). Chest radiographs demonstrate infiltrates with cavitation. Serologic tests are available to help establish the diagnosis. Disseminated disease involves the kidney in up to 65%, the adrenal in 16–32%, and the prostate in 6%. Renal coccidiomycosis may cause similar changes, as seen in renal TB (moth-eaten calyces, infundibular stenosis, ureteral stricture, and calcifications). Prostatic infection with occasional abscess and scrotal infections with fistulas have been reported. Epididymal and prostatic involvement can demonstrate necrotizing and nonnecrotizing granulomas. Therapy includes up to 2 g of amphotericin, with 1 year of ketoconazole (200 mg/d).

REFERENCE

Wise GJ, Freyle J. Changing patterns in genitourinary fungal infections. *AUA Update.* Vol. XVI, Lesson 1, 1997.

COHEN ("CROSS-TRIGONAL") URETERAL REIMPLANTATION

DESCRIPTION Through a transvesical approach, the ureter is mobilized from its hiatus and delivered through a submucosal tunnel to the contralateral side of the trigone. A cross-trigonal reimplantation is then carried out by reanastomosing the ureter to the bladder.

REFERENCE

Khoury AE, Bagli DJ. Vesicoureteral Reflux. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3267–3309.

COITAL INCONTINENCE (COITAL LEAKAGE/INTERCOURSE INCONTINENCE)

DESCRIPTION Recent attention has focused on loss of urine during intercourse termed "coital incontinence." Loss of vaginal fluids during sexual activity is not well studied and the term "female ejaculation" has become a popular term. Although the exact pathophysiology is poorly understood this phenomenon may include urinary incontinence during sexual activity. In 1 series 60% of women with a history of urinary incontinence reported urinary leakage during intercourse. Coital incontinence is considered in the spectrum of stress urinary incontinence (SUI) and pelvic organ prolapse by some authors. Urethral sphincter incompetence has also been suggested as part of the pathophysiology. Many women with detrusor overactivity (DO) leak during sex; however, the potential role of associated urethral incompetence needs further investigation. Quality of life appears negatively impacted by this condition. (See also Section I: "Incontinence, Urinary, Adult Female and Section II; "Ejaculation, Female.")

REFERENCES

El-Azab AS, Yousef HA, Seifeldein GS. Coital incontinence: Relation to detrusor overactivity and stress incontinence. *Neurourol Urodyn.* 2011;30(4):520–524.

Jha S, Strelley K, Radley S. Incontinence during intercourse: Myths unravelled. *Int Urogynecol J.* 2012;23(5):633–637.

COLLECTING SYSTEM DUPLICATION, COMPLETE

DESCRIPTION Duplicated collecting systems (also known as duplex collecting systems) can be defined as renal units containing 2 pyelocaliceal systems that are associated with a single ureter or with double ureters. The 2 ureters empty separately into the bladder or fuse to form a single ureteral orifice. Associated problems include upper-pole hydronephrosis from stenosis, ectopic insertion of the upper-pole ureter, ureterocele of the upper-pole ureter, and reflux involving the lower pole. Duplex collecting systems can be unilateral or bilateral and can be associated with obstruction, reflux, and infection. Caused by early ureteral bud bifurcation or the occurrence of 2 ureteral buds from the wolffian duct during renal

embryogenesis.

REFERENCE

Glassberg KI, Braren V, Duckett JW, et al. Suggested terminology for duplex systems, ectopic ureters and ureteroceles. *J Urol*. 1984;132(6):1153–1154.

COLON AND RECTAL CANCER, UROLOGIC CONSIDERATIONS

DESCRIPTION Colorectal cancer may present as locally invasive lesions that involve the bladder and/or prostate. En-bloc resection (pelvic exenteration) of the bladder and rectum/colon is sometimes indicated. In colorectal malignancies, a 7–12% incidence of locoregional extension into the adjacent organs has been reported, with the bladder as the most commonly involved organ. In women, the interposition of the uterus between the colon and bladder makes the incidence lower. In cases of more proximal colon cancers, ureteral and renal involvement may require localization with ureteral catheters. After extensive colorectal dissection, erectile and bladder dysfunction may occur secondary to disruption of the pelvic plexus up to 70% of the time. (See also Section I: “Neurogenic Bladder, General” and Section VII: “TNM.”)

REFERENCE

Calpista A, Lai S, Agostini A, et al. Functional urological complications after colorectal cancer surgery. *Pelviperineology*. 2007;26(1):38–40.

COLUMN OF BERTIN, HYPERTROPHIED

DESCRIPTION A normal anatomic structure of the kidney, which, if enlarged, can be mistaken for a renal mass. It normally appears as granular material in the renal sinus, which is simply cortex. The column of Bertin is located between the pyramids. (See also Section II: “Renal Pseudotumors.”)

REFERENCE

Anderson JK, Cadeddu JA. Surgical Anatomy of the Retroperitoneum, Adrenals, Kidneys and Ureters. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3–32.

COMPARTMENT SYNDROME, UROLOGIC CONSIDERATIONS

DESCRIPTION Compartment syndrome, defined by the rise of pressure in a tissue compartment compromising circulation, can result in devastating consequences, especially in the urologic setting. Reports of compartment syndrome leading to rhabdomyolysis, renal failure, and limb loss have been reported with the dorsal lithotomy position, flank position during open or laparoscopic procedures, prolonged reconstructive pediatric procedures, and urethral and perineal surgeries. Recently there has been an increase in reports relating to robotic prostatectomy. In abdominal compartment syndrome, a Foley catheter can be used to provide continuous abdominal compartment pressure readings.

The etiology of compartment syndrome is multifactorial and prevention is the mainstay of treatment. Positioning and other efforts to prevent acute lower extremity compartment

syndrome include limiting the time of leg elevation, positioning the leg below the level of the atrium and postoperative monitoring of patients at risk. Pulse oximetry to detect hypoperfusion has been reported. The 6 "Ps" associated with compartment syndrome are: Pain out of proportion based on exam, paresthesia, pallor, paralysis, pulselessness, and pressure. Fasciotomy may be necessary to relive pressure and restore extremity perfusion. Although debated, measured compartment pressure of 30 mm Hg is a generally accepted indication for lower extremity fasciotomy. (See also Section I: "Rhabdomyolysis.")

REFERENCES

Bocca G, van Moorselaar JA, Feitz WF, et al. Compartment syndrome, rhabdomyolysis and risk of acute renal failure as complications of the lithotomy position. *J Nephrol*. 2002;15:183–185.

Sukhu T, Krupski TL. Patient positioning and prevention of injuries in patients undergoing laparoscopic and robot-assisted urologic procedures. *Curr Urol Rep*. 2014;15(4):398.

COMPULSIVE MASTERBATION

DESCRIPTION Masturbation is the deliberate stimulation of the genitalia in order to achieve sexual arousal. Compulsive masturbation, like all compulsive behaviors, may be included in the spectrum of anxiety disorders. Compulsive behaviors are meant to reduce anxiety, fear, worry, or apprehension. Patients with compulsive disorders are unable to inhibit their behaviors, even after they become maladaptive, regardless of consequences. Most frequently seen in patients with psychiatric disorders such as autism, schizophrenia, and personality disorders. May be seen with dementia and Parkinson disease.

REFERENCE

Calabro RS, Galì A, Marino S, et al. Compulsive masturbation and chronic penile lymphedema. *Arch Sex Behav*. 2012;41(3):737–739.

CONDYLOMATA LATA

DESCRIPTION Also called *flat condyloma*, these moist or mucous papules are found in the skin folds of syphilis patients and reflect the secondary stage of syphilis. They secrete serous fluid and can be covered by a layer of epidermal debris. They represent the hematogenous spread of spirochetes. (See also Section I: "Syphilis.") (Image ☼)

TREATMENT

- Single dose of penicillin G (benzyl penicillin) 2.4 million units IM *OR*
- IM ceftriaxone 1,000 mg/d for 10 days *OR*
- Oral tetracycline 500 mg QID for 14 days *OR*
- Oral doxycycline 100 mg BID for 14 days

REFERENCE

Lautenschlager S. Cutaneous manifestations of syphilis: Recognition and management. *Am J Clin Dermatol*. 2006;7(5):291–304.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

DESCRIPTION The adrenal cortex secretes 2 compounds, DHEA and androstenedione, that require conversion to testosterone in peripheral tissues for their androgenic effects. CAH represents a group of autosomal-recessive, inherited metabolic errors, each characterized by a deficiency or total lack of a particular enzyme involved in the biosynthesis of cortical steroids, particularly cortisol. Steroidogenesis is then channeled into other pathways, leading to increased production of androgens, which accounts for virilization. Simultaneously, the deficiency of cortisol results in increased secretion of ACTH, resulting in adrenal hyperplasia. Certain enzyme defects may also impair aldosterone secretion, adding salt wasting to the virilizing syndrome. The most commonly recognized forms are 21-hydroxylase deficiency (>90%) and 11-hydroxylase deficiency (5–8%). The spectrum of presentation is substantial, resulting from the compound heterozygosity and multiple etiologies in this disease continuum. Phenotypic manifestations include ambiguous genitalia (CAH is the most common reason in newborns), clitoromegaly, labioscrotal fusion, and hypospadias. Clinical CAH subtypes include (1) salt wasters (virilization and aldosterone deficiency), (2) simple virilizers (virilization without salt wasting), and (3) nonclassic patients (no virilization or wasting). In the salt-wasting variant, symptoms begin weeks after birth with weight loss, failure to thrive, vomiting, dehydration, and life-threatening adrenal crisis. In virilizers, sexual precocity is the hallmark of disease. Diagnosis is often made from markedly elevated levels of serum 17-hydroxyprogesterone and progesterone (with 21-OH deficiency), but may also present as elevated 11-deoxycortisol and 11-DOC (with 11-OH deficiency). (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "11β-hydroxylase (CYP11B1) deficiency and 21-Hydroxylase (CYP21A2) Deficiency.")

Congenital Adrenal Hyperplasia: Features for Each Enzyme Defect

Feature	21-Hydroxylase Deficiency	11β-Hydroxylase Deficiency	17α-Hydroxylase Deficiency	3β-Hydroxysteroid Deficiency	Lipoid Hyperplasia	Aldosterone Synthase Deficiency
Incidence	1:15,000	1:100,000	Rare	Rare	Rare	Rare
Defective gene	CYP21	CYP11B1	CYP17	HSD3B2	StAR	CYP11B2
Chromosomal localization	6p21.3	8q24.3	10q24.3	1p13.1	8p11.2	8q24.3
Ambiguous genitalia	+ (female)	+ (female)	+ (male) Absent puberty (female)	+ (male) Mild in female	+ (male) Absent puberty (female)	No
Acute adrenal insufficiency	+	Rare	No	+	++	Salt wasting only
Hormones:						
Glucocorticoids	Reduced	Reduced	Reduced	Corticosterone normal	Reduced	Normal
Mineralocorticoids	Reduced	Increased	Reduced	Increased	Reduced	Reduced
Androgens	Increased	Increased	Reduced	Reduced (male) Increased (female)	Reduced	Normal
Elevated hormonal metabolite	17-Hydroxy-progesterone	DOC, 11-deoxycortisol	Corticosterone, DOC	DHEA, 17Δ^5-pregnenolone	None	Corticosterone, 18-OHB
Blood pressure	Decreased	Increased	Decreased	Increased	Decreased	Decreased
Potassium	Increased	Decreased	Increased	Decreased	Increased	Increased

DOC, deoxycorticosterone; DHEA, dehydroepiandrosterone; 18-OHB, 18-hydroxycorticosterone.

TREATMENT

- Monitor for severe, life-threatening salt wasting and dehydration in the 1st wk of life. Follow electrolytes.
- Monitor for adrenal crisis.
- Determination of etiology (measure 17-hydroxyprogesterone, ACTH, cortisol, 11-DOC, DHEA)

- Genetic analysis (karyotype, FISH for SRY region)
- Sex assignment. Girls with classic CAH typically undergo reconstructive surgery, usually clitoroplasty and vaginoplasty.
- Glucocorticoid replacement therapy: Hydrocortisone 12–18 mg/m^2/d infants. In older children, dexamethasone 0.25–0.50 mg at bedtime. Stress dose increases for illness or surgery to avoid adrenal crisis.
- Mineralocorticoid replacement fludrocortisone 0.05–0.20 mg/d

REFERENCES

MacLellan DL1, Diamond DA, et al. Recent advances in external genitalia. *Pediatr Clin N Am.* 2006;53(3):449–464.

Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *Lancet.* 2005;365(9477):2125–2136.

Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(9):4133–4160.

CONGENITAL NEPHROSIS/NEPHROTIC SYNDROME

DESCRIPTION Congenital nephrotic syndrome is a rare condition affecting children from birth to the 3rd month of life. Familial incidence occurs as an autosomal recessive mode of inheritance. This disease is seen most frequently in Finland (1:8,000 live births). Clinical manifestations include wide anterior and posterior fontanelles, generalized edema, abdominal distention, anasarca, and malnutrition. Characteristic lab findings include proteinuria, hypoalbuminemia, and hyperlipidemia. Long-term survival is dependent on the correction of nutritional deficits and renal transplantation.

REFERENCE

Ramirez-Seijas F, Granado-Villar D, Cepero-Akselrad A, et al. Congenital nephrotic syndrome. *Intern Pediat.* 2000;15(2):121–122.

CONSTIPATION, UROLOGIC CONSIDERATIONS

DESCRIPTION Constipation is associated with bladder storage symptoms and increased risk of urinary tract infections. Urodynamic studies in children with functional constipation have revealed detrusor overactivity (DO) and small bladder capacity, both of which improve with improved bowel function. In addition, the same holding behavior that leads to functional constipation often alters bladder habits as well, as seen with dysfunctional elimination syndrome. Treatment of bowel dysfunction alone can resolve chronic recurrent UTI and urinary incontinence in some children. It is important to rule out neurologic and bowel disease as causes of constipation before making the diagnosis of functional constipation. (See also Section I: “Dysfunctional Elimination Syndrome.”)

TREATMENT

- Diet changes
- Laxatives, stool softeners
- Toilet schedules

REFERENCES
Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. *Pediatrics*. 1997;100:228–232.
Veiga ML, Lordêlo P, Farias T, et al. Constipation in children with isolated overactive bladder. *J Pediatr Urol*. 2013;9(6 Pt A):945–949.

CONTACT DERMATITIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Contact dermatitis is caused by an external irritant or allergen, and the patient complains of itching and burning or stinging. The findings are inflammation, scaling, and crust formation. Extreme reactions can result in blistering and necrosis. Allergic agents typically induce dermatitis after repeated contact with the skin.

CAUSES
- Common irritant agents cause immediate symptoms and include industrial chemicals, soaps, cleansing products, spermicides and lubricants, perfumes, urogenital secretions, and feces.
- Sensitizing agents for the genital skin include cleansing agents and disinfectants, lubricants and emollients, spermicides and other topical ointments, perfumes and fragrances, latex and other types of rubber, clothing, dyes, poison ivy (direct contact or indirect contact from the hand), met als such as nickel, and sanitary napkins.

TREATMENT
- Attempt to identify and remove the offending agent from contact with the skin.
- Topical corticosteroids, emollients, and antihistamines give symptomatic relief. Severe allergic contact dermatitis may require oral corticosteroids.
- Severe reactions (rarely) may require debridement and grafting.
- Patch testing of uninvolved skin to common antigens is often helpful.

REFERENCES
Buechner SA. Common skin disorders of the penis [review]. *BJU Int*. 2002;90(5):498–506.
Burrows LJ, Shaw HA, Goldstein AT. The vulvar dermatoses. *J Sex Med*. 2008;5(2):276–283.

CONTRAST-INDUCED NEPHROPATHY (CIN)

DESCRIPTION An acute and usually reversible form of acute kidney injury following the administration of radiocontrast media. Onset is often 12–24 hr after the contrast study, with renal recovery typically beginning within 3–5 days; it is nonoliguric. The process behaves as a clinical acute tubular necrosis (ATN) with decreased GFR and increased FENa. Risk factors include renal insufficiency (Cr >1.5 mg/dL, GFR <60 mL/min), diabetes, heart failure, dehydration, and multiple contrast studies within 72 hr. The mechanisms of the injury are thought to be renal vasoconstriction with resulting medullary hypoxemia and direct cytotoxic effects of contrast material. Older agents are hyperosmolar and ionic and carry a higher risk of nephrotoxicity, whereas newer agents are iso-osmolar and nonionic and have a lower risk of renal injury. (See also Section I: “Contrast allergy and reactions” and Section II: “Nephrogenic Systemic Fibrosis/Fibrosing Dermatopathy.”)

TREATMENT

- Preventative:
  - Avoid contrast material if possible; consider alternative imaging modalities such as ultrasound or CT/MRI without contrast
  - Avoid dehydration and NSAIDs, as both increase renal vasoconstriction
  - IV saline or sodium bicarbonate (154 mEq/L in D_5W, 3 mL/kg/h 1 hr prior, 1 mL/kg/h 6 hr following) before and after the administration of contrast
  - Antioxidant acetylcysteine [600–1,200 mg PO BID] 1 day prior and following contrast study
  - Use low- or iso-osmolal contrast agents and avoid frequent repeat dosing intervals of contrast (ie, <48 hr).
- Contrast-induced nephropathy diagnosed following a procedure should be managed as ATN:
  - Do not biopsy kidney; injury is usually transient.
  - Carefully control fluid and electrolyte balance; hemodialysis is usually unnecessary.
  - Avoid further nephrotoxic insults and/or medications.

REFERENCE

Asif A, Epstein M. Prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis.* 2004;44:12.

CORDONNIER AND NESBIT URETERAL ANASTOMOSIS

DESCRIPTION A direct ureteral colonic refluxing anastomosis incorporating full-thickness ureteral and intestinal wall.

REFERENCE

Dahl DM, et al. Use of intestinal segments and urinary diversion. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011:2411–2449.

CORPORA AMYLACEA (CA)

DESCRIPTION Small, round, ovoid bodies, lamellar in structure, located in the alveoli of the prostate. Composed of lecithin, albumin, and nitrogenous substances, they may precipitate around sloughed and degenerated prostatic epithelial cells. Recently noted is a high prevalence of calcium phosphate in the form of hydroxyapatite. CAs become more common with age, and act as the nidus for the development of prostatic calculi formation. Although often observed histologically to be associated with inflammation, the contribution of CA to prostatitis-related symptoms of unknown etiology or to prostate carcinogenesis remains unclear.

REFERENCE

Sfanos KS, Wilson BA, De Marzo AM, et al. Acute inflammatory proteins constitute the organic matrix of prostatic corpora amylacea and calculi in men with prostate cancer. *Proc Natl Acad Sci U S A*. 2009;106(9):3443–3448.

CORTICAL NECROSIS, ACUTE (RENAL CORTICAL NECROSIS)

DESCRIPTION Acute cortical necrosis is a rare form of acute renal failure (ARF) characterized by necrosis of the cortex with sparing of the medulla. It is thought to be the result of selective arterial spasm of the cortical vasculature with continued perfusion of the renal medulla via the medullary arterioles. Pathologically, necrosis of the glomeruli, tubules, and arterioles occurs. A cortical rim sign can be seen on contrast-enhanced CT scan, indicating spared perfusion of the renal capsule. Factors that can predispose a patient to acute cortical necrosis include shock, placental abruption, peritonitis, transfusion reaction, pancreatitis, and toxins. (See also Section I: "Renal Failure, Acute.")

REFERENCE

Wilck EJ, Gerard PS. Acute cortical necrosis. *Urology*. 1997;49(3):116.

COSTOVERTEBRAL ANGLE TENDERNESS

DESCRIPTION Costovertebral angle (CVA) tenderness is a clinical sign elicited by percussion of the CVA and often accompanied by symptoms of flank pain. The CVA is defined by the area formed by the 12th rib and vertebral column. CVA tenderness is a manifestation of renal capsular distension resulting in innervation of afferent T11–L2 nerve roots. Common causes include pyelonephritis, perirenal abscess, urolithiasis, acute hydronephrosis, renal artery occlusion, and renal vein thrombosis. (See also Section I: "Flank Pain.")

REFERENCE

Follin SA. *Professional Guide to Signs & Symptoms*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

COUGH STRESS TEST

DESCRIPTION The cough stress test involves filling the patient's bladder to at least 300 mL or to subjective fullness. The patient is then asked to cough as the physician directly visualizes the urethral meatus. The test can be performed with the patient in an upright position or in dorsal lithotomy on an exam table (supine stress test). If urine leakage is noted, the test is positive. The cough stress test has been compared with other more sophisticated testing methods (multichannel urodynamic studies) and has demonstrated good sensitivity and specificity. This test can be used not only as part of the clinician's physical exam, but as an outcome measure after treatment.

REFERENCE

Ghoniem G, GhoniStanford E, Kenton K, et al. Evaluation and outcome measures in the treatment of female urinary stress incontinence: International Urogynecological Association (IUGA) guidelines for research and clinical practice. *Int Urogynecol J Pelvic Floor Dysfunct.* 2008;19(1):5–33.

COWPER DUCT CYST

DESCRIPTION The Cowper glands are paired periurethral structures located in the urogenital diaphragm and are drained by 2–3-cm long ducts that empty into the bulbous urethra through small, flush openings. These glands secrete a clear fluid that functions as a

lubricant and a coagulation factor for semen during ejaculation and to neutralize traces of acidic urine in the urethra. Abnormalities of these glands and their ducts may result from obstruction and, less frequently, trauma and infection. This diagnosis should be considered in any male presenting with irritative or obstructive urinary symptoms, particularly when there is a complaint of persistent postvoid dribbling or incontinence. Urethrography and cystourethroscopy are the diagnostic studies of choice.

SYNONYMS
- Cowper syringocele
- Bulbourethral gland duct ectasia

TREATMENT
Endoscopic unroofing of the syringocele (marsupialization) into the bulbar urethra

REFERENCE
Bevers F, Abbekerk EM, Boon TA. Cowper's syringocele: Symptoms, classification and treatment of an unappreciated problem. *J Urol.* 2000;163:782–784.

COWPER GLAND CARCINOMA

DESCRIPTION Rare tumor that can present with obstructive symptoms, pain with defecation, or constipation. Most have a palpable perineal mass. Microscopically, these appear as adenocarcinoma. However, local necrosis and tissue destruction may prevent exact localization of the site of origin. Combined surgical and radiation therapy has been employed.

REFERENCE
Mitsumori K, Elwell MR. Tumours of the male accessory sex glands. *IARC Scientific Pub.* 1994;111:431–449.

COWPERITIS (INFLAMMATION OF BULBOURETHRAL GLAND)

DESCRIPTION Normally, the bulbourethral glands are not palpable. 1 gland lies on each side of the membranous urethra, between the inferior edge of the prostate and the inner border of the anal canal. When they are inflamed, they are exquisitely tender and palpable. In chronic inflammation, they enlarge from the size of a pea to that of a hazelnut. With a finger in the rectum, the thumb is held outside on the median raphe of the scrotum just anterior to the anus and the tissue is compressed to detect tenderness or a mass.

REFERENCE
Chughtai B, Sawas A, O'Malley RL, et al. A neglected gland: A review of Cowper's gland. *Int J Androl.* 2005;28(2):74–77.

CREATININE, SERUM, INCREASED/DECREASED

DESCRIPTION Serum creatinine represents the breakdown product of muscle creatine and is an ideal marker of glomerular filtration rate (GFR). 5–10% of excreted creatinine is secreted in the proximal tubule, rather than filtered through the glomerulus. Serum creatinine can estimate the GFR (eGFR) by 2 methods: The modification diet of renal disease (MDRD) or the

Cockcroft–Gault formula. Increased levels can signify renal failure, renal infection, rhabdomyolysis, urinary tract obstruction, acute tubular necrosis, dehydration, eclampsia, drug toxicity, etc. Decreased levels may reflect female gender, advanced age, late stages of muscular dystrophy, or myasthenia gravis. (See also Section IV: "Urine Studies III Creatinine Clearance and Glomerular Filtration Rate.")

REFERENCE

Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. *Ann Intern Med*. 2004;141(12):929–937.

CREDé MANEUVER

DESCRIPTION Used to facilitate voiding in those patients with decreased bladder tonicity and low outlet resistance. The maneuver involves placing the thumb of each hand over the left and right anterior superior iliac spine, and the fingers over the suprapubic area and pressing into the abdomen. Both hands are then pressed downward into the pelvis. It may not always be an effective technique to empty the bladder, since the external urethral sphincter may contract during the maneuver.

SYNONYM

Manual compression of bladder

REFERENCE

Moy LM, Wein AJ. Additional therapies for storage and emptying failure. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011:2298.

CREMASTERIC REFLEX

DESCRIPTION The cremasteric reflex is a useful sign in the evaluation of the acute scrotum. The classic presentation of testicular torsion is sudden onset of severe unilateral pain, often associated with nausea or vomiting. The normal reflex consists of cremasteric contraction with elevation of the testis, elicited by stroking the ipsilateral upper medial thigh. The innervation is carried via the genital branch of the genitofemoral nerve. The reflex was previously reported to be absent in 100% of cases of testicular torsion; however, there have been reported cases of preserved cremasteric reflex in the setting of testicular torsion. As such, the presence or absence of this reflex should not influence the decision to perform a scrotal exploration when there is a clinical suspicion of torsion.

REFERENCE

Nelson CP, Williams JF, Bloom DA. The cremasteric reflex: A useful but imperfect sign in testicular torsion. *J Pediatr Surg.* 2003;38(8):1248–1249.

CRIBRIFORM CLEAR CELL HYPERPLASIA OF THE PROSTATE

DESCRIPTION This condition may be misdiagnosed as cribriform prostate carcinoma, but anticytokeratin staining of the basal cell layer distinguishes the 2 lesions. Also, hyperplasic

cells lack cytologic atypia, which is in contrast to carcinoma. The natural history is unknown; the lesion is usually found in the central area of the gland.

REFERENCE

Epstein J. Precursor lesions to prostatic adenocarcinoma. *Virchows Arch*. 2009;454(1):1–16.

CRYPTOCOCCUS, GENITOURINARY

DESCRIPTION An opportunistic fungal infection, *Cryptococcus neoformans* thrives in areas inhabited by birds. A pulmonary site is most common primary infection site, but immunocompromised patients can develop disseminated disease (AIDS, transplant). Adrenal insufficiency has been reported, but the most common sites of GU involvement are the prostate and kidney. The prostate may be a reservoir in patients with AIDS. Epididymis and penis involvement have also been reported. GU involvement is considered a manifestation of systemic disease. (See also Section I: "Fungal Infections, Genitourinary.")

TREATMENT

- Systemic antifungal therapy with IV amphotericin B, flucytosine, fluconazole, or combination of drugs
- Surgical drainage of large abscesses may be considered

REFERENCE

Traboulsi R, Kanafani ZA, Kanj SS. Fungal infections of the genitourinary tract [review]. *J Med Liban*. 2004;52(4):202–209.

CRYSTAL-INDUCED ACUTE KIDNEY INJURY (ACUTE RENAL FAILURE)

DESCRIPTION Intratubular precipitation of crystals poorly soluble in human urine can lead to AKI. This form of AKI most commonly occurs as a result of acute uric acid nephropathy (tumor lysis syndrome) or following the administration of other drugs/toxins, such as acyclovir, sulfonamides, methotrexate, indinavir, triamterene, ethylene glycol, and high doses of Vitamin C. The presentation is usually asymptomatic and detected by worsening serum creatinine, although renal colic symptoms may be present. Severe volume depletion (prerenal state) is the most important predisposing factor to crystal-induced AKI when patients are receiving the above medications. Likewise, the 1st step in treatment is correction of volume status, usually with isotonic saline and loop diuretics in order to wash out crystals. (See also Section I: "Acute Kidney Injury, Adult [Renal Failure, Acute].")

REFERENCE

Lochy S, Jacobs R, Honoré PM, et al. Phosphate induced crystal acute kidney injury – an under-recognized cause of acute kidney injury potentially leading to chronic kidney disease: case report and review of the literature. *Int J Nephrol Renovasc Dis*. 2013;6:61–64.

CT SCAN, UROLOGIC CONSIDERATIONS

DESCRIPTION A computed tomography (CT) of the abdomen and pelvis can be performed with and without IV or PO contrast. Noncontrast studies are most useful in the evaluation of

nephrolithiasis. IV contrast is useful to delineate vascular, renal, and collecting system anatomy. Delayed images (excretory phase) provide information on urinary tract drainage and ureteral anatomy. Protocols have been developed to delineate renal tumors, stones, urothelial tumors, and arterial supply by adjusting the presence of contrast and the timing of the study. Modern CT machines can provide detailed images quickly and efficiently, but the clinician must be aware of contrast complications and contrast-induced nephropathy (see also Section I: "Contrast Allergy and Reactions"; Section II: "Contrast Induced Nephropathy [CIN].") and the increased risk of malignancy with repeat scans, especially in children. Approximate CT radiation exposure varies with type. Some radiation exposure comparisons average, in MilliSieverts (mSv):

- CT electron beam (EBT): 11 mSv Chest, 26 mSv Abdomen
- CT Sequential: 4 mSv Chest, 20 mSv Abdomen
- CT Spiral: 2 mSv Chest, 7 mSv Abdomen
- CT Pelvis: 7 mSv
- Intravenous pyelogram: 8 mSv
- Standard chest x-ray (2 view): 0.06–0.25 mSv
- Natural sources: Annual (Germany): 2.4 mSv/yr
- Survivors of Hiroshima and Nagasaki Atomic bombings: 50–150 mSv
- Mean lethal dose radiation (kills 50% within 60 days): 3,500–4,000 mSv

REFERENCES

Blake MA, Kalra MK. Imaging of urinary tract tumors. *Cancer Treat Res*. 2008;143:299–317.

Brenner DJ, Hall EJ. Computed tomography: An increasing source of radiation exposure. *N Engl J Med*. 2007;357(22):2277–2284.

Cancer Risk due to Diagnostic Radiology in Family Practice notebook. http://fpnotebook.com/Rad/HemeOnc/CncrRskDTDgnstcRdlgy.htm, Accessed March 2, 2014.

CULP-DEWEERD PYELOPLASTY

DESCRIPTION A pyeloplasty technique best suited for management of UPJ obstruction in the setting of a long segment of strictured proximal ureter. A spiral incision is carried out over the anterior and medial aspect of the renal pelvis and continued down across a point beyond the UPJ obstruction. The apex of the flap is brought down to the apex of the ureterotomy, where a 5-0 chromic stay suture is placed. The posterior and anterior anastomoses are completed with interrupted 5-0 chromic sutures.

REFERENCE

Nakada SY, Hsu TH. Management of Upper Urinary Tract Obstruction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:1143.

CUNNINGHAM CLAMP

DESCRIPTION A clamp device designed to compress the penile urethra and prevent urinary incontinence in males only. The clamp is usually placed on the midshaft of the penis and requires the user to have manual dexterity, intact penile skin, good cognition, and a sensate

penis and bladder. The clamp has a ratchet-type closure with foam padding and comes in small, medium, and large sizes. It is inexpensive and the most commonly used clamp device. Other types are commercially available based on this urethral compression concept.

REFERENCE

Moore KN, Schieman S, Ackerman T, et al. Assessing comfort, safety, and patient satisfaction with 3 commonly used penile compression devices. *Urology*. 2004;63(1):150–154.

CYCLOPHOSPHAMIDE (CYTOXAN) TOXICITY

DESCRIPTION Cyclophosphamide (sometimes referred to through the historic brand name Cytoxan) is an alkylating chemotherapeutic agent used to treat many blood cell cancers and as an effective immunosuppressant for other diseases such as rheumatoid arthritis. Common side effects include bone marrow suppression, diarrhea, alopecia, and lethargy. However, Cytoxan has unique toxicities, including the development of hemorrhagic cystitis and secondary cancers such as urothelial carcinoma of the bladder and leukemia. Acrolein, a metabolite of Cytoxan, is the main cause of acute hemorrhagic cystitis (and thought to be the cause of long-term increased risk of urothelial carcinoma in patients treated with Cytoxan). Hemorrhagic cystitis can be prevented by administering Mesna at the time of Cytoxan readministration; Mesna binds the toxic metabolite acrolein. (See also Section I: “Cystitis, Hemorrhagic [Infectious, Noninfectious, Radiation]”; Section II: “Chemotherapy Toxicity, Urologic Considerations.”)

TREATMENT

- Mesna can be given either PO or IV, and its routine concurrent use is recommended in the treatment of patients receiving cyclophosphamide and ifosfamide. It should be discontinued when hemorrhagic cystitis is present as it can prevent the development of the cystitis but is ineffective in treating active bleeding.
- Hydration: Forced saline diuresis and the medication Mesna were similar in preventing the incidence of cyclophosphamide-induced hemorrhagic cystitis in some studies.
  – ASCO recommends that patients receiving high-dose cyclophosphamide in the setting of hematopoietic cell transplantation receive Mesna in conjunction with saline diuresis.

REFERENCES

Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: Use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27(1):127–145.

Hu RQ, Mehter H, Nadasdy T, et al. Severe hemorrhagic cystitis associated with prolonged oral cyclophosphamide therapy: Case report and literature review. *Rheumatol Int*. 2008;28(11):1161–1164.

CYSTADENOCARCINOMA, GENITOURINARY

DESCRIPTION Commonly seen in other organ systems, such as the ovary, pancreas, appendix, and thyroid. In the GU system, cystadenocarcinoma has been reported in testes, prostate, paratesticular structures, and kidney. Grossly, multilocular cystic masses are noted.

Microscopically, cuboidal to columnar epithelium is seen lining the cysts. These cells can secrete serous or mucinous substances. Malignant cells will demonstrate multilayering of epithelium, nuclear atypia, and invasion of surrounding stroma. It is treated by primary surgical resection.

REFERENCE

Yu CC, Huang JK, Chiang H, et al. Papillary cystadenocarcinoma of the epididymis: A case report and review of the literature. *J Urol*. 1992;147(1):1622–1625.

CYSTADENOMA, GENITOURINARY

DESCRIPTION A benign cystic epithelial-lined mass that has been described in the kidney, seminal vesicle, prostate, and epididymis (most common GU tract site). It is often described as a papillary cystadenoma and represents benign epithelial hyperplasia. It usually causes very few symptoms. Lesions can be bilateral, and 2/3 may be associated with Von Hippel–Lindau syndrome. Grossly, the lesion appears cystic. Microscopically, it demonstrates cells with clear, vacuolated cytoplasm arranged in glandular or papillary structures. It appears as a cystic to solid mass at the head of the epididymis on ultrasound. Treatment is observation or radical orchiectomy, if the diagnosis is in doubt.

REFERENCE

Choyke PL, Glenn GM, Wagner JP, et al. Epididymal cystadenomas in von Hippel-Lindau disease. *Urology*. 1997;49(6):926–931.

CYSTADENOMA/CYSTADENOCARCINOMA, RETROPERITONEAL

DESCRIPTION Primary retroperitoneal tumors of mucinous type are extremely rare. They can be sub-divided into cystadenoma (a benign cystic epithelial-lined mass), borderline, and cystadenocarcinoma (multilocular cystic masses with multilayer epithelium, nuclear atypia, and invasion of surrounding stroma). Prompt diagnosis is important, as the majority of cystadenocarcinomas are malignant. Presenting symptoms can be vague. Given their malignant nature, they should be considered in the differential diagnosis of chronic abdominal pain. Cross-sectional abdominal imaging is the primary diagnostic modality. Radical resection remains the treatment of choice. (See also Section I: “Retroperitoneal Masses, Fluid and Cysts.”)

REFERENCE

Navin P, Meshkat B, McHugh S, et al. Primary retroperitoneal mucinous cystadenoma: a case study and review of literature. *Int J Surg Case Rep*. 2012;3(10):486–488.

CYSTATIN C

DESCRIPTION A 13 kDa nonglycosylated endogenous protein found in all nucleated cells that has a constant rate of production unaffected by diet. Its clearance is not affected by renal tubular functions. It is not currently widely available, but it will likely replace serum creatinine as the standard test in GFR measurement.

REFERENCE
Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008;51(3):395.

CYSTIC FIBROSIS, UROLOGIC CONSIDERATIONS

DESCRIPTION In this genetic disease affecting 1 in 2,000 Caucasian births, defective chloride transport across the epithelium occurs. This leads to complications involving the pancreas, liver, salivary glands, and lungs. Urogenital findings include bilateral absence of the vas deferens, leading to infertility. Abnormal development of the mesonephric system, inguinal hernias, hydroceles, and undescended testes are also seen. Risk of testicular cancer may be increased. (See also Section I: “Vas Deferens, Congenital Absence.”)

REFERENCE
Oates RD. Clinical evaluation of the infertile male with respect to genetic etiologies. *Syst Biol Reprod Med*. 2011;57:72–77.

CYSTINOSIS

DESCRIPTION Rare autosomal recessive metabolic disorder involving lysosomal storage of the amino acid cysteine due to a defective membrane transport protein: Cystinosin. There are 3 types described, based on the age at diagnosis. Nephropatic or infantile–the most severe, inevitably leading to terminal renal failure in the 1st decade of life, and major identifiable cause of Fanconi syndrome in children. Intermediate–resembles the nephropathic form but onset is during adolescence. Nonnephropathic or ocular cystinosis—usually occurs in adulthood is characterized by corneal crystals and photophobia. The condition is characterized by the intracellular accumulation of excessive quantities of cystine. Daily excretion of cystine is only 5–10% of that found in cystinuria. Stone formation is rare. This condition has a varied range of severity, with severe forms progressing to end stage renal disease (ESRD). Medical management includes hydration, potassium, bicarbonate, vitamin D, and calcium supplementation. Cysteamine bitartrate (Cystagon) is a cysteine depleting medication. ESRD may require real transplantation.

REFERENCE
Nestorave G, Gahl WA. Cystinosis: The evolution of a treatable disease.*Pediatr Nephrol*. 2013;28(1):51–59.

CYSTITIS CYSTICA

DESCRIPTION Similar to von Brunn nests, which are areas of benign urothelium in the submucosa, except that in cystitis cystica the centers of the nests have undergone eosinophilic liquefaction (degeneration) to form small cystic mucin cavities; when intestinal metaplasia with gland formation is found it is described as *cystitis glandularis*. Both conditions are thought to be benign. Found in 60% of normal bladders at autopsy, cystoscopically they appear as small pearly white or yellowish lesions, usually <5 mm, but occasionally larger.

No clear relation to malignant transformation is noted. There is no specific treatment; diagnosis is usually established by biopsy to rule out cancer.

REFERENCE

Alijani M, Ng KJ, Dickinson IK, et al. An unusual case of cystitis cystica. *BJU International.* 2002;89:634.

CYSTITIS, EMPHYSEMATOUS

DESCRIPTION A rare UTI with gas formation in the bladder wall or bladder lumen. Predominant in older women with diabetes. Presents with abdominal pain, dysuria, and possibly pneumaturia; gas can be seen on imaging studies. *Escherichia coli* and *Klebsiella pneumoniae* are most common pathogens and medical management is similar to acute complicated pyelonephritis. (See also Section I: "Pneumaturia [Gas in Urine].")

REFERENCE

Thomas AA, Lane BR, Thomas AZ, et al. Emphysematous cystitis: A review of 135 cases. *BJU Int.* 2007;100(1):17–20.

CYSTITIS, EOSINOPHILIC

DESCRIPTION A rare and severe form of allergic cystitis. Symptoms include hematuria, urgency, dysuria, and suprapubic discomfort. Urine analysis may show eosinophiluria. Cystoscopic findings may reveal raised plaques or ulcers that mimic CIS or invasive bladder cancer. Bladder biopsy revealing eosinophilic infiltrate is pathognomonic. Potential causes include food or drug allergies (including methicillin, anthranilic acid, intravesical mitomycin, and thiotepa). Parasitic infections should also be considered as etiologies. Some confusion in the literature exists between this entity and granulomatous cystitis. Conservative medical management with oral antibiotics, antihistamines, and steroids with an allergy evaluation are required. (See also Section II: "Cystitis Granulomatous.")

TREATMENT

- Conservative medical management with oral antibiotics, antihistamines, and steroids
- A full allergy evaluation is required

REFERENCE

Zaman SR, Vermeulen TL, Parry J. Eosinophilic cystitis: Treatment with intravesical steroids and oral antihistamines. *BMJ Case Rep.* 2013; pii: bcr2013009327. doi: 10.1136/bcr-2013-009327.

CYSTITIS FOLLICULARIS

DESCRIPTION Cystitis follicularis (also called "bacteriuric bumps" or "follicular cystitis") is characterized by the formation of lymphoid follicles in the lamina propria of the trigonal region of the bladder. It is caused by repeated or chronic UTIs. It may appear grossly as punctate, yellow submucosal nodules. It is not associated with malignancy, and treatment of the underlying infection is curative.

REFERENCE

McIntire M, Scudiere JR, Gattuso P. Cystitis follicularis in bladder washings: Report of 2 cases and review of the literature. *Diagn Cytopathol*. 2007;35(8):537–538.

CYSTITIS GLANDULARIS AND CYSTITIS GLANDULARIS OF INTESTINAL TYPE

DESCRIPTION Similar to von Brunn nests, which are areas of benign urothelium in the submucosa, except these urothelial cells have undergone glandular metaplasia. It is usually only detected microscopically, but occasionally can appear as a grossly visible lesion and may appear papillary. *Typical cystitis glandularis* is the most common form. Diffuse *cystitis glandularis of the intestinal type* is seen in chronically irritated bladders, and is associated with an increased risk of bladder cancer (adenocarcinoma) and may be associated with pelvic lipomatosis. No specific treatment except follow-up due to cancer risk. (Image ☼)

REFERENCE

Rau AR, Kini H, Pai RR. Morphological evaluation of cystitis glandularis. *Indian J Pathol Microbiol*. 2009;52(2):203–205.

CYSTITIS, GRANULOMATOUS

DESCRIPTION Granulomatous cystitis (sometimes called *eosinophilic cystitis* or *eosinophilic granulomatous cystitis* in the literature, thus leading to some confusion of this entity) is a rare allergic cystitis in patients who often have a significant allergic history. It mimics other forms of intractable cystitis, such as interstitial cystitis, TB, and bladder neoplasms. The cause is unknown, but believed to be various antigens that form immune complexes and stimulate eosinophilic infiltration. It can be seen in some patients after the use of intravesical BCG for bladder cancer as a thickened, edematous bladder with erythematous plaques, ulcerations, and submucosal hemorrhage. Microscopy reveals fibrosis and inflammatory cells with extensive eosinophil infiltration of bladder wall. Patients present with frequency, dysuria, and hematuria.

TREATMENT

- Condition is usually benign with self-limited course
- Optimal management is unclear; usually NSAIDs, steroids, and antihistamines

REFERENCES

Ladocsi LT, Sullivan B, Hanna MK. Eosinophilic granulomatous cystitis in children. *Urology*. 1995;46(5):732–735.

Littleton R, Farah RN, Cerny JC. Eosinophilic cystitis: An uncommon form of cystitis. *J Urol*. 1982;127(1):132–133.

CYSTITIS, POLYPOID AND PAPILLARY

DESCRIPTION These benign lesions may appear cystoscopically as papillary urothelial neoplasms and are a reaction to urothelial injury. Polypoid cystitis becomes papillary cystitis when the condition becomes chronic. Similar lesions occur throughout the urothelial tract

and are referred to as *polypoid urethritis, polypoid ureteritis,* and *polypoid pyelitis* when present in the urethra, ureter, and renal pelvis, respectively; these are clinically and diagnostically similar lesions. Clinical settings for this diagnosis include evaluation of gross hematuria, bladder and/or urethral stones, prostate cancer with radiation therapy, history of urothelial carcinoma treatment, long-term urinary stents, and colovesical fistulas. Proper diagnosis relies on low-power microscopic identification of the reactive process with an inflamed background that is edematous or densely fibrous with predominantly simple, nonbranching, broad-based fronds of relatively normal-thickness urothelium. If the tissue is examined at higher power, some fronds may appear to resemble a urothelial neoplasm. Treatment is directed at the inciting cause.

REFERENCE

Lane Z, Epstein JI. Polypoid/papillary cystitis: A series of 41 cases misdiagnosed as papillary urothelial neoplasia. *Am J Surg Pathol.* 2008;32(5):758–764.

CYSTITIS, RADIATION

DESCRIPTION Radiation cystitis can be caused during the treatment of pelvic malignancies (prostate, cervical, colorectal) when the bladder is in the radiation treatment field. Patients may experience urgency, frequency, dysuria, and urination of small volumes. Bladder spasms may also be present. This can progress to hemorrhagic cystitis with diffuse bladder mucosal inflammation and hemorrhage. The initial response of the bladder to radiation exposure results in an edematous and friable bladder. There can be extensive endarteritis with friable mucosa. Long-term radiation cystitis may present with delayed bleeding remote from the exposure to radiation (6 mo–20 yr after). The hallmark is neovascularity that bleeds easily, however when bladder bleeding occurs long term, bladder cancer should be ruled out. Life-threatening hemorrhage is a possible consequence of radiation-induced hemorrhagic cystitis. Amifostine has shown potential in prevention of GI and acute bladder toxicity from radiation. (See Section I: “Cystitis, Hemorrhagic Infectious, Noninfectious, Radiation.”)

TREATMENT

- Local irrigation with evacuation of clots is the initial intervention along with the correction of any coagulopathy if present should be the initial conservative management based on the clinical presentation
- Endoscopic electrocoagulation or laser ablation of bleeding sites
- Intravesical alum
- Hyperbaric oxygen (100% oxygen at higher than atmospheric pressure) 60–93% effective
- Pentosan polysulfate 100 mg 3 times a day; conjugated estrogens
- Intravesical instillation of formalin (37% solution of formaldehyde) in the absence of reflux
- Refractory life-threatening hemorrhage may require more aggressive intervention: Using selective embolization of the vesical or internal iliac arteries, diversion of the urinary stream (nephrostomy tubes, ileal conduit) with or without cystectomy (Image ☼)

REFERENCES

Mendenhall WM, Henderson RH, Costa JA, et al. Hemorrhagic radiation cystitis. *Am J Clin Oncol.* 2013 Dec 7. [Epub ahead of print].

Smit SG, Heyns CF. Management of radiation cystitis. *Nat Rev Urol.* 2010;7(4):206–214.

CYSTITIS, VIRAL

DESCRIPTION Viruses are increasingly recognized as the cause of lower UTIs—especially hemorrhagic cystitis among immunocompromised patients. Viral cystitis is caused most commonly by adenovirus, papovavirus, or influenza A. BK virus, adenovirus, and CMV are predominant pathogens involved in hemorrhagic cystitis after stem cell and solid-organ transplantation, and their early diagnosis and treatment may prevent significant morbidity. These can produce clinically significant symptoms, such as dysuria, hematuria, and frequency. Standard urine culture is negative. Urine analysis may show WBCs and RBCs. Cytology may be suspicious for malignancy, with abnormally large cells having prominent nuclei. The diagnosis of viral lower UTI is based on molecular techniques, and real-time polymerase chain reaction is often the method of choice because it allows for quantification of viral load. (See also Section I: "Cystitis, Hemorrhagic"; "Polyoma virus (BK, JC), urologic considerations"; Section II: "BK Virus, Urologic Considerations.")

TREATMENT

- Viral cystitis is usually self-limited
- In immunosuppressed patients, the use of antiviral agents (cidofovir, vidarabine, ribavirin) administered by PO, IV, or intravesical routes is recommended

REFERENCE

Paduch DA. Viral lower urinary tract infections. *Curr Urol Rep*. 2007;8(4):324–335.

CYSTOCELE GRADING: BADEN–WALKER, PELVIC ORGAN PROLAPSE QUANTIFICATION (POP-Q)

DESCRIPTION The grading and evaluation of cystoceles have evolved from the Baden–Walker grading scale to the current Pelvic Organ Prolapse Quantification (POP-Q) system. Although the 2-staging systems are widely used in clinical practice, POP-Q is more commonly used in the literature. The classic Baden–Walker grading system was 1st described in 1968. POP-Q was later developed in 1996. Both staging systems base the degree of prolapse on the leading edge during a Valsalva maneuver. (See also Section I: "Pelvic Prolapse [Cystocele and Enterocele]"; Section II: "Pelvic Organ Prolapse Quantification System [POPQ]."") (Image☼ Cystocele/Pelvic Organ Prolapse Classification)

Baden–Walker Grading	
Grade 0:	No prolapse
Grade 1:	Leading edge descends halfway to the hymen
Grade 2:	Leading edge descends to the hymen
Grade 3:	Leading edge descends halfway past the hymen
Grade 4:	Procidentia or vault eversion

POP-Q Staging	
Stage 0:	No prolapse
Stage I:	Leading edge is >1 cm above the hymen
Stage II:	Leading edge is between 1 cm above and 1 cm below the hymen
Stage III:	Leading edge is >1 cm below the hymen but less than total vaginal length – 2 cm (TVL (total vaginal length) – 2 cm)
Stage IV:	Leading edge is below hymen by more than TVL – 2 cm

REFERENCES

Bump RC, Mattiasson A, Bø K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175(1):10–17.

Theofrastou JP, Swift SE. The clinical evaluation of pelvic floor dysfunction. *Obstet Gynecol Clin North Am.* 1998;25(4):783–804.

CYSTOGRAM, INDICATIONS AND TECHNIQUE

DESCRIPTION A cystogram is a radiologic exam of the urinary bladder that can show the bladder's position, shape, presence of vesicoureteral reflux, bladder perforation and/or filling defects. A catheter is inserted into the bladder and used to fill the bladder with a contrast agent under gravity drainage. Typically, 300–350 mL of contrast is utilized depending on the patient's anatomy. Fluoroscopic images are then taken of the opacified bladder in the AP and oblique views. A postdrainage view is important to evaluate residual volume and to ensure no missed contrast extravasation behind the bladder. Common indications include abdominal/pelvic trauma, infection, fistula, reflux disease, and incontinence. Cystography has been largely replaced by the use of the CT cystogram.

REFERENCE

Chan DP, Abujudeh HH, Cushing GL Jr, et al. CT cystography with multiplanar reformation for suspected bladder rupture: Experience in 234 cases. *AJR Am J Roentgenol.* 2006;187(5):1296–1302.

CYSTOMETROGRAM

DESCRIPTION A cystometrogram evaluates the filling and/or storage phases of detrusor function. Catheters to measure intravesical pressure, abdominal pressure and to fill the bladder with saline, water, or CO_2 are utilized. The bladder filling rate is 1–50 mL/min.

Simultaneous measurements of pressure and volume are recorded and a curve is created. Variables observed are compliance, contractility, sensation, and capacity. During filling, the bladder volumes are recorded at (1) the 1st sensation of filling, (2) sensation of urgency to void, and (3) sensation of maximum capacity. Abnormalities that may be detected include altered sensation, changes in detrusor compliance, disorders of detrusor contractility, and/or presence of detrusor overactivity (DO).

REFERENCE

Pressure/flow cystometry. In: Chapple CR, MacDiarmid SA, Patel A, eds. *Urodynamics Made Easy.* 3rd ed. London: Elsevier; 2009.

CYSTOSARCOMA PHYLLODES, PROSTATE

DESCRIPTION Histopathologically resembles its counterpart in the breast: Distinctive biphasic pattern with hyperplastic epithelium-lined cysts, leaf-like intraluminal epithelium-lined stromal projections, and variable spindle cell stroma. Grossly, the tumor is unusually soft, cystic, and spongy. It can present with LUTS. Case reports indicate normal PSA levels or only slightly elevated. It can range from benign to malignant and its treatment is surgical resection.

REFERENCE

Fujii T, Shimada K, Tanaka N, et al. Phylloides tumor of the prostate. *Pathol Int.* 2012;62(3):204–208.

CYSTOSCOPE PROCESSING

DESCRIPTION Flexible fiberoptic cystoscopes are a major component of urology practice used for both diagnostic and therapeutic procedures. The American Urologic Association (AUA) and Society of Urologic Nurses and Associates (SUNA) have issued joint recommendations for reprocessing flexible cystoscopes. The key findings are summarized here:

- Cystoscopes as "semi-critical" devices requiring high-level disinfection or sterilization between patients. High-level disinfection differs from sterilization: High-level disinfection does not kill large numbers of bacterial spores; sterilization is the complete destruction of all microbial life.
- In the office setting, high-level disinfection (using glutaraldehyde or another chemical disinfectant) should include precleaning, leak testing, cleaning, disinfection, rinsing, and drying.
- Glutaraldehyde "soak times" are 20–45 min. With no precleaning a 45-min glutaraldehyde soak is required. A 20-min soak is adequate if recommended reprocessing steps are followed prior to immersion in glutaraldehyde.
- One chemical disinfectant (ortho-phthalaldehyde [OPA]) has been associated with anaphylaxis in bladder cancer patients, and should be avoided in these patients.

REFERENCE

Clemens JQ, Dowling R, Foley F, et al. Joint AUA/SUNA white paper on reprocessing of flexible cystoscopes. *J Urol.* 2010;184(6):2241–2245.

CYTOKERATIN STAINING

DESCRIPTION Commonly used in prostate cancer diagnosis (ie, to differentiate PIN from basal cell hyperplasia or distinguish various forms of acinar proliferations that are not cancer on needle biopsy) 34β3E12, which detects basal cell–specific CK, is commonly used. If basal cell staining is present, this helps to rule out carcinoma; it is also used to examine lymph nodes or periprostatic tissues for prostate cancer and may increase the accuracy of lymph node staging. It has shown promise in breast cancer staging, where up to 1/3 of patients have unsuspected micrometastasis to lymph nodes. Its utility in prostate cancer metastasis is being

investigated. (See also Section II: “Immunohistochemical Staining, Urologic Considerations.”)

REFERENCE

Moul JW, Lewis DJ, Ross AA, et al. Immunohistologic detection of prostate cancer pelvic lymph node micrometastases: Correlation to preoperative serum prostate-specific antigen. *Urology*. 1994;43(1):68–73.

CYTOLOGY, PROSTATE

DESCRIPTION Exam of cells, usually obtained by fine-needle aspiration (FNA), for the detection of malignancy. Characteristics that can be determined include DNA ploidy status, cell cycle distribution, and cytologic grade. Its advantages over standard pathologic techniques include ease and rapidity of technique; when used in combination with flow cytometry, it seems to increase accuracy. The findings must be read by an experienced cytopathologist to ensure reliability. The use of this technique has declined greatly in favor of needle biopsy. (See also Section II: “Fine-Needle Aspiration, Prostate.”)

REFERENCE

Paz-Bouza JI, Orfao A, Abad M, et al. Transrectal fine needle aspiration biopsy of the prostate combining cytomorphologic, DNA ploidy status and cell cycle distribution studies. *Pathol Res Pract*. 1994;190(7):682–689.

CYTOLOGY, URINARY

DESCRIPTION Microscopic exam of the urine, usually performed for the detection of malignant cells during follow-up of urothelial carcinoma. Criteria for malignancy include increased cytoplasmic-to-nuclear ratio, eccentric nucleus, nuclear pleomorphism and irregularity, hyperchromasia, chromatin clumping, nuclear crowding and overlapping, prominent nucleoli, mitotic figures, lack of cytoplasmic vacuolization, and loss of cell cohesion. Highly accurate (95%) in high-grade carcinoma and CIS but less (10–50%) accurate in low-grade bladder cancer, it is also useful in detecting unresected residual tumor, and may predict future tumor recurrence after transurethral resection (Image ☼).

REFERENCE

Jones JS, Larchian WA. Non-Muscle Invasive Bladder Cancer (Ta, T1, and CIS). In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:2351.

CYTOMEGALOVIRUS (CMV), UROLOGIC CONSIDERATIONS

DESCRIPTION CMV is the most important infectious threat to renal transplant recipients. Risk factors include the serologic status of donor and recipient, as well as the immunosuppressive regimen utilized. Other effects include voiding dysfunction by invading peripheral nerves. CMV cystitis has been reported to occur in AIDS, and it is 1 of the TORCH infections that can cause fet al malformations. CMV has been associated with perinatal renal vein thrombosis, and it can be a cause of virally induced hemorrhagic cystitis. Ganciclovir has been effective in transplant patients. (See also Section I: “Immunocompromised Patients, Urologic Considerations.”)

REFERENCE

Xu LP, Zhang HY, Huang XJ, et al. Hemorrhagic cystitis following hematopoietic stem cell transplantation: incidence, risk factors and association with CMV reactivation and graft-versus-host disease. *Chin Med J*. 2007;120(19):1666–1671.

DAVIS INTUBATED URETEROTOMY

DESCRIPTION Rarely used today, it was developed for surgical repair of lengthy or multiple ureteral strictures. An incision is carried out over the strictured area. A flap is then created attempting to maximally preserve its blood supply. Nephrostomy tube drainage is placed to avoid urinoma formation. A stenting catheter is passed through the cortex of the kidney, down the stenotic segment, and into the distal ureter/bladder. Apex of the flap is brought over the stent as far down as possible over the ureterotomy and closed with interrupted or running absorbable suture. The stenting catheter can be removed at 6 wk, after which an antegrade nephrostogram is done to ensure patency of the ureter. Nephrostomy catheter is removed afterward.

REFERENCE

Nakada SY, Thomas HH. Management of upper urinary tract obstruction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:1122–1168.

DAYTIME FREQUENCY SYNDROME (POLLAKIURIA)

DESCRIPTION The complaint of frequent daytime voiding or *pollakiuria* (from the Greek pollakis, meaning often) is a fairly common pediatric complaint. Other terms to describe the condition include extraordinary *daytime urinary frequency*, and in early literature, *sham urinary tract infection*. It is seen somewhat more often in boys usually between 4 and 10 yr. In children the differential includes UTI, diabetes mellitus, detrusor instability (DI), constipation, and bladder detrusor instability. If no cause can be determined simple behavioral regimen has demonstrated effectiveness including reassuring the parents and child and waiting for the condition to self-resolve. Reducing dietary intake of oxalate-rich beverages such as, tea and acidic juices such as apple in children who consume large amounts of them, along with liberal intake of water, have been proposed as ancillary approaches. The child needs to learn to ignore the urges and postpone voiding with some type of reward system.

REFERENCE

Farber JM. A strategy to treat pollakiuria. Contemporary Pediatrics. March 1, 2013.

DEEP VENOUS THROMBOEMBOLISM (DVT) PROPHYLAXIS: AUA GUIDELINES

DESCRIPTION Venous thromboembolism (DVT or PE) can occur in 1–5% of patients after major urologic surgery. Risk factors include advanced age, prior venous thromboembolism, cancer, hypercoagulable states, immobilization, obesity, smoking, pelvic dissection, lithotomy position, and many others. Bleeding risk must be weighed against the benefits of prophylaxis. Risk stratification:

- Low risk: Minor surgery, <40 yo, no additional risk factors
- Moderate risk: Minor surgery with additional risk factors or patients 40–60 yo with no additional risk factors

- High risk: Patients >60 yo OR patients 40–60 yo with additional risk factors
- Very high risk: Patients with multiple risk factors

RECOMMENDATIONS
- Transurethral or low-risk procedures: Early and frequent ambulation only
- Moderate Risk: Heparin 5,000 U SQ q12h start post op OR Enoxaparin 40 mg SQ/daily (if CrCL <30 mL/min 30 mg)
- High risk: Heparin 5,000 U SQ q8h start post op OR Enoxaparin 40 mg SQ/daily (if CrCL <30 mL/min 30 mg)
- Very high risk: Heparin 5,000 U SQ q8h start post op OR Enoxaparin 40 mg SQ/daily (if CrCL <30 mL/min 30 mg) AND adjuvant pneumatic compression device
- Active bleeding: Compression stockings and/or intermittent pneumatic compression
- Selected very high-risk patients: Consider postdischarge enoxaparin or warfarin

REFERENCE

Best Practice Statement 2008: Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery. Available at www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm, Accessed March 3, 2014.

DEHYDROEPIANDROSTERONE (DHEA) AND DHEA SULFATE (DHEA-S) BLOOD TEST

DESCRIPTION Because they are produced in the adrenal cortex, serum levels of DHEA and the sulfated form (DHEA-S) reflect adrenal gland function. Normal value ranges differ by age and sex. Common clinical reasons to measure these levels include female virilism, hirsutism, precocious puberty, CAH, and adrenal cancer. DHEA-S is the major form in serum. Generally, blood levels of both forms decrease in the aging male, and replacement has been linked with improved outcomes in Alzheimer disease and systemic lupus.

	DHEA (ng/mL)	DHEA-S (μg/mL)
Child	1–3	N/A
Male	1.7–9.5	80–560
Female	2–10	35–430

REFERENCE

Baulieu E, Thomas G, Legrain S, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci U S A.* 2000;97(8):4279–4284.

DELAYED NEPHROGRAM

DESCRIPTION In most imaging studies, contrast is typically appreciated within a few minutes of injection. In a delayed nephrogram, contrast appearance in the kidney is delayed. The most common cause is obstruction of the collecting system or ureter by calculus, tumor, or clot. Other causes are:
- Extraluminal obstruction of the collecting system by extrinsic mass
- Intrarenal obstruction, usually by precipitated substances in the tubules, such as Tamm–

Horsfall protein
- Azotemia
- Hypotension
- Renal vein thrombosis
- Rarely, acute kidney injury (AKI)

REFERENCE

Friedenberg RM. Excretory urography in the adult. In: Pollack HM, et al., eds. *Clinical Urography*. 1st ed. Philadelphia, PA: Saunders; 1990.

DEMENTIA AND VOIDING DYSFUNCTION

DESCRIPTION Dementia represents a debilitating neurologic cognitive disability, which can be associated with Alzheimer disease, Parkinson disease, and Lewy body disease. These patients typically develop lowerurinary tract symptoms (LUTS) of urgency, frequency, and urge incontinence. The incontinence may be a result of urgency and/or functional status. The more advanced the dementia and lack of mobility, the greater the role of functional incontinence. These patients are very difficult to manage successfully and require significant ancillary care. Incontinence in patients with a neurologic diagnosis is typically caused by DO. (See also Section I: "Neurogenic Bladder, General Considerations.").

TREATMENT
- Anticholinergic medication
- α-Blocker medication
- Behavioral modifications
- Address underlying cause of dementia

REFERENCE

Ransmayr GN, Holliger S, Schletterer K, et al. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. *Neurology*. 2008;70(4):299–303.

DENT DISEASE

DESCRIPTION Characterized by hypercalciuria, nephrocalcinosis, kidney stones, renal failure, and rickets. It is a disorder of the proximal tubules with X-linked recessive inheritance. Symptomatic disease is almost exclusively confined to males. Typical childhood presentation is polyuria, microscopic hematuria, asymptomatic proteinuria, or urolithiasis. Treatment is focused on reducing the hypercalciuria. (See Section II: "Hypercalciuria [Absorptive, Renal, and Resorptive].")

REFERENCE

Stechman MJ, Loh NY, Thakker RV, et al. Genetic causes of hypercalciuric nephrolithiasis. *Pediatr Nephrol*. 2009;24(12):2321–2332.

DENYS-DRASH SYNDROME (DDS), UROLOGIC CONSIDERATIONS

DESCRIPTION Also called Drash syndrome, a rare disorder consisting of congenital

nephropathy, Wilms tumor, and DSD (male pseudohermaphroditism) resulting from WT-1 gene mutations on chromosome 11p13. Patients develop hypertension, end stage renal disease (ESRD), and gonadoblastomas in their dysgenetic gonads.

TREATMENT
- Early prophylactic bilateral nephrectomy
- Gonadectomy
- Chemotherapy based on National Wilms Tumor protocol
- Renal transplantation after 2 yr of disease free on dialysis

REFERENCE
Shapiro O, Welch TR, Sheridan M, et al. Mixed gonadal dysgenesis and Denys-Drash syndrome: Urologists should screen for nephrotic syndrome. *Can J Urol.* 2007;14(6):3767–3769.

DERMATITIS HERPETIFORMIS

DESCRIPTION Dermatitis herpetiformis (also called Duhring disease) is an autoimmune blistering disorder associated with gluten sensitivity, and autoimmune and lymphoproliferative disorders. It is characterized by grouped excoriations, urticarial plaques, and papules with vesicles, and has been described on the external genitalia. It is extremely pruritic, and the vesicles are often excoriated to erosions by the time of physical exam. Diagnosis is made by the presence of IgA deposits in the upper papillary dermis seen on direct immunofluorescence of a skin biopsy specimen. The mainstays of treatment are dapsone and a gluten-free diet.

REFERENCE
Alonso-Llamazares J, Gibson LE, Rogers RS 3rd. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: Review of the Mayo Clinic experience. *Int J Dermatol.* 2007;46(9):910–919.

DERMATOPHYTE, EXTERNAL GENITALIA

DESCRIPTION Dermatophytes are the most common type of fungi that cause skin and nail infections, and they can involve the external genitalia. The irritation is often caused by the dermatophyte, *Trichophyton rubrum.* They typically present in obese adults with excessive perspiration as a major risk factor. Skin manifestations include red, raised, sharply defined, itchy lesions in the groin that may extend to the buttocks, inner thighs, and external genitalia. Warm weather and tight clothing encourage fungus growth. Also consider treating tinea pedis ("athlete's foot"), as this is often the original site of the offending organism.

SYNONYMS
- Tinea cruris
- Ringworm
- Jock itch

TREATMENT
- Weight loss; improved personal hygiene; talcum, cornstarch, or other desiccant powders to

keep the area dry
- Topical antifungals (powders, creams, lotions, solutions) such as terbinafine (Lamisil), clotrimazole (Lotrimin), econazole (Spectazole), ciclopirox (Loprox)

REFERENCE

Nadalo D, Montoya C, Hunter-Smith D. What is the best way to treat tinea cruris? *J Fam Pract.* 2006;55(3):256–258.

DERMOID CYST, TESTICULAR

DESCRIPTION Dermoid cysts (*epidermoid cyst*) are benign intratesticular neoplasms and a variant of cystic teratomas that contain ectodermic derivatives. Patients present with a palpable, firm, nontender testicular mass. Case reports indicate occurrence over a wide range of ages, from 5–85 yr. Dermoid cysts are typically well-encapsulated and unilocular. They occur more often in the right testicle (upper/lower pole) and are usually treated with focal excision or enucleation.

REFERENCE

Viganò P, Picozzi SC, Manganini V, et al. 7-year history of an intratesticular mass: Patient description and review of the literature about dermoid cysts of the testis. *Urol Int.* 2006;77(3):281–283.

DESMOPLASTIC SMALL ROUND CELL TUMOR

DESCRIPTION Rare, usually very aggressive mesenchymal tumor that typically presents in the abdominal cavity but might involve the GU system. Those patients with GU involvement tend to be younger men. Histologically, irregular nests of small round cells surrounded by fibrous connective tissue are seen. Immunohistochemical studies reveal both epithelial and nonepithelial origins. Associated with a unique translocation between chromosomes 11 and 22, that involves EWSR1 and WT1 genes. Prognosis is particularly poor, largely due to majority of patients presenting with metastatic disease. Surgical resection and multidrug chemotherapy have been employed with poor success.

REFERENCE

Dufresne A, Cassier P, Couraud L, et al. Desmoplastic small round cell tumor: current management and recent findings. *Sarcoma.* 2012;2012:714986.

DE TONI-FANCONI-DEBRE SYNDROME

DESCRIPTION Syndrome of multiple defects of tubular function, characterized by aminoaciduria, phosphaturia, glycosuria, osteomalacia, and renal tubular acidosis. The proximal renal tubule is shortened and replaced by a thin tubular structure, constituting the swan-neck deformity.

TREATMENT
- Replacement of cation deficits (especially potassium)
- Correction of acidosis with bicarbonate or citrate

- Replacement of phosphate loss with isoionic neutral phosphate solution
- Encouragement of liberal calcium intake with added vitamin D

REFERENCE

Ogier H, Lombes A, Scholte HR, et al. De Toni-Fanconi-Debre syndrome with Leigh syndrome revealing severe muscle cytochrome C oxidase deficiency. *J Pediatr*. 1988;112(5):734–739.

DETRUSOR OVERACTIVITY

DESCRIPTION Involuntary or uninhibited contraction of the detrusor muscle (as seen with multichannel urodynamics) in the absence of a neurologic cause. According to the Incontinence Society definition: DO is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Clinically, DO usually presents as urinary urgency, with or without urinary frequency urgency incontinence. (See also Section I: "Overactive Bladder.") The etiology of DO can be either neurogenic or idiopathic.

SYNONYM

Overactive bladder

TREATMENT

- Behavior modification: Fluid restriction, avoidance of bladder irritant
- Pelvic floor exercises
- Anticholinergic/antimuscarinic therapy
- β3-Adrenergic receptor agonist therapy
- Botulinum toxin type A
- Sacral neuromodulation
- Posterior tibial nerve stimulation
- Surgical treatments: Ileovesicostomy, augmentation cystoplasty

REFERENCES

Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61(1):37–49.

Ginsberg D, Cruz F, Herschorn S, et al. OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor activity regardless of concomitant anticholinergic use or neurologic etiology. *Adv Ther*. 2013;30(9):819–833.

DEXAMETHASONE SUPPRESSION TEST

DESCRIPTION The dexamethasone suppression test is designed to diagnose and differentiate among the various types of Cushing syndrome and other hypercortisolism states. Results indicative of Cushing disease involve no change in cortisol on low-dose dexamethasone but inhibition of cortisol on high-dose dexamethasone. If the cortisol levels are unchanged by both low- and high-dose dexamethasone, then a cortisol-secreting adrenocortical tumor is suspected or an ectopic ACTH source. Occasionally, other conditions (such as major depression, alcoholism, stress, obesity, kidney failure, pregnancy, or

uncontrolled diabetes) may interfere with cortisol levels.

The low-dose test depends on the fact that only the correct dose of dexamethasone will suppress ACTH – and thus cortisol release in normal subjects – whereas patients with corticotrophic adenomas will not suppress below a specified cutoff. Traditionally, high-dose dexamethasone has been used to suppress pituitary sources of ACTH and thus serum cortisol levels to help distinguish Cushing disease from the ectopic ACTH syndrome. 2 mg of dexamethasone is given q6h for 48 hr, after which urinary cortisol is measured. Suppression of basal urinary cortisol levels (measured in the initial screening) by 90% is the commonly quoted cutoff for this test. It is advised that high-dose dexamethasone suppression be used more as a confirmatory test, if at all, for the diagnosis of Cushing disease.

REFERENCE

Gross BA, Mindea SA, Pick AJ, et al. Diagnostic approach to Cushing disease. *Neurosurg Focus*. 2007;23(3):E1.

DIABETES INSIPIDUS (DI), UROLOGIC CONSIDERATIONS

DESCRIPTION DI may cause polyuria. DI is further distinguished as neurogenic or nephrogenic in origin. Of urologic interest, the IVP can show marked hydronephrosis, dilated ureters, and megacystis secondary to the great increase in urine flow. Signs include hypernatremia and hyperosmolarity. The condition is diagnosed by the inability to concentrate urine despite water deprivation and administration of ADH. Neurogenic DI is caused by the loss of ADH secretion from trauma, tumor, or for iatrogenic reasons. Nephrogenic DI can be idiopathic, due to medications, or a result of obstructive uropathy.

TREATMENT

- Neurogenic: Replace ADH
- Nephrogenic:
  - Remove the underlying cause
  - Chlorothiazide with low sodium diet

REFERENCE

Garofeanu CG, Weir M, Rosas-Arellano MP, et al. Causes of reversible nephrogenic diabetes insipidus: A systematic review. *Am J Kidney Dis*. 2005;45(4):626–637.

DIETL CRISIS

DESCRIPTION The most severe manifestation of nephroptosis, originally described by Jozef Dietl in 1864. Classically described as colicky flank pain, nausea, chills, tachycardia, oliguria, and transient hematuria or proteinuria. Hydronephrosis secondary to vascular obstruction of the ureter is the postulated cause. Physical exam reveals an enlarged, tender kidney.

TREATMENT

- Manual reduction of the ptotic kidney was initially used
- Nephropexy has been used for nephroptosis and was 1 of the most commonly performed operations of the early 20th century; uncommon procedure today

REFERENCE

Moss S. Floating kidneys: A century of nephroptosis and nephropexy. *J Urol*. 1997;158:699–702.

DIMERCAPTOSUCCINIC ACID (DMSA) RENAL SCAN

DESCRIPTION DMSA allows the visualization of detailed renal cortical anatomy because it accumulates in the kidney at the proximal renal tubules and is slowly excreted in the urine. DMSA renal imaging is the most sensitive radiologic study used to detect pyelonephritic changes and scarring in the kidneys.

REFERENCE

Hardy R, Austin J. DMSA renal scans and the top-down approach to urinary tract infection. *Pediatr Infect Dis J*. 2008;27(5):476–477.

DIURETIC RENOGRAM

DESCRIPTION A noninvasive nuclear medicine study that provides functional information regarding upper urinary tract obstruction (sometimes referred to as “Lasix renogram”). This test is most commonly utilized to determine obstruction in the setting of hydronephrosis. A tubular agent is preferred, therefore MAG3 is widely used for its high extraction fraction, rapid parenchymal transit, low radiation absorbed dose, and excellent imaging properties. The recommended dose of furosemide (Lasix) in adults is 40 mg IV. In the standard protocol, Lasix is injected when the collecting system appears to be full (usually 15–20 min after tracer injection, called F + 20). In patients with equivocal results, a 2nd study with administration of Lasix 15 min before tracer injection (called F – 15) is performed to maximize the diuretic stress, which improves the sensitivity and specificity and reduces the chances of equivocal outcome. Quantitative parameters, such as time to peak (TTP), 20 min to peak activity ratio (20/MAX), pelvic T1/2 clearance time, and parenchymal transit time (PTT) are calculated (Image ☼).

REFERENCE

Foda MM, Gatfield CT, Matzinger M, et al. A prospective randomized trial comparing 2 diuresis renography techniques for evaluation of suspected upper urinary tract obstruction in children. *J Urol*. 1998;159(5):1691–1693.

DOPPLER, PENILE

DESCRIPTION Currently, the most widely utilized method to measure arterial flow and prove arterial insufficiency as an etiology of impotence. It allows visualization of individual arteries and measurement of flow. Performed in the flaccid and erect states (after the intracavernosal injection of vasoactive agents). An increase in mean arterial diameter of >75% of the flaccid value and a mean peak flow velocity of >25 cm/s after vasoactive agent injection is used to determine adequate arterial capacity. A wide variability in some patients has been shown.

REFERENCE

Burnett AL. Evaluation and management of erectile dysfunction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:721–748.

DOWN SYNDROME, UROLOGIC CONSIDERATIONS

DESCRIPTION Also known as trisomy 21, the findings of this commonly seen trisomy include brachycephalic skull; congenital nasal hypoplasia; broad, short hands; and GU anomalies in the form of undescended testicles and a small penis. Males affected are hypogonadal with a smaller than average phallus. Approximately 25% will have cryptorchidism. Microscopic renal cysts, usually of the glomerular space, can also occur.

REFERENCE

Rabinowitz R. General consideration of congenital anomalies. In: Gillenwater JY, Grayhack JT, Howards SS, Duckett JW, eds. *Adult and Pediatric Urology*. 3rd ed. St. Louis, MO: Mosby; 1996.

DRIBBLING, POSTVOID

DESCRIPTION A complaint of loss of urine that occurs after completion of voiding, thought to be caused by retained urine in the urethra distal to the sphincter in men and retained urine in the vagina or urethral diverticulum in women. In men, it is a complaint associated clinically with BPH, following radical prostatectomy and stricture disease. Recent data suggests it may be a surrogate for median lobe hypertrophy in BPH.

REFERENCE

Ablove T. Post void dribbling: Incidence and risk factors. *Neurourol Urodyn*. 2010;29(3):432–436.

DROMEDARY HUMP

DESCRIPTION A normal anatomic variant of the left kidney consisting of a bulge of normal tissue that mimics a tumor. Dromedary humps arise from the superolateral aspect of the left kidney secondary to molding by the spleen. It is usually mistaken for tumors on IVP or kidney tomograms. Other imaging, such as CT, MRI, or renal US can be used to rule out a tumor. Appropriately named after the dromedary camel. (See also Section II: “Renal Pseudotumor.”)

REFERENCE

Dyer R, Chen MY, Zagoria RJ. Classic signs in uroradiology. *Radiographics*. 2004;24:S247–S280.

DROOPING LILY SIGN

DESCRIPTION Excretory urographic description for the lower pole moiety in a duplicated collecting system. The nonfunctioning upper pole produces a mass effect that pushes the lower pole downward. The lower pole ureter tends to be orthotopic, whereas the upper pole is typically ectopic.

REFERENCE

Amis ES, Newhouse JH. *Essentials of Uroradiology*. 1st ed. Boston, MA: Little Brown; 1991:263.

DROP METASTASES

DESCRIPTION Upper tract urothelial tumors can spread to urothelial structures that are either distal or proximal to the primary tumor called "drop metastases." Upper urinary tract tumors frequently are multiple or can occur synchronously with bladder tumors. This may reflect the propensity of neoplastic cells to flow down from the renal pelvis or reflux from the bladder to the ureter, forming an invasive implant. However drop metastases may be difficult to differentiate from separate primary lesions. Recurrent bladder tumors tend to cluster around the ureteral orifice of an affected ureter. This suggests their origin as metastases from the original primary tumor.

REFERENCE

Ritchei, JP, Kantoff PW. Malignancies of the renal pelvis and ureter. UpToDate.com, Accessed March 8, 2014.

DRUG ERUPTION, FIXED

DESCRIPTION This sharply localized dermatitis characteristically recurs at the same site each time the offending drug is administered (penis is most common site), with an acute phase followed by desquamation and hyperpigmentation. Symptoms usually appear after 6 hr, although lesions can occur 24–48 hr later. A macrophage migration inhibition factor (MIF) assay is essential for diagnosis.

Common medications responsible include phenolphthalein, trimethoprim-sulfamethoxazole, antipyrine, quinine, tetracycline, salicylates/NSAIDS, and hydroxyzine hydrochloride. Discontinuation of the drug causing the reaction results in complete resolution of the fixed drug eruption. Supportive topical therapy (steroids) is used, as needed.

REFERENCE

Cohen HA, Barzilai A, Matalon A, et al. Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother*. 1997;31(3):327–329.

DYSFUNCTIONAL VOIDING

DESCRIPTION Dysfunctional voiding is characterized by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals. Although dysfunctional voiding is not a very specific term, it is preferred to terms such as "nonneurogenic neurogenic bladder". Other terms such as " idiopathic detrusor sphincter dyssynergia," or "sphincter overactivity voiding dysfunction," may be preferable. However, the term dysfunctional voiding is very well established. The condition occurs most frequently in children. While it is felt that pelvic floor contractions are responsible, it is possible that the intraurethral striated muscle may be important. It was originally described by Hinman and Bauman in 1973 after a review of similar reported cases. Upper tract damage can occur. Diagnosis is through

videourodynamics. (See also Section II: “Hinman Syndrome [Hinman–Allen Syndrome].”)

REFERENCE

Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology.* 2003;61(1):37–49.

DYSGERMINOMA

DESCRIPTION Malignant tumor of the ovary, which is roughly the counterpart of seminoma of the testes, occurring in children and young women. It is occasionally seen in gonadal dysgenesis or testicular feminization syndrome. Patients may present with pelvic mass or abdominal pain. Pure dysgerminomas do not secrete tumor markers such as AFP or hCG.

TREATMENT

- Surgical resection for local disease
- Radiation therapy or chemotherapy for advanced disease

REFERENCE

Berek JS. Ovarian cancer. In: Hacker NF, et al., eds. *Essentials of Obstetrics and Gynecology*. 2nd ed. Philadelphia, PA: Saunders; 1992.

DYSORGASMIA

DESCRIPTION Pain with orgasm can affect both men and women and is not well described in the literature. In men, largely self-limited if experienced after radical prostatectomy (RP). Some reports that seminal vesiculectomy following RP can be therapeutic. In women often manifests as lower abdominal cramping pain.

REFERENCE

Matsushita K, Tal R, Mulhall JP. The evolution of orgasmic pain (dysorgasmia) following radical prostatectomy. *J Sex Med.* 2012;9(5):1454–1458.

DYSPAREUNIA, MALE (PARTNER DYSPAREUNIA, HISPAREUNIA)

DESCRIPTION The term dyspareunia means “bad or difficult mating.” Pain with intercourse is traditionally ascribed to female complaints. Recently cases of male dyspareunia and penile trauma have been reported due to the use of alloplastic materials in female pelvic floor surgery. This is often related to prominence or frank exposure of the sling material. Changes of male sexual function and particularly pain after sling insertion in their female partners may be due to sling exposure. Sexual interest and drive may be negatively influenced and can be treated effectively by correcting the sling exposure.

REFERENCE

Mohr S, Kuhn P, Mueller MD, et al. Painful love-”hispareunia” after sling erosion of the female partner. *J Sex Med.* 2011;8(6):1740–1746.

DYSRAPHISM, SPINAL

DESCRIPTION Most common cause of neurogenic bladder dysfunction in childhood, dysraphism is defined as failure of closure of the vertebral canal during embryonic development, leading to spinal cord dysfunction. The most common dysraphism, myelodysplasia, includes meningoceles, myelomeningoceles, and lipomeningoceles. Reflux, continence, sexuality, and bowel function are often important issues with these patients. Many rarer forms also exist, including tight filum terminale, dermoid cysts, and aberrant nerve roots with varying levels of resulting dysfunction. (See also Section II: "Myelodysplasia [Myelomeningocele], Urologic Considerations"; Section III: "Tethered Cord Syndrome.")

REFERENCE

Bauer SB, MacLellan DL. Neuropathic dysfunction of the lower urinary tract In: Wein AJ, et al., *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3431–3456.

DYSTHYROIDISM (HYPO/HYPERTHYROIDISM) UROLOGIC CONSIDERATIONS

DESCRIPTION Thyroid disease (hyper/hypo) may occasionally be associated with male factor infertility and erectile dysfunction (ED). Hyperthyroidism is commonly associated with diminished libido (may be caused by increased circulating estrogen levels). In hypothyroidism, low testosterone secretion and elevated prolactin levels contribute to ED. Subclinical hypothyroidism does not impact semen parameters. In patients undergoing urologic surgery, they should be euthyroid prior to their intervention. Thyrotoxicosis or thyroid storm can present with fevers, tachycardia, confusion, and cardiovascular collapse. Hypothyroidism is generally associated with an increased sensitivity to medications such as anesthetic agents and narcotics; its severe form can be associated with myocardial dysfunction, coagulopathy, electrolyte imbalance, and decreased gastrointestinal motility.

REFERENCE

Vira MA, Steckel J. Core principles of perioperative care. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:159–176.

ECCHYMOSIS, FLANK

DESCRIPTION The presence of ecchymosis in the flank region (*Grey–Turner sign*) is a physical sign of retroperitoneal bleeding. Common associations may include renal trauma, ruptured abdominal aortic aneurysm, and acute pancreatitis.

REFERENCE

Bonani M, Franzen D, Anabitarte P, et al. Images in emergency medicine. Cullen's sign and Grey–Turner's sign. *Ann Emerg Med*. 2008;51(4):448–458.

ECHINOCOCCUS, RENAL

DESCRIPTION Renal hydatid disease is a parasitic tapeworm infestation that results in renal cysts that occupy space and cause local mass symptoms. This infection is caused by the larval stage of the cestode *Echinococcus granulosus*, whose definitive host is the dog and principal intermediate is the sheep. Common symptoms include flank pain, hematuria, and local pressure. The diagnosis of renal echinococcus requires a high index of suspicion and despite a complete clinical history, serologic, radiologic, and urine data, the yield is only 50%. Radiographic findings include a calcified, curvilinear cystic mass in the kidney. During cyst excision, great care must be taken to not spill or rupture the cyst, because the liberated parasites could be spread and cause anaphylaxis. (See also Section II: "Hydatid Cysts.")

SYNONYMS

- Cystic hydatid disease
- Hydatid cysts

TREATMENT

- Surgical excision of intact cyst, with care not to spill or rupture cyst (praziquantel and albendazole may be given preoperatively 7–10 days before surgery)
- Medical treatment is reserved for nonsurgical candidates (albendazole 400 mg twice daily for 1–6 mo)

REFERENCE

Angulo J, Sanchez-Chapado M, Diego A, et al. Renal echinococcosis: Clinical study of 34 cases. *J Urol*. 1997;157(3):787–794.

EDEMA, LOWER EXTREMITY, UROLOGIC CONSIDERATIONS

DESCRIPTION Edema of the lower extremity can present bilaterally or unilaterally and can have multiple urologic implications, depending on the clinical presentation. Unilateral edema in the peri- or postoperative period may be a manifestation of deep venous thrombosis or an expected result after lymphadenectomy. Bilateral edema may be a result of underlying congestive heart failure or generalized anasarca. Postoperative fluid management should be closely monitored with this finding. In endemic regions, filariasis may present with significant bilateral lower extremity edema.

CAUSES

- Anasarca
- Congestive heart failure
- Deep venous thrombosis
- Filariasis
- IVC thrombosis/obstruction
- Lymphadenectomy (retroperitoneal, pelvic, inguinal)
- Superficial thrombophlebitis
- Urinary obstruction/retention

REFERENCE

Ely J, Osheroff JA, Chambliss ML, et al. Approach to leg edema of unclear etiology. *J Am Board Fam Med*. 2006;19(2):148–160.

EDWARD SYNDROME

DESCRIPTION Also known as *trisomy* 18, it is the 2nd most common autosomal trisomy after Down syndrome. Characterized by structural heart defects, kidney malformations, esophageal atresia, omphalocele, facial clefts, diaphragmatic hernias, and genital hypoplasia among other signs. High incidence of urologic abnormalities noted with Horseshoe kidney in about 20% of cases; hydronephrosis, hypospadias, and cryptorchidism are also common. Up to 90% of patients die within the 1st yr of life, usually secondary to cardiopulmonary problems. Uterine and vaginal abnormalities are common in females.

REFERENCE

Surányi A, Bitó T, Vajda G, et al. Unusual clinical history of a male infant with Edwards syndrome. *Pathol Oncol Res*. 2009;15(1):147–152.

EJACULATION, FEMALE

DESCRIPTION So called “female ejaculation" is the expulsion of fluid by females during or before sexual orgasm. The prevalence varies between 10–54%, whereas the amount of fluid ranges from 1–900 mL. These are natural sexual responses but may also represent symptoms of urinary incontinence. The term encompasses various phenomena with different underlying pathophysiologic mechanisms noted below:

- Vaginal lubrication: Vaginal fluid is forced out by the contractions of perivaginal muscles.
- Ejaculation orgasm: Either orgasmic expulsion of whitish secretion produced by the “female prostate” (known as Skene glands), or orgasmic expulsion of diluted urine (squirting/gushing), or the combination of both.
- Coital incontinence: Leakage of urine that occurs during penetrations or orgasm. Usually associated with stress or urge urinary incontinence.

Penetration incontinence occurs more frequently and is usually caused by SUI. Urodynamic diagnoses of detrusor overactivity (DO) and SUI are observed in orgasmic incontinence. (See also Section I: “Incontinence, Urinary, Adult Female”; Section II; “Coital Incontinence [Coital Leakage/Intercourse Incontinence].”)

REFERENCE

Pastor Z. Female Ejaculation Orgasm vs. Coital Incontinence: A Systematic Review. *J Sex Med.* 2013;10(7):1682–1691.

EJACULATION, PAINFUL

DESCRIPTION The incidence of pain associated with or immediately after ejaculation is 1–9.7%. Can be iatrogenic, physiologic, or psychogenic in nature. Ejaculatory or postorgasmic pain is believed to arise from interference with the coordination of the muscles of the pelvic floor and male genitalia that are responsible for semen transport during ejaculation. (See also Section II: "Dysorgasmia.")

CAUSES
- Prostatitis
- BPH
- Ejaculatory duct obstruction (EDO) by calculi
- Postoperative (prostatectomy)
- Antidepressants
- Pudendal neuropathy

TREATMENT
- α-Adrenoreceptor inhibitors
- Rule out and treat EDO
- Pudendal nerve injection with bupivacaine/triamcinolone
- Pudendal nerve release

REFERENCE

Ilie CP, Mischianu DL, Pemberton RJ. Painful ejaculation. *BJU Intern.* 2007;99(6):1335–1339.

EJACULATORY ANHEDONIA

DESCRIPTION A rare condition, affecting males predominantly, in which ejaculation occurs without an accompanying sense of orgasmic pleasure. Most common causes are psychogenic in origin or related to SSRI antidepressants usage.

REFERENCE

Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med.* 2004;1(1),6–23.

EJACULATORY DUCT OBSTRUCTION (EDO)

DESCRIPTION EDO is found in 1–5% of infertile men, producing azoospermia with low-volume, acidic ejaculate that has no fructose. Obstruction of the ejaculatory ducts prevents the emission of sperm and seminal fluid into the posterior urethra during ejaculation. Congenital causes include utricular, müllerian and wolffian duct cysts; ejaculatory duct stenosis; or atresia. Acquired causes include infection, calculus, trauma, or prior instrumentation. Physical exam is usually normal, with the occasional palpable midline mass or dilated seminal vesicles. Semen analysis shows low-volume, acidic pH, absent fructose, and failure to coagulate. Transrectal ultrasonography (TRUS) demonstrates a cystic midline

structure within the prostate, with dilated seminal vesicles. When TRUS is equivocal, additional tests include TRUS-guided seminal vesicle aspirate (demonstrates abundant spermatozoa) or vasography. (See also Section II: "Vasography, Technique and Indications.")

TREATMENT
Through transurethral resection of ejaculatory duct, in which the ejaculatory duct cyst is unroofed by transurethral resection at the level of the verumontanum, until efflux from the ducts is seen.

REFERENCE
Fisch H, Lambert SM, Goluboff ET. Management of ejaculatory duct obstruction: Etiology, diagnosis, and treatment [review]. *World J Urol.* 2006;24(6):604–610.

ELECTROEJACULATION

DESCRIPTION Procedure for obtaining sperm for ARTs in patients who cannot ejaculate on their own, such as SCI patients, typically used after failure of vibratory penile stimulation. General anesthesia is used, except in cases of complete spinal cord compromise. A transrectal probe is positioned with electrodes against the anterior rectal wall. Electrical stimulation causes erection and ejaculation in >80% of patients. Rectosigmoidoscopy is performed before and after the procedure to rule out rectal injury. Blood pressure monitoring is essential during the procedure for patients who may have autonomic dysreflexia.

REFERENCE
Sønksen J, Ohl DA. Penile vibratory stimulation and electroejaculation in the treatment of ejaculatory dysfunction. *Int J Androl.* 2002;25(6):324–332.

ELECTROMYOGRAPHY, EXTERNAL SPHINCTER

DESCRIPTION Generally, electromyography is the measurement of bioelectric potentials generated by the depolarization of muscle. During urodynamics, the activity of the external sphincter can be monitored by transperineal needle electrodes or surface electrodes. During filling, there should be increase in activity, which will reach maximum near capacity. During voiding, there should be a persistent cessation of sphincter activity. At the end of the voiding phase, sphincter activity returns to baseline. To assess external sphincter activity, the patient may be asked to interrupt voiding in the middle of the stream, at which point there should be an abrupt increase in sphincter activity sufficient to stop the flow. Abnormal EMG patterns may be detected in detrusor sphincter dyssynergia and dysfunctional voiding. EMG monitoring may also be used during biofeedback therapy for dysfunctional voiding.

REFERENCE
Voiding disorders and bladder outlet obstruction. In: Chapple CR, MacDiarmid SA, Patel A, eds. *Urodynamics Made Easy.* 3rd ed. London, Elsevier, 2009:127–148.

ELEJALDE SYNDROME

DESCRIPTION Also known as *acrocephalopolydactylous dysplasia,* this exceedingly rare

autosomal recessive syndrome is characterized by craniosynostosis and fibroblast hyperproliferation in organs such as skin, liver, kidney, and pancreas. High birth weight, craniofacial dysmorphism, polydactyly, hepatomegaly, splenic abnormalities, hypertrophic kidneys, and renal cysts are also common features.

REFERENCE

Silhánová E, Plevová P, Curík R, et al. 2006. Elejalde syndrome: A case report. *Am J Med Genet Part A*. 140A:2223–2226.

ELEPHANTIASIS, SCROTUM (ELEPHANTIASIS SCROTI)

DESCRIPTION Also called *elephantiasis scroti*, this is the end result of a progressive lymphatic obstruction in which the scrotum and penis can become massively enlarged. Usually associated with filariasis, which is uncommon in the United States. Differential includes filariasis and other infectious causes; malignancy obstructing lymphatics; surgical therapy that has altered lymphatic drainage; and idiopathic, such as Milroy disease. (See also Section I: "Edema, External Genitalia (Lymphedema, Peno-Scrotal Edema)"; Section II: "Filariasis, Urologic Considerations." and (Image ☼))

TREATMENT

- Drug therapy for any infectious etiology
- Surgery for resection of redundant scrotum with flap coverage of testes

REFERENCE

Zacharakis E, Dudderidge T, Zacharakis E, et al. Surgical repair of idiopathic scrotal elephantiasis. *South Med J*. 2008;101(2):208–210.

ENCOPRESIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Children who are incontinent of stool, even with minor fecal soiling, usually have significant constipation. Occult pathology of the bowel or nervous system must be ruled out as a possible cause. Encopresis usually is helpful in identifying bowel problems when the parents of a child are not aware of the child's stool habits. Children with encopresis and constipation have a higher risk of UTI and urinary incontinence. Successful treatment of functional constipation will usually resolve encopresis and associated urinary tract problems. The term "fecal incontinence" is sometime used as the preferred term over encopresis or soiling. (See also Section I: "Dysfunctional Elimination Syndrome.")

TREATMENT

- Diet changes
- Laxatives, stool softeners
- Toilet schedules

REFERENCE

Combs AJ, Van Batavia JP, Chan J, et al. Dysfunctional elimination syndromes: how closely linked are constipation and encopresis with specific lower urinary tract conditions? *J Urol*. 2013;190(3):1015–1020.

ENCRUSTED CYSTITIS AND PYELITIS

DESCRIPTION Inflammatory ulcerating condition of the bladder and pelvicalyceal system characterized by encrustation with calcium deposits (struvite and apatite calculi). Commonly, the presence of alkaline urine, infection by urea-splitting Corynebacterium urealyticum (formerly called Corynebacterium group D2), a multiple antibiotic-resistant urea-splitting bacterium, is the most frequently incriminated agent, and recent history of a urologic procedure in a immunocompromised host (eg, renal transplant) is found. Clinical manifestations of encrusted cystitis are often fever, dysuria, and gross hematuria. Encrusted pyelitis may have lumbar pain in addition to symptoms of encrusted cystitis. Imaging on US and CT may reveal calcific encrustations with thick-walled edema of the bladder and/or pyelocaliceal system. Calcifications seldom appear on plain abdominal radiographs unless in association with staghorn calculi. The endoscopic appearance is of calcified white plaques adherent to a severely inflamed and ulcerated mucosa. Bacteriologic diagnosis of *Corynebacterium* group D2 requires culture for 48–72 hr at 37°C on media enriched with 5% carbon dioxide (CO_2) or sheep blood agar.

TREATMENT

- Treat *Corynebacterium* infection according to sensitivity; most are susceptible to vancomycin and teicoplanin (not available in the United States)
- Acidify urine through irrigation (eg, Suby's solution G, Thomas C24) or PO acetohydroxamic acid
- Remove calcified plaques where bacteria harbor: TUR, endoscopic

REFERENCE

López-Medrano F, García-Bravo M, Morales JM, et al. Urinary tract Infection due to Corynebacterium urealyticum in kidney transplant recipients: An underdiagnosed etiology for obstructive uropathy and graft dysfunction—Results of a prospective cohort study. *Clin Infect Dis*. 2008;46(6):825–830.

ENCRUSTED URETERAL STENT

DESCRIPTION Indwelling ureteral stents are routinely employed for the prevention and treatment of ureteral obstruction secondary to intrinsic, extrinsic, and iatrogenic causes such as urolithiasis, strictures, and/or malignancy. Indwelling time seems to affect rate of encrustation: Consensus is that stents should not remain in place longer than 3–6 mo (high degree of variation according to different series). Reported risk factors include urinary tract infections (urease-producing microorganisms) and pregnancy. Site and degree of encrustation will guide the appropriate approach (single or multimodal). For this purpose several grading systems and management algorithms have been proposed. Good communication between physician and patient is imperative in preventing this challenging complication.

REFERENCE

Acosta-Miranda AM, Milner J, Turk TM. The FECal Double J: A simplified approach in the management of encrusted and retained ureteral stents. *J Endourol*. 2009;23(3):409–415.

ENDOCARDITIS (SBE) PROPHYLAXIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Antimicrobial prophylaxis for genitourinary procedures solely to prevent infectious endocarditis is no longer recommended by the American Heart Association; the risk of adverse events exceeds the benefit. The AHA guidelines concluded that bacteremia resulting from random daily activities are much more likely to cause infectious endocarditis than bacteremia associated with GU procedures.

REFERENCE

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council. *Circulation*. 2007;116(15):1736–1754.

ENDOCERVICOSIS, BLADDER

DESCRIPTION This rare mucinous analog of endometriosis histologically demonstrates glandular lesions characterized by a prominent endocervical-type epithelium that may involve the urinary bladder in women of reproductive age. Typically are observed in the posterior wall of the bladder or the dome. Lack of awareness may lead to confusion with an adenocarcinoma, particularly of urachal origin given its location. Because of this, patients are presumed to have an underlying malignancy and are treated surgically. Patients usually present with irritative voiding symptoms and pelvic pain. Transurethral resection or partial cystectomy is curative, and close follow-up is recommended.

REFERENCE

Young RH. Tumor-like lesions of the urinary bladder. *Modern Pathology*. 2009;22:s37–s52.

ENDOMETRIOSIS, GENITOURINARY

DESCRIPTION Endometriosis is a condition in which endometrial tissue is found outside the uterus. Most common sites in the GU system are the bladder and distal 3rd of ureter. Symptoms are variable and may include dysmenorrhea and pelvic pain with or without urinary symptoms of gross hematuria, flank pain, frequency, or urgency. Urinary symptoms may or may not be exacerbated with menstruation, and the classic symptom of “cyclical hematuria” is uncommon. Diagnosis is through IVP/CT urography and urine analysis, laparoscopy to inspect the pelvis and obtain tissue biopsy, or cystoscopy or ureteroscopy to evaluate hematuria and obtain biopsy.

TREATMENT

- Hormonal therapy with oral contraceptives, danocrine, or GNRH agonists
- Surgery when medical treatment fails
- Partial cystectomy, ureterolysis, ureteric reimplantation, or ureteral stenting may be performed

REFERENCE

Umar SA, MacLennan GT, Cheng L. Endometriosis of the ureter. *J Urol.* 2008;179(6):2412.

EPCA-2 (EARLY PROSTATE CANCER ANTIGEN)

DESCRIPTION A nuclear matrix protein (NMP) that showed promise as a new serum-based biomarker of prostate cancer, which was postulated to have better sensitivity and specificity than PSA. However, at the request of the authors (Leman et al., *Urology*. 2012;79(2):490), the original article was retracted as there were inconsistencies in validating their data collection.

REFERENCE

Leman ES, Cannon GW, Trock BJ, et al. EPCA-2: A highly specific serum marker for prostate cancer. *Urology*. 2007;69:714–720.

EPIDIDYMAL CYST

DESCRIPTION Epididymal cysts tend to occur in the head of the epididymis and may be mistaken for a testicular mass. They are increased in male offspring of mothers who used DES during pregnancy. They are often asymptomatic. The distinction between a spermatocele and an epididymal cyst is based on size; epididymal cystic masses > 2 cm are called spermatoceles. Spermatoceles are always located superior to the testis and are palpated as distinct from the testis, which differentiates them from hydroceles. Transscrotal ultrasound is diagnostic and no treatment is necessary. (See also Section I: "Scrotum and Testicle, Mass" and "Spermatocele"; Section II: "Epididymal Cystadenoma/Papillary Cystadenoma.")

REFERENCE

Eyre RC. Evaluation of nonacute scrotal pathology in adult men. www.UpToDate.com. Wolters Kluwer, Accessed April 1, 2014.

EPIDERMOID CYST, TESTICLE

DESCRIPTION Epidermoid cysts account for ~1% of testicular tumors. Producing keratinizing, stratified, squamous cell–lined cysts supported by fibrous tissue, these cysts are considered special cases of teratoma, but are not truly considered a teratoma since only a single germinal layer and not the required 2 layers is represented. Benign in behavior; scrotal US is suggestive of the diagnosis but not usually definitive. (See also Section I: "Scrotum and Testicle, Mass.")

TREATMENT

- Inguinal orchiectomy
- Some advocate organ-sparing surgery if the diagnosis is definitively proven by frozen section

REFERENCE

Heidenreich A, Engelmann UH, Vietsch HV, et al. Organ preserving surgery in testicular epidermoid cysts. *J Urol.* 1995;153(4):1147–1150.

EPIDIDYMAL CYSTADENOMA/PAPILLARY CYSTADENOMA

DESCRIPTION This is a benign tumor that accounts for 1/3 of all primary epididymal

tumors. Epididymal cystadenomas are seen in up to 2/3 of patients with von Hippel–Lindau disease and are often bilateral with this syndrome. They have a cystic appearance on ultrasound and can be up to 6 cm. Cut surface is gray-brown and contain fluid. The histologic appearance is that of dilated tubules with a single or double layer of cuboidal or low columnar epithelium. Rarely can be mistaken for metastatic RCC. Papillary cystadenomas are benign and generally asymptomatic and no treatment is required. (See also Section I: "Scrotum and Testicle, Mass," "Spermatocele," and "Von Hippel–Lindau Disease/Syndrome" and Section II: "Epididymal Cysts.")

REFERENCES

Bostwick DG. Chapter 14. Spermatic cord and testicular adnexae. In: Bostwick DG, Cheng L, eds. *Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier: 2008.
Eyre RC. Evaluation of nonacute scrotal pathology in adult men. www.UpToDate.com. Wolters Kluwer. Accessed April 1, 2014.

EPIDIDYMIS, METASTASIS TO

DESCRIPTION Extremely rare, with primary sites reported to include colon, stomach, kidney, prostate, carcinoid, and pancreatic tumors. Prognosis is related to that of the primary disease. Patients can present with pain and swelling or as an incidental finding on orchiectomy for prostate cancer. 4 mechanisms for spread have been proposed, including direct extension, retrograde venous extension, retrograde lymphatic extension, and arterial embolism.

REFERENCE

Powell BL, Craig JB, Muss HB. Secondary malignancies of the penis and epididymis: A case report and review of the literature. *J Clin Oncol*. 1985;3:110–116.

EPIDIDYMIS, OBSTRUCTION

DESCRIPTION A cause of obstructive azoospermia. Most common cause is vasectomy, which results in a fixed obstruction and elevated vessel pressures resulting, in the blowout of the epididymal tubules. Other causes include trauma, congenital malunion of the vas and epididymis, infection, inflammatory damage to the epididymis, and idiopathic. Epididymovasostomy is the treatment of choice. (See also Section I: "Infertility, Urologic Considerations" and "Vas Deferens, Congenital Absence"; Section II: "Azoospermia.")

REFERENCE

Kim ED, Winkel E, Orejuela F, et al. Pathological epididymal obstruction unrelated to vasectomy: Results with microsurgical reconstruction. *J Urol*. 1998;160(6, Part 1):2078–2080.

EPITHELOID HEMANGIOMA, PENIS AND SCROTUM

DESCRIPTION Rare vascular lesion, typically arising on the head and distal extremities, whose pathogenesis is not fully understood. Genital involvement has rarely been reported. These lesions do not recur following excision and no metastasis has been reported.

Macroscopically, the lesions are described as an inflammatory red to brown nodule. Microscopically, the lesions are characterized by endothelial cells arranged in nests surrounded by immature vessels and eosinophilic cell infiltrate. Differential diagnosis includes epithelioid hemangio-endothelioma, epithelioid hemangiosarcoma, Kimura's disease, and bacillary angiomatosis. Treatment is local excision.

REFERENCE

Ismail M, Damato S, Freeman A, et al. Epithelioid hemangioma of the penis: case report and review of literature. *J Med Case Rep*. 2011;5:260.

ERECTILE DYSFUNCTION INVENTORY OF TREATMENT SURVEY (EDITS)

DESCRIPTION A validated satisfaction questionnaire for both patient (11 items) and partner (5 items) based on their subjective evaluation of the treatment for ED. Few of the disease-specific instruments used to assess ED address sexual dysfunction related quality of life, psychosocial impact, and satisfaction. EDITS attempts to address both patient and partner satisfaction with ED treatment, in addition to sexual functioning.

REFERENCE

Althof SE, Corty EW, Levine SB, et al. EDITS: Development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. *Urology*. 1999;53(4):793–799.

ERECTION HARDNESS SCORE (EHS) FOR ED

DESCRIPTION The EHS was developed as a single-item, patient-reported outcome to quantify erection hardness data. It is easy to use and highly responsive to treatment. Psychometric analysis supports its use as a simple, valid, reliable, and responsive tool for the assessment of erection hardness in clinical research.

REFERENCE

Mulhall JP, Goldstein I, Bushmakin AG, et al. Validation of the erection hardness score. *J Sex Med*. 2007;4(6):1626–1634.

ERYSIPELAS, EXTERNAL GENITALIA

DESCRIPTION Superficial bacterial infection of the dermis with marked dermal lymphatic involvement. The irritation afflicts extremes of ages, and the most common site of involvement is the face. Typically heralded by pain, superficial erythema, and plaque-like edema with a sharply defined margin to normal skin, it may often be described as a *peau d'orange* appearance. The clinician must differentiate erysipelas from cellulitis and Fournier gangrene (exclusion of this diagnosis is a priority in all cutaneous infections of the external genitalia). It is usually caused by Group A hemolytic streptococcus (eg, *S. pyogenes*), or rarely *S. aureus*.

TREATMENT

- Mild infection: PO penicillin, macrolides, or clindamycin
- Severe infection: Parenteral penicillin or vancomycin

REFERENCE

Link RE. Cutaneous disease of the external genitalia. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:416–467.

ERYTHEMA MULTIFORME (EM), EXTERNAL GENITALIA

DESCRIPTION EM is a common acquired blistering skin condition that affects all age groups, ethnicities, and sex. EM minor is a mild subtype that usually is confined to skin and oral involvement. EM major (Stevens–Johnson syndrome) affects skin and often other mucoepithelial-lined surfaces including the eyes, oral cavity, and external genitalia. The hallmark of EM is a target lesion, a circular erythematous macular lesion resembling a bulls-eye, commonly occurring on the hands. Painful rash is characteristic, and macules, papules, urticaria, vesicles, bullae, purpura, or petechiae are pleomorphic. In EM major, large tracts of skin and oral mucosa may be denuded, along with conjunctivitis, and GU and upper GI involvement. HSV is the most common cause but virtually any infectious agent or drug can cause EM. Main differential is toxic epidermal necrolysis.

TREATMENT

- EM minor: Wet compress with topical astringent, topical acyclovir (for HSV-related EM)
- EM major (Stevens–Johnson syndrome): Hospitalization required, nutrition, hydration, aggressive topical nursing care equivalent to burn protocols

REFERENCE

Fine JD. Blistering diseases. In: Kerdel FA, FJimenez-Acosta, eds. *Dermatology: Just the Facts.* New York, NY: McGraw-Hill; 2003:143–145.

ERYTHRASMA

DESCRIPTION Superficial, asymptomatic cutaneous infection by the diphtheroid Corynebacterium minutissimum. Physical exam reveals sharply delineated, round to oval patches with scales in the intertriginous or interdigital regions. Wood's lamp exam reveals coral-red fluorescence. Histologically, only the stratum corneum is affected, with all other layers normal. More common in tropical climates. Despite there being no consensus on the ideal treatment for the condition, usually it consists of topical or oral antibiotic therapy for 14 days (erythromycin or tetracycline). Recent evidence suggests single-dose clarithromycin may be an alternative regimen.

REFERENCE

Blaise G, Nikkels AF, Hermanns-Lê T, et al. Corynebacterium-associated skin infections. *Int J Dermatol.* 2008;47(9):884–890.

EXCRETORY UROGRAM, INTRAOPERATIVE ("ON TABLE IVP"/"SINGLE-SHOT IVP")

DESCRIPTION The preferred imaging study for renal trauma is contrast-enhanced CT, and the indications for intraoperative excretory urography is uncommon. However, a "single-shot" IVP may be performed in a setting in which renal trauma is suspected during abdominal

exploration for a trauma patient too unstable for CT. A single film is shot on the operative table at 10 min after administration of 2 mL/kg of IV contrast. An abnormal or inconclusive study should prompt renal exploration to complete staging of the renal injury and perform appropriate repairs; a properly performed study can potentially reduce the need for renal exploration by 32%. The study is also valuable in confirming the presence of a normal contralateral renal unit before renal exploration.

REFERENCES

Jankowski JT, Spirnak JP. Current recommendations for imaging in the management of urologic traumas. *Urol Clin N Am.* 2006;33(3):365–376.

Morey AF, McAninch JW, Tiller BK, et al. Single shot intraoperative excretory urography for the immediate evaluation of renal trauma. *J Urol.* 1999;161(4):1088–1092.

EXPRESSED PROSTATIC SECRETIONS (EPS)

DESCRIPTION EPS represents prostatic fluid expressed after vigorous prostatic massage. Evaluation of this fluid is part of the Stamey test used in the evaluation of prostatitis. Note that prostate massage is contraindicated in the setting of acute bacterial prostatitis. The WBC count in an EPS for a diagnosis of chronic bacterial prostatitis (NIH category II) is >10 WBCs/hpf (40× objective) or clumping of WBCs with the presence of oval fat bodies and a positive EPS bacterial culture. NIH category III prostatitis is divided into IIIa and IIIb, based on whether greater or fewer than 10 WBCs are seen on microscopic exam of the EPS, respectively. The pH of prostatic fluid increases with infection (6.5–>8.0).

REFERENCE

Nickel JC, Shoskes D, Wang Y, et al. How does the premassage and postmassage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? *J Urol.* 2006;176(1):119–124.

EXSTROPHY–EPISPADIAS COMPLEX (EEC)

DESCRIPTION EEC is a rare congenital urogenital anomaly with a spectrum of complexity ranging from epispadias and bladder exstrophy to cloacal exstrophy. Incidence of bladder exstrophy is between 1 in 10,000 and 1 in 50,000 live births, with a male preponderance. The risk of recurrence in a family is 1 in 100. The condition is believed to be due to failure of the cloacal membrane to be reinforced by in growth of mesoderm, therefore preventing the medial migration of mesenchymal tissues and lower abdominal wall development. The defective cloacal membrane ruptures prematurely and, depending on the stage of development during which the rupture occurs, a variant of the complex will result. Most anomalies relate to defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum, and anus. (See also Section I: “Epispadias” and “Exstrophy, Bladder [Classic Exstrophy].”)

TREATMENT

- Immediate at birth: Prevent irritation/trauma to exposed mucosal surfaces (eg, Saran wrap)
- Surgical reconstruction must consider appearance of lower abdomen and genitalia, pelvic bone reconstruction, continence, and subsequent sexual function

- Staged reconstruction: Early bladder, abdominal wall, and posterior urethral closure, with osteotomy. Epispadias repair between 6 and 12 mo. Reconstruction of continent bladder neck and ureteric reimplantation, usually at age 4–5 yr.
- Single-stage reconstruction

REFERENCE

Eeg K, Khoury A. The exstrophy-epispadias complex. *Curr Urol Rep*. 2008 9;9(2):158–164.

EXTRAGONADAL GERM CELL TUMORS (EGCT)

DESCRIPTION Rare entity representing 3–5% of all GCT. There is a clinical association with Klinefelter syndrome, and testicular ultrasound is necessary to exclude primary tumor. Extragonadal GCT must show no evidence of a primary tumor in the testes (or ovaries in females). Primary EGCT are usually midline in decreasing frequency: Mediastinum, retroperitoneum, pineal/suprasellar region, and the sacrococcygeal region. All tumor types are reported, with nonseminomatous being most common. They can present with wide local invasion and advanced metastasis with few symptoms. Transformation to sarcoma or carcinomas has been reported with chemotherapy resistance common in these cases. 1 or both testicular tumor markers (β-HCG or AFP) are elevated in 85% of cases of EGCT. Management of EGCT parallels that of metastatic testicular GCT, however EGCT have a worse prognosis.

TREATMENT

- Surgical excision, if feasible
- Chemotherapy, irradiation, or combination based on histology and in general follows testicular cancer regimens.

REFERENCE

Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: Results from an international analysis. *J Clin Oncol*. 2002;20(7):1864–1873.

EXTRAMAMMARY PAGET DISEASE, UROLOGIC CONSIDERATIONS

DESCRIPTION A rare cutaneous malignancy arising from ducts of apocrine-gland bearing skin, most often involving the anogenital region, more commonly seen in the elderly and women. The condition presents with a well-circumscribed erythematous scaly patch, similar in appearance to mammary Paget disease. There is a 10% association with underlying metachronous GU (most commonly bladder) or GI (most commonly colon) malignancy. Differential diagnoses include SCC in situ or malignant melanoma.

TREATMENT

- Surgical excision with wide margin, Moh's microsurgical excision, or radiation
- Screen for occult GU and GI malignancy

REFERENCE

Smoller BR. Paget's disease. In: Morgan MB, et al. eds. *Deadly Dermatologic Diseases:*

Clinicopathologic Atlas and Text. New York, NY: Springer; 2007:43–50.

EXTRAMEDULLARY HEMATOPOESIS, RENAL

DESCRIPTION This is a reactive process in response to the failure of hematopoiesis in the bone marrow. It commonly occurs in organs such as the liver, spleen, and kidney. It commonly occurs in the presence of myelofibrosis (most common), chronic myeloproliferative disorder, polycythemia vera, and essential thrombocytosis. Considered a cause of renal pseudotumor, a renal mass in association with any of these disorders should raise the possibility of an extramedullary hematopoiesis. Biopsy confirmation is usually required.

REFERENCE

Bhatt S, MacLennan G, Dogra V. Renal pseudotumors. *AJR Am J Roentgenol.* 2007;188:1380–1387.

EXTRAVASATION DURING UROLOGIC SURGERY

DESCRIPTION Perforation of the urinary tract can lead to extravasation of irrigation fluid, contrast, urine, and/or blood. This can lead to flank pain, fever, and ileus, depending on the site of perforation. Potential complications include formation of an infected urinoma or hematoma. The extent of fluid collection can be documented by imaging studies in the form of CT scan or ultrasound. Fluid collections due to extravasation can be managed with either observation, when appropriate, or drainage.

REFERENCE

Lytton B, Weiss RM, Green DF, et al. Complications of ureteral endoscopy. *J Urol.* 1987;137:649–653.

FABRY DISEASE/SYNDROME

DESCRIPTION Fabry disease is a rare X-linked disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A. Progressive accumulation of the substrate Globotriasylceramide (Gb3) leads to progressive organ failure and premature death. Findings consist of multiple cutaneous lesions (*angiokeratoma corporis diffusum*), corneal opacification, and progressive renal insufficiency. Symptoms of severe burning pain in the extremities usually begin in the 1st decade, and can cause febrile episodes. Cardiovascular effects include coronary artery disease and congestive heart failure. Renal failure leads to uremia and hypertension in the 3rd–5th decades.

TREATMENT

- Enzyme replacement therapy with agalsidase-β
- Renal replacement therapy

REFERENCE

Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest.* 2004;34(3):236–242.

FAMILIAL TESTOTOXICOSIS

DESCRIPTION Cause of isosexual precocity inherited as an autosomal dominant pattern. Markedly elevated levels of testosterone with normal LH secretion are noted, but sleep-associated LH pulses are absent. Patients typically present with family history and testicular enlargement around ages 3–4. Diagnosis is a lack of testosterone response to hCG administration, despite a measurable increase in LH. Hyperplasia of Leydig cells is noted on biopsy. Ketoconazole, antiandrogens, aromatase inhibitors, and/or medroxyprogesterone acetate have been used in different combinations with success.

REFERENCE

Lenz AM, Shulman D, Eugster EA, et al. Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. *Pediatrics*. 2010;126(3):728–733.

FANCONI SYNDROME

DESCRIPTION An acquired or inherited disorder characterized by abnormalities of renal proximal tubular function, including glucosuria, phosphaturia, aminoaciduria, and bicarbonate wasting. The aminoaciduria is generalized, and defects in uric acid, water, potassium, and sodium absorption can also occur. The basic abnormality is unknown. Acquired disease is caused by 6-mercaptopurine or outdated tetracycline, renal transplantation, multiple myeloma, amyloidosis, intoxication with heavy met als or other chemical agents, and vitamin D deficiency. Inherited form (usually seen with other disorders) presents in infancy with proximal tubular acidosis, hypophosphatemic rickets, hypokalemia, polyuria, and polydipsia. In the nephropathic form, failure to thrive and growth retardation are common, with progressive renal failure. Diagnosed by demonstrating the abnormalities of renal function.

TREATMENT

- Sodium bicarbonate for acidosis
- Renal transplantation has been successful

REFERENCES

Bickel H, Manz F. Hereditary tubular disorders of the Fanconi type and the idiopathic Fanconi syndrome. *Prog Clin Biol Res*. 1989;305:111–335.

Palmer LS, Trachtman H. Renal functional development and diseases in children. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011:3002–3027.

FATTY CASTS

DESCRIPTION Fatty casts contain fat globules embedded within tubular epithelial casts. Polarized light microscopy may reveal a "Maltese cross" appearance if cholesterol is present. These are most commonly associated with nephrotic syndrome, but occasionally seen also after long-bone fractures, and classically seen in fat embolism syndrome.

REFERENCE

Schrier RW. Clinical evaluation. In: *Diseases of the Kidney and Urinary Tract.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:294.

FECAL INCONTINENCE, UROLOGIC CONSIDERATIONS

DESCRIPTION Numerous studies have identified a relationship between urinary symptoms and fecal incontinence. In the Nurses' Health Study of over 64,000 women ages 62–87 yr, the prevalence of dual urinary and fecal incontinence was 7% (fecal incontinence alone was 4% and urinary incontinence alone was 38%). Risk factors for dual incontinence in women included: age >80 yr; depression; neurologic disease; functional limitations, multiparity; and childbirth of a heavy newborn (>9.5 lb). As compared with white race, black race was associated with a decreased risk of dual incontinence. Men and women with overactive bladder (OAB) are significantly more likely to report having chronic constipation or fecal incontinence compared with those without OAB. Causes of fecal incontinence include vaginal delivery with anal sphincter damage, surgical trauma, diabetes mellitus, decreased rectal compliance (ulcerative proctitis and radiation proctitis), impaired rectal sensation (diabetes, MS, demential, meningo-myelocele, SCI), fecal impaction, medications, food intolerance, and idiopathic. Stool impaction with the rectum in close proximity to the bladder can elicit local, spontaneous neurogenic activity, prompting urinary frequency, and/or incontinence.

In children with fecal incontinence urinary tract issues are often present. Up to 29% children have daytime wetting and 34% have nighttime wetting. Urinary tract infections have been associated with fecal incontinence in 33% of girls and 3% of boys. (See also Section I: "Dysfunctional elimination Syndrome.")

REFERENCES

Ferry GD. Definition, clinical manifestations, and evaluation of functional fecal incontinence in infants and children. www.UpToDate.com; Wolters Kluwer, Accessed April 1, 2014.

Robson K, Lembo AJ. Fecal incontinence in adults. www.UpToDate.com; Wolters Kluwer, Accessed April 1, 2014.

FECALURIA

DESCRIPTION The presence of fecal matter passed per urethra, suggestive of a fistulous communication between the urinary and intestinal tract. Etiologies include a pathologic process such as Crohn's disease, diverticulitis, and cancer, or iatrogenic causes such as perineal surgery, radiation, or trauma. Initial evaluation should include cross-sectional imaging in the form of CT (modality of choice) or MRI to help delineate the location of the fistulous tract.

REFERENCE

Rovner ES. Urinary tract fistulae. In: Wein AJ, Kavoussi LR, Novick AC, et al. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:2223–2261.

FEMALE HYPOACTIVE SEXUAL DESIRE DISORDER

DESCRIPTION Female sexual dysfunction has been defined in the DSM-IV manual as persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty. Prevalence ranges from 39–43% in recent studies. The operational definition of desire/arousal is currently being reviewed. The DSM-V is scheduled for release in May 2013.

CAUSES

- Hormonal: Hypothalamic/pituitary dysfunction, menopause, chronic oral contraceptive pills
- Musculogenic: Hyper- or hypotonicity of pelvic floor
- Neurogenic: Spinal cord injury (SCI), other nervous system disorders (DM, CVA)
- Psychogenic: Relationship problems, poor body image/self-esteem, mood disorders
- Vasculogenic: Poor blood flow, pelvic atherosclerosis, trauma
- Iatrogenic: Medication use (antidepressants, esp. SSRIs)

TREATMENT

- Education: Desire-arousal-orgasm axis, emotional intimacy, anatomic explanation
- Lifestyle modification: Stress management, adequate rest, regular exercise
- Pharmacology: Topical/vaginal estrogens improve vaginal lubrication and atrophy, but have shown no effect on sexual desire. Testosterone (300 μg/d transdermally) has shown benefit in postmenopausal women, but remains unapproved by the FDA. Phosphodiesterase inhibitors have not shown improvement for women with diminished desire.

REFERENCE

Frank JE, Mistretta P, Will J. Diagnosis and treatment of female sexual dysfunction. *Am Fam Physician*. 2008;77(5):635–642.

FEMALE SEX FUNCTION INDEX (FSFI)

DESCRIPTION The FSFI is a validated questionnaire to assess female sexual function. It was developed for the specific purpose of assessing domains of sexual functioning (eg, desire,

sexual arousal, lubrication, orgasm, satisfaction, pain) in clinical trials. It was not designed for use as a diagnostic instrument and should not be used as a substitute for a complete sex history in clinical evaluation. The FSFI was validated in 2 groups of women, including subjects with sexual arousal disorder (determined by history) and age-matched controls. The instrument reliably differentiated these 2 groups in all domains of sexual functioning.

REFERENCE

Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000;26(2);191–208.

FEMINIZING GENITOPLASTY

DESCRIPTION Surgical treatment of ambiguous genitalia may be indicated in the genetic female with virilization of external genitalia for psychosocial development. The most common cause of virilization in the female newborn is CAH. Feminizing genitoplasty may be performed early in infancy to facilitate gender-appropriate upbringing, or delayed until adolescence when the patient can participate in consent. Extensive counseling of parents of any infant with a disorder of sexual development is critical before considering genitoplasty. Goals of surgery are to create external genitalia with an esthetic female appearance, and permit sexual function and, if possible, fertility. (See also Section I: “Disorders of Sexual Development [DSD]”; Section II: “Congenital Adrenal Hyperplasia.”)

REFERENCE

Schober JM. Feminization (surgical aspects). In: Stringer MD, Oldham KT, Mouriquand PDE, eds. *Pediatric Surgery and Urology: Long-term Outcomes*. New York, NY: Cambridge; 2006:595–611.

FERTILE EUNUCH DISEASE/SYNDROME

DESCRIPTION Syndrome characterized by prepubertal androgen deficiency or eunuchoidism caused by LH deficiency but pubertal or almost adult-sized testes in which advanced-stage spermatogenesis is present due to relatively preserved FSH secretion. However, spermatogenesis usually is not completely normal in these men, and they are not fertile. Because there is only relative gonadotropin deficiency and some spermatogenesis is present, treatment with LH-like activity (hCG) stimulates Leydig cell testosterone production and ameliorates androgen deficiency, stimulating spermatogenesis sufficient for induction of fertility.

REFERENCE

Matsumoto AM, et al. Testicular disorders. In: Melmed S, lonsky KS, Larsen PR, et al. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia, PA: Elsevier; 2011.

FIBROEPITHELIAL POLYP, GENITOURINARY

DESCRIPTION The most common benign ureteral tumor, arising from the upper 3rd of the ureter, these polyps resemble a smooth nodule or may be pedunculated. Histologically, a

central fibrous core surrounded by normal or hyperplastic urothelium is seen. Patients present with flank pain and hematuria, usually as a young adult. Radiographically, smooth filling defects are seen. Hydroureteronephrosis can be seen, as well as ureteral intussusception. They can recur locally.

TREATMENT
Ureteroscopic resection, open ureterotomy with polypectomy, or partial ureterectomy if the diagnosis cannot be confirmed preoperatively.

REFERENCE
Sun Y, Xu C, Wen X, et al. Is endoscopic management suitable for long ureteral fibroepithelial polyps? *J Endourol.* 2008;22(7):1459–1462.

FIBROEPITHELIAL POLYP, PENIS

DESCRIPTION Fibroepithelial polyp of the penis is a rare benign finding with only a few reported cases in the literature. Most of these patients have a long-term history of usage of condom catheter. The possible pathogenesis is a chronic irritation. Histologically, it contains loosely arranged spindle to stellate cells in a collagenous and edematous stroma with variable-sized thin-walled vascular channels, with perivascular hyalinization. Fibroepithelial polyp of prepuce differ from conventional cutaneous fibroepithelial polyp (also known as a skin tag, acrochordon) by being larger, having notable stromal edema and vascular dilatation and by having greater stromal cellularity. Skin tags are usually <5 mm in size and they have a predilection for the axilla, neck, and eyelid.

REFERENCE
Banerji JS, Shah S, Kekre NS. Fibroepithelial polyp of the prepuce: A rare complication of long-term condom catheter usage. *Indian J Urol.* 2008;24(2):263–264.

FIBROUS HAMARTOMA OF INFANCY

DESCRIPTION Uncommon subcutaneous and lower dermis proliferative lesion, with the most common anatomic distributions being the axillary region, upper arm, upper trunk, inguinal region, and external genital area. Vast majority of cases occur within the 1st year of life and present as a painless nodule with rapid growth. There is a predilection for boys with a male/female ratio of 2.4. Local excision is curative with very low recurrence rates even in the setting of incomplete excision. Should be in the differential diagnosis of genital masses. Histologically, it demonstrates mature adipose tissue, scattered mesenchymal cells, and bundles of fibrous tissue.

REFERENCE
Dickey GE, Sotelo-Avila C. Fibrous hamartoma of infancy: Current review. *Pediatr Dev Pathol.* 1999;2(3):236–243.

FIBROUS PSEUDOTUMOR OF TESTICULAR TUNIC

DESCRIPTION Reactive, benign process of the tunica vaginalis in which multiple firm

nodules occur in the tunica or within it. Presents as testicular mass, sometimes associated with trauma or hydrocele. It may be difficult to distinguish from malignant processes. Histologically, the lesion can demonstrate granulation tissue, fibroblastic proliferation, and nodules of hyalinized tissue.

SYNONYMS
- Fibrous pseudotumors
- Multiple fibromas of the tunica vaginalis testes
- Reactive periorchitis

TREATMENT
Orchiectomy usually necessary to confirm diagnosis but local excision can be considered.

REFERENCE
Parker PM. Benign fibrous pseudotumor of tunica vaginalis testis. *Urology*. 2006;68(2):427:e17–e19.

FIDUCIAL MARKERS

DESCRIPTION External beam radiotherapy is a valuable tool in the treatment of localized prostate cancer; however, this form of treatment is limited by the difficulty in accurately localizing the prostate gland. The implantation of intraprostatic gold fiducial markers under transrectal ultrasound guidance is a safe outpatient procedure that aids in identifying anatomic structures of interest during radiation treatment (most importantly the prostate-rectal interface). Markers are usually cylindrical allowing ease of placement with a hollow bore needle. Surface features prevent migration. The preprocedure regimen is similar to transrectal ultrasound-guided prostate biopsy. Prophylactic antibiotics are administered, anticoagulant medications withheld 7 days before procedure, and cleansing enemas given to empty the rectal vault. Patients are routinely placed in the left lateral decubitus position. A transrectal ultrasound probe is utilized to calculate prostate volume in the standard fashion. Local anesthesia should be placed bilaterally at the level of the neurovascular bundles. An 18-gauge implant needle is utilized to place markers into the right base, left base, and apex of the prostate. Standard prostate biopsy discharge instructions are given. Patients then follow up with a radiation oncologist for pretreatment planning imaging and subsequent radiotherapy (Image ☼).

REFERENCE
Linden RA, Weiner PR, Gomella LG, et al. Technique of outpatient placement of intraprostatic fiducial markers before external beam radiotherapy. *Urology*. 2009;73(4):881–886.

FILARIASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Filariasis is transmitted by mosquitoes, most commonly *Wuchereria bancrofti,* endemic to areas of the Caribbean, Venezuela, Colombia, the Guianas, Brazil, Central America, sub-Saharan Africa, North Africa, Turkey, and Asia. Filariasis (Bancroftian, Malayan, and Timorian) is often asymptomatic. The parasite causes symptoms due to inflammation and dysfunction of the lymphatics, where the adult worms develop (fever, headache, myalgia, and

lymphadenitis). In lymphatic disease, manifestations usually occur 3 mo–1 yr after acquisition. Occasionally, moderate lymphadenopathy, particularly involving the inguinal lymph nodes, occurs. Inflammation of the lymphatics of the extremities and genitalia leads to retrograde adenolymphangitis. Epididymitis, orchitis, and funiculitis can also occur, along with fever, chills, and other nonspecific systemic symptoms. Lymphatic dysfunction, with resulting chronically progressive edema of the limbs and genitalia, is relatively infrequent in children. Elephantiasis can result from fibrosis caused by chronic dysfunction of the lymphatic channels. Chyluria can occur as a manifestation of bancroftian filariasis. Lymphatic filariasis must be diagnosed clinically because serologic assays are not available, and in elephantiasis the microfilariae may no longer be present. Eosinophilia of 25% frequently occurs in early disease. (See also Section I: “Edema, External Genitalia [Peno-Scrotal Edema].”)

TREATMENT

- Diethylcarbamazine citrate is the drug of choice. The late obstructive phase of the disease is not affected by chemotherapy.
- Ivermectin, an investigational drug in the United States, is effective against the microfilariae of *W. bancrofti*, but is unlikely to become the drug of choice for lymphatic filariasis.
- Complex, decongestive physiotherapy may be effective in treating elephantiasis.
- Plastic surgical repair of the genitalia gives variable results.
- Chyluria originating in the bladder responds to fulguration; chyluria originating in the kidney is much more difficult to correct.

REFERENCE

Kehinde EO, Anim JT, Hira PR. Parasites of urological importance. *Urol Int.* 2008;81(1):1–13.

FINE-NEEDLE ASPIRATION (FNA) OF PROSTATE

DESCRIPTION In the detection of prostatic carcinoma, FNA cytology of the prostate has largely been replaced by core needle biopsy of the prostate, as cytology does not allow Gleason grading. However, the detection rates of prostatic carcinoma by either core needle biopsy or FNA appear to be comparable. Largely replaced by core biopsy techniques. (See also Section II: “Cytology, Prostate.”)

REFERENCE

Hautmann SH, Conrad S, Henke RP, et al. Detection rate of histologically insignificant prostate cancer with systematic sextant biopsies and fine needle aspiration cytology. *J Urol.* 2000;163:1734–1738.

FISH: URINARY FLUORESCENT IN SITU HYBRIDIZATION (UROVYSION TEST)

DESCRIPTION Cytogenetic studies describe frequent alterations in chromosomes 1, 3, 4, 7, 8, 9, 11, 17, etc., in urothelial cancers. FISH allows the study of genetic abnormalities within formalin-fixed cancer cells. UroVysion test is a multitargeted multicolor FISH assay that stains exfoliated cells from urine specimens with probes for chromosome 3, 7, 17, and 9p21, and

allows observation of the cells under a fluorescence microscope. Reported sensitivity of UroVysion test is higher for higher-grade tumors (83–97%) and CIS (almost 100%), than with low-grade low-stage tumors (36–57%). Specificity is high (89–96%). A false-positive UroVysion test may predict for future recurrence or simply reflect urothelium that is at risk of malignant transformation. A study to detect bladder cancer in a high-risk population showed FISH to be comparable to urine cytology with a higher false-positive rate (Image ☼).

REFERENCE

Banek S, Schwentner C, Täger D, et al.; UroScreen Study Group. Prospective evaluation of fluorescence-in situ-hybridization to detect bladder cancer: Results from the Uroscreen-Study. *Urol Oncol.* 2013;31(8):1656–1662.

FISTULA, ENTEROVESICAL

DESCRIPTION An abnormal fistulous communication between the bowel (such as *colovesical fistula*) and urinary bladder due to various inflammatory and neoplastic causes. Usually presents with fecaluria, pneumaturia, and/or recurrent UTI. Gouverneur syndrome is the "classic" presentation of vesicoenteric fistula: Suprapubic pain, urinary frequency, dysuria, and tenesmus. Causes include inflammatory processes (diverticulitis, Crohn disease), neoplasia (bladder or colonic malignancy), and radiation. Diagnosis may require the use of ≥1 diagnostic modality, such as endoscopy (colonoscopy, cystoscopy), contrast imaging (cystography, contrast enema), and CT. Oral-activated charcoal and urinary straining on a stone filter may be useful, as well as the Bourne test. (See Section II: "Bourne Test" and (Image ☼).)

TREATMENT

- Surgical resection of fistulous tract with or without fecal and urinary diversion
- Fecal and urinary diversion
- Conservative management

REFERENCES

Kavanagh D, Neary P, Dodd JD, et al. Diagnosis and treatment of enterovesical fistulae. *Colorectal Dis.* 2005;7(3):286–291.

Randall D, Tittle V, Wright G, et al. Crohn's disease and enterovesical fistulae: Common things are common. *Br J Hosp Med.* 2010;71(9):530–531.

FISTULA, RECTOURETHRAL

DESCRIPTION An abnormal communication between the urethra and rectum, almost exclusively in males due to anatomic reasons. May present with passage of urine in the stools. Causes include iatrogenic (transurethral instrumentation and surgery, RP, cryosurgery or radiotherapy of prostate), trauma, inflammatory bowel disease, pelvic infection, or congenital malformations. Diagnosis may require the use of ≥1 diagnostic modality, such as endoscopy (proctosigmoidoscopy, cystoscopy), contrast imaging (urethrocystography, contrast enema), CT or MRI with endorectal coil.

TREATMENT

- Surgical excision of fistulous tract, urethral repair, tissue interposition, and rectal closure with possible use of advancement flaps or vascularized flaps
- Posterior trans-ano-sphincteric, transperineal, transanal, transabdominal approaches described
- Possible vascularized flaps include dartos flap, scrotal myocutaneous flap, island groin flap, gracilis flap, and omental flap
- Proximal bowel diversion usually recommended
- Fecal and urinary diversion
- Conservative management

REFERENCE

Gupta G, Kumar S, Kekre NS, et al. Surgical management of rectourethral fistula. *Urology.* 2008;71(2):267–271.

FISTULA, URETEROARTERIAL

DESCRIPTION May present with microscopic hematuria, intermittent gross hematuria, or torrential hemorrhage in extremis. Risk factors include prior pelvic surgery, chronic indwelling ureteric stents, pelvic irradiation, and arterial disease. Rarely, this is the etiology for hematuria, but should be considered for persistent gross hematuria or torrential bleeding in a patient with associated risk factors. General guideline to reduce the risk of fistula development is the use of the smallest caliber, softest flexible ureteric stent for the shortest possible period. In a stable patient, CT, retrograde uretero-pyelography, and angiography may be nonspecific but aid in planning reconstructive options. Removal of stents and ureteral manipulation should be performed with caution and in a facility where immediate angiographic or surgical intervention is available.

TREATMENT

- If stable, early reconstruction of vascular and urinary structures:
  - Vascular occlusion with angiographic stent or embolization; *OR*
  - Vascular ligation, with or without bypass procedure
  - Ureteric reconstruction by uretero-ureterostomy, cutaneous ureterostomy, transverse ureteroureterostomy, or ureteric ligation with nephrostomy
  - Endovascular stenting is increasingly used in lieu of open techniques due to the high operative risk and comorbidities in patients with ureteroarterial fistulas
- In the actively bleeding patient, immediate surgical intervention or angiographic occlusion

REFERENCE

Fox JA, Krambeck A, McPhail EF, et al. Ureteroarterial fistula treatment with open surgery versus endovascular management: Long-term outcomes. *J Urol.* 2011;185(3):945–950.

FISTULA, VESICOCUTANEOUS

DESCRIPTION An abnormal communication between the urinary bladder and skin of the anterior abdominal wall or groin. The fistulous tract that exists after placement of suprapubic catheter is the most commonly seen. Causes include urinary diversion (suprapubic

catheterization); infected urachal remnant; radiation; dehiscence of urinary bladder repair, usually in association with complex pelvic and bowel surgery; and others (bladder calculus, inguinoscrotal hernia). Diagnosis is made by cystoscopy and CT contrast imaging.

TREATMENT

- Surgical excision of fistulous tract and repair
- Conservative management

REFERENCE

Kobori Y, Shigehara K, Amano T, et al. Vesicocutaneous fistula caused by giant bladder calculus. *Urol Res.* 2007;35(3):161–163.

FISTULA, VESICOUTERINE

DESCRIPTION Rare, usually caused by simultaneous injury to uterus and bladder. Urinary incontinence is present if the cervical os is incompetent. The lesion occasionally presents with Youseff syndrome, which describes menouria (urine in menses), cyclic hematuria with apparent amenorrhea, infertility, and urinary incontinence in patients with prior low-segment cesarean section, which is the most common cause. Other causes include uterine rupture during obstructed labor tearing the posterior bladder wall, placenta percreta, and others (IUD, brachytherapy, traumatic bladder catheterization). Differential diagnosis includes vesicovaginal fistula (VVF), ureterovaginal fistula (UVF), and endometriosis of bladder. Diagnosis is made by cystography, cystography, and contrast CT or MRI of the pelvis, which helps exclude concomitant ureteric injury and (Image ☼).

TREATMENT

- Prolonged bladder drainage with or without fulguration of fistula tract, and await spontaneous resolution. Option of hormonal induction of menopause to help induce involution of uterus
- Surgical management:
  - Hysterectomy and bladder repair, if fertility not desired
  - Uterine-sparing surgery if fertility preferred

REFERENCE

Rao MP, Dwivedi US, Datta B, et al. Post caesarean vesicouterine fistulae-Youssef syndrome: Our experience and review of published work. *ANZ J Surg.* 2006;76(4):243–245.

FISTULA, VESICOVAGINAL AND URETEROVAGINAL

DESCRIPTION Vesicovaginal fistula (VVF) is an abnormal communication between the urinary bladder and vagina that may be associated with urethrovaginal fistula (UVF) in 12%. Patients present with continuous urinary incontinence, with prior history of recent pelvic or gynecologic surgery or other causes.

CAUSES

- Iatrogenic following obstetric and gynecologic surgery
- Pelvic malignancy
- Pelvic radiation

- Inflammatory: Pelvic and abdominal infections
- Penetrating trauma
- Foreign body

DIAGNOSIS
- Pelvic exam
- Cystoscopy with cystography and/or retrograde pyelography
- Contrast imaging (eg, CT urography with delayed imaging, CT cystogram)

TREATMENT
UVF should be managed by reimplantation of ureter. Before undergoing a ureteral reimplantation, a patient can be temporarily managed with ipsilateral percutaneous nephrostomy drainage. Small VVFs may close spontaneously with prolonged bladder drainage. If a VVF requires primary repair, a multilayer closure can be achieved through a transvaginal or transabdominal approach. If diagnosis has been delayed by several weeks, then it is prudent to delay repair for approximately 3 mo. Principles of VVF repair include:
- Demarcation of fistula
- Approaches: Transvaginal, transabdominal
- Excise diseased tissue if present
- Multilayered closure with interrupted absorbable sutures and nonoverlapping suture lines
- Consider vascularized tissue interposition (eg, Martius flap, pedicled muscle flap, peritoneal flap, omental flap), especially when quality of tissue healing is expected to be compromised (eg, previous failed repair, postirradiation)
- Adequate postoperative bladder drainage (Image ☼)

REFERENCE
Wong MJ, Wong K, Rezvan A, et al. Urogenital fistula. *Female Pelvic Med Reconstr Surg.* 2012;18(2):71–78.

FITZ–HUGH–CURTIS SYNDROME

DESCRIPTION Perihepatic inflammation and right upper quadrant pain found in a small segment of patients with pelvic inflammatory disease (PID). PID is a polymicrobial, ascending, postcoital infection of the upper genital tract usually associated with gonorrhea, *Chlamydia*, *Haemophilus,* or *Streptococcus*. Fitz–Hugh–Curtis is believed to occur from transperitoneal or vascular dissemination of PID organisms, often suggesting a profound pathologic inoculation. The diagnosis is confirmed by laparoscopic visualization of filmy perihepatic adhesions.

REFERENCE
Torrealday S, Torrealday S. Benign gynecologic conditions. *Surg Clin North Am.* 2008;88:245–264.

FLANK HERNIA FOLLOWING NEPHRECTOMY

DESCRIPTION True flank hernias are rare, and careful palpation may reveal the fascial edges. Obesity, immunocompromised states, and poor nutrition status are risk factors. Flank

"bulge" is not a true hernia and is believed to be due to laxity of the transversus and oblique abdominal wall muscles, caused by injury to the intercostal nerves, in particular the 11th intercostal, and accentuated in part by unopposed contraction of contralateral musculature. About 15% of patients develop flank bulge after a retroperitoneal flank incision. Care should be taken to avoid injury to the intercostal nerves during incision and closure.

TREATMENT

- Flank hernia: Generally should be repaired with or without mesh, based on surgeon preference, patient comorbidities, and clinical factors specific to each case. If the patient is asymptomatic or debilitated, a corset can be offered
- Flank bulge: Repair seldom needed except for cosmesis (Image ☼)

REFERENCE

Baumann DP, Butler CE. Lateral abdominal wall reconstruction. *Semin Plast Surg.* 2012;26(1):40–48.

FLUORESCENT (BLUE LIGHT) CYSTOSCOPY

DESCRIPTION Drugs for fluorescence diagnosis, such as 5-ALA and hexaminolevulinate (Hexvix [EU]; Cysview [US]), are placed intravesically where they preferentially stain malignant or premalignant tissue and emit a red fluorescence when excited by visible blue light. Requires specific endoscopic equipment fitted with the blue light, camera, and lens with filters. In a meta-analysis, fluorescent cystoscopy (92.4%) sensitivity was superior to white-light cystoscopy (60.5%). Reports have shown fluorescent cystoscopy to be limited by specificity, which is equivalent to or poorer than white-light cystoscopy. Fluorescent cystoscopy can enhance the diagnosis of patients with positive cytology and no visible lesion on white-light cystoscopy, and for surveillance of high-risk bladder cancers and/or CIS (Image ☼).

REFERENCE

Isfoss BL. The sensitivity of fluorescent-light cystoscopy for the detection of CIS of the bladder: A meta-analysis with comments on gold standard. *BJU Int.* 2011;108(11):1703–1707.

FOLEY Y-V PYELOPLASTY

DESCRIPTION The triangular portion of the Y is incised in the dependent portion of the pelvis, with the apex pointing to the stricture, and a single 2- to 3-cm longitudinal incision is continued from the apex anteriorly down across the stricture to complete the Y configuration. The apex of the triangle flap is then brought down to the lower apex of the ureterotomy and a 5-0 chromic stay suture is placed. Interrupted 5-0 chromic sutures are used to complete the anastomosis. Used for UPJ repair.

REFERENCE

Tsivian A, Tsivian M, Sidi AA. The Y-V pyeloplasty revisited. *Urology.* 2010;75(1):200–202.

FORDYCE SPOTS (ECTOPIC SEBACEOUS GLANDS), PENIS

DESCRIPTION Fordyce spots are ectopic sebaceous glands on the lips and buccal and genital mucosa (glans penis and labia minor). Lesions are multicentric and whitish to yellowish in color with slightly elevated papules and plaques with sizes ranging from 1–3 mm. Most patients are asymptomatic but some consider receiving treatment for cosmetic reasons since the lesions do not resolve spontaneously. CO_2 laser can be used for ablation.

REFERENCE

Lee JH, Lee JH, Kwon NH, et al. Clinicopathologic manifestations of patients with Fordyce's Spots. *Ann Dermatol.* 2012;24(1):103–106.

FOREIGN BODY, BLADDER AND URETHRA

DESCRIPTION Almost every conceivable foreign body has been inserted into the urinary bladder and urethra, usually for erotic exploration and curiosity, or because of psychiatric disorder or mental retardation. Amazonian parasitic catfish (*Candiru*) and leeches have also been reported to enter the urethra while bathing in a river. Symptoms include urethral pain, dysuria, urinary retention, hematuria, frequency, painful voiding, weak stream, and sepsis. (See also Section II: "Bladder Filling Defect.")

TREATMENT

- Urethral foreign body: Endoscopic retrieval may be easier by 1st pushing back into bladder; alternatively, urethrotomy, especially when periurethral abscess is present
- Bladder foreign body: Endoscopic retrieval; open vesicostomy (Image ☼)

REFERENCE

Van Ophoven A, DeKernion JB. Clinical management of foreign bodies of the genitourinary tract. *J Urol.* 2000;164(2):274–287.

FORMALIN INSTILLATION, INDICATIONS AND TECHNIQUE

DESCRIPTION Formalin (37% formaldehyde) instillation is an option in the management of hemorrhagic cystitis which is refractory to more conservative measures. A solution of 50 mL of 1% formalin is typically utilized. Instillation must be done in the operating room and usually with general anesthesia, as the procedure may cause pain. Prior to instillation, a cystogram must be performed to rule out vesicoureteral reflux. If reflux is present, then formalin may cause damage to the ureters and intrarenal collecting system. Use of Fogarty catheters to occlude the ureters in the case of reflux has been reported. Bladder fibrosis with reduced capacity and increased urinary frequency is a common outcome after formalin instillation. (See also Section II: Cystitis, Hemorrhagic.")

REFERENCE

Joseph CM, Bowley DM. Formalin treatment of refractory hemorrhagic cystitis. *J Pediatr Urol.* 2005;1(5):365–367.

FOSSA NAVICULARIS DIVERTICULUM

DESCRIPTION 1st described by Guérin (1864), this diverticulum is partially separated from the urethra by a septum. On voiding cystorethrogram (VCUG), it can often be seen as a small spherical collection of contrast at the tip of the penis. It is thought to result embryologically from an incomplete breakdown of the wall between the ectoderm and the urethra being formed by the urethral folds. It is a common anatomic finding with rare symptoms, including dysuria, gross hematuria, spotting of blood, or hematospermia.

SYNONYMS

- Valve of Guérin
- Dorsal urethral diverticulum
- Lacuna magna

TREATMENT

If symptomatic, the wall can be divided with tenotomy scissors or under direct vision with a resectoscope.

REFERENCE

Seskin FE, Glassberg KI. Lacuna magna in 6 boys with postvoid bleeding and dysuria: Alternative approach to treatment. *J Urol.* 1994;152(3):980–982.

FOWLER SYNDROME (PRIMARY DISORDER OF URETHRAL SPHINCTER RELAXATION)

DESCRIPTION This syndrome describes young women (usually under the age of 30) with idiopathic urinary retention and no evidence of neurologic disease. The classic patient will present with the inability to void for an entire day and will have a large volume of urine in her bladder. For diagnosis, a retained urine volume of 1 L or more and lack of sensation or urgency is necessary. EMG activity of the urethral sphincter indicates abnormally increased sphincter activity making appropriate relaxation difficult. There is an association with polycystic ovarian syndrome.

TREATMENT

Use of botulinum toxin, pharmacotherapy, and hormonal modulation have not proven to be successful. Sacral neuromodulation has proven to be successful. 1 study reported efficacy approaching 70%.

REFERENCES

De Ridder D, Ost D, Bruyninckx F. The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. *Eur Urol.* 2007;51(1):229–233.

Fowler CJ, Christmas TJ, Chapple CR, et al: Abnormal electromyographic activity of the urethral sphincter, voiding dysfunction, and polycystic ovaries: A new syndrome? *BMJ.* 1988;297:1436–1438.

FOWLER–STEPHENS ORCHIOPEXY

DESCRIPTION This procedure is used in the treatment of high intra-abdominal testes. It

entails ligating the spermatic vessels and hinges on the premise that the testicle will survive from the vasal and cremasteric collaterals. The operation was originally described as a 2-stage procedure in which the vessels are divided, and then 6 mo later the testicle is brought down to the scrotum, after collaterals have become well developed. However, the procedure is now performed also a 1-stage procedure. Both techniques have a fairly high success rate, but 2-stage is reported to have a slightly better success rate (85% for 2-stage vs. 80% for 1-stage). It is now commonly performed using laparoscopy.

REFERENCES

Elyas R, Guerra LA, Pike J, et al. Is staging beneficial for Fowler-Stephens orchiopexy? A systematic review. *J Urol.* 2010: 183(5):2012–2018.

Esposito C, Vallone G, Savanelli A, et al. Long-term outcome of laparoscopic Fowler-Stephens orchiopexy in boys with intra-abdominal testis. *J Urol.* 2009;181(4):1851–1856.

FRACTURE RISK ASSOCIATED WITH PROSTATE CANCER AND ANDROGEN DEPRIVATION THERAPY

DESCRIPTION Androgen deprivation therapy (ADT) for treatment of prostate cancer leads to a hypogonadal state. This state predisposes men to osteopenia or osteoporosis with subsequent increased risk of fracture. There is a direct correlation between length of time on ADT and risk of fracture. 1 study reported that after 5 yr on ADT, the risk of fracture rises nearly 7% compared to controls.

TREATMENT

Men being treated with ADT should be considered for a baseline DEXA scan to assess bone mineral density (BMD). Increased weight-bearing exercise and cessation of smoking should be encouraged. Also, calcium and vitamin D supplementation can help improve BMD. Daily supplementation of calcium (1,200 mg/d with most taken through dietary means) and vitamin D (1,000–1,200 IU daily) is recommended. Systemic therapy (bisphosphonate or denosumab) therapy has also been shown to play a role in the prevention of osteoporosis and reduce fracture risk. Densoumab is approved for men on ADT or with osteoporosis 60 mg SC Q 6 mo (Prolia). Bisphosphonates such as zoledronic acid (Reclast) can be given IV 5 mg/yr, alendronate (Fosamax, Fosamax Plus D) and risedronate (Actonel) are given orally weekly. Alternative dosing forms are given with the presence of bone metastasis to decrease skelet al related events (SRE). Densosumab (Xgeva) is given 4 mg SC monthly and zoledronic acid (Zometa) is administered IV 4 mg monthly.

REFERENCES

Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med.* 2005;352:154–164.

Suzman DL, et al. Bone-targeting agents in prostate cancer. *Cancer Metastasis Rev*. 2014 Jan 8 [Epub ahead of print]

Zhumkhawala AA, Gleason JM, Cheetham TC, et al. Osteoporosis management program decreases incidence of hip fracture in patients with prostate cancer receiving androgen deprivation therapy. *Urology*. 2013;81(5):1010–1015.

FRAGILE X SYNDROME

DESCRIPTION The most common cause of inherited mental retardation. The affected gene encodes a protein known as FMR1, which is required for normal cognitive development. Facial dysmorphism and bilateral macro-orchidism (MO) are also seen. Measurement of testis size in mentally retarded males has been suggested as a simple screening test for this condition.

REFERENCE

Healy A, Rush R, Ocain T. Fragile X syndrome: an update on developing treatment modalities. *ACS Chem Neurosci.* 2011;2(8):402–410.

FRALEY SYNDROME

DESCRIPTION A condition in which vascular obstruction of the superior infundibulum might lead to hydrocalyx, bleeding, and intermittent flank pain or infection. Vessels causing obstruction may be arteries, veins, or both. Impaired drainage on delayed films or isotope renography must be confirmed before surgery. On ultrasound, diuretics will accentuate the caliectasis.

TREATMENT

Surgery can provide relief in severely symptomatic patients. Various techniques including infundibulo-infundibulostomy, infundibulopyelostomy, infundibulorrhaphy, and vasopexy have been reported to be successful in treating symptoms.

REFERENCES

D'Amico A, Lusuardi L, Ficarra V, et al. Experience in the surgical treatment of Fraley's syndrome. *Eur Urol.* 2000;38(4):410–414.

Fraley EE. Vascular obstruction of superior infundibulum causing nephralgia: A new syndrome. *N Engl J Med.* 1966;275:1403–1409.

FRENCH CATHETER SCALE

DESCRIPTION Used to measure the outer diameter of catheters, cystoscopes, and other endoscopes. The diameter in millimeters of the instrument is determined by dividing the French size by 3 (eg, an 18 Fr catheter has a diameter of 6 mm). The system was introduced by a 19th century French medical instrument manufacturer. (See Section VII: "Catheter Guide.")

REFERENCE

Bedside procedures. In: Gomella LG, Haist SA, eds. *Clinicians Pocket Reference.* 11th ed. New York, NY: McGraw-Hill; 2007.

FREQUENCY, URINARY

DESCRIPTION Urinary frequency is defined as the patient's perception that he/she voids too often by day. Although often associated with an overactive bladder and/or bladder outlet obstruction, urinary frequency is 1 of many complaints included in the nonspecific,

nondiagnostic symptom complex known as lower urinary tract symptoms or LUTS. Frequency is further categorized as 1 of the storage symptoms (experienced during the bladder filling phase or storage phase of micturition), as opposed to a voiding or postmicturition symptom.

REFERENCE
Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report of the terminology for female pelvic floor dysfunction. *Neurourol Urodyn.* 2010;29(1):4–20.

FREQUENCY–DYSURIA SYNDROME

DESCRIPTION Occurring in children and women, this is also referred to as the "urethral syndrome." Patients present with complaints of frequency and dysuria, but evaluation finds no infectious, anatomic, functional, or physiologic abnormalities. Because this term is so nonspecific, it is not a currently accepted meaningful term for diagnosis or treatment planning. In childhood, hypercalciuria was theorized and in adults, fastidial organisms were once thought to be the cause. (See also Section II: "Urethral Syndrome.")

REFERENCE
Brock JW III. The frequency and frequency dysuria syndromes of childhood: Hypercalciuria as a possible etiology. *Urology.* 1994;44(3):411–412.

FUHRMAN NUCLEAR GRADING CLASSIFICATION, RENAL CELL CARCINOMA (RCC)

DESCRIPTION A classification used to grade renal cell carcinoma, based on the concept that nuclear features correlate with survival, this scale consists of 4 grades based on size, contour, and conspicuousness of nucleoli. Large series have confirmed the correlation with survival. Grade 1 is round, uniform nuclei with minute or absent nucleoli. Grade 2 is slightly irregular nuclei about 15 μm, with nucleoli visible at 400×. Grade 3 is more irregular nuclei, 20 μm, with nucleoli visible at ×. Grade 4 is similar to grade 3, with bizarre features noted. There is a noted correlation between tumor size and Fuhrman grade (Image ☼).

REFERENCE
Zhang, C, Li X, Hao H, et al. The correlation between size of renal cell carcinoma and its histopathological characteristics: a single center study of 1867 renal cell carcinoma cases. *BJU Int.* 2012;110(11 Pt b):E481–E485.

FUNGURIA

DESCRIPTION Funguria (sometimes called candiduria due to the frequent finding of *Candida* species) refers to fungus in the urine (fungal UTI of the bladder or kidney). It is a common nosocomial infection. Organisms are typically *C. albicans* and *C. glabrata*. Other organisms can involve the kidney through disseminated infection (eg, *Aspergillus* sp., *Fusarium*, others). Associated predisposing factors include catheters, antibiotics, diabetes mellitus, hospitalization, and immunocompromised states. Urinary colonization is usually

asymptomatic, whereas invasive fungal infection of bladder may have irritative voiding symptoms. Fungal infection of the kidney is often hematogenous in origin from other sources or the GI tract; fungal renal or perirenal abscesses present similar to pyelonephritis. Infection should be suspected when urine microscopy shows budding fungal hyphae. Positive fungal urine culture demands investigation. (See Section I: "Fungal Infections, Genitourinary"; Section II: "Bezoars, Genitourinary.")

TREATMENT

- Remove predisposing factors
- Asymptomatic candiduria rarely requires antifungal therapy (unless in the setting of neutropenia, neonates, or urinary tract instrumentation):
  - Fluconazole, 200–400 mg (3–6 mg/kg) daily for several days if urinary tract instrumentation is planned
- Symptomatic cystitis: Fluconazole 200 mg (3 mg/kg) daily for 2 wk or amphotericin B 0.3–0.6 mg/kg for 1–7 days; or flucytosine 25 mg/kg QID for 7–10 days. Amphotericin B bladder irrigation is recommended only for fluconazole-resistant organisms (eg, *C. krusei* and *C. glabrata*).
- Symptomatic infections should be treated
- Bezoars should be removed

REFERENCE

Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503–535.

FUNICULITIS

DESCRIPTION Inflammation of the spermatic cord; the entire spermatic cord is subject to inflammatory diseases, usually as a result of trauma or pyogenic bacteria, and this condition is occasionally seen with scrotal inflammation or epididymitis. Parasitic infections (filariasis, schistosomiasis) can also induce inflammatory changes in the cord (see also Section I: "Spermatic Cord Mass and Tumors.")

REFERENCE

Sabiston D. *Textbook of Surgery*. 19th ed. Philadelphia, PA: Saunders; 2012.

GAMETE INTRAFALLOPIAN TRANSFER (GIFT)

DESCRIPTION GIFT is similar to IVF but is rarely performed currently with the improved pregnancy rates in IVF. Current indications for GIFT include patients who have ethical or religious objections to IVF and prefer fertilization in vivo rather than in vitro. Technique involves inducing superovulation, aspirating the ovarian follicles vaginally under US guidance, and identifying eggs. Sperm is collected and capacitated. During laparoscopy, sperm and eggs are mixed and transferred into 1 of the fallopian tubes, allowing in vivo fertilization. A 20–30% pregnancy rate per cycle is reported. Limitations of GIFT are that patients must have normal fallopian tubal function and the procedure requires general anesthesia and laparoscopy.

REFERENCE

DeUgarte CM, et al. Assisted reproductive technologies: In vitro fertilization & related techniques. In: DeCherney AH, Nathan L, eds. *Current Diagnosis & Treatment Obstetrics & Gynecology*. 10th ed. New York, NY: McGraw-Hill; 2006.

GANGLIONEUROBLASTOMA, ADRENAL

DESCRIPTION Extremely rare tumor originating from neural crest cells, this ganglioneuroblastoma exists on a spectrum of diseases between neuroblastoma and ganglioneuroma. It is varied in appearance and malignant potential, with prognosis and behavior depending on histology. The cause is unknown, but it has been reported to have a genetic predisposition. Treated by surgical resection.

REFERENCE

Koike K, Iihara M, Kanbe M, et al. Adult-type ganglioneuroblastoma in the adrenal gland treated by a laparoscopic resection: Report of a case. *Surg Today*. 2003;33(10):785–790.

GANGLIONEUROMA, ADRENAL

DESCRIPTION A tumor originating from neural crest cells, this is the benign counterpart of neuroblastoma. It does not metastasize, but can locally recur after resection and be locally aggressive. It most commonly presents as an abdominal mass. Histologically, the lesion is composed of ganglion cells with abundant cytoplasm and large nuclei. Treatment is by surgical resection.

REFERENCE

Gupta R, Dinda AK. Ganglioneuroma of the adrenal gland: A rare case. *Indian J Pathol Microbiol.* 2007;50(4):782–784.

GARTNER DUCT CYST

DESCRIPTION Gartner duct cyst is a rare congenital anomaly associated with urogenital maldevelopment, usually located posterior to the urinary bladder. It is caused by a failure of separation of the ureteric bud from the mesonephric duct that leads to persistence of the

Gartner duct, often with cystic dilation. The Gartner duct is associated with müllerian duct developmental anomalies and with abnormal ureteric development, such as ureteric ectopia. Abnormal development of the ureter also results in the maldevelopment, ectopic kidney, or absence of the ipsilateral kidney. The usual presentation is an anterior vaginal wall mass with ipsilateral renal dysgenesis with or without urinary incontinence. Differential diagnoses include ectopic ureterocele, urethral diverticulum, urethral tumor, Skene gland cyst or abscess, and vaginal wall cysts or tumors. Diagnosis is by voiding cystourethrography, cystourethroscopy, and retrograde pyelography (maldevelopment of the bladder neck and hemitrigone; ureteric ectopia or ureteric dysgenesis) and renal and bladder US (a cystic lesion behind bladder is suggestive of Gartner duct cyst and ipsilateral renal agenesis or ectopic kidney). Treated surgically, depending on anatomic anomalies, including transvaginal or transabdominal excision of the Gartner duct and closure of any associated urinary fistula; reconstruction of bladder neck and urethra; reimplantation of ipsilateral and/or contralateral ureter; or removal of nonfunctioning renal unit and ectopic ureter.

REFERENCE

Dwyer PL, Rosamilia A. Congenital urogenital anomalies that are associated with the persistence of Gartner's duct: A review. *Am J Obstet Gynecol.* 2006;195:354–359.

GENITAL AROUSAL DISORDER (PERSISTENT)

DESCRIPTION A condition of spontaneous, intrusive, and frequently unwanted genital arousal including throbbing, pulsating, and tingling. These feelings are usually unrelated to any sexual arousal. Physical arousal caused by this syndrome can persist for extended periods of time. Orgasm can sometimes provide temporary relief, but within hours the symptoms return suddenly. Can be debilitating and negatively impact quality of life.

TREATMENT

While not well-studied, treatment options include antidepressants, antiandrogens, psychotherapy, and local nerve blocks (pudendal nerve is most frequent)

REFERENCE

Basson R, Leiblum S, Brotto L, et al. Definitions of women's sexual dysfunctions reconsidered: advocating expansion and revision. *J Psychosom Obstet Gynaecol.* 2003;24:221–229.

GENITAL PIERCING, UROLOGIC CONSIDERATIONS

DESCRIPTION Urologists must be familiar with complications from genital piercing. In males, piercings include the penile glans, shaft, urethra, scrotum, and combinations of these. Clitoral and labial piercings in females are also performed. Complications include:

- Transmission of infectious agent: HIV, Hepatitis B and C, or an STD
- Bleeding
- Cellulitis
- "Cutting-out" or erosion
- Priapism
- Paraphimosis

- Recurrence of condyloma acuminatum
- Urethral fistula
- Hypertrophic scarring, keloid
- Trauma during intercourse: To partner or self

REFERENCE

Anderson W, Summerton DJ, Sharma DM, et al. The urologist's guide to genital piercing. *BJU Int.* 2003;91(3):245–251.

GENITAL SKIN LOSS

DESCRIPTION Genital skin loss is most commonly iatrogenic, as the result of skin debridement for necrotizing infection by polymicrobial infection—Fournier gangrene. Skin loss can less commonly occur as a result of trauma, usually blunt; however, penetrating trauma can also result in skin loss. Burns can also lead to genital skin loss.

TREATMENT

Reconstruction is the mainstay of treatment. In the case of skin loss to due to debridement for infection, the infection should be stable prior to reconstruction being performed. In the case of penile skin loss in an uncircumcised male, a flap using redundant foreskin may be harvested to address a proximal defect. Flaps may also be created using scrotal, abdominal, or thigh tissue. Split-thickness skin grafts can be used to address both penile and scrotal skin defects. Vacuum-assisted closure therapy has been effective in early management with skin grafts (see also Section I: "Scrotum and Testicle, Trauma.")

REFERENCES

Czymek R, Schmidt A, Eckmann C, et al. Fournier's gangrene: Vacuum-assisted closure versus conventional dressings. *Am J Surg.* 2009;197:168–176.

McAninch JW, Kahn RI, Jeffrey RB, et al. Major traumatic and septic genital injuries. *J Trauma.* 1984;24:291–298.

GENITAL ULCERS

DESCRIPTION Genital ulcers may be due to multiple causes: Infection, Behçet syndrome, erythema multiforme, Crohn disease, lichen planus, amebiasis, drug reaction, trauma, and carcinoma in situ are all possible causes. They are most commonly a manifestation of sexually transmitted infections, including chancroid, genital herpes, lymphogranuloma, and primary syphilis. Characteristics of the ulcers associated with sexually transmitted infections are as follows:

- Chancroid: Tender papule that turns painful which has a purulent ulcer underneath; may be single or multiple
- Genital herpes: Multiple painful vesicles
- Lymphogranuloma: A small painless papule or vesicle that ulcerates
- Primary syphilis: Painless, indurated ulcer; usually single

TREATMENT

If a sexually transmitted infection is suspected, empiric antibiotic therapy should be initiated

even before confirmatory testing. Chancroid is treated with a single oral dose of azithromycin, or a single intramuscular dose of ceftriaxone, or oral erythromycin for 7 days. Genital herpes is treated with antiviral drugs such as Acyclovir. Lymphogranuloma is usually treated with tetracycline or erythromycin. Primary syphilis is treated with a single dose of intramuscular penicillin G or a single dose of oral azithromycin in a penicillin allergic patient. (See also Section I: “Sexually Transmitted Infections [STIs]; Sexually Transmitted Diseases [STDs], General.”)

REFERENCES

DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. *Clin Infect Dis.* 1997;25:292–298.

Workowski KA, Berman S; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(No. RR-12)1–110.

GENITOURINARY PAIN INDEX (GUPI)

DESCRIPTION GUPI is a validated 9 question instrument to assess severity of symptoms, in men and women with urologic pain conditions. The GUPI can differentiate men with chronic prostatitis or interstitial cystitis, those with other symptomatic conditions (dysuria, frequency, chronic cystitis), and those with none of these diagnoses. It can discriminate between women with interstitial cystitis, those with incontinence, and those with none of these diagnoses.

REFERENCE

Clemens JQ, Calhoun EA, Litwin MS, et al.; Urologic Pelvic Pain Collaborative Research Network. Validation of a modified National Institutes of Health chronic prostatitis symptom index to assess genitourinary pain in both men and women. *Urology*. 2009;74(5):983–987.

GENOMIC TESTING, PROSTATE CANCER

DESCRIPTION A variety of genomic tests have been recently approved. The more common tests are shown in the table. All rely on either needle biopsy or radical prostatectomy tissue analysis. Their role in the definitive management of patients with prostate cancer is currently evolving.

Common Prostate Cancer Genomic Tests Comparisons		
	ConfirmMDx (MDxHealth)	**Decipher (GenomeDx)**
Indications	To reduce unnecessary repeat biopsies. Performed on previous negative biopsy tissue.	Treatment decisions after radical prostatectomy
Outcome predicted	Presence or absence of occult cancer detection; direct follow up biopsy based on "halo" effect	Risk of clinical metastasis following radical prostatectomy
Assay	3 epigenetic methylation markers	22 genetic markers on RP specimen
	Prolaris (Myriad)	**Oncotype DX (Genomic Health)**
Indications	Biopsy and post RP risk of disease progression; active surveillance decision	Risk assessment on biopsy; active surveillance decision
Outcome predicted	PCa-specific mortality, metastasis, recurrence, progression	Adverse pathology: Primary Gleason 4, any 5, pT3
Assay	46 gene Cell Cycle Progression (CCP) panel	17 gene Genomic Prostate Score (GPS)

REFERENCE

http://www.cancernetwork.com/oncology-journal/new-biomarkers-prostate-cancer/page/0/2, Accessed April 1, 2014.

GERM CELL APLASIA (SERTOLI CELL ONLY SYNDROME)

DESCRIPTION Total absence of germ cells within a normal interstitium. Patients present with infertility, and usually with small to normal testes and azoospermic semen specimens. Phenotypically, these patients are normally virilized males. Histologically, Sertoli cells line the seminiferous tubules with a complete absence of germ cells and normal interstitium. Plasma FSH is usually elevated due to the absence of germ cells. Plasma testosterone and LH are normal. Diagnosis is based on an elevated FSH and FNA of the testis. Aplasia may represent the endpoint of various etiologies, resulting in this histologic appearance. Adoption or use of donor sperm is necessary if children are desired.

REFERENCE

Odabas O, Ugras S, Aydin S, et al. Assessment of the testicular cytology by fine-needle aspiration and the imprint technique: Are they reliable diagnostic modalities? *Br J Urol.* 1997;79(3):445–448.

GESTATIONAL AGE ASSESSMENT, UROLOGIC CONSIDERATIONS

DESCRIPTION Gestational age assessment can be derived from 3 clinical methods: (1)

physical exam, (2) ultrasound, and (3) history, using the date of the last menstrual period (LMP) to calculate the estimated date of delivery ("due date" or EDD). The clinical assessment of gestational age or duration of pregnancy reflects the "menstrual age." Studies have shown ultrasound to be superior to physical exam or history. Rapid determination of gestational age in the delivery room includes assessment of soles of the feet, breast nodules, earlobe, hair, and the external genitalia of males. Babies born 36 wk and earlier the testes are usually partially descended, the scrotum is small with very few rugae. Term infants (39 wk and beyond) should have the testes fully descended, the scrotum should appear normal sized with prominent rugae.

REFERENCE

Gomella, TL ed. *Assessment of Gestational Age in Neonatology*. 7th ed. New York, NY: McGraw Hill, 2013.

GIBBON CLASSIFICATION OF VOIDING DYSFUNCTION

DESCRIPTION Historic classification based in large part on the system proposed by Bors-Comarr. 5 categories are proposed to be important: (1) Full general and neurologic diagnosis, (2) state of the bulbocavernosus and anal reflexes in cord injuries, (3) presence or absence of reflex detrusor contractions, (4) urodynamic findings, and (5) failure of storage, emptying, or control when dealing with incontinence.

REFERENCE

Gibbon NOK. Nomenclature of neurogenic bladder. *Urology*. 1976;8:423–431.

GIBSON INCISION

DESCRIPTION A curvilinear incision is made starting 2–3 cm medial to the anterior superior iliac spine, running parallel to the inguinal ligament down to 2–3 cm superior and just lateral to the pubic tubercle. The external and internal obliques and the transversalis muscle are bluntly opened along their fibers. After transecting the transversalis fascia, the peritoneum is swept medially to expose the ureter at its midsection. Useful for distal ureteral stones, distal ureterectomy and renal transplant.

REFERENCE

Yang WH, Ou CH. A muscle sparing modified Gibson incision for hand-assisted retroperitoneoscopic nephroureterectomy and bladder cuff excision–an approach through a window behind the rectus abdominus muscle. *Urology*. 2012;79(2):470–474.

GIGGLE INCONTINENCE (ENURESIS RISORIA)

DESCRIPTION Giggle incontinence, also referred to as enuresis risoria, is urinary leakage that occurs only with laughter in children with rare exception exclusively occurs in girls. It is characterized by large-volume voids. These children have normal bladder function when the child is not laughing. The disorder is thought to be mediated by the central nervous system and has similarities to detrusor instability.

TREATMENT

- Treatment of this condition is not well studied
- Anticholinergics (eg, oxybutynin)
- Methylphenidate
- Biofeedback was effective in 1 series in patients refractory to medical management

REFERENCE

Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006;176(1):314–324.

GIL-VERNET EXTENDED PYELOLITHOTOMY

DESCRIPTION An open approach to remove a large renal calculi, such as a staghorn calculi. Using a flank incision, the kidney is exposed and freed at the upper pole, lower pole and posteriorly. The ureter is identified and traced to the renal pelvis. The renal pelvis is incised and the incision can be continued to include the calices to allow for removal of more significant calculi.

REFERENCE

Gil-Vernet J. New surgical concepts in removing renal calculi. *Urol Int.* 1965;20:255–288.

GIL-VERNET ORTHOTOPIC URINARY DIVERSION

DESCRIPTION A continuous segment of terminal ileum, cecum, and ascending colon are isolated. The unit is rotated 180° to allow anastomosis of the reduced end of the ascending colon to the urethra and the ureters to the terminal ileum.

REFERENCE

Benson MC, Olsson CA. Continent urinary diversion. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*, 7th ed. Philadelphia, PA: Saunders; 1998:3190–3245.

GIL-VERNET URETERAL REIMPLANTATION

DESCRIPTION Through a transvesical approach, the ureters are dissected free from their hiatus. The principle involves advancing the ureters across the trigone to the midline such that both ureteral orifices are juxtaposed. A single incision is made in the trigone mucosa, which will serve to join traction sutures from each ureter that are anchored in the midline.

REFERENCE

Khoury AE, Bagli DJ. Vesicoureteral reflux. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:3267–3309.

GITELMAN SYNDROME

DESCRIPTION Gitelman syndrome is an autosomal recessive disorder characterized by

hypokalemia, hypocalciuria, and hypomagnesemia with metabolic alkalosis. It is caused by loss of function mutations of a thiazide sensitive sodium-chloride symporter found in the distal convoluted tubule of the kidney.

TREATMENT
Replacement of respective electrolytes.

REFERENCE
Nakhoul F, Nakhoul N, Dorman E, et al. Gitelman's syndrome: A pathophysiological and clinical update. *Endocrine.* 2012;41(1):53–57.

GITTES NEEDLE URETHROPEXY

DESCRIPTION Historically used to treat female stress incontinence. A Stamey needle is delivered through a stab incision at the upper border of the pubis, then transferred under digital guidance through the anterior vaginal wall at the level of the bladder neck. A No. 2 proline suture is used to suspend the bladder neck on both sides, and the vaginal sutures eventually cut through the wall and become buried in the scar.

REFERENCE
Benson JT, Agosta A, McClellan E. Evaluation of a minimal-incision pubovaginal suspension as an adjunct to other pelvic-floor surgery. *Obstet Gynecol.* 1990;75(5):844–847.

GLEASON GRADE, TERTIARY PATTERN

DESCRIPTION The standard Gleason grading system reports the primary and secondary Gleason pattern. The tertiary pattern (3rd most prevalent) is noted if it is high grade. Retrospective data suggest that a high-grade tertiary component after RP, even when present in a small percentage of total tumor volume, has prognostic significance. Its presence is associated with biochemical recurrence and adverse pathologic features such as seminal vesicle invasion, extraprostatic extension, and positive surgical margins.

REFERENCES
Harnden P, Shelley MD, Coles B, et al. Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. *Lancet Oncol.* 2007;8(5):411–419.
Sim HG, Telesca D, Culp SH, et al. Tertiary Gleason pattern 5 in Gleason 7 prostate cancer predicts pathological stage and biochemical recurrence. *J Urol.* 2008;179:1775–1779.

GLEASON GRADING/SCORING SYSTEM

DESCRIPTION A widely accepted system to describe the aggressiveness of prostatic adenocarcinoma was developed by Dr. Donald Gleason between 1969 and 1974, in which prostate cancer mortality data were correlated to low-magnification architectural patterns of prostate carcinoma. 5 grades are described, ranging from well differentiated to undifferentiated. To account for variations within tumors, 2 grades are recorded: The predominant, or primary, grade and the less extensive, or secondary, grade. These are

summated to give the Gleason score (or Gleason sum). Gleason system, the most prevalent and the 2nd most prevalent pattern (if at least 5% of the tumor) are added together to obtain a Gleason score (eg, Gleason grade 3 + 4 = 7). The Gleason score is a strong independent predictor of cancer behavior and treatment outcome for prostate cancer patients. Pattern 3 is separated from pattern 4 because this separation usually distinguishes Gleason score 6 from Gleason score 7 tumors, with the latter having a significantly worse prognosis.

- **Gleason pattern 1:** Very well-circumscribed nodule of single, separate, closely packed, back-to-back glands. There is no infiltration into adjacent benign prostatic tissue. The glands are fairly large, round or oval, and are approximately equal in size and shape. Gleason pattern 1 is usually found in transition zone cancers and is rare. When present, it is usually associated with a pattern 2 tumor. Distinction from pattern 2 is not critical, as they have a similar prognosis.
- **Gleason pattern 2:** Usually, but not always, seen in transition zone carcinomas. Well-circumscribed nodule of single, separate glands with the glands more loosely arranged and not as uniform as in pattern 1. Minimal invasion by neoplastic glands into the surrounding benign prostatic tissue. The cells are smoothly rounded or oval with open lumens and are not angular, as seen in pattern 3. The cytoplasm is more abundant and pale staining than intermediate-grade tumors.
- **Gleason pattern 3:** Infiltrative with extension into adjacent benign prostatic tissue. The glands vary in size and shape and are often elongated or angular. These small glands are often called microglands and are usually smaller than Gleason pattern 1 or 2 glands. However, some of the glands of pattern 3 may be moderate to large sized. The small glands of pattern 3, in contrast to small poorly defined glands of pattern 4, are distinct glandular units and 1 should be able to draw an imaginary circle around each of them. Cribriform glands may also be Gleason pattern 3, with these glands being slightly larger than benign glands and having regular outer contours. They resemble intraductal cribriform carcinoma of the breast. Cribriform pattern 3 must be separated from cribriform pattern 4, intraductal cribriform proliferations, and prostatic duct adenocarcinoma.
- **Gleason pattern 4:** The glands are no longer single and separate as seen in pattern 1–3. They are fused, poorly defined with only occasional lumen formation, or cribriform. Fused glands are chains, nests, or masses of glands that are no longer completely separated by intervening stroma. Fused glands contain rare strands of residual stroma that may give the appearance of partial separation of the glands. Consequently, fused glands may have a scalloped appearance peripherally. The “hypernephromatoid” pattern described by Gleason is an uncommon variant of fused glands and resembles RCC. Cribriform glands of pattern 4 are either large cribriform glands (cribriform sheets) or small cribriform glands with irregular infiltrating borders. The small cribriform glands with irregular infiltrating borders of pattern 4 must be distinguished from cribriform pattern 3, in which the small cribriform glands have regular borders. Fragments of cribriform carcinoma in needle biopsies of the prostate imply a cribriform cancer and are designated pattern 4.
- **Gleason pattern 5:** The tumor has virtually no glandular differentiation. It is composed of solid sheets, solid cords, or single cells. Nests of tumor with central comedonecrosis are also classified as pattern 5. It is controversial whether cribriform glands of cancer that otherwise would be considered Gleason pattern 4 should be considered Gleason pattern 5 if

comedonecrosis is present. Separating poorly defined pattern 4 glands from cords and nests of tumor with virtually no glandular differentiation or with only vacuoles is a problem, but usually not critical because any combination of the 2 patterns will lead to a Gleason score of 8–10, all of which are poorly differentiated (Image ☼).

REFERENCE

Egevad L, et al. Gleason Grading of prostate carcinoma. Available at http://web.archive.org/web/20051016170005/pathology2.jhu.edu/gleason/patterns.cfm (archive accessed March 2, 2014).

GLEASON GRADING SYSTEM, MODIFIED

DESCRIPTION The International Society of Urologic Pathology held a consensus conference in 2005 at which the "old Gleason grading system" for prostatic carcinoma from 1966 underwent its 1st major revision. With this modified grading system, a shift of the most frequent Gleason scores from 6–7a (3 + 4) in biopsy specimens and an increased degree of agreement between specimens of biopsies and radical prostatectomies with carcinoma of the prostate could be demonstrated. After modified grading of GS 3 + 4 = 7a tumors, 95% were stage pT2, whereas 79% of GS 4 + 3 = 7b tumors were stage pT3–4. In cases with PSA <10 ng/mL and tumor extent <20%, the most frequent Gleason scores were 6 and 7a. Cases with serum PSA >10 ng/mL or tumor extent of >20% had higher scores (7b or higher). Cancers with tumor infiltration of <1 mm in 1 of 12 cores and PSA <10 ng/mL were mainly low grade (Gleason scores 6 and 7a) and may correspond to so-called insignificant carcinoma of the prostate. Using the modified Gleason system, grade, stage, tumor extent, and serum PSA show good correlations and characterize the difference between low- and high-grade malignancy of the prostate.

REFERENCE

Helpap B, Egevad L. Modified Gleason grading. An updated review. *Histol Histopathol.* 2009;24(5):661–666.

GLENN-ANDERSON URETERONEOCYSTOSTOMY

DESCRIPTION Through a transvesical approach, the ureter is mobilized from its hiatus and advanced toward the bladder neck through a submucosal tunnel, where it is reimplanted. Used to treat vesicoureteral reflux or resection of a ureteral orifice.

REFERENCE

Kay R. Reimplantation of the ureter. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989: 526–538.

GLOMERULOCYSTIC KIDNEY DISEASE (CORTICAL MICROCYSTIC DISEASE)

DESCRIPTION Rare, bilateral cystic kidney disease that can be inherited (autosomal dominant) or sporadic. Presents most commonly in childhood with bilateral flank masses,

which are large kidneys with many cysts. Seen rarely in adults with hypertension, hematuria, and end stage renal disease (ESRD). Cysts are confined to the cortex and arise from the Bowman space. Renal biopsy may be necessary to confirm diagnosis. Radiologically, the lesions are similar to autosomal-dominant polycystic kidney disease (ADPKD). Treatment is supportive, with renal replacement therapy if renal failure occurs.

REFERENCE

Gusmano R, Caridi G, Marini M, et al. Glomerulocystic kidney disease. *Nephrol Dial Transplant.* 2002;17:813–818.

GLOMERULOSCLEROSIS

DESCRIPTION An accumulation of homogeneous eosinophilic material in the glomerulus, made up of plasma proteins that have exuded from the plasma into glomerular structure; this is a light microscopic feature known as hyalinization. This change contributes to obliteration of capillary lumina of the glomerular tuft, a feature of glomerulosclerosis. Hyalinization and glomerulosclerosis are a consequence of endothelial or capillary wall injury and the end result of various forms of glomerular damage.

REFERENCE

Alpers CE. The kidney. In: Kumar V, Abbas AK, Fausto N, eds. *Robbins and Cotran: Pathologic Basis of Disease.* 7th ed. Philadelphia, PA: Elsevier Saunders; 2005.

GLUCAGON STIMULATION TEST

DESCRIPTION Indicated when the diagnosis of pheochromocytoma is highly suspected by history and clinical findings but blood pressure is normal and diagnostic biochemical tests are equivocal (catecholamines only modestly elevated). The mode of action is the stimulation of glucagon-sensitive adenylate cyclase receptors expressed on the tumor, which can lead to dangerous rises in blood pressure; thus, this test is rarely used. A physician must be present throughout the test, and it should only be performed in patients whose blood pressure is well controlled. A rise in plasma norepinephrine to $>$3-fold or $>$2,000 pg/mL is diagnostic of pheochromocytoma.

REFERENCE

Guber HA, Farag AF, Lo J, et al. Evaluation of endocrine function. In: McPherson RA, Pincus MR, eds. Henry's *Clinical Diagnosis and Management by Laboratory Methods*. 21st ed. China: Saunders Elsevier; 2007.

GLYCOSURIA, RENAL

DESCRIPTION Normal urine contains small amounts of glucose. Increased amounts represent either inefficient handling by the tubule or hyperglycemia. Diabetes is the most common cause of glycosuria. Causes of primary glycosuria are either intestinal glucose–galactose malabsorption or benign familial renal glycosuria. Some substances are known to cause false-positive glucose readings on dipstick, such as ascorbic acid and salicylates. Medications such as ACE inhibitors may also have a direct effect on the kidney and cause

glycosuria. Pregnancy can be causative. Glycosuria may also be part of Fanconi syndrome or RTA.

SYNONYM
Glucosuria

REFERENCE
Bakris GL, Fonseca VA, Sharma K, et al. Renal sodium-glucose transport: Role in diabetes mellitus and potential clinical implications. *Kidney Int.* 2009;75(12):1272–1277.

GOLDSTEIN TEST

DESCRIPTION Intraoperative diagnostic pneumoperitoneum, also known as Goldstein test, is done in the a setting of pediatric open inguinal hernia repair. To prevent unnecessary contralateral inguinal exploration, the test is performed by introducing a soft rubber catheter through the ipsilateral hernia sac. Air is insufflated into the peritoneal cavity, distending it, and the contralateral groin is palpated for crepitus. The presence of crepitus constitutes a positive test and necessitates repair of a metachronous hernia. Currently, this practice has been largely supplanted by the use of laparoscopy.

REFERENCE
Haynes JH. Inguinal and scrotal disorders. *Surg Clin North Am.* 2006;86(2):371–381.

GOLDSTON SYNDROME

DESCRIPTION Rare syndrome with principal features of kidney, liver, and brain abnormalities. The kidneys are cystic and large bilaterally. Histologic lesions of the liver are triads with a double band of fibrous tissue without bile ducts. The brain shows the Dandy–Walker malformation, which is the cystic dilation of the 4th ventricle, secondary to obstruction of the foramina of Luschka and Magendie. Renal replacement therapy, as indicated, and hydrocephalus requiring a shunt are standard treatments.

REFERENCE
Gloeb DJ, Valdes-Dapena M, Salman F, et al. The Goldston syndrome: Report of a case. *Pediatr Pathol* 1989;9(3):337–343.

GONADAL DYSGENESIS, MIXED

DESCRIPTION Gonadal dysgenesis syndromes include Turner syndrome (45, XO), 46, XX "pure" gonadal dysgenesis, mixed gonadal dysgenesis (45, XO/46, XY), partial gonadal dysgenesis (aka, dysgenetic male pseudohermaphroditism), and bilateral vanishing testis syndrome. It is the 2nd most common cause of ambiguous genitalia in the newborn after CAH. Mixed gonadal dysgenesis is characterized by unilateral testis, often intra-abdominal; contralateral streaked gonads; and persistent müllerian structures with varying degrees of inadequate masculinization ("testis plus streak gonad"). A *streak gonad* is dysgenetic and resembles ovarian stromal tissue, but no germ cells are present. Usual karyotype is 45, XO/46, XY mosaicism. Phenotype is variable, ranging from a female with Turner syndrome,

to ambiguous genitalia, to (rarely) normal-appearing males. Almost all have a uterus, vagina, and fallopian tubes, but with varying degrees of phallic development, labioscrotal fusion, and undescended testis. Increased risk exists of gonadoblastoma (incidence 20%) in either dysgenetic testis or streak gonad (more frequently testis), as well as an increased risk of Wilms tumor. Clinical diagnosis is at birth and with confirmatory karyotyping. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Gonadal Dysgenesis, Pure.")

TREATMENT

- Determine gender assignment, based upon potential for normal function of external genitalia and gonads
- Perform appropriate gonadectomy (if male, consider prophylactic gonadectomy versus bringing testis down to scrotum for purpose of screening of gonadoblastoma)
- Screen for Wilms tumor
- Initiate appropriate sex and growth hormone replacement

REFERENCE

Kolon TF. Disorders of sexual development. *Curr Urol Rep.* 2008;9(2):172–177.

GONADAL DYSGENESIS, PURE

DESCRIPTION 46, XX "pure" gonadal dysgenesis ("bilateral streak gonads") is closely related to Turner syndrome, except that it lacks the somatic stigmata associated with Turner syndrome. Patients present with amenorrhea and lack of pubertal development. Evaluation reveals normal female external genitalia and müllerian ducts, absent wolffian ducts, normal height, sexual infantilism, bilateral streaked gonads, and 46, XX karyotype. A streak gonad is dysgenetic and resembles ovarian stromal tissue, but no germ cells are present. This is an autosomal recessive trait with no increased risk of gonadoblastoma (unlike in mixed gonadal dysgenesis). It is treated with cyclic estrogen and progesterone replacement. (See also Section I: "Disorders of Sexual Development [DSD]"; Section II: "Gonadal Dysgenesis, Mixed.")

REFERENCE

Kolon TF. Disorders of sexual development. *Curr Urol Rep.* 2008;9(2):172–177.

GONADOBLASTOMA

DESCRIPTION Rare tumor comprising 0.5% of all testes tumors that occurs almost always in gonadal dysgenesis (intersex disorders). This is a benign tumor that has the potential for malignant transformation. Patients present either with a palpable mass or virilization secondary to androgen production. It has 2 distinct cell types: Large germ cells (similar to dysgerminoma and seminoma) and small cells resembling immature Sertoli or granulosa cells. Tubules microscopically contain PAS-positive staining Call–Exner bodies. Upregulation of the TSPY gene is implicated in this tumor. (See also Section I: "Testis Cancer, Adult General Considerations" and "Testis Cancer, Pediatric, General Considerations"; Section II: "Turner Syndrome.")

SYNONYMS

- Tumors of dysgenetic gonads

- Mixed germ-cell tumor
- Gonadocytoma

TREATMENT
- With an intersex disorder or Turner syndrome: Prophylactic removal of the dysgenic gonad before developing gonadoblastoma
- Radical orchiectomy with possible contralateral orchiectomy secondary to high incidence of bilaterality

REFERENCE
Brant WO, Rajimwale A, Lovell MA, et al. Gonadoblastoma and Turner syndrome. *J Urol.* 2006;175(5):1858–1860.

GOODPASTURE SYNDROME

DESCRIPTION Characterized by a triad of pulmonary hemorrhage, iron deficiency anemia, and glomerulonephritis (GN), representing <1% of all cases of GN. Anti-GBM antibody deposition in the lungs and kidneys is the cause. Antibody production appears to be self-limited. Histologically, it shows focal proliferative and necrotizing glomerular lesions that progress rapidly to diffuse proliferation with crescents. Immunohistochemical studies show diffuse linear deposition of IgG along the GBM. Primarily a disease of young white males (Male > Female, 6:1) with a mean age of 21. About 1/3 of patients die of pulmonary involvement. Renal involvement is usually severe and progressive, with rapid development of oliguria and renal failure.

TREATMENT
- Steroid pulse therapy with prednisone
- Plasma exchange therapy to remove circulating anti-GBM antibody
- Cyclophosphamide to inhibit further antibody production
- Renal replacement therapy for ESRD

REFERENCE
Shah MK, Hugghins SY. Characteristics and outcomes of patients with Goodpasture's syndrome. *South Med J.* 2002;95(12):1411–1418.

GOODWIN URETERAL ANASTOMOSIS

DESCRIPTION Through a transcolonic approach, a nonrefluxing anastomosis is performed by raising a tunnel of mucosa with a mosquito hemostat for a 3–4-cm distance, then exiting the bowel wall. The ureter is grasped and pulled through the tunnel. The spatulated ureter is anastomosed to the colonic mucosa while incorporating some muscularis for security.

REFERENCE
Dahl DM, McDougal WS. Use of intestinal segments in Urinary Diversion. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: Saunders; 2012:2411–2449.

GORLIN SYNDROME

DESCRIPTION Autosomal dominant cancer condition characterized by an increased risk of multiple basal cell carcinomas. Features include disorders of the skin, skelet al, eye, nervous system, and endocrine glands. The lesions are sensitive to ionizing radiation.

SYNONYMS
- Nevoid basal cell carcinoma syndrome
- Basal cell nevus syndrome

REFERENCE
Mitchell G, Farndon PA, Brayden P, et al. Genetic predisposition to cancer: The consequences of a delayed diagnosis of Gorlin syndrome. *Clin Oncol (R Coll Radiol).* 2005;17(8):650–654.

GOUT, UROLOGIC CONSIDERATIONS

DESCRIPTION An inherited disorder of purine metabolism characterized by elevated serum urate levels and severe recurrent arthritis, gout leads to an increased risk of urate urolithiasis and uric acid nephropathy. Most patients with uric acid stones, however, do not have gout. About 20% of patients with gout will develop a stone. Gout may also produce a type IV RTA, resulting in hyperkalemia and a mild metabolic acidosis. (See Section I: "Renal Tubular Acidosis"; Section I: "Urolithiasis, Uric Acid.")

TREATMENT
- Alkalinization of urine and increasing urine output help prevent stones.
- Allopurinol or following a low-purine diet will decrease serum urate levels.

REFERENCE
Liebman SE, Taylor JG, Bushinsky DA. Uric acid nephrolithiasis [review]. *Curr Rheumatol Rep.* 2007;9(3):251–257.

GOUVERNEUR SYNDROME

DESCRIPTION Classic presentation of vesicoenteric fistula, with suprapubic pain, urinary frequency, dysuria, and tenesmus.

REFERENCE
Vidal Sans J, Pradell Teigell J, Palou Redorta J, et al. Review of 31 vesicointestinal fistulas: Diagnosis and management. *Eur Urol.* 1986;12(1):21–27.

GRANULOMA INGUINALE (DONOVANOSIS)

DESCRIPTION Ulcerative disease of the genitals with significant locoregional lymphadenopathy, caused by *Klebsiella granulomatis* (*formerly known as Calymmatobacterium granulomatis).* The disease occurs rarely in the United States and is endemic in some tropical and developing areas (India; Papua, New Guinea; the Caribbean; central Australia; and southern Africa). Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudoboboes) might also occur. The lesions are highly vascular (ie, beefy red appearance) and bleed easily on contact. Ulceration at site inoculation may be

on the genitals or extragenital sites, and prominent lymphadenopathy often results in further skin ulceration over the nodes. Untreated, it results in lymphedema and genital mutilation. (See also Section I: "Sexually Transmitted Infections [STIs]; Sexually Transmitted Diseases [STDs], General.")

Diagnosis is based on rapid Giemsa stained-smear of ulcer (RapiDiff), to look for Donovan bodies. For smear-negative cases, biopsy of the ulcer is necessary. Culture and PCR are available only in specialized centers.

TREATMENT

- Doxycycline 100 mg orally twice a day for at least 3 wk and until all lesions have completely healed
- Alternative regimens (treat until all lesions healed): Azithromycin 1 g orally once per week for at least 3 wk OR ciprofloxacin 750 mg orally twice a day for at least 3 wk OR erythromycin base 500 mg orally 4 times a day for at least 3 wk OR trimethoprim-sulfamethoxazole 1 double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 wk

REFERENCES

O'Farrell N. Donovanosis. *Sex Transm Infect.* 2002;78:452–457.

Workowski KA, Berman S; Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR Recomm Rep*. 2010;59(No. RR-12):1–110.

GRANULOSA CELL TUMORS

DESCRIPTION The most common ovarian neoplasm. Usually small, cystic, unilateral, and secretes estrogens. Often presents in childhood as precocious puberty or as postmenopausal bleeding in older women. During the reproductive years, prolonged and irregular bleeding and a pelvic mass are most common. These tumors can also present with urinary symptoms, and they can rarely be present in the testes.

TREATMENT

- Surgical excision is usually curative.
- Close follow-up of the contralateral ovary is necessary.

REFERENCE

Chan YF, Restall P, Kimble R. Juvenile granulosa cell tumor of the testis: Report of 2 cases in newborns. *J Pediatr Surg.* 1997;32(5):752–753.

GRAPEFRUIT AND GRAPEFRUIT JUICE, INTERACTION WITH UROLOGIC MEDICATIONS

DESCRIPTION Grapefruit or grapefruit juice can affect the metabolism of many medications, increasing the risk of toxicity and adverse events. These oral medications tend to be metabolized through the intestinal cytochrome P450 3A4 (CYP3A4) system and can also inhibit the drug concentration for up to 72 hr. The following mediations are used in urologic practice and do not represent an exhaustive listing. Typically there is increased drug levels by grapefruit interaction.

- Immunosuppressive agents:
  – Cyclosporine everolimus, sirolimus, tacrolimus, temsirolimus
- Phosphodiesterase Type 5 inhibitors (PDE-5I)
  – Tadalafil, vardenafil
- Tyrosine kinase inhibitors (TKI)
  – Axitinib, everolimus, pazopanib, sunitinib, temsirolimus

REFERENCE

Stump AL, Mayo T, Blum A. Management of grapefruit-drug interactions. *Am Fam Physician*. 2006;74(4):605–608.

GRATIFICATION DISORDER

DESCRIPTION Also known as *infantile masturbation*, usually peaks at 4 yo but can be seen as early as 3 mo of age. The disorder may occur in the absence of genital manipulation and can consist of vocalizations with quiet grunting, diaphoresis, and pressure on the perineum with characteristic posturing of the lower extremities. The patient is commonly referred for seizures or a movement disorder because of the recurrent paroxysmal movements.

REFERENCE

Yang ML, Fullwood E, Goldstein J, et al. Masturbation in infancy and early childhood presenting as a movement disorder: 12 cases and review of the literature. *Pediatrics*. 2005;116:1427–1432.

GRIESS TEST

DESCRIPTION Detects the presence of nitrite in urine, which is formed when bacteria reduce the normally present nitrate. With a lower sensitivity and specificity than microscopy and culture, this test in combination with leukocyte esterase has been used to screen asymptomatic patients. Microscopy is indicated for the higher-risk population for UTI.

REFERENCE

Schaeffer AJ. Urinary tract infections. In: Gillenwater JY, Grayhack JT, Howards SS, et al., eds. *Adult and Pediatric Urology*. 3rd ed. St. Louis, MO: Mosby; 1996.

GRISS SEX FUNCTION INDEX (GOLOMBOK–RUST INVENTORY OF SEXUAL SATISFACTION)

DESCRIPTION Golombok–Rust Inventory of Sexual Satisfcation (GRISS) is a validated psychometric instrument intended for heterosexual couples or individuals. The questionnaire is based on a 28-item scale, with separate forms for men and women. It contains subscales of ED, orgasmic disorders, vaginismus, and male and female nonsensuality. It may be used in individuals undergoing marital or sex therapy.

REFERENCE

Wiegel M, Wincze JP, Barlow DH. Sexual dysfunction. In: Barlow D, ed. *Assessment and Treatment Planning for Psychological Disorders.* New York, NY: Guilford Press; 2002.

GROIN HERNIA, PEDIATRIC

DESCRIPTION The most common surgery in the pediatric age group. Most hernias in this population are indirect and congenital. The incidence is higher in preterm births, with a male to female ratio of 6:1. The hernia is formed from the persistence of the processus vaginalis and can present as a communicating hydrocele, hydrocele of the cord, simple hydrocele, or incarceration and strangulation of intraperitoneal contents. Surgical repair is usually indicated.

REFERENCE

Warner BW. Pediatric surgery. In: Townsend CM, Sabiston DC, eds. *Sabiston Textbook of Surgery*. 18th ed. Philadelphia, PA: Saunders; 2008.

GROWING TERATOMA SYNDROME

DESCRIPTION Refers to an enlarging mature teratoma arising during or after chemotherapy for a nonseminomatous germ-cell tumor. The AFP and β-HCG serum levels are normal. The preferred treatment is complete surgical resection as teratomas are chemotherapy and radiation therapy resistant.

REFERENCE

Vaughn DJ, Flaherty K, Lal P, et al. Treatment of growing teratoma syndrome. *N Engl J Med.* 2009;360:423–424.

GUILLAIN–BARRé (TRANSVERSE MYELITIS) SYNDROME: UROLOGIC CONSIDERATIONS

DESCRIPTION Also known as *acute inflammatory demyelinating polyneuropathy*, an inflammatory demyelinating disorder of the autonomic and peripheral nervous system. It is thought to be triggered by a bacterial or viral antigen, causing the immune system to cross-react and attack neural tissue. Symptoms may include muscle weakness, respiratory difficulties, autonomic neuropathy, and cardiac, bowel, bladder, and sexual dysfunction. Lower urinary tract dysfunction can range from urgency and stress incontinence to urinary retention.

TREATMENT

- Manage lower urinary tract dysfunction (Clean intermittent catherization (CIC), anticholinergics, etc.)
- Plasmapheresis
- IV immunoglobulin

REFERENCE

Ganesan V, Borzyskowski M. Characteristics and course of urinary tract dysfunction after acute transverse myelitis. *Dev Med Child Neurol.* 2001;43(7):473–475.

GUN SHOT WOUND, EXTERNAL GENITALIA

DESCRIPTION The genitalia have several characteristics that are somewhat protective against sustained injury. Characteristics such as the laxity of skin, flaccidity, and multiple sources of blood supply assist with dampening the blow of trauma and help with reconstruction efforts. Nevertheless, the location of major vasculature and visceral organs make these injuries potentially life-threatening. Greater than 50% of injuries to the penis have urethral injuries and 75% have other significant associated injuries. A majority of these injuries require exploration with copious irrigation, excision of foreign material, antibiotics, and primary closure. In injuries to the urethra, imaging such as retrograde urethrogram should be implemented and, if warranted, abdominal/pelvic imaging should be obtained. (See also Section I: "Penis, Trauma"; Section I: "Scrotum and Testicle, Trauma.")

REFERENCE

Phonsombat S, Master VA, McAninch JW. Penetrating external genital trauma: A 30-year single institution experience. *J Urol.* 2008;180(1):192–195.

GUN SHOT WOUND, KIDNEY

DESCRIPTION The kidney is subject to the majority of external injuries in the GU system. Hematuria is a good indicator of injury but its amount or absence does not eliminate renal injury nor does it dictate the degree of injury. Any degree of hematuria in penetrating trauma should prompt imaging. Kidney injury is graded from I–V in accordance with the American Association for Surgery of Trauma Organ Injury Severity Scale for the Kidney. In carefully selected patients, management can be nonoperative, with careful observation or segmental embolization used. Absolute indications for surgical exploration include expanding perirenal hematoma, evidence of persistent renal bleeding, and pulsatile perirenal hematoma. Relative indications include urinary extravasation, nonviable tissue, delayed diagnosis of arterial injury, segmental arterial injury, and incomplete staging. (See also Section I: "Renal Trauma, Adult"; Section I: "Renal Trauma, Pediatric"; Section II: "American Association for Surgery of Trauma Organ Injury Severity Scale.")

REFERENCE

Voelzke BB, McAninch JW. Renal gunshot wounds: Clinical management and outcome. *J Trauma.* 2009;66(3):593–600.

HAILEY–HAILEY DISEASE (BENIGN FAMILIAL PEMPHIGOID)

DESCRIPTION Autosomal dominant skin disease arising from mutations of the *ATP2C1* gene. The appearance begins as a flaccid vesicle or bulla with associated itching, irritation, and a possible odor. The lesions may erupt and leave crusted erosions, and some may have a dry center and inflammatory periphery. The onset usually occurs within the 2nd–3rd decades of life, and lesions are seen in intertriginous areas (ie, axillary fold, groin, and perianal areas). Lesions heal without scarring. Treatment involves antibiotics for superinfection, steroids, and dermabrasion.

REFERENCE

McKibben J, Smalling C. Hailey-Hailey. *Skinmed.* 2006;5(5):250–252.

HALD–BRADLEY CLASSIFICATION OF VOIDING DYSFUNCTION

DESCRIPTION Based on the anatomic location of the neurologic lesion, voiding dysfunction is broken down into 5 classes: (1) Suprasacral, (2) suprasacral spinal, (3) infrasacral, (4) peripheral autonomic neuropathy, and (5) muscular lesions. Examples include coordinated voiding with hyperreflexia in suprasacral lesions, whereas muscular lesions may be a decompensated bladder from long-standing bladder outlet obstruction.

REFERENCE

Hald T, Bradley WE. The neurogenic bladder. In *The Urinary Bladder, Neurology and Urodynamics*. Baltimore, MD: Williams and Wilkins; 1982.

HAND FOOT SYNDROME

DESCRIPTION Many oncologic medications have been implicated (such as capecitabine, fluorouracil, others), but this condition appears to be a relatively common problem with multikinase inhibitors such as sunitinib and sorafenib, which are used to treat tumors such as metastatic renal cell carcinoma (RCC). Symptoms include tingling or burning, redness, flaking, swelling, and small blisters and sores on the palms of the hands or soles of the feet. Some patients experience eventual skin hardening (Image ☼).

SYNONYMS

- Palmar–plantar erythrodysesthesia (PPE)
- Plantar–palmar toxicity
- Palmoplantar keratoderma

TREATMENT

- Reduce exposure of hands and feet to friction and heat (ie, hot water, avoid pressure on feet, avoid using tools, cool hands and feet with an ice pack, moisturizing creams).
- Stopping the medication temporarily reduces the symptoms. The drug can often be restarted at a lower dose.

REFERENCE

Hutson TE, Figlin RA, Kuhn JG, et al. Targeted therapies for metastatic renal cell carcinoma:

An overview of toxicity and dosing strategies. *Oncologist.* 2008;13(10):1084–1096.

HAUTMANN POUCH

DESCRIPTION This ileal neobladder is created from 70 cm of ileum, starting 15 cm from the ileocecal junction. The bowel is opened up along the antimesenteric border, and is arranged into an M or W shape. The limbs are sutured to each other with absorbable suture material to form a broad ileal plate. A preselected segment is anastomosed to the urethra, and the ureters are implanted in a LeDuc fashion. The plate is then closed into a pouch and anastomosed to the urethra.

REFERENCE

Hautmann RE, Egghart G, Frohneberg D, et al. The ileal neobladder. *J Urol.* 1988;139(1):39–42.

HEIKEL–PARKKULAINEN REFLUX CLASSIFICATION SYSTEM

DESCRIPTION Described by Heikel and Parkkulainen in 1966, this system is used to grade vesicoureteral reflux based on ureteral diameter and pelvicalyceal dilatation. It gained much popularity in Europe. Later, features of this system were used to create the International Classification System, which is now the standard.

REFERENCE

Heikel RE, Parkkulainen KV. Vesico-ureteric reflux in children: A classification and results of conservative treatment. *Ann Radiol.* 1966;9:37–40.

HEMATOCELE

DESCRIPTION Collection of blood within the layers of the tunica vaginalis. Hematocele can present as scrotal swelling and may be asymptomatic. It may be difficult to distinguish from tumor, in which case transcrotal ultrasound (US) is helpful. Causes include trauma, infection, bleeding disorders, tumor, and rarely uremia. (See also Section I: “Scrotum and Testicle, Mass”; Section I: “Scrotum and Testicle, Trauma.”)

TREATMENT

Conservative management if patient asymptomatic and diagnosis confirmed. Often, diagnosis by surgical exploration

REFERENCE

Chaudhary S, Bhullar JS, Subhas G, et al. Hematocele after laparoscopic appendectomy. *JSLS.* 2012;16(4):660–662.

HEMATURIA, ATHLETIC (RUNNERS’ HEMATURIA)

DESCRIPTION Described mostly in adults after strenuous exercise. The phenomenon of gross or microscopic hematuria can occur in contact or noncontact sports. The RBCs seen in the urine may be glomerular or nonglomerular in shape. The cause of the hematuria can be from trauma of the posterior bladder wall hitting against the bladder base. Nontraumatic

causes are hypothesized to be from hypoxic changes secondary to the vasoconstriction of the splanchnic and renal vessels or to constriction of the efferent glomerular arteriola resulting in increased filtration pressures in the kidney. The hematuria should be distinguished from myoglobinuria and hemoglobinuria.

SYNONYMS
- Sports hematuria
- Athletically induced hematuria

TREATMENT
- Should be self-limited and provoked by strenuous exercise.
- Co-existing urologic pathology should be ruled out if history or physical exam is suspicious.

REFERENCE
Abarbanel J, Benet AE, Lask D, et al. Sports hematuria. *J Urol.* 1990;7143:65887–65890.

HEMATURIA–DYSURIA SYNDROME

DESCRIPTION Hematuria–dysuria syndrome is the most common reported complication of gastrocystoplasty. The syndrome of dysuria and hematuria is defined as 1 or a combination of the following symptoms: Bladder spasm or suprapubic, penile or periurethral pain, coffee brown or bright red hematuria without infections, skin irritation or excoriation, and dysuria without infections.

REFERENCE
Chadwick PJ, Snodgrass WT, Grady RW, et al. Long-term follow-up of the hematuria-dysuria syndrome. *J Urol.* 2000;164(3 Pt 2):921–923.

HEMATURIA–LOIN PAIN SYNDROME

DESCRIPTION A cause of recurrent gross hematuria that may be confused with IgA nephropathy, loin pain-hematuria syndrome generally affects young women and is characterized by recurrent episodes of gross hematuria associated with dull unilateral or bilateral loin pain and sometimes low-grade fever. BP and renal function are usually normal. The syndrome has been associated most often with the use of oral contraceptive agents and generally resolves when these agents are discontinued. Renal autotransplantation has been described as a treatment modality.

REFERENCE
Chin JL, Kloth D, Pautler SE, et al. Renal autotransplantation for the loin pain-hematuria syndrome: Long-term followup of 26 cases. *J Urol.* 1998;160(4):1232–1235.

HEMIZONA ASSAY

DESCRIPTION This assay assesses the ability of sperm to bind to the zona pellucida of the egg. It is performed by dividing intact zona pellucida and incubating it separately with donor sperm and the patient's sperm. A hemizona index is derived by dividing the number of bound donor sperm by the number of bound patient sperm. An index <0.60 is seen in males who

failed IVF. Its use is limited by the availability of human ova. Since this technique potentially bypasses the step of zona binding, men whose sperm cannot bind may be good candidates for these procedures.

REFERENCE

Yao YQ, Yeung WS, Ho PC. The factors affecting sperm binding to the zona pellucida in the hemizona binding assay. *Hum Reprod.* 1996;11(7):1516–1519.

HEMORRHAGE, POSTOPERATIVE, UROLOGIC CONSIDERATIONS

DESCRIPTION Postoperative hemorrhages can occur after any urologic procedure, but are most common and significant with percutaneous procedures of the kidney. The risk of hemorrhage increases in patients with underlying coagulopathy, aberrant anatomy, multiple needle passages, tract dilation, or nephrostomy tube placement. Parenchymal bleeding can be persistent, and a large high-pressure balloon can be placed through the nephrostomy tube tract to promote tamponade and hemostasis. Not uncommonly, venous lacerations may occur and can be managed by placing a large nephrostomy tube and clamping the tube to allow for tamponade. If arterial bleeding is persistent, selective arterial embolization may be employed. Delayed bleeding can occur soon after surgery, or weeks to months later in the setting of renal pseudoaneurysms or arteriovenous fistulas. If these diagnoses are suspected, evaluation with angiography and treatment with selective embolization can be performed.

REFERENCE

Srivastava A, Singh KJ, Suri A, et al. Vascular complications after percutaneous nephrolithotomy: Are there predictive factors. *Urology.* 2005;66:38–40.

HEMORRHAGE, RETROPERITONEAL AND PERINEPHRIC

DESCRIPTION Retroperitoneal and perinephric hemorrhage are uncommon in the absence of trauma. Spontaneous retroperitoneal and perinephric hemorrhage is most commonly from the kidney. The most common renal causes are angiomyolipoma (AML) and renal cell carcinoma (RCC). Vascular diseases such as polyarteritis nodosa (PAN), renal artery aneurysm, infections of kidney such as cortical abscess, pyelonephritis, and renal cysts are occasional etiologic factors. Adrenal hemorrhage (AH) is seen with severe stress conditions (sepsis, burns, trauma), pheochromocytoma, adrenal carcinomas, myelolipoma, and cortical adenomas. Clinical presentation depends on the amount of bleeding ranging from mild flank pain to shock and oliguria. CT scan is considered the gold standard for diagnosis. (See also Section I: “Retroperitoneal Masses, Fluid and Cysts” and Section II: “Retroperitoneal Hematoma.”)

REFERENCE

Goyal A, et al. Spontaneous retroperitoneal haemorrhage: Diagnostic and therapeutic approach. *Indian J Urol.* 2001;18:70–73.

HEMOSIDERIN, URINARY

DESCRIPTION Hemosiderin occurs when hemoglobin is reabsorbed by the proximal tubular

cells and then catabolized into ferritin and hemosiderin. Urinary hemosiderin can occur up to 2 days after an acute hemolytic episode, and is also demonstrated in chronic hemolytic states and hemochromatosis.

REFERENCE

McPherson R, Threatte G. Urine and other body fluids. In: McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 21st ed. Philadelphia, PA: Saunders; 2006.

HENOCH–SCHöNLEIN PURPURA (HSP)

DESCRIPTION HSP is a form of purpura with an underlying pathologic feature of vasculitis, affecting mainly small blood vessels. The disease is predominately seen in children. Clinically, the purpuric skin lesions are typically located on the lower extremities. However, the hands, arms, and trunk can be affected. Joint pain, abdominal pain, and GI bleeding may be present. Hematuria denotes a renal lesion, which is usually reversible. HSP is similar to IgA nephropathy, but somewhat more severe, particularly in adults. Progressive renal failure occurs in at least 25%. Kidney biopsy reveals segmental glomerulonephritis with crescents and mesangial deposition of IgA and sometimes IgG. Lab tests reveal high ESR and normal to high platelet counts. If renal involvement is not severe, the disease will subside without sequelae within 6 wk.

TREATMENT

- Currently no effective treatment is available.
- Immunosuppressive (steroids, cytotoxics) drugs have shown some success in nephropathies caused by that disorder.

REFERENCE

Assadi F. Childhood Henoch-Schönlein nephritis: A multivariate analysis of clinical features and renal morphology at disease onset. *Iran J Kidney Dis.* 2009;3(1):17–21.

HEPATITIS A & B (HAV/HBV), UROLOGIC CONSIDERATIONS

DESCRIPTION HAV and HBV both belong to a family of 5 hepatropic viruses. HAV is a picornavirus and is mostly enterically transmitted by fecal–oral routes. Transmission has been noted in men who have sex with men and with oral–anal contact regardless of sexual preference. No significant transmission occurs through semen or vaginal secretions, but transmission through blood products is rare but possible. Extrahepatic manifestations include vasculitis, cardiac abnormalities, Guillain–Barré (transverse myelitis), and renal failure. HBV is a double-shelled hepadnavirus and is mostly transmitted parenterally, which can take place from mother to fetus, through blood products, and through cutaneous and mucosal exposure to infectious blood or bodily fluid. Unlike HAV, HBV has a chronic phase that may lead to hepatocellular carcinoma.

REFERENCE

Curry M, Chopra S. Acute viral hepatitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia, PA: Churchill Livingstone; 2005.

HEPATORENAL SYNDROME

DESCRIPTION Known as progressive oliguric renal failure complicating the course of end-stage liver disease, the cause is thought to be functional, due perhaps to discharge of the sympathetic nervous system and/or metabolic imbalances, including endothelin and nitric oxide. The prognosis usually involves recovery of renal function and for survival overall. Urine is characteristically hyperosmolar, with a high creatine-to-plasma ratio and a very low sodium concentration.

TREATMENT

- A transjugular intrahepatic portosystemic shunt has been attempted in the past
- Orthotopic liver transplantation

REFERENCE

Lata J. Hepatorenal syndrome. *World J Gastroenterol.* 2012;18(36):4978–4984.

HEREDITARY LEIOMYOMA RENAL CELL CARCINOMA (HLRCC) SYNDROME

DESCRIPTION HLRCC syndrome is manifested by uterine leiomyomas, multiple cutaneous leiomyomas, and RCC (papillary cell carcinoma). The disorder results from an autosomal dominant germline mutation encoding for fumarate hydratase. The renal tumors have been found to be aggressive, leading to early metastases and death. (See also Section I: “Renal Cell Carcinoma, General.”)

TREATMENT

- Early diagnosis and close follow-up
- Nephrectomy (partial or radical) when indicated

REFERENCE

Hayedeh G, Fatemeh M, Ahmadreza R, et al. Hereditary leiomyomatosis and renal cell carcinoma syndrome: A case report. *Dermatol Online J.* 2008;14(1):16.

HEREDITARY PAPILLARY RENAL CELL CARCINOMA (HPRCC)

DESCRIPTION HRPCC is an autosomal dominant disorder associated with type 1 papillary RCC. Activation of a proto-oncogene, rather than inactivation of a tumor suppressor gene, is the inciting event. Missense mutations of the c-MET proto-oncogene on chromosome 7 at 7q31 have been described as the relevant genetic locus causing the disorder. A majority of the mutations were isolated on the tyrosine kinase domain of the c-MET gene. Tumors linked to these mutations are thought to be less aggressive than the sporadic type. (See also Section I: “Renal Cell Carcinoma, General.”)

REFERENCES

Sudarshan S, Linehan WM. Genetic basis of cancer of the kidney. *Semin Oncol.* 2006;33:544–551.

Vira MA, Novakovic KR, Pinto PA, et al: Genetic basis of kidney cancer: A model for developing molecular-targeted therapies. *BJU Int.* 2007;99:1223–1229.

HERNIA UTERINE INGUINALE

DESCRIPTION A cause of male pseudohermaphroditism, thought to be due to an isolated defect in the production of müllerian inhibition substance or the response to müllerian inhibiting factor (MIF). This is a rare syndrome of müllerian ducts persistence. Affected males are not ambiguous at birth and generally present later, most commonly with an inguinal hernia on 1 side and an impalpable contralateral testes. Hernia sac may contain the uterus. Karyotype is 46, XY. The gonadal tissue is exclusively testicular. Both wolffian and müllerian duct derivatives are present, with a vas and epididymis alongside an ipsilateral uterus, fallopian tube, and upper vagina. Testes have malignant potential. No uterine or vaginal malignancies have been reported.

TREATMENT

- Sex assignment as male
- Primary or staged orchidopexy
- Müllerian structures do not require removal, as the vas deferens may be damaged.

REFERENCE

Snyder HM. Intersex. *Practical Cases in Urology.* Series XIX, Course 4, 1996.

HERPES ZOSTER, GENITOURINARY

DESCRIPTION If the herpes zoster virus invades the sacral dorsal root ganglia and posterior nerve roots, then detrusor areflexia and urinary retention can result. These symptoms are usually noted days to weeks after the onset of primary viral symptoms, such as painful cutaneous lesions. The urologic symptoms usually spontaneously resolve in 4–8 wk. Cystoscopy may reveal bladder lesions similar to the cutaneous lesions.

REFERENCE

Broseta E, Osca JM, Morera J, et al. Urological manifestations of herpes zoster. *Eur Urol.* 1993;24(2):244–247.

HIDRADENITIS SUPPURATIVA (ACNE INVERSA), UROLOGIC CONSIDERATIONS

DESCRIPTION A chronic suppurative disease of the apocrine gland–bearing areas of the body, such as the axilla, buttocks, and groin. Not primarily infectious; caused by plugging of the follicles. Secondary infection can occur after the follicle plugs, with resultant inflammatory response. Lesions resemble boils and can resolve without scarring but more typically result in fibrosis, keloids, and sinus tract formation. Mild cases resemble simple boils (furunculosis). Diagnosed primarily by location and clinical course. Pain, fluctuation, discharge, and sinus tract formation are characteristic. In chronic cases, coalescence of inflamed nodules may cause palpable cordlike bands. The condition may become extensive and disabling; if the pubic and genital areas are severely involved, walking may be difficult.

TREATMENT

- Avoid irritants such as antiperspirants

- Conservative treatment with rest, moist heat, and prolonged antibiotics (tetracycline or erythromycin)
- Oral isotretinoin and intralesional corticosteroids may be effective
- Surgical excision and plastic repair of the affected areas may be necessary

REFERENCE

Goldberg JM, Buchler DA, Dibbell DG. Advanced hidradenitis suppurativa presenting with bilateral vulvar masses. *Gynecol Oncol.* 1996;160(3):494–497.

HINMAN SYNDROME (HINMAN–ALLEN SYNDROME) (NONNEUROGENIC NEUROGENIC BLADDER) (OCCULT NEUROPATHIC BLADDER)

DESCRIPTION 1st described in 1937 by Hinman and Bauman, this is a syndrome of vesicourethral dysfunction (dysfunctional voiding) that is associated with recurrent UTIs, vesical trabeculation, poor emptying, and hydronephrosis with possible progression to renal failure. Hinman syndrome is thought to occur from bladder sphincteric dysfunction with no signs of neurologic cause and may begin in the neonate or in the child around the time of toilet training.

SYNONYM

Nonneurogenic neurogenic bladder

TREATMENT

- Clean intermittent catheterization (CIC)
- Cutaneous vesicostomy

REFERENCE

Mosawi AJ. Identification of nonneurogenic neurogenic bladder in infants. *Urology.* 2007;70:356–357.

HISPAREUNIA (MALE DYSPAREUNIA)

DESCRIPTION Sling erosion/extrusion is a recognized complication after suburethral sling insertion to treat female stress urinary incontinence (SUI). Erosion occurs in up to 6% of patients. Female symptoms may include discharge, infections, postcoital bleeding, and alterations of the sexual function. Changes of male sexual function and particularly pain after sling insertion in their female partners may be due to sling exposure and has been termed “hispareunia.” Sexual interest and drive may be negatively influenced. Male dyspareunia is a complaint that appears to be effectively treated by correcting the sling exposure in the female partner.

REFERENCE

Mohr S, Kuhn P, Mueller MD, et al. Painful love-”hispareunia” after sling erosion of the female partner. *J Sex Med.* 2011;8(6):1740–1746.

HISTOPLASMOSIS, GENITOURINARY

DESCRIPTION *Histoplasma capsulatum* grows in soil enriched by bird guano, with outbreaks reported in caves, construction sites, and on bird farms. Disseminated virulent disease is seen in AIDS, children, and immunosuppressed individuals. GU involvement is a manifestation of systemic disease and can result in sloughed papilla, prostatic obstruction, or prostatic abscess. Epididymitis can resemble sperm granulomas. Up to 7% can experience adrenal insufficiency from adrenal destruction. (See also Section I: "Fungal infections, Genitourinary.")

TREATMENT

2 g of amphotericin B with maintenance therapy with itraconazole to prevent relapse

REFERENCE

Wise GJ, Freyle J. Changing patterns in genitourinary fungal infections. *AUA Update.* Vol. XVI, Lesson 1, 1997.

HIV NEPHROPATHY

DESCRIPTION HIV nephropathy (HIVAN) is the most common cause of chronic renal failure among HIV seropositive patients. It can occur in both the chronic and acute phase of the illness. Presentation may include nephrotic syndrome, hypertension, hematuria, and renal insufficiency. Pathologically, there is a focal segmental glomerulosclerosis, collapsing nephropathy with podocyte hypertrophy, and hyperplasia. (See also Section I: "HIV/AIDS, Urologic Considerations.")

TREATMENT

- Highly active antiretroviral therapy
- Steroids
- ACE inhibitor

REFERENCE

Audard B, Avouac J, Wirden M, et al. HIV-related nephropathies associated with changes in blood and kidney tissue virus load. *Kidney Int.* 2008;73:651–655.

HODGKIN DISEASE, UROLOGIC CONSIDERATIONS

DESCRIPTION Hodgkin disease is a type of lymphoma differentiated from other lymphomas partially on the basis of the presence of Reed–Sternberg cells. It has become 1 of the most curable forms of malignancy. It has many urologic associations, and an association with a higher incidence in RCC patients has been proposed. Treatment with radiation for Hodgkin may predispose to bladder cancer. The kidney and bladder have been reported to be primary sites of Hodgkin disease. Extensive retroperitoneal lymphadenopathy may cause ureteral obstruction. Renal radiation-induced arterial stenosis can be a treatment effect. (See also Section II: "Lymphoma, Urologic Considerations.")

REFERENCE

Jones MW. Primary Hodgkin's disease of the urinary bladder. *Br J Urol.* 1989;63(4):438.

HODGSON TYPES I, II, III HYPOSPADIAS REPAIR

DESCRIPTION Type I: Chordee is repaired. A longitudinal tube along the urethral axis is formed on the inner surface of the prepuce, which is then transferred to the ventrum through a buttonhole incision at the base of the tube. The proximal neourethra is anastomosed to the proximal native urethra, and the distal neourethral tube is used to create the meatus.

Type II: Hodgson modified type I for the very distal hypospadias where no chordee exists, and the native urethral plate remains intact. The inner surface of the prepuce is again transferred to the ventrum via a buttonhole at the base. In this repair, the prepuce flap is sutured onto the urethral plate.

Type III: This is modified for the more proximal hypospadias repair. Here, the buttonhole is created at the base of the penis, and a longer tubular neourethral is created, based on preputial and shaft skin.

REFERENCE

Devine CJ, Horton CE. Repair of hypospadias and epispadias. In: Novick AC, Streem SB, Pontes JE, et al., eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:689–714.

HONEYMOON CYSTITIS

DESCRIPTION Urinary tract infection which affects young sexually active women. It accounts for 4% of UTIs and for 75–90% of episodes in young sexually active women. The pathogenesis of this disorder involves transmission of bowel flora from the perineum into the female's introitus during sexual intercourse. The proximity of the bladder to the perineum enables the development of an ascending infection through the female's short urethra. Spermicide use, independent of sexual frequency, increases the risk of UTIs. (See also Section I: "Urinary Tract Infection [UTI], Adult Female"; Section II: "Postcoital Prophylactic Antibiotics.")

TREATMENT

- High fluid intake
- Postcoital voiding (controversial if useful)
- Identify any triggers (Spermacide, positioning during sexual activity, etc.)
- Consider single dose of antibiotic before or after intercourse if >3 symptomatic UTIs/yr (eg, Trimethoprim/sulfamethoxazole, trimethoprim, nitrofurantoin, cephalexin, ciprofloxacin, others)

REFERENCE

Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am.* 2008;35(1):1–12.

HORSESHOE KIDNEY

DESCRIPTION The most common fusion anomaly, present in 1 in 400 births, with a male predominance. Usually, this represents a true fusion of the lower poles, which may be composed of thick functioning parenchyma or merely a fibrous band. Associated anomalies are seen in 1/3 of patients and include multisystem disturbances of the skelet al and

cardiovascular systems and GI tract, as well as GU abnormalities, such as an increased frequency of ureteral duplication, reflux, and dysplasia. Usually asymptomatic, a horseshoe kidney may be associated with urolithiasis and UPJ obstruction. Radiographic diagnosis can be made with IVP or CT, which reveals deviation of the axis of the kidneys. Renal scan may be helpful in surgical decision making, if necessary. The condition is caused by fusion of poles during ascent of the kidneys. (See also Section I: "Renal Fusion Anomalies.")

TREATMENT

- Pyeloplasty and ureteral implantation may be required for proven UPJ obstruction or severe reflux, respectively
- Can affect management of many other disease conditions, such as neoplasm, aortic aneurysm, and transplantation

REFERENCE

O'Brien J, Buckley O, Doody O, et al. Imaging of horseshoe kidneys and their complications. *J Med Imaging Radiat Oncol.* 2008;52(3):216–226.

HORTON-DEVINE "FLIP-FLAP" HYPOSPADIAS REPAIR

DESCRIPTION The distal ventral skin over the urethra is mobilized, and the distal urethra is also mobilized. Parallel incisions are made in the glans to create a urethral plate, and the proximal flap is flipped over and sutured onto the urethral plate. The wings of the glans are then approximated over this distal repair.

REFERENCE

Devine CJ, Horton CE. Repair of hypospadias and epispadias. In: Novick AC, Streem SB, Pontes JE, et al., eds. *Stewarts Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:689–714.

HOUNSFIELD UNITS

DESCRIPTION Named after Sir Godfrey Newbold Hounsfield, the inventor of the CT scanner, this is an arbitrary scale created to compare density of different substances seen on CT. Water is represented by 0 HU. Air is –1,000 HU. Bone is 1,000 HU. Fat is in the range of –100 to 0 HU, whereas water with electrolytes is slightly above 0 HU. Soft tissue is in the range of 35 HU.

REFERENCE

Miraldi F. Imaging principles in computed tomography. In: Haaga JR, Alfidi RJ, eds. *Computed Tomography of the Whole Body*. 1st ed. St. Louis, MO: Mosby; 1983.

HPC-1 (HEREDITARY PROSTATE CANCER 1 LOCUS)

DESCRIPTION A locus found on chromosome 1q24–25, which has been potentially linked to inherited prostate cancer. Families in which this altered gene is found were determined to have a lower age at diagnosis, a higher grade of cancer, and more cases of advanced disease than normal.

REFERENCE

Gronberg H, Isaacs SD, Smith JR, et al. Characteristics of prostate cancer in families potentially linked to the hereditary prostate cancer 1 (HPC1) locus. *JAMA*. 1997;278(15):1251–1255.

HPV (HUMAN PAPILLOMA VIRUS), UROLOGIC CONSIDERATIONS

DESCRIPTION This family of viruses, with double-stranded DNA, causes various warts, papillomas, and cervical cancer. Types 6, 11, 42, and 44 are associated with condyloma acuminatum. Types 16, 18, 31, 33, 35, and 39 have an association with cancer. Types 6 and 11 have been associated with Buschke–Lowenstein tumor. Subclinical condyloma can be detected with application of 5% acetic acid and inspection with a magnifying glass. HPV is associated also with Bowenoid papulosis and squamous cell carcinoma of the penis and urethra. Bladder cancer association is controversial. (See also Section I: “Condylomata Acuminata [Venereal Warts]”; “Penis, Lesion, General”; and Section II: “Buschke-Lowenstein Tumor.”)

TREATMENT

- Podophyllin or trichloroacetic acid for condyloma
- Laser therapy is also effective

REFERENCES

Abol-Enein H. HPV Infection: Is it a cause of bladder cancer? *Scand J Urol Nephrol Suppl.* 2008;(218):79–84.

Kayes O, Ahmed HU, Arya M, et al. Molecular and genetic pathways in penile cancer. *Lancet Oncol.* 2007;8(5):420–429.

HUMAN GROWTH HORMONE (hGH), UROLOGIC CONSIDERATIONS

DESCRIPTION Use of hGH has been approved for children with short stature. There are multiple off-label uses; hGH has also been used in the aging patient to increase energy and possibly libido, and to add muscle mass in athletes. These therapeutic applications are not supported by evidence-based studies. There have been some concerns expressed that the use of hGH may increase the risk of germ cell tumors (GCT’s) anywhere in the body; vigilant monitoring is mandatory in treated GCTs who are hGH replaced.

REFERENCES

Allen DB, Fost N. hGH for short stature: Ethical issues raised by expanded access. *J Pediatrics*. 2004;144(5):648–652.

Chung, TT, Drake WM, Plowman PN, et al. No clear evidence for an association between GH replacement and relapse of intracranial germ cell tumours: single centre and KIMS experience. *Eur J Endocrinol.* 2010;163:357–358.

HUNNER ULCER

DESCRIPTION Cystoscopic finding of ulceration of the bladder mucosa in patients with interstitial cystitis/painful bladder syndrome (IC/PBS). This fulfills 1 of the NIH criteria for

IC/PBS. Found in a variable number of patients with IC/PBS, it was 1st described by Hunner in 1918, when he noted the ulcer in association with the constellation of clinical findings of IC/PBS. (See also Section I: "Interstitial Cystitis.")

REFERENCE

Hillelsohn JH, Rais-Bahrami S, Friedlander JI, et al. Fulguration for Hunner ulcers: Long-term clinical outcomes. *J Urol.* 2012;188(6):2238–2241.

HUTCH DIVERTICULUM

DESCRIPTION Herniation of the bladder mucosa through the weakest point of the hiatus, in the detrusor above the intramural ureter, producing a Hutch diverticulum and reflux. The condition is usually due to a chronic increase in intravesical pressure as a result of bladder outlet obstruction. (See also Section I: "Vesicoureteral Reflux, Adult" and "Vesicoureteral Reflux, Pediatric.")

REFERENCE

Hutch JA, Ayres RD, Loquvam GS. The bladder musculature with special reference to the uretero vesical junction. *J Urol.* 1961;85:531.

HYDATID CYST (HYDATID DISEASE)

DESCRIPTION Infection occurs after ingestion of the dog parasite, *Echinococcus granulosus* (tapeworm). Sheep are the intermediate hosts. Cases occur in the Middle East, Australia, and Argentina. The hydatid is the larval form of *E. granulosus*, and the cysts represent a thick parasitic membrane that is enveloped in fibrous tissue. The cysts are fluid filled and contain the parasites. They grow slowly over many years and typically involve the kidney (2% incidence with echinococcus), with cases of seminal vesical involvement also reported. 3% affect the kidneys. Large cysts form that can be asymptomatic or present with flank pain. Renal cysts may cause pressure and chronic pain but do not affect renal function. They may rupture, causing new metastatic cysts. A peripheral eosinophilia is seen with a positive hydatid complement-fixation test. X-rays and CT show a thick-walled, fluid-filled spherical cyst with a calcified wall. (See also Section II: "Echinococcus, Renal.")

TREATMENT

- Medical therapy is with albendazole.
- Where surgical excision is indicated, cysts can be 1st sterilized with formalin or alcohol. Praziquantel is also recommended preoperatively or if cyst contents are spilt (which can cause systemic anaphylaxis).

REFERENCE

Kaya K, Gokce G, Kaya S, et al. Isolated renal and retroperitoneal hydatid cysts: A report of 23 cases. *Trop Doct.* 2006;36(4):243–246.

HYDROCALYCOSIS

DESCRIPTION A relatively rare cystic dilation of a major calyx. A calyceal diverticulum is

distal to a minor calyx, whereas the hydrocalyx is a dilation of a major calyx. Caused by a congenital anomaly secondary to acquired intrinsic obstruction from a parapelvic cyst or crossing vessel causing infundibular stenosis. Differential diagnoses includes megacalycosis, ureteral obstruction and hydronephrosis, calyceal clubbing due to pyelonephritis or medullary necrosis, renal TB, or calyceal diverticulum. Patients may complain of flank pain, hematuria, or infection. Dismembered pyeloplasty or percutaneous treatment of the narrowed infundibulum is curative.

REFERENCE

Craver R, Boyd R, Ward K, et al. Renal hypertrophic infundibular stenosis. *Fet al Pediatr Pathol.* 2004;23(4):285–292.

HYDROCELE OF THE SPERMATIC CORD

DESCRIPTION A loculated fluid collection along the spermatic cord, the process is caused by a failure of the process vaginalis to close during development. The hydrocele can be in communication with the peritoneum at the internal inguinal ring (funicular) or may be encysted, where the fluid collection does not communicate with the peritoneum or the tunica vaginalis. Patients usually present with groin swelling and should be evaluated with US, which will exhibit an oval anechoic mass in the groin along the spermatic cord and above and separated from the testis and the epididymis. (See also Section I: "Hydrocele, Adult and Pediatric"; Section I: "Spermatic Cord Mass.")

REFERENCE

Rathaus V, Konen O, Shapiro M, et al. US features of spermatic cord hydrocele in children. *Br J Radiol.* 2005;74:818–820.

HYMENAL SKIN TAGS

DESCRIPTION A polypoid lesion of the hymenal ring. A normal variant and rarely symptomatic (ie, bleeding, irritation), treatment involves observation or excision when symptomatic or to exclude malignancy.

REFERENCE

Rink RC, Kaefer M. Surgical management of disorders of sexual differentiation, cloacal malformation and other abnormalities of the genitalia in girls. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders, 2012:3629–3666.

HYPERBARIC OXYGEN, UROLOGIC CONSIDERATIONS

DESCRIPTION This therapy involves use of oxygen at higher than atmospheric level. A variety of uses have been reported. Mainly, hyperbaric oxygen has been used to aid in wound healing. Reports of its efficacy in healing after radiation-induced wounds and iatrogenic debridement following necrotizing fasciitis of the genitourinary tract (Fournier gangrene) have been described. Hyperbaric oxygen has also been reported in the treatment of hematuria from radiation cystitis. (See also Section I: "Fournier gangrene"; "Cystitis, Hemorrhagic [Infectious, Noninfectious, Radiation"] and Section II: "Cystitis: Radiation.")

REFERENCES
Jallali N, Withey S, Butler PE. Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg.* 2005;189:462–466.
Neheman A, Nativ O, Moskovitz B, et al. Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis. *BJU Int.* 2005;96:107–109.

HYPERCALCEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION In urology, hyperuricemia is generally the result of metastatic lesions to bone, hydrochlorothiazide therapy, hyperparathyroidism, or chronic renal failure. Symptoms include anorexia, weakness, somnolence, polyuria, and coma. This condition may also occur as a paraneoplastic syndrome from RCC and can lead to hypercalciuria, which can increase chances of urolithiasis.

TREATMENT
- Initial therapy involves diuresis by nonthiazide diuretics and IV saline.
- Inorganic phosphate and EDTA may be used for an emergency.
- Mithramycin, steroids, and etidronate disodium have also been used.

REFERENCE
Assadi F. Hypercalcemia: An evidence-based approach to clinical cases. *Iran J Kidney Dis.* 2009;3(2):71–79.

HYPERCALCIURIA (ABSORPTIVE, RENAL, AND RESORPTIVE)

DESCRIPTION Hypercalciuria is the most commonly encountered metabolic abnormality in patients with calcium nephrolithiasis. Defined as urinary excretion of >275–300 mg of calcium per day in men or >250 mg of calcium per day in women on a regular unrestricted diet. An alternative definition in patients on a calcium-restricted diet (400 mg calcium, 100 mEq sodium) is a urinary calcium level of >4 mg/kg/d or with a urinary level >200 mg calcium/L of urine. Hypercalciuria consists of several types:
- **Absorptive hypercalciuria.** Caused by the intestinal hyperabsorption of calcium. Hypercalciuria results from the increased filtered load and reduced renal tubular reabsorption of calcium, caused by parathyroid suppression. Absorptive hypercalciuria type I is a severe, uncommon form; type II is mild–moderate and the most common form of this condition. Type III, sometimes called *renal phosphate leak*, is uncommon.
- **Renal hypercalciuria.** Also called *renal calcium leak*, this is caused by impairment in the renal tubular reabsorption of calcium. There may be excessive mobilization of calcium from bone and an enhanced intestinal absorption of calcium because of the parathyroid hormone excess and the stimulation of the renal synthesis of 1,25–$(OH)_2D$. Unlike primary hyperparathyroidism, serum calcium is normal and the hyperparathyroidism is secondary.
- **Resorptive hypercalciuria.** The hypercalciuria is due to primary hyperparathyroidism with excessive resorption of bone resulting from hypersecretion of PTH. Intestinal absorption of calcium is frequently elevated because of the PTH-dependent stimulation of the renal synthesis of 1,25–$(OH)_2D$.

As a guide to testing for hypercalciuria, calcium load usually consists of 1 g of oral calcium gluconate.

Hypercalciuria Type	Urinary Calcium on 400-mg Calcium Diet (Normal = <200 mg/24 h)	Fasting Calcium/ Creatinine Ratio (Normal = <0.11)	Postcalcium Load Calcium/Creatinine Ratio (Normal = <0.20)
Normal	Normal	Normal	Normal
Absorptive type I	High	Normal	High
Absorptive type II	Normal	Normal	High
Absorptive type III (renal phosphate leak)	High	High	High
Renal calcium leak	High	High	High
Resorptive (hyperparathyroidism)	High	High	High

Based on data from Leslie SW. Hypercalciuria. http://www.emedicine.com/med/TOPIC1069.HTM, Accessed May 18, 2013.

TREATMENT

- General recommendations include increased urine volume to >2 L/d, do not use calcium-restricted diet, but avoid excessive intake of dairy products, salty foods, and red meat protein. (Note: A low calcium intake increases intestinal oxalate absorption, with a subsequent increase in urinary oxalate stone formation.) Patients may be at risk for osteoporosis and osteopenia.
- Absorptive hypercalciuria:
  - Thiazide is not a selective therapy for absorptive hypercalciuria, since it does not decrease intestinal calcium absorption. However, this drug is used because of its hypocalciuric action and the high cost and inconvenience of alternative therapy (sodium cellulose phosphate).
- Absorptive hypercalciuria type I:
  - Thiazide does not correct the basic, underlying physiologic defect in absorptive hypercalciuria.
  - Potassium supplementation (as potassium citrate), should be employed when using thiazide therapy to prevent hypokalemia and hypocitraturia (eg, potassium citrate 15–20 mEq BID)
  - Amiloride in combination with thiazide may be more effective than thiazide alone in reducing calcium excretion.
  - Potassium supplementation should be used with caution in patients taking amiloride.
  - Thiazides may lose their hypocalciuric effect over time and cause hypokalemia, hypocitraturia, and increased uric acid.
  - Recent data suggest bisphosphonates (eg, alendronate [Fosamax], risedronate [Actonel], and ibandronate [Boniva] increase bone deposition of calcium and reduce urinary calcium levels.
- Absorptive hypercalciuria type II:
  - No specific drug treatment may be necessary since the physiologic defect is not as severe as in absorptive hypercalciuria type I. Low calcium intake (400–600 mg/d) and high fluid intake (sufficient for a minimum urine output >2 L/d) is helpful. Normo-calciuria can be restored by dietary calcium restriction alone, and increased urine volume has been shown to reduce urinary saturation of calcium oxalate.
- Absorptive hypercalciuria type III (renal phosphate leak) is treated with slow-release neutral

potassium phosphate (Neutra-Phos K) that corrects the hyperphosphatemia.

- Renal hypercalciuria:
  - Thiazide diuretic augments calcium reabsorption in the distal tubule, causes extracellular volume depletion, and stimulates proximal tubule reabsorption of calcium. Agents include hydrochlorothiazide 50 mg BID, chlorthalidone 50 mg/d, or indapamide 1.25–2.5 mg/d. Potassium supplementation (~40 mEq/d) is required to prevent hypokalemia and attendant hypocitraturia. Potassium citrate has been shown to be effective in averting hypokalemia and in increasing urinary citrate when administered to patients with calcium nephrolithiasis taking thiazide.
  - Triamterene is contraindicated because of the risk of triamterene renal stone formation.
- Resorptive hypercalciuria: Parathyroidectomy is the optimum treatment.

REFERENCE

Pak CY. Pharmacotherapy of kidney stones. *Expert Opin Pharmacother*. 2008;9(9):1509–1518.

HYPERCARBIA DURING LAPAROSCOPY

DESCRIPTION CO_2 is the most abundantly used insufflant in the United States for laparoscopic surgery. CO_2 has the ability to diffuse easily into body tissues and out of the peritoneum during surgery. This can lead to increases in blood levels or hypercarbia that can stimulate the sympathetic nervous system, leading to increases in vascular resistance, tachycardia, and impaired cardiac contractility. Patients who have pulmonary compromise (ie, COPD, fibrosis) may have difficulty compensating for the increased CO_2 levels. Rarely a CO_2 gas embolism may occur.

REFERENCE

Bandi G, Gomella LG. Basic principles of laparoscopy: Transperitoneal, extraperitoneal and hand-assisted techniques. In: Graham S, Keane T, eds. *Glenn's Operative Urology*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.

HYPERCONTINENCE

DESCRIPTION A condition described in the literature referring to the increased likelihood that females are more likely to require intermittent catheterization than men following continent urinary diversion such as orthotopic neobladder. Hypercontinence is reported in up to 31% of females and is much less common in men.

REFERENCE

Rouanne M, Legrand G, Neuzillet Y, et al. Long-term women-reported quality of life after radical cystectomy and orthotopic ileal neobladder reconstruction. *Ann Surg Oncol*. 2014;21(4):1398–1404.

HYPERKALEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hyperkalemia usually occurs in urologic patients as a result of renal insufficiency, addisonian crisis, trauma, shock, and diabetic acidosis. It can also be a

consequence of small bowel substitution used in urinary diversion. ECG changes are characteristic, including peaked T waves, long PR interval, long QRS complex, and absent P wave.

TREATMENT

- Monitor patient on ECG if symptomatic or if K^+ is >6.5 mEq/L; discontinue all K^+ intake, including IV fluids; order a repeat stat K^+ to confirm.
- Pseudohyperkalemia should be ruled out. If doubt exists, obtain a plasma K^+ in a heparinized tube; the plasma K will be normal if pseudo-hyperkalemia is present.
- Rapid correction: These steps only protect the heart from K^+ shifts, and total body K^+ must be reduced by 1 of the treatments shown under slow correction:
  - Calcium chloride, 500 mg, slow IV push
  - Alkalinize with 50 mEq (1 amp) Na^+ bicarbonate (causes intracellular K^+ shift)
  - 50 mL D50W, IV push, with 10–15 units regular insulin, IV push (causes intracellular K^+ shift)
- Slow correction:
  - Sodium polystyrene sulfonate (Kayexalate) 20–60 g PO with 100–200 mL of sorbitol or 40 g Kayexalate with 40 g sorbitol in 100-mL water given as an enema. Repeat doses QID as needed.
- Dialysis (hemodialysis or peritoneal):
  - Correct underlying cause, such as stopping K-sparing diuretics, ACE inhibitors, mineralocorticoid replacement for hypokalemia

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 11th ed. New York, NY: McGraw-Hill; 2007.

HYPERMAGNESEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hypermagnesemia (Mg >2.5 mEq/L [mmol/L]) usually results from excessive intake (including laxatives, enemas, antacids), renal failure, hypothyroidism, or adrenal insufficiency. Symptoms include nausea and vomiting, weakness, and hyporeflexia. At higher serum levels, cardiac arrhythmias and severe cardiovascular abnormalities can result.

TREATMENT

- Stop administration of any magnesium containing medications.
- Maximize excretion of magnesium—for patients with normal renal function diuretics are used and for patients in renal failure dialysis should be initiated.
- Calcium gluconate can be administered as a cardioprotective agent.

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 10th ed. New York, NY: McGraw-Hill; 2007.

HYPERNATREMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hypernatremia in the urologic patient can result from iatrogenic causes and various disease states. Classified according to the mechanisms described below, the symptoms depend on the absolute level and also how rapidly the Na^+ level has changed. Symptoms may include confusion, irritability, lethargy, stupor, coma, muscle twitching, and seizures. Signs can include hyperreflexia and mental status changes:

- Combined sodium and water losses (hypovolemic hypernatremia): Water loss in excess of Na^+ loss results in low total body Na^+. Due to renal (diuretics, osmotic diuresis due to glycosuria, mannitol, post-obstructive diuresis, etc.) or extrarenal (sweating, GI [vomiting, NG suction], respiratory) losses.
- Excess water loss (isovolemic hypernatremia): Total body Na^+ remains normal, but total body water is decreased. Caused by diabetis insipudus (DI) (central and nephrogenic), excess skin losses, respiratory loss, others.
- Excess sodium (hypervolemic hypernatremia): Total body Na^+ increased. Caused by iatrogenic Na^+ administration (ie, hypertonic dialysis, hypertonic saline enemas, Na-containing medications) or other exogenous sources (seawater ingestion, salt tablets) or adrenal hyperfunction (Cushing syndrome, hyperaldosteronism).

TREATMENT

- Check the serum Na^+ levels frequently while attempting to correct hypernatremia:
  - Hypovolemic hypernatremia. Determine if the patient's volume is depleted by determining if orthostatic hypotension is present; if volume is depleted, rehydrate with NS until patient is hemodynamically stable, then administer hypotonic saline (1/2 NS).
  - Euvolemic/isovolemic (no orthostatic hypotension): Calculate the volume of free water needed to correct the Na^+ to normal as follows:

    Body water deficit = Normal total body water - Current TBW
    Normal TBW = 0.6 - Body weight in kg
  - Give free water as D5W, 1/2 the volume in the 1st 24 hr and the full volume in 48 hr. (Caution: The rapid correction of the Na^+ level using free water (D5W) can cause cerebral edema and seizures.)
  - Hypervolemic hypernatremia: Avoid medications that contain excessive Na^+ (carbenicillin, etc.). Use furosemide along with D5W.

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 11th ed. New York, NY: McGraw-Hill; 2007.

HYPEROXALURIA, UROLOGIC CONSIDERATIONS

DESCRIPTION The greatest significance of hyperoxaluria is the increased risk of urolithiasis, which is more significant than calcium in the formation of most kidney stones. Oxalate and calcium form an insoluble compound that can result in urolithiasis. The normal upper level of urinary oxalate excretion is 40 mg (440 μmol)/24 hr. Hyperoxaluria is caused

by dietary excess, bowel disorders such as extensive ileal resection, and primary hyperoxaluria. Primary hyperoxalurias are disorders associated with a congenital defect in the oxalate pathway. (See also Section I: "Urolithiasis, Calcium Oxalate/Phosphate."):

- Enteric hyperoxaluria: Accounts for a relatively small number of cases of hyperoxaluria (5%). Caused by chronic diarrhea and malabsorption (colitis or jejunoileal bypass), through the reduced GI calcium availability to bind oxalate and keep it from being absorbed systemically.
- Dietary hyperoxaluria: Caused by increased intake of foods high in oxalates (eg, nuts, chocolate, tea, spinach, rhubarb, beets, wheat bran, strawberries, and other plant products). Reduced dietary calcium intake can also result in hyperoxaluria due to reduced intestinal binding of oxalate and increased oxalate absorption.
- Idiopathic: The most common cause; may be due to increased dietary absorption or due to increased intrinsic production of oxalate, with some suggestions of a genetic predisposition.
- Primary hyperoxaluria type I (also called *glycolic aciduria*): A form of primary hyperoxaluria caused by an enzymatic deficiency of glyoxylate carboligase transmitted as an autosomal recessive trait. Caused by a deficiency of the peroxisomal liver-specific alanine-glyoxylate aminotransferase (AGT) gene. Pyridoxine (vitamin B6) is a cofactor in this pathway that normally converts glyoxylic acid to glycine. With a block in this conversion, because of deficiency or absence of this enzyme, high levels of glycolic and oxalic acids result that are converted to oxalate that is then excreted in the urine. This causes extensive nephrocalcinosis with kidney failure common in childhood. Most patients die at <30 yr. The condition often presents with stone disease in childhood. Type I can be associated with ESRD secondary to stones and interstitial deposits of calcium oxalate.
- Primary hyperoxaluria type II: Less common than type I hyperoxaluria, this entity is caused by deficiency of D-glyceric dehydrogenase that causes the conversion of glyoxylate to oxalate. Type I and II primary hyperoxaluria result in about the same degree of hyperoxaluria, with renal failure slightly less common in patients with type II disease. Pyridoxine is generally not effective in type II primary hyperoxaluria.
- Other: Increased hepatic conversion, due to pyridoxine deficiency, type I glycol ingestion, and methoxyflurane anesthesia

TREATMENT

- Primary hyperoxaluria: Oral phosphates and dietary oxalate restriction are usually unsuccessful. Increase urine flow. Prescribe high-dose pyridoxine (vitamin B6) 150–500 mg/d. Liver–kidney transplantation is often required at end stage.
- Enteric hyperoxaluria: Calcium citrate without vitamin D, potassium citrate 40–60 mEq/d in divided doses (increases urinary pH and citrate). Dietary restriction of oxalate with low fat and reduced meat protein diet.
- Idiopathic hyperoxaluria: Increase urine flow. Avoid excess Vitamin C (can be converted to oxalate). Prescribe high-dose pyridoxine (vitamin B6) 150–500 mg/d.

REFERENCE

Beck BB, Hoyer-Kuhn H, Göbel H, et al. Hyperoxaluria and systemic oxalosis: an update on current therapy and future directions. *Expert Opin Investig Drugs*. 2013;22(1):117–129.

HYPERPARATHYROIDISM, UROLOGIC CONSIDERATIONS

DESCRIPTION Hyperparathyroidism can cause a variety of urologically related conditions and problems, including nephrolithiasis, hypercalciuria, nephrocalcinosis, chronic renal insufficiency, and abnormalities in renal tubular function (decreased concentrating ability). Also associated in the MEN1 syndrome. About 5% of new stone formers have hyperparathyroidism, whereas up to 20% of patients with hyperparathyroidism will have stones (most common calcium oxalate). These patients usually exhibit elevated serum and urine calcium with an inappropriately normal or elevated serum PTH level and elevated calcitriol level. Treatment is through parathyroidectomy and workup for MEN when appropriate. (See also Section II: "Hypercalciuria and Multiple Endocrine Neoplasia.")

REFERENCE

Reinmark L, Vestergaard P, Mosekilde L. Nephrolithiasis and renal calcifications in primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2011;96(8):2377–2385.

HYPERPHOSPHATEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hyperphosphatemia (>1.6 mmol/L) can result from hypoparathyroidism, osteomalacia, medications, and chronic renal failure. Signs include muscle cramps, tetany, perioral numbness, renal osteodystrophy, and secondary hyperparathyroidism.

TREATMENT

Dietary restriction, stopping medications that include phosphate, and binding agents are the mainstays of therapy.

REFERENCE

Prie D, Beck L, Urena P, et al. Recent findings in phosphate homeostasis. *Curr Opin Nephrol Hypertens*. 2005;14:318–324.

HYPERSPERMIA AND HYPOSPERMIA

DESCRIPTION Hyperspermia is a poorly studied condition characterized by an excessive volume of ejaculate defined in studies as >5.5–6.5 mL/semen analysis. Hypospermia is generally defined as a total ejaculate of <1.5 mL. (See also Section II: "Semen Analysis, Abnormal Findings and Terminology"; Section II: "Semen Analysis, Technique and Normal Values.")

REFERENCE

Cooke S, Tyler JP, Driscoll GL. Hyperspermia: The forgotten condition? *Human Reprod.* 1995;10(2):367–368.

HYPERTENSION, UROLOGIC CONSIDERATIONS

DESCRIPTION Primary hypertension is the most common form of this disease, but when significant findings on evaluation are present or if the hypertension is refractory to intensive multiple-drug therapy or requires hospitalization, a secondary cause should be sought. Common urologic considerations are primary aldosteronism, congenital adrenal hyperplasia

(CAH), Cushing syndrome, pheochromocy-toma, and renovascular disease. Workup entails physical exam, endocrinologic workup, and imaging.

REFERENCE

Victor G. Arterial hypertension. In: Goldman L, ed. *Cecil Medicine*. 23rd ed. Philadelphia, PA: Saunders; 2007.

HYPERURICOSURIA

DESCRIPTION Hyperuricosuria refers to the uric acid excretion in the urine of >800 mg/d in men and >750 mg/d in women. Uric acid, the end product of purine metabolism, is relatively insoluble in water and can lead to the formation of uric acid calculi. Overproduction and over-excretion of uric acid can be due to excess dietary intake of purine-rich foods and in patients with malignancies (such as lymphoma, leukemia, myeloproliferative disease) especially after chemo or radiation induces rapid cell lysis (tumor lysis syndrome). Inherited enzyme defects can also lead to hyperuricosuria and hyperuricemia such as hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch–Nyhan syndrome) and glucose-6-phosphatase deficiency (glycogen storage disease, type I). Hyperuricosuria can be associated with hyperuricemia. The term "gouty diathesis" refers to the formation of urinary stones in persons with gout. These patients may present with other manifestations of gout such as "gouty arthritis." These high levels of uric acid can predispose to urolithiasis that can be uric acid, calcium or a combination of both. Uric acid stones are more likely with a low urine pH (ie, <6) where the solubility of uric acid is low. Allopurinol and febuxostat reduce urinary levels of uric acid. Urate crystals in the urine tend to be needle-shaped or appear as flat, square plates. (See also Section I: "Urolithiasis, Uric Acid.")

Society Definitions of Hypogonadism Based on Serum Testosterone	Total Testosterone		
	ng/dL	ng/mL	nmol/L
European Academy of Andrology (EAA), International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM)	<340	<3.40	<12 (mild)
European Association of Urology (EAU), American Society of Andrology (ASA), International Society for Sexual Medicine (ISSM)	<231	<2.31	<8 (severe)
Endocrine Society (ES)	<300	<3.00	<10.4
American Association of Clinical Endocrinologists (AACE)	<200	<2.00	7

Based on data from Miner M. Low Testosterone Medscape CME Expert Column Series. Issue 2: Screening and Workup for Testosterone Deficiency available at http://www.medscape.org/viewarticle/749240, Accessed March 27, 2014.

REFERENCE

Mehta TH, Goldfarb DS. Uric acid stones and hyperuricosuria. *Adv Chronic Kidney Dis*. 2012;19(6):413–418.

HYPOCITRATURIA

DESCRIPTION Citrate is a urinary inhibitor of crystal formation. Hypocitraturia is defined as urinary citrate excretion of <320 mg/d, but the absolute value can vary. It is a common cause of calcium urolithiasis, because citrate combines with calcium to form a nondissociable soluble complex with less calcium to combine with oxalate. Citrate also inhibits crystal agglomeration, in which individual calcium oxalate crystals combine to form a stone. Hypocitruria may develop from distal renal tubular acidosis (type I), chronic diarrhea,

thiazide use, very high animal protein diet, and gastrocystoplasty, or it may be idiopathic.

TREATMENT

- Correction of acidosis in RTA
- Replacement therapy with potassium citrate (powder: 1 packet in water after meals and at bedtime; adjust dose to urinary pH; solution: 15–30 mL after meals and at bedtime; adjust dose based on urinary pH)

REFERENCE

Pak CY. Pharmacotherapy of kidney stones. *Expert Opin Pharmacother.* 2008;9(9):1509–1518.

HYPOGONADISM, SOCIETY DEFINITIONS

DESCRIPTION The lab diagnosis of testosterone/androgen deficiency is a challenge. The Endocrine Society defines male hypogonadism as a clinical syndrome that results from failure of the testis to produce physiologic levels of testosterone (androgen deficiency) and the normal number of spermatozoa caused by disruption of 1 or more levels of the hypothalamic–pituitary–gonadal (HPG) axis. Unfortunately there is no consensus among specialists (endocrinologists, urologists, pathologists) as to what lab values defines a "low" testosterone level. Serum testosterone levels are subject to many variables including diurnal, seasonal, and age-related variations. Illness and medications (opiates, glucocorticoids), may impact testosterone levels. In addition testosterone levels are impacted by alterations in sex-hormone binding globulin (SHBG). Further there are a variety of assays that differ in their measurement of testosterone levels leading to a wide variety of normal ranges reported by different labs. The Food and Drug Administration (FDA) uses a cut-off value of 300 ng/dL to define hypogonadism for clinical trial development and enrollment. Society definitions of testosterone levels and hypogonadism are summarized in the table. (See also Section I: "Andropause [Late Onset Male Hypogonadism]," "Testosterone, Decreased [Hypogonadism]," "Sex-Hormone Binding Globulin," and "Testosterone [Free and Total] Lab Testing.")

REFERENCE

Paduch D, et al. The Laboratory Diagnosis of Testosterone Deficiency: AUA White Paper available at http://www.auanet.org/common/pdf/education/clinical-guidance/Testosterone-Deficiency-WhitePaper.pdf, Accessed March 27, 2014.

HYPOKALEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hypokalemia (K^+ of <3.6 mEq/L [mmol/L]) can result from excessive upper GI losses, diarrhea, diuretic therapy, steroid administration, and hyperaldosteronism. Metabolic alkalosis is often associated and causes an intracellular redistribution of potassium. Other high-renin states, such as renin-secreting tumors, have been reported as a cause. A serum K^+ level of 2 mEq/L (mmol/L) probably represents a deficit of at least 200 mEq (mmol) in a 70-kg adult; to change K^+ from 3–4 mEq/L (mmol/L) takes about 100 mEq (mmol) of K^+ in a 70-kg adult.

TREATMENT

- Treat underlying cause.

- Hypokalemia potentiates the cardiac toxicity of digitalis. In the setting of digoxin use, hypokalemia should be aggressively treated.
- Treat hypomagnesemia if present. It will be difficult to correct hypokalemia in the presence of hypomagnesemia.
- Rapid correction: Give KCl IV. Monitor heart with replacement at >20 mEq/h; IV KCI can be painful and damaging to veins:
  - Patient <40 kg: 0.25 mEq/kg/h × 2 hr
  - Patient >40 kg: 10–20 mEq/h × 2 hr
  - Severe [<2 mEq/L (mmol/L)]: Maximum 40 mEq/h IV in adults. In all cases, check a stat K^+ following each 2–4 hr of replacement.
- Slow correction: Give KCl PO:
  - Adult: 20–40 mEq BID or TID
  - Pediatric patients: 1–2 mEq/kg/d in divided doses. Potassium supplementation either with PO or IV forms

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 10th ed. New York, NY: McGraw-Hill; 2007.

HYPOMAGNESEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hypomagnesemia (Mg of <0.7 mEq/L [mmol/L]) can result from inadequate magnesium intake, malabsorption, chronic diarrhea, stress, alcoholism, and medications such as diuretics. Symptoms of hypomagnesemia include weakness, muscle cramps, muscle tetany, confusion, hallucinations, hypertension, and arrhythmias. Often accompanied by hypokalemia.

TREATMENT

Replacement can be either oral for patients with mild symptoms or parenterally for more severe symptoms.

- Tablet (Mag-Ox): 1–2 tablets PO daily or capsule (Uro-Mag): 4–5 capsules PO daily
- Parenteral replacement: Mild 1 g IM q6h × 4 doses; More severe: 5 g IV over 3 hr
- Changing diuretics to agents such as amiloride (a potassium-sparing diuretic with mild hypocalciuric activity) reduces the magnesium loss caused by thiazides.

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 10th ed. New York, NY: McGraw-Hill; 2007.

HYPONATREMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hyponatremia is a sodium/Na^+ level of <136 mEq/L (mmol/L). Many causes exist, but an acute cause in urology is a result of excessive nonelectrolyte irrigant absorption during endourologic procedures. As the fluid is absorbed, volume expansion and dilutional hyponatremia occur. Known as transurethral resection (TUR) syndrome, nausea, mental confusion, and sensory disturbances are seen, and, if allowed to progress, blindness,

convulsions, hypotension, coma, oliguria, and death can occur. Other causes include nephrotic syndrome, renal failure, SIADH, adrenal insufficiency, diuretics, renal tubular acidosis (RTA), GI losses, and mineralocorticoid insufficiency. (See also Section I: "Transurethral Resection [TUR] Syndrome.")

TREATMENT

- Treat the underlying cause.
- Therapy is based on determination of volume status. Evaluate volume status by physical exam: HR and BP lying and standing after 1 min, skin turgor, and edema, and by determination of the plasma osmolality. It is not necessary to treat hyponatremia from pseudo-hyponatremia (increased protein or lipids) or hypertonic hyponatremia (hyperglycemia); treat underlying disorder (see above):
  - Life-threatening (seizures, coma): 3–5% NS can be given in the ICU setting. Attempt to raise the Na to at least 125 mEq/L with 3–5% NS.
  - Isovolemic hyponatremia (SIADH): Restrict fluids (1,000–1,500 mL/d). Demeclocycline can be used in chronic SIADH.
  - Hypervolemic hyponatremia: Restrict Na and fluids (1,000–1,500 mL/d). Treat with furosemide.
  - Hypovolemic hyponatremia: Give D_5NS or NS.
    - Arginine vasopressin antagonists are indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia
      - Conivaptan (Vaprisol) Load: 20 mg IV infusion over 30 min the 20 mg IV continuous infusion over 24-hr period for 2–4 days
      - Tolvaptan (Samsca) Initial: 15 mg PO daily followed by maintenance. Increase dose PRN after >24 hr to 30 mg qDay; may increase further 60 mg/d maximum dose. Not to exceed 30 days.

REFERENCE

Fluids and electrolytes. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference.* 11th ed. New York, NY: McGraw-Hill; 2007.

HYPOPHOSPHATEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Hypophosphatemia (<1.0 mmol/L) can result from inadequate intake, malabsorption, alcohol abuse, and hyperparathyroidism. It may manifest as muscle weakness, or mental status changes. More severe states can produce problems at the cellular level leading to white blood cell dysfunction or anemia.

TREATMENT

Replacement can be either oral for patients with mild symptoms or parenterally for more severe symptoms.

- Potassium phosphate/sodium acid phosphate (K-Phos Neutral, Neutra-Phos) 1–2 tablets PO QID; also lowers urinary calcium level in idiopathic hypercalciuria
- Parenteral: KPO_4 Phos or Na PO_4 (mixed 15 mmol/250 mL) 0.25 mmol/kg IBW infused over 4–6 hr

REFERENCE

Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. *Am J Kidney Dis*. 2012;60(4):655–661.

HYPOSPADIAS, FREE GRAFT REPAIR

DESCRIPTION When local skin is not available or the quality of the preputial flap is poor during planned hypospadias repair, the use of free grafts from the bladder (1st introduced in 1947 by Memmelaar) or buccal mucosa tissue is generally employed. From a historical perspective, genital skin or bladder mucosa was commonly utilized during free graft repair. However, buccal mucosa has now become the graft of choice in the modern era. The preferred harvesting area is the inner cheek, taking care to avoid Stensen's duct. Multiple small incisions are then made in the harvested graft to prevent hematoma formation after placement. Excellent results have been reported in both the single and 2 step stages utilizing free buccal mucosa graft for repair.

REFERENCES

Gargollo P, Borer J. Two-stage repair of hypospadias. In: Smith J, Howards S, Preminger G, eds. *Hinman's Atlas of Urologic Surgery*. Philadelphia, PA: Elsevier Saunders; 2012.

Zhao M, Li Y, Tang Y, et al. Two-stage repair with buccal mucosa for severe and complicated hypospadias in adults. *Int J Urol*. 2011;18(2):155–161.

HYPOSPADIAS, TUBULARIZED INCISED PLATE (TIP) REPAIR

DESCRIPTION For distal hypospadias repairs, the most commonly performed operation is the tubularized incised plate or TIP repair. The penis is degloved and a midline incision of the urethral plate is made from within the meatus to the end of the plate without entering the glans. This incision allows for easier tubularization of the tissue and creates less tension on the ventral reconstruction. Urethral plate tubularization is then performed from the end of the plate to create a rounded meatus. Subepithelial running is used to complete a 2-layer closure. A dartos flap is then created and rotated ventrally to cover the neo-urethra. Glansplasty and shaft skin closure and reconstruction complete the procedure. Sponge bathing and antibiotic therapy are advised until the urethral catheter is removed. Oxybutynin is also provided to older patients to reduce bladder spasms. As with other hypospadias techniques, the most common complications from TIP urethroplasty is fistula formation, which can be low as 2% in the hands of an experienced surgeon. It has proven to be a versatile procedure used in both distal and midshaft hypospadias repairs.

REFERENCE

Snodgrass WT. Snodgrass technique for hypospadias repair. *BJU Int.* 2005;95(4):683–693.

HYPOSPADIAS, 2-STAGE REPAIR

DESCRIPTION The basic tenet of the 2-stage hypospadias repair is to create a new urethral plate with a graft of alternative tissue in the 1st stage and then tubularize this tissue to create a neo-urethra in the 2nd stage. The main grafts for the 1st-stage repair can be categorized

into the following:
- Byars' flap—pedicled flaps of the dorsal hood foreskin rotated ventrally
- Mesh free skin graft in an onlay fashion
- Buccal mucosa free graft in an onlay fashion
- Bracka graft—a free partial-thickness skin graft

The choice of graft depends on a multitude of factors including surgeon experience or preference, availability of preputial skin, and history of previous surgeries.

During the 1st stage, an orthoplasty is performed and a chosen graft is placed on the ventral penis. The next stage is generally performed 6 mo or more after completion of the 1st stage where the main goal is to create a neo-urethra that corrects the hypospadias. Tubularization of local skin proceeds in a Thiersch–Duplay fashion. This step is followed by reapproximation of the glans over the newly formed urethra and 2nd layer coverage with local subcutaneous tissue or a tunica vaginalis flap. Finally, urinary diversion with either a urethral or suprapubic catheter should be done for 1–2 wk postoperatively. Daily meatal dilation for 6 mo is recommended to prevent meatal stenosis. Complications include urethrocutaneous fistula, bleeding, infection, meatal stenosis, urethral stricture, and partial or complete breakdown of the repair.

REFERENCE

Gargollo P, Borer J. Two-stage repair of hypospadias. In: Smith J, Howards S, Preminger G, eds. *Hinman's Atlas of Urologic Surgery*. Philadelphia, PA: Elsevier Saunders; 2012.

HYPOSPADIAS, URETHRAL ADVANCEMENT FOR SUBGLANULAR AND MIDSHAFT DEFECTS

DESCRIPTION The meatal advancement and glanuloplasty incorporated (MAGPI) procedure was 1st described by Duckett in 1981 as an option for patients with a glanular or subcoronal hypospadias. A dorsal meatotomy with glanulopasty is performed to advance the neo-urethra distally. This was later modified by Zaontz in 1989 for patients with a coronal or glanular hypospadias with a deep glanular groove and a fish mouth meatus as the glans approximation or "GAP procedure". For midshaft defects, rolled mid-line tube techniques based on the initial reports of Thiersch–Duplay in the 1800s have gained renewed popularity. The Snodgrass incised plate procedure (TIP), a variant of the Thiersch-Duplay technique, is now among the most popular methods of hypospadias repair. Other techniques include meatal based flap procedures (eg, Mathieu) and on-lay flap repairs with native tissue or free grafts.

REFERENCE

Belman A. Hypospadias. In: Graham S, Glenn J, Keane T, eds. *Glenn's Urologic Surgery*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:792–801.

HYSTERECTOMY, UROLOGIC CONSIDERATIONS

DESCRIPTION Hysterectomy is among the most frequent surgeries performed on female patients and has been reported to contribute to up to 54% of all ureteral injuries. The reported rates of ureteral injury vary between 0.5 and 14% during laparoscopic hysterectomy.

Whereas at least 1/3 of ureteral injuries are recognized intraoperatively during open operations, fewer are identified during laparoscopy. Therefore, a high index of suspicion with intimate knowledge of anatomy is critical during gynecologic surgery. Repair of the ureter is determined by location and extent of injury and can include ureteroureterostomy, ureteroneocystostomy with or without a Boari flap or psoas hitch, or even more extreme examples such as kidney autotransplantation or bowel interposition.

Nearly half of all bladder injuries result from iatrogenic causes, mainly obstetric or gynecologic complications during surgery. Again, a high index of suspicion along with knowledge of the anatomy is crucial in recognizing these injuries. Tests with indigo carmine can be utilized to assist in identification of either ureteral or bladder injuries. In addition, blood or gas (during laparoscopic surgery) in the foley bag can be a sign of a potential injury. When identified, intraperitoneal bladder injuries during hysterectomy should repaired in the same operative setting.

REFERENCE

Leonard F, Fotso A, Borghese B, et al. Ureteral complications from laparoscopic hysterectomy indicated for benign uterine pathologies: A 13-year experience in a continuous series of 1,300 patients. *Hum Reprod.* 2007;22:2006–2011.

IC (INTERSTITIAL CYSTITIS) SYMPTOM INDEX

DESCRIPTION Also called the *Oleary–Sant Symptom Index*, this is a validated questionnaire for patients with IC/PBS (interstitial cystitis/painful bladder syndrome) to measure urinary and pain symptoms. It is based on 4 questions that are graded from 0–5, with 5 being the most severe. It is frequently used with the IC problem index.

REFERENCE

O'Leary MP, Sant GR, Fowler FJ Jr, et al. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(5A Suppl):58–63.

ICE WATER TEST

DESCRIPTION Historically performed after standard cystometrogram, this test may aid in differentiation of upper and lower motor neuron lesions. Ice water is rapidly instilled into the bladder and left for 1 min. If the water is ejected or the bladder pressure rapidly rises, the test is positive. Most patients with upper motor neuron/suprasacral lesions (eg, Parkinson, MS, CVA) have a positive test. Patients with lower motor neuron lesions almost never have a positive test.

REFERENCE

Petersen T, et al. The ice-water test in detrusor hyper-reflexia and bladder instability. *Br J Urol*. 1997;79(2):163–167.

ICIQ-MLUTS (INTERNATIONAL CONSULTATION ON INCONTINENCE QUESTIONNAIRE-MALE LOWER URINARY TRACT SYMPTOMS)

DESCRIPTION The ICIQ-MLUTS is a patient questionnaire used to evaluate men with LUTS and impact on quality of life. The original questionnaire compromised of 22 items and was shortened to 11 items in 2 distinct factors of voiding and incontinence. Unlike other questionnaires, such as the American Urological Association symptom score, the ICIQ-MLUTS contains separate subscores for the domains of incontinence and voiding with separate consideration of frequency, nocturia, and impact on quality of life. It has been shown to be a validated and reliable instrument for evaluating men with LUTS.

REFERENCE

Donovan JL, Peters TJ, Abrams P, et al. Scoring the short form ICS male SF questionnaire. International Continence Society. *J Urol.* 2000;164(6):1948–1955.

IIEF (INTERNATIONAL INDEX OF ERECTILE FUNCTION)

DESCRIPTION The IIEF is a validated self-administered patient questionnaire useful in the assessment of male sexual dysfunction. A score of 0–5 is given to each of 15 questions in 4 main male sexual function domains: Erectile function, orgasmic function, sexual desire, and intercourse satisfaction. The IIEF questionnaire is limited by a superficial assessment of psychosexual issues and also partner relationship factors which can both impact male sexual

dysfunction. The abridged 5-item questionnaire was subsequently developed to specifically diagnose the presence and severity of erectile dysfunction.

REFERENCES

Rosen R, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49:822–830.

Rosen R, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res*. 1999;11(6):319–326.

IMMUNOHISTOCHEMICAL STAINING, UROLOGIC CONSIDERATIONS

DESCRIPTION The following are common markers and patterns of immunohistochemical (IHC) and other staining patterns commonly used in urologic pathology. Individual labs and pathologists may use individual panel testing with selective staining (Image ☼).

Tumor Type	IHC Stains Positive	IHC Stains Negative
Prostate adenocarcinoma	AMACR (P504S), PSA, pPSA, PSAP, PSMA, ERG, NK3.1	Basal cell markers: HMWK and P63 or CK14, CK5/6; CK7, CK20
Prostate small-cell carcinoma	Chromogranin, synaptophysin, CD56, NSE, TTF1, AMACR, CK7, AE1/AE3	CD45, CD99
RCC, clear cell	RCC, CD10, vimentin, EMA, AE1/AE3, CAM5.2, CAIX, PAX2, PAX8	CK7, CK20, CEA, C-Kit, Ksp-cadherin, HMWK
RCC, papillary and papillary adenoma	CK7, vimentin, AMACR, EMA, AE1/AE3	RCC, Ksp-cadherin, HMWK, WT1
RCC, chromophobe	CK7, C-Kit, Ksp-cadherin, EMA, CAM5.2, AE1/AE3, EpCAM, Hale's Colloidal Iron[a]	Vimentin, RCC, CD10
Renal oncocytoma	C-Kit, Ksp-cadherin, EMA, CAM5.2, AE1/AE3	CK7, EpCAM, vimentin, RCC, CAIX, Hale's Colloidal Iron[a]
Renal metanephric adenoma	WT1, AE1/AE3, vimentin	EMA, CK7
Renal MITF/TFE family translocation-associated carcinoma	TFE3, TFEB, CD10, RCC, AMACR (TFEB tumors show + Melan-A and HMB45)	AE1/AE3, CK7, EMA, vimentin. (TFEB tumors: CD10, RCC)
Renal angiomyolipoma	HMB45, Melan-a	AE1/AE3, EMA
Urothelial carcinoma	CK7, CK20, HMWK, p63, p53, uroplakin, thrombomodulin, GATA-3	Vimentin, CDX2, PSA, PSAP, PSMA, NK3.1
Testis, seminoma	PLAP, C-kit, OCT4	AE1/AE3, EMA, CD30, AFP, inhibin
Testis, embryonal carcinoma	PLAP, CD30, AE1/AE3, CAM5.2, OCT4	EMA, AFP
Testis, yolk sac	PLAP, AFP, AE1/AE3, CAM5.2, α1-antitrypsin	EMA, CD30
Testis, choriocarcinoma	PLAP, β-HCG, EMA, AE1/AE3, CAM5.2, inhibin, CEA	
Testis, Leydig cell tumor	Inhibin, CD99, vimentin, S100, CAM5.2	PLAP, EMA
Testis, Sertoli cell tumor	Inhibin α, CD99, vimentin, S100, CAM5.2, NSE, synaptophysin	PLAP

AE1/AE3, pan-cytokeratin; AFP, α-fetoprotein; AMACR, alpha-methylacyl CoA racemase; CAIX, carbonic anhydrase IX; C-Kit, CD117; EMA, epithelial membrane antigen; ERG, erythroblast transformation-specific (ETS) transcription factor; GATA, endothelial transcription factor 3; HMWK, high–molecular-weight keratin (34βE12); Ksp-cadherin, kidney-specific cadherin; MITF, microphthalmia-associated transcription factor; NSE, neuron-specific enolase; OCT4 (OCT3/4); PAX, paired box gene; PLAP, placental like alkaline phosphatase; pPSA, pro prostate-specific antigen; PSA, prostate-specific antigen; PSAP (PAP), prostatic acid phosphatase; PSMA, prostate surface membrane antigen; RCC, renal cell carcinoma and RCC antibody; TFE, transcription factor binding; TFE3, transcription factor binding to IGHM enhancer 3; TFEB, transcription factor EB; TTF1, transcription termination Factor 1; WT1, Will's tumor 1; β-HCG, human chorionic gonadotropin β-subunit;
[a] histochemical stain.

REFERENCES

Bostwick D, et al. Immunohistochemistry of the prostate and bladder, testis, and renal tumors. In: Dabbs D, ed. *Diagnostic Immunohistochemistry*. Philadelphia, PA: Churchill Livingstone; 2002:407–434.

Liu, Qian J, Singh H, et al. Immunohistochemical analysis of chromophobe renal cell carcinoma, renal oncocytoma, and clear cell carcinoma: An optimal and practical panel for differential diagnosis. *Arch Pathol Lab Med*. 2007;131(8):1290–1297.

IMPERFORATE HYMEN

DESCRIPTION The hymen is composed of endoderm from the urogenital sinus epithelium and is located between the vaginal canal and vestibule. Normally, it opens during embryonic development. If it does not open, the hymen is called imperforate. Patients may present with hydrocolpos or mucocolpos that may obstruct the urinary tract. At puberty, females may present with primary amenorrhea and cyclic abdominal pain. Treatment is surgical if it causes symptoms.

REFERENCE

Katz V, Lentz G. Congenital abnormalities of the female reproductive system. In: Katz VL, ed. *Comprehensive Gynecology*. St. Louis, MO: Mosby; 2007.

IN VITRO FERTILIZATION (IVF) AND EMBRYO TRANSFER

DESCRIPTION Currently IVF is used for women with nonfunctioning oviducts, severe endometriosis, and in couples with male factor infertility or unexplained infertility. In most clinics, the female patient undergoes ovarian hyperstimulation with hormonal agents to increase the number of oocytes for follicle aspiration. The oocyte retrieval is performed by aspiration through the vagina with US guidance of needle placement. After aspiration of the oocyte, the eggs are incubated and placed in culture media. Sperm from the male is then integrated into the culture media after being separated from the semen. After about 48–96 hr, 1–4 splitting embryos are placed in the uterus via transcervical injection. (See also Section II: "Assisted Reproductive Techniques [ARTs].")

REFERENCE

Lobo R. Infertility: Etiology, diagnostic evaluation management, prognosis. In: Katz VL, ed. *Comprehensive Gynecology*. 5th ed. St. Louis, MO: Mosby, 2007.

INCONTINENCE CLAMPS

DESCRIPTION The underlying pathophysiology of male incontinence is related to either detrusor over activity or external sphincter weakness, or a combination of the 2. Incontinence clamps are external devices that are used to treat male incontinence by increasing outflow resistance. They are applied externally to the penis to exert nonsurgical compression of the urethra, thereby preventing leakage of urine. The safety, efficacy, comfort, and patient satisfaction with 3 types of commercially available penile incontinence clamps (C3, U-Tex Male Adjustable Tension Band, and Cunningham clamp) has been studied in a small 12 patient trial. Results indicated that the Cunningham clamp was the most efficacious and most accepted by users. There was a concern over reduced distal blood flow velocity. None of the devices completely eliminated urine leakage when applied at a comfortable pressure. Complications of penile clamps can include edema, pain, urethral erosion, and obstruction.

Penile clamps should not be used for >4 hr at a time. (See also Section I: "Incontinence, Urinary, Adult Male" and Section II: "Cunningham Clamp.")

REFERENCES

Campbell SE, Glazener CM, Hunter KF, et al. Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev.* 2012;1:CD001843.

Moore KN, Schieman S, Ackerman T, et al. Assessing comfort, safety, and patient satisfaction with three commonly used penile compression devices. *Urology*. 2004;63:150–154.

INCONTINENCE IMPACT QUESTIONNAIRE (IIQ-7)

DESCRIPTION Short version of the IIQ (Incontinence Impact Questionnaire). A 7-question validated questionnaire to assess the impact of female urinary incontinence on activities of daily living. Commonly used in a perioperative setting for patients undergoing anti-incontinence procedures and for research purposes.

REFERENCE

Ubersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: The Incontinence Impact Questionnaire and the Urogenital Distress Inventory. *Neurourol Urodyn*. 1995;14(2):131–139.

INCONTINENCE (URINARY) WITH ORGASM (CLIMACTURIA)

DESCRIPTION Coital urinary incontinence can be divided into 2 forms: Incontinence at penetration and incontinence during orgasm. Incontinence during orgasm has been associated with detrusor overactivity (DO), whereas female incontinence during penetration has been associated with stress incontinence. The term *climacturia* is used mostly when referring to males who have incontinence associated with orgasm; this condition is seen mostly after radical prostatectomy. (See also Section II: "Coital Incontinence [Coital Leakage/Intercourse Incontinence].")

REFERENCE

Serati M, Salvatore S, Uccella S, et al. Female urinary incontinence during intercourse: A review on an understudied problem for women's sexuality. *J Sex Med*. 2009;6(1):40–48.

INDEVUS URGENCY SEVERITY SCALE (IUSS)

DESCRIPTION A validated patient-reported questionnaire for the report of urgency severity associated with overactive bladder. This scale has been validated to capture the urgency severity per toilet void. This scale, when combined with a 24-hr diary of frequency and urge incontinence episodes, creates the Overactive Bladder Symptom Composite Score (OAB-SCS).

REFERENCE

Zinner N, Harnett M, Sabounjian L, et al. The overactive bladder-symptom composite score: A composite symptom score of toilet voids, urgency severity and urge urinary incontinence in patients with overactive bladder. *J Urol*. 2005;173(5):1693–1643.

INDIANA POUCH

DESCRIPTION A urinary reservoir is created from the right colon, and the ileal cecal apparatus is used as a continent catheterizable limb. Originally described by Gilchrist et al. in 1950, the pouch was modified by Rowland and co-workers at the University of Indiana. Modifications included detubularizing the colon with subsequent closure in a Heineke–Mikulicz configuration, strengthening of the ileocecal valve with imbricating sutures (which are performed on the ileal limb), and then performing a tunneled ureterocolonic anastomosis (Image ☼).

REFERENCE

Bihrle R. The Indiana pouch continent urinary reservoir. *Urol Clin North Am*. 1997;24(4):773–779.

INFERTILE MALE SYNDROME

DESCRIPTION Syndrome caused by mutations in the androgen receptor gene, leading to partial androgen insensitivity and infertility. This is the mildest form of partial androgen insensitivity syndrome (PAIS) and has been termed the infertile male syndrome. Described as phenotypically normal males with azoospermia or oligospermia, and high/normal serum gonadotropins and testosterone. Testicular histology varies from complete absence of germinal elements to maturation arrest of spermatogenesis.

REFERENCE

Aiman J, Griffin JE, Gazak JM, et al. Androgen insensitivity as a cause of infertility in otherwise normal men. *N Engl J Med*. 1979;300:223–227.

INFLAMMATORY BOWEL DISEASE, UROLOGIC CONSIDERATIONS

DESCRIPTION Crohn disease and ulcerative colitis are inflammatory diseases of the GI tract. The inflammatory response in ulcerative colitis is mostly confined to the mucosa and submucosa, as opposed to Crohn disease, which can be transmural. These diseases can give rise to a number of urologic manifestations including fistula to the urinary tract, malabsorption syndromes leading to nephrolithiasis, and pyoderma gangrenosum of the genitalia (Image ☼).

REFERENCE

Stenson P. Inflammatory bowel disease In: Goldman L, ed. *Cecil Medicine*. 23rd ed. Philadelphia, PA: Saunders; 2007.

INFLAMMATORY PSEUDOTUMOR (PSEUDOSARCOMATOUS FIBROMYXOID TUMOR)

DESCRIPTION A benign mesenchymal tumor of the bladder also referred to by many other names: Postoperative pseudosarcomatous response or lesion, spindle cell nodule, pseudosarcomatous or atypical fibromyxoid tumor, atypical myofibroblastic tumor, plasma cell granuloma, nodular fasciitis, and pseudosarcomatous myofibroblastic proliferation. The

differential diagnosis of benign inflammatory pseudotumors primarily includes the spindle variant of carcinoma and sarcomas. Immunohistochemical stains are used to distinguish spindle variants of carcinoma from benign inflammatory pseudotumors. These can be seen endoscopically as pedunculated nonpapillary intraluminal lesions or as difficult to identify submucosal lesions. These are more common in females. Management is by compete transurethral resection as inflammatory pseudotumors are benign lesions that grow slowly and do not metastasize or undergo malignant transformation.

REFERENCES

Lakshmanan Y, Wills ML, Gearhart JP, et al. Inflammatory (pseudosarcomatous) myofibroblastic tumor of the bladder. *Urology*. 1997;50:285–288.

Zubac DP, Malmfred S, Nerstrøm B. Inflammatory pseudotumor of the bladder: A case report. *Scand J Urol Nephrol*. 2000;34:72–74.

INFUNDIBULAR STENOSIS

DESCRIPTION Infundibular stenosis can be characterized by a narrow infundibulum leading to a nondilated calyx which may or may not contain stones. Etiologies include extrinsic compression by either malignancy or retroperitoneal fibrosis or from intrinsic narrowing from TB, nephrolithiasis, or infection chronic scarring from renal surgery (eg, PCNL) and local neoplasm. The condition can be rarely caused by a crossing segmental artery. Patients can present with flank pain, hematuria, or deterioration of global kidney function. Indications for surgery include obstruction or to allow access to treat stones in an obstructed calyx. The use of a holmium:YAG laser or balloon is generally employed to incise or dilate the stenosis.

REFERENCE

Walsh RM, Kelly CR, Gupta M. Pecutaneous renal surgery: Use of flexible nephroscopy and treatment of infundibular stenosis. *J Endourol*. 2009;23(10):1679–1685.

INFUNDIBULOPELVIC DYSGENESIS

DESCRIPTION This is an obstructive process secondary to narrowing of the infundibulopelvic system that produces various congenital anomalies such as hydrocalycosis, calyceal diverticula, ureteropelvic junction stenosis, and multicystic kidney.

REFERENCE

Uhlenhuth E, Amin M, Harty JI, et al. Infundibulopelvic dysgenesis: A spectrum of obstructive renal disease. *Urology*. 2007;35:334–337.

INGUINAL HERNIA, ADULT, UROLOGIC CONSIDERATIONS

DESCRIPTION A direct hernia is the most common inguinal hernia in adult males. It occurs when there is a protrusion of intra-abdominal contents in an area called the Hesselbach triangle (formed by the rectus abdominis muscle, inferior epigastric artery, and inguinal ligament). Untreated bladder outlet obstruction can lead to recurrent hernia. In addition, urinary retention can occur after hernia repair. In cases of a large inguinal hernia, a portion of a distended bladder can herniate into the groin. Indirect inguinal hernias are more

common in infants and children and are caused by a patent processus vaginalis.

REFERENCE

Jeyarajah R, Harford WV Jr, et al. Abdominal hernias and gastric volvulus In: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 8th ed. Philadelphia, PA: Saunders; 2006.

INGUINAL HERNIA, PEDIATRIC, UROLOGIC CONSIDERATIONS

DESCRIPTION Typically, an indirect hernia is the most common type of inguinal hernia in the pediatric population. During embryologic development, the spermatic cord and testis descend through the anterior abdominal wall to the inguinal canal through the projection of the process vaginalis. If the process vaginalis persists, an indirect inguinal hernia may form and is always associated with a hydrocele.

REFERENCE

Jeyarajah R, Harford WV Jr. Abdominal hernias and gastric volvulus In: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 8th ed. Philadelphia, PA: Saunders; 2006.

INJECTION THERAPY FOR VESICOURETERAL REFLUX

DESCRIPTION Endoscopic treatment of vesicoureteral reflux disease was 1st described in 1981 by Matouschek using polytetrafluoroethylene (PTFE) paste at the ureteral orifice. The primary principle behind injection therapy is to endoscopically inject a bulking agent beneath the ureteral orifice, which then helps to coapt the distal ureter. The technique involves placement of the needle approximately 2 mm distal to the 6 o'clock position of the ureteral orifice. The objective is to create a "volcano" like mound appearance of the ureteral orifice. Agents used for endoscopic correction of ureteral reflux should be nontoxic, cause minimal local inflammation, not migrate to other organs, and should be easy to inject. Broadly they can be categorized into 2 main categories: Nonautologous and autologous. PTFE (Teflon), bovine collagen, dextranmoer hyaluronic copolymer (Deflux), and coaptite are all examples of nonautologous materials. Chondrocytes, fat, collage, and muscles are some of the autologous materials that have been used (Image ☼).

REFERENCE

Molitierno JA, Scherz HC, Kirsch AJ. Endoscopic treatment of vesicoureteral reflux using dextranomer hyaluronic acid copolymer. *J Pediatric Urol*. 2008;4(3):221–228.

INSECT BITE, PENIS AND SCROTUM

DESCRIPTION Insect bites and stings are typically acute processes with rapid onset of various symptomatologies, including pain, pruritus, signs of ecchymosis, and edema preceding exfoliating dermatitis. While this is a benign process requiring only analgesics and antihistamines for its treatment, it is imperative to rule out pathologic events such as testicular torsion or cancer.

REFERENCE

Moran ME, Ehreth JT, Drach GW. Venomous bites to the external genitalia: An unusual cause

of acute scrotum. *J Urol.* 1992;147(4):1085–1086.

INTERMITTENT HORMONAL THERAPY (IHT)/INTERMITTENT ANDROGEN DEPRIVATION (IAD)

DESCRIPTION The role of testosterone and prostate cancer has been well established. The role of androgen deprivation therapy (ADT) is to achieve serum testosterone levels similar to that induced by surgical castration. The impact of ADT in patient overall survival is not well known and the ideal serum testosterone level is debated. Intermittent ADT is an alternative to continuous ADT. ADT is continued until PSA reaches a nadir level. ADT is then stopped and restarted when PSA rises to pretreatment levels. In general, intermittent ADT is better tolerated and improves overall quality of life when compared to standard ADT. A recent review stated: "There is fair evidence to recommend use of IAD instead of continuous androgen deprivation (CAD) for the treatment of men with relapsing, locally advanced, or metastatic prostate cancer who achieve a good initial response to androgen deprivation. This recommendation is based on evidence against superiority of either strategy for time-to-event outcomes and substantial decrease with IAD in exposure to androgen deprivation, resulting in less cost, inconvenience, and potential toxicity."

REFERENCES

Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. *J Clin Oncol.* 2013;31(16):2029–2036.

Dason S, Allard CB, Wang JG, et al. Intermittent androgen deprivation therapy for prostate cancer: Translating randomized controlled trials into clinical practice. *Can J Urol.* 2014;21(Suppl 1):28–36.

INTERNATIONAL CHILDREN'S CONTINENCE SOCIETY (ICCS), TERMINOLOGY

DESCRIPTION The ICCS has developed standardized definitions for bladder dysfunction symptoms. These generally apply to children who are 5 or more years of age (unless noted otherwise). (See also Section I: "Incontinence, Urinary, Pediatric.")

- Daytime frequency: Voiding 8 or more times during waking hours. Decreased daytime frequency is defined as 3 or fewer voids. (Note: Pollakiuria is also used to define abnormally frequent small voids in a previously toilet-trained child without evidence of polyuria or UTI).
- Hesitancy: Difficulty in the initiation of voiding or if a child must wait a considerable amount of time before voiding begins. Hesitancy can be applied to children who have achieved bladder control regardless of age.
- Holding maneuvers: Observed behavior used to either postpone voiding or suppress urgency. These maneuvers include: Standing on tiptoe, forcefully crossing the legs, or squatting with a hand or heel pressed into the perineum (also referred to as "Vincent's curtsy"). These may be observed in children who have achieved bladder control regardless of age.
- Incontinence: Uncontrolled leakage of urine. Incontinence can be continuous or intermittent.

- Intermittent stream (Intermittency): A voiding stream of urine that occurs in several discrete bursts rather than in the normal continuous stream. Considered a normal physiologic pattern in children 3 yr of age or younger.
- Nocturia: Awakening to void at night.
- Postmicturition dribbling: Involuntary urine leakage immediately after completion of voiding in children who have achieved bladder control regardless of age.
- Straining: The application of abdominal pressure (a.k.a. Valsalva maneuver) to initiate and maintain voiding. Considered a pertinent finding in all age groups.
- Urgency: The sudden and unexpected experience of the immediate need to void.
- Weak stream: The observed ejection of urine with a weak force. Considered a pertinent finding in all age groups.

REFERENCE

Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006;176(1):314–324.

INTERNATIONAL GERM CELL CANCER COLLABORATIVE GROUP (IGCCCG)

DESCRIPTION Effective chemotherapy regimens for germ cell tumors (GCT) resulted in the development of prognostic groups for patients with metastatic disease. With good-risk disease, the goal is to minimize the toxicity of current regimens, while preserving the high cure rates. In patients with high-risk disease, investigational studies have been designed to improve long-term response rates. In the IGCCCG staging system, patients are divided into good-, intermediate-, and poor-risk groups, based upon primary site of the GCT, sites of metastasis, and serum tumor markers. Within each risk group, criteria differ for seminomas and nonseminomatous GCT. Survival in >5,200 patients is correlated with risk status: Good-risk disease, 91% 5-yr survival; intermediate-risk disease, 79% 5-yr survival; poor-risk disease, 48% 5-yr survival. (See also Section I: "Testis, Cancer, General"; Section I: "Testis, Nonseminomatous Germ Cell Tumors, General"; Section I: "Testis, Seminoma.")

SEMINOMA: GOOD RISK

All of the following:
- Any primary site
- No nonpulmonary visceral metastases
- Normal serum AFP

SEMINOMA: INTERMEDIATE RISK

All of the following:
- Any primary site
- Nonpulmonary visceral or brain metastases present
- Normal serum AFP

NONSEMINOMATOUS GERM CELL TUMORS: GOOD RISK

All of the following;

- Testicular or retroperitoneal primary tumors
- No nonpulmonary visceral metastases
- Serum AFP <1,000 ng/mL and β-hCG <5,000 mlU/mL and LDH <1.5 × upper limit of normal

NONSEMINOMATOUS GERM CELL TUMORS: INTERMEDIATE RISK

All of the following:

- Testicular or retroperitoneal primary tumors
- No nonpulmonary visceral metastases
- Intermediate level of any of the following: AFP 1,000–10,000 ng/mL or β-hCG 5,000–50,000 mlU/mL or LDH 1.5–10 × upper limit of normal

NONSEMINOMATOUS GERM CELL TUMORS: POOR RISK

Any of the following:

- Mediastinal primary germ cell tumor
- Nonpulmonary visceral metastases,
- Serum AFP >10,000 ng/mL
- Serum β-hCG >50,000 mlU/mL
- LDH >10 × upper limit of normal

REFERENCES

Bhala N, Coleman JM, Radstone CR, et al. The management and survival of patients with advanced germ-cell tumours: Improving outcome in intermediate and poor prognosis patients. *Clin Oncol (R Coll Radiol)*. 2004;16(1):40–47.

International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol*. 1997;15(2):594–603.

INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

DESCRIPTION A patient self-scoring instrument used for assessment of symptom severity in men with LUTS. The symptoms are scored from mild (0–7), moderate (8–19), to severe (20–35); the score can also be used to measure treatment response. The I-PSS uses the same 7 questions as the AUA Symptom Index for BPH with the addition of the disease-specific QoL question (known as the *bother score*), scored on a scale from 0–6 points (delighted to terrible). (See Section VII: “AUA Symptom Index for BPH” and “the I-PSS Appendix VII.”)

REFERENCES

Hakenberg OW, Pinnock CB, Marshall VR. Does evaluation with the International Prostate Symptom Score predict the outcome of transurethral resection of the prostate? *J Urol*. 1997;158(1):94–99.

Kapoor A. Benign prostatic hyperplasia (BPH) management in the primary care setting. *Can J Urol*. 2012;19(Suppl 1):10–17.

INTERSTITIAL NEPHRITIS

DESCRIPTION Acute interstitial nephritis is most commonly caused by drugs, but

autoimmune diseases (eg, lupus) and a variety of infections (eg, streptococcal or legionella) can also be the cause. Many drug-related causes have been described, but the most common are penicillins, cephalosporins, NSAIDs, ciprofloxacin, rifampin, sulfonamides, allopurinol, cimetidine, and indinavir. Nonspecific symptoms and signs, along with acute renal dysfunction include nausea, vomiting, and malaise. Urine analysis reveals WBCs, RBCs, WBC casts. Proteinuria is usually absent or mild (<1 g/d). With drug-related interstitial nephritis, allergic-type reactions may be present, such as rash, fever, and eosinophilia. Diagnosis can only be confirmed on renal biopsy. Chronic interstitial nephritis is typically caused by long-term exposure to medications such as analgesics, anticonvulsants, and Chinese herbal medications; heavy met al exposure; chronic obstruction; and other causes. Presentation is insidious with hypertension, inability to concentrate urine, acidosis, and anemia being the more common symptoms. Treatment involves stopping the offending medication or treating the underlying infection or condition (eg, lupus or sarcoidosis). Steroids are controversial in treating acute interstitial nephritis but they may benefit chronic interstitial nephritis; most cases resolve spontaneously, although persistent renal dysfunction may remain.

REFERENCE

Patel N, Menolasino, M. Interstitial nephritis. In: Domino FJ, ed. *The 5-Minute Clinical Consult*. 22nd ed. Philadelphia, PA: Lippincott; 2014.

INTRACYTOPLASMIC SPERM INJECTION (ICSI)

DESCRIPTION An assisted repoduction technique (ARRT) in which a single spermatozoon is injected into the cytoplasm of an ovum. This technique is typically utilized in males with severe oligospermia or azoospermia, as the cost is high. (See also Section II: “Assisted Reproductive Techniques [ARTs].”)

REFERENCE

Lobo R. Infertility: Etiology, diagnostic evaluation, management, prognosis. In: Katz VL, ed. *Comprehensive Gynecology*. 5th ed. St. Louis, MO: Mosby, 2007.

INTRAOPERATIVE FLOPPY IRIS SYNDROME (IFIS)

DESCRIPTION The triad of intraoperative observations of flaccid iris stroma that undulates and billows in response to ordinary intraocular fluid currents, a propensity for the floppy iris to prolapse toward the phacoemulsification tip and incision, and progressive intraoperative pupil constriction. This syndrome has been associated with α-blocker therapy in men with BPH, especially tamsulosin and is due to relaxation of the dilator muscle. Discontinuation of tamsulosin appears to be unpredictable and may not reliably reduce the severity. To mitigate the intraoperative problems, pharmacologic and mechanical strategies are used.

REFERENCE

Friedman AH. Tamsulosin and the intraoperative floppy iris syndrome. *JAMA*. 2009;301(19):2044–2045.

INTRAUTERINE INSEMINATION (IUI)

DESCRIPTION An ART in which the placement of spermatozoa that have been separated from the seminal fluid are placed into the endometrial cavity through a small catheter. Typically used to treat male factor infertility caused by oligospermia and abnormalities of semen volume or viscosity. Also used with cervical stenosis or "hostile cervical mucous" in females (See also Section II: "Assisted Reproductive Techniques [ARTs].")

REFERENCE

Lobo R. Infertility: Etiology, diagnostic evaluation, management, prognosis. In: Katz VL, ed. *Comprehensive Gynecology*. 5th ed. St. Louis, MO: Mosby; 2007.

INTRINSIC SPHINCTER DEFICIENCY (ISD)

DESCRIPTION ISD is one of many components that contribute to stress urinary incontinence (SUI) and is defined as the loss of coaptation and compression of the urethra along its length. Its etiology is usually multifactorial. ISD in women may occur simultaneously with urethral hypermobility, but should be differentiated, as the latter is an anatomic cause of SUI and not synonymous with ISD. After radical prostatectomy, SUI caused by ISD in most cases. The clinical parameters for ISD are loosely defined as a Valsalva leak-point pressure <60 cm H_2O or a maximal urethral closure pressure <20 cm H_2O, consensus is lacking.

CAUSES

- Complete loss of urethral tone (catheter trauma, surgical trauma)
- Pudendal nerve dysfunction and denervation of the mid-urethral complex (external sphincter)
- Estrogen deficiency (resulting in mucosal changes effecting coaptation)
- Diabetes (autonomic dysfunction of smooth and nonstriated skelet al muscle)
- Parity (pudendal neuropathy and pelvic floor destruction)
  - Sphincteric injury during RP or other transurethral procedure
  - Traumatic injury (ie, pelvic fracture)

TREATMENT

- Conservative management including Kegel exercises and biofeedback
- Females: Retropubic and needle suspension; periurethral bulking agents; synthetic (mesh) urethral sling; fascial urethral sling; artificial urinary sphincter
- Males: Male sling; artificial urinary sphincter (Image ☼)

REFERENCE

Shah SM, Gaunay GS. Treatment options for intrinsic sphincter deficiency. *Nat Rev Urol.* 2012;9(11):638–651.

INVERTED PAPILLOMA, BLADDER

DESCRIPTION An uncommon tumor of the urinary tract characterized by proliferating urothelium arranged as inverting cords and nests with an intact overlying urothelium. Inverted papilloma is thought to be a benign lesion but because of reports of multiplicity, recurrence, and associated TCC have been seen in the literature. Its management has been controversial (Image ☼).

REFERENCE
Picozzi S, Casellato S, Bozzini G, et al. Inverted papilloma of the bladder: A review and an analysis of the recent literature of 365 patients. *Urol Oncol.* 2013;31(8):1584–1590.

INVERTED PAPILLOMA, URETER AND RENAL PELVIS

DESCRIPTION Considered by most researchers to be benign, this lesion can coexist with malignant tumors. These rare, benign lesions have a presentation similar to that of other upper tract tumors. Papillary fronds project opposite into the mucosa, appearing as smooth-surfaced, pedunculated, or sessile lesions of the urothelium. There is a strong male predominance (91%). The lesions are typically small (<3 cm), pedunculated, and polypoid. Muscularis invasion is not seen microscopically. Inverting cords and nests of urothelial cells continuous with the urothelium is a typical finding. The etiology is unknown, but probably generated by reaction to inflammation. Although benign, the lesions have a high association with urothelial carcinoma (TCC). Diagnosis is by ureteroscopy for direct visualization and biopsy. Treatment has been nephroureterectomy; however, local excision is possible, but careful follow-up for other sites of cancer along the urinary tract is essential.

REFERENCE
Luo JD, Wang P, Chen J, et al. Upper urinary tract inverted papillomas: Report of 10 cases. *Oncol Lett.* 2012;4(1):71–74.

IRS (INTERGROUP RHABDOMYOSARCOMA STUDY) CLINICAL CLASSIFICATION

DESCRIPTION A generally accepted classification and staging system used in the IRS. (See Section I: "Rhabdomyosarcoma, Pediatric [Sarcoma Botryoides].")

- Group I: Localized disease, completely removed, regional nodes not involved
  - A: Confined to muscle or organ of origin
  - B: Contiguous involvement, with infiltration outside the muscle or organ of origin; this group includes both gross impression of complete removal and microscopic confirmation of complete removal
- Group II:
  - A: Grossly removed tumor with microscopic residual disease; no evidence of gross residual tumor; no evidence of regional node involvement
  - B: Regional disease, completely removed (regional nodes involved and/or extension of tumor into an adjacent organ; no microscopic residual disease)
  - C: Regional disease with involved nodes, grossly removed, but with evidence of microscopic residual disease
- Group III: Incomplete removal or biopsy with gross residual disease
- Group IV: Distant metastatic disease present at onset

REFERENCE
Andrassy RJ, Hays DM, Raney RB, et al. Conservative surgical management of vaginal and vulvar pediatric rhabdomyosarcoma: A report from the Intergroup Rhabdomyosarcoma Study III. *J Pediatr Surg.* 1995;30:1034–1036.

JABOULAY/WINKELMAN PROCEDURE (HYDROCELECTOMY)

DESCRIPTION Hydrocelectomy is performed by incision of the hydrocele sac after complete mobilization of the hydrocele. Partial resection of the sac is then performed and the edges are sewn together behind the spermatic cord in the Jaboulay/Winkelman technique. Care is taken not to injure any spermatic cord contents.

REFERENCE

Ku JH, Kim ME, Lee NK, et al. The excisional, placation, and internal drainage techniques: A comparison of the results for idiopathic hydrocele. *BJU Int.* 2001;87(1):82–84.

JACK STONES

DESCRIPTION A term that refers to irregular, spiculated calcium oxalate stones, resembling children's jacks, which are sometimes seen in the bladder.

REFERENCE

Dyer RB, Chen MY, Zagoria RJ. Classic Signs in Uroradiology. *Radiographics*. 2004;24:S247–S280.

JARISCH–HERXHEIMER REACTION

DESCRIPTION Originally observed by Jarisch in 1895 and later by Herxheimer and Kraus, this reaction occurs after patients are given mercury for the treatment of syphilis. The reaction is now associated with the antimicrobial treatment of spirochete infections such as leptospirosis, Lyme disease, tick-borne relapsing fever, and also syphilis. The reaction mostly occurs within 12–24 hr after treatment, and presents with symptoms such as rigors, malaise, headache, hypotension, and sweating. The reaction may be caused by a release of endotoxins or a transient elevation of cytokines, and it may be prevented with TNF-α antibodies or steroids.

REFERENCE

Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. *J Clin Pharm Ther*. 2005;30:291–295.

JEJUNAL–ILEAL BYPASS, UROLOGIC CONSIDERATIONS

DESCRIPTION Jejunal–ileal bypass is a form of bariatric surgery for treatment of morbid obesity. The complications following jejunal-ileal bypass center on a malabsorptive state and include mineral and electrolyte imbalances, protein malnutrition, enteric complications, and a list of other extra-intestinal manifestations (eg, arthritis, peripheral neuropathy, liver disease, etc.). Bariatric surgery has more recently developed newer techniques (eg, gastric sleeve, Roux-en-y bypass) which limit these complications and the jejunal-ileal bypass procedure has fallen out of favor. From a urologic perspective, bariatric bypass surgery can lead to a state of enteric hyperoxaluria and result in an increased risk of kidney stone formation. For patients with a prior history of nephrolithiasis, a 31.4% recurrence rate has been reported after bypass

surgery. It is important for the urologist to establish appropriate prevention techniques and institute treatment when necessary for this high-risk group. (See also Section II: “Bariatric Surgery, Urologic Considerations.”)

REFERENCE

Whitson JM, Stackhouse GB, Stoller ML. Hyperoxaluria after modern bariatric surgery: case series and literature review. *Int Urol Nephrol.* 2010;42(2):369–374.

JEUNE SYNDROME (ASPHYXIATING THORACIC DYSPLASIA)

DESCRIPTION Jeune syndrome is a form of lethal, short-limbed dwarfism with features that include constriction of the upper thorax and polydactyly. It has autosomal recessive inheritance. Of urologic interest, renal dysplasia, sometimes leading to end stage renal disease (ESRD), is associated with the condition.

REFERENCE

Ring E, Zobel G, Ratschek M, et al. Retrospective diagnosis of Jeune’s syndrome in 2 patients with chronic renal failure. *Child Nephrol Urol.* 1990;10(2):88–91.

JOINT REPLACEMENT, UROLOGIC CONSIDERATIONS

DESCRIPTION Prophylaxis is no longer routinely indicated for patients receiving orthopedic pins, plates, and screws or even total joints. Antimicrobial prophylaxis is intended to reduce the risk of hematogenous joint infection in patients who fit the criteria for increased risk of total joint infection and who have an increased risk of bacteremia and who meet *BOTH* sets of criteria in the table here. For patients *NOT* meeting both these criteria, antimicrobial prophylaxis still may be indicated to reduce the risk of other infections. (Based on AUA Guidelines Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis.)

Increased Risk of Hematogenous Total Joint Infection	Increased Risk of Bacteremia Associated with Urologic Procedures
Patients during the 1st 2 yr after prosthetic joint replacement Immunocompromised patients with prosthetic joint replacements: • Inflammatory arthropathies (eg, rheumatoid arthritis, systemic lupus erythematosus) • Drug-induced immunosuppression • Radiation-induced immunosuppression Patients with prosthetic joint replacements and comorbidities: • Previous prosthetic joint infections • Malnourishment • Hemophilia • HIV infection • Diabetes • Malignancy	Any stone manipulation (includes shock-wave lithotripsy) Any procedure with transmural incision into urinary tract (does not include simple ligation with excision or percutaneous drainage procedure) Any endoscopic procedures of upper tract (ureter and kidney) Any procedure that includes bowel segments Transrectal prostate biopsy Any procedure with entry into the urinary tract (except for urethral catheterization) in individuals with higher risk of bacterial colonization: • Indwelling catheter or intermittent catheterization • Indwelling ureteral stent • Urinary retention • History of recent recurrent urinary tract infection or prostatitis • Urinary diversion

TREATMENT

Recommended antimicrobial regimens:

- A single systemic level dose of a quinolone (eg, ciprofloxacin, 500 mg; levofloxacin, 500 mg; ofloxacin, 400 mg) PO 1–2 hr preoperatively.
- Ampicillin 2 g IV (or vancomycin 1 g IV over 1–2 hr in patients allergic to ampicillin) plus gentamicin 1.5 mg/kg IV 30–60 min preoperatively.
- For some procedures, additional or alternative agents may be considered for prophylaxis against specific organisms and/or other infections.

REFERENCE

Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol.* 2007;179:1379–1390.

JUVENILE GANGRENOUS VASCULITIS, SCROTAL (PYODERMA GANGRENOSUM)

DESCRIPTION A variant of scrotal gangrene of unknown etiology, which is thought to be a variant of pyoderma gangrenosum. The lesions usually occur in healthy individuals <30 yo, following an upper respiratory infection. The lesions can present with scrotal itching or stinging, with ≥ 1 skin lesions. Lab findings can show an increased erythrocyte sedimentation

rate (ESR) with normal microbiologic tests. Biopsy of the lesions reveals mostly neutrophilic dermal infiltrate and fibrinoid necrosis of small blood vessels without vasculitis. Treatment is systemic corticosteroids. The condition is often self-limited.

REFERENCE

Caputo R. Juvenile gangrenous vasculitis of the scrotum: Is it a variant of pyoderma gangrenosum? *J Am Acad Dermatol.* 2006;55(2 Suppl):S50–S53.

JUXTAGLOMERULAR CELL TUMOR, KIDNEY

DESCRIPTION Rare but important benign renal mass caused by the secretion of renin and generally affects adolescents and young adults. The ultimate cause is surgically curable hypertension. Patients (typically young females) present with severe diastolic hypertension, hypokalemia, and elevated plasma renin levels. CT, renal angiography, and renal vein sampling may be helpful in localization. The tumor is well circumscribed with fibrous capsule and the cut surface shows yellow or gray-tan color with frequent hemorrhage. The tumor is composed of monotonous polygonal cells with entrapped normal tubules. Immunohistochemically, tumor cells exhibit a positive reactivity for renin, vimentin, and CD34. Infrequent aggressive forms have been reported. Partial nephrectomy or enucleation is the treatment of choice.

REFERENCES

Dong D, Li H, Yan W, et al. The diagnosis and surgical management of juxtaglomerular cell tumor of the kidney. *J Hypertens.* 2010;28(3):628–632.

Kuroda N, Gotoda H, Ohe C, et al. Review of juxtaglomerular cell tumor with focus on pathobiological aspect. *Diagn Pathol.* 201126;6:80.

KALLMANN SYNDROME

DESCRIPTION Also known as *hypogonadotropic hypogonadism with anosmia,* caused by failure of GnRH secretion by the hypothalamus, leading to testicular failure. KAL1, encoding the extracellular glycoprotein anosmin-1, is responsible for the X-linked recessive form of the disease. It is a cause of male infertility due to the defect in the short arm of the X chromosome, and has variable inheritance and penetrance. Anosmia, cleft palate, renal anomalies, microphallus, cryptorchidism, blindness, and deafness are also associated conditions. Testes are typically small. Delayed puberty is often an initial presenting sign.

TREATMENT

- Androgens can virilize but will not promote spermatogenesis.
- hCG with FSH and LH may help fertility.

REFERENCE

Dodé C, Hardelin JP. Kallmann syndrome. *Eur J Hum Genet.* 2009;17(2):139–146.

KAPOSI SARCOMA, UROLOGIC CONSIDERATIONS

DESCRIPTION A tumor of reticuloendothelial system that presents as a raised, painful papule or ulcer with a bluish hue. In the United States, it is seen most commonly in association with AIDS. Most common site in the GU system is the penis, with a much higher incidence in homosexual males. It may cause urethral obstruction. (See also Section I: "HIV/AIDS, Urologic Considerations.")

TREATMENT

- Radiation or penectomy (partial or total) aimed at palliation
- Proximal urethrostomy for obstruction not responsive to other treatment

REFERENCE

Woldrich JM, Silberstein JL, Saltzstein SL, et al. Penile Kaposi sarcoma in the state of California. *Can J Urol.* 2012;19(2):6178–6182.

KARTAGENER SYNDROME (IMMOTILE CILIA SYNDROME)

DESCRIPTION Also called *primary ciliary dyskinesia syndrome,* this syndrome is characterized by situs inversus, chronic sinusitis, otitis media, airway disease, and immotile sperm leading to infertility. The absence of the inner and outer dynein arm of cilia is the primary pathology. Most men have live but immotile spermatozoa and are infertile, whereas some have motile spermatozoa but immotile cilia. Women have decreased fertility, with $<50\%$ completing pregnancy. This is the most common of a group of inherited ciliary defects that lead to respiratory disorders called primary ciliary dyskinesias. ICSI may be used for reproduction, but genetic counseling should be offered.

REFERENCE

Haddad G, Kashgarian M. Primary ciliary dyskinesia (immotile cilia syndrome). In: Kliegman R, et al., eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA: Saunders; 2007.

KEGEL EXERCISES

DESCRIPTION 1st described by Arnold Kegel in 1948, these exercises can be used as treatment for both stress and urgency urinary incontinence. Modern cure/improvement rates range from 50–80%. The usual regimen consists of multiple contractions of the pelvic floor muscles ≥3 times a day. Patients can practice by starting and stopping their urinary stream. Biofeedback, electrical stimulation, and cystometry are adjuncts to Kegel exercises.

SYNONYM

Pelvic floor exercises

REFERENCES

Bump RC, Hurt WG, Fantl JA, et al. Assessment of Kegel pelvic muscle exercise performance after brief verbal instruction. *Am J Obstet Gynecol*. 1991;165(2):322–327.

Park SW, Kim TN, Nam JK, et al. Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology*. 2012;80(2):299–305.

KELAMI CLASSIFICATION SYSTEM (MODIFIED)

DESCRIPTION A classification system developed by Kelami to define the severity of penile curvature. The system consists of a grading system from 1–3: Grade 1, curvature of ≤30°; grade 2, curvature of 30–60°; and grade 3, ≥60° curvature. (See also Section I: "Penis, Curvature and/or Pain.")

REFERENCE

Usta MF, Bivalacqua TJ, Jabren GW, et al. Relationship between the severity of penile curvature and the presence of comorbidities in men with Peyronie's disease. *J Urol*. 2004;171(2 Pt 1):775–779.

KELLY PLICATION

DESCRIPTION A transvaginal surgical technique to treat female SUI. The fibromuscularis tissue underlying the bladder neck is plicated in the midline through an anterior vaginal wall incision. No longer a commonly used treatment modality for SUI due to the availability of superior treatment modalities and the risk of postoperative voiding dysfunction.

REFERENCE

Thaweekul Y, Bunyavejchevin S, Wisawasukmongchol W, et al. Long term results of anterior colporrhaphy with Kelly plication for the treatment of stress urinary incontinence. *J Med assoc Thai*. 2004;87(4):357–360.

KERR KINKS

DESCRIPTION Kinking of the renal pelvis due to a deformity of the pyelocalyceal system, caused by traction of a strictured infundibulum and parenchymal fibrosis of a tuberculous kidney. The deformity leads to obstruction and dilatation of areas not directly affected by

tuberculous ulcerations and eventual pressure atrophy of renal tissue.

REFERENCE

Barrie HJ, Kerr WK, Gale GL. The incidence and pathogenesis of tuberculous strictures of the renal pelvis. *J Urol.* 1967;98:584–589.

KETAMINE ABUSE, UROLOGIC CONSIDERATIONS

DESCRIPTION Ketamine is generally used as a dissociative anesthetic compound by licensed anesthesiologists. When used recreationally, it can cause hallucinations, derealization, and thought disorders. It has seen an increase in use in young adults. Ketamine abuse can cause urinary tract changes. These include findings of bilateral upper tract narrowing, hydronephrosis, and contracted bladder states on urodynamic studies.

REFERENCE

Lai Y, Wu S, Ni L, et al. Ketamine-associated urinary tract dysfunction: an under-recognized clinical entity. *Urol Int.* 2012;89(1):93–96.

KIBRICK TEST

DESCRIPTION A test designed to evaluate circulating immune factors, as an aid to diagnosing causes of infertility. Dilutions of serum from both partners are combined with semen samples in a medium with an agglutinating gelatin. Agglutination will occur if antibodies in the serum are reactive against the sperm. Controls are usually also run with the samples to prevent errors.

REFERENCE

Kalaydjiev SK, Dimitrova DK, Trifonova NL, et al. The age-related changes in the incidence of 'natural' anti-sperm antibodies suggest they are not auto-/isoantibodies. *Am J Reprod Immunol.* 2002;47(2):65–71.

KIDNEY, METASTASIS TO

DESCRIPTION Kidney metastases may present as a renal mass and grossly appear as a renal primary neoplasm. Discovered most often at autopsy, with an incidence of about 7%. They are frequently asymptomatic, but flank pain, hematuria, or hemorrhage may occur. Common primary tumors are lung (bronchogenic carcinoma most common), ovary, bowel, breast, and lymphoma. Virtually any origin is possible.

REFERENCE

Campbell SC, Lane BR. Malignant renal tumors. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:1413–1474.

KIDNEY, SUPERNUMERARY

DESCRIPTION One of the least common genitourinary anomalies, this mass of renal tissue has no parenchymatous connection with the definitive kidney (unlike a horseshoe kidney).

The supernumerary kidney is usually in a caudal position relative to the normal kidney and rarely is in a more cephalad position. The kidney is usually smaller or hypoplastic than a normal kidney and can function normally or not function at all. The ureter can insert into a normal ureter or bladder. It is usually associated with other GU anomalies, such as duplicated renal pelvis, vaginal atresia, and duplicated female urethra. Treatment is unnecessary unless disease is present. (See also Section I: "Renal Ectopia and Renal Fusion Anomalies.")

REFERENCE

Favorito LA, Morais AR. Evaluation of supernumerary kidney with fusion using magnetic resonance image. *Int Braz J Urol.* 2012;38(3):428–429.

KLINEFELTER SYNDROME

DESCRIPTION A syndrome characterized by small, firm testes, gynecomastia, and elevated urinary gonadotropins; it is present in 1 out of 600 male births. Usually presents as incomplete virilization, infertility, or rarely as male pseudohermaphroditism. Mental retardation and low bone mineral density (BMD) are associated. A testicular biopsy usually shows sclerosis of tubules. The condition is caused by a nondisjunction of the meiotic chromosome, resulting in XXY karyotype and its variants. FSH is markedly elevated. Azoospermia is traditionally described on semen analysis, but recent series indicate that sperm can be found in over 50% of men with Klinefelter syndrome; thus, these men are not always sterile. Recent evidence suggests that children with Klinefelter syndrome are born with spermatogonia and lose large numbers of germ cells during puberty. No treatment can improve spermatogenesis. (See also Section II: "XXY Syndrome.")

REFERENCE

Paduch DA, Fine RG, Bolyakov A, et al. New concepts in Klinefelter syndrome. *Curr Opin Urol.* 2008;18(6):621–627. Review.

KLIPPEL–TRENAUNAY–WEBER SYNDROME

DESCRIPTION Klippel–Trenaunay–Weber syndrome was 1st described by French physicians in 1900. It consists of cutaneous vascular malformations in combination with soft tissue and bone hypertrophy. The defects are present at birth and most commonly involve the lower extremities. The vascular lesions have a propensity for hemorrhage. In a study of 214 patients by Husmann et al., 30% had genital cutaneous involvement. Of these patients, 36% developed intractable bleeding. Surgical excision of these vascular malformations was associated with significant blood loss.

REFERENCE

Husmann D, Rathburn SR, Driscoll DJ. Klippel-Trenaunay syndrome: incidence and treatment of genitourinary sequelae. *J Urol.* 2007;177(4):1244–1249.

KOCK POUCH AND HEMI-KOCK NEOBLADDER

DESCRIPTION A Kock continent catheterizable urinary reservoir (pouch) is created from 70–80 cm of small bowel. The mid 45-cm portion is folded into a U-shaped configuration and

opened along its antimesenteric border, and the adjoining edges of the U are sutured together. The resulting U patch is folded again from top to bottom to form a reservoir. The 17-cm end limbs are intussuscepted and stapled to create nipple valves at each end. The ureters are anastomosed in the proximal afferent limb, where the nipple prevents reflux and the efferent limb is used to create a continent stoma, which is catheterized to empty the pouch.

The hemi-Kock neobladder is an orthotopic neobladder constructed based on the theme of the Kock pouch. In this diversion, a single intussuscepted ileal nipple valve is used to create a nonrefluxing ureteroileal anastomosis. The remainder of the pouch is made from a detubularized ileum, which is configured into a pouch and anastomosed to the urethra. It is not currently a recommended form of urinary diversion due to complications related to intussuscepted nipple valves.

REFERENCE

Hautmann RE, Abol-Enein H, Hafez K, et al.; World Health Organization (WHO) Consensus Conference on Bladder Cancer. Urinary diversion. *Urology*. 2007;69(1 Suppl):17–49.

KOYLE STENT

DESCRIPTION The Koyle diaper stent (Cook Medical Inc., Bloomington, IN, USA) is used for stenting the urethra after hypospadias repair. It has an 8-Fr circumference in the fossa navicularis to minimize distal meatal or urethral stenosis while providing excess tubing externally to allow drainage into a 2nd or outside diaper while keeping the inside diaper dry to allow healing.

REFERENCE

Koyle MA. Hypospadias: A 30 year personal journey. *Scand J Surg*. 2011;100(4):250–255.

KRUGER STRICT SPERM MORPHOLOGY

DESCRIPTION Some fertility experts use the test to decide between intrauterine insemination (IUI) and in vitro fertilization (IVF) although the test is controversial. This test examines sperm morphology more in-depth than the standard WHO method. Freshly ejaculated sperm are smeared on a slide and stained. Sperm are judged as normal based on the following criteria:

- Head must be oval in shape with smooth contours, 5–6 μm in length and 2.5–3.5 μm wide with the acrosome taking up 40–70% of the head.
- Neck and mid-piece must have no abnormalities and a cytoplasmic droplet (a remnant from sperm production) if present must not be larger than 1/2 the size of the head.
- Tail must not be coiled or bent and should not have a droplet at the end.

After 200 individual sperm are counted at 1,000 X, the percent normal forms are calculated. The IUI prognosis is based on the following scale:

≥15% normal	Normal range: Good prognosis
5–14% normal	Sub optimal range: Prognosis is fair to good, however, the lower the percent normal, the lower the chance of successful fertilization
0–4% normal	Poor prognosis: Will usually need IVF with intracytoplasmic sperm injection (ICSI)

REFERENCE

Ghirelli-Filho M, Mizrahi FE, Pompeo AC, et al. Influence of strict sperm morphology on the results of classic in vitro fertilization. *Int Braz J Urol*. 2012;38(4):519–528.

LABIAL ADHESIONS AND FUSION

DESCRIPTION Complete (fusion) or partial adherence of labia minora. Low estrogen levels contribute to a thin atrophic lining, which is easily denuded and later heals with adhesions. The condition is acquired, not found at birth, and occurs in prepubescent girls and postmenopausal women. Fecal soiling as an infant, vulvovaginitis, eczema, dermatitis, and sexual abuse may be inciting factors. It may cause voiding dysfunction in severe cases, with resulting hydroureteronephrosis.

SYNONYMS

- Acquired postinflammatory cohesion of the labia minora
- Vulvar fusion
- Synechiae of the vulva

TREATMENT

- Conjugated estrogen cream locally applied
- Surgical treatment for severe cases

REFERENCE

Tebruegge M, Misra I, Nerminathan V. Is the topical application of oestrogen cream an effective intervention in girls suffering from labial adhesions? *Arch Dis Child.* 2007;92(3):268–271.

LACTATE DEHYDROGENASE (LDH), UROLOGIC CONSIDERATIONS

DESCRIPTION LDH is a cellular enzyme useful in monitoring the treatment of GCT. It tends to have a low specificity (further impaired in smokers), and therefore must be correlated with other clinical findings and lab markers (ie, α-fetoprotein and β-hCG). Some correlation has been made between LDH and tumor bulk. LDH can also be elevated in cases of liver involvement by other tumors such as RCC.

REFERENCE

Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. *Nat Rev Urol.* 2010;7(11):610–617.

LAPIDES CLASSIFICATION OF VOIDING DYSFUNCTION

DESCRIPTION A historic system for categorizing neurogenic voiding dysfunction into 5 areas:

- Sensory neurogenic bladder: Interrupted afferent bladder sensation can lead to chronic bladder distension and deterioration. Common processes include diabetes mellitus, tabes dorsalis, and pernicious anemia.
- Motor paralytic bladder: Destruction of parasympathetic motor innervation to the bladder results in painful overdistension initially and inability to initiate and maintain micturition. Common processes include pelvic surgery or trauma and possibly herpes zoster.
- Uninhibited neurogenic bladder: Injury to the corticoregulatory tract of the sacral spinal cord (micturition reflex center) leads to frequency, urgency, and urge incontinence.

Common processes include cerebrovascular accident, brain or spinal cord tumor, Parkinson disease, and demyelinating disease.

- Reflex neurogenic bladder: Complete interruption of sensory and motor pathways between the sacral spinal cord and brainstem leads to lack of bladder sensation and inability to voluntarily micturate. Common processes include trauma and transverse myelitis.
- Autonomous neurogenic bladder: Complete motor and sensory separation from the sacral spinal cord leads to inability to voluntarily micturate and lack of reflex bladder activity and bladder sensation.

REFERENCE

Voiding dysfunction: Diagnosis, Classification and management. In: Gillenwater JY. *Adult and Pediatric Urology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.

LASER TECHNOLOGIES AND UROLOGIC APPLICATIONS

DESCRIPTION The use of laser (short for "light amplification by stimulated emission of radiation") systems in urologic surgical practice has gained widespread acceptance. The primary mechanism of laser operating systems is based on the process of stimulated emission of radiation where excited electrons rapidly decay and emit photon energy, which leave a resonator cavity as a coherent laser beam.

Lasers impart 4 different effects: Thermal, mechanical, photochemical, and tissue-welding effects. The thermal effect is most commonly employed. The laser light energy is absorbed and transformed into heat. The heat denatures proteins at 42–65°C, shrinks arteries and veins at 70°C, and cellular dehydration at 100°C. After water has evaporated from the tissue, the temperature rapidly rises, with carbonization at 250°C, and vaporization occurs at 300°C. Mechanical effects are used to create a plasma bubble that expands rapidly to disrupt stones. Photochemical effects involve laser activation of specific drugs or compounds taken up by the tissue and tissue welding relies upon collagen cross-linking using materials activated by a lasers specific wavelength.

Conditions such as nephrolithiasis, benign prostatic obstruction (BPO), bladder cancer, kidney cancer, urothelial cancer, and stricture disease have all been treated by laser therapy. Some modern laser systems include potassium titanyl phosphate (KTP), neodymium:yttrium-aluminum-garnet (Nd:YAG), holmium:yttrium-aluminum-garnet (Ho:YAG), and semiconductor diode lasers. The frequency-doubled, double-pulse Nd:YAG (FREDDY) laser is a short-pulsed, double-frequency solid-state laser with wavelengths of 532 and 1064 nm. It is a low-power, low-cost laser developed for intracorporeal lithotripsy. CO_2 lasers are used for ablation of skin lesions such as condylomata. The thulium:YAG laser has been developed improve on some of the shortcomings of the Ho:YAG laser. This new laser more closely matches the water absorption peak in soft tissue to minimize collateral tissue damage. The methods of laser delivery can include end firing, side firing, and interstitial technologies with many fibers designed to fit trough endoscopes. Specific clinical applications:

- Soft tissue incisions (eg, strictures, posterior urethral valves, endopyelotomy, bladder neck contractures): Ho:YAG, Nd:YAG, or KTP.
- Resection and tissue ablation (eg, BPH, bladder cancer, condylomata, penile cancer, hemangiomata), use Nd:YAG, Ho:YAG, KTP:YAG, semiconductor diode, or CO_2.

- Lithotripsy (renal pelvis, ureter, bladder stones): Ho:YAG, FREDDY, pulsed dye, or alexandrite.
- Tissue welding (eg, vasovasotomy; urethral reconstruction for hypospadias): Diode, KTP, Nd:YAG, or CO_2.
- Laser hair removal (eg, perineal skin used for local urethral grafts): Alexandrite, semiconductor diode, or Nd:YAG.

REFERENCES

Zarrabi A, Gross AJ. The evolution of lasers in urology. *Ther Adv Urol.* 2011;3(2):81–89.
Grasso, M. Lasers in Urology in Medscape. http://emedicine.medscape.com/article/445722-overview, Accessed March 3, 2014.

LAURENCE–MOON–BARDET–BIEDL SYNDROME

DESCRIPTION This autosomal recessive disease was initially described in 1860 by Laurence–Moon and received a more exact description in 1920 by Bardet–Biedl. A wide variety of manifestations include retinal pigmentary dystrophy (previously termed *retinitis pigmentosa*), postaxial polydactyly, central obesity, mental retardation, and hypogenitalism. More recently, renal abnormalities have been described, including chronic glomerulonephritis, characteristic cystic tubular disease, lower urinary tract malformations, and defects of tubular concentrating ability. Renal failure is the major cause of morbidity and early mortality. Undescended or maldescended testes can be present neonatally in up to 25% of males.

SYNONYMS

- Bardet–Biedl syndrome: More general, including all of the above description
- Laurence–Moon syndrome: Much rarer; differs with the above description, including progressive spastic paraparesis and distal muscle weakness but without polydactyly

REFERENCES

Beales PL, Warner AM, Hitman GA, et al. Bardet-Biedl syndrome: A molecular and phenotypic study of 18 families. *J Med Genet.* 1997;34(2):92–98.
Bahceci M, Dolek D, Tutuncuoglu P, et al. A case series of Bardet-Biedl syndrome in a large Turkish family and review of the literature. *Eat Weight Disord.* 2012;17(1):e66–e69.

LAZY BLADDER SYNDROME (NURSE'S BLADDER)

DESCRIPTION 1st described by Swenson in 1962, this condition occurs when children exhibit holding behavior and void infrequently. Thought to be caused by the continuous voluntary suppression of the normal desire to void, it is more common in girls. Patients are prone to develop UTIs due to urinary stasis and often have problems with constipation. Some patients have overflow or stress incontinence. The VCUG shows a large smooth-walled bladder, and US of the upper tract is usually normal. Urodynamic studies show large bladders with decreased sensation during bladder filling, low pressures, and large postvoid residuals. Timed voiding schedules, antibiotic suppression, biofeedback bladder training, and intermittent catheterization are all options for treatment.

REFERENCES
Grasso M, Torelli F, Blanco S, et al. Vesicoureteral reflux in the child with lazy bladder syndrome: The infrequent voider. *Adv Urol.* 2008:432576.
Bauer SB, Retik AB, Colodny AH, et al. The unstable bladder of childhood. *Urol Clin North Am.* 1980;7:321–336.

LEADBETTER–CLARKE URETERAL ANASTOMOSIS

DESCRIPTION A nonrefluxing anastomosis is created by making a longitudinal incision through the taenia, just outside the mucosa. The ureter is laid over the mucosa and a small buttonhole is made through the mucosa to anastomose the spatulated end of the ureter. The taenia is closed over the ureter.

REFERENCE
Porena M, Mearini L, Zucchi A, et al. Ureterointestinal anastomosis in orthotopic neobladders. *Urol Int.* 2000;64(4):181–184.

LEADBETTER–POLITANO URETERONEOCYSTOSTOMY

DESCRIPTION Through a transvesical exposure, the ureter is mobilized from the bladder wall and surrounding peritoneum. A new ureteral hiatus is created 2–3 cm above the old hiatus. The ureter is then delivered behind the entire bladder, through the new hiatus and tunneled submucosally toward the old hiatus, where it is reimplanted.

REFERENCE
Kay R. Reimplantation of the ureter. In: Novick AC, Streem SB, Pontes JE, et al., eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:526–538.

LEAK POINT PRESSURE (LPP)/ABDOMINAL LEAK POINT PRESSURE (ALPP)

DESCRIPTION LPP is a urodynamic variable. Abdominal leak point pressure (ALPP), related to stress urinary incontinence (SUI), is the lowest abdominal pressure required to cause urinary leakage during either a Valsalva maneuver or a cough in the absence of a detrusor contraction. An ALPP of <60 cm H_2O suggests significant intrinsic sphincter deficiency (ISD). If the ALPP is –90, it suggests mild sphincter deficiency. Sphincter deficiency is minimal with an ALPP >90 cm H_2O. Detrusor leak point pressure (DLPP) is the lowest detrusor pressure required to cause urinary leakage in the absence of a detrusor contraction or increased abdominal pressure. High DLPP (>40 cm H_2O) may put patients at a higher risk for upper urinary tract deterioration.

REFERENCE
Kim SO, Kim YJ, Yoo DH, et al. Clinical factors associated with low valsalva leak point pressure among women with stress urinary incontinence. *Int Neurourol J.* 2011;15(4):211–215.

LeBAG NEOBLADDER

DESCRIPTION This is a modification of the Mainz I orthotopic neobladder, which uses only 1 ileal limb instead of 2. The detubularized colon and a single segment of ileum can be joined using met al staplers to create a broad intestinal plate, which is then converted into a pouch with a ureterocolonic and urethral anastomosis.

REFERENCE

Pannek J, Senge T. History of urinary diversion. *Urol Int.* 1998;60(1):1–10.

LeDUC URETERAL ANASTOMOSIS

DESCRIPTION The end of the small bowel segment is opened 4–5 cm and a longitudinal incision is made in the mucosa, which is then raised. At the distal end of this incision, a hole is made through the wall. The ureter is pulled through this opening and laid in the mucosal incision. The mucosa is then sutured to the side of the ureter.

REFERENCE

Evangelidis A, Lee EK, Karellas ME, et al. Evaluation of ureterointestinal anastomosis: Wallace vs Bricker. *J Urol.* 2006;175(5):1755–1758.

LEIOMYOMATOSIS, HEREDITARY

DESCRIPTION Familial cancer syndrome of a triad of cutaneous leiomyomas, uterine leiomyomas, and type 2 papillary RCC. Renal tumors tend to be solitary and unilateral and are likely to be aggressive; collecting duct RCCs have also been observed. The lesions are usually seen in women 20–35 yo. Given their aggressive nature, the prompt surgical resection of renal tumors is recommended. (See also Section II: “Reed Syndrome.”)

REFERENCE

Coleman JA. Familial and hereditary renal cancer syndromes. *Urol Clin N Am.* 2008;35(4):563–572.

LEOPARD SYNDROME

DESCRIPTION An autosomal dominant condition similar to Noonan syndrome, except for multiple lentigines (macule pigment accumulation within the dermis and epidermis). LEOPARD syndrome is the mnemonic for lentigines, ECG abnormalities, ocular hypertelorism/obstructive cardiomyopathy, pulmonary valve stenosis, abnormalities of genitalia in males, retardation of growth, and deafness. Cardiomyopathy is an important feature because it is associated with significant mortality. Genital hypoplasia in males, including a small penis and small, often undescended testicles, is the most common association. Hypospadias and delayed puberty may also be found.

SYNONYMS

- Multiple lentigines syndrome
- Progressive cardiomyopathic lentiginosis

TREATMENT
Orchiopexy, repair of hypospadias

REFERENCE
Coppin BD, Temple IK. Multiple lentigines syndrome (LEOPARD syndrome or progressive cardiomyopathic lentiginosis). *J Med Genet.* 1997;34(7):582–586.

LERICHE SYNDROME

DESCRIPTION Described in 1923 as symptoms characteristic of thrombotic occlusion of the terminal aorta, this syndrome is caused by atherosclerosis of the arterial wall, with thrombus and gradual occlusion. Symptoms include fatigue of both lower limbs, symmetrical atrophy of lower extremities, pallor of legs/feet, and an inability to maintain a stable erection due to inadequate arterial flow to the penis (hypogastric arterial obstruction). Gradual occlusion allows for collateral circulation; therefore, acute symptoms are unlikely.

SYNONYM
Gradual thrombotic obliteration of the abdominal aorta and iliac arteries

TREATMENT
Bypass graft from the aorta to iliac or common femoral arteries

REFERENCE
Setacci C, Galzerano G, Setacci F, et al. Endovascular approach to Leriche syndrome. *J Cardiovasc Surg (Torino)*. 2012;53(3):301–306.

LESCH–NYHAN SYNDROME

DESCRIPTION 1st described in 1964 as an X-linked recessive disorder associated with failure to form hypoxanthine phosphoribosyltransferase, this disorder is caused by loss of function of the enzyme hypoxanthine guanine posphoribosyltransferase. Manifestations are hyperuricemia and uric acid lithiasis, choreoathetosis, mental retardation, spastic cerebral palsy, and self-mutilation of fingers and lips by biting. Allopurinol is the main urologic intervention to reduce hyperuricemia.

REFERENCE
Ngo TC, Assimos DG. Uric acid nephrolithiasis: recent progress and future directions. *Rev Urol.* 2007;9(1):17–27.

LEUKEMIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Leukemic infiltration of the testicle can be seen in children with acute lymphoblastic leukemia (ALL). The typical presentation is testicular enlargement, typically bilateral. Open testicular biopsy, bilaterally, should be performed along with bone marrow and CSF analysis for tumor recurrence. Orchiectomy is not indicated for leukemic infiltration. Testes were once a common site of relapse, but with current intensive chemotherapy regimens, the testicular relapse rate is $<5\%$. No strong evidence suggests an increase in birth defects in the children of leukemia survivors. Patients treated with cyclophosphamide-

containing regimens are at risk for hemorrhagic cystitis and long-term urothelial tumors. (See also Section I: "Cystitis, Hemorrhagic [Infectious, Noninfectious].")

TREATMENT

- If the testicle is the isolated site of relapse, local irradiation (up to 20 Gy) to both testes and reinstitution of systemic chemotherapy can be curative.
- Therapy can cause irreversible damage to seminiferous tubules and Leydig cells.

Patients can develop hypogonadotropic hypogonadism and low testosterone with azoospermia.

REFERENCES

Kulkarni RK, Marwaha RK, Trehan A, et al. Testicular relapse in childhood acute lymphoblastic leukemia: The challenges and lessons. *Indian J Cancer.* 2010;47:134–138.

Pui CH, Rivera GK. Acute lymphoblastic leukemia. In: Rudolph AM, ed. *Rudolph's Pediatrics.* 19th ed. Norwalk, CT: Appleton & Lange; 1991.

LEUKOPLAKIA, PENIS

DESCRIPTION Solitary or whitish plaques with hyperkeratosis, parakeratosis, and hypertrophy of the squamous rete pegs, with edema and lymphocytic infiltration. The condition often involves the penile meatus and has been associated with in situ squamous cell carcinoma (SCC) and verrucous carcinoma.

TREATMENT

- Eliminate chronic irritation
- Circumcision
- Surgical excision with periodic biopsy of incompletely excised lesions

REFERENCE

Bissada NK. Conservative extirpative treatment of cancer of the penis. *Urol Clin N Am.* 1992;19(2):283–290.

LEUKORRHEA

DESCRIPTION Generally refers to nonmalodorous, mucous like, white, or yellowish vaginal discharge in the absence of any pathologic cause. The quantity and quality vary among individuals, and mild irritative symptoms can be normal. Leukorrhea is also seen during infancy secondary to maternal estrogens, as well as during puberty secondary to estrogen surges. Reassurance is all that is necessary if the cervical and vaginal exam is normal, vaginal pH is normal (<4.5), and there are normal findings on microscopy and a negative amine test. (See also Section II: "Vaginosis"; Section III: "Vaginal Discharge Algorithm.")

REFERENCE

Anderson AU, Karasz A, Friedland S. Are vaginal symptoms ever normal? A review of the literature. *MedGenMed.* 2004;22:49.

LICHEN NITIDUS, PENIS

DESCRIPTION An uncommon chronic inflammation appearing as flesh-colored papules with sharp demarcations and flat, shiny, and slightly elevated surfaces. The etiology is unknown, but it is believed to be a variant of lichen planus. Histologically, lymphocytes, histiocytes, and melanophages form a ball-like structure covered by epidermis with a characteristic claw-like projection of the rete ridges. The condition is usually asymptomatic.

TREATMENT

- Spontaneous healing is common
- Oral histamines
- Topical antipruritics and topical corticosteroids may be helpful

REFERENCE

Davis DA, Skidmore RA, Woosley JT. Lichen nitidus. *Urology*. 1996;47(4):573.

LICHEN PLANUS, PENIS

DESCRIPTION An uncommon pruritic inflammation of the skin, which typically occurs on the penile glans. Benign, it is characterized by pruritic, violaceous, and flat-topped papules. Histologically, there can be degeneration of the basal cell-layer keratinocytes and dense infiltration of lymphocytes in the upper dermis hugging the epidermis. Multiple lesions occur and can ulcerate. Differential diagnoses include secondary syphilis, bowel disease, psoriasis, Zoon balanitis, and squamous cell carcinoma (SCC). There is no specific treatment; symptomatic relief is obtained through antihistamines, ataractics, and topical lotions.

REFERENCE

Hoshi A, Usui Y, Terachi T. Penile carcinoma originating from lichen planus on glans penis. *Urology*. 2008;71(5):816–817.

LICHEN SCLEROSIS ET ATROPHICUS

DESCRIPTION An uncommon cutaneous disorder with a female predominance. Early lesions are characterized as either white macules, which may coalesce into patches, or flat, white, or pink-depressed papules and plaques. Confluence of the papules and marked hyperkeratosis and atrophy may develop. Extra-genital areas (eg, arms, shoulders, trunk, neck, and face) are less commonly affected in men. Dysuria, pruritus, and pain are associated with the disease process. Squamous cell carcinoma (SCC) has been reported to occur.

SYNONYMS

- Lichen sclerosis
- The late stage evolves into balanitis xerotica obliterans

TREATMENT

- Circumcision
- Topical treatments for nongenital areas

REFERENCE

West DS, Papalas JA, Selim MA, Vollmer RT. Dermatopathology of the foreskin: An institutional experience of over 400 cases. *J Cutan Pathol.* 2013;40(1):11–18.

LICHEN SIMPLEX CHRONICUS (LICHEN SIMPLEX COMPLEX)

DESCRIPTION Localized chronic pruritus with patches of dermatitis, resulting from chronic scratching/rubbing. Common sites are the perineum, thigh, scrotum, and vulva. The lesions appear as multiple oval plaques that become thickened and scaly. There is a whitish gray discoloration caused by lichenification and maceration. The skin may become more susceptible to secondary infection and allergic contact dermatitis. Etiologies include contactants (irritant and allergic), infection, and underlying dermatoses. Microscopically, the lesions resemble chronic dermatitis with hyperkeratosis and parakeratosis. Diagnosis is usually clinical, but biopsy may be necessary.

SYNONYM
Circumscribed neurodermatitis

TREATMENT
- Break the scratch-itch cycle
- Stop all irritants
- Sitz baths or soaks
- Open wet compresses to affected areas
- Systemic antipruritics and/or sedating medications may be necessary to lessen the itching
- Topical and occasionally systemic steroids are necessary

REFERENCE
Margesson LJ. Vulvar disease pearls. *Dermatol Clin.* 2006;24(2):145–155.

LICH–GREGOIR URETERAL REIMPLANTATION

DESCRIPTION This extravesical, less invasive repair does not disrupt the ureteral trigonal continuity. A 4–5-cm trough is created by dissecting the detrusor of the mucosa, and the mobilized ureter is placed in the trough with the detrusor closed over it.

REFERENCE
Kay R. Reimplantation of the ureter. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore: Williams & Wilkins; 1989:526–538.

LIDDLE'S SYNDROME

DESCRIPTION Liddle's syndrome is an autosomal dominant disorder of the sodium channels of the collecting duct. Mutations in the epithelial sodium channels in the kidney result in increased activity and severe hypertension is typically the result. Features of hypokalemia and metabolic alkalosis can also occur mimicking primary hyperaldosteronism. Treatment generally focuses on a low salt diet in conjunction with a potassium-sparing diuretic.

REFERENCE
Guay-Woodford L. Hereditary nephropathies and developmental abnormalities of the urinary

tract. In: Goldman L, Schafer A, eds. *Goldman's Cecil Medicine.* Philadelphia, PA: Elsevier Saunders; 2011:802.

LIFE EXPECTANCY, UROLOGIC CONSIDERATIONS

DESCRIPTION Life expectancy is commonly used by urologists when determining therapy for localized prostate cancer, as age may influences choice of treatment.

Current Age	Life Expectancy (yr) Male	Life Expectancy (yr) Female
65	17.19	19.89
66	16.48	19.10
67	15.77	18.32
68	15.08	17.55
69	14.40	16.79
70	13.73	16.05
71	13.08	15.32
72	12.44	14.61
73	11.82	13.91
74	11.21	13.22
75	10.62	12.55
76	10.04	11.90
77	9.48	11.26
78	8.94	10.63
79	8.41	10.03
80	7.90	9.43
81	7.41	8.86
82	6.94	8.31
83	6.49	7.77
84	6.06	7.26
85	5.65	6.77
86	5.26	6.31
87	4.89	5.87
88	4.55	5.45
89	4.22	5.06
90	3.92	4.69

REFERENCE

Social Security Administration. Available at www.socialsecurity.gov, Accessed May 15, 2013.

LIPOMA, BLADDER

DESCRIPTION Bladder lipoma is a rare entity. It can be associated with a pelvic lipoma, and has been reported to cause bladder outlet obstruction. A capsule circumscribes the homogeneous, sharply marginated fat. It is benign and must be distinguished from liposarcoma, angiolipoma, and cystic teratoma, usually by CT. Treatment is by surveillance, unless symptomatic. (See also Section II: "Bladder Mass.")

REFERENCE

Kunkle DA, Mydlo JH. Bladder wall lipoma in patient with irritative voiding symptoms. *Urology*. 2005;66(3):653–654.

LIPOMA, SPERMATIC CORD

DESCRIPTION Benign lobulated preperitoneal fat that can project down the cord. Accounts for up to 90% of spermatic cord tumors and is most commonly seen in adults. Histologic variants include angiolipoma, fibrolipoma, fibromyxolipoma, myxolipoma, and myxoid

myolipoma. The lesion can present as a mass, and must be distinguished from adenomatoid tumor, leiomyoma, fibroma, liposarcoma, leiomyosarcoma, and fibrosarcoma. (See also Section I: "Spermatic Cord Mass.") Complete excision at time of surgery is recommended.

REFERENCE

Cavazzola LT, Lieberknecht M, Machado AS, et al. Giant lipoma of the spermatic cord. *Am J Surg.* 2009;198(5):e54–e55.

LIPOMATOSIS, PELVIC

DESCRIPTION Pelvic lipomatosis was 1st described in 1959 as an overgrowth of fat in the perirectal and perivesical regions that can cause compression of the lower urinary tract and lead to uremia. Rare disease found primarily in men in the 3rd–6th decades of life. Approximately 2/3 of patients are African American, with an 18:1 male-to-female ratio. Lipomatous tissue is composed of mature adipose and may be associated with inflammation. Histopathologically, it is found to be dense, vascular, unencapsulated lipomatous tissue that commonly envelops the pelvic viscera. It differs from a simple lipoma by the fact that it does not arise from a single focus, is not encapsulated, and does not expand centrifugally. Clinical features vary from urinary frequency to constipation. Pelvic lipomatosis has been associated with a higher incidence of hypertension. On a plain abdominal x-ray, it presents with radiolucency of the perivesical areas. Other radiographic signs include an elongation and elevation of the bladder, and the rectum and sigmoid colon. There is widening of the retrorectal space with increased lucency of the pelvic sidewalls. On cystography, a full bladder has an abnormal shape (banana shape) and position (superiorly as well as anteriorly). Cystoscopy should be performed, as there are reports of associated cystitis glandularis. Surgical removal of the fat (difficult and feasible in selected few patients) may be possible. For those patients with obstructive uropathy, treatment options include ureteral stenting, nephrostomy tubes, ureteral reimplantation, or urinary diversion. Pelvic exploration is done with caution as the normal anatomic planes are disrupted by the infiltrating fat.

REFERENCE

Trilla Herrera E, Torrecilla Ortíz C, Muñoz Seguí J, et al. Pelvic lipomatosis: Clinical review and report of four new cases. *Actas Urol Esp.* 2000;24(5):423–428.

LIPOMENINGOCELE, UROLOGIC CONSIDERATIONS

DESCRIPTION A meningocele associated with an overlying lipoma. This condition belongs to the family of occult spinal dysraphisms in which the formation of the spinal column is affected but does not result in an open vertebral canal. Outward signs and symptoms may be subtle, and the neurologic exam may be normal. As children get older, they may present with absent perineal sensation, back pain, secondary incontinence (incontinence after initial period of dryness), recurrent UTIs, or fecal soiling. In children <3 yo, urodynamic testing may be normal but it is usually abnormal in children >3 yr.

Address urinary symptoms as appropriate after urodynamic testing, and refer to a neurosurgeon for evaluation of tether release to prevent further injury and growth.

REFERENCE

Rendeli C, Ausili E, Tabacco F, et al. Urodynamic evaluation in children with lipomeningocele: Timing for neurosurgery, spinal cord tethering and follow-up. *J Urol.* 2007;177(6):2319–2324.

LIVER METASTASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION The liver is a primary site for many malignant neoplasms, including those arising in the GU tract. Urothelial carcinoma (TCC), renal cell carcinoma (RCC) and testicular carcinoma may spread to the liver, but metastasis is most commonly seen in prostate cancer. In addition to bone pain and spinal cord compression, liver metastasis can be very painful. A liver lesion itself should not affect the urinary tract, but extensive disease may be reflected in increased bilirubin and urobilinogen levels on urine analysis.

TREATMENT

- Evaluate and treat primary tumor.
- Segmental resection or locally ablative therapies may be appropriate (Image ☼).

REFERENCE

Campbell SC, Lane BR. Malignant renal tumors. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:1413–1474.

LOBAR NEPHRONIA

DESCRIPTION A renal mass caused by acute focal infection without liquefaction. Clinical characteristics most frequently encountered are fever, flank pain, or back pain. Uroradiographic findings in this condition can mimic a renal abscess or neoplasm. Bacterial infection (*E. coli, Klebsiella, Aerobacter aerogenes, Proteus, Pseudomonas*) and *Candida albicans* are common causes. Appropriate medical treatment will cause the infected mass to disappear, but scarring may occur. (See also Section I: “Pyelonephritis, Acute, Adult.”)

SYNONYMS

- Acute lobar nephronia
- Acute focal bacterial nephritis

TREATMENT

- IV antibiotics
- Radiologic surveillance: CT or US

REFERENCE

Papanicolaou N, Pfister RC. Acute renal infections. *Radiol Clin North Am.* 1996;34(5):965–995.

LORD PROCEDURE (HYDROCELECTOMY)

DESCRIPTION During the Lord procedure for hydrocelectomy, radial sutures are used to gather the sac around the posterior aspect of the testis and epididymis. It was initially developed in 1964 to reduce the rate of postoperative hematoma formation after

hydrocelectomy. This technique does not require dissection of the hydrocele sac and therefore can be relatively bloodless. Generally this technique is recommended for thin-walled hydroceles.

REFERENCE

Singh DR, Gupta SK, Gupta S. Lord's procedure: a curative outpatient operation for primary hydrocele. *J Indian Med Assoc*. 1996;94(4):141–142.

LOWE SYNDROME

DESCRIPTION Also called *oculocerebrorenal syndrome*, it was 1st described in 1952 as an X-linked recessive disorder manifested by congenital cataracts, hypotonia, developmental delay, poor growth, and renal tubular dysfunction. Proteinuria and aminoaciduria are present by 1 yr of age, with gradual progression of Fanconi syndrome (typically failure to reabsorb water, electrolytes, bicarbonate, glucose, calcium, phosphorus, and small molecules). Polyuria, metabolic acidosis, hypophosphatemia with rickets, hypercalciuria, and sodium and potassium wasting can occur, leading eventually to end stage renal disease (ESRD). Nephrolithiasis has been reported due to the hypercalciuria. Vitamin D supplements and surveillance for nephrolithiasis are recommended.

REFERENCE

Sliman GA, Winters WD, Shaw DW, et al. Hypercalciuria and nephrocalcinosis in the oculocerebrorenal syndrome. *J Urol.* 1995;153(4):1244–1246.

LUB SYNDROME

DESCRIPTION Very rare, incomplete androgen insensitivity of karyotype XY with testes but ambiguous genitalia. Nonfertile, with elevated testosterone and LH levels, these children are usually raised as female and early gonadectomy and feminizing genitoplasty is performed in infancy. (See Section I: "Disorders of Sexual Development [DSD].")

REFERENCE

Snyder HM. Management of ambiguous genitalia in the neonate. In: Snyder NM, ed. *Urologlic Surgery in Neonates and Young Infants*. 19th ed. Philadelphia, PA: Saunders; 1988:346–348.

LYME DISEASE, UROLOGIC CONSIDERATIONS

DESCRIPTION Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is a multisystem inflammatory disorder. Urinary dysfunction is rarely reported but has been linked to detrusor hyperreflexia or, less commonly, hyporeflexia. Detrusor external sphincter dyssynergia has not been described. The urinary tract may be part of the neuroborreliosis phase or the spirochete may directly invade the urinary tract.

SYNONYMS

- Neuroborreliosis
- Bannwarth syndrome
- Acrodermatitis chronica atrophicans

TREATMENT

- Therapy is aimed at stage of dissemination and symptomatology; 1st-line therapy is doxycycline 100 mg BID or amoxicillin 500 mg QID for 10–15 days; a longer course or IV antibiotics are required for more severe disease.
- Conservative bladder management including clean intermittent catheterization (CIC) guided by urodynamic evaluation.

REFERENCE

Puri BK, Shah M, Julu PO, et al. Urinary bladder detrusor dysfunction symptoms in lyme disease. *Int Neurourol J.* 2013;17(3):127–129.

LYMPHANGIOGRAM, PEDAL

DESCRIPTION Contrast injection into lymphatic channels on the dorsum of foot to visualize retroperitoneal lymph nodes. This technique has been largely replaced by CT, but it can be used to assess the retroperitoneal lymph nodes in patients with testicular and prostatic cancer. Its major advantage over CT scan is the detection of architectural changes in nonenlarged lymph nodes. It is time-consuming, invasive, does not opacify sentinel nodes, cannot differentiate between malignant and nonmalignant changes, and may cause fibrosis of lymph nodes due to reaction to the contrast medium (Image ☼).

REFERENCE

Pollack H. Tumors of the testis and testicular adnexa. In: Pollack H, ed. *Clinical Urography*. Philadelphia, PA: Saunders; 1990:1424–1428.

LYMPHANGIOMA, BLADDER

DESCRIPTION This rare bladder lesion presents with hematuria, and several cases are reported in children. Treatment is by partial cystectomy. The lesion is composed of multiple small cystic cavities filled with proteinaceous material, typical of cavernous lymphangiomas.

REFERENCE

Bolkier M, Ginesin Y, Lichtig C, et al. Lymphangioma of bladder. *J Urol.* 1983;129(5):1049–1050.

LYMPHANGIOMA, RENAL

DESCRIPTION A rare tumor, with 1/3 occurring in children and 2/3 in adults. The lesion appears as a solitary encapsulated mass with multiple cysts. Microscopy reveals benign endothelial cells with septa, which may contain smooth muscle. If within the renal sinus, the mass may cause obstruction.

REFERENCE

Chaabouni A, Rebai N, Fourati M, et al. Cystic lymphangioma of the kidney: diagnosis and management. *Int J Surg Case Rep.* 2012;3(12):587–589.

LYMPHANGIOMA, RETROPERITONEAL

DESCRIPTION Lymphangiomas are benign cystic tumors of the lymphatic system. They are rare tumors and retroperitoneal lesions account for only 1% of all lymphangioma lesions. <200 cases have been reported in the literature. They typically present clinically with a palpable abdominal mass, abdominal pain or distention, anorexia, nausea/vomiting, or diarrhea. These lesions can easily be confused with other retroperitoneal cystic tumors, including those arising from the liver, kidney, or pancreas. Surgical excision is generally required for definitive diagnosis and treatment. (See also Section I: "Retroperitoneal Masses and Cysts.")

REFERENCE

Bhavsar T, Saeed-Vafa D, Harbison S, et al. Retroperitoneal cystic lymphangioma in an adult: A case report and review of the literature. *World J Gastrointest Pathophysiol*. 2010;1(5):171–176.

LYMPHANGIOMA, SCROTAL

DESCRIPTION Congenital malformations of the intrascrotal lymphatic system, which may form cystic masses. These lymphangiomas are benign tumors, occurring mostly in children. They are found relatively infrequently in the scrotum. Treatment consists of surgical excision; unless completely removed, recurrences are common.

REFERENCE

MacMillan RW, MacDonald BR, Alpern HD. Scrotal lymphangioma. *Urology*. 1984;23(1):79–80.

LYMPHATIC ASCITES

DESCRIPTION Nonmalignant ascites is the most common form (80–90%) and can be the result of cardiac, liver, or renal failure. Malignant ascites accounts for 10–20% . Lymphatic ascites can be the result of obstruction of lymphatic vessels or, less frequently, a surgical complication following retroperitoneal surgery or trauma. Persistent lymphatic fluid leakage with ascites has been described following both nephrectomy and retroperitoneal lymph node dissections and other surgical procedures (colorectal, gynecologic). The cisterna chyli (enlarged lymphatic vessel within the lumbar region) is the transition point between chylomicron rich or poor lymphatic fluid. When lymphatic fluid is encountered superior to the cisterna chyli, it is termed "chylous" (milky white appearance due to high cholesterol) and in urology is most often seen associated with retroperitoneal lymph node dissection for testicular cancer. When the fluid is distal to this transition point, the condition is classified as lymphatic (minimal cholesterol, straw-colored or clear fluid) (See Section I: "Chylous Ascites.") (Image ☼)

REFERENCE

Micha JP, Mendivila AA, Cupp JS, et al. Recurrent lymphatic ascites in a patient cured of cervical carcinoma. *Gynecologic Oncology Case Reports*. 2012;2(3):105–106.

LYMPHOGRANULOMA VENEREUM

DESCRIPTION Lymphogranuloma venereum (LGV) is a relatively uncommon STI/STD caused by *Chlamydia trachomatis* (L1, L2, and L3 serovariants). While uncommon in the United States, it is endemic in parts of Africa, India, Southeast Asia, South America, and the Caribbean and is diagnosed more often in men than women. It is also known as lymphogranuloma inguinale, tropical bubo, and Nicolas–Favre disease. Initial infection (after 3 d) is a painless herpetiform lesion on the penis or scrotum in males and rarely presents initial symptoms in females. This is followed by a secondary stage (2–4 wk later) of tender groin lymphadenitis (buboes) and malaise in heterosexual males. Suppurative granulomatous lymphadenitis and matted draining nodes are seen. Genital swelling is common due to obstructed lymphatics. Females and anal receptive homosexual males are more likely to develop pelvic and perianal abscesses with proctocolitis in tertiary disease. Potentially fatal bowel obstruction with perforation if rectal stenosis is severe. The main differential is between syphilis and chancroid. Nucleic acid amplification testing is the diagnostic test of choice; screening for other STI/STD including HIV should be considered. Fluctuant buboes can be aspirated to reduce morbidity.

TREATMENT

Doxycycline is the treatment of choice and erythromycin, sulfisoxazole, and azithromycin are alternatives and should be used for at least 3 wk. Treat contacts within the last 30 d as well.

REFERENCE

MedlinePlus. http://www.nlm.nih.gov/medlineplus/ency/article/000634.htm (Accessed August 24, 2014)

LYMPHOMA, UROLOGIC CONSIDERATIONS

DESCRIPTION Lymphoma can involve any part of the urinary tract, but is more commonly seen in the testicle and kidney:

- Lymphoma represents a common cause of testicular cancer in older men. It may be a local tumor growth or a late manifestation of widespread disease. >50% of testicular tumors in men >60 are lymphomas; these must be differentiated from seminoma. In adults, most are diffuse, large B-cell lymphomas; children can have Burkitt lymphoma involving the testicle.
- Bladder involvement is usually secondary to systemic disease and is present in 13% of patients dying of non-Hodgkin lymphoma. Primary bladder lymphoma occurs almost exclusively in females. Lesions may be sessile or polypoid and should be differentiated from chronic inflammatory bladder involvement, small cell carcinoma, and a rare entity called *lymphoma-like carcinoma.*
- Prostate lymphoma typically presents in older men, with symptoms of bladder outlet obstruction. PSA is rarely elevated. This is usually a manifestation of systemic disease, with primary prostate disease rare. The differential diagnosis includes chronic prostatitis with follicular hyperplasia, neuroendocrine prostate cancer, and granulomatous prostatitis.
- Adrenal involvement is present in up to 25% dying of systemic disease. The adrenals are a rare primary site of disease, with bilateral, clinical, adrenal involvement in 18% of non-Hodgkin lymphoma and 9% of Hodgkin lymphoma. (See also Section II: “Hodgkin

Lymphoma, Urologic Considerations.")

TREATMENT

- Testicular lymphomas: radical orchiectomy followed by systemic chemotherapy, depending on the extent of the disease. For stage I disease, 5-yr survival is >60%; if advanced, survival at 5 yr is <20%.
- Bladder lymphoma: Treated with radiation. If the bladder site is part of systemic disease, use systemic therapy.
- Prostatic lymphoma: Systemic therapy with TUR is used for obstructive symptoms. A poor prognosis, regardless of primary site; most die in <24 mo.

REFERENCE

Wang Y, Li ZM, Huang JJ, et al. Three prognostic factors influence clinical outcomes of primary testicular lymphoma. *Tumour Biol.* 2013;34(1):55–63.

LYMPHORETICULAR MALIGNANT NEOPLASM, PENIS

DESCRIPTION Rarely, lymphoreticular malignancies (eg, leukemia) may infiltrate the penis. Primary disease is rare, and a search for systemic disease is mandatory. The most common presentation is priapism, a painful prolonged erection. Treatment involves chemotherapy for primary lesions combined with local low-dose radiation.

REFERENCE

Begun FP, Derus J, Toorkey B, et al. Leukemia of the penis. *J Urol.* 1989;142(1):123–124.

LYMPHOVASCULAR INVASION (LVI), UROLOGIC CONSIDERATIONS

DESCRIPTION LVI describes an important feature for many aspects of urologic oncology, because it is an adverse prognostic indicator in urothelial carcinoma of the bladder and upper tracts, prostate cancer, and testicular cancer. In upper tract TCC, it has been found to be an independent prognostic factor for disease-specific survival. In noninvasive bladder cancer, it is a relative indication for early cystectomy. In testicular cancer, it is a risk factor for retroperitoneal and/or systemic failure.

REFERENCE

Sheinfeld J, Bosl GJ. Surgery of testicular tumors. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2012:871–892.

LYNCH SYNDROME

DESCRIPTION An autosomal dominant genetic syndrome caused by mutations in mismatch-repair enzymes, most commonly MSH2 and MLH1. This creates DNA MSI (Microsatellite instability) and increases the risk of colon and endometrial malignancy. An increased risk of upper tract urothelial carcinoma (TCC) is also observed and these cases can be successfully managed with ureteroscopic treatment/surveillance. In addition, these patients are at increased risk of developing bladder lesions as well.

SYNONYMS

- Hereditary nonpolyposis colorectal cancers
- Hereditary site-specific colon cancer

TREATMENT

- Screening for mutation can be performed via genetic testing.
- If screening is positive, surveillance colonoscopy is recommended.
- Netherlands Surveillance Protocol for specific individuals (includes regimented colonoscopies, urine cytologies, upper endoscopy, and US of the endometrium).

REFERENCE

Hubosky SG, Boman BM, Charles S, et al. Ureteroscopic management of upper tract urothelial carcinoma (UTUC) in patients with Lynch Syndrome (hereditary nonpolyposis colorectal cancer syndrome). *BJU Int.* 2013;112(6):813–819.

MACE (MALONE ANTEGRADE CONTINENCE ENEMA)

DESCRIPTION The Malone antegrade continence enema (MACE) procedure is performed mostly in children with complex constipation or fecal incontinence secondary to neurogenic dysfunction. Using the appendix, a continent catheterizable colonic stoma is made. Antegrade enemas delivered by this route produce complete colonic emptying and minimize fecal soiling.

REFERENCE

Hoy NY, Metcalfe P, Kiddoo DA, et al. Outcomes following fecal continence procedures in patients with neurogenic bowel dysfunction. *J Urol.* 2013;189(6):2293–2297.

MACRO-ORCHIDISM (MO)

DESCRIPTION Macro-orchidism (MO) is an increase of testicular volume, up to 25 mL, seen in the adult male. It is frequently associated with mental retardation with fragile X-chromosome. MO has also been described in association with bilateral testicular tumors, idiopathic precocious puberty, juvenile hypothyroidism, and, more rarely, with congenital testicular cysts (cystic testicular dysplasia). Management of MO must be conservative in all cases, and testicular biopsy must only be performed to diagnose leukemic infiltration, carcinoma in situ, or as part of a fertility workup. MO may be related pathogenically to some hormonal regulation mechanism or to higher seminiferous tubule sensitivity to FSH.

REFERENCE

Martinez-Garcia F, Regadera Gonzalez J, Cobo Nuñez P, et al. Macro-orchidism: New pathogenetic and histopathologic aspects. *Espanol Urol.* 1994;47(1):59–65.

MAG 3 RENAL SCAN

DESCRIPTION A nuclear medicine study is used to evaluate renal function and the presence of obstruction. MAG3 (technetium^{99m}-mercaptoacetyltriglycine) is a nuclear isotope secreted by the renal tubules. Multiple images are taken over time to give anatomic details, including scarring and function of the kidney. A split differential function between the 2 kidneys is obtained. Commonly, furosemide is administered to induce diuresis, and the time for the kidney to clear 1/2 of the tracer is calculated ($t_{1/2}$). A $t_{1/2}$ of 0–10 min indicates nonobstructive drainage, 10–20 min is indeterminate, and >20 min is consistent with obstruction.

REFERENCE

Hubert KC, Palmer JS. Current diagnosis and management of fet al genitourinary abnormalities. *Urol Clin North Am.* 2007;34(1):89–101.

MAGPI HYPOSPADIAS REPAIR

DESCRIPTION The meatal advancement and glanuloplasty procedure (MAGPI) was 1st described by Duckett in 1981. After a circumferential subcoronal incision, the bridge of tissue

immediately distal and dorsal to the meatus is split in a vertical fashion and closed in a horizontal orientation (Heineke–Mikulicz closure). The ventral edge of the new meatal opening is pulled up, and the glans is reapproximated ventrally, which, in effect, advances the meatus.

REFERENCE

Duckett JW. MAGPI (meatoplasty and glanuloplasty) a procedure for subcoronal hypospadias. 1981. *J Urol.* 2002;167(5):2153–2158.

MAINZ I, II, III POUCH URINARY DIVERSION

DESCRIPTION The Mainz I (ileocecal pouch) is an orthotopic pouch created by opening the cecum and 2 limbs of distal ileum; the limbs are then sutured to create a broad intestinal plate. After a tunneled ureterocolonic anastomosis is made, the cecal portion of the plate is anastomosed to the male urethral stump and the plate is closed into a sphere. The Mainz II (sigma rectum pouch) is an augmented valved rectum created by making a 10–12-cm rectosigmoid opening. The sigmoid colon is configured into a U shape, and the medial plate is closed. Ureters are implanted through submucosal tunnels. After securing the apex of the pouch to the sacral promontory, the remaining plate is closed. The Mainz III is a continent cutaneous pouch made exclusively of colon (transverse-ascending colon pouch or transverse-descending colon pouch) with the efferent segment created from a tapered bowel segment embedded in the pouch wall.

REFERENCE

Bader P, Westermann D, Frohneberg D. Urinary diversions: Which one is right for which patient? *Urologe A.* 2009;48(2):127–136.

MALACOPLAKIA, GENITOURINARY

DESCRIPTION Malacoplakia, derived from the Greek term for soft plaque, is a chronic inflammatory disease, the etiology of which remains obscure. It appears related to an underlying infectious process. It has a very low incidence and affects primarily the GU tract. The diagnosis is made by biopsy. The pathologic specimens typical of malacoplakia consist of large histiocytes known as *von Hansemann cells* and intracytoplasmic inclusions known as *Michaelis–Gutmann bodies*. The goal of treatment is to stabilize the disease process by controlling UTI (Image ☼).

REFERENCES

Guner G, Akdogan B, Baydar DE. Malakoplakia of prostate as a complication of transrectal needle biopsy. *Can J Urol.* 2012;19(1):6124–6127.

Long JP Jr., Althausen AF. Malacoplakia: A 25-year experience with a review of the literature. *J Urol.* 1989;141(6):1328–1331.

MALARIA (BLACK WATER FEVER), UROLOGIC CONSIDERATIONS

DESCRIPTION The protozoan *Plasmodium falciparum* is the parasite responsible for malaria. From a urologic perspective, malaria can cause hemoglobinuria. Treatment includes full dose

antimalarials with supportive care. Acute renal tubular necrosis can occur if the infection is left untreated and some patients with chronic malaria develop nephrotic syndrome. (See Section II: “Black-Water Fever.”)

REFERENCE

Kehinde EO, Anim JT, Hira PR. Parasites of urological importance. *Urol Int.* 2008;81:1–13.

MALE SEXUAL FUNCTION SCALE

DESCRIPTION An 8-question sexual health inventory completed by the patient, which assesses core components of male sexual function including desire, erection, ejaculation, and satisfaction. The scale is meant to screen for sexual health in both the primary care and urologic practice settings.

REFERENCE

Lue TF, Broderick GA. Evaluation and nonsurgical management of erectile dysfunction and premature ejaculation. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.

MALE SEXUAL HEALTH QUESTIONNAIRE (MSHQ) AND THE MSHQ SHORT FORM

DESCRIPTION A patient self-administered test developed in 2004, the MSHQ is a 25-question questionnaire that evaluates sexual function and satisfaction in older men with LUTS. It provides more in-depth assessment of ejaculatory function than previous measures of sexual dysfunction, mainly the International Index of Erectile Function (IIEF). A 4-item version is called the MSHQ short form, and both forms can be used in research settings as well as in clinical practice to assess ejaculatory dysfunction. (See Section VII: “Reference Tables: Male sexual health questionnaire, Short Form".)

REFERENCE

Rosen RC, Catania JA, Althof SE, et al. Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. *Urology*. 2007;69(5):805–809.

MALROTATED KIDNEY/RENAL MALROTATION

DESCRIPTION Malrotated kidney occurs when the kidney does not rotate 90° medially during fet al development. As a result, the renal pelvis, which normally lies medial to the parenchyma, is located anterior to the parenchyma. Often a malrotated kidney is an incidental finding. Malrotation makes the kidney more susceptible to trauma, and is also commonly observed in ectopic kidneys. (See also Seection I: “Renal Ectopia.”) (Image ☼)

REFERENCE

Graham SD, Glenn JF, Keane TE. *Glenn’s Urologic Surgery*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

MARSHALL–MARCHETTI–KRANTZ (MMK) CYSTOURETHROPEXY

DESCRIPTION A historical procedure for the treatment of stress incontinence in women performed through a Pfannenstiel incision. The retropubic space is exposed and the urethra, vaginal wall, bladder neck, and bladder are identified. The original description reports placement of interrupted sutures to attach the paraurethral tissue to the back of the symphysis pubis, with the most proximal suture being at the bladder neck.

REFERENCE

Parnell JP 2nd, Marshall VF, Vaughan ED Jr. Primary management of urinary stress incontinence by the Marshall-Marchetti-Krantz vesicourethropexy. *J Urol.* 1982;127(4):679–682.

MARTIUS GRAFT

DESCRIPTION A surgical technique used to repair urinary-vaginal fistulae. The flap is a well-vascularized fat pad from the labia majora and receives its blood supply from the branches of the pudendal artery. It is tunneled beneath the labia minora into the vaginal lumen, where it is used an interposition graft at the site of the fistula repair. It serves as a well-vascularized barrier between suture layers to prevent recurrent fistula formation.

SYNONYMS

- Martius labial pedicle graft
- Martius labial fat pad
- Martius flap

REFERENCE

Rangnekar NP, Imdad Ali N, Kaul SA, et al. Role of the Martius procedure in the management of urinary-vaginal fistulas. *J Am Coll Surg.* 2003;191(3):259–263.

MATHIEU HYPOSPADIAS REPAIR

DESCRIPTION A ventral flap is mobilized based on the dartos blood supply, and it is transposed over the urethral plate to advance the meatus. The lateral wings of the glans are reapproximated over the repair.

REFERENCE

Minevich E, Pecha BR, Wacksman J, et al. Mathieu hypospadias repair: Experience in 202 patients. *J Urol.* 1999;162(6):2141–2142.

MATURATION ARREST

DESCRIPTION The term *maturation arrest* has been used to describe testicular biopsies in cases of infertility. 2 forms of maturation arrest have been described: Spermatogenic arrest and spermatocytic (meiotic) arrest. The arrest is most frequently observed at the primary spermatocyte level. Reversible arrest at that level can be due to heat, infections, and hormonal and nutritional factors. Irreversible arrest at the primary spermatocyte or spermatid level has a genetic origin due to chromosomal anomalies. The dysfunction occurs in somatic

and germ cells.

REFERENCE

Martin-du Pan RC, Campana A. Physiopathology of spermatogenic arrest. *Fertil Steril.* 1993;60(6):937–946.

MAXIMUM ANDROGEN BLOCKADE (MAB)/COMBINED HORMONAL THERAPY (CHT)

DESCRIPTION The main concept behind maximum androgen blockade (MAB), sometimes referred to as combined hormonal therapy (CHT) or total androgen blockade is that by adding an antiandrogen in conjunction with surgical castration or LHRH agonist therapy, urologists can minimize the effects of any extragonadal sources of androgen production in patients with prostate cancer. This source was traditionally noted to be the adrenal gland. Studies have been conflicting with some showing prolonged survival in patients treated with MAB with advanced prostate cancer and others demonstrating no significant difference. In a large meta-analysis published by the Prostate Cancer Trialists' Collaborative group, a nonsignificant 1.8% 5-yr survival was found in the MAB group. This study included 27 randomized trials and over 8,200 patients.

Short-term MAB (1–2 wk) is generally agreed to in men with newly diagnosed metastatic disease when starting androgen deprivation with an LHRH analog to block the so-called "flare" reaction. Most RTOG trials that combine radiation therapy and external beam radiation therapy for intermediate and high-risk disease are performed using MAB (6 mo to 2–3 yr based on the risk and protocol).

REFERENCES

Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of randomized trials. *Lancet.* 2000;255:1491–8.

Kollmeier MA, Zelefsky MJ. What is the role of androgen deprivation therapy in the treatment of locally advanced prostate cancer? *Nat Clin Pract Urol.* 2008;5(11):584–585.

MAYER–ROKITANSKY–KUSTER–HAUSER SYNDROME (ROKITANSKY—KUSTER–HAUSER SYNDROME)

DESCRIPTION A congenital absence of the vagina. The uterus is either abnormal or absent. The diagnosis is usually made when amenorrhea is noted in a normal pubertal XX person with a female phenotype. Renal and skelet al anomalies are a common association. The defect involves mesodermal development and the mesonephric kidney, the latter resulting in abnormalities in the paramesonephros (uterus and vagina) and in the metanephric kidney.

REFERENCE

Griffin JE, Edwards C, Madden JD, et al. Congenital absence of the vagina. The Mayer-Rokitansk-Kuster-Hauser syndrome. *Ann Intern Med.* 1976;85(2):224–236. Review.

MAYO CLINIC GRADING SYSTEM FOR PROSTATE CANCER

DESCRIPTION A grading system for prostate cancer that uses not only assessment of glandular architecture similar to Gleason's grading system, but also histologic criteria. Grading is done on a scale of 1–4, with 4 having the worst prognosis. Cellular features, such as cytoplasmic-nuclear-nucleolar morphology, mitotic activity, and tumor invasiveness, are all used to assign grade.

REFERENCES

Kozlowski JM, Grayhack JP. Carcinoma of the prostate. In: Gillenwater JY, Grayhack JT, Howards SS, et al., eds. *Adult and Pediatric Urology*. 2nd ed. St. Louis, MO: Mosby; 1991.

Utz DC, Farrow GM. Pathologic differentiation and prognosis of prostatic carcinoma. *JAMA*. 1969;209(11):1701–1703.

McCUNE–ALBRIGHT SYNDROME

DESCRIPTION A syndrome characterized by a classic triad of fibrous dysplasia (cystic bone lesions), gonadotropin-independent precocious puberty, and cutaneous pigmentation with cafe-au-lait spots. It is caused by a mutation of chromosome 20q13, coding for the α-subunit of G-proteins that are involved with many hormone receptor signaling pathways.

SYNONYMS

- Polyostotic fibrous dysplasia
- Osteitis fibroso cystica

TREATMENT

Treatment is targeted at the specific endocrinopathy and may include:

- Hyperthyroidism surgery
- Adrenalectomy
- Aromatase inhibitors, anti-estrogens, and ant-iandrogens

REFERENCE

Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskelet al manifestations of fibrous dysplasia. *Orphanet J Rare Dis*. 2012;7:S4. Published online May 24, 2012.

McGUIRE URINAL

DESCRIPTION An external male urine collection device consisting of a reusable latex urinal sheath that is either self-contained or attached directly to a leg bag. It is often supported by fabric suspensions in a jock-strap type fashion.

REFERENCE

Tanagho EA, McAininch JW. Neuropathic bladder disorders. In: Tanagho EA, McAininch JW, eds. *Smith's General Urology*. 17th ed. New York, NY: McGraw-Hill; 2007.

MEATAL STENOSIS, URETHRAL, FEMALE

DESCRIPTION Distal urethral (meatal) stenosis is a recognized entity. Females with this condition present clinically with complaints ranging from UTI to enuresis. Distal urethral

stenosis may be associated with the radiographic appearance of a prominent, collar-like bladder neck, which reflects generalized detrusor hypertrophy. When treatment is deemed necessary, the distal urethra is calibrated with bougies or female urethral sounds. (See also Section III: "Urethra, Meatus, Normal Caliber.")

REFERENCE

Perlmutter AD, Colodny A, Harris PD, et al. Urethral meatal stenosis in female children simulating bladder-neck obstruction. *J Pediatr.* 1966;69(5):739–743.

MEATAL STENOSIS, URETHRAL, MALE

DESCRIPTION Most commonly seen after neonatal circumcision, this acquired condition is theorized to follow a postsurgical inflammatory reaction at the glans, resulting in an extremely narrow meatus. Meatal stenosis is usually not apparent until the child is toilet trained. Strength and/or direction of stream can be affected. Dysuria, frequency, incontinence, and hematuria are symptoms that have been associated with this condition. Meatal stenosis rarely causes obstructive changes in the urinary tract. Meatoplasty is the corrective procedure for those requiring surgical correction. (See also Section II: "Calibration, Meatus and Urethra.")

REFERENCE

Brem J, Jaffee SR. Hidden meatal stenosis in male infants and children. *Am Fam Physician (GP).* 1970;2(2):72–73.

MECKEL–GRUBER SYNDROME (MECKEL SYNDROME)

DESCRIPTION Meckel–Gruber syndrome is a rare, lethal, autosomal recessive disorder with major characteristic features consisting of the triad of occipital encephalocele, polydactyly, and bilateral polycystic kidneys. Prenatal sonographic exam has been demonstrated to be of reliable diagnostic accuracy. For this reason, appropriate prenatal counseling is advocated for those at high risk.

REFERENCE

Sepulveda W, Sebire NJ, Souka A, et al. Diagnosis of the Meckel-Gruber syndrome at eleven to fourteen weeks' gestation. *Am J Obstet Gynecol.* 1997;176(2):316–319.

MEDIAN BAR

DESCRIPTION Median bar refers to prostatic posterior commissural hyperplasia, an acinar hyperplasia involving the posterior bladder lip that produces a wide bar. Patients suffering enlargement of the middle lobe or posterior commissure are more likely to develop obstructive symptoms due to the tissue location, which easily obstructs the bladder neck. This explains the correlation between the size of the gland and the degree of obstruction.

REFERENCE

Randall A. *Surgical Pathology of Prostatic Obstruction.* Baltimore, MD: Williams & Wilkins; 1931.

MEDIAN RAPHE CYST

DESCRIPTION Median raphe cysts are uncommon congenital lesions of the male genitalia. Theories proposing its origin include the development of embryologic outgrows of epithelium after primary closure of urethral folds, or that they arise from epithelial remains caused by incomplete closure of the folds. Cysts can be found anywhere from the distal penis to anus at the midline. They are usually asymptomatic until adulthood, when they can be traumatized or secondarily infected, producing swelling, tenderness, and purulent discharge. Treatment is simple excision followed by primary closure.

REFERENCE

Krauel L. Median raphe cysts of the perineum in children. *Urology*. 2008;71(5):830–831.

MEDICATIONS THAT CAN IMPACT VOIDING FUNCTION

DESCRIPTION A variety of agents can impact on urinary function. Some can worsen incontinence, others can cause retention and difficulty voiding.

Medications That Can Impact Voiding Function

Medication	Effect on Voiding Function
Alcohol	Frequency, urgency, sedation, delirium, immobility
Angiotensin-converting enzyme inhibitors	Associated cough worsens stress and possibly urge leakage in persons with impaired sphincter function
Anticholinergics	Impaired emptying, retention, delirium, sedation, constipation, fecal impaction
Antipsychotics	Anticholinergic effects plus rigidity and immobility
β-Blockers	Urge incontinence
Calcium channel blockers	Impaired detrusor contractility and retention; the dihydropyridine agents can cause pedal edema, leading to nocturnal polyuria
Cholinesterase inhibitors	Alone may increase incontinence; increased functional impairment when combined with anti-incontinence antimuscarinic agents
Estrogen	Worsens stress and mixed leakage in women
GABAergic agents (gabapentin, pregablin)	Pedal edema causing nocturia and nighttime incontinence
Histamine 1 receptor antagonists	Confusion
Latanoprost	Urge incontinence
Lithium	Polyuria
Loop diuretics	Polyuria, frequency, urgency
Narcotic analgesics	Urinary retention, fecal impaction, sedation, delirium
Nonsteroidal anti-inflammatory drugs	Pedal edema causing nocturnal polyuria
Opioid analgesics	Sedation, anticholinergic effects
Oral contraceptives	Stress, urge, and mixed incontinence
Sedative hypnotics	Sedation, delirium, immobility
Thiazolidinediones	Pedal edema causing nocturnal polyuria
Tricylic antidepressants	Anticholinergic effects, sedation
α-Adrenergic agonists	Outlet obstruction (men)
α-Adrenergic blockers	Stress leakage (women)

REFERENCE

Reprinted with permission from DuBeau CE. Urinary incontinence. In: Pompei P, Murphy JB, eds. *Geriatrics Review Syllabus: A Core Curriculum in Geriatric Medicine*. 6th ed. New York, NY: American Geriatrics Society; 2006: 185. Table based on data from Resnick NM. Geriatric medicine. In: Isselbacher JK, Braunwald E, Wilson JD, et al. eds. *Principles of Internal Medicine*. New York, NY: McGraw-Hill; 1994: p. 34.

MEDULLARY CYSTIC KIDNEY

DESCRIPTION A form of progressive renal disease with up to 75% of cases having

medullary cysts, although it is primarily a tubulointerstitial disease. Juvenile nephronophthisis and medullary cystic disease are similar anatomically and clinically, but they have different modes of transmission and different clinical presentations. Juvenile nephronophthisis usually is inherited as an autosomal recessive trait (onset age: 6–20 yr), and medullary cystic disease typically is inherited as an autosomal dominant trait that presents after the 3rd decade. Patients present with polyuria and polydipsia due to salt wasting, a concentrating defect, anemia, and profound growth retardation. Juvenile nephronophthisis often is associated with disorders of the retina (ie, retinitis pigmentosa), skelet al abnormalities, hepatic fibrosis, and Bardet–Biedl syndrome (obesity, mental retardation, polydactyly, retinitis pigmentosa, and hypogenitalism). On US or CT, the medullary cysts can be seen with parenchyma and may appear hyperechogenic due to tubulointerstitial fibrosis.

SYNONYMS
- Juvenile nephronophthisis
- Uremic medullary cystic disease
- Salt-losing enteropathy
- Uremic sponge kidney

TREATMENT
Sodium replacement initially, with dialysis and transplantation later. The transplant graft appears to be resistant to the disease.

REFERENCE
Bernstein J, Gardner KD Jr. Familial juvenile nephronophthisis: Medullary cystic disease. In: Edelman CM Jr., ed. *Pediatric Kidney Disease*. Boston: Little, Brown; 1979:580.

MEGAPREPUCE (CONGENITAL MEGA PREPUCE)

DESCRIPTION Also known as *megameatus intact-prepuce variant*, this is a variant of hypospadias in which the ventral prepuce is intact and characterized by intermittent ballooning of the genital area. It may only be discovered following a dorsal slit at the time of circumcision. Associated anomalies include chordee, penoscrotal inversion, bifid scrotum, and cryptorchidism. One surgical repair consists of limited preputial resection of the phimotic ring, wide dissection of the outer prepuce to the base of the penis, fixation of the proximal outer prepuce to Buck's fascia to create a new penoscrotal junction. Next step is unfurling and wide tailoring of the inner prepuce in the ventral midline to resurface the whole elongated penile shaft. A catheter is left in place for 5 or 6 days.

REFERENCES
Mesrobian HO. Urologic problems of the neonate: An update. *Clin Perinatol.* 2007;34(4):667–679.

Ruiz E, Vagni R, Apostolo C, et al. Simplified surgical approach to congenital megaprepuce: fixing, unfurling and tailoring revisited. *J Urol.* 2011;185(6 Issue):2487–2490.

MEGACALYCOSIS

DESCRIPTION A nonobstructive enlargement of the calyces due to a congenital

malformation of the renal papillae. There is no dilation of the renal pelvis, and no evidence of UPJ obstruction. Found almost exclusively in males (6:1), it often presents in children due to a UTI workup or in adults with hematuria and renal calculi. The clinician must differentiate between hydronephrosis and UPJ obstruction.

TREATMENT
Not necessary. A diuretic renogram should fail to demonstrate any obstruction.

REFERENCE
Redman JF, Neeb AD. Congenital megacalycosis: a forgotten diagnosis? *Urology*. 2005;65(2):384–385.

MEGACYSTIS, CONGENITAL

DESCRIPTION A dilated, thin-walled bladder with a wide and poorly developed trigone. Because of the laterally displaced ureters, vesicoureteral reflux is commonly seen. Bladder contractility is normal, but most urine refluxes retrograde into the collecting system. Correction of the reflux often restores normal bladder dynamics. It is most often diagnosed on prenatal US. It is associated with *megacystis-microcolon-intestinal hypoperistalsis syndrome,* a rare congenital disorder characterized by a dilated, nonobstructive urinary bladder and hypoperistalsis of the GI tract.

TREATMENT
Correction of vesicoureteral reflux after 6 mo of age.

REFERENCE
Frimberger D, Kropp BP. Bladder anomalies in children. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.

MEGACYSTIS-MEGAURETER SYNDROME

DESCRIPTION The term *megacystis-megaureter* describes the radiologic appearance of a large-capacity, thin-walled bladder, and massive primary vesicoureteral reflux. The pathophysiology of these massively dilated ureters and the large-capacity bladder is the constant recycling of large volumes of refluxed urine. Bladder contractility is normal, even with a poorly developed trigone. Surgical correction of the reflux usually leads to a normal voiding pattern. (See also Section I: “Vesicoureteral Reflux, Pediatric.”)

TREATMENT
Correction of the reflux surgically should lead to a normal voiding pattern.

REFERENCE
Burbige KA, Lebowitz RL, Colodny AH, et al. The megacystis-megaureter syndrome. *J Urol.* 1984;131(6):1133–1136.

MEGALOURETHRA

DESCRIPTION Megalourethra is an extremely rare congenital deficiency of the mesodermal

tissues of the phallus. It can best be described as a urethral diverticulum that affects the entire penile urethra. 2 types have been described, scaphoid and fusiform. Scaphoid megalourethras are more common and have an absence of corpus spongiosum, whereas fusiform megalourethras lack both spongiosum and corpora cavernosa. Often associated with lethal congenital anomalies, fusiform megalourethras are present in some stillborns. Transient obstruction during early development may be responsible for the fusiform type. With the scaphoid type, a failure of development of erectile tissue is present, a mesenchymal defect similar to the pathophysiology of prune belly syndrome (PBS). Many other conditions are associated, such as PBS, renal agenesis, hypospadias, cryptorchidism, and others. For PBS, urethrostomy may be needed secondary to bladder outlet obstruction and renal failure. In surgical repair of the scaphoid type, longitudinal reduction urethroplasty over a catheter to decrease urethral caliber or plication techniques can be used.

For the fusiform variant, each case is managed based on the amount of tissue present and the severity of disease (Image ☼).

REFERENCE

Vaghefi H, Simmons MN, Hsia MH, et al. Two extremes of the megalourethra spectrum. *Urology.* 2006;67:614–616.

MELANOMA, ADRENAL

DESCRIPTION Primary malignant melanoma of the adrenal gland is an established entity. It originates in the adrenal medulla from cells derived from the neural crest. Because of the high frequency of metastatic involvement of the adrenal by cutaneous and ocular melanomas, diagnosis can be difficult. Primary adrenal melanoma is a highly malignant tumor of middle age that often manifests as a painful flank mass. Distant lymph node metastases can be seen as a presenting sign. Treatment is not effective, with a mortality rate approaching 100% within 2 yr.

REFERENCE

Dao AH, Page DL, Reynolds VH, et al. Primary malignant melanoma of the adrenal gland. A report of two cases and review of the literature. *Am Surgeon.* 1990;56(4):199–203.

MELANOMA, GENITOURINARY

DESCRIPTION Malignant melanoma of the GU tract is rarely a primary disease. However, lesions of the penis, scrotum, and urethra can present as primary sites of disease. Secondary melanoma metastatic to the GU tract is a common autopsy finding. The majority of patients whose secondary melanoma is discovered clinically die of metastatic disease within 2 yr.

REFERENCE

Stein BS, Kendall AR. Malignant melanoma of the genitourinary tract. *J Urol.* 1984;132(5):859–868.

MELANOMA, URETHRAL

DESCRIPTION A malignant degeneration of melanocytes and nevus cells, primary

malignant melanomas are rare. The urethra is the preferred site of the urinary tract and accounts for ~4% of urethral cancers. A urethral melanoma is more likely to be primary compared with cases in the bladder or kidney. It is 3 times more common in women, more frequent in the white population, and most commonly affects the distal urethra. Presentation is similar to that of other urethral tumors, but melanuria is sometimes seen. It may be confused with urethral polyps, caruncles, mucosal prolapse, chancre, or more common malignant urethral tumors. It is most commonly unifocal. These are usually deeply invasive; local extension is common and inguinal lymph node metastases are present at diagnosis in 1/2 of the cases. Most patients do not survive >3 yr. (See also Section I: "Urethra, Carcinoma, General Considerations.")

TREATMENT

- Limited data are available; most are treated with radical surgery and frequently bilateral lymph node dissection.
- Chemotherapy, immunotherapy, radiotherapy, or a combination of all 3 is experimental.

REFERENCE

Oliva E, Quinn TR, Amin MB, et al. Primary malignant melanoma of the urethra: A clinicopathologic analysis of 15 cases. *Am J Surg Pathol.* 2000;24(6):785–796.

MENKES SYNDROME (MENKES KINKY HAIR DISEASE)

DESCRIPTION A rare congenital disorder of copper metabolism with an X-linked recessive inheritance. Symptoms appear in the neonatal period and include hypothermia, poor feeding, and impaired weight gain. Neurogenic function progressively deteriorates. A colorless and friable hair is characteristically found. There tends to be a high incidence of GU conditions, including bladder diverticula, UTI, UPJ obstruction, vesicoureteral reflux, and cryptorchidism.

TREATMENT

- Parenteral copper therapy
- Bladder diverticula generally are treated with clean intermitent catheterization (CIC), as well as open cutaneous vesicostomy. Excision of the bladder diverticula is usually hazardous because of the generally poor health of these patients.

REFERENCE

Oshio T, Hino M, Kirino A, et al. Urologic abnormalities in Menkes' kinky hair disease: Report of three cases. *J Pediatr Surg.* 1997;32(5):782–784.

MENOPAUSE, UROLOGIC CONSIDERATIONS

DESCRIPTION Menopause is the cessation of the menstrual cycle and is caused by reduced secretion of the ovarian hormones estrogen and progesterone. This causes a variety of symptoms, including those that affect the GU tract. Vaginal side effects such as dyspareunia (~40%), itching, and vaginal dryness (~55%) occur secondary to reduced estrogen and androgen secretions. A change in the pH of vaginal fluid from acidic to neutral occurs that increases urinary infections. Decreased estrogen contributes to collagen loss and subsequent

pelvic organ prolapse and urinary symptoms. Urinary incontinence and irritative bladder symptoms occur in 20–40% of perimenopausal and postmenopausal women.

TREATMENT

- Topical estrogen therapy has been shown to decrease the incidence of urinary infections, increase bladder control with reduction in urge and irritative symptoms, and improve vaginal dryness and atrophy. It has no effect on stress urinary incontinence (SUI).
- The use of hormone therapy is generally on a short-term basis and only for symptomatic individuals. Although it has been shown to possibly have cardioprotective effects, an increase in breast cancer risk is also seen.

REFERENCE

Lobo RA. Menopause: Endocrinology, consequences of estrogen deficiency, effects of hormone replacement therapy, treatment regimens. In: Katz VL, et al. *Comprehensive Gynecology*. 5th ed. Philadelphia, PA: Mosby Elsevier; 2007.

MESOTHELIOMA, BENIGN, TESTICULAR TUNIC

DESCRIPTION Both a benign papillary, nonpapillary (adenomatoid tumor), and benign multicystic varieties exist. The nonpapillary tumor is the most common tumor of the epididymis and cord. All arise from the tunica vaginalis and are usually seen in young men 20–50 yr of age. The most common clinical presentation is associated with a painless scrotal mass or hydrocele. Benign multicystic mesothelioma has a recurrence rate of 27–75% in 3 mo–19 yr. (See also Section I: “Paratesticular Tumors.”)

REFERENCE

Aber A, Tahir A, Arumuham V, et al. Benign cystic mesothelioma: A rare cause for scrotal swelling. *Case Rep Med.* 2012;2012:572186.

MESOTHELIOMA, MALIGNANT, TESTICULAR TUNIC

DESCRIPTION Mesothelioma is a rare tumor (<100 cases reported), affecting the serosal surface of pleura, pericardium, peritoneum, and tunica vaginalis (an extension of the peritoneum). It usually presents as an incidental finding at the time of hydrocele surgery. It most commonly presents in the 5th–7th decades, although it has been reported in a patient 10 yo. Patients typically present with a hydrocele, but the initial physical exam rarely suggests malignancy. Metastatic spread occurs early via the lymphatic system to the paraaortic, inguinal, and supraclavicular nodes. The tumor spreads less commonly via the bloodstream to the lungs and liver. In the absence of metastatic spread, aggressive local surgery seems to yield the best results. The role of adjuvant chemotherapy and radiotherapy is less clear. (See also Section I: “Paratesticular Tumors.”) (Image ☼)

REFERENCE

Brimo F, Illei PB, Epstein JI. Mesothelioma of the tunica vaginalis: A series of eight cases with uncertain malignant potential. *Modern Pathology*. 2010;21:1165–1172.

METABOLIC STONE EVALUATION (24-HR URINE STUDIES)

DESCRIPTION Patients with urolithiasis should be encouraged to retrieve stones or stones removed surgically should be submitted for stone analysis. The extent of further evaluation is somewhat controversial. It is generally agreed that all patients who present with nephrolithiasis undergo a basic evaluation to rule out a systemic disease. This limited evaluation include history, physical exam, imaging for any residual stones, electrolytes, creatinine, calcium, uric acid, phosphorus, stone analysis and urinalysis, including urine pH. This may diagnose uncommon, but potentially serious, systemic conditions (eg, primary hyperparathyroidism or distal renal tubular acidosis). Patients with complex anatomy should undergo a comprehensive evaluation with their first episode of urolithiasis. In contrast, a comprehensive metabolic stone evaluation goes beyond the limited evaluation. The results of the metabolic stone evaluation can provide information on the best strategy to reduce future stone formation and allow monitoring of therapeutic interventions.

- Two 24-hr urine collections on a random diet with components noted below with initial quantitative cystine determination (optional)
- Serum calcium, phosphorus, uric acid, HCO_3, BUN, creatinine, albumin, alkaline phosphate, intact PTH (optional), 1,25-di-OH-vitamin D2 (optional)

Metabolic Stone Evaluation

Urine	Normal (24-hr collection)	Clinical Implications
Urine volume	0.5–4 L/d	Increase daily urine output to at least 2L. Low urine output as an isolated condition can result in urolithiasis. Consider diarrheal disease, very poor fluid intake or occupational causes
pH	5.8–6.2	If <5.8 consider K or Na citrate 25–30 mEq BID; > 6.5, RTA if citrate is low; >8, consider urea splitting infection
Urine ammonium	15–60 mmol/d	High level with pH >7, urea splitting infection; low level with pH <5.5 consider: Renal disease, uric acid stones, gout
Urine calcium	male <250, female <200 mg/dL	Idiopathic hypercalciuria, consider hydrochlorothiazide 25 mg BID or chlorthalidone 12.5–25 mg QAM. Keep urine Na <100 by sodium restriction
Urine chloride	70–250 mmol/d	Varies with sodium and potassium intake
Urine citrate	male >450, female >550 mg/d	Consider K citrate 20–30 mEq BID; if due to RTA (urine pH >6.5) also use K citrate
Urine creatinine	mg/d; varies with body weight	Used as a check for day to day consistency of urine collection (see urine creatinine/kg)
Urine creatinine/kg	male 18– 24, female 15–20 mg/kg/d	Low in obesity, incomplete urine collection.
Urine magnesium	30–120 mg/d	Low with poor nutrition, some laxatives, malabsorption syndrome
Urine oxalate	20–40 mg/d	If elevated, usually dietary; if enteric, consider cholestyramine, oral calcium 1–2 g with meals; if >80 mg/d, may be primary hyperoxaluria
Urine phosphorus	0.6–1.2 g/d	Low in bowel disease, malnutrition, high with large food intake
Urine potassium	20–100 mmol /d	If <20, consider bowel disease, diuretics, laxatives
Urine sodium	50–150 mmol/d	When high raises urine Ca, and K loss from thiazide; ideal is <100
Urine sulfate	20–80 mmol /d	When high indicates a high protein diet
Urine urea nitrogen	6–17 g/d	Measures urea production from diet protein
Urine uric acid	male <0.800 g/d, female <0.750 g/d	Often due to diet; if stones are severe and low protein diet fails try allopurinol 200 mg/d

Cystine screening is performed on an optional basis and is not part of standard metabolic stone evaluation unless following patients with cystinuria.		
Qualitative cystinuria screen	Negative	Sodium cyanide–nitroprusside test detects urinary cystine >75 mg/g of creatinine
Urine cysteine	<75 mg/d	Most stone formers are >300 mg/d. Heterozygotes excrete 200–400 mg/d; Homozygotes excrete 600–1,400 mg/d. Basic treatments are high fluids to achieve a urine volume >3.5 L daily, and increased urine pH to 7–7.5 using potassium alkali; K or Na citrate 25–30 mEq BID; to keep pH above 7.0 in cystinuria patients. Sulfhydryl drugs (tiopronin, penicillamine, and captopril) may interfere with assay results.

d = day.
Values and recommended clinical implications based on data from Litholink; https://www.litholink.com/en/OurReports0, (Accessed April 5, 2014.

REFERENCE

Paterson RF. Arguments for a comprehensive metabolic evaluation of the first-time stone former. *Can Urol Assoc J*. 2010;4(3):209–210.

METABOLIC SYNDROME, UROLOGIC CONSIDERATIONS

DESCRIPTION An increasingly more prevalent disease affecting ~22% of American adults, metabolic syndrome is characterized by having any 3 of the following: Abnormal waist circumference, hypertriglyceridemia, low HDL, hypertension, or abnormal fasting glucose parameters. Sexual dysfunction can occur, including hypogonadism and erectile dysfunction (ED). Many patients have a low urinary pH, thus increasing the risk of uric acid stones. Subclinical Cushing syndrome accounts for 3–5% of metabolic syndrome and should be in the differential diagnosis. ADT can contribute to metabolic syndrome.

SYNONYMS

- Syndrome X
- Insulin resistance syndrome
- Obesity dyslipidemia syndrome

TREATMENT

- Lifestyle modifications with dietary changes, increased physical activity, and smoking cessation
- Obesity: Goal of gradual 5–10% weight reduction. Consider bariatric surgery in extreme cases if conservative management fails.
- Pharmacologic therapy: aimed at hypertension, hyperlipidemia/dyslipidemia, other
- Impaired glucose tolerance: initial management with diet and exercise
  - Prothrombotic states: Consider low-dose aspirin in high coronary artery disease risk
  - Testosterone for hypogonadism may have protective cardiovascular effects (controversial)
- Oral hydration and urine alkalinization can be considered for uric acid stone formers.

REFERENCE

Tukaye DN. Metabolic syndrome. In: Domino FJ, ed. *5 Minute Clinical Consult 2014*. 22nd ed. Philadelphia, PA: Wolters Kluwer; 2014.

METANEPHRIC ADENOFIBROMA, KIDNEY (NEPHROGENIC

ADENOFIBROMA)

DESCRIPTION A pediatric benign renal tumor with stromal features resembling congenital mesoblastic nephroma. The epithelial component has varying levels of activity ranging from inactive metanephric adenoma to Wilms tumor. Some masses contain areas identical to papillary RCC. Lesions with a Wilms tumor component occur at a young age (mean of 12 mo). No tumors have recurred after nephrectomy, but all have been treated with Wilms tumor chemotherapy. There has been 1 case described with nodal metastasis of the papillary RCC component of their tumor.

REFERENCE

Argani P. Metanephric neoplasms: The hyperdifferentiated, benign end of the Wilms Tumor spectrum? *Clin Lab Med.* 2005;25(2):379–392.

METANEPHRIC ADENOMA

DESCRIPTION A recently recognized renal tumor originally described in 1980; it bears a cytologic resemblance to early metanephric tubular differentiation and to the metanephric hamartomatous element of nephroblastomatosis. Fewer than 100 cases have been reported, with a 2:1 female-to-male predominance. Most cases present in the 5th–6th decades of life, and the lesion is often discovered incidentally. An association with polycythemia has been reported in 12% of the cases that resolves after surgical resection. These adenomas are typically unilateral and rarely multifocal. The majority are either unencapsulated or have only a limited and discontinuous pseudocapsule. It is largely regarded as a benign neoplasm but in 1 case lymph node metastases were reported. It cannot be differentiated from RCC on imaging studies. WT1 and CD57 immunohistochemical staining aids in the diagnosis of metanephric adenoma (Image ☼).

REFERENCE

Hartman DJ, MacLennan GT. Renal metanephric adenoma. *J Urol.* 2007:178(3):1058.

METAPYRONE TEST

DESCRIPTION Cushing syndrome describes the symptom complex caused by excess circulating glucocorticoids. Metapyrone is a blocking agent used to reduce the secretion of functional steroids, thereby lessening the severity of symptoms. Metapyrone blocks the conversion of 11-deoxycortisol to cortisone. It is a diagnostic test for hypothalamic–pituitary ACTH function:

- Day 1: Control period: Collect 24-hr urine to measure 17-hydroxycorticosteriods or 17-ketogenic steroids.
- Day 2: ACTH test: 50 units ACTH infused over 8 hr and measure 24-hr urinary steroids.
- Days 3–4: Rest period.
- Day 5: Administer metyrapone with milk or snack. (Adult: 750 mg PO q4h for 6 doses; Pediatric: 15 mg/kg q4h for 6 doses [min 250 mg dose]).
- Day 6: Determine 24-hr urinary steroids.
- Normal 24-hr urine 17-OHCS is 3–12 mg; following ACTH, it increases to 15–45 mg/24 hr; normal response to metyrapone is a 2–4-fold increase in 17-OHCS excretion; drug

interactions with phenytoin, cyproheptadine, and estrogens may lead to subnormal response.

REFERENCE

Scott HW Jr., Orth DN. Hypercortisolism. In: *Surgery of the Adrenal Glands*. Philadelphia, PA: JB Lippincott; 1990.

MEYER–WEIGERT LAW

DESCRIPTION In cases in which separate ureteric buds on the same mesonephric duct form a completely duplicated collecting system, separate investigators (Weigert and then Meyer) noted that there exists a consistent relationship between the upper and lower pole orifices as they relate to 1 another on the trigone. The caudad, or distally placed, orifice actually drains the upper pole moiety; whereas the cranial, or superior, orifice drains the lower pole moiety. The distal orifice is more medial on the trigone, as opposed to the laterally placed cranial orifice. This is a reliable rule for cases of ureteral duplication.

REFERENCE

Glassberg KI, Braren V, Duckett JW, et al. Suggested terminology for duplex systems, ectopic ureters and ureteroceles. *J Urol*. 1984;132 (6):1153–1154.

MIBG SCAN

DESCRIPTION A form of molecular imaging using metaiodobenzylguanidine (MIBG), an analog of guanethidine. MIBG accumulates into cells via norepinephrine transporters and is collected into secretory granules. It is useful in identifying primary and metastatic pheochromocytoma, paraganglioma, and neuroblastoma.

REFERENCE

Chen CC, Carrasquillo JA. Molecular imaging of adrenal neoplasms. *J Surg Onc*. 2012;106:532–542.

MICHAELIS–GUTMANN BODIES

DESCRIPTION Michaelis–Gutmann bodies are the pathognomonic finding in the benign inflammatory process known as ***malakoplakia***. Light microscopy demonstrates a granulomatous inflammatory process, characterized by the accumulation of large mononuclear cells with abundant granular cytoplasm and PAS-positive calcific intracytoplasmic inclusions (so-called Michaelis–Gutmann bodies). On electron microscopy, such inclusions appear as concentric lamellated structures with a mineralized core (Image ☼).

REFERENCE

Lambird PA, Yardley JH. Urinary tract malakoplakia: Report of a fatal case with ultrastructural observations of Michaelis-Gutmann bodies. *Johns Hopkins Med J*. 1970;126(1):1–14.

MICROCYSTIC/NESTED VARIANT UROTHELIAL CARCINOMA

DESCRIPTION Microcystic and nested variant urothelial carcinoma are rare histologic subtypes of bladder cancer that appear similar to benign conditions of the bladder, however demonstrate aggressive behavior. Microcystic urothelial cancer has an inverted growth pattern that resembles cystitis cystica. It has been identified in bladder, upper tract, and prostatic urethra. Nested variant urothelial carcinoma is easily mistaken for reactive von Brunn nests. Lesions have a low-grade appearing cytology even when invasive. Lymphovascular invasion (LVI) is usually present at the time of diagnosis (Image ☼).

REFERENCE

Shanks JH, Iczkowski KA. Divergent differentiation in urothelial carcinoma and bladder cancer subtypes with selected mimics. *Histopathology*. 2009;54:885–900.

MICROLITHIASIS, TESTIS

DESCRIPTION Testicular microlithiasis is an uncommon condition characterized by the presence of calcifications within degenerating seminiferous tubules. There is a reported incidence of between 2 and 6% of males. Microlithiasis is often found in conjunction with other testicular pathologies, with testicular malignancy being the most concerning, however, there are conflicting reports. Currently, no guidelines exist for follow-up of patients diagnosed with microlithiasis of the testis. Recommendations range from no follow-up to a staging workup for testicular carcinoma. At a minimum, testicular self-exams are important and annual physical exam by a physician is recommended. Some authors suggest annual exam by a urologist in conjunction with annual ultrasound for patients with risk factors for testicular cancer (Image ☼).

REFERENCE

Rashid HH, Cos LR, Weinberg E, et al. Testicular microlithiasis: A review and its association with testicular cancer. *Urol Oncol.* 2004; 22(4):285–289.

MICROPAPILLARY BLADDER CANCER

DESCRIPTION A variant of bladder cancer 1st described in 1994. The histologic features closely resemble papillary serous carcinoma of the ovary. It accounts for 0.7–2.2% of all urothelial tumors and is nearly always associated with an advanced stage of disease and aggressive clinical course. A recent review of 100 consecutive patients at MD Anderson Cancer Center indicated an average age of 64.7 yr, with a male-to-female ratio of 10:1. 5 and 10-yr survivals of 51% and 24%, respectively. Intravesical therapy appears to be ineffective. Radical cystectomy provides a chance of cure in these patients. (See also Section I: “Bladder Cancer, General.”) (Image ☼)

TREATMENT

Expeditious radical cystectomy in patients with surgically resectable disease

REFERENCE

Kamat AM, Dinney CP, Gee JR, et al. Micropapillary bladder cancer: A review of the

University of Texas MD Anderson Cancer Center experience with 100 consecutive patients. *Cancer.* 2007;110(1):62–67.

MICTURITION SYNCOPE

DESCRIPTION Syncopal episodes occurring during voiding are known as micturition syncope. This was originally though to be a disorder of young healthy men, however additional studies have found micturition syncope to span ages and gender. Several mechanisms have been suggested in the literature. 1 is that decompression of the bladder results in a decreased intra-abdominal pressure therefore decreasing blood return and causing a sudden decrease in cerebral blood flow. Another is that increased vagal tone during voiding results in a syncopal episode. Finally, micturition syncope could be an orthostatic event as a result of waking from sleep that occurs during the 1st void of the day immediately after wakening. Rarely, micturition syncope can be a symptom of a pheochromocytoma/paraganglioma of the bladder. Further investigation with urinalysis and cystoscopy are warranted in addition to workup of a cardiovascular source of syncope.

REFERENCE

Kapoor WN, Peterson JR, Karpf M. Micturition syncope. *JAMA*. 1985;253:796–798.

MILK OF CALCIUM, URINARY TRACT

DESCRIPTION The crystallization of calcium salts without actual stone formation. These usually accumulate in simple renal cysts or calyceal diverticula. On ultrasound, it is an echogenic focus or layer within the cyst. On IVP, it appears as a crescent-shaped density whose meniscus may adjust relative to patient positioning.

TREATMENT

Endoscopic, percutaneous, or ablative procedures may be performed if clinically indicated (ie, pain, infection).

REFERENCE

Sidhu R, Bhatt S, Dogra V, et al. Renal colic. *Ultrasound Clin.* 2008;3:159–170.

MILK–ALKALI SYNDROME

DESCRIPTION Hypercalcemia and alkalosis associated with the ingestion of large amounts of milk and antacids containing calcium and absorbable alkali. Patients can develop nephrocalcinosis and renal insufficiency, but typically do not have hypercalciuria. The associated vomiting and dehydration can produce further volume contraction and alkalosis. (See also Section I: “Nephrocalcinosis, Adult.”)

TREATMENT

- Withdrawal of milk and alkali, with gentle hydration to lower serum calcium
- Vigorous hydration can result in rebound hypocalcemia due to the chronic suppression of the parathyroid glands

REFERENCE

Smith SG. Milk-alkali syndrome. In: Domino FJ M, ed. *The 5-Minute Clinical Consult 2014*. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2014.

MITROFANOFF PRINCIPLE

DESCRIPTION A surgical procedure, originally described by Mitrofanoff, in which the appendix is excised with a button of cecum, reversed, and tunneled to create a catheterizable channel with a reported continence rate of 93–100%. Stomal stenosis is an early complication affecting 7–24% within 3 yr in published series.

REFERENCE

Harris CF, Cooper CS, Hutcheson JC, et. al. Appendicovesicostomy: The mitrofanoff procedure – A 15 year perspective. *J Urol.* 2000;163(6):1922–1926.

MIXED EPITHELIAL STROMAL TUMOR OF THE KIDNEY (MESTK)

DESCRIPTION MESTK is a subset of benign renal tumors composed mainly of smooth muscle cells in which epithelial structures are embedded. It is usually found in middle-aged and perimenopausal women. Grossly, MESTK is well-circumscribed but unencapsulated, and cystic on a cut surface. Microscopically, it is composed both of epithelial structures similar to renal tubules and stroma comprising nonspecific spindle cells. The differential diagnosis for these tumors includes cystic nephroma and cystic partially differentiated nephroblastoma.

REFERENCE

Michal M, Hes O, Bisceglia M, et al. Mixed epithelial and stromal tumors of the kidney. A report of 22 cases. *Virchows Arch.* 2004;445(4):359–67.

MOLLUSCUM CONTAGIOSUM

DESCRIPTION A benign, self-limited skin tumor or papular eruption caused by a virus. Infection occurs after breakage of the skin and characteristically begins as a small papule. When mature, it is a discrete 2–5 mm smooth, dome-shaped, pearly or flesh-colored nodule that is often umbilicated. Single to hundreds of lesions may track alone the line of a scratch. In adults, they occur on the trunk, thighs, and pubic areas. Lesions usually disappear by themselves within 6–12 mo, although this may take up to 4 yr with impaired cell-mediated immunity. Diagnosis is usually clinical, but brick-shaped virions can sometimes be seen under negative-stain electron microscopy. Henderson–Paterson bodies are characteristically seen on pathology. (See also Section I: “Sexually Transmitted Diseases [STDs], General.”)

TREATMENT

- Observation is reasonable for nongenital lesions.
- Curettage is useful for treating a few lesions; scarring may develop.
- Liquid nitrogen therapy, cantharidin 0.7%, tretinoin 0.025% gel, or 0.1% cream; laser therapies are also common.

REFERENCE

Damon I. Other poxviruses that infect humans: Parapoxvirus, molluscum contagiosum, and

tanapox. In: Mandell GL, et al., eds. *Mandell, Douglas, & Bennett's Principles and Practice of Infectious Diseases.* 6th ed. Philadelphia, PA: Elsevier; 2005.

MONDOR DISEASE

DESCRIPTION Mondor disease is superficial thrombophlebitis of the dorsal vein of the penis. It is typically diagnosed in young males after excessive sexual activity and can be diagnosed in older males due to venous obstruction secondary to bladder distention. Physical exam typically reveals a tender palpable cord on the dorsal surface of the penis as well as distal penile edema. Treatment is conservative with abstinence of sexual activity until completely resolved. Anticoagulation and antiplatelet medications have not been shown to be of benefit. Vein stripping surgery is indicated for patients with associated cellulitis.

REFERENCE

Dicuio M, Pomara G, Cuttano MG, et al. Penile Mondor's disease after intensive masturbation in a 31 and a 33 year old man. *Thromb Haemost.* 2003;90(1):155–156.

MONFORT TECHNIQUE

DESCRIPTION A type of abdominal wall reconstruction in patients with prune belly syndrome. This technique utilizes an elliptical incision that preserves the umbilicus and thickens and strengthens the anterior abdominal wall. Full-thickness resection of skin from the central abdomen is performed, and the anterior wall is sutured in a double-breasted fashion preserving vascularity and the umbilicus. This technique offers excellent exposure for concomitant intra-abdominal surgery.

REFERENCE

Monfort G, Guys JM, Bocciardi A, et al. A novel technique for reconstruction of the abdominal wall in the prune belly syndrome. *J Urol.* 1991;146(2):639–640.

MONTI PROCEDURE

DESCRIPTION Also known as the *Monti ileovesicostomy,* a technique most often used in children to create a continent catheterizable stoma. A short segment of bowel (2–3 cm of ileum) is incised along the antimesenteric border and then closed transversely to create a uniform tube that can be tunneled into the bladder and out through the abdominal wall. This allows preservation of the appendix for the Malone antegrade continent enema (MACE) procedure. A review of 199 patients undergoing Monti ileovesicostomy at a single institution reported a revision rate of 8.5% and a continence rate of 96.5% with mean follow-up of 28 mo.

REFERENCE

Rink RC, Dussinger AM, Gitlin J, et al. Updated Experience with the Monti catheterizable channel. *Urology*. 2008;72(4):782–785.

MORRIS SYNDROME

DESCRIPTION An intersex disorder that affects 1 in 20,000 live male births; it is caused by a mutation in the androgen receptor gene located on the long arm of the X chromosome. This prevents appropriate androgen binding and/or function. If complete androgen insensitivity occurs, the child will appear to have a normal female phenotype and the testes are located internally. Many children are diagnosed at the time of hernia repair as infants or not diagnosed until puberty during an evaluation for primary amenorrhea.

SYNONYMS
- Testicular feminization syndrome
- In class of male pseudohermaphroditism

REFERENCE
Hyun G, Kolon TF. A practical approach to intersex in the newborn period. *Urol Clin N Am.* 2004;31(3):435–443.

MOSKOWITZ VAGINAL PROLAPSE REPAIR

DESCRIPTION Through a transabdominal exposure, the procedure entails closing the cul-de-sac through placement of a series of purse-string sutures. The procedure was initially described to treat rectal prolapse by securing the rectum to the fixed vagina, and the same logic has been used to correct vaginal prolapse by fixing it to the rectum. Unfortunately, the rectum is not well anchored. (See also Section I: “Pelvic Prolapse [Cystocele and Enterocele].”)

REFERENCE
Raz S, et al. Vaginal reconstructive surgery for incontinence and prolapse. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell’s Urology*. 7th ed. Philadelphia, PA: Saunders; 1998:1066–1094.

MOSTOFI (WHO) GRADING SYSTEM, PROSTATE CANCER

DESCRIPTION Traditional prostate cancer grading system, generally replaced by the Gleason grading system:
- Grade I: Well differentiated, with slight nuclear anaplasia
- Grade II: Moderately to poorly differentiated, with moderate nuclear anaplasia
- Grade III: Poorly differentiated, with marked nuclear anaplasia, or undifferentiated carcinoma

SYNONYM
World Health Organization Grading System

REFERENCE
Mostofi FK. Grading of prostatic carcinoma. *Cancer Chemother Rep.* 1975;59(Pt I):111–117.

MOWAT–WILSON SYNDROME

DESCRIPTION A syndrome of multiple congenital anomalies due to a heterozygous mutations or deletions in *ZEB2*, or Zinc finger E-box-biding homeobox 2 gene. It is generally

discovered on genetic workup for Hirschsprung disease. Patients present with a distinct facial phenotype, mental retardation, epilepsy, agenesis of corpus callosum, and congenital heart defects. Roughly 50% of patients have genitourinary anomalies with hypospadias being the most prominent (52%). Another common anomaly is cryptorchidism (36%). Bifid scrotum, vesicoureteral reflux and micropenis are rare but have been reported.

REFERENCE

Garavelli L, Mainardi PC. Mowat- Wilson syndrome. *Orphanet J Rare Dis.* 2007;2:42.

MUCORMYCOSIS, GENITOURINARY

DESCRIPTION A fungal infection that usually affects immunocompromised patients. Patients receiving hemodialysis and deferoxamine are at particular risk for disseminated disease. The kidneys are the organs most often involved in the GU system, but penile involvement has also been reported. The course is usually fatal. (See also Section I: "Fungal Infections, Genitourinary.")

TREATMENT

Amphotericin B systemically; nephrectomy for involved kidney

REFERENCE

Wise GJ, Freyle J. Changing patterns in genitourinary fungal infections. *AUA Update Series.* Vol. XVI, Lesson 1; 1997.

MUCOSURIA (MUCINURIA)

DESCRIPTION Passage of mucous during urination. This is a normal finding in patients who have undergone bladder replacement surgery using bowel segments. Mucosuria can be a symptom of mucinous adenocarcinoma of the urinary tract, most commonly of the urachus however mucin producing tumors of the prostate and renal pelvis have been reported. Other sources of mucin production in the bladder include invasive colorectal cancer and colovesical fistulas. (See also Section I: "Bladder Cancer, Adenocarcinoma.")

REFERENCE

Bohman KD, Osunkoya AO. Mucin-producing tumors and tumor-like lesions involving the prostate: A comprehensive review. *Adv Anat Pathol.* 2012;19(6):374–387.

MUIR–TORRE SYNDROME

DESCRIPTION An autosomal dominant skin condition characterized by tumors of the sebaceous gland or keratoacanthoma associated with ≥ 1 visceral malignancies including colorectal, endometrial, urologic, and upper GI. Usually considered a subtype of hereditary nonpolyposis colorectal cancer syndrome; $\sim 25\%$ of the visceral cancers are associated with the urogenital tract, the most common of which are urothelial carcinoma.

REFERENCE

Ponti G, Ponz de Leon M. Muir-Torre syndrome. *Lancet Oncol.* 2005;6:980–987.

MULBERRY STONES

DESCRIPTION A term that refers to the surface appearance of irregular calcium oxylate dihydrate stones often seen in the bladder. Based on their less well-developed spikes than seen on jackstones; the spikes possess more of a mamillated appearance.

REFERENCE

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston: Little-Brown; 1991:224.

MULCAHY PROTOCOL

DESCRIPTION Infection of a penile prosthesis is suspected when there is local pain and erythema, fever and cutaneous fixation of the prosthesis components. In this situation there are 2 main options. The 1st is to remove the prosthesis and reinsert it at least 6–8 mo later. This repeat surgery can be difficult due to formation of scar tissue in the corpora. Another option is to remove the prosthesis, perform a copious antibiotic washout of the corpora cavernosa with an antibiotic solution, then place a "tutor" cylinder inside the corpora to prevent shortening and scarring. Another approach to the management of an infected penile prosthesis is the Mulcahy protocol. This involves complete removal of the infected part of the prosthesis and all other components followed by the use of the specific Mulcahy salvage procedure outlined below with reinsertion of a new penile prosthesis in the same sitting with a reported success rate of 85%. (See also Section I "Penile Prosthesis Problems [Infection/Extrusion/Malfunction]".)

- Remove all prosthetic parts and foreign material
- Irrigate wounds using 5 antiseptic solutions:
  - Antibiotic solution (1 g vancomycin and 80 mg gentamicin in 1 L of normal saline)
  - 1/2 strength hydrogen peroxide
  - Pressure washing with 1 g vancomycin and 80 mg gentamicin in 5 L irrigation
  - 1/2 strength Povidone-iodine (Betadine or similar)
  - Antibiotic solution rinse
- Change gowns, gloves, surgical drapes, and instruments immediately before prosthesis insertion
- Insert new prosthesis
- Close wounds with no drains or catheters
- Administer oral antibiotics for 1 month

REFERENCES

Mulcahy JJ. Current approach to the treatment of penile implant infections. *Ther Adv Urol.* 2010;2(2):69–75.

Natali A. Management of the complications of penile prosthesis implantation. *World J Men's Health.* 01/2010;7(3). doi:10.1016/j.jomh.2010.07.003

MÜLLERIAN DUCT REMNANTS AND SYNDROME (PMDS)

DESCRIPTION Refers to the persistence of the müllerian duct structures (uterus, fallopian tubes) in the genotypically and phenotypically normal male. The remnants persist due to the

absence of müllerian inhibiting substance. It is an autosomal recessive inherited disorder. Patients present with cryptorchidism and hernia, and the persistent müllerian structures are found within the hernia sac. Increasing evidence is mounting that persistent müllerian structures are at risk for malignant transformation. 11 cases of malignancy have been reported in the literature out of 200 reported cases of persistent Müllerian dcut syndrome (PMDS).

SYNONYMS
- Prostatic utricular cyst
- Müllerian duct cyst (Image ☼)

REFERENCE
Farikullah J, Ehtisham S, Nappo S, et al. Persistent Müllerian duct syndrome: lessons learned from managing a series of eight patients over a 10-year period and review of literature regarding malignant risk from the Müllerian remnants. *BJU Int.* 2012;110(11 Pt C):E1084–E1089.

MULTILOCULAR CYSTIC NEPHROMA (CYSTIC NEPHROMA, MULTILOCULAR CYST)

DESCRIPTION A round, well-encapsulated multilocular cystic mass whose septa are composed of well-differentiated tissues, without blastemal elements. The current thinking is that multilocular cystic nephroma is at the benign end of a spectrum that includes cystic partially differentiated nephroblastoma (CPDN) and Wilms tumor on the malignant end. Grossly, multilocular cystic nephroma and CPDN look identical. The contents of the cysts consist of either clear to yellow fluid or thick myxomatous gel. The lesion is usually solitary but rarely can be multiple. Cystic nephroma presents in a bimodal age distribution of 3 mo–2 yr (2:1 male-to-female) and in adulthood (8:1 female-to-male). Children usually present with a palpable mass and adults with pain, hematuria, or infection. Imaging cannot distinguish between cystic nephroma and CPDN. The lesion often is close to the renal pelvis, and herniation of the renal pelvis is a pathognomonic finding on IV urography, CT, or MRI. The nephromas contain noncommunicating cysts with thin septa separating the cysts. On US, multiple anechoic spaces are seen, separated by hyperechoic septa. CT reveals a well-marginated, rounded, or polycyclic cortical mass that extends beyond the normal renal outline. Enhancement of the septa may be seen due to the presence of thin vessels. Imaging cannot reliably predict malignant potential.

SYNONYMS
- Cystic kidney, cystic nephroma
- Focal polycystic kidney
- Multicystic or cystic adenoma

TREATMENT
- Partial nephrectomy or radical nephrectomy is indicated.
- Follow-up is required because of local recurrence (Image ☼).

REFERENCE

Stamatiou K, Polizois K, Kollaitis G, et al. Cystic nephroma: A case report and review of the literature. *Cases J.* 2008;1(1):267.

MULTIPLE ENDOCRINE NEOPLASIA (MEN I, MEN II)

DESCRIPTION A group of inherited syndromes primarily consisting of endocrine tumors of both benign and malignant nature. MEN syndrome lesions are of urologic interest because of the possibility of adrenal involvement, hyperparathyroidism, renal stones, and hyperlactatemia:

- MEN I (Wermer syndrome): Autosomal dominant condition with neuroendocrine parathyroid, pancreas, duodenal, and pituitary lesions. Cutaneous tumors may also be seen (angiofibromas, others). Hyperparathyroidism is the most common presentation of this syndrome, but overall this is a rare cause of hyperparathyroidism in the general population. Pituitary lesions may cause hyperprolactinemia and ACTH-producing lesions.
- MEN II (Sipple syndrome): Autosomal dominant:
  - Type IIA triad: Pheochromocytoma, medullary carcinoma of the thyroid, parathyroid adenoma
  - Type IIB: Pheochromocytoma, medullary carcinoma of the thyroid (but not parathyroid hyperplasia) with mucosal neuromas, intestinal ganglioneuromas, and occasionally marfanoid habitus. Some literature refers to this as MEN III (mucosal neuroma syndrome).

REFERENCE

Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. *Surg Clin N Am.* 2008;88(4):863–895.

MULTIPLE MYELOMA, UROLOGIC CONSIDERATIONS

DESCRIPTION A malignant proliferation of plasma cells derived from a single clone. The classic triad involves marrow plasmacytosis, lytic bone lesions, and a serum and/or urine M component. Renal failure occurs in 25% of patients. Hypercalcemia is the most common cause, but hyperuricemia is also present and a likely cause. Tumor lysis syndrome is uncommon with multiple myeloma. There may be tubular precipitation of light-chain proteins (myeloma kidney), urinary obstruction due to uric acid or calcium-containing stones, or recurrent pyelonephritis. Glomerular, tubular, and interstitial involvement can cause renal insufficiency. The development of a myeloma kidney can lead to adult Fanconi syndrome, which is a type II proximal renal tubular acidosis. NSAIDs are to be avoided. Renal failure is rare but has been reported after the use of contrast agents in patients with multiple myeloma.

REFERENCE

Sakhuja V, Jha V, Varma S, et al. Renal involvement in multiple myeloma: A 10-year study. *Ren Fail.* 2000;22(4):465–477.

MUMPS ORCHITIS

DESCRIPTION Mumps is a single-stranded RNA (paramyxo) virus. After the prodromal period, 1 or both parotid glands begin to enlarge. Mumps orchitis follows the development of

parotitis by 4–7 days, with about 20% of males developing orchitis (10% bilateral and 80–90% unilateral). It has been reported following mumps vaccination. The presentation is high fever, testicular pain, and swelling. The management of mumps orchitis is supportive (bedrest, scrotal support, analgesics) with resolution in about 7 days. Unilateral testicular atrophy occurs in 60%. Impaired fertility can affect up to 13%, but sterility is rare. (See also Section I: "Orchitis, General.")

REFERENCE

Masarani M, Wazait H, Dinneen M. Mumps orchitis. *J R Soc Med.* 2006;99(11):573–575.

MURCS ASSOCIATION (MüLLERIAN DUCT, RENAL, AND CERVICAL VERTEBRAL DEFECTS)

DESCRIPTION MURCS association consists of a nonrandom association of müllerian duct aplasia, renal aplasia/agenesis, and cervicothoracic somite dysplasia. The incidence of cervicothoracic vertebral defects, especially from C5–T1, is 80%. Other abnormalities may include Sprengel deformity, upper limb defects, and moderately frequent rib anomalies. It is the 2nd most frequent cause of primary amenorrhoea after Turner syndrome.

REFERENCE

Braun-Quentin C, Billes C, Böwing B, et al. MURCS association: Case report and review. *J Med Genet.* 1996;33(7):618–620.

MUSCLE FLAP TYPES, UROLOGIC CONSIDERATIONS

DESCRIPTION Muscle flaps are a reconstructive technique using local or distant muscle donor sites to provide tissue coverage in complex reconstructive procedures. The most simple muscle flaps are local and regional flaps where blood supply of the muscle is not interrupted when the flap is repositioned to its new location. Pedicle and micro vascular free flaps are more complicated forms of tissue transfer that are finding new indications in reconstructive urologic procedures. Tissue transfer has become increasingly used in centers for complex repair of fistula disease following radiation. In addition, clinical study has shown latissimus dorsi transferred to acontractile detrusor tissue with microsurgical coaptation of the thoracodorsal nerve to low intercostal nerves innervating the rectus abdominus has restored voluntary voiding in patients with detrusor areflexia.

REFERENCE

Ninkovic M, Dabernig W. Flap technology for reconstructions of urogenital organs. *Curr Opin Urol.* 2003;13:483–488.

MUSTARDé HYPOSPADIAS REPAIR

DESCRIPTION A more extensive Mathieu technique in which the ventral flap is tubularized to form a neourethra and then transposed distally. The glans wings are again approximated over the neourethra.

REFERENCE

Belman AB. The modified Mustardé hypospadias repair. *J Urol.* 1982;127(1):88–90.

MYCOPLASMA GENITALIUM INFECTION

DESCRIPTION *Mycoplasma genitalium* is a common organism that resides within the genital tracts of both men and women. However, it may be a cause of chronic prostatitis in men or urgency and frequency in women. Identifying and culturing this organism is difficult. Initial treatment includes doxycycline 100 mg BID for 2 wk or azithromycin 1 g in a single dose.

REFERENCE

Moi H, Reinton N, Moghaddam A. Mycoplasma genitalium is associated with symptomatic and asymptomatic nongonococcal urethritis in men. *Sex Transm Infect.* 2009;85(1):15–18.

MYCOPLASMA HOMINIS, URINARY TRACT INFECTION

DESCRIPTION *Mycoplasma hominis* commonly resides in the genital tracts of both men and women. This organism is often found in women with bacterial vaginosis and can be a cause of PID and dyspareunia. It is generally susceptible to tetracycline and quinolones.

REFERENCE

Kenny GE. Genital mycoplasmas: *Mycoplasma genitalium, Mycoplasma hominis,* and *Ureaplasma* species. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Bennett, & Dolin: Principles and Practice of Infectious Diseases.* 6th ed. Philadelphia, PA: Elsevier, 2005:2280–2282.

MYOCUTANEOUS FLAPS

DESCRIPTION Myocutaneous flaps, such as rectus flap, gracilis flap, or tensor fascia flap, can be utilized during urologic reconstructive surgery. Common applications are for skin coverage during ilioinguinal node dissections for penile cancer, closure of urinary fistulae, and reconstruction after Fournier gangrene:

- Rectus abdominis flap: The blood supply of the rectus abdominis is the superior and deep inferior epigastric vessels. The deep superior epigastric vessels are not utilized as a vascular pedicle for the free flap because of their smaller caliber and a greater amount of skin can be transferred by relying on the interior epigastric pedicle.
- Gracilis flap: The origin of the gracilis muscle is the ischium and inferior ramus of the pubis and the insertion is the medial tibia. The gracilis muscle is 4–8 cm wide and is harvested from the inner thigh. It can be utilized either as a muscle flap or myocutaneous flap and leaves the patient without any functional deficit. The nerve supply to the gracilis muscle is a branch of the obturator nerve, and its blood supply is a single artery from the profunda femoral system.
- Tensor fascia lata flap: The tensor fascia lata can be harvested from the lateral aspect of the upper leg. The vascular pedicle is comprised of the transverse branch of the lateral circumflex femoral artery, and the sensory supply is the lateral femoral cutaneous nerve of the thigh, which originates from T12. A skin island of up to 15 cm can be harvested and leaves the patient without any functional deficit.

REFERENCE

Smith HO, Genesen MC, Runowicz CD, et al. The rectus abdominis myocutaneous flap: Modifications, complications, and sexual function. *Cancer.* 1998;83(3):510–520.

MYOFASCIAL PAIN, UROLOGIC CONSIDERATIONS

DESCRIPTION Myofascial sources of pain have been defined in women with myofascial pelvic pain syndrome (MPPS) (see below) and new evidence is mounting that myofascial pain may be a contributing factor in a constellation of chronic male pelvic pain syndromes previously diagnosed as prostatitis or orchitis. Trigger points, defined as hyperirritable, sensitive, or tender spots usually associated with a taut band of skelet al muscle or fascia, have been identified in women with MPPS. A recent study has identified several reproducible trigger points in males with chronic pelvic pain (CPP) on external and internal pelvic exam and an initial investigation has shown improved response to internal and external myofascial physical therapy compared to external massage (57–28%).

REFERENCE

Anderson RU, Sawyer T, Wise D, et al. Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome. *J Urol.* 2009;182:2753–2758.

MYOFASCIAL PELVIC PAIN SYNDROME (MPPS)

DESCRIPTION MPPS is a disorder in which pelvic pain is attributed to short, tight, tender pelvic floor muscles, usually with hypersensitive trigger points. Pelvic floor trigger points refer pain to the vagina, vulva, perineum, rectum, and bladder. Pain can be also be referred to the thighs, buttocks, or lower abdomen. Irritative symptoms (eg, urinary urgency, vulvovaginal burning, rectal fullness) may be more prominent than pain. The diagnosis is clinical. Treatment is customized and based on reducing the response of the trigger point. Stress reduction (meditation, relaxation exercises), physical therapy (stretch/massage), heat, ice, or NSAIDs are recommended for mild cases. Pelvic floor physical therapy (manual myofascial release, stretching, and strengthening) is useful for many patients. More severe cases may require trigger point injections (bupivacaine), gabapentin, or botulinum toxin if muscle spasm can be identified. (See also Section I: “Pelvic Pain, Female.”)

REFERENCE

Srinivasan AK, Kaye JD, Moldwin R. Myofascial dysfunction associated with chronic pelvic floor pain: Management strategies. *Curr Pain Headache Rep.* 2007;11(5):359–364.

MYOGLOBIN NEPHROTOXICITY

DESCRIPTION Renal failure associated with the excessive deposit of myoglobin into the serum following massive muscle necrosis/rhabdomyolysis. Renal failure is initiated by acute tubular obstruction, and necrosis is caused by free chelatable iron and ischemia. Granular casts are found in the urine. Renal failure is initially manifested by oliguria and followed later by a polyuric state. (See also Section II: “Myoglobinuria and Rhabdomyolysis.”)

TREATMENT

- Myoglobin nephrotoxicity is prevented by maintaining fluid balance through the use of

diuretics and hydration, using isotonic saline initially.
- If renal failure develops, fluid retention should be avoided by limiting infusion rates.
- In polyuric states, vigilant replacement of electrolytes is required.

REFERENCE

Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)*. 2005;84(6):377–385.

MYOGLOBINURIA

DESCRIPTION 1st described by Fleischer in 1881, myoglobinuria refers to the presence of excessive amounts of myoglobin, a protein found in muscle, in the urine. Myoglobinuria occurs when serum levels exceed the renal threshold. Myoglobin is released into the serum following massive muscle necrosis (rhabdomyolysis) from crush, compartment syndrome, electrical injury, toxins, malignant hyperthermia, and other causes, and imparts a cola-like color to the urine. Diagnosis is made by electrophoresis separation and radioimmunoassay of urinary myoglobin. Serum creatinine kinase is elevated, and there is an absence of red cells in the urine. (See also Section I: “Rhabdomyolysis”; Section II: “Myoglobin Nephrotoxicity.”)

CAUSES
- Diabetic acidosis
- Fluid/electrolyte imbalance
- Infectious myositis
- Ischemia
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Rhabdomyolysis or compartment syndrome
- Toxins
- Trauma

TREATMENT
- Remove the causative agent.
- Protect against renal failure through correction of electrolyte imbalances, alkalinization of urine with sodium bicarbonate, hydration, and diuretics.

REFERENCE

Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)*. 2005;84(6):377–385.

NAGAMATSU INCISION

DESCRIPTION A dorsolumbar incision is made over either the 11th or 12th rib, which is resected. After rib removal, the diaphragm and pleura are retracted superiorly, and the kidney and the adrenal may be exposed.

REFERENCE

Montague DK. Surgical incisions. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:15–40.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES

DESCRIPTION The NCCN is a nonprofit alliance of NCI-designated Comprehensive Cancer Centers devoted to improving care for cancer patients. This includes the development of treatment guidelines for most cancers, including GU cancers such as prostate, bladder, kidney, and testes as well as screening guidelines. Patient friendly information is also available. Useful treatment algorithms are available on their site or as an app for mobile devices. Registration (no charge) is required. (See also Section II: "Prostate Cancer Screening Guidelines.")

REFERENCE

Online at www.nccn.org.

NATIONAL INSTITUTES OF HEALTH (NIH) CHRONIC PROSTATITIS SYMPTOM INDEX (CPSI)

DESCRIPTION The CPSI is a validated and reproducible measure of outcomes for men with prostatitis. With 9 questions, it captures the 3 domains of the prostatitis experience: Pain, urinary function, and quality of life. While not a diagnostic aid, it is useful for both research studies and clinical practice, in initially assessing patients, subsequently following their progress, and providing specific treatment. (See Section VII.)

REFERENCE

Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: Development and validation of a new outcome measure. *J Urol*. 1999;162:369–375.

NECROSPERMIA

DESCRIPTION A condition in which the sperm are both nonmotile and nonviable. The etiology of this condition is variable.

REFERENCE

Chavez-Badiola A, Drakeley AJ, Finney V, et al. Necrospermia, antisperm antibodies, and vasectomy. *Fertil Steril.* 2008;89(3):723.e5–e7.

NELSON SYNDROME

DESCRIPTION The development of pituitary tumors (usually a chromophobe adenoma) seen in 10–20% of patients originally treated with bilateral adrenalectomy for Cushing disease. Believed to be caused by a lack of hypothalamic/pituitary feedback and resultant high levels of ACTH and related compounds, patients must be followed with ACTH levels and imaging of the sella turcica. Patients usually present 1–4 yr after bilateral adrenalectomy. Common symptoms include visual deficits (57%), hyperpigmentation, and headaches, however most patients are diagnosed based on screening labs and imaging. ACTH levels above 200 ng/L and evidence of pituitary mass enlargement on MRI are diagnostic.

TREATMENT

- Surgical excision
- Radiation therapy
- Prophylactic pituitary radiotherapy (shown to reduce the incidence of Nelson syndrome by 50%)

REFERENCE

Banasiak MJ, Malek AR. Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management. *Neurosurg Focus.* 2007;23(3):E13.

NEPHRITIS, RADIATION

DESCRIPTION Renal dysfunction occurs if ≥23 Gy of radiation therapy is administered to both kidneys during a period of ≤5 wk. Histologic exam shows hyalinized glomeruli, atrophic tubules, interstitial fibrosis, and hyalinization of the media of renal arterioles. Radiation-induced renal ischemia causes tubulointerstitial damage, which may take months to manifest. Acute radiation nephritis presents with rapidly progressing azotemia, moderate to malignant hypertension, anemia, and proteinuria. More than 50% of patients progress to chronic renal failure. Malignant hypertension may follow unilateral radiation and resolve with nephrectomy. This entity has essentially vanished due to refinement in radiation therapy techniques.

REFERENCE

Kelly CJ, Neilson EG. Tubulointerstitial diseases. In: Brenner BM, ed. *The Kidney*. 5th ed. Philadelphia, PA: Saunders; 1996:1655–1679.

NEPHROCALCINOSIS, NEONATAL

DESCRIPTION Nephrocalcinosis with or without nephrolithiasis are commonly observed in both term and premature infants who have had difficult neonatal courses. Neonates with prolonged illness are at particular risk, especially those who still require oxygen at 28 days. While multifactorial, such as high calcium and phosphorous intake, loop diuretics appear to be the major cause in this group of patients. Loop diuretics (furosemide most commonly used) predispose to nephrocalcinosis by increasing urinary calcium excretion. Other factors such as immature renal function and physiologic hypercalciuria that occurs between 32 and 40 weeks of gestation contribute.

Nephrocalcinosis in infants with a birth weight <1,500 g may be as high as 64% and may be independent of diuretic use. In infants born <32 wk gestation, 27% had nephrocalcinosis with 70% having been treated with a loop diuretic. Other causes of neonatal nephrocalcinosis include William syndrome (supravalvular aortic stenosis and hypercalcemia), neonatal primary hyperparathyroidism and distal (type 1) renal tubular acidosis. The loop diuretic-induced hypercalciuria can be diminished and radiologic appearance of renal calcifications diminished by administrating a thiazide diuretic in place of or alternating with a loop diuretic. The long-term impact of nephrocalcinosis on renal outcome is unclear because data are limited and inconsistent. Long-term follow-up is recommended.

REFERENCE

Smith J, Stapleton FB. Nephrocalcinosis in neonates. www.UpToDate.com; Wolters Kluwer, Accessed March 29, 2014.

NEPHROGENIC ADENOMA (NA) AND METAPLASIA

DESCRIPTION A rare lesion occurring in the urinary tract that was once thought to be a metaplastic reaction to chronic irritation and has now been shown to originate from exfoliated and implanted renal epithelial cells. It is named for its histologic similarity to renal tubules and can cause hematuria, dysuria, and urinary frequency. On cystoscopy nephrogenic adenoma can appear papillary, nodular, or sessile and is very friable. It is typically unifocal. It is considered a benign lesion, however malignant transformation has been reported and therefore requires complete resection and long-term follow-up due to recurrence rates from 0.5–80% (Image ☼).

REFERENCE

Alexiev BA, LeVea CM. Nephrogenic adenoma of the urinary tract: A review. *Int J Surg Pathol.* 2012;20(2):123–131.

NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS

DESCRIPTION A clinical disorder of water balance resulting in an inability to excrete a free water load. Clinically patients appear similar to those with SIADH, however they have low serum levels of circulating vasopressin. Activating mutations of the V2R (vasopressin type 2 receptor) have been identified as a cause of this chronic condition. Treatment of this condition includes free water restriction and osmotic diuresis with urea. Targeted treatment with compounds that might inhibit V2R are under investigation.

REFERENCE

Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med.* 20005;352:1885–1890.

NEPHROGENIC SYSTEMIC FIBROSIS/FIBROSING DERMATOPATHY (NSF/NFD)

DESCRIPTION NSF is a scleroderma-like skin disease that affects patients with renal

insufficiency. There is a strong association between the development of NSF and exposure to gadolinium contrast agents used in performing MRI in patients with advanced kidney disease. The skin lesions begin as patches, plaques, or papules, then coalesce to form a woody skin appearance. The skin thickening can limit joint motion. There is no known effective treatment. (See also Section I: "Contrast Allergy and Reactions.")

REFERENCE

Kurtkoti J, Snow T, Hiremagalur B. Gadolinium and nephrogenic systemic fibrosis: Association or causation. *Nephrology*. 2008;13:235–241.

NEPHROMETRY SCORING SYSTEMS (PADUA, C-INDEX, RENAL)

DESCRIPTION Nephrometry is an attempt to create a common classification system to describe renal masses based on anatomical characteristics. 3 prominent scoring systems have emerged. PADUA (Preoperative aspects and dimensions used for anatomic classification), C-Index (centrality index), and RENAL (radius, exophytic/endophytic, nearness, anterior/posterior, location) all attempt to score and categorize renal tumors in an attempt to predict complexity of nephron-sparing surgery and surgical outcomes of these lesions.

REFERENCE

Okhunov Z, Rais-Bahrami S, George AK, et al. The comparison of three renal tumor scoring systems: C-index, P.A.D.U.A., and R.E.N.A.L. nephrometry scores. *J Endourol*. 2011;25(12):1921–1924.

NEPHRONOPHTHISIS (JUVENILE, INFANTILE, AND ADOLESCENT)

DESCRIPTION A group of 4 diseases, known as the juvenile nephronophthisis–renal medullary cystic disease complex, that result in ESRD. Nephronophthisis is the most common cause of tubointerstitial nephropathy in children, and is inherited in an autosomal recessive pattern mapped to chromosome 2. 3 subtypes of nephronophthisis exist, based on the age of onset of ESRD. Juvenile nephronophthisis is the most common (1 in 50,000 births), with a median onset of 13 yr; infantile nephronophthisis usually causes ESRD by 5 yr; and adolescent nephronophthisis has a mean onset of 19 yr. The disease presents as failure to thrive, azotemia, polyuria, and polydipsia. Hypertension is less common. Microscopically, it resembles an interstitial nephritis with cysts. US reveals muddling of corticomedullary junction and small reniform kidneys with cysts found at the corticomedullary junction. Retinitis pigmentosa hepatic fibrosis and Bardet–Biedl syndrome are associated. Renal replacement therapy, as needed, is the treatment of choice. Extrarenal involvement is described and can involve the retina, liver, and brain. (See also Section I: "Medullary Cystic Kidney Disease.")

REFERENCE

Saunier S, Salomon R, Antignac C. Nephronophthisis. *Curr Opin Gen Dev*. 2005;15:324–331.

NEPHROPATHY, ANALGESIC

DESCRIPTION A chronic interstitial nephritis seen in patients who consume large quantities

of analgesics over many years. They usually suffer from chronic headaches or low back pain and have consumed a mixture of analgesics, including acetaminophen, aspirin, and NSAIDs. Their chronic use leads to recurrent papillary necrosis with impaired concentrating ability, sterile pyuria, and renal insufficiency. Removal of phenacetin from OTC pain medications has dramatically reduced the incidence of this condition. During periods of acute necrosis, patients may have flank pain, pyuria, hematuria, and acute ureteral obstruction from passage of sloughed, necrotic papillary tissue. IVP shows the ring sign, which refers to the contrast agent surrounding sloughed papilla, although the current use of IVP is limited due to contrast load. Renal US shows small kidneys, with irregular thinning of the renal cortex. Renal biopsy shows interstitial infiltrates and fibrosis. Noncontrast CT shows bilateral reduced renal size, bumpy renal contours, and papillary calcifications (ie, small, indented, and calcified kidneys). The mechanism of injury is believed to be a combination of injury from the production of toxic metabolites and medullary ischemia. These patients are at increased risk of developing TCC of the urinary tract. Cessation of drug use can lead to stabilization of renal function.

REFERENCE

Mihatsch MJ, Khanlari B, Brunner FP. Obituary to analgesic nephropathy—an autopsy study. *Nephrol Dial Transplant.* 2006;21(11):3139–3145.

NEPHROPATHY, ISCHEMIC

DESCRIPTION Ischemic nephropathy is described as a deterioration of renal function due to a reduction in renal blood flow, commonly caused by atherosclerotic renovascular disease or renal artery stenosis. The disease progresses with worsening renal failure and decreased overall survival. It can present as hypertension (HTN) with unexplained renal insufficiency, worsening azotemia with HTN, azotemia in the setting of coronary artery disease or peripheral vascular disease, ACE inhibitor-induced ARF, or flash pulmonary edema. Numerous tests are used to define the presence, size, and function of the kidneys, as well as to establish the presence of a vascular lesion and its clinical significance, including CT or MR angiography, conventional angiography, Doppler US, ACE-I renography or renal vein renin measurements. Controversy still exists on the appropriate management of renal artery stenosis. Options include medical therapy, percutaneous transluminal angioplasty with or without stent placement, as well as surgical revascularization or nephrectomy. (See also Section I: “Renal Artery Stenosis/Renovascular Hypertension.”)

REFERENCE

Chonchol M, Linas S. Diagnosis and management of ischemic nephropathy. *Clin J Am Soc Nephrol.* 2006;1:172–181.

NEPHROPATHY, MEMBRANOUS

DESCRIPTION Renal disease that manifests with nephrotic syndrome. Affecting mainly middle-aged adults, it can progress to either spontaneous remission or ESRD. It is the most common cause of nephrotic syndrome in nondiabetic adults. Proteinuria with microscopic hematuria is often present; massive proteinuria, hypertension, and impaired renal function on presentation, and male gender, are all poor prognostic factors. Believed to be related to in

situ formation of immune complexes, it is most commonly idiopathic, but may be secondary to diseases (malignancy, infection, systemic lupus erythematosus [SLE]) or drug use (gold, penicillamine). Immunofluorescence often reveals deposits of IgG and complement. Treatment is based on the risk of progression associated with proteinuria (low risk <4 g/protein/d; moderate 4–8 g/protein/d; high risk >8 g/protein/d, lasting >3 mo or associated with a reduced creatinine clearance). Low-risk patients are at high likelihood of spontaneous remission and are treated with nonimmunosuppressive therapy, including ACE inhibitors or angiotensin II receptor blockers. In high-risk disease, cyclophosphamide and chlorambucil, both given with glucocorticoids, are effective in inducing remission of proteinuria and preventing progression to ESRD. Other agents reported include cyclosporine and tacrolimus (plus low-dose prednisone 10 mg/d max). (See also Section I: "Nephrotic Syndrome.")

REFERENCE

Glassock RJ. Diagnosis and natural course of membranous nephropathy. *Semin Nephrol.* 2003;23(4):324–332.

NEPHROPATHY, MINIMAL CHANGE

DESCRIPTION A common cause of nephrotic syndrome, most often affecting children but can account for up to 15% of adult nephrotic syndrome. Sometimes called *minimal change disease*, this condition manifests as nephrotic syndrome, with massive proteinuria and anasarca without hypertension. RBCs in the urine are a common finding; histologic evaluation shows essentially no changes on light microscopy. Electron microscopy shows epithelial foot process fusion. The pathogenesis is unknown, but T-cell dysfunction is theorized. The nephropathy can be primary or secondary to medications, neoplasm, infection, allergy, or other renal glomerular diseases; it frequently undergoes spontaneous remission, is responsive to corticosteroid therapy, and rarely progresses to chronic renal failure. (See also Section I: "Nephrotic Syndrome.")

REFERENCE

Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: Clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol.* 2007;2(3):445–453.

NEPHROPATHY, OBSTRUCTIVE

DESCRIPTION Obstructive nephropathy occurs when renal deterioration is due to obstruction of the urinary system. The point of obstruction can be in the upper or lower urinary tract. Congenital, inflammatory, neoplastic, and anatomic etiologies of urinary obstruction are all common. Obstruction of the outflow from the kidney results in several changes that lead to renal fibrosis. The tubular injury in obstructive nephropathy is caused initially by the increased intratubular pressure and later by atrophy induced by reduced perfusion, inflammation, and ischemia. The recovery of renal function after relief of the obstruction is determined by the duration of the obstruction, baseline renal function, patient age, and degree of obstruction. With total obstruction of the ureter, relatively complete recovery of GFR can be achieved within 1 wk, whereas after 12 wk, little or no recovery is

seen. (See also Section I: “Hydronephrosis/Hydroureteronephrosis [Dilated Ureter/Renal Pelvis], Adult.”)

REFERENCE

Better OS, Arieff AI, Massry SG, et al. Studies on renal function after relief of complete unilateral ureteral obstruction of three months duration in man. *Am J Med.* 1973;54(2):234–240.

NEPHROPATHY, URATE (URATE NEPHROPATHY)

DESCRIPTION A disorder in which an abrupt deterioration in renal function occurs due to the renal tubular deposition of urate and uric acid crystals. Chronic renal injury from uric acid deposition is most often associated with gout and is uncommon today. 2 forms are recognized, acute and chronic. Acute urate nephropathy occurs almost exclusively in the setting of malignancies, such as leukemias and lymphomas, with rapid cell turnover leading to increased purine metabolism and loss of nucleotides in the plasma. This is further enhanced by added acceleration of cell lysis, which occurs with chemotherapy and radiation used in these patients, producing the so-called *tumor lysis syndrome*. Nucleotides are converted to urate by xanthine oxidase, resulting in hyperuricemia with levels of 25–90 mg/dL at the time of onset of renal dysfunction. Diagnosis requires the appropriate clinical setting of increased cell lysis (usually with chemotherapy), oliguria, marked hyperuricemia, and hyperuricosuria. A urinary uric acid-to-creatinine ratio >1 distinguishes this from other catabolic states with elevated serum urate levels and renal failure, such as trauma with rhabdomyolysis. (See also Section I: “Urolithiasis, Uric Acid”; Section II: “Gout, Urologic Considerations,” “Hyperuricosuria,” and Tumor Lysis Syndrome [TLS].”)

TREATMENT

- Prevention is the key, using xanthine oxidase inhibition with allopurinol and alkaline diuresis prior to initiation of chemotherapy.
- Alkalinization of urine in the acute tumor lysis syndrome is not possible in the setting of brisk diuresis.
- Rasburicase (Elitek) is recombinant urate oxidase that converts uric acid to water-soluble allantoin.
- Occasionally, dialysis is required to correct azotemia and reduce urate levels.

REFERENCE

Conger JD. Acute uric acid nephropathy. *Med Clin North Am* 1990;74:859–871.

NEPHROPTOSIS

DESCRIPTION Nephroptosis, also referred to as *floating kidney* or *renal ptosis,* is a condition in which the kidney drops into the pelvis when the patient stands up. It tends to be more common in women and is thought to be caused by a lack of perirenal fat. Patients are usually asymptomatic but colicky type pain can be attributed to this conditions, similar to a Dietl crisis. The pain is classically relieved by lying down. Imaging can demonstrate the renal descent and aid in diagnosis. Conservative management had been the mainstay of treatment,

although laparoscopic nephropexy is now recommended for symptomatic patients. (See also Section II: “Dietl Crisis.”)

REFERENCE

Barber NJ, Thompson PM. Nephroptosis and nephropexy-hung up on the past? *Eur Urology*. 2004;46:428–433.

NESBIT CHORDEE REPAIR

DESCRIPTION A surgical procedure in which ≥1 vertical ellipses are removed from the Tunica Albuginea on the longer convex side, and the ellipses are closed transversely, which results in shortening of the longer side to correct the penile curvature.

REFERENCE

Montague DK. Correction of chordee. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart’s Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:822–825.

NEUROENDOCRINE TUMORS, GENITOURINARY

DESCRIPTION A group of tumors that share a characteristic morphology, often being composed of clusters and trabecular sheets of round blue cells, granular chromatin, and an attenuated rim of poorly demarcated cytoplasm. Neuroendocrine tumors include carcinoids, small (oat) cell carcinomas, medullary carcinoma of the thyroid, Merkel cell tumor, cutaneous neuroendocrine carcinoma, pancreatic islet cell tumors, and pheochromocytoma. Small (oat) cell carcinomas have been described most often in the prostate and bladder. Prostate cancer with neuroendocrine differentiation is considered a variant of Gleason 5 adenocarcinoma of the prostate. Undifferentiated carcinomas of the urinary bladder and prostate should be analyzed not only by means of hematoxylin and eosin but also by immunohistochemical staining for chromogranin A (Chr A) and synaptophysin (SNP), to demonstrate a neuroendocrine origin. Because the prognosis of small cell neuroendocrine cancers is very poor, aggressive multimodal therapy is often employed. (See also Section I: “Pheochromocytoma”; Section II: “Multiple Endocrine Neoplasia [MEN I, MEN II]”; “Prostate Cancer, Small Cell [Neuroendocrine].”)

REFERENCE

Helpap B. Morphology and therapeutic strategies for neuroendocrine tumors of the genitourinary tract. *Cancer*. 2002;95(7):1415–1420.

NEUROFIBROMATOSIS, UROLOGIC CONSIDERATIONS

DESCRIPTION A hereditary disorder characterized by cafe-au-lait spots, cutaneous fibromas, and neurofibromas; it is associated with renovascular lesions and pheochromocytomas. Vascular lesions are characterized by endothelial proliferation, with or without aneurysmal formation and cellular nodules in the vessel walls. The aorta is frequently involved, and the renal arteries may demonstrate long areas of stenosis that are generally best treated with revascularization rather than angioplasty. In addition, a 30-fold increase in the incidence of neurofibromatosis in patients with Wilms tumor has been reported.

REFERENCE

Saborio P, Scheinman J. Genetic renal disease. *Curr Opin Pediat.* 1998;10:174–183.

NEUROGENIC DETRUSOR OVERACTIVITY (NDO)

DESCRIPTION NDO patients are a heterogeneous group with both storage and voiding dysfunction. The NDO symptoms include urinary frequency, urgency, and incontinence. Neurologic conditions associated with NDO include multiple sclerosis (MS), spinal cord injury (SCI) Parkinson disease, cerebral palsy, and myelomeningocele. Neurogenic bladder dysfunction is present in 80.8% of individuals with MS, 90% with myelodysplasia, virtually all SCI patients with persistent neurologic deficits and 70% of ambulatory SCI patients. NDO impacts quality of life and can also result in risk of UTI and upper urinary tract damage.

Anticholinergic therapies such as oxybutynin are primarily used for patients with DO and poor compliance. CIC may be best for those who have poor bladder emptying. Although not FDA-approved neuromodulation via sacral nerve stimulation is useful in patients who have failed anticholinergics. Intra-detrusor injection of onabotulinum toxin-A is FDA approved in the management of NDO in patients refractory or intolerant of anticholinergics. In selected individuals, a chronic indwelling catheter may be the best management therapy. Surgical intervention (bladder augmentation, urinary diversion, continent urinary diversion, and ileovesicostomy) may be indicated for protection of the upper urinary tract in high-risk patients or to achieve continence. (See also Section I: “Neurogenic Bladder, General Considerations.”)

REFERENCE

Cone E, Ellsworth P. Neurogenic detrusor overactivity: An update on management options. *R I Med J*. 2013, Available at www.rimed.org, Accessed March 29, 2014.

NEUROMODULATION, UROLOGIC CONSIDERATIONS

DESCRIPTION Neuromodulation involves the use of electrical current to alter physiologic properties. This technology has been applied to lower urinary tract voiding dysfunction for the past decade by stimulation of the sacral nerve roots. Sacral neuromodulation was approved for use in patients with overactive bladder refractory to medical and behavioral therapy by the FDA in 1997. A recent multi-institutional clinical trial shows success rates as high as 68% for urge urinary incontinence, 56% for urgency–frequency, and 71% with unobstructive urinary retention at 5 yr after implantation. Posterior tibial nerve stimulation is also being used. (See also Section II: “Posterior Tibial Nerve Stimulation: Urgent PC [PTNS].”)

REFERENCE

Hubsher CP, Jansen R, Riggs DR, et al. Sacral nerve stimulation for neuromodulation of the lower urinary tract: How I do it. *Can J Urol.* 2012;19(5):6480–6484.

NEVES–ZINCKE CLASSIFICATION

DESCRIPTION A largely historic classification system for describing the level of tumor thrombus associated with a renal mass. The categories are renal vein, ≤2 cm above the renal

vein, infrahepatic >2 cm but below the intrahepatic vena cava, intrahepatic but below the diaphragm and atrial above the diaphragm. (See also Section I: "Renal Cell Carcinoma with Tumor Thrombus.")

REFERENCE

Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. *BJU*. 1987;59(5):390–395.

NMP-22 TESTING

DESCRIPTION NMP-22 has been found to serve as a urinary marker for TCC. The NMP-22 test (Matritech, Inc., Newton, MA) is a quantitative immunoassay that measures NMP-22. The addition of NMP-22 testing to cytology may increase the sensitivity for recurrence detection in patients with superficial transitional cell bladder cancer. Patients with positive NMP-22 findings developed significantly more recurrences compared with those with negative NMP-22 findings in several studies.

REFERENCE

Gupta NP, Sharma N, Kumar R. Nuclear matrix protein 22 as adjunct to urine cytology and cystoscopy in follow-up of superficial TCC of urinary bladder. *Urology*. 2009;73(3):592–596.

NOCTURNAL ERECTIONS, NORMAL AND ABNORMAL

DESCRIPTION Nocturnal erections occur at night during REM sleep. The number of erections peak during puberty. Various criteria exist for what is considered normal erectile activity at night, but normal is usually 4–5 erectile episodes per night with a mean duration >30 min and an increase in circumference of >3 cm at the base and >2 cm at the tip, as well as maximal rigidity above 70% at both base and tip. (See also Section II: "Nocturnal Penile Tumescence Testing.")

REFERENCE

Lue TF, Broderick GA. Evaluation and nonsurgical management of erectile dysfunction and premature ejaculation. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007:765.

NOCTURNAL PENILE TUMESCENCE (NPT) TESTING

DESCRIPTION NPT refers to a recurring cycle of penile erections associated with rapid eye movement sleep. The primary goal of NPT testing is to distinguish between psychogenic and organic causes of impotence. Nocturnal monitoring devices measure the number of erectile episodes, maximal penile rigidity, tumescence, and duration of erections. This testing assumes that the mechanism for nocturnal erections is the same as that for erotically induced erections. (See also Section II: "Nocturnal Erections, Normal and Abnormal.")

REFERENCE

Greenstein A, Mabjeesh NJ, Sofer M, et al. Are consecutive nightly recordings required for

valid evaluation of sleep-associated erections? *Int J Impot Res.* 2007;19(2):196–199.

NOCTURNAL POLYURIA (NP)

DESCRIPTION NP is a condition in which the rate of urine output is excessive only at night, and total 24-hr output is within normal limits. NP is defined as the production of >1/3 of total 24-hr urine output between midnight and 8 AM (normal physiologic response is reduced urine output at night). A voiding diary (*frequency volume chart* or FVC) that records time and volume of each void over a 24-hr period for 7 days establishes if the patient is polyuric or nonpolyuric. True polyuria is present throughout the 24-hr period, whereas NP is confined to elevated night-time output. Altered sleep patterns caused by frequent trips to the bathroom can cause problems staying alert at work, major depression, and hypertension. Although traditional therapies in men have been directed toward medical or surgical treatment, NP does not respond well to these standard interventions. (See also Section II: "Polyuria and Voiding Diary [Frequency Volume Chart, FVC].")

TREATMENT

- Lifestyle changes: Limiting fluids in the late afternoon and evening, such as coffee, soft drinks, or tea.
- Taking diuretics early in the day.
- Desmopressin mimics the action of vasopressin in reducing nocturnal urine production.

REFERENCE

Kujubu DA, Aboseif SR. An overview of nocturia and the syndrome of nocturnal polyuria in the elderly. *Nat Clin Pract Nephrol.* 2008;4(8):426–435.

NOMOGRAMS, UROLOGIC

DESCRIPTION Nomograms are mathematical tools that allow for the prediction of various outcomes. Validated nomograms have been developed for all major urologic cancers, as well as for some benign urologic diseases. Useful online prediction tools are available on several sites including Memorial Sloan Kettering Cancer Center (www.mskcc.org/mskcc/html/5794.cfm) for prostate, bladder, and kidney cancer. SWOP is sponsored by the Prostate Cancer Research Foundation, Rotterdam (www.prostatecancer-riskcalculator.com/). It is an online multi-step Prostate Cancer Risk Calculator and assesses a man's prostate cancer risk and helps to avoid unnecessary biopsy.

REFERENCE

Kattan MW, Scardino PT. Evidence for the usefulness of nomograms. *Nat Clin Pract Urol.* 2007;4(12):638–639.

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

DESCRIPTION NAION describes the acute, painless loss of vision in 1 eye associated with optic disc edema (crowded optic disk). It is a common cause of acute optic neuropathy in adults. Associations have been found between NAION and the phosphodiesterase inhibitors sildenafil, vardenafil, and others. The mechanism and exact nature of this association are still

under investigation.

REFERENCE

Seftel AD, Miner MM, Kloner RA, et al. Office evaluation of male sexual dysfunction. *Urol Clin N Am.* 2007;34:463–482.

NONSACRAL NEUROMODULATION

DESCRIPTION Neuromodulation involves the use of electrical current to alter physiologic properties. This technology has been applied to lower urinary tract voiding dysfunction for the past decade by stimulation of the sacral nerve roots. There has been recent interest into stimulation of more distal branches of the sacral nerve roots as well, including the pudendal, dorsal genital, and posterior tibial nerves. (See also Section II: “Neuromodulation, Urologic Considerations” and “Posterior Tibial Nerve Stimulation: Urgent PC [PTNS].”)

REFERENCE

Bennett RC, et al. Nonsacral neuromodulation. In: Goldman HB, Vasavada SP, eds. *Female Urology: A Practical Clinical Guide.* Totowa, NJ: Humana Press; 2007.

NOONAN SYNDROME

DESCRIPTION This autosomal dominant syndrome consists of multiple congenital anomalies, including characteristic facial features, short stature, and chest deformity. Over 1/2 of males with Noonan syndrome have unilateral or bilateral cryptorchidism. Females can have delayed sexual maturation, but normal development is expected. Renal anomalies occur in 10% of children. Because congenital cardiac anomalies are found in 1/2 of the patients, all patients with this syndrome should have cardiac evaluation and close follow-up. Growth hormone replacement may have value in treating short stature.

REFERENCE

Noonan JA. An update and review for the primary pediatrician. *Pediatrics*. 1997;33:549.

N-TELOPEPTIDE, URINARY (NTX)

DESCRIPTION NTX is a product of type I collagen breakdown that can be measured in the urine. Several studies suggest its utility as a marker for bone turnover in osteoporosis, and for response to treatment of bony metastasis and bisphosphonate therapy. Typical reference ranges are (bone collagen equivalent [BCE]): Normal adult male 21–83 nM BCE/mM creatinine; adult female premenopausal: 17–94 nM BCE/mM creatinine; postmenopausal 26–124 nM BCE/mM creatinine. A decrease of 30–40% from the NTX baseline after 3 mo of therapy is typical for treatment with bisphosphonate.

REFERENCE

Rubin CT, Rubin JE. Biology, physiology, and morphology of bone. In: Harris ED, Budd RC, Genovese MC, et al., eds. *Kelley’s Textbook of Rheumatology*. 7th ed. Philadelphia, PA: Saunders; 2005.

NUTCRACKER SYNDROME

DESCRIPTION This syndrome occurs secondary to compression of the left renal vein by the superior mesenteric artery and the aorta. Patients are usually young and previously healthy. Presentation classically is due to gross hematuria caused by left renal vein hypertension. Pelvic pain may be present. Various modalities, including nephrectomy, autotransplantation, renocaval reimplantation, and venolysis have been employed. Gore-Tex graft renal vein interposition and anterior nephropexy have been successful (Image ☼).

REFERENCE

Wang L, Yi L, Yang L, et al. Diagnosis and surgical treatment of nutcracker syndrome: A single-center experience. *Urology*. 2009;73(4):871–876.

OBESITY, UROLOGIC CONSIDERATIONS

DESCRIPTION It is estimated that 300,000 deaths a year in the United States are associated with elevated body mass index (BMI). Cardiovascular comorbidities of obesity have been well established and there is mounting evidence that obesity impacts a number of urologic diseases. Strong correlations had been shown between obesity in women and stress urinary incontinence (SUI) secondary to increased abdominal pressure. Similarly, obese males have been shown to have increased lower urinary tract symptoms (LUTS). This may be attributable to an increase in adenoma size in BPH, although there is conflicting data regarding the effect of size on symptoms.

A direct link to obesity has also been shown in urologic stone formation. Obese patients with a stone to skin length >10 cm have poorer clearance rates with extracorporeal shock wave lithotripsy (ESWL). In addition, percutaneous nephrolithotomy (PCNL) is limited to patients who are not too obese for standard sheath and nephroscope lengths.

Research has shown an increase number of malignancies in patients who are obese. This is true with some urologic cancers. Prostate cancer has been shown to be more prevalent in obese patients as is adverse pathology. Renal cell carcinoma (RCC) is also associated with obesity.

The increased incidence in prostate cancer in obese men is postulated to result, at least partially, by conversion of testosterone to estradiol in adipocytes. Likewise, this aromatization of androgens leads to decreased fertility in young males. Sexual dysfunction is observed in obese men as a result of increased rates of hypertension, diabetes, and vascular disease. (See also Section II: “Body Mass Index (BMI), Urologic Considerations.”)

REFERENCE

Mydlo JH. The impact of obesity in urology. *Urol Clin N Am.* 2004;31:275–287.

OBTURATOR NERVE INJURY, INTRAOPERATIVE

DESCRIPTION The obturator nerve, which provides motor innervation of medial thigh adductor muscles, can be injured in surgeries involving pelvic lymphadenectomy, such as prostatectomy and cystectomy. In addition, excessive hip flexion or cautery injury during surgery can cause neurapraxia of the obturator nerve. Postoperatively, EMG can be helpful in making the diagnosis. Symptoms include gait disturbance, pain, or anesthesia along the nerve’s sensory distributions along the inner thigh and scrotum. Thigh adduction will be impacted. The incidence of intraoperative obturator nerve injury is not well documented but thought to be rare. When transection of the obturator nerve is identified intraoperatively, surgical repair may be done by end-to-end anastomosis or grafting when achieving tension-free anastomosis is not possible. Nerve transection can be repaired with end-to-end approximation of nerve edges with four 6–0 to 10–nylon or Prolene epineural stitches, using magnification if possible. Efforts must be made to align the nerve fibers prior to approximation. An absorbable collagen implant nerve wrap/protector (NeuraWrap™), can facilitate the repair when applied to the new anastomosis. If the nerve is frayed and grossly devitalized, efforts can be made to trim both segments sharply. In the event of a significant gap, nerve-grafting techniques can be performed at a later date using a sural nerve (which is

a nonessential nerve) graft.

REFERENCE

Spaliviero M, Steinberg AP, Kaouk JH, et al. Laparo-scopic injury and repair of obturator nerve during radical prostatectomy. *Urology.* 2004;64(5):1030.

OBTURATOR REFLEX, UROLOGIC CONSIDERATIONS

DESCRIPTION Stimulation of the obturator nerve during surgical procedures (eg, transurethral resection of bladder tumors located on the posterolateral wall, or laparoscopic pelvic lymph node dissection) can cause unexpected adduction of the thigh. Surgeons must be aware of this response so as not to cause inadvertent injury, such as perforation of the bladder. The response can usually be prevented by muscle-paralyzing anesthetic agents.

REFERENCE

Jones JS, Campbell SC. Non-Muscle-Invasive Bladder Cancer (Ta, T1, and CIS). In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology.* 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.

O'LEARY–SANT SCORES (O'LEARY–SANT INTERSTITIAL CYSTITIS SYMPTOM INDEX [ICSI])

DESCRIPTION The ICSI is a validated questionnaire that documents and scores patient's urinary symptoms as well as the level those symptoms cause a problem in their life. The questionnaire can be administered without the supervision of a professional interviewer. It focuses on the symptoms of urinary urgency, frequency, nocturia, and dysuria/ pain over a 30-day period. It has been found useful as a tool to follow symptoms of but not the diagnosis of interstitial cystitis.

REFERENCE

O'Leary MP, Sant GR, Fowler FJ Jr, et. al. The interstitial cystitis symptom index and problem index. *Urology.* 1997;49(5A Suppl):58–63.

OLIGOASTHENOTERATOSPERMIA

DESCRIPTION Oligoasthenoteratospermia describes very generalized abnormalities in sperm concentration, motility, and morphology. The cause of these combined defects in sperm parameters are commonly caused by the effects of a varicocele (most commonly cited cause), cryptorchidism, and other transient insults such as heat, drugs, or environmental toxins. *Trichomonas* has been implicated in some studies. Treatment involves the removal of potentially offending spermatotoxins and a repeat semen analysis in 3 mo. No good data exist on the use of agents such as bromocriptine, clomiphene citrate, human chorionic gonadotropin (hCG), or tamoxifen. (See also Section I: "Infertility"; Section II: "Semen Analysis, Abnormal Findings and Terminology"; "Semen Analysis, Technique, and Normal Values.")

REFERENCE

Cavallini G, Crippa A, Magli MC, et al. A study to sustain the hypothesis of the multiple genesis of oligoasthenoteratospermia in human idiopathic infertile males. *Biol Reprod.* 2008;79(4):667–673.

OLIGOSPERMIA

DESCRIPTION Oligospermia occurs when sperm density is <20 million/mL or with a total count of <50 million sperm. Severe oligospermia occurs if counts are <10 million/mL, and may be due to hormone deficiency. A count of <20 million/mL is associated with substantially decreased fertility rates. (See also Section I: "Infertility"; Section II: "Semen Analysis, Abnormal Findings and Terminology"; "Semen Analysis Technique, Normal Values.")

REFERENCE

Grimes DA. Oligozoospermia, azoospermia, and other semen-analysis terminology: The need for better science. *Fertil Steril.* 2007;88(6):1491–1494.

OMPHALOCELE-EXSTROPHY OF THE BLADDER—IMPERFORATE ANUS-SPINA BIFIDA DEFECTS (OEIS) COMPLEX

DESCRIPTION This complex represents the most severe end of a spectrum of birth defects, the exstrophy-epispadias sequence, which, in order of increasing severity, includes phallic separation with epispadias, pubic diastasis, vesical exstrophy of the bladder and cloacal exstrophy, and OEIS complex. The incidence of the OEIS complex is rare (1 of 200,000–400,000 pregnancies). Exstrophy of the cloaca includes the persistence and exstrophy of a common cloaca that receives ureters, ileum, and a rudimentary hindgut and is associated with failure of fusion of the genital tubercles and pubic rami. Other anomalies include incomplete development of the lumbosacral vertebrae with spinal dysraphism; imperforate anus; cryptorchidism and epispadias in males; anomalies of the müllerian duct derivatives in females; and a wide range of urinary tract anomalies including renal defects. Omphalocele (a defect in the umbilical ring, through which the peritoneum and an amnion-covered sac herniate) is common, and most patients have a single umbilical artery. The etiology of the OEIS complex is still unclear; single defects in blastogenesis and mutations in homeobox genes, such as *HLXB9*, have been suggested as responsible. Although often fatal, extensive surgical reconstruction has been successful.

REFERENCE

Keppler-Noreuil K. Prenatal ascertainment of OEIS complex/cloacal exstrophy: 15 new cases and literature review. *Am J Med Genet A.* 2007;143A(18):2122–2128.

OPIOID-INDUCED HYPOGONADISM

DESCRIPTION Opioids are a considerable source of drug abuse and addiction worldwide. Chronic use of opiate medication whether under supervision or illicit causes hypogonadism by actions on opioid receptors in the hypothalamus with additional actions of elevating prolactin levels and direct suppression of the pituitary and testes. Testosterone levels have

been decreased as low as 50% after a single dose of opiate. Testosterone levels recover in 24–72 hr but can be suppressed up to a month depending on dose. Hypogonadism induced by opioids can be treated with hormone replacement therapy.

REFERENCE

Reddy RG, Aung T, Karavitaki N, et al. Opioid induced hypogonadism. *BMJ.* 2010;341:605–606.

OPITZ–FRIAS SYNDROME

DESCRIPTION Also called the *G syndrome* (named for 1 of the 1st patients), this condition is due to a defect of midline development, characterized by numerous congenital abnormalities, especially of the face. Many patients have hypertelorism and posteriorly rotated ears; hypospadias is almost always present. Other manifestations include cleft lip and palate, high tracheal bifurcation, duodenal stricture, imperforate anus, lung hypoplasia, and cardiac abnormalities. Inheritance is autosomal dominant with incomplete penetrance. Carriers show minimal abnormalities. It is more common in males, and perinatal mortality is around 30%.

REFERENCE

Conlon BJ, O'Dwyer TH. The G syndrome, Opitz oculo-genital-laryngeal syndrome, Opitz BBB/G syndrome, Opitz-Frias syndrome. *J Laryngol Otol.* 1995;109(3):244–246.

ORAL–FACIAL–DIGITAL (OFD) SYNDROME

DESCRIPTION At least 11 different types of oral–facial–digital (OFD) syndromes have been described. OFD type I is an X-linked dominant condition characterized by malformations of the face, oral cavity, and digits with polycystic kidney disease and variable involvement of the CNS. Facial milia, orofacial defects such as cleft palate, hand deformities, including shortening of the phalanges, and CNS defects are noted. Of urologic interest, renal cystic disease is found that resembles autosomal dominant polycystic kidney disease in appearance and course. Liver and pancreatic cysts may be observed. Polycystic kidney disease occurs in fewer than 50% of individuals with OFD type 1; the exact frequency is unknown. Renal cysts can develop from both tubules and glomeruli. The age of onset is most often in adulthood, but renal cysts in children have been described. ESRD has been reported in affected girls and women ranging in age from 11–70 yr. Recently it has been emphasized that the risk for significant renal disease may be greater than previously reported. Close monitoring of renal function if renal cystic disease present and renal replacement therapy, as needed.

REFERENCE

Toprak O, Uzum A, Cirit M, et al. Oral-facial-digital syndrome type 1, Caroli's disease and cystic renal disease. *Nephrol Dialys Transplant.* 2006;21(6):1705–1709.

ORCHITIS, GRANULOMATOUS

DESCRIPTION This condition encompasses a group of disorders that have similar clinical and pathologic findings. It is usually of sudden clinical onset during the 6th–7th decades of life. The patient may complain of a painful and swollen scrotum, and occasionally fever

and/or skin changes may be present. Often, the diagnosis is rendered postoperatively after inguinal orchiectomy is performed for presumed malignancy and histology shows chronic inflammation with granuloma. The most common cause is *Mycobacterium tuberculosis*. Less commonly, brucellosis, actinomycosis, and sarcoidosis are found. The condition can be a rare complication of intravesical bacillus calmette-Guérin therapy for urothelial cancer. If TB is suspected, antitubercular chemotherapy is warranted, with operative treatment for medical failures. For other causes, medical and/or surgical therapy can be utilized.

REFERENCE

Harving SS, Asmussen L, Roosen JU, et al. Granulomatous epididymo-orchitis, a rare complication of intravesical bacillus Calmette-Guérin therapy for urothelial cancer. *Scand J Urol Nephrol.* 2009;24:1–3.

ORGASMIC PAIN (PAINFUL EJACULATION)

DESCRIPTION Pain associated with ejaculation and orgasm is widely underreported. The nature, duration, and location of the pain can vary widely between patients. The exact cause of the pain is unknown but can be related to previous surgery (including RP), ejaculatory duct stones, pudendal nerve neuropathy, and antidepressant medications. Treatments include the use of conservative measures, anti-inflammatory medications, α-blockers, topiramate, steroid injections, relief of seminal duct obstruction, and surgical interventions such as neurolysis and fasciotomy of Alcock canal. (See also Section I: “Ejaculatory Disturbances [Delayed, Decreased, or Absent].”)

REFERENCE

Ilie CP, Mischianu DL, Pemberton RJ. Painful ejaculation. *BJU Int.* 2007;99:1335–1339.

ORTHO-PHTHALALDEHYDE (OPA) CHEMICAL DISINFECTANT

DESCRIPTION OPA 0.55% is a chemical disinfectant for instruments such as cystoscopes. It can irritate eyes, skin, nose, and other tissues. OPA is FDA approved as a high-level disinfectant (12 min at 20°C and 5 min at 25°C). Anaphylactic reactions have been reported in patients with bladder cancer who underwent repeated cystoscopy with scopes sterilized with OPA. OPA is contraindicated in patients with a history of bladder cancer but can be used in manual or automated reprocessing protocols.

REFERENCE

http://www.auanet.org/education/guidelines/flexible-cystoscopes.cfm, Accessed January 25, 2014.

OSSIFYING RENAL TUMOR OF INFANCY

DESCRIPTION Rare, calcified tumor of infancy, usually resembling a renal pelvis calculus. Occurs usually in 1st year of life, with gross hematuria as the most common presenting symptom. Anatomic and histologic origins are unclear but are thought to be of urothelial origin. Lesions are apparently benign, with no reported cases of recurrence or metastasis. Surgical enucleation with renal-sparing procedure is the treatment, with careful follow-up

using renal sonograms, as necessary.

REFERENCE

Hu J, Wu Y, Qi J, et al. Ossifying renal tumor of infancy (ORTI): A case report and review of the literature. *J Pediatr Surg.* 2013;48(2):e37–e40.

OSTEONECROSIS OF THE JAW (ONJ), UROLOGIC CONSIDERATIONS

DESCRIPTION Osteonecrosis is a newly recognized complication of long-term therapy with bone strengthening agents in patients with metastatic cancer to the bone such as prostate, breast and renal cell carcinoma and in multiple myeloma. Bisphosphonates and denosumab decrease cancer-induced bone resorption thereby reducing SREs, pain, and improving quality of life. Initially identified as bisphosphonate-induced ONJ, it now recognized as a potential complication of denosumab as well. ONJ is classified as exposed necrotic maxillofacial bones for >8 wk in patients treated with bisphosphonates or denosumab who have not had radiation to the jaws. The exposed bone becomes infected with oral flora resulting in significant pain and need for oral surgery. A new term is bisphosphonate-related osteonecrosis of the jaws (BRONJ). Symptoms include pain, swelling, redness, or other signs of infection in the gums; gums or sockets that don't heal after dental work; loose teeth and numbness or a heavy feeling in the jaw. The risk of developing ONJ is related to the potency of the antiresorptive, the duration of exposure, and dentoalveolar trauma. Prospective studies of patients taking bisphosphonates for metastatic prostate cancer that include regular exam by dentists estimate an incidence as high as 20% which is much higher than retrospective studies that suggested an incidence of 3–6%. Dental clearance before initiating therapy is recommended as well as avoiding extensive dental work while on therapy.

REFERENCE

Walter C, Al-Nawas B, Grötz KA, et al. Prevalence and risk factors of bisphosphonate – associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with Zoledronate. *Eur Urol.* 2008;54:1066–1072.

OSTEOPOROSIS AND OSTEOPENIA, UROLOGIC CONSIDERATIONS

DESCRIPTION Osteoporosis and osteopenia are conditions of decreased bone mineral density (BMD) that lead to an increased risk of fracture. Although traditional emphasis has been placed on diagnosing osteoporosis in women, as the male population ages, increased numbers of men are at risk for developing skelet al fractures. In addition, more men are being placed on long-term androgen-deprivation therapy (orchiectomy of LHRH analog) as treatment for prostate cancer, which further increases the risk for osteopenia and osteoporosis. A DEXA scan can be used prior to treatment to measure BMD. Central DEXA is the gold standard and measures the spine and hip BMD. The T-score is the number of SDs by which the patient's bone mass falls above or below the mean peak bone mass for a 30-yr-old healthy adult. For every 1 SD decrease in T-score, relative risk of fracture increases ~1.5–2.5-fold. According to the National Osteoporosis Foundation, a normal T-score is >–1, osteopenia is –1 to –2.5, and osteoporosis is <–2.5. Further, it is recognized that, in addition to cancer treatment–induced bone loss, many men may suffer skelet al related events (SRE's) as a

consequence of bony metastatic disease. Improving BMD may also decrease SREs (radiation for bone pain or to treat pathologic fractures or spinal cord compression, pathologic fractures, spinal cord compression, and vertebral body collapse or surgery to bone). (See also Section II: "Bone Mineral Density, Urologic Considerations.")

TREATMENT

- Calcium: 1,200 mg/d; it is recommended most cal-cium come from foods (dairy, green leafy vegetables)
- Vitamin D: At least 800–1,000 IU/d preferable from foods (fatty fish and oils, liver, fortified milk) with sun exposure of 30 min/d or supplements
- Exercise to include weight bearing
- Stop smoking; limit alcohol and caffeine
- Consider bisphosphonates:
  - Alendronate (Fosamax, Fosamax Plus D) approved for treatment of men with osteoporosis and treatment/prevention of osteoporosis in men taking glucocorticoids
  - Risedronate (Actonel, Atelvia) approved for treatment of men with osteoporosis and treatment/prevention of osteoporosis in men taking glucocorticoids.
  - Pamidronate (Aredia) for men with Paget disease, hypercalcemia of malignancy, malignant myeloma
  - Zoledronic acid (Zometa); 4 mg/monthly IV approved for bony metastasis but not male osteoporosis
  - Zoledronic acid (Reclast); 5 mg/yr IV in men with Paget disease and osteoporosis
- Consider denosumab: Injectable monoclonal antibody to RANK ligand, decreases osteoclast activity
  - Prolia: Men on ADT or osteoporosis 60 mg SC Q 6 mo
  - Xgeva : Men with metastasis, not men with osteoporosis: 120 mg SC Q every 4 wk.

REFERENCES

National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis. Online guidelines. Available at http://www.nof.org/hcp/practice/practice-and-clinical-guidelines/clinicians-guide, Accessed March 17, 2013.

Tombal B. Practical guide to bone health in spectrum of advanced prostate cancer. *Can J Urol.* 2014;21(2 Suppl 1):84–92.

OSTEOTOMY, UROLOGIC CONSIDERATIONS

DESCRIPTION Osteotomy is the surgical techn-ique of cutting bone to its shape, length, or alignment. This becomes of particular necessity in surgical repair of bladder exstrophy to correct a wide pubic diastasis. Advantages of pelvic osteotomy include decreased bladder dehiscence, improved continence, and less late pelvic organ prolapse in females.

REFERENCE

Vining NC, Song KM, Grady RW. Classic bladder exstrophy: Orthopaedic surgical considerations. *J Am Acad Orthop Surg.* 2011;19:518–526.

OVARIAN CANCER, UROLOGIC CONSIDERATIONS

DESCRIPTION Ovarian cancer is the leading cause of death from gynecologic cancer and is usually of epithelial origin. These tumors can often involve adjacent structures or cause extrinsic compression of the urinary tract, including the bladder and ureters, with the resultant need for urologic intervention.

REFERENCE

Coleman RL, Gershenson DM. Neoplastic diseases of the ovary: Screening, benign and malignant epithelial and germ cell neoplasms, sex-cord stromal tumors. In: Katz VL, et al., eds. *Comprehensive Gynecology*. 5th ed. St. Louis, MO: Mosby; 2007.

OVARIAN REMNANT SYNDROME

DESCRIPTION This condition is a rare complication of bilateral oophorectomy and occurs when remnants of ovarian cortex are inadvertently left behind. The remaining ovarian tissue becomes functional and cystic. Typically, patients present with pelvic pain that can be chronic or intermittent and a pelvic mass. Symptoms may begin weeks to 5 yr postoperatively. Ureteral obstruction has been reported. Excision of the ovarian remnant is the most widely accepted treatment method. Preoperative ovarian stimulation can help intraoperative identification of retained tissue. Surgery is associated with an 8–10% recurrence rate.

REFERENCES

Kho RM, Abrao MS. Ovarian remnant syndrome: Etiology, diagnosis, treatment and impact of endometriosis. *Curr Opin Obstet Gynecol.* 2012;24(4):210–214.

Magtibay PM, Magrina JF. Ovarian remnant syndrome. *Clin Obstet Gynecol.* 2006;49(3):526–534.

OVARIAN VEIN SYNDROME

DESCRIPTION Ureteral obstruction, usually right-sided, occurring secondary to occlusion by dilated ovarian veins. The ovarian veins lie adjacent to the ureters, and dilation of these veins, especially during pregnancy, is thought to result in ureteral obstruction. The obstruction is usually seen around the L3–L4 vertebral level. Symptoms include chronic flank pain, but colicky pain has also been found. The symptoms can also begin several days prior to menses and then regress. Diagnosis can be made by IV urogram, retrograde ureteropyelogram, and simultaneous angiography. Ureterolysis and ovarian vein resection can be performed using open or laparoscopic techniques.

REFERENCE

Sato F, Nomura T, Shin T, et al. Retroperitoneoscopic treatment of ovarian vein syndrome. *J Laparoendosc Adv Surg Tech A.* 2008;18(5):739–742.

OXALATE-ASSOCIATED RENAL DISEASE

DESCRIPTION Hyperoxaluria is associated with calcium oxalate nephrolithiasis. An increased oxalate production or absorption, or an idiopathic form, might be responsible for the disease. In cases of primary hyperoxaluria, stone formation usually starts during

childhood, with eventual tubulointerstitial nephropathy and chronic renal failure. Oxalate deposition in heart, joints, and other tissues (*oxalosis*) may occur. (See Section II: "Hyperoxaluria," for the causes of increased urinary oxylate.)

TREATMENT

- Pyridoxine supplements (200–400 mg/d) for primary hyperoxaluria
- Oral hydration; low-oxalate, low-fat diet for enteric hyperoxaluria
- Pyridoxine and thiazides for idiopathic hyperoxaluria

REFERENCES

Danpure CJ. Molecular and cell biology of primary hyperoxaluria type I. *Clin Invest Med.* 1994;72:725.

Scheinman JI. Primary hyperoxaluria: Therapeutic strategies for the 90s. *Kidney Int.* 1991;40:389–399.

OXALATE, DIETARY

DESCRIPTION An excessive intake of oxalate-rich products, should be limited or avoided to prevent an oxalate load. This includes fruits and vegetables rich in oxalate such as wheat bran. This is particularly important in patients in whom an high oxalate excretion has been demonstrated. Vitamin C is a precursor of oxalate, but its role as a risk factor in calcium oxalate stone formation remains controversial. Some studies have shown that a daily intake of up to 4 g might be allowed without risk. However, a recent study demonstrated an increased risk in stone formation for men taking 1 g/d or more of vitamin C vs. <90 mg. It therefore seems justified to advise calcium oxalate stone formers to avoid excessive intake of vitamin C. (See also Section I: "Urolithiasis, Calcium Oxalate/Phosphate.") The following products have high oxalate content:

- Rhubarb, 530 mg oxalate/100 g
- Spinach, 570 mg oxalate/100 g
- Cocoa, 625 mg oxalate/100 g
- Tea leaves, 375–1,450 mg oxalate/100 g
- Nuts, 200–600 mg oxalate/100 g

REFERENCE

Tiselius HG, Alken P, Buck C, et al. EAU Guidelines on Urolithiasis. http://www.uroweb.org/fileadmin/user_upload/Guidelines/Urolithiasis.pdf, Accessed April 6, 2014.

P53, UROLOGIC CONSIDERATIONS

DESCRIPTION The p53 gene produces a nuclear phosphorylation protein that has a tumor-suppression function. Loss of wild-type p53 is the most common genetic abnormality associated with TCC. Its presence is associated with high grade, late stage, and relapse. Potentially, it may be useful in grading tumors. In prostate cancer, p53 is associated with an increased probability of biochemical relapse and is found in a higher percentage of hormone-refractory cancers.

REFERENCE

Minimo C, Tawfiek ER, Bagley DH, et al. Grading of upper urinary tract transitional cell carcinoma by computed DNA content and p53 expression. *Urology*. 1997;50:869–874.

PAD TESTING

DESCRIPTION Used as a clinical tool to assess the severity of urinary incontinence, often in association with a micturition diary. The pad test provides a gross/semi-quantitative measurement of urine loss over a given period of time. Several types have been described, but none has met with widespread approval. 1 technique has a patient take Pyridium 200 mg TID and then change pads every 6 hr for a 24-hr period. The amount of staining is an estimate of incontinence. Another approach is to weigh the pads (1 g = 1-mL urine).

REFERENCE

Ryhammer AM, Djurhuus JC, Laurberg S. Pad testing in incontinent women: A review. *Int Urogynecol J Pelvic Floor Dysfunct.* 1999;10(2):111–115.

PAGANO URETERAL ANASTOMOSIS

DESCRIPTION A 4–5-cm linear incision is made through the taenia of the colon, and the mucosa is dissected from the submucosa to the level of the mesentery. The ureters are pulled through the lateral muscular wall and implanted distally into the mucosa. The serosa is reapproximated while incorporating mucosa in the midline.

REFERENCE

Pagano F. Ureterocolonic anastomosis: Description of a technique. *J Urol.* 1980;123(3):355–356.

PAGE KIDNEY

DESCRIPTION This condition was 1st described in 1939, after hypertension was created by wrapping cellophane around a canine kidney. Applied clinically, this term was given to hypertension secondary to subcapsular or perirenal compression resulting in renal ischemia. Elevated renin secretion from the compromised kidney and decreased renin production from the contralateral renal unit result. Diagnosis can be made with US, CT, or MRI, demonstrating a surrounding hematoma or fibrous capsule. Clinical causes include blunt trauma, closed renal biopsy, anticoagulation, or tumor bleed. Treatment is directed at the primary cause.

Further therapy may include ACE inhibitors, open or percutaneous drainage, or nephrectomy. Spontaneous resolution can occur secondary to reabsorption of the hematoma.

REFERENCE

Sterns RH, Rabinowitz R, Segal AJ, et al. "Page kidney." Hypertension caused by chronic subcapsular hematoma. *Arch Intern Med.* 1985;145(1):169–171.

PAGET DISEASE, ANOGENITAL/EXTRAMAMMARY

DESCRIPTION Extramammary Paget disease is an adenocarcinoma of the epidermis that can exist in numerous areas, including the penis, scrotum, bladder, vulva, perianal area, umbilicus, axilla, and conjunctiva. An underlying adnexal neoplasm is associated 1/2 the time with an increased risk of other malignancies. Generally considered an adenocarcinoma that occurs in apocrine gland areas of the body, the mammary type originates from lactiferous ducts and extends into epidermis. The anogenital type is usually slow growing and resembles dermatitis clinically, rarely involving the penile or scrotal skin. Often associated with underlying carcinoma such as bladder, prostate, and urethral cancers. Typically presents in the 60s or 70s with lesions that appear as crusted, indurated, erythematous to whitish patches. Histologically, the intraepithelial neoplastic cells contain mucin and are PAS positive. Differential diagnosis includes SCC in situ or malignant melanoma. The lesions originate from pluripotent cells in epidermis that formed apocrine glands and may also result from extracutaneous adenocarcinoma that spread into the epidermis. Excision of skin lesion and evaluation for underlying malignancy should be performed.

REFERENCE

Balducci L, Crawford ED, Smith GF, et al. Extramammary Paget's disease: An annotated review. *Cancer Invest.* 1988;6:293–303.

PAGET DISEASE, BONE

DESCRIPTION This condition affects up 10% of elderly individuals, with a 3:1 male-to-female ratio. Bone pain is the most common presenting symptom. Paget disease of the spine may also be a cause of low back pain. The disorder is due to increased bone remodeling, bone hypertrophy, and bone deformity of uncertain origin. Paget disease, also called *osteitis deformans,* is characterized by an initial phase of intense osteoclastic resorption, followed by an increase in bone formation, but the new skelet al tissues are deformed and prone to inducing pain and fracture. Approximately 1/3 of Paget disease cases have monostotic disease, with pelvic involvement in 72%. In these cases, the lumbar spine is involved in 58%, the thoracic spine in 45%, and the femur and skull in 55% and 42%, respectively. Patients' elevated alkaline phosphatase or bone pain may be due to Paget disease or other diseases, such as liver disease, renal disease, or metastatic prostate cancer. Radiographically, the localized enlargement of bone is a characteristic feature. Areas of lysis due to osteoclastic reabsorption can also be present. It can be confused with metastatic prostate cancer to bone. Suspect Paget disease over metastatic prostate cancer when there is widening of the bone, thickening of the cortex, and a prominent trabecular pattern. MRI of the bone may help in differentiating the processes.

TREATMENT

- Pain reduction and decreasing long-term complications are the main goals.
- Inhibitors of osteoclastic bone resorption, such as bisphosphonates (zoledronic acid, risedronate, alendronate) are now the treatment of choice. (See Section II: "Osteoporosis and Osteopenia, Urologic Considerations.") Calcitonin is reserved for those intolerant of bisphosphonates.

REFERENCE

Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. *Lancet.* 2008;12;372(9633):155–163.

PAINFUL BLADDER SYNDROME (PBS)

DESCRIPTION The ICS defines PBS as suprapubic pain related to bladder filling, accompanied by other symptoms such as increased day- and night-time frequency, in the absence of proven urinary infection or other obvious pathology. According to the ICS, PBS differs from interstitial cystitis in that the latter has cystoscopic and histologic findings. Treatment begins with conservative measures including dietary modifications, behavioral changes, and nonprescription medications, followed by intravesical therapy and prescription medications. Patients who fail these therapies can move to more invasive therapies including hydrodistention, neuromodulation, and finally urinary diversion or augmentation.

REFERENCE

Chuang YC, Chancellor MB. Treatment of painful bladder syndrome and pelvic organ prolapse: Highlights of the 4th international consultation on incontinence, July 5–8, 2008, Paris, France. *Rev Urol.* 2009;11(1):28–32.

PALLIATIVE RADIATION, UROLOGIC CONSIDERATIONS

DESCRIPTION The symptoms of advanced urologic malignancies are often treated with palliative radiation. Approximately 1/2 of prescribed radiotherapy is given for palliation of symptoms from incurable cancer. For example, 90% of patients with symptomatic bone metastases, commonly seen in metastatic prostate cancer, obtain some pain relief with a low-dose, brief course of palliative radiotherapy. Bone metastases can also result in erosion of cortical bone and tumor invasion into the extradural space, which elicits edema within the spinal cord and compression of the neurologic structures. The degree of edema within the cord is directly related to the neurologic impairment. Spinal cord compression from malignancy requires early diagnosis and treatment with emergency radiotherapy to prevent irreversible neurologic injury. Radiation therapy has also been shown to relieve clinical symptoms in 70–90% of patients with brain metastases, sometimes seen in patients with metastatic RCC.

REFERENCE

Hoegler D. Radiotherapy for palliation of symptoms in incurable cancer. *Curr Probl Cancer.* 1997;21(3):129–183.

PANCREATITIS, AUTOIMMUNE UROLOGIC CONSIDERATIONS

DESCRIPTION Autoimmune pancreatitis (AIP) has been referred to by a variety of names including sclerosing pancreatitis, tumefactive pancreatitis, and nonalcoholic destructive pancreatitis. It is recognized to be an immunoglobulin G4-related disease (IgG4-RD). IgG4-related kidney disease can include tubulointerstitial nephritis and membranous glomerulonephritis.

REFERENCE

Khosroshahi A, Stone JH. A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol.* 2011;23(1):57–66.

PANETH CELL-LIKE CHANGE, PROSTATE

DESCRIPTION Describes the observation of prostatic glandular epithelium with distinct eosinophilic intracytoplasmic granules resembling Paneth cells, found in crypts of Lieberkühn in the small intestine. These cells are thought to represent a morphologic similarity to Paneth cells, rather than true Paneth cell metaplasia of the prostatic epithelium, due to the presence of PSA and PAP on immunohisto-chemistry. These changes have been described in normal, hyperplastic, dysplastic, and malignant prostate tissue, and must be differentiated from other prostatic intracytoplasmic inclusions including secretory vacuoles, melanin, CMV viral inclusions, or virus-like particles.

REFERENCE

Weaver MG, Abdul-Karim FW, Srigley J, et al. Paneth cell-like change of the prostate gland. *Am J Surg Pathol.* 1992;16(1):62–68.

PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL (PUNLMP)

DESCRIPTION The World Health Organization defines PUNLMP as a papillary urothelial tumor that resembles an exophytic urothelial papilloma, but shows increased cellular proliferation exceeding the thickness of normal urothelium. They are typically small (1–2 cm) and have little, if any, cytologic atypia. Treatment and follow-up are the same as for low-grade noninvasive urothelial carcinoma. (See also Section II: “WHO/ISUP Classification of Urothelial Neoplasms” [1998 and 2004].) (Image ☼)

REFERENCE

Eble JN, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon: IARC Press; 2004.

PAPILLOMA, BLADDER

DESCRIPTION A controversial diagnostic entity of the urinary bladder. The papillary lesion is small and unifocal, with a delicate fibrovascular stalk, and covered in cytologically and architecturally normal urothelium. Typically found in a younger age group than bladder cancer. Recurrences are common, and future development of invasive urothelial tumors of the

urinary tract occurs in <10%. Many consider the lesion to be a very low-grade bladder cancer (grade I TCC) with limited potential to progress. Others propose that the terms low- and high-grade papillary urothelial carcinoma be replaced by low- and high-grade papillary intraurothelial neoplasia for all noninvasive urothelial cancers. (See also Section II: "WHO/ISUP Classification of Urothelial Neoplasms" [1998 and 2004].) (Image)

SYNONYMS
- WHO grade I papillary urothelial carcinoma
- Urothelial papilloma

TREATMENT
- Transurethral surgical resection is the main modality, with no defined role for intravesical therapy.
- These patients must be followed, due to the possible increased risk of having a urothelial malignancy.

REFERENCE
Van der Kwast TH, Zlotta AR, Fleshner N, et al. Thirty-five years of noninvasive bladder carcinoma: A plea for the use of papillary intraurothelial neoplasia as new terminology. *Anal Quant Cytol Histol.* 2008;30(6):309–315.

PAPILLOMA, RENAL PELVIS

DESCRIPTION An extraordinarily rare urothelial lesion in the upper urinary tract. A papilloma is a small, delicate proliferation with a fibrovascular core lined by normal urothelium. By WHO criteria, this is considered a benign lesion.

REFERENCE
Eble JN, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon: IARC Press, 2004.

PAPILLORENAL SYNDROME

DESCRIPTION Also called *renal coloboma,* this is an autosomal dominant disorder characterized by bilateral congenital optic disc anomalies and hypoplastic kidneys. It is associated with mutations in the PAX2 gene. Many patients suffer from renal failure due to renal hypoplasia or chronic pyelonephritis from vesicoureteral reflux.

REFERENCE
Nguyen D, Riordan-Eva P. Abnormal optic discs and renal failure: Papillorenal syndrome. *Acta Ophthalmol Scand.* 2006;84:823–824.

PAQUIN URETERAL REIMPLANTATION

DESCRIPTION This repair is done using combined extravesical ureteral mobilization and intravesical implantation. A submucosal plane is developed toward the trigone with tenotomy scissors, and the freshly spatulated ureter is reimplanted.

REFERENCE
Atala A, Keating MA. Vesicoureteral reflux and megaureter. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders, 1998:1882–1896.

PARAPHILIAS, UROLOGIC CONSIDERATIONS

DESCRIPTION Paraphilias are psychosocial conditions referring to abnormal sexual behavior. These may be encountered in daily urologic practice and are often referred for psychologic intervention. Different kinds of paraphilias, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR) classification are noted in the accompanying table.

SYNONYM
Sexual Deviation

Paraphilia Designation	Description
Exhibitionism	Exposure of genital to unsuspecting strangers (not considered the same as public urination).
Fetishism	Use of nonliving objects as repeatedly preferred or exclusive method of sexual excitement (eg, leather goods, clothing, undergarments, fabrics, shoes). (If female clothing is used in cross-dressing or devices are used for genital stimulation [eg, vibrator] this is not considered as fetishism).
Frotteurism	Touching and rubbing against a nonconsenting person.
Pedophilia	Children are the sexual target (perpetrator is ≥16 yo and ≥5 than 5 years older than the prepubescent child).
Sexual masochism	Perpetrator receives the humiliation/suffering (practice can lead to death, especially during "hypoxyphilia" or sexual arousal during hypoxia).
Sexual sadism	Perpetrator inflicts the humiliation/suffering on another.
Transvestic fetishism	Wearing clothing of the other sex for sexual arousal.
Voyeurism	Observing sexual activity or naked/disrobing individuals.
Paraphilias Not Otherwise Specified	Paraphilias that do not meet criteria for a specific DSM category such as telephone scatologia or coprolalia (obscene phone calls), necrophilia (corpses), partialism [exclusive focus on part of body], zoophilia [animals], coprophilia [feces], klismaphilia [enemas], and urophilia [urine]).

REFERENCE
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision (DSM-IV-TR) Arlington VA (2000).

PARASTOMAL HERNIA

DESCRIPTION A parastomal hernia is an incisional hernia related to an abdominal wall stoma. In urologic surgery, parastomal hernias occur infrequently (<5% of cases) and are more likely to arise in loop-type stomas than in end-type stomas. To prevent parastomal herniation, it is recommended that the stoma be placed through the rectus muscle and that the opening in the abdominal wall not be too large. In addition, some have placed mesh at the time of stoma creation to prevent hernia formation. Repair of a parastomal hernia follows the same principles as treating other types of incisional hernias and can be completed in an open or laparoscopic fashion, with or without mesh. (See also Section I: "Urostomy Problems.")

REFERENCE

Israelsson LA. Parastomal hernias. *Surg Clin N Am.* 2008;88:113–125.

PARATESTICULAR RHABDOMYOSARCOMA

DESCRIPTION Rhabdomyosarcoma is the most common spermatic cord sarcoma, arising from the mesenchymal elements of the paratesticular tissues and representing 40% of all paratesticular malignancies and 5% of all testicular and paratesticular malignancies. There is a bimodal age distribution, with peaks at 3–4 mo and yr. Patients present with a painless firm mass which can be a wide range of sizes. Roughly 40% have metastases at presentation. Ultrasounds reveals a heterogeneous mass. CT scan of the abdomen and pelvis, liver function tests, bone scan, and chest x-ray are required for staging. Several histologic patterns are described, with almost all being embryonal. After treatment, cross-sectional imaging and liver function tests are needed every 2–3 mo. (See also Section I: "Tunica Albuginea/Paratesticular Tumors and Cysts.")

TREATMENT

- Radical orchiectomy
- Boys 10 yr or older or those with evidence of retroperitoneal disease should undergo retroperitoneal lymph node dissection (RPLND)
- Those with evidence of lymphatic spread should undergo radiotherapy and multiagent chemotherapy

REFERENCE

Ahmed HU, Arya M, Muneer A, et al. Testicular and paratesticular tumours in the prepubertal population. *Lancet Oncol.* 2010;11(5):476–483.

PARAURETHRAL AND VAGINAL WALL MASSES

DESCRIPTION Paraurethral masses can be benign (urethral caruncles, Skene's gland abscess/cysts, mucosal prolapsed, ectopic ureterocele, urethral diverticulum, vaginal wall cyst, Gartner's duct cyst, leiomyoma, and hamartoma) or malignant (adenocarcinoma, SCC, TCC, histiocytoma, and sarcoma) and treatment varies upon the etiology of the lesion. The most common paraurethral mass is the urethral diverticulum, followed by the leiomyoma and the vaginal wall cyst. Masses may be asymptomatic or may cause pain and voiding

dysfunction. VCUG, MRI, CT, and double-balloon retrograde urography all have a high detection rate for urethral diverticula. Videourodynamics and cystoscopy are useful tools, particularly for masses causing voiding dysfunction. Physical exam may help distinguish benign from malignant conditions. Urethral malignancies do not normally present as paraurethral masses, but more commonly with complaints of bleeding and discharge.

REFERENCE

Blaivas JG, Flisser AJ, Bleustein CB, et al. Periurethral masses: Etiology and diagnosis in a large series of women. *Obstet Gynecol.* 2004;103(5 Pt 1):842–847.

PARTIN TABLES

DESCRIPTION Nomograms for patients with biopsy-proven prostate cancer, developed by Dr. Partin and associates at Johns Hopkins University, these charts incorporate PSA, TNM stage, and Gleason score. They are used to predict rate of lymph node and distant spread or whether patients have organ-confined cancer, and to aid in making accurate treatment decisions. The tables have been updated several times, using larger patient cohorts. Information is available online: http://urology.jhu.edu/prostate/partintables.php, Accessed March 3, 2014.

REFERENCE

Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int.* 2013;111(1):22–29. Erratum in: *BJU Int.* 2013;111(3):524.

PATAU SYNDROME

DESCRIPTION This rare syndrome is associated with trisomy 13 and has a median survival of 3 mo. The incidence is 1 in 6,000 live births and is associated with multiple cardiac, neurologic, and renal abnormalities. Renal anomalies occur in about 80% of children. Unilateral renal agenesis, renal duplication, hydronephrosis, and polycystic kidneys have been associated with Patau syndrome.

REFERENCE

Martlew RA, Sharples A. Anesthesia in a child with Patau's syndrome. *Anesthesia.* 1995;50:980.

PATIENT PERCEPTION OF BLADDER CONDITION (PPBC)

DESCRIPTION The Patient Perception of Bladder Condition (PPBC) is a questionnaire that attempts to obtain a global assessment of the patient's bladder condition. It has been validated and shown to be responsive to changes. It has been translated into many languages and is widely available for use.

Which of the following statements describes your bladder condition best at the moment? Please mark X in 1 box only.
• My bladder condition does not cause me any problems at all. (1 pt)
• My bladder condition causes me some very minor problems. (2 pt)
• My bladder condition causes me some minor problems. (3 pt)
• My bladder condition causes me (some) moderate problems. (4 pt)
• My bladder condition causes me severe problems. (5 pt)
• My bladder condition causes me many severe problems. (6 pt)

REFERENCE

Coyne KS, Matza LS, Kopp Z, et al. The validation of the patient perception of bladder condition (PPBC): A single-item global measure for patients with overactive bladder. *Eur Urol*. 2006;49:1079–1086.

PATIENT PERCEPTION OF INTENSITY OF URGENCY SCALE (PPIUS)

DESCRIPTION A single-question tool to assess the patient's perception of the degree of urgency. PPIUS as a reliable measure of urgency in both clinical trials and real life settings. The question is as follows:

Patient Perception of Intensity of Urgency Scale	
0.	No urgency: I felt no need to empty my bladder but did so for other reasons.
1.	Mild urgency: I could postpone voiding as long as necessary without fear of wetting myself.
2.	Moderate urgency: I could postpone voiding for a short while without fear of wetting myself.
3.	Severe urgency: I could not postpone voiding but had to rush to the toilet in order not to wet myself.
4.	Urge incontinence: I leaked before arriving at the toilet.

REFERENCE

Notte S, Marshall TS, Lee M, et al. Content validity and test-retest reliability of patient perception of intensity of urgency scale (PPIUS) for overactive bladder. *BMC Urology*. 2012;12:26.

PCA3 (PROSTATE CANCER GENE 3 URINE ASSAY)

DESCRIPTION Prostate cancer antigen 3 (PCA3) is a gene that expresses a noncoding RNA. PCA3 is over expressed in 95% of prostate cancers and is upregulated 66-fold in cancerous tissue as compared to normal tissue. No other human tissues have yet been shown to produce PCA3. While serum PSA levels are known to be influenced by volume of BPH tissue, age, inflammation, trauma, and use of 5α-reductase inhibitors (finasteride, dutasteride), preliminary data indicate that these factors do not appear to influence PCA3 scores. Urine samples are collected after an "attentive" digital rectal exam (3 sweeps on each side of the prostate). 1st voided urine is then collected and sent to labs for analysis. PCA3 and PSA can

be detected in the urine utilizing reverse transcriptase PCR techniques on the collected cells. PCA3 expression is denoted against a background of prostate-specific genetic material, a PCA3 score (ie, a ratio of PCA3 to PSA mRNA). Studies have shown excellent specificity and sensitivity in men undergoing confirmatory prostate biopsy, and its role in the diagnosis of prostate cancer is currently evolving. A useful role of the new marker appears to be in men with persistently elevated serum PSA levels, but a negative initial biopsy.

PCA3/PSA mRNA Ratio vs. Serum PSA in Men with Previous Negative Biopsy

	Serum PSA	PCA3 Assay
Cut Point	4.0 ng/mL	PCA3/PSA = 35×10^{-3}
Sensitivity	83%	58%
Specificity	17%	74%
Odds Ratio of a Positive Rebiopsy	1.2	3.6

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group in 2013 found insufficient evidence to recommend PCA3 testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men. (See Also Section II: "Attentive Digital Rectal Exam (DRE)," "TMPRSS2-ERG Gene Fusion, Prostate Cancer," "Attentive Digital Rectal Exam Image." ☼)

REFERENCES

Groskopf J, Aubin SM, Deras IL, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem*. 2006;52:1089–1095.

Parekh DJ, Ankerst DP, Troyer D, et al. Biomarkers for prostate cancer detection. *J Urol*. 2007;178:2252–2259.

Recommendations from the EGAPP Working Group: does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes? Genetics in Medicine (2013) doi:10.1038/gim.2013.141 Published online 26 September 2013.

PEARLY PAPULES OF PENIS

DESCRIPTION These are normal anatomic structures located on the proximal glans penis or corona. They appear as minute, dome-shaped, flesh-colored papules. The incidence is 19–30%. These lesions are asymptomatic and can be confused with genital warts. Histologically, these papules are angio-fibromas. No treatment is usually needed. Although these lesions represent a benign condition, psychological and cosmetic concerns often prompt patients to seek therapeutic removal. Multiple therapeutic modalities have been reported; however, use of CO_2 laser has proven to be the most effective to date.

REFERENCE

Lane JE, Peterson CM, Ratz JL. Treatment of pearly penile papules with CO_2 laser. *Dermatol Surg*. 2002;28(7):617–618.

PEDIATRIC-MODIFIED RISK INJURY FAILURE LOSS END-STAGE RENAL DISEASE (pRIFLE)

DESCRIPTION Acute kidney injury (AKI) is defined as a decrease in GFR, manifested by an elevated or rising creatinine. However, serum creatinine is often a delayed and imprecise test as it reflects GFR in individuals at steady state with stable kidney function, and may not estimate the GFR in a patient whose renal function is changing. Recognizing a need for a consensus definition of AKI called the RIFLE classification of AKI based on changes in creatinine and urine output were developed. The RIFLE criteria consists of 3 graded levels of injury (Risk, Injury, and Failure) based upon either the magnitude of elevation in serum creatinine or urine output, and 2 outcome measures (Loss and End-stage renal disease). This is a pediatric modification of the adult RIFLE classification (see table). The use of pRIFLE has been strongly advocated as a research and clinical tool. AKI defined by the pRIFLE criteria has been shown as an independent risk factor for mortality and morbidity. (See also Section I: "Acute Kidney Injury, Pediatric [Renal Failure, Acute].")

REFERENCE

Akcan-Arikan A, Zappitelli M, Loftis LL, et al. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int.* 2007;71(10):1028–1035.

Pediatric Rifle (pRIFLE) Classification of Acute Kidney Injury

pRIFLE Stage	Estimated Creatinine Clearance (eCCl)	Urine Output
R = Risk for renal dysfunction	eCCl decreased by 25%	<0.5 mL/kg/h for 8 hr
I = Injury to the kidney	eCCl decreased by 50%	<0.5 mL/kg/h for 16 hr
F = Failure of kidney function	eCCl decreased by 75% or eCCl <35 mL/min/1.73 m^2	<0.3 mL/kg/h for 24 hr or anuria for 12 hr
L = Loss of kidney function	Persistent failure >4 wk	
E = End-stage renal disease	Persistent failure >3 mo	

Devarajan P. Acute kidney injury in children: Clinical features, etiology, evaluation, and diagnosis.www.UpToDate.com, Accessed March 29, 2014. Reproduced with permission of Wolters Kluwer.

PEDICULOSIS PUBIS (CRAB LICE/PUBIC LICE)

DESCRIPTION Ectoparasitic infection (*Phthirus pubis*), marked by severe pruritus and tending to have an incubation period of ~4 wk. Signs include observation of the lice, 1–2 mm long gray-brown organisms, on the skin or on the hair shafts or the presence of "nits" (egg stage) on the hair shaft. The recommended regimens should not be applied to the eyes. Pediculosis of the eyelashes should be treated by applying occlusive ophthalmic ointment to the eyelid margins twice a day for 10 days. Bedding and clothing should be decontaminated (ie, either dry cleaned or machine-washed and dried using the heat cycle) or removed from body contact for at least 72 hr. Fumigation of living areas is not necessary. Nits need to be mechanically removed with a fine-toothed comb. Patients with pediculosis pubis should be

evaluated for other STI/STDs. Patients should be evaluated after 1 wk if symptoms persist. Retreatment might be necessary if lice are found or if eggs are observed at the hair-skin junction. Patients who do not respond to 1 of the recommended regimens should be retreated with an alternative regimen. Sex partners that have had sexual contact with the patient within the previous month should be treated. (See also Section I: "Sexually Transmitted Infections [STI] (Sexually Transmitted Diseases [STD]), general.")

TREATMENT

- CDC-recommended regimens: Permethrin 1% cream rinse applied to affected areas and washed off after 10 min OR Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 min
- CDC Alternative Regimens: Malathion 0.5% lotion applied for 8–12 hr and washed off OR Ivermectin 250 μg/kg orally, repeated in 2 wk

REFERENCE

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010;59(No. RR-12).

PELIOSIS HEPATIS

DESCRIPTION Peliosis hepatis is a condition in which liver and splenic tissue is replaced with blood-filled cysts. This has been reported in patients receiving androgenic anabolic steroid therapy and other conditions. These cysts are sometimes present with hepatic dysfunction, or may be associated with liver failure. Can be easily confused with malignancy on imaging studies. Cysts are often not recognized until life-threatening liver failure or intra-abdominal hemorrhage develops. Withdrawal of drug usually results in complete disappearance of lesions.

REFERENCE

Neri M, Bello S, Bonsignore A, et al. Anabolic androgenic steroids abuse and liver toxicity. *Mini Rev Med Chem*. 2011;11(5):430–437. Review.

PELVIC FLOOR DYSFUNCTION

DESCRIPTION Pelvic floor dysfunction represents a constellation of symptoms that include lower urinary tract, bowel, sexual, and other local symptoms, including pelvic organ prolapse. These conditions are all associated with damage to the pelvic floor through disruption of the connective tissues or by primary or secondary neuropathy and myopathy. Many predisposing, inciting, and promoting factors can lead to pelvic floor dysfunction. Treatments range from conservative/behavioral therapies, to medications and surgical interventions.

REFERENCE

Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin*. 1998;25:723–746.

PELVIC FRACTURE, UROLOGIC CONSIDERATIONS

DESCRIPTION Pelvic fractures can result in bladder and urethral injury. The length and tethered anatomy of the male urethra makes it more vulnerable to injury. Blood at the urethral meatus is the cardinal sign of urologic injury. For patients suspected of having a urethral injury, a retrograde urethrogram should be performed prior to insertion of a Foley catheter. This should be followed by a cystogram. Depending on the location and extent of trauma, several options exist for treatment including drainage of the bladder with a Foley catheter or suprapubic cystotomy, primary repair of the injury, or delayed repair after stabilization. (See also Section I: "Urethra, Trauma [Anterior AND Posterior].")

REFERENCE

Cass AS. The multiple injured patient with bladder trauma. *J Trauma.* 1984;24:731.

PELVIC LIPOSARCOMA

DESCRIPTION Liposarcoma can present as a tumor of the spermatic cord or as a paratesticular tumor. Treatment includes inguinal orchiectomy with high ligation of the cord; adjuvant treatment is controversial but could include postoperative radiotherapy. Chemotherapy options are limited. (See also Section I: "Tunica Albuginea/Paratesticular Tumors and Cysts.")

REFERENCE

Richie JP, Steele GS. Neoplasms of the testis. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology.* 9th ed. Philadelphia, pa: Saunders Elsevier; 2007.

PELVIC ORGAN PROLAPSE QUANTIFICATION SYSTEM (POP-Q)

DESCRIPTION A quantitative description of pelvic support using the hymenal ring as the reference point. Negative numbers are assigned to structures that have not prolapsed beyond the hymen, and positive numbers to those that are protruding. 3 reference points are defined anteriorly and 3 points posteriorly. Once the measurements are complete, the patient is assigned to 1 of 4 stages as noted below. (See also Section I: "Pelvic Organ Prolapse (Cystocele and Enterocele)" and Section II: "Cystocele Grading: Baden–Walker, Pelvic Organ Prolapse Quantification (POP-Q).")

POP-Q Grading System

Stage	Degree of Prolapse
0	No prolapse demonstrated
I	The most distal portion of the prolapse is >1 cm above the level of the hymen
II	The most distal portion of the prolapse is ≤1 cm proximal or distal to the hymenal plane
III	The most distal portion of the prolapse protrudes >1 cm below the hymen but protrudes no farther than 2 cm less than the total vaginal length
IV	Complete vaginal eversion

This classification system exhibits excellent reliability, but it is more cumbersome to use than other systems and patient positioning can alter the results. (See also Section I: "Pelvic Prolapse, Cystocele and Enterocele.")

REFERENCE

Bump RC, Mattiasson A, Bø K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175:10–17.

PELVIC PAIN AND URGENCY/FREQUENCY (PUF) PATIENT SYMPTOM SCALE

DESCRIPTION Instrument for the evaluation and treatment of patients with Interstitial cystitis (IC)/Painful Bladder syndrome (PBS).

REFERENCE

Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology*. 2002;60(4):573–578.

PELVIC PAIN, MALE

See Section I: “Prostatitis, Chronic Nonbacterial, Noninflammatory (NIH CP/CPPS III A and B).”

PELVIS, BIFID, RENAL

DESCRIPTION A normal variant seen in ~10% of patients in which the renal pelvis is divided into 2 major calyces just inside the kidney. (See Pelvis, bifid, renal image ☼)

REFERENCE

Dähnert W. *Radiology Review Manual.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2007.

PELVIS, EXTRARENAL

DESCRIPTION Most often a normal anatomic variant and can be mistaken for a pathologic condition (hydronephrosis, parapelvic, or renal cyst, etc.). Calyces are normal appearing on imaging with an unobstructed extrarenal pelvis but will be dilated with hydronephrosis. The extrarenal pelvis can also be associated with conditions such as renal malrotation or ectopic kidney and rarely may cause urinary stasis and difficulties with infection and stones.

REFERENCE

Kidneys. In: Dalrymple NC, et al., eds. *Problem Solving in Abdominal Imaging.* Philadelphia, PA: Elsevier; 2009.

PEMPHIGUS FOLIACEUS AND VULGARIS

DESCRIPTION Pemphigus foliaceus and vulgaris refer to a group of rare autoimmune intraepidermal blistering diseases involving the skin and mucous membranes. The difference between pemphigus foliaceus and vulgaris involves the level of epidermis at which loss of cell–cell cohesion occurs. Almost all patients will have painful oral mucosal erosions and 50% may have cutaneous blisters involving the genitalia. The diagnosis is confirmed by light

microscopy and immunofluorescence. Pemphigus carries a high mortality rate of 10% from sepsis as a result of skin breakdown and treatment-associated side effects.

TREATMENT

- Topical steroids (eg, clobetasol propionate 0.05% cream [mild cases])
- Glucocorticoids (prednisone) and immunosuppressants (cyclophosphamide, azathioprine, and IV immunoglobulin) for severe cases

REFERENCE

Habif TP. Vesicular and bullous diseases. In: Habif TP, ed. *Clinical Dermatology*. 4th ed. Philadelphia, PA: Mosby; 2004.

PENILE AND CORPORAL BODY MASS

DESCRIPTION Penile masses are relatively rare lesions. Benign solid tumors of the penis include angioma, fibroma, lipoma, and myoma, as well as other dermatologic lesions. Abscesses and granulomas should be included in the differential. Malignant tumors of the penis are more often seen in adults and include squamous cell carcinoma (SCC), melanoma, and soft tissue sarcoma. Cystic lesions are usually periurethral gland and retention cysts due to sebaceous glands in the skin. For malignant lesions, wide excision is recommended. (See also Section II: “Penis, Mass [Noncutaneous].”)

REFERENCE

Kocakoc E, Kazez A, Dagli AF, et al. Postcircumcision granuloma: A rare cause of a penile mass in a boy. *J US Med.* 2006;25(12):1611–1613.

PENILE BRACHIAL PRESSURE INDEX (PBI)

DESCRIPTION The PBI can be defined as the penile systolic BP divided by the brachial systolic BP. A penile brachial index of ≤ 0.7 has been suggested to indicate arteriogenic impotence. However, due to several limitations, this test is considered an unreliable tool to exclude arteriogenic impotence.

REFERENCE

Metz P, Bengtsson J. Penile blood pressure. *Scand J Urol Nephrol.* 1981;15:161.

PENILE DOPPLER ULTRASOUND INDICATIONS AND PARAMETERS

DESCRIPTION This type of minimally invasive vasculogenic imaging is used for men with ED who have a potentially surgically treatable cause (eg, younger men who may have suffered traumatic straddle injuries and do not respond to oral or intracavernosal therapy). Penile Doppler US is used for evaluation of penile blood flow and requires intracavernous injection of vasodilators. Peak systolic velocity (PSV) in healthy individuals varies from 35–47 cm/s. A PSV <25 cm/s has a sensitivity of 100% and specificity of 95% in patients with abnormal pudendal arteriography. Patients with severe ED will have a cavernous artery luminal diameter <0.7 mm and an increase of $<75\%$ in diameter post-injection. Patients with veno-occlusive dysfunction will exhibit good PSV (>25 cm/s) and have persistent end

diastolic flow velocity of >5 cm/s with quick detumescence after stimulation. A resistive index calculation (RI = PSV – EDV/PSV) >0.9 (where EDV is end diastolic velocity) usually indicates no evidence of veno-occlusive dysfunction, whereas an RI of <0.75 was associated with venous leakage in 95% of cases.

REFERENCE

Wein AJ, Kavoussi LR, Novick AC, et al. Vascular surgery for erectile dysfunction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.

PENILE ENHANCEMENT AND LENGTHENING

DESCRIPTION Penile lengthening can be accomplished by release of the suspensory ligament of the penis and the use of penile weights. Increased girth can be obtained by the use of circumferential dermal fat grafts. There are reports of significant complications from lengthening and girth procedures including scarring, skin deformities, irregular fat nodules, scrotalization of the penis, and ED.

REFERENCE

Van Driel MF, Schultz WC, Van de Wiel HB, et al. Surgical lengthening of the penis. *Br J Urol.* 1998;82(1):81–85.

PENILE INTRAEPITHELIAL NEOPLASIA

DESCRIPTION Penile intraepithelial neoplasia is squamous cell carcinoma in situ and encompasses 3 clinical entities: Bowenoid papulosis (BP), erythroplasia of Queyrat (EQ), and Bowen Disease (BD), which vary in their epidemiology, clinical presentation, and malignant potential. BP is seen in young men and occurs on the penile shaft, but can also be seen on the glans or prepuce. Lesions are multiple, small, well-demarcated papules with a relatively benign course. EQ occurs in older uncircumcised men with plaques that are solitary, sharply defined, velvety, and red with malignant transformation in 10–33% of cases. While EQ refers to lesions of the mucocutaneous epithelium, BD refers to penile intraepithelial neoplasia on the follicle-bearing skin of the penis. BD is seen more commonly in elderly men and typically appears as a single, red, sharply defined plaque that can have areas of oozing or crusting and undergoes malignant transformation in approximately 5% of cases.

REFERENCE

Brady KL, Mercurio MG, Brown MD. Malignant tumors of the penis. *Dermatol Surg.* 2013;39(4):527–547.

PENILE NECROSIS (GANGRENE) NON-FOURNIER GANGRENE

DESCRIPTION Penile gangrene is a rare, but serious consequence following infection or ischemic injury. Vascular compromise may be caused by tourniquet syndrome, priapism, venous thrombosis, anticoagulants, and can be seen in diabetics with ESRD. Color Doppler ultrasonography can provide important information regarding thrombosis or rupture of cavernosal and dorsal penile vessels. Treatment involves correction of the underlying etiology and debridement of the nonviable tissue.

REFERENCE
Sabharwal S, Banerji JS, Kekre NS. Penile skin necrosis mimicking penile gangrene: an unusual case. *Urol J.* 2013; 10(1):755.

PENILE PAIN SYNDROME

DESCRIPTION In contrast to other chronic pain syndromes of reproductive organs, chronic penile pain seems to be extremely rare. Penile pain can be understood by etiology, which includes *local conditions* such as dermatitis, infection, and ischemia; *referred pain* from bladder, prostate, lower back, and hips; *neuropathic pain* resulting from injury to dorsal nerve, pudendal nerve, or cauda equina; and *psychiatric conditions* that may lead to extreme hypersensitivity and allodynia. Persistent pain can be treated by treating the underlying disease (paraphimosis, priapism, Peyronie disease, herpes). 1 case in the literature described a patient with episodic penile pain attacks and an inguinal hernia whose pain resolved after herniorrhaphy. His pain was likely due to the irritation of the ilioinguinal nerve in the inguinal canal, which also supplies the ventral base of the penis. In psychosomatic pain, analgesics may be helpful; however tricyclic antidepressants or anticonvulsants have also proven effective.

REFERENCE
Baranowski AP, Abrams P, Fall M. *Urogenital Pain in Clinical Practice.* Boca Raton, FL: CRC Press, 2007:248–252.

PENILE PROSTHESIS, MODELS AND DESCRIPTIONS

DESCRIPTION The earliest attempts of implantable devices began in the 1930s with the 1st viable and widespread adoption of the Carrian intracorporal silicone-based prosthesis in the 1970s. A variety of commercial implantable penile prosthesis are available with the majority used inflatable units. Self-contained inflatable units are no longer manufactured. They are in 3 categories: Semi-rigid, 2-piece, and 3-piece inflatable (see table) (Image ☼).

Prosthesis Type	American Medical Systems	Mentor Corporation	Description	Advantages	Disadvantages
Semi-rigid	AMS Malleable 600 AMS Malleable 650	Acu-form	Malleable core rods that can be bent up and down	Low mechanical failure rate, easy to insert	Constant penile rigidity, increased risk of penile erosion
2-piece inflatable	Ambicor		2 cylinders connected to a small scrotal pump	Easy to insert	Increased risk of mechanical failure
3-piece inflatable	AMS 700 CX AMS 700 CXM AMS 700 CXR (65 mL reservoir) AMS 700 Ultrex	Alpha I Titan Titan Narrow Base	2 cylinders, large abdominal fluid reservoir, and scrotal pump	Penile girth and rigidity most similar to normal erection As above; increased penile length	Highest risk of mechanical failure, technically more difficult, risk of autoinflation with physical activity

[a] Commonly used systems as of March 2014.

REFERENCE
Ellsworth PI. Penile Prosthesis http://emedicine.medscape.com/article/1987058-overview

(Accessed April 17, 2014)

PENILE REHABILITATION

DESCRIPTION Erectile dysfunction (ED following radical prostatectomy (RP) is believed to include neuropraxia, which results in temporarily reduced oxygenation and subsequent structural changes in penile tissue. Penile rehabilitation management of this veno-occlusive dysfunction has focused on tissue oxygenation. Cavernosal hypoxia, resultant fibrosis, and venous leak are hypothesized as the predominant mechanisms for postprostatectomy ED. While animal studies support the use of phosphodiesterase type 5 inhibitors (PDE5Is) in the setting of cavernous nerve damage but results from human studies are contradictory. Penile rehabilitation has been classically defined as the use of a device or pharmacologic agent to aid erectile function recovery after RP. A scheduled regimen of early pharmacologic (PDE5 inhibitors, prostaglandins) therapy, nonpharmacologic (vacuum erection devices) therapy, or a combination thereof immediately following RP is thought to increase potency rates and help maintain penile length and girth. PDE5 inhibitors may help with maintaining penile length. (See Section II: “Penile Shortening.”) The largest study to date found no long-term effect of either daily or on-demand PDE5I use after RP compared with placebo and the utility of prostaglandin and vacuum erection devices are questionable and high-quality studies are lacking.

REFERENCES

Fode M, Ohl DA, Ralph D, et al. Penile rehabilitation after radical prostatectomy: what the evidence really says. *BJU Int*. 2013;112(7):998–1008.

Hakky TS, Baumgarten AS, Parker J, et al. Penile rehabilitation: the evolutionary concept in the management of erectile dysfunction. *Curr Urol Rep*. 2014;15(4):393. doi: 10.1111/bju.12228. Epub 2013 Jul 4.

PENILE SHORTENING

DESCRIPTION Penile shortening may occur congenitally in patients with bladder exstrophy and more commonly after radical prostatectomy (RP) and penile revascularization. Patients with bladder exstrophy have penile shortening because of diastasis of the pubic symphysis and short corporal lengths (<50% the size of controls). More commonly, patients may have shortening of the penis following RP because of unopposed sympathetic stimulation of the penis, fibrosis resulting from hypoxia (as a consequence of denervation), or possibly as a result of retraction of the penile structures into the pelvis. Treatment of Peyronie disease may result in minor penile shortening. Arterial revascularization surgery for vascular ED may result in penile shortening in 20% of patients as a result of scar formation.

In a prospective study of stretched flaccid penile length changes after RP, there was evidence of stretched flaccid penile length loss at 2 mo, but not at 6 mo after RP. PDE5 inhibitors use moderated stretched flaccid penile length loss, with patients who regularly used PDE5 inhibitors having no loss in stretched flaccid penile length.

REFERENCE

Berookhim BM, Nelson CJ, Kunzel B, et al. Prospective analysis of penile length changes after

radical prostatectomy. *BJU Int.* 2013;113(5b):E131–e136. doi: 10.1111/bju.12443 [Epub ahead of print].

PENILE SKIN BRIDGES (PENILE BANDS)

DESCRIPTION Penile skin bridges are a rare complication of neonatal circumcision. They are caused by skin adhesions that occur during childhood. With aging, the adhesions separate partially at the corona to form skin bridges. Treatment involves surgical excision with attachment of the skin edges to the distal penile shaft proximally and the glans distally. Careful surgical technique and proper dressing at the time of initial circumcision are simple procedures that may help prevent adherence of the distal preputial skin flap to the glans penis.

REFERENCE

Kamal BA. Penile skin bridges: causes and prevention. *Int Surg.* 2009;94(1):35–37.

PENILE, MASS (NONCUTANEOUS)

DESCRIPTION Penile soft tissue tumors are rare and comprise approximately 5% of penile tumors and most have been reported as isolated case reports. These tumors can be classified as benign or malignant, superficial or deep, and in terms of age at presentation. The most common benign soft tissue tumors are vascular neoplasms, followed by tumors of neural, myoid, and fibrous origin. The most commonly reported malignant soft tissue tumors are Kaposi sarcoma and leiomyosarcoma. Correct diagnosis of these tumors, by considering clinical information, histopathologic findings, and immunohistochemical stains, is important because their behavior and clinical management vary considerably. (See also Section II: “Penile and Corporal Body Mass.”)

REFERENCE

Katona TM, Lopez-Beltran A, MacLennan GT, et al. Soft tissue tumors of the penis: a review. *Anal Quant Cytol Histol.* 2006;28(4):193–206.

PENIS, AGENESIS (APHALLIA)

DESCRIPTION Penile agenesis is a rare anomaly with an estimated incidence of about 1 in 10 million live births. Most cases have a 46, XY karyotype. The usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft. Associated anomalies are common. Associated urethral absence is usually accompanied by fatal anomalies. Immediate investigations for associated anomalies and karyotype are essential. Caused by failure of development of the genital tubercle, surgical reconstruction/gender reassignment is recommended in the newborn.

REFERENCE

Oesch IL, Pinter A, Ransley PG. Penile agenesis: A report of six cases. *J Pediatr Surg.* 1987;2:172–174.

PENIS, ANGIOSARCOMA

DESCRIPTION Approximately 32 cases of penile angiosarcoma have been reported. No site of predilection is demonstrated, and the tumor may be well circumscribed or diffuse. Death may occur 1 wk to 5 yr after presentation (mean: 13 mo). The application of immunoperoxidase staining for factor VIII, present in normal endothelial cells, aids in diagnosis.

TREATMENT

- Local excision with lymph node dissection
- Local radiotherapy
- Systemic chemotherapy with more widespread tumor

REFERENCE

Wu X, Chen Z, Ji H, et al. Angiosarcoma of the penis: a case report and literature review. *Int Urol Nephrol.* 2012;44(5):1341–1343.

PENIS, ARTIFICIAL NODULES (TANCHO NODULES, BULLETUS, FANG MUK, CHAGAN BALLS)

DESCRIPTION Tancho nodules are spherical foreign objects, in the form of beads, implanted in the subcutaneous tissue of the shaft of the penis proximal to the glans. They are placed to allegedly enhance the sexual pleasure of females during sexual intercourse. It is a practice common in southeast Asia, especially Thailand. However, non-Asian groups in Romania, Russia, and Middle East have adopted this practice as well. The incidence and severity of early or delayed complications are unknown but are probably underreported.

REFERENCES

Wilcher G. Artificial penile nodules: A forensic pathosociology perspective: Four case reports. *Med Sci Law.* 2006;46(4):349–356.

Fischer N, Hauser S, Brede O, et al. Implantation of artificial penile nodules–a review of literature. *J Sex Med.* 2010;7(11):3565–3567.

PENIS, BASAL CELL CARCINOMA

DESCRIPTION Basal cell carcinoma is a common cutaneous malignancy, but is very rare at the penis. Ultraviolet radiation is an important risk factor. Basal cell carcinoma of the penis most likely presents in the 5th–7th decades of life. The natural history is that of a slowly growing tumor with little propensity to metastasize. Lesions are successfully treated with simple local excision. (See also Section I: “Penis, Lesion, General.”)

REFERENCES

Bañón Pérez VJ, Martínez Barba E, Rigabert Montiel M, et al. Basal cell carcinoma of the penis. *Arch Esp Urol.* 2000;53(9):841–843.

Lidder S, Lang KJ, Nakhdjevani A. Basal cell carcinoma of the penis. *Singapore Med J.* 2011;52(10):e201–E202.

PENIS, BOWENOID PAPULOSIS

DESCRIPTION Bowenoid papulosis of the penis are benign lesions that appear as rounded, reddish, single, or multiple papules on the glans or shaft of penis, although they can occur anywhere on the external genitalia or perianal regions of both male and females. These papules typically occur in sexually active patients who are 20–35 yr of age. They are caused by HPV and maybe confused with carcinoma in situ (CIS) of the penis. Histologically, these lesions show parakeratosis and acanthosis in squamous epithelium with disorganization of the epithelial cells. They can be distinguished from CIS by possessing less mitotic figures and cellular dysplasia. Treatment is local destruction, including superficial excision, laser surgery, and use of topical retinoic acid, podophyllum resin, and topical 5-fluorouracil. The recurrence rate is 20%.

REFERENCE

Bhojwani A, Biyani CS, Nicol A, et al. Bowenoid papulosis of the penis. *Br J Urol.* 2003;80(3):508.

PENIS, BURIED (CONCEALED/HIDDEN/TRAPPED)

DESCRIPTION This condition must be differentiated from an abnormally small penis. A buried or concealed penis refers to a normal-sized penis that is hidden because of the prepubic fat pad. Congenital causes or obesity can hide the penile shaft. The penis can usually be exposed by retracting skin lateral to the penile shaft. The iatrogenic hidden penis after circumcision is more properly called a *trapped penis*. Children who undergo neonatal circumcision with testicular swelling or with a hernia or a webbed penis are at risk for excess penile shaft skin loss and a trapped penis. Congenital buried penis is a spectrum characterized by a longer inner prepuce and may include in addition; short penile shaft, abnormal attachment of fundiform, and suspensory ligaments and excess supra-pubic fat. Congenital mega prepuce (CMP) is a variant. Theoretically, obese adults who undergo circumcision are also at risk for removal of excess shaft skin. Symptoms can sometimes be associated (balanitis, UTI, painful voiding, ballooning of the foreskin, and urinary retention) with the condition.

SYNONYM

Inconspicuous penis (general term for buried, trapped, or webbed penis)

TREATMENT

- Surgical correction is optional and controversial.
- Liposuction has been used in cases of extreme obesity.

REFERENCES

Donatucci CF, Ritter EF. Management of the buried penis in adults. *J Urol.* 1998;159(2):420–424.

Hadidi AT. Buried penis: Classification surgical approach. *J Pediatr Surg.* 2014;49(2):374–379. doi: 10.1016/j.jpedsurg.2013.09.066. Epub 2013 Nov 7.

PENIS, CUTANEOUS HORN

DESCRIPTION Cutaneous horn is a clinical diagnosis referring to a conical projection above the skin that resembles a miniature horn. The lesions usually arise in sun-exposed skin and are benign. Penile cutaneous horn is rare and is characterized by overgrowth of epithelium above a lesion that may be a wart, nevus, or tumor. It is important to note that the incidence of SCC is 33% when penile horn is present. Treatment is surgical excision with a margin of tissue at base. Careful histologic evaluation of the base and close clinical follow-up of the excision site are highly recommended.

REFERENCE

Vera-Donoso CD, Lujan S, Gomez L, et al. Cutaneous horn in glans penis: A new clinical case. *Scand J Urol Nephrol.* 2009;43(1):92–93.

PENIS, CYSTS

DESCRIPTION Epidermal cysts found on the ventral surfaces of the penis have been attributed to defective embryologic closure of the median raphe, anomalous developmental rests of the periurethral glands of Littré, development of apocrine cystadenomas ectopically, and anomalous budding and separation of urethral columnar epithelium from the urethra. Penile cysts are commonly found lying just beneath the median raphe and are most likely derived from urethral columnar epithelium. Patients are most often asymptomatic.

TREATMENT

Surgical excision

REFERENCE

Paslin D. Urethroid cysts. *Arch Dermatol.* 1983;119(1): 89–90.

PENIS, DUPLICATION (DIPHALLUS)

DESCRIPTION This is an extremely rare anomaly, with an incidence of 1 in 5–6 million births. According to Aleem's classification, the condition may be true diphallia (complete or partial), or bifid phallus (complete or partial bifid glans or bifid penis). Usually, the penises are unequal in size and lie side by side. Associated anomalies are frequent. Ultrasound may help in differentiating true complete diphallia (2 corpora cavernous in each penis) from complete bifid phallus (only 1 corpus cavernous in each penis). The condition is caused by a failure of fusion of paired mesodermal anlagen of the genital tubercle and treated by surgical reconstruction.

REFERENCE

Aleem AA. Diphallia: Report of a case. *J Urol.* 1972;108:357.

PENIS, FIXED DRUG ERUPTIONS

DESCRIPTION A fixed drug eruption is an allergy that produces a plaque or blister at the same cutaneous site each time the drug is ingested. The most common drugs with side effects afflicting the penis are tetracycline, phenolphthalein, sulfonamides, barbiturates, salicylates, penicillins, foscarnet, and Coumadin. Foscarnet can cause periurethral ulcerations and

coumadin can cause a hemorrhagic necrosis of the penis.

REFERENCE

English JC 3rd, Laws RA, Keough GC, et al. Dermatoses of the glans penis and prepuce. *J Am Acad Dermatol.* 1997;37(1):1–24.

PENIS, HEMANGIOMA (CAVERNOUS HEMANGIOMA)

DESCRIPTION Penile hemangiomas are rare, occurring in 1% of all patients with hemangiomas. They should be differentiated from cutaneous hemangiomas, which are more common and tend to involute with time. By contrast, penile hemangiomas tend to become larger and may require surgical intervention. The physical exam often does not reveal the extent of the lesion, and ultrasound or angiography should be performed to delineate the anatomy. Treatment is surgical excision or laser ablation.

SYNONYMS

- Cavernous hemangiomas
- Subcutaneous hemangiomas
- Penile hemangiomas

TREATMENT

Surgical excision or laser ablation

REFERENCE

Alter GJ, Trengove-Jones G, Horton CE Jr. Hemangioma of penis and scrotum. *Urology.* 1993;42(2):205–208.

PENIS, HIRSUTE PAPILLOMA (PEARLY PENILE PAPULES, CORONAL PAPILLAE)

DESCRIPTION Hirsute papillomas of the penis, more commonly known as *pearly penile papules*, are asymptomatic acral angiofibromas, typically distributed circumferentially on the corona and sulcus of the glans penis. The lesion is often confused with STI/STD's, and persists through life, gradually becoming less noticeable with increased age. Treatment is not required, but sometimes offered for cosmetic reasons. CO_2 laser is effective.

REFERENCE

Bylaite M, Ruzicka T. Images in clinical medicine. Pearly penile papules. *N Engl J Med.* 2007;357(7):691.

PENIS, HYPOPLASIA

DESCRIPTION A small or hypoplastic penis may be the result of gonadotropin deficiency, hypospadias, or epispadias. (See Section I: "Micropenis [Microphallus].")

REFERENCE

Schneck FX, Bellinger MF. Anomalies of the testes and scrotum and their surgical

management. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.

PENIS, KAPOSI SARCOMA

DESCRIPTION Kaposi sarcoma of the penis is rare, with only 37 cases reported in literature. Although most are associated with HIV, cases have been described in immunocompetent patients. It is clinically identified by painless, red-violaceous nodules, as well as papules, plaques, and wart-like pedunculated lesions. The lesions are most commonly found on the glans, although the foreskin, urethral meatus, and scrotum can also be affected. Treatments described include local surgery, radiotherapy, electrocoagulation, laser, and injection of interferon-α into the lesion. (See also Section I: "Penis, Lesion, General.")

REFERENCE

Hernández-Bel P, López J, Sánchez JL, et al. Primary Kaposi sarcoma of the penis in an HIV-negative patient. *Actas Dermosifiliogr.* 2008;99(8):662–663.

PENIS, LEIOMYOMA

DESCRIPTION Penile leiomyoma is a rare benign tumor of smooth muscle that commonly involves the shaft, with glans penis involvement being next in frequency. These lesions tend to be small (1 cm in diameter), well-circumscribed, rubbery in consistency, with light yellow to white cut surfaces. Electron microscopy and immunohistochemistry should be used to confirm diagnosis. Multiple recurrences are rare. Primary excision of the tumor is the treatment of choice.

REFERENCE

Leoni S, Prandi S, Mora A. Leiomyoma of the prepuce. *Eur Urol.* 1980;6(3):188–189.

PENIS, LEIOMYOSARCOMA

DESCRIPTION Penile leiomyosarcoma is a very rare malignant smooth muscle tumor that usually occurs on the 5th–7th decades. Superficial lesions commonly arise from the dermis of the shaft or the smooth muscle of the glans penis and usually form subcutaneous-nodules. Deep leiomyosarcoma is less common, arising from the smooth muscle of the corpora cavernosa, and tends to invade the urethra and metastasize early. These tumors are firm, gray-white, lobulated, and poorly circumscribed, and can range in size from 3–8 cm. Electron microscopy and immunohistochemistry should be used to confirm diagnosis.

TREATMENT

- Primary excision of the tumor is the treatment of choice in low-grade (superficial) tumors; however, the tumor tends to recur locally.
- In high-grade (deep) malignancies, the treatment depends on the age of the patient, size, location of the tumor, and the degree of invasiveness.

REFERENCE

Kathuria S, Jablokow VR, Molnar Z. Leiomyosarcoma of the penile prepuce with

ultrastructural study. *Urology.* 1986;27(6):556–557.

PENIS, LENGTH, NORMAL

DESCRIPTION Data on pediatric penile length considerations are discussed in Section I: "Microphallus (Micropenis)." At birth, dimensions of the normal-term infant phallus are 3.5 ± 0.7 cm in stretched length and 1.1 ± 0.2 cm in diameter. In adults, concern over phallus size can direct some men to seek penile augmentation. There is no real delineation between normal and abnormal, since many variables (fat pad, erect vs. flaccid length) are present. For example, a large fat pad can cause a penis to become buried and give a shorter appearance. (See Section II: "Penis, Buried [Concealed, Trapped, or Hidden].") 1 recent study provided the following data for mean measurements in adults (length from penopubic skin to the meatus):

- Flaccid length: 8.85 cm; stretched length: 12.45 cm
- Erect length: 12.89 cm; flaccid girth: 9.71 cm; erect girth: 12.3 cm

REFERENCE

Wessels H, McAninich JW. Penis size: What is normal? *Contemp Urol.* 1997;6671.

PENIS, LEUKOPLAKIA

DESCRIPTION These lesions present as solitary or multiple white plaques, usually involving the penile meatus. Histologically, parakeratosis, hyperkeratosis, and hypertrophy of the rete pegs are present, with dermal edema and lymphocytic infiltration. Leukoplakia is commonly associated with in situ SCC and verrucous carcinoma of the penis. Thus, close follow-up of the excision site with periodic biopsy of incompletely excised lesions is necessary to detect early malignant change.

TREATMENT

- Elimination of chronic irritation and circumcision may be indicated.
- Surgical excision and radiation have been used in the treatment of leukoplakia.

REFERENCE

Bain L, Geronemus R. The association of lichen planus of the penis with squamous cell carcinoma in situ and with verrucous squamous carcinoma. *J Dermatol Surg Oncol.* 1989;15(4):413–417.

PENIS, MALIGNANT FIBROUS HISTIOCYTOMA (MFH)

DESCRIPTION MFH is a rare sarcoma of the penis that may present as a subcutaneous penile mass in a patient with penile pain, priapism, or urinary retention.

TREATMENT

- Superficial tumors are treated with wide local excision vs. total amputation.
- Deep tumors arising from the corpora are treated with total penile amputation.
- Local recurrence is common, and complete amputation should be considered even for superficial tumors.
- Regional metastases are rare, and lymphadenectomy is unnecessary unless adenopathy is palpable.

REFERENCE

Katona TM, Shienbaum AJ, Wyatt LL, et al. Malignant fibrous histiocytoma of the glans penis: A case report. *Anal Quant Cytol Histol.* 2006;28(1):39–42.

PENIS, MELANOMA

DESCRIPTION Melanoma of the penis is extremely rare. It presents as a reddish brown or blue black pigmented papule, plaque, or ulceration on the glans penis and less commonly on the prepuce. The depth of skin invasion (Clark classification) and thickness of the tumor (Breslow classification) are of prognostic importance.

TREATMENT

- Surgery is the mainstay of therapy via partial or total penile amputation.
- Foreskin lesions may be treated with circumcision.
- Glanular lesions may be treated with partial penectomy.
- Lesions on the shaft often require total penile amputation.

REFERENCE

Te CC, Vemulapalli S, Confer SD, et al. Recurrent malignant melanoma of the penis. *Urology*. 2008;72(5):1185, e15–16.

PENIS, METASTASIS TO

DESCRIPTION Metastatic disease to the penis is rare, with roughly 200 cases reported during the past 100 yr. The bladder, prostate, rectum, and rectosigmoid are responsible for the greatest number of metastases. However, distal primaries (eg, lung) have been reported. Several mechanisms might lead to this condition: Direct extension, retrograde lymphatic spread, retrograde venous spread, direct arterial extension, secondary embolism, tertiary embolism, instrumental spread, and paradoxical spread. Patients may develop masses or malignant priapism. Most patients die within 6 mo of presentation. Penectomy may be indicated for pain or relief of urinary obstruction (Image ☼).

REFERENCE

Bachrach P, Dahlen CP. Metastatic tumors to the penis. *Urology*. 1973;1(4):359–362.

PENIS, NEURILEMOMA (SCHWANNOMA)

DESCRIPTION Penile neurilemmoma, also known as schwannoma, is a rare entity. It is an encapsulated tumor that arises from the sheaths of peripheral nerves. These are solitary, slow-growing, and often asymptomatic lesions. Most penile schwannomas are unifocal, benign, and tend to occur on the dorsal penile shaft, where the penile dorsal nerve is located, although cases on the glans penis have also been reported. A family history of neurofibromatosis is usually present. Malignant schwannomas are often associated with neurofibromatosis type I. Surgical excision is the treatment of choice, and regular follow-up is recommended because recurrence of benign schwannomas has been reported.

REFERENCE

Loeser A, Katzenberger T, Meuller JG, et al. Solitary schwannoma of the glans. *Urology.* 2007;70(5):1007.e5–e6.

PENIS, NEUROFIBROSARCOMA (MALIGNANT SCHWANNOMA)

DESCRIPTION A malignant nerve sheath tumor arising from Schwann cells that very rarely occurs on the penis. These lesions most commonly occur on the dorsal aspect of the penis, near the dorsal nerve. Nodules from Peyronie disease are uncommon in this location. Patients may have a history of von Recklinghausen disease or neurofibromatosis, and an exam for café au lait spots and other nodules should be undertaken.

TREATMENT
- Complete excision
- Careful follow-up for recurrence
- Recurrent schwannomas may require total penectomy

REFERENCE

Suzuki Y, Ishigooka M, Tomaru M, et al. Schwannoma of the penis: Report of a case and review of the literature. *Int Urol Nephrol.* 1998;30(2):197–202.

PENIS, SCLEROSING LIPOGRANULOMA (PARAFFINOMA)

DESCRIPTION This is a foreign-body reaction resulting from injection of paraffin, petroleum jelly, bear grease, or other materials into penile shaft, in an attempt to increase penile girth. Injections of oil-based substances may also be performed for therapeutic or cosmetic purposes, but these procedures are usually performed by the patient or an untrained person practicing medicine fraudulently. Complications usually occur, including penile deformity, skin necrosis, ED, and painful intercourse (Image ☼).

TREATMENT
- Complete excision of affected skin and subcutaneous tissue
- Skin graft coverage (full- or split-thickness skin graft)
- Flap coverage (usually scrotal) is required if skin graft does not take.

REFERENCE

Jeong JH, Shin HJ, Woo SH, et al. A new repair for penile paraffinoma: Bilateral scrotal flaps. *Ann Plast Surg.* 1996;37(4):386–393.

PENIS, SCLEROSING NONVENEREAL LYMPHANGITIS

DESCRIPTION Sometimes referred to as *Mondor phlebitis of the penis,* these are firm and often asymptomatic subcutaneous cordlike swellings along the dorsal shaft of the penis or around the coronal sulcus. They can be confused with *lymphangioma circumscriptum*, a uncommon tumor of the lymphatic channels. The lesion is caused by thickening or thrombosis of the superficial veins of the penis, probably secondary to trauma. Treatment is not usually necessary, and the condition usually resolves in several weeks. Avoid vigorous sexual activity. Failure to resolve in a timely manner may require biopsy.

REFERENCE
Kumar B, Narang T, Radotra BD, et al. Mondor's disease of penis: A forgotten disease. *Sex Transm Infect.* 2005;81:480–482.

PENIS, STRANGULATION

DESCRIPTION Penile strangulation is caused by attachment of and encircling by a foreign object around the penis, which leads to entrapment and distal ischemia. These efforts are usually associated with an attempt to maintain a longer erection and sexual interest. Foreign objects used include iron rings, rubber bands, steel washers, and strings. Wearing constricting rings on the flaccid penis often result in the impossibility of their removal after erection, leading to vascular complications usually within a few hours. These injuries range from simple penile engorgement to ulceration, necrosis, urinary fistula, or even gangrene. The main objective in the treatment is acute decompression to avoid potential ischemic necrosis and autoamputation. Removing the constricting device is a challenge to the urologic surgeon, and each case requires an individual approach. Methods used include aspiration of the corpora, or the use of saws, grinders, and dental drills to remove object. The outcome is often good, but some can have serious complications such as penile amputation and urethrocutaneous fistula.

REFERENCE
Ivanovski O, Stankov O, Kuzmanoski M, et al. Penile strangulation: Two case reports and review of the literature. *J Sex Med.* 2007;4(6):1775–1780.

PENIS, SYRINGOMA

DESCRIPTION Syringomas are benign appendageal tumors that normally occur in adolescents on the face, neck, axillae, or abdomen. They are extremely rare on the penis; only 6 cases have been reported in the literature to date. On exam, 2–5-mm flesh-colored papules are seen. A punch biopsy can be obtained to relieve patient fears of STI/STD and cancer, and to rule out condyloma, lichen planus, and bowenoid papulosis, which may appear similarly. Because they are benign, treatment is usually considered cosmetic. CO_2 laser has proved effective, as well as surgical excision and cryotherapy with liquid nitrogen.

REFERENCE
Olson JM, Robles DT, Argenyi ZB, et al. Multiple penile syringomas. *J Am Acad Dermatol.* 2008;59(2 Suppl 1):S46–S47.

PENIS, THROMBOSIS OF DORSAL VEIN

DESCRIPTION Thrombosis of the superficial dorsal vein of the penis, also known as *Mondor disease*, is a rare, poorly understood clinical entity. Some predisposing factors include vigorous sexual activity, trauma, and surgery to the pelvis or external genitalia. It can also be a manifestation of metastatic pancreatic cancer, or can be associated with bladder and prostate cancers. Clinically, the patient complains of swelling and pain on the dorsal aspect of the penis. On exam, a cordlike structure is palpated. Doppler US can demonstrate a

noncompressible portion of the superficial dorsal vein, as well as a lack of venous flow signals. Treatment is conservative, as the disease is self-limited and often spontaneously resolves. Abstinence from sex and anticoagulation with heparin is sometimes recommended. NSAIDs may relieve pain and diminish inflammation. Thrombus excision may be the last resort in cases without resolution. Spontaneous thrombosis of the deep dorsal penile vein has also been described following trauma, or in a patient with thrombophilia. This condition improves with anticoagulation treatment.

REFERENCE

Kartsaklis P, Konstantinidis C, Thomas C, et al. Penile Mondor's disease: A case report. *Cases J.* 2008;1(1):411.

PENIS, TORSION

DESCRIPTION Congenital rotation of the penile shaft such that the median raphe spirals obliquely around the penile shaft. The external genitalia are otherwise normal, but this condition may be associated with hypospadias or ventral hood penile deformity. The torsion tends to occur in a counterclockwise direction (ie, the twist is to the left). Mainly a cosmetic issue, repair is usually not necessary if the rotation is $<60–90^{\circ}$.

TREATMENT

Mild cases require only simply freeing the penile shaft of its investing tissue.

REFERENCE

Pomerantz P, Hanna M, Levitt S, et al. Isolated torsion of penis. Report of six cases. *Urology.* 1978;11(1):37–39.

PENIS, VERRUCOUS CARCINOMA

DESCRIPTION Squamous cell carcinoma (SCC) of the penis represents about 1% of cancers in men in USA and 11–12% of all cancers in men in countries where circumcision is not routinely practiced. Verrucous carcinoma is an uncommon variant that accounts for only 5–16% of all penile SCCs. Diagnosis of verrucous carcinoma may be difficult because biopsies are usually performed on the superficial portion of the lesion. Therefore, it is crucial to perform a deep biopsy. Verrucous carcinoma exhibits an exophytic warty lesion of SCC and endophytic growth where cellular atypia is noted. (See also Section I: "Penis Cancer, General" and "Penis, Squamous Cell Carcinoma.")

SYNONYMS

- Giant condyloma
- Buschke–Lowenstein tumor

CAUSES

- Lack of circumcision
- Prior trauma
- Previous disease
- Poor hygiene
- Phimosis

- Tight prepuce

TREATMENT
Partial penectomy

REFERENCE
Kanik AB, et al. Penile verrucous carcinoma in a 37-yr-old circumcised man. *J Am Acad Dermatol.* 1997;37(2):329–331.

PENIS, WEBBED

DESCRIPTION A congenital condition in which the scrotal skin extends onto the ventral aspect of the penile shaft. Although there are usually no associated abnormalities, there are a few reports of hypoplasia of the distal urethra. Occasionally, a webbed penis is the result of a circumcision in which there was excess removal of ventral penile shaft skin. Cosmetic repair is performed, as needed.

REFERENCE
Dilley AV, Currie BG. Webbed penis. *Pediatr Surg Int.* 1999;15(5–6):447–448.

PENN POUCH

DESCRIPTION A continent urinary reservoir is created based on the Mitrofanoff principle, which uses the appendix as the catheterizable continent apparatus. The pouch is made from joining a detubularized colon and ileum.

REFERENCE
Benson MC, Olsson CA. Continent urinary diversion. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders, 1998:3190–3245.

PEREYRA URETHROPEXY

DESCRIPTION Pereyra, in 1959, was 1st to present a transvaginal approach to a urethropexy using a needle suture carrier, obviating the need for a transabdominal exposure. Through a T vaginal incision, the bladder neck and periurethral tissue are exposed. The suture carrier is passed through a suprapubic stab incision and, under digital guidance, delivered through the periurethral tissue. The bladder neck is then suspended with absorbable suture.

REFERENCE
Duggan ML. Another look at Pereyra's Stint urethropexy. *South Med J.* 1975;68(11):1381–1384.

PERINEAL GROOVES

DESCRIPTION Perineal groove is a rare congenital malformation characterized by a wet sulcus lined by mucous membrane, extending from the posterior fourchette to the anterior edge of the anus. There are 2 reasons for surgical correction: Cosmetic reasons and the groove

mucosa is often infected due to colonization by rectal germs. Patients present with inflammatory aspects of the groove mucosa, infection of the external genitalia, and urinary tract infection. Considering that infectious complications occur in about 50% of patients, surgical excision is often recommended. Generally, the tissue defect is closed by interrupted sutures and some advocate the use of surgical glue over the suture line to help prevent infection/movement of the skin edges and, therefore, the development of subsequent dehiscence.

REFERENCE

Esposito C, Giurin I, Savanelli A, et al. Current trends in the management of pediatric patients with perineal groove. *J Pediatr Adolesc Gynecol.* 2011; 24(5):263–265.

PERINEAL MASS

DESCRIPTION Perineal masses are classified as either benign or malignant and can arise from the perineum directly or from pelvic extension of gastrointestinal, genitourinary, or gynecologic structures. Benign conditions include soft tissue masses, traumatic saddle injury, infections leading to abscess formation, various fistulae, granulomatous disease, urethral foreign body, urolithiasis, Bartholin gland or prostatic cyst, and condyloma. Neoplasms that present as a perineal mass include sarcomas as well as malignancies of the prostate, urethra, anus, vagina, and metastases from other pelvic structures. Patients typically present with a palpable mass or with perineal, gluteal, or labial swelling. On occasion, clinical findings and symptoms suggest the underlying cause, such as inflammatory changes associated with infection. Cross-sectional imaging, with CT scan or MRI, is usually required to further define the anatomic origin, extent, and radiologic features of the lesion. Aggressive surgical treatment of mass lesions, in the form of wide local excision, is often the treatment of choice with the aim of negative resection margins without causing disturbances to urinary or anorectal function (Image ☼).

REFERENCE

Tappouni RF, Sarwani NI, Tice JG, et al. Imaging of unusual perineal masses. *AJR Am J Roentgenol.* 2011;196(4):W412–W420.

PERINEAL PAIN, DIFFERENTIAL DIAGNOSIS

DESCRIPTION According to the ICS, *perineal pain syndrome* is the occurrence of persistent or recurrent episodic perineal pain which is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. Perineal pain is felt in the female, between the posterior fourchette (posterior lip of the introitus) and the anus, and in the male, between the scrotum and the anus. There is no proven infection or other obvious pathology. The ICS suggests that in men, the term prostatodynia (prostate-pain) should not be used as it leads to confusion between a single symptom and a syndrome. The differential diagnosis of perineal pain is long, with infectious, inflammatory, iatrogenic, anatomic, and other causes as listed below:

Infectious:

- Prostatitis

- Cystitis
- Epididymitis
- Orchitis
- Fournier gangrene
- Abscess
- Sexually transmitted infections (herpes, syphilis, chancroid)

Inflammatory:
- Interstitial cystitis (IC)/Painful bladder syndrome (PBS)
- Inflammatory dermatoses (lichen planus, lichen sclerosis, SLE, Behcet disease)

Iatrogenic:
- Sacral nerve stimulation
- Perineal sling
- Radiation therapy
- Cryotherapy
- Pelvic surgery

Prolapse:
- Bladder
- Urethra
- Vagina
- Uterus
- Rectum

Other:
- Ureteral stone
- Torsion (testicular, ovarian, appendix testis, appendix epididymis)
- Pudendal nerve entrapment
- Diabetic and HIV/AIDS neuropathy

REFERENCE

Warfield CA, Bajwa ZH. Perineal pain. In: Warfield CA, Bajwa ZH, eds. *Principles and Practice of Pain Medicine.* 2nd ed. New York, NY: McGraw-Hill; 2005.

PERINEAL TRAUMA (STRADDLE INJURY)

DESCRIPTION This refers to fracture of all 4 pubic rami or simply to blunt force trauma to the perineum causing urethral injury or high-flow priapism. Patients with blood at the urethral meatus, perineal hematoma, or urinary retention after blunt force trauma should be suspected of having a urethral injury. A retrograde urethrogram should be performed in males and urethroscopy in females. Patients with urethral injuries may have an attempt at primary realignment with a catheter but suprapubic cystotomy remains the standard of care. Anastomotic urethroplasty should be considered the gold standard, with endoscopic treatments reserved for posterior urethral strictures <1 cm or strictures following anastomotic repair. Straddle injury may also cause nonischemic high-flow priapism from a cavernosal artery–corpora cavernosa fistula. This may require angiographic embolization if it fails to resolve on its own. (See also Section I: “Urethra, Trauma [Anterior and Posterior].”) (Image ☼)

REFERENCE

Park S, Mc Aninch JW. Straddle injuries to the bulbar urethra: Management and outcomes in 78 patients. *J Urol.* 2004;171(2 pt 1):722–725.

PERINEPHRIC MASS

DESCRIPTION Masses in the perinephric space may be due to tumor, fluid, inflammation, various proliferative disorders, or subcapsular renal diseases. Neoplasms include renal tumors, perinephric lymphoma, posttransplantation lymphoproliferative disorder, metastases, and various retroperitoneal tumors. Fluid may be present from hematoma, urinoma, abscess, or lymphangiomatosis. Inflammation is seen in conditions such as xanthogranulomatous pyelonephritis or pancreatitis. Proliferative diseases that appear as perinephric masses include extramedullary hematopoiesis, retroperitoneal fibrosis, sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease), and lipoid granulomatosis (Erdheim–Chester disease). In addition, subcapsular diseases, such as renal cortical necrosis or nephroblastomatosis, may also present as perinephric masses on cross-sectional imaging.

REFERENCE

Westphalen A, Yeh B, Qayyum A, et al. Differential diagnosis of perinephric masses on CT and MRI. *AJR Am J Roentgenol.* 2004;183(6):1697–1702.

PERINEPHRIC STRANDING

DESCRIPTION Fat stranding is seen on cross-sectional imaging as a linear or hazy increased attenuation within a region of fat, usually caused by fluid or inflammatory cells infiltrating the tissues and often accompanied by thickening of nearby fascial planes. Focal fat stranding can signal a focus of acute disease and should prompt inspection of adjacent structures. Perinephric stranding is commonly seen in healthy individuals, but when asymmetric, it may be secondary to an obstructive urinary calculus, pyelonephritis, inflammatory nephritis, renal infarction, neoplasm, or renal vein thrombosis.

REFERENCE

Leyendecker JR, Dalrynmple NC. Computed tomography incidentalomas. In: Dalrymple NC, et al., eds. *Problem solving in abdominal imaging*. Philadelphia, PA: Mosby Elsevier; 2009.

PERINEURAL INVASION, UROLOGIC CONSIDERATIONS

DESCRIPTION Perineural invasion most commonly refers to a pathologic finding on needle biopsy of prostate or radical prostatectomy specimens. Perineural invasion on needle biopsy specimens correlates with an increased risk of extraprostatic extension, lymph node metastases, and postoperative progression. Surprisingly, perineural invasion in RP specimens does not have any prognostic significance, perhaps because it represents spread of tumor along a plane of decreased resistance, as opposed to invasion into vascular or lymphatic structures, which portends a worse prognosis.

TREATMENT

Patients should be counseled on treatment options, nerve-sparing vs. non–nerve-sparing

surgery, and prognosis based upon PSA, Gleason score, and TNM stage and possibly perineural invasion.

REFERENCES

Ng JC, Koch MO, Daggy JK, et al. Perineuralinvasion in radical prostatectomy specimens: Lack of prognostic significance. *J Urol.* 2004;172:2249–2251.

Stone NN, Stock RG, Parikh D, et al. Perineural invasion and seminal vesicle involvement predict lymph node metastasis in men with localized carcinoma of the prostate. *J Urol.* 1998;160:1722–1726.

PERIPHERAL NEUROPATHY, UROLOGIC CONSIDERATIONS

DESCRIPTION As it pertains to urology, peripheral neuropathy classically affects bladder and sexual function. The most common causes of peripheral neuropathy are diabetes, HIV/AIDS, alcoholism, side effects of chemotherapy, and B12 deficiency. The classic description of diabetic cystopathy is impaired bladder sensation, increased bladder capacity, decreased contractility, decreased flow rate, and increased residual volume. Patients may have involuntary bladder contractions and eventually develop areflexic bladders. Sexual function may be impaired, and patients may have ED or anorgasmia.

TREATMENT

- The underlying cause of neuropathy should be identified and treated, if possible.
- Careful evaluation for progression of disease should be sought, and patients may need to be on timed voiding or intermittent catheterization.
- Erectile dysfunction (ED) may require a vacuum erection device, medical therapy, or surgical intervention.

REFERENCE

Sasaki K, Yoshimura N, Chancellor MB. Implications of diabetes mellitus in urology. *Urol Clin North Am.* 2003;30(1):1–12.

PERIURETERITIS

DESCRIPTION Most cases of periureteritis, or inflammatory changes surrounding the ureter, are secondary to infection from microorganisms that cause infections elsewhere in the genitourinary tract. Any associated anatomic abnormality of the ureter, including stricture, megaloureter, and ureterocele, predisposes an individual to ureteritis. Urinary obstruction, trauma, and abdominopelvic radiation are other causes for periureteral inflammation. The 1st step in treatment of periureteritis is treating the underlying etiology, including the treatment of infection, stricture, stone, or tumor. This term is not used in current peer-reviewed literature.

REFERENCE

Giambroni L, Monticelli L, Simeone C, et al. Ureteritis. *Arch Ital Urol Nefrol Androl.* 1993;65(1):31–33.

PERIURETHRAL ABSCESS

DESCRIPTION A life-threatening infection of the urethra and periurethral tissues that can spread rapidly to the adjacent soft tissues. It most commonly presents with scrotal edema (94%), fever (70%), urinary retention (19%), a draining abscess (11%), dysuria, and urethral discharge. Periurethral abscesses have been associated with gonococcal urethritis infections, urethral strictures, periurethral bulking agent injections, and urethral diverticulum. Drainage and broad spectrum antibiotics are the mainstay of treatment.

REFERENCE

Kenfak-Foguena A, Zarkik Y, Wisard M, et al. Periurethral abscess complicating gonococcal urethritis: Case report and literature review. *Infection*. 2010;38:497–500.

PERLMAN SYNDROME

DESCRIPTION An overgrowth syndrome characterized by fet al gigantism, visceromegaly, distinct facial features, and nephroblastomatosis. Similar overgrowth syndromes include Beckwith–Weidemann, Sotos, and the Simpson–Golabi–Behemel syndromes. Neonatal mortality is extremely high. The kidneys are often dysplastic, with numerous cysts and nephrogenic rests. The cause is unknown, and the diagnosis is based entirely on the phenotypic description.

REFERENCE

Schilke K, Schaefer F, Waldherr R, et al. A case of Perlman syndrome: Fet al gigantism, renal dysplasia, and severe neurological deficits. *Am J Med Genet.* 2000;91(1):29–33.

PFANNENSTIEL INCISION

DESCRIPTION A transverse incision is centered ~2 fingerbreadths above the pubic symphysis. A transverse incision is made through the anterior rectus fascia, and entry into the retropubic space can be gained by separating the rectus muscle in the midline. Useful for bladder and other lower abdominal procedures.

REFERENCE

Montague DK. Surgical incisions. In: Novick AC, Streem SB, Pontes JE, eds. *Stewarts Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:15–40.

PHI (PROSTATE HEALTH INDEX) (SEE SECTION II: "PROSTATE HEALTH INDEX (*PHI*) AND [-2] PROPSA")

PHIMOSIS, CLITORAL

DESCRIPTION Phimosis should be suspected in women with clitoral pain, itching, or burning. A physical exam may reveal a mild, moderate, or severe degree of an inability to visualize the entire clitoris. Initial conservative treatment involves testosterone and estrogen creams to improve the elasticity of the prepuce and potentially antifungal agents such as nystatin or fluconazole. Rarely, lichen planus may result in a white scarring of the clitoris, prepuce, and perineum. Treatment with clobetasol cream may improve symptoms. Women with refractory symptoms may require a dorsal slit.

REFERENCE

Munarriz R, Talakoub L, Kuohung W, et al. The prevalence of phimosis of the clitoris in women presenting to the sexual dysfunction clinic: Lack of correlation to disorders of desire, arousal and orgasm. *J Sex Marital Ther.* 2002;28(1):181–185.

PHOSPHATE NEPHROPATHY, ACUTE

DESCRIPTION Acute phosphate nephropathy is characterized by acute and subsequent chronic renal failure following exposure to oral sodium phosphate (OSP) bowel purgatives. Renal biopsy demonstrates acute and chronic tubular injury with prominent tubular and interstitial calcium phosphate deposits. Risk factors include older age, female gender, hypertension (HTN), chronic kidney disease (CKD) and treatment with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and diuretics. The pathologic mechanism of action involves hypovolemia-induced proximal salt and water reabsorption, delivery of a large phosphate load to the distal nephron, and precipitation of calcium phosphate in the distal tubule and collecting duct. Prevention of acute phosphate nephropathy is best achieved by avoiding sodium phosphate purgatives in high-risk patients, aggressive hydration, minimizing the dose, and maintaining a minimum of 12 hr between administrations.

REFERENCE

Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int.* 2009; 76(10):1027–1034.

PINWORMS, UROLOGIC CONSIDERATIONS

DESCRIPTION Approximately 209 million people are infected with intestinal pinworms (*Enterobius vermicularis*) worldwide. They most commonly reside in the large intestine, and females lay ~15,000 eggs nightly on the perineum, causing intense perineal itching and sleep disturbances. Occasionally, worms may ascend the vagina and uterus and enter the peritoneal cavity through the fallopian tubes, where they may lay eggs causing an intense inflammatory response resulting in fever, abdominal pain, adhesions, and granulomas. Involvement of the urinary tract is rare, and only 1 report exists of *Enterobius* in the bladder.

TREATMENT

- Mebendazole 100 mg PO once (1st-line) or pyrantel pamoate 11 mg/kg up to 1 g PO once (2nd-line)
- Treat household contacts
- Clean bedrooms and bedding

REFERENCES

Ben Musa NA. Intestinal parasites in school aged children and the 1st case report on amoebiasis in urinary bladder in Tripoli, Libya. *J Egypt Soc Parasitol.* 2007;37(3):775–784.

Kucik CJ, Martin GL, Sortor BV. Common intestinal parasites. *Am Fam Physician.* 2004;69(5): 1161–1168.

PIPE STEM URETHRA

DESCRIPTION A form of intrinsic sphincter deficiency (ISD) caused by a fixed, open, and nonfunctioning urethra. This is usually the result of prior pelvic surgery, irradiation, or long-standing indwelling catheter drainage. Patients typically have a high bladder neck on cystoscopic exam and severe urinary incontinence.

TREATMENT

- Mid-urethral sling
- Urethrolysis
- Artificial urinary sphincter

REFERENCE

Ghoniem GM, Shaaban A. Sub-urethral slings for treatment of stress urinary incontinence. *Int Urogynecol J.* 1994;5(4):228–239.

PI-RADS PROSTATE MRI SCORING SYSTEM

DESCRIPTION The European Society of Urogenital Radiology (ESUR) developed a scoring system to present multi-parametric prostate MRI data in a simple but meaningful way in the diagnosis of prostate cancer. The system is similar to that used by breast radiologist (BI-RADS for x-ray mammography, breast ultrasound, and MRI). Multiple parameters for each lesion are scored on a 5-point scale and the overall score predicts the chance of the lesion being a clinically significant cancer.

- Score 1 = Clinically significant disease is highly unlikely to be present.
- Score 2 = Clinically significant cancer is unlikely to be present.
- Score 3 = Clinically significant cancer is equivocal.
- Score 4 = Clinically significant cancer is likely to be present.
- Score 5 = Clinically significant cancer is highly likely to be present.

REFERENCE

Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22(4):746–757.

PLAP (PLACENTAL ALKALINE PHOSPHATASE)

DESCRIPTION PLAP is a fet al isoenzyme that has a different structure than the adult alkaline phosphatase. It is 1 of many tumor markers used for the diagnosis, staging, and monitoring of treatment response in patients with GCT, and it may be useful as a prognostic index. Although the individual sensitivity of PLAP is low, when combined with gamma-glutamyl transpeptidase, simultaneous determinations have shown elevations of 1 or both in 80% of patients with active disease.

REFERENCE

Javadpour N. Multiple biochemical tumor markers in testicular cancer. *Cancer.* 1983;52:887.

PLASMACYTOID UROTHELIAL CARCINOMA

DESCRIPTION Plasmacytoid urothelial carcinoma (PUC) is a rare and recently described histologic variant of urothelial carcinoma (TCC). Tumor tissue is predominantly manifested by infiltrating tumor cells with characteristics of plasmacytoid morphology. Cells appear medium-sized and dyscohesive with abundant eosinophilic cytoplasm, small hyperchromatic nuclei, and frequent mitotic features. In addition, immunohistochemical staining plays an important role in the diagnosis of PUC. The most common presenting symptom is hematuria, generally accompanied by irritative lower urinary tract symptoms. However, early diagnosis cannot be made due to the absence of hematuria until the later stages of disease. Due to the highly metastatic potential and poor prognosis of this variant of TCC, treatment options include deep TURBT for initial diagnosis, followed by radical cystectomy with adjuvant therapy.

REFERENCE

Wang Z, Lu T, Du L, et al. Plasmacytoid urothelial carcinoma of the urinary bladder: A clinical pathological study and literature review. *Int J Clin Exp Pathol.* 2012;5(6):601–608

PLASMACYTOMA, BLADDER

DESCRIPTION This tumor is characterized by a monotonous proliferation of plasma cells at variable stages of differentiation, with predominance of the immature variety. 5 cases have been reported in the literature, with a mean age of 54 yr, none of which had multiple myeloma at the time of diagnosis. Local suprapubic recurrences and regional lymph node metastasis may occur. Survival up to 12 yr after diagnosis has been reported.

TREATMENT

- Subtotal cystectomy
- Radiation and chemotherapy

REFERENCE

Yang C, Motteram R, Sandeman TF. Extramedullary plasmacytoma of the bladder: A case report and review of literature. *Cancer.* 1982;50:146–149.

PLASMACYTOMA, TESTICULAR

DESCRIPTION Neoplastic collections of plasma cells occurring in the testicles. Plasmacytomas are most commonly found in the head and neck region. These are very rare tumors, with an incidence of ~1 in 1,000 testicular tumors. They are most commonly associated with a previous or concurrent diagnosis of multiple myeloma and are generally not believed to occur as primary tumors. Presentation is a painless testicular mass. Treatment is radical orchiectomy and monitoring or management of multiple myeloma.

REFERENCE

Berrondo C, Gorman TE, Yap RL. Primary plasmacytoma of the testicle: a case report. *J Med Case Rep*. 2011;5:494.

PLOIDY ANALYSIS, BLADDER CANCER

DESCRIPTION *Ploidy* is the chromosomal content of cells, which can be measured using flow cytometry. Ploidy analysis, when considered as an independent variable, is a fair predictor of clinical outcome. Tumor stage and grade are considered to be the most important predictors of survival. Although ploidy may be more significant in predicting survival than grade, the addition of ploidy to the known stage and grade of a bladder tumor usually does not drastically alter the clinical management of a patient.

REFERENCE

Bittard H, Lamy B, Billery C. Clinical evaluation of cell deoxyribonucleic acid content measured by flow cyto-metry in bladder cancer. *J Urol.* 1996 ;(155):1887–1891.

PLOIDY ANALYSIS, PROSTATE CANCER

DESCRIPTION *Ploidy* is a variation in the number of chromosomes in a cell. *Aneuploidy* is a variation in the number of chromosomes in a cell that is other than a simple multiple of the number of chromosomes. In a prostate specimen, flow cytometry is used to measure the DNA content of the cells. *DNA ploidy* in addition to the histologic grading may improve the ability to predict the pathologic state and ultimately the prognosis of any given lesion. The frequency of aneuploidy increases with advancing tumor stage. Inherent problems with ploidy analysis include heterogeneity of DNA cell sampling, as well as whether it will change clinical management.

REFERENCE

Dejter SW, Cunningham RE, Noguchi PD, et al. Prognostic significance of DNA ploidy in carcinoma of prostate. *Urology.* 1989;33:361–366.

PNEUMORETROPERITONEUM

DESCRIPTION Pneumoretroperitoneum, the presence of air in the retroperitoneal space, unless immediately postoperatively, is always considered an abnormal finding. It can be due to a perforated retroperitoneal viscus or from residual air following a retroperitoneal surgical procedure. Duodenal, colonic, or rectal perforation can result from peptic ulcer disease, abdominal trauma, endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), colonoscopy, colorectal carcinoma, diverticulitis, ischemic colitis, or foreign-body insertion.

Often accompanied by pneumoperitoneum, pneumomediastinum, or subcutaneous emphysema. Early diagnosis and treatment are important, as certain unrecognized conditions may become life-threatening (viscous perforation with sepsis). Treatment of the underlying etiology may be conservative or surgical, and allows for the pneumoretroperitoneum to resolve.

REFERENCE

Pretre R, Robert J, Mirescu D, et al. Pathophysiology, recognition and management of pneumoretroperitoneum. *Br J Surg*. 1993;80(9):1138–1140.

PNEUMOSCROTUM

DESCRIPTION Pneumoscrotum, the presence of air within the scrotum, can result from both pathologic and iatrogenic etiologies. This term includes both *scrotal emphysema*, which is subcutaneous air palpated as crepitus, and *pneumatocele*, where air is present within the tunica vaginalis and not directly palpable. Air may come from extraperitoneal (thoracic [pneumothorax], retroperitoneal), intraperitoneal (perforated viscus), or local (air-producing microorganisms) sources. The underlying cause must be recognized early, as certain conditions may be life-threatening (pneumothorax, Fournier gangrene, intestinal perforation) and treatment of the underlying cause allows the pneumoscrotum to resolve. Today, pneumoscrotum is sometimes seen after laparoscopic or robotic transperitoneal or extraperitoneal procedures and resolves spontaneously.

REFERENCES

Watson HS, Klugo RC, Coffield KS. Pneumoscrotum: review of two cases and review of mechanisms of its development. *Urology*. 1992;40(6):517–521.

Wilson C, Green A, Bader S, et al. Pneumoscrotum as the presenting symptom of pneumothorax and pneumoperitoneum after jet ventilation. *Anesthesiology*. 2012;117(2):408.

POLYARTERITIS NODOSA (PAN), UROLOGIC CONSIDERATIONS

DESCRIPTION PAN can affect many organ systems but usually presents with a systemic illness characterized by malaise, weight loss, myalgia, arthralgia and signs of end-organ damage. PAN is not well understood, but is believed to be caused by the deposition of immune complexes on the walls of primarily medium-sized arteries, causing deformative changes in those walls. This may lead to thickening and aneurysmal changes, causing acute renal hemorrhage and often leading to chronic renal failure. When left untreated, the 5-yr survival rate of PAN is 13% with some renal features being associated with poor prognosis: Renal insufficiency (serum creatinine >1.58 mg/dL) and proteinuria (>1 g/d). Corticosteroids and azathioprine are used in the treatment of PAN. The majority of patients with PAN have renal involvement. Flank pain is sometimes present and glomerular ischemic changes and renal artery vasculitis can cause renal failure (a small percentage of patients may require dialysis), hypertension, or both. Infrequently patients may develop pain over the testicular or ovarian area with testicular infarction reported. Spontaneous renal hemorrhage is also reported. Steroids with or without cyclophosphamide is the standard treatment.

REFERENCE

Pettigrew HD, Teuber SS, Gershwin ME. Polyarteritis nodosa. *Compr Ther*. 2007 Fall;33(3):144–149.

POLYEMBRYOMA

DESCRIPTION A mixed germ cell tumor (GCT) of the testis, containing embryonal carcinoma and yolk sac tumor. Histologic analysis reveals a distinctive, well-organized pattern of embryoid bodies in a myxoid stroma, which resembles extraembryonic mesenchyme. Due to the yolk sac component there may be substantial alpha fetoprotein (AFP) elevation. Treatment mirrors that for GCT.

REFERENCE

Ulbright TM. Germ cell neoplasms of the testis. *Am J Surg Pathol.* 1993;17(11):1075–1091.

POLYOMA VIRUS (BK, JC), UROLOGIC CONSIDERATIONS

DESCRIPTION The polyoma viruses may cause transplant renal nephropathy, ureteral obstruction or stricture, and hemorrhagic cystitis. BK virus may cause transplant renal nephropathy in up to 6% of transplant recipients, and may cause ureteral obstruction secondary to fibrosis. It is also thought to be the causative agent in the majority of patients with hemorrhagic cystitis following immunosuppression for bone marrow or solid organ transplantation. BK virus causes clinical disease of the genitourinary tract, due in part to its tropism for genitourinary epithelium. The JC virus causes a similar disease pattern but is less common. BK nephropathy occurs in up to 10% of kidney transplant recipients and causes graft failure in as many as 50% of individuals affected. BK and JC viruses can be diagnosed with PCR of the urine or blood. Urine cytology may demonstrate the so-called “decoy cells.’ Most renal transplant programs employ posttransplant screening programs. Decreasing immunosuppressive medications is essential. Additional therapies include agents such as

ciprofloxin and IVIG. (See also Section I: “Immunocompromised Patients, Urologic Considerations” and Section II: “BK Virus, Urologic Considerations.”)

REFERENCE

Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: Interdisciplinary analyses and recommendations. *Transplantation*. 2005;79:1277–1286.

POLYORCHIDISM

DESCRIPTION This is a very rare condition characterized by multiple (>2) testicles. It may be the result of transverse division of the urogenital ridge. The majority of cases are asymptomatic and associated with inguinal hernia, torsion, or cryptorchidism. It is most often discovered as an asymptomatic swelling in the scrotum; the supernumerary testis usually occurs with its own separate epididymis and vas deferens. If a testicular tumor can be ruled out using US or MRI, and if surveillance indicates no other associated disorders, surgical exploration is not necessary.

TREATMENT

Surveillance, exploration, and biopsy, if indicated

REFERENCE

Arlen AM, Holzman SA, Weiss AD, et al. Functional supernumerary testis in a child with testicular torsion and review of polyorchidism. *Pediatr Surg Int*. 2014;30(5):565–568. [Epub ahead of print]

POLYTHELIA, UROLOGIC CONSIDERATIONS

Polythelia (the presence of extra nipples) is linked with abnormalities of the urinary tract and is usually found within the milk line extending from the axilla to pubic region. Urologic abnormalities include supernumerary kidneys, failure of renal formation, and carcinoma of the kidney. The association of polythelia and renal anomalies is not uniform but is supported by some studies. 1 group reported 40% of children with polythelia had obstructive renal anomalies or duplications of the excretory system. The presence of extra nipples in children should heighten the clinician’s suspicion of possible renal anomalies.

REFERENCE

Grossl NA. Supernumerary breast tissue: Historical perspectives and clinical features. *South Med J*. 2000;93(1):29–32.

POLYURIA

DESCRIPTION Generally defined as >3 L of urine output from a person without excessive fluid intake (2 L/m^2 in children). It is necessary to differentiate it from nocturnal polyuria (NP) (the production of >1/3 of total 24-hr urine output between midnight and 8 AM). Normally, a person’s urine output is decreased overnight, when compared to daytime urine output. It is useful to measure the urine osmolality to determine whether the polyuria is due

to a water diuresis (urine osmolality <250 mOsmol/kg) or a solute diuresis (urine osmolality >300 mOsmol/kg). Polyuria has numerous causes. A solute diuresis may be caused by excessive hypertonic saline infusion, high-protein feedings, uncontrolled diabetes, or postobstructive diuresis. A water diuresis can be caused by multiple conditions, including polydipsia, loop diuretics, diabetes insipidus, and infusion of hypotonic solutions. Correct the underlying cause. (See also Section II: "Nocturnal Polyuria.")

REFERENCE

Kujubu DA, Aboseif SR. An overview of nocturia and the syndrome of nocturnal polyuria in the elderly. *Nat Clin Pract Nephrol.* 2008;4(8):426–435.

POSITRON EMISSION TOMOGRAPHY (PET) IMAGING, CHOLINE C 11

DESCRIPTION Choline C 11 injection is a radiotracer where choline is labeled with carbon C 11, a positron-emitting isotope. An active, carrier-mediated transport mechanism for choline allows for uptake into tumor cells where it is phosphorylated by choline kinase, an enzyme that is often upregulated in cancer. Therefore, these lesions can be differentiated from normal tissue on PET imaging. C-Choline PET/CT has been FDA approved in the detection of distant relapses in prostate cancer patients with a biochemical recurrence. In addition, accurate imaging of cancers within the prostate is important for patients with a high clinical suspicion for prostate cancer, but previous negative core biopsies. For these patients, targeted biopsy may improve detection rates of prostate cancer. This imaging study has been shown to accurately detect and locate major areas of prostate cancer and differentiate segments with prostate cancer from those with benign hyperplasia, chronic prostatitis, or normal prostatic tissue.

REFERENCE

Kitajima K, Murphy RC, Nathan MA. Choline PET/CT for imaging prostate cancer: an update. *Ann Nucl Med.* 2013;27(7):581–589.

POSITRON EMISSION TOMOGRAPHY (PET) IMAGING, UROLOGIC CONSIDERATIONS

DESCRIPTION The most common urologic applications for the PET scan are in seminoma, kidney cancer, and prostate cancer. Patients who are treated for seminoma and have a residual retroperitoneal mass >3 cm should have a PET scan performed. A positive scan implies viable tumor, whereas a negative scan implies freedom from disease. Emerging data from combination PET/CT scans show potential in identifying small renal masses with reported 94% sensitivity and 100% specificity rates for clear cell RCC, but is still considered experimental. PET scans may also be useful in prostate cancer for distinguishing local vs. distant failure, determining progression of disease, and assessing the degree of androgen receptor expression but are not yet standard of care studies.

REFERENCE

Larson SM, Schöder H. Advances in positron emission tomography applications for urologic cancers. *Curr Opin Urol.* 2008;18(1):65–70.

POST MICTURITION SYMPTOMS

DESCRIPTION LUTS are conventionally classified into symptoms of storage, voiding, and postmicturition symptoms. Postmicturition symptoms include the sensation of incomplete bladder emptying and postmicturition dribble. These symptoms have an overall prevalence of ~10% of the population, are most often present in the setting of other storage or voiding symptoms, and are noted to increase with age in men. Incomplete bladder emptying is seen more commonly in women whereas men more often experience postmicturition dribbling. Despite the fact that the importance of these symptoms is not always highlighted, studies have shown that their presence can have a significant adverse effect on patient health-related quality of life.

REFERENCE

Maserejian NN, Kupelian V, McVary KT, et al. Prevalence of postmicturition symptoms in association with lower urinary tract symptoms and health-related quality of life in men and women. *BJU Int.* 2011;108(9):1452–1458.

POSTORGASMIC ILLNESS SYNDROME (POIS)

DESCRIPTION Post orgasmic illness syndrome (POIS) is characterized by debilitating mental and physical symptoms following orgasm that may last from a few hours to several days. Mental symptoms include cognitive dysfunction, irritability, discomfort, anxiety, and depression. Physical symptoms include fatigue, headache, and allergic or flu-like symptoms. Patients typically avoid sexual activity altogether or plan to engage in intercourse when they have adequate time to recover. Some hypothesize that allergy to one's own semen may contribute to the illness. Others believe that a lack of the neurosteroid progesterone, or defect in neurosteroid precursor synthesis, leads to the observed pathophysiology.

REFERENCE

Waldinger MD, Meinardi MM, Zwinderman AH, et al. Postorgasmic illness syndrome (POIS) in 45 Dutch Caucasian males: Clinical characteristics and evidence for an immunogenic pathogenesis (Part 1). *J Sex Med.* 2011;8(4):1164–1170.

POSTATROPHIC HYPERPLASIA OF THE PROSTATE

DESCRIPTION Postatrophic hyperplasia is a histologic pattern showing atrophic and hyperplastic glands, sometimes with a small acinar configuration. Atrophy followed by hyperplasia results in acini with nuclear enlargement. Nucleoli are enlarged as well. The basal cell layer may be difficult to see, but its presence rules out prostate cancer. Immunohisto-chemistry with 34βE12 stain, which stains for basal cell CK, may be helpful. This entity can be confused with prostate cancer on needle biopsy, but is a benign condition. (See also Section III: "Atypical Small Acinar Proliferation, Prostate [ASAP]"; "Atypical Adenomatous Hyperplasia of the Prostate.")

REFERENCE

Amin MB, Tamboli P, Varma M, et al. Postatrophic hyperplasia of the prostate gland: A detailed analysis of its morphology in needle biopsy specimens. *Am J Surg Pathol.*

1999;23(8):925–931.

POSTCOITAL PROPHYLACTIC ANTIBIOTICS

DESCRIPTION Women who suffer recurrent UTIs (≥2 infections in 6 mo or ≥3 infections in 1 yr) may have an association of their UTIs with sexual activity. Gram-negative organisms colonizing the vagina are often the cause. The problem is typically seen in premenopausal women. (See also Section I: "Urinary Tract Infection [UTI], Adult Female.")

TREATMENT

- Hydrate well and empty bladder immediately after intercourse (have not been proven to be uniformly effective in clinical trials).
- Cranberry juice/supplements have not been proven beneficial in trials
- Suppressive antibiotic therapy immediately after intercourse; single dose of the following has been reported: Trimethoprim-sulfamethoxazole, nitrofurantoin, cephalexin, and the fluoroquinolones; if pregnant: Cephalexin (250 mg) or nitrofurantoin (50 mg).

REFERENCE

Fiore DC, Fox CL. Urology and nephrology update: recurrent urinary tract infection. *FP Essent.* 2014;416:30–37.

POSTCOITAL TEST

DESCRIPTION A test that evaluates the interaction between sperm and cervical mucus. It determines the adequacy of sperm and the receptivity of cervical mucus. Testing consists of retrieving specimens from the posterior vaginal fornix, exocervix, and endocervical canal ~6–8 hr after intercourse. The test should be performed close to the time of ovulation, and couples are asked to abstain from sex for 48 hr prior to the test. These specimens are examined to determine the number of motile sperm, with 10 sperm/hpf considered adequate and excluding the cervical mucosa as cause of infertility. When these test results are poor, the specimens may be repeated on another occasion, 1–3 hr after coitus.

SYNONYM

Sims–Huhner Test

REFERENCE

Leushuis E, van der Steeg JW, Steures P, et al.; CECERM study group. Prognostic value of the postcoital test for spontaneous pregnancy. *Fertil Steril.* 2011;95(6):2050–2055.

POSTERIOR TIBIAL NERVE STIMULATION (PTNS)

DESCRIPTION PTNS provides retrograde stimulation to the sacral plexus through stimulation of the posterior tibial nerve. The currently available United States system is the Urgent PC (Uroplasty, Minnetonka, MN). It is FDA approved for the treatment of urinary urgency, urinary frequency, and urge incontinence (overactive bladder). Other uses described include nonobstructive urinary retention, neurogenic bladder, pediatric voiding dysfunction and chronic pelvic pain syndrome (CPP)/Painful bladder syndrome (PBS). The PTNS mechanism of action is unclear, and may be due to effects on different areas of the CNS or a

peripheral effect on the target organ. The -gauge disposable needle insertion point is 4–5 cm cephalad to the medial malleolus. The current is a continuous, square wave (duration of 200 μs, frequency of 20 Hz). The current is determined by the highest level that is tolerated by the patient. The stimulations sessions last for 30 min and are performed once a week for 10–12 wk PTNS was found to be effective in 37–100% of patients with OAB, in 41–100% of patients with nonobstructive urinary retention and in up to 100% of patients with CPP/PBS. (See also Section I: "Overactive Bladder (OAB)" and Section II: "Sacral Neuromodulation.") (Image ☼)

REFERENCE

Gaziev G, Topazio L, Iacovelli V, et al. Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. *BMC Urol.* 2013;13:61.

POSTOPERATIVE SPINDLE CELL NODULE, BLADDER

DESCRIPTION These benign lesions appear 5 wk to 3 mo after surgical procedures in the lower urogenital tract. They grossly resemble a sarcoma and develop after damage to the bladder wall. Microscopically, they appear as intersecting spindle cells intermingled with inflammatory infiltrates. The main differential diagnosis is leiomyosarcoma. They have been reported most commonly in the bladder and prostate.

SYNONYMS

- Postoperative spindle cell nodule of Proppe
- Pseudosarcoma

TREATMENT

Transurethral resection

REFERENCE

Young, RH. Non-neoplastic disorders of the urinary bladder (Chapter 5). In: Bostwick DG, ed. *Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008:238.

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

DESCRIPTION Posttransplant lymphoproliferative disorder (PTLD) is a heterogeneous disease that may occur in recipients of solid organ transplants and hematopoietic stem cell transplants. The risk of lymphoma is increased 20–120% compared with the general population. Epstein–Barr virus infection at the time of transplantation appears to be a significant risk factor. Based on morphologic, immunophenotypic, and molecular criteria, PLTD are classified into 4 pathologic categories: Early lesions, polymorphic, monomorphic, and classical Hodgkin lymphoma. A mainstay of therapy is reduction of immune suppression but often single-agent rituximab or even combination chemotherapy is needed.

REFERENCE

Jagadeesh D, Woda BA, Draper J, et al. Post transplant lymphoproliferative disorders: Risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol.* 2012;13(1):122–136.

POSTVOID DRIBBLING

DESCRIPTION Urine that leaks out or the urethra at the end of micturition. It may be caused by bladder outlet obstruction, a urethral diverticulum, or vesicovaginal reflux of urine. Recent data suggests it may be a surrogate for median lobe hypertrophy.

REFERENCE

Hassler E, Krakau I, Häggarth L, et al. Questioning questions about symptoms of benign prostatic hyperplasia. *Fam Pract.* 2001;(3):328–332.

POTASSIUM SENSITIVITY TESTING

DESCRIPTION A diagnostic test proposed for Interstitial cystitis (IC)/Painful Bladder syndrome (PBS). The pathogenic mechanism of PBS/IC may involve increased epithelial permeability or loss of tight junctions between epithelial cells. Patients with a normal urothelium and sensory nerves will have no pain associated with the instillation of 400 mM (0.4 M) of potassium chloride solution into the bladder, whereas those with PBS/IC may have pain. Patients may be asked to rank their degree of pain on a visual analog scale. More recently, potassium chloride has been used to predict the responsiveness of patients to intravesical hyaluronic acid therapy.

REFERENCE

Parsons CL, Greenberger M, Gabal L, et al. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol.* 1998;159(6):1862–1866.

POTTER SYNDROME/POTTER SEQUENCE

DESCRIPTION A fetus with Potter syndrome (oligohydramnios sequence) a rare fatal disorder that occurs in sporadic and autosomal recessive forms with an incidence of 1 in 4,000 births may show signs of Potter facies (a flat nose, recessed chin, epicanthal folds, low-set ears) and limb abnormalities. These deformities are believed to be secondary to compression of the fetus due to severe oligohydramnios resulting from bilateral renal agenesis. Skelet al malformations may include hemivertebrae, sacral agenesis, and limb anomalies. Babies are often stillborn or die early in the neonatal period. Death usually results from respiratory insufficiency from lack of development of the alveolar sacs. (See also Section II: “Renal Agenesis [Bilateral and Unilateral].”)

REFERENCES

Potter EL. Bilateral renal agenesis. *J Pediatr.* 1946;29:68–76.
Shastry SM, Kolte SS, Sanagapati PR. Potters Sequence. *J Clin Neonatol.* 2012;1(3):157–159.

POUCHITIS

DESCRIPTION Pouchitis is the most common long-term complication in patients with restorative proctocolectomy and ileal pouch-anal anastomosis and is more completely described in the literature for this population. In patients undergoing continent catheterizable stoma, pain in the region of the stoma, along with an increase in pouch contractility is also

referred to as *pouchitis*. The increased intestinal segment contractility can cause temporary loss of the continence mechanism. The patient may complain of sudden, explosive loss of urine through the catheterizable stoma. Anecdotal reports of continent orthotopic neobladder also exist. Most cases involving urinary diversion are caused by a bacterial infection that responds to a 10-day course of antibiotics based on sensitivity testing.

REFERENCE

Colwell JC, et al. eds. *Fecal & Urinary Diversions: Management Principles*. Philadelphia, PA: Mosby Elsevier; 2012.

PRADER–WILLI SYNDROME

DESCRIPTION This is secondary to a chromosomal abnormality consisting of partial deletion of the long arm of chromosome 15 (q11–13). Children often present as obese, hypotonic, and retarded, with hypogonadism, and cryptorchidism. Obesity and behavioral problems are the major cause of morbidity and mortality in affected individuals.

REFERENCE

Cassidy SB. Prader-Willi syndrome. *J Med Genet.* 1997;34(11):917–923.

PRECOCIOUS PUBERTY

DESCRIPTION Precocious puberty is sexual development at an earlier age than expected. In general, signs of secondary sexual development in boys <9 and breast or pubic hair development in white girls <7 or in black girls <6 is precocious. Common causes include medications (exogenous estrogen or testosterone), idiopathic causes, pituitary and CNS tumors (hamartomas, others), CAH, adrenal tumor, ovarian cysts and tumors, McCune–Albright syndrome, Leydig cell tumors, hCG-secreting GCT, testotoxicosis, or pseudoprecocious puberty.

REFERENCE

Carel JC, Leger J. Clinical practice. Precocious puberty. *N Engl J Med.* 2008;358(22):2366–2377.

PREGNANCY, BACTERIURIA, PYURIA, AND URINARY TRACT INFECTION

DESCRIPTION Pregnant women with asymptomatic bacteriuria have a higher likelihood of developing a UTI and should be treated to reduce the incidence of pyelonephritis, sepsis, and fet al complications (low birth weight, prematurity, death). Pyuria in the presence of bacteriuria indicates UTI. Pyuria in the absence of bacteriuria should raise suspicion for nephrolithiasis, TB, or less commonly, malignancy of the urinary tract. Penicillins and cephalosporins (FDA category B) are generally agreed to be safe in pregnancy. Drugs with very high protein binding (eg, Ceftriaxone), may be inappropriate the day before parturition because of the possibility of bilirubin displacement and kernicterus risk. Fluoroquinolones should be AVOIDED in pregnancy. (See also Section I: “Bacteruria and Pyuria” and

"Pregnancy, Urolithiasis.")

TREATMENT

The following regimens have been reported in eradicating asymptomatic bacteriuria in pregnancy:

- Nitrofurantoin 100 mg BID × 5 days
- Amoxicillin 500 mg PO BID 3–7 days
- Amoxicillin-clavulanate 500 mg PO BID 3–7 days
- Cephalexin 500 mg 500 mg PO BID 3–7 days
- Fosfomycin 3 g orally as a single dose

The following regimens have been reported in treating cystitis in pregnancy modified based on urine culture results:

- Nitrofurantoin 100 mg orally every 12 hr for 5 days
- Cefpodoxime: 100 mg twice daily for 3–7 days
- Amoxicillin-clavulanate: 500 mg orally every 12 hr for 3–7 days
- Fosfomycin: 3 g orally as a single dose

The following regimens are reported for mild to moderate pyelonephritis in pregnancy:

- Ceftriaxone: 1 g every 24 hr
- Cefepime: 1 g every 12 hr
- Aztreonam: 1 g every 8 to 12 hr

The following regimens are reported for severe pyelonephritis with immunocompromise and/or incomplete urinary drainage.

- Ticarcillin-clavulanate: 3.1 g every 6 hr
- Piperacillin-tazobactam: 3.375 g every 6 hr
- Meropenem: 500 mg every 8 hr
- Ertapenem: 1 g every 24 hr
- Doripenem: 500 mg every 8 hr

REFERENCES

Hooton TM, Gupta K. Urinary tract infections and asymptomatic bacteriuria in pregnancy in UpToDate.com. Accessed March 5, 2015.

Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am.* 2007;(341):35–42.

PREGNANCY, HEMATURIA

DESCRIPTION Microscopic hematuria is a common finding during pregnancy, however it rarely impacts the outcome of the pregnancy. However, these patients should be assessed postpartum for continued microscopic hematuria to assess for further urologic or kidney disease.

REFERENCE

Brown MA, Holt JL, Mangos GJ, et al. Microscopic hematuria in pregnancy: Relevance to pregnancy outcome. *Am J Kid Dis.* 2005;45:667–673.

PREGNANCY, RADIOLOGIC CONSIDERATIONS

DESCRIPTION Urologists are commonly confronted with pregnant patients with hydronephrosis, renal colic, and stone disease. Imaging is difficult to interpret due to anatomic and physiologic changes in the gravid patient, as well as because of the concern of exposing a fetus to ionizing radiation. The maximum safe dose of radiation allowable to the fetus in the 1st trimester is thought to be 20,000 mrads, and 50,000 mrads in the 2nd and 3rd trimesters. The initial imaging modality of choice should be abdominal ± transvaginal color Doppler ultrasound (US) to evaluate renal resistive indices, ureteral dilation distal to the iliac vessels, and ureteral jets in the bladder. If further evaluation is needed, a diuretic magnetic resonance urogram (MRU) or low-dose CT reported average exposure 705 mrads) can be performed. In the OR, stent placement can be done with intraoperative US and, if absolutely necessary, fluoroscopy with shielding of the fetus by placement of lead below the patient's lower abdomen and pelvis. Iodinated contrast materials may be used in pregnancy, when indicated. Gadolinium is not recommended for use in the pregnant patient unless benefit justifies the potential fet al risk.

REFERENCES

Goldstone K, Yates SJ. Radiation issues governing radiation protection and patient doses in diagnostic imaging. In: Grainger RG, Allison DJ, et al. *Diagnostic Radiology*. 5th ed. Philadelphia, PA: Elsevier; 2008.

White WM, Zite NB, Gash J, et al. Low-dose computed tomography for the evaluation of flank pain in the pregnant population. *J Endourol.* 2007;21(11):1255–1260.

PREGNANCY, RENAL TRANSPLANTATION

DESCRIPTION Successful renal transplantation restores normal ovulatory function and the potential for successful conception. Pregnancy does not appear to affect long-term graft survival. However, pregnancies after renal transplant are at significant risk for maternal and fet al complications including hypertension, preeclampsia, and infection, as well as preterm delivery and fet al growth restriction. Renal transplantation is not a contraindication to vaginal delivery and care should be taken during cesarean section not to injure the renal unit. General safe guidelines for pregnancy after renal transplantation are good health and functioning renal unit 2 yr after transplantation without any evidence of infection or obstruction and on low doses of immunosuppression.

REFERENCE

Fuchs KM, Wu D, Ebcioglu Z. Pregnancy in renal transplant recipients. *Semin Perinatol.* 2007;31:339–347.

PREGNANCY, URINARY DIVERSION

DESCRIPTION Pregnancy after urinary diversion has not been well studied, and only 250 cases have been reported in the literature thus far. Patients have more difficulty getting pregnant because of their inherent underlying disease process, metabolic changes from urinary diversion, and because of the fixed position of the uterus from prior surgery. These

patients have special antepartum considerations from decreased perfusion of the bowel segment from compression of the conduit or neobladder by the uterus, malabsorption of food due to use of the terminal ileum, stomal prolapse from increased intra-abdominal pressure, stomal stenosis from impaired blood flow, difficulty catheterizing continent pouches from stretching of the efferent limb, and an increased risk of UTI from the presence of bacteriuria. Unique postpartum issues include adhesions of the small intestine that may complicate cesarean section, increased residual urine volumes from stretching of conduits or neobladders, and an increased risk of pelvic organ prolapse.

REFERENCE

Hautmann RE, Volkmer BG. Pregnancy and urinary diversion. *Urol Clin North Am.* 2007;31:71–88.

PREGNANCY, URINARY TRACT OBSTRUCTION

DESCRIPTION Urinary tract obstruction during pregnancy most commonly occurs from a ureteral stone or extrinsic compression from the gravid uterus. Patients will commonly present with flank pain. US, magnetic resonance urography, or low-dose CT may be used to evaluate for a ureteral stone and evidence of obstruction. Hydronephrosis is a common finding in pregnancy and may be found in 15%, 20%, and 50% of patients in their 1st, 2nd, and 3rd trimesters, respectively. It is more common on the right side, and is commonly thought to occur from progesterone-mediated ureteral dilation and extrinsic compression. (see also Section I: “Pregnancy, Urolithiasis” and Section II: “Pregnancy, Radiologic Considerations.”)

TREATMENT

- Initially, conservative with IV hydration and analgesic therapy.
- Patients who fail may require stent or nephrostomy tube placement. Stents can rapidly encrust due to increased urinary calcium excretion and should be changed in a timely fashion.
- Ureteroscopy and laser lithotripsy.

REFERENCE

McAleer SJ, Loughlin KR. Nephrolithiasis and pregnancy. *Curr Opin Urol.* 2004;14(2):123–127.

PREGNANCY, UROLOGIC MALIGNANCY

DESCRIPTION Urologic malignancies are rare in pregnancy but often misdiagnosed due to overlapping signs and symptoms with preeclampsia and eclampsia. The most common tumor is RCC, which may present as flank pain, hematuria, and a palpable mass. It is often identified incidentally on imaging. Pheochromo-cytomas have been reported to occur in 1 of 50,000 term pregnancies. They present with severe hypertension, headaches, palpitations, vomiting, visual changes, and without proteinuria unlike preeclampsia. Adrenal adenomas may present with Cushing syndrome. Renal angiomyolipoma may present with flank pain, hematuria, and retroperitoneal hemorrhage, although it is sometimes incidentally diagnosed on imaging.

Urothelial carcinoma of the upper or lower tracts is rare and presents with hematuria. If urine analysis reveals hematuria and the culture is negative, cytology, cystoscopy, and upper tract imaging are warranted.

TREATMENT

- Removal of pheochromocytomas is controversial, but medical therapy may be used until the 3rd trimester or delivery of the fetus.
- The size and type of tumor should dictate management for RCC, and laparoscopic nephrectomy has been shown to be safe in pregnant women.
- Angiomyolipoma (AML) with hemorrhage may be managed with embolization or partial or total nephrectomy.
- Urothelial cancer should be managed endoscopically given its propensity for aggressive growth and lymphatic invasion. Mitomycin should be avoided, and only 1 case report exists of using BCG.

REFERENCE

Martin FM, Rowland RG. Urologic malignancies in pregnancy. *Urol Clin North Am.* 2007;341):53–59.

PREGNANCY, UROLOGIC MEDICATIONS

DESCRIPTION Medications in pregnancy have not been well studied or documented. Urologic issues include antibiotics for UTIs and anesthesia for surgical procedures. Macrobid is a safe, well-tolerated antibiotic classified as a category B (no evidence of harm to human fetus) drug by the FDA. There is a recommendation against using this in the 3rd trimester because of the risk of hemolytic anemia in patients with G6PD deficiency. Fluoroquinolones are considered category C medications, but multiple studies have failed to demonstrate any evidence of harm. Penicillins are category B drugs, and often the medication of choice in pregnancy. General anesthesia may carry a slightly higher risk of fet al malformations and premature labor; this effect is directly related to the complexity and length of the procedure but the overall increased risk is thought to be minimal. (See also Section II: “Pregnancy, Bacteruria, Pyuria, and UTI.”)

REFERENCE

Shrim A, Garcia-Bournissen F, Koren G. Pharmaceutical agents and pregnancy in urology practice. *Urol Clin North Am.* 2007;34(1):27–33.

PREHN SIGN

DESCRIPTION Prehn sign is a clinical test used to aid in distinguishing epididymitis from testicular torsion although it is not always reliable. The physical lifting of the testicles is said to relieve the pain of epididymitis (positive Prehn sign), but does not relieve the pain of testicular torsion (negative Prehn sign). It is important to note that Prehn sign is not always reliable and Doppler ultrasound is a valuable tool in confirming the diagnosis.

REFERENCE

Lavallee ME, Cash J. Testicular torsion: Evaluation and management. *Curr Sports Med Rep*.

2005; 4(2):102–104.

PRENTISS MANEUVER

DESCRIPTION Additional cord length in an orchiopexy operation can be gained by incising the inguinal floor and ligating the inferior epigastric vessels. The internal ring and transversalis fascia are then closed lateral to the cord.

REFERENCE

Kelly CE. The relationship between pressure flow studies and ultrasound-estimated bladder wall mass. *Rev Urol.* 2005;Suppl 6:S29–S34.

PREPUTIAL STONES

DESCRIPTION Preputial stones (*preputial calculi*) are rare occurrences, generally found in adults and associated with poor genital hygiene, low socioeconomic status, and phimosis. Factors in preputial stone formation include obstruction, stasis, foreign body, nidus formation, and infection. Removal of stone and elimination of the predisposing condition is the treatment.

REFERENCE

Ellis DJ, Siegel AL, Elder JS, et al. Preputial calculus: A case report. *J Urol.* 1986;1362:464–465.

PRESSURE–FLOW STUDIES

DESCRIPTION The simultaneous measurement of bladder pressure and uroflow throughout the entire voiding cycle. Performed as part of urodynamic study, these studies improve on some of the imitations of uroflowmetry alone. Measurements for this study can include the variables that affect the study: Intravesical pressure, rectal pressure, intraurethral pressure, sphincter electromyogram, and urine flow rate. A small catheter is placed to fill the bladder and measure the flow. All variables are plotted and recorded simultaneously to compare the various readings during various points in the micturition study.

REFERENCE

Nitti VW. Pressure Flow urodynamic studies: the gold standard for diagnosing bladder outlet obstruction. *Rev Urol.* 2005;7(Suppl 6): S14–S21.

PRIAPISM, STUTTERING (INTERMITTENT PRIAPISM)

DESCRIPTION Priapism that is recurrent in nature should be treated initially as for ischemic priapism. Emphasis should be placed on long-term prevention using medical or self-injection therapy. (See also Section I: “Priapism.”)

SYNONYMS

- Recurrent priapism
- Intermittent priapism

TREATMENT

- Hormonal therapy (leuprolide, flutamide, bicalutamide)
- Self-injection therapy with phenylephrine

REFERENCE

Burnett AL, Bivalacqua TJ. Priapism: Current principles and practice. *Urol Clin North Am.* 2007;344:61–62.

PRIMITIVE NEUROECTODERMAL TUMORS (PNET) (EXTRASKELET AL EWING SARCOMA)

DESCRIPTION Primitive neuroectodermal tumors are part of the Ewing family of tumors (EFT) that include Ewing's sarcoma of the bone. Peripheral PNET is a very aggressive neoplasm that predominantly affects children and adolescents. Renal PNET is the most reported PNET of the genitourinary tract, however bladder, prostate, ureter, and seminal cord PNETs have also been reported. PNETs are often diagnosed as metastatic disease (25–50%) and the outcome is often poor; with a 5-yr survival rate (45–55%).

TREATMENT

Multimodal therapy including surgical resection, chemotherapy, and radiation.

REFERENCE

Ellinger J, Bastian PJ, Hauser S, et al. Primitive neuroectodermal tumor: Rare, highly aggressive differential diagnosis in urologic malignancies. *Urology*. 2006;68:257–262.

PRINCETON III CONSENSUS RECOMMENDATIONS: ERECTILE DYSFUNCTION (ED) AND CARDIOVASCULAR DISEASE

DESCRIPTION The recommendations of the 3rd Princeton Consensus Conference focus on (1) evaluation and management of cardiovascular risk in men with ED and no known CVD, (2) reevaluation and modification of the 2nd conference recommendation for evaluation of cardiac risk associated with sexual activity in men with known CVD, and (3) the role of testosterone replacement therapy (TRT) in ED and CVD management (Image ☼).

REFERENCE

Nehra A, Nehra A1, Jackson G, Miner M, et al. The princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*. 2012;87(8):766–778.

PROLACTIN, SERUM LEVEL

DESCRIPTION Elevated prolactin levels are associated with infertility and ED. Hyperprolactinemia may be caused by a pituitary tumor, stress, medications, hypothyroidism, or idiopathic causes. A pituitary tumor will result in low serum gonadotropin and testosterone levels and elevated prolactin levels. The mainstay of therapy for prolactinomas is medical management.

Elevated prolactin levels >50 ng/mL suggest a prolactinomas. Renal failure, stress,

medications, and hypothyroidism have serum prolactin value <50 ng/mL.

TREATMENT
- Cabergoline
- Bromocriptine
- Surgical excision

REFERENCE
Verhelst J, Abs R. Hyperprolactinemia: Pathophysiology and management. *Treat Endocrinol.* 2003;2(1):23–32.

PROLAPSE, STAGING SYSTEMS

DESCRIPTION Since the early 1960s multiple practitioners including Porges, Baden, Walker, and Beecham have attempted to classify pelvic organ prolapse. Then in 1996 the American Urogynecologic Society, the Society of Gynecologic Surgeons, and the ICS adopted the Pelvic Organ Prolapse Quantitation (POP-Q) exam. The POP-Q exam, in which 9 specific points of measurement are obtained in relation to the hymenal ring, has been demonstrated to be learned easily and performed quickly with highly reproducible exam findings. The most widely used classification systems used today are the Baden–Walker and POPQ systems. (See also Section II: “Cystocele Grading: Baden–Walker, Pelvic Organ Prolapse Quantification [POP-Q].”)

REFERENCE
Theofrastous JP, Swift SE: The clinical evaluation of pelvic floor dysfunction. *Obstet Gynecol Clin North Am.* 1998;25:783–804.

PROPANTHELINE STIMULATION TEST

DESCRIPTION This test is used when involuntary detrusor contractions are demonstrated during cystometry to predict the outcome of pharmacologic treatment with anticholinergics. Propantheline bromide is an anticholinergic with side effects that include dry mouth and blurred vision. Once involuntary detrusor contractions have been confirmed, 15 mg of propantheline bromide are administered parenterally. Once effects of the drug are noticed, cystometry is repeated. A positive response is defined as the complete abolition of involuntary detrusor contractions, or a 200% increase in the bladder volume at which they occur. If the parenteral dosage is effective, a favorable clinical response to the orally administered dose can be expected in most patients.

REFERENCE
Blaivis JG, Scott RM, Labib KB. Urodynamic evaluation as a test of sacral cord function. *Urology*. 1979;13:682–687.

PROPHYLACTIC ANTIBIOTICS, AUA GUIDELINES

DESCRIPTION Recommendations include limiting antibiotic prophylaxis to a maximum of 24 hr, no prophylaxis solely to prevent infectious endocarditis, and defining characteristics

for patients at higher risk. These characteristics include advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, distant coexistent infection, and prolonged hospitalization.

Recommendations for specific procedures and agents are found in Section VII: "Reference Tables: Antibiotic Prophylaxis: AUA guidelines."

REFERENCE

Wolf JS Jr., Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol.* 2008;179(4):1379–1390.

PROSTASCINT SCAN

DESCRIPTION A nuclear medicine imaging study designed to localize prostate cancer cells using a radiolabeled monoclonal antibody to PSMA (prostate-specific membrane antigen) called indium-111 capromab pendetide. Patients are injected, and single photon emission computed tomography is performed immediately after scan and 4–5 days later. This allows for washout of antibody from the blood and bowel. The test was initially designed to identify extraprostatic disease, and current applications include identifying the location of cancer recurrence following definitive therapy for prostate cancer. It has traditionally suffered from poor specificity and interobserver reliability and issues concerning uptake of mid abdominal lymph nodes. Recent data suggest that there may be renewed interest in integrating the ProstaScint scan in clinical decision making for deciding between local vs. systemic salvage therapy for PSA recurrence following definitive management of prostate cancer (Image ☼).

REFERENCE

Taneja S. ProstaScint Scan: Contemporary use in clinical practice. *Rev Urol.* 2004;S10:19–28.

PROSTATE CANCER SCREENING GUIDELINES

DESCRIPTION Screening asymptomatic men for prostate cancer is controversial. Concerns about over diagnosis and overtreatment of clinically important cancers are part of this reason. Many professional organizations have developed guidelines concerning prostate cancer screening that are summarized in the table. (See also Section II: "PSA, General Considerations" and Section VII: Reference Tables: Prostate Cancer Screening Guidelines.)

Organization	Recommendation (all PSA values in ng/mL)
American Cancer Society (ACS) (2010)	• No routine screening; After informed discussion for those who wish to be screened: – Screen with PSA, w/or w/o DRE, at age 50 with >10 yr life expectancy – Screen at age 45 with high risk[a]; age 40 with highest risk[b] – No screening with <10 yr life expectancy (age 75)
American College of Physicians (2013)	• Inform men age 50–69 about limited benefits and harms; screen only if patient wants it • Do not screen <age 50 if average risk, over 69, or <10–15-yr life expectancy
American Urological Association (2013)	• No screening under 40; not recommended if average risk 40–54; individualize if high risk[c] • Shared decision making for men age 55–69 • No screening over age 75 or any man <10–15-yr life expectancy • Reduce the harms of screening, a screening interval of 2 yr or more may be preferred
National Comprehensive Cancer Network (NCCN)(2014)	• Informed discussion with all • Baseline DRE & PSA age 45; if PSA <1 repeat age 50; if PSA >1, repeat every 1–2 yr • Age 50–70 with normal DRE & PSA <3, repeat every 1–2 yr • Use caution screening if >age 70 and only if very healthy; few >age 75 benefit from screening
USPSTF (2012)	• No role in any man unless symptoms (Grade D)

[a] African-American or have a 1st degree relative diagnosed with PCa at <65 yr of age
[b] Several 1st degree relatives diagnosed with PCa at <65 yr of age
[c] Positive family history or African-American race
Modified from Gomella LG, et al. *CJU*. 2011;18(5):5875; ACP 2013 guidelines (www.acponline.org); NCCN 2014 Prostate Cancer Early Detection Guidelines Version 1.2014 (www.nccn.org).

REFERENCES

Gomella LG, Liu XS, Trabulsi EJ, et al. Screening for prostate cancer: the current evidence and guidelines controversy. *Can J Urol*. 2011;18(5):5875–5883. Review

ACP 2013 Prostate Cancer Screening Guidelines (www.acponline.org); NCCN 2014 Prostate Cancer Early Detection Guidelines Version 1.2014 (www.nccn.org) Accessed March 30, 2014.

PROSTATE CANCER, ACTIVE SURVEILLANCE AND WATCHFUL WAITING

DESCRIPTION Screening for prostate cancer can result in the diagnosis of prostate cancer in many men who are not likely to suffer any consequences or die from the disease. This often results in overtreatment of many men with prostate cancer. Deferred therapy for prostate cancer generally involves 2 different approaches although the terms are often used interchangeably, they are not completely identical:

- *Active surveillance* is a strategy aiming to individualize the management of early prostate cancer by selecting only those men with significant cancers for curative therapy. This involves actively monitoring the course of prostate cancer with the intent of intervention with definitive local therapy (eg, radiation therapy, RP) if cancer progression is documented.
- *Watchful waiting* uses less aggressive follow-up until the patient develops symptomatic disease progression, at which time he is often placed on hormonal treatment. (See also Section I: “Prostate Cancer, General” and “Prostate Cancer, Very Low Risk and Active Surveillance”; Section II: “Life Expectancy, Urologic Considerations.”)

REFERENCE

NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer V.1.2014. Available at www.nccn.org. Accessed March 4, 2014)

PROSTATE CANCER, BASAL CELL CARCINOMA

DESCRIPTION A very rare variant of prostate cancer comprising $<0.01\%$ of malignant tumors. Lesions exist in 2 distinct forms, adenoid cystic carcinoma (ACC), and basaloid carcinoma (BC), that may occur clinically separate or as mixed tumors with 1 dominant pattern. Immunohistochemical analysis reveals strongly positive results for both 34βE12 and p63. Once thought to be a more indolent form of prostate cancer, current evidence supports the potential for local recurrence and metastasis and therefore suggests radical surgery with life-long follow-up as 1st-line management.

REFERENCE

Montironi R, Mazzucchelli R, Stramazzotti D, et al. Basal cell hyperplasia and basal cell carcinoma of the prostate: A comprehensive review and discussion of a case with c-erbB-2 expression. *J Clin Pathol.* 2005;58:290–296.

PROSTATE CANCER, CIRCULATING TUMOR CELLS (CTC's)

DESCRIPTION Circulating tumor cells (CTC) can be detected using molecular techniques such as RT-PCR. An identification assay for actual circulating cells (CellSearch) is commercially available for use in patients with hormone-refractory prostate cancer. In patients with advanced prostate cancer, men with ≥ 5 CTCs per 7.5 mL blood prior to chemotherapy had a significantly shorter median survival (10 vs. 21 mo in those with <5 CTCs). The role of the CTC assay continues to evolve in the management of prostate cancer; it appears to be only valid at present for men with advanced, castrate resistant prostate cancer disease and is not as useful for earlier stages of disease. (See also Section II: "PSA, RT-PCR.")

REFERENCE

de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2008;14(19):6302–6309.

PROSTATE CANCER, DUCTAL ADENOCARCINOMA

DESCRIPTION These terms have been replaced by *ductal adenocarcinoma of the prostate.* It accounts for 0.2–0.8% of prostate adenocarcinoma. Due to its appearance, ductal adenocarcinoma was previously thought to arise from müllerian remnants and possess unique clinical features related to its origin. While further analyses have shown that these tumors do in fact arise from prostatic tissue. The lesion originates from periurethral prostatic ducts and may grow into an exophytic urethral lesion around the verumontanum. A mixture of cribriform and papillary structures is seen on microscopy, resembling endometrial adenocarcinoma of the uterus and hence the earlier descriptive terms. Histologically, these tumors are composed of tall columnar cells with clear to eosinophilic cytoplasm and large nucleoli. The cells form glands with scant intervening stroma. Prostatic ductal carcinoma cells express PSA. Prostate adenocarcinoma is also present in 77% of cases.

Early presentation is hematuria, irritative and obstructive symptoms and it tends to occur in older men (60–80 yr). Serum PSA levels and DRE at the time of diagnosis tend to underestimate disease. Cystoscopically it may appear multiple polypoid friable protruding from near the mouth of the prostatic utricle but often there are no defining endoscopic

findings. Sources are conflicting concerning the clinical presentation with some stating due to the early symptom presentation most are organ confined and others more likely to present with advanced stage cancer. The behavior has been compared to behaved similar to Gleason's 8 (4 + 4) acinar prostate adenocarcinoma.

SYNONYMS

- Ductal carcinoma of the prostate
- Endometrioid carcinoma, prostate
- Endometrial carcinoma of the prostate
- Papillary adenocarcinoma of the prostatic utricle

TREATMENT

Similar to high-grade acinar adenocarcinoma of prostate. Most in the literature have been managed by radical prostatectomy. Ductal carcinoma of the prostate tends to be hormone sensitive and advanced disease is initially responsive to androgen deprivation. The overall mortality was significantly worse in men with ductal prostate adenocarcinoma, almost 3-fold higher rate of death, as compared to acinar prostate adenocarcinoma.

REFERENCES

Bostwick DG, Meiers I. Neoplasms of the prostate. Chapter 9 in Bostwick DG, ed. *Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008:493–495.

Morgan TM, Welty CJ, Vakar-Lopez F, et al. Ductal adenocarcinoma of the prostate: Increased mortality risk and decreased PSA secretion *J Urol*. 2010;184(6):2303–2307.

PROSTATE CANCER, FAMILIAL

DESCRIPTION The risk of prostate cancer is directly dependent upon the number of affected 1st-degree relatives, the age of the relative when diagnosed, and whether the relative is a father or brother. Risk is also associated with a family history of breast cancer.

Relations	Risk of Prostate Cancer	Relations	Risk of Prostate Cancer
Any relative	1.93	Brother	2.84
Any 1st degree	2.22	1st degree dx <60 yr	2.16
Any 2nd degree	1.88		
Father	2.12	1st degree with breast cancer	1.24

REFERENCE

Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: Systematic review and meta-analysis. *Int J Cancer*. 2003;107:797–803.

PROSTATE CANCER, LEIOMYOSARCOMA, AND OTHER UNCOMMON SARCOMAS

DESCRIPTION Leiomyosarcoma of the prostate is extremely rare and a highly aggressive neoplasm, accounting for <0.1% of primary prostate malignancies. It is the most common primary prostatic sarcoma of the prostate in adults and comprises 38–52% of adult prostatic sarcomas. Rhabdomyosarcoma most common in pediatric patients and can be seen in adults.

Other less common prostate sarcomas include MFH and prostatic stromal sarcoma. Presentation can include urinary obstruction frequency, urgency, hematuria, perineal and/or rectal, pain, constipation, burning on ejaculation, and constitutional symptoms. The diagnosis of prostate sarcoma was usually established with ultrasound-guided biopsy or transurethral resection, and PSA is usually normal. Multimodality therapy using surgery RP, radical cystectomy, pelvic exenteration with pre- or postoperative radiation and pre- or postoperative chemotherapy have been used with no standard of care. Doxorubicin-based combinations with agents such as cyclophosphamide, ifosfamide, vinblastine, or vincristine have been reported with mixed results.

REFERENCES

Pace G, Pomante R, Vicentini C. Sarcoma of prostate: Case report and review of the literature. *Arch Ital Urol Androl.* 2010;82(2):105–108.

Sexton WJ, Lance RE, Reyes AO, et al. Adult prostate sarcoma: The MD Anderson cancer center experience. *J Urol.* 2001;166(2):521–525.

PROSTATE CANCER, MUCINOUS ADENOCARCINOMA

DESCRIPTION These very rare tumors are histopathologically defined as having lakes of extracellular mucin comprising at least 25% of the primary prostate tumor. They generally are considered to have a slightly worse prognosis than typical adenocarcinoma of the prostate but other literature states the behavior is similar to adenocarcinoma of the prostate with no statistically significant difference in biochemical failure or survival. They can be hormonally refractory, and bone metastasis are common. Radiation and/or surgery can be considered.

REFERENCES

Ro JY, Grignon DJ, Ayala AG, et al. Mucinous adenocarcinoma of the prostate: Histochemical and immunohistochemical studies. *Hum Pathol.* 1990;21:593–600.

Lane BR, Magi-Galluzzi C, Reuther AM, et al. Mucinous adenocarcinoma of the prostate does not confer poor prognosis. *Urology.* 2006;68(4):825–830.

PROSTATE CANCER, PREVENTION (CHEMOPREVENTION)

DESCRIPTION Numerous medications and nutraceuticals, including selenium, statins, and green teas, have been evaluated for the prevention of prostate cancer, but the most notable remain the 5α-reductase inhibitors (5 ARIs) finasteride and dutasteride. The Prostate Cancer Prevention Trial (PCPT) using finasteride demonstrated an almost 25% reduction in the incidence of prostate cancer but a slightly increased incidence of higher Gleason score cancers. Some have hypothesized that this may be due to selective inhibition of low-grade cancers along with a smaller prostate size resulting in less sampling error and better detection of higher-grade cancers already present. This is supported by whole-mount correlation from RP specimens. The REduction DUtasteride of prostate Cancer (REDUCE) trial using dutasteride (a dual 5α-reductase inhibitor) reported a 23% reduction in prostate cancer in high-risk men with a slight increase in high-grade cancers. The large SELECT trial using selenium and vitamin E was stopped prematurely because it did not appear that either agent alone or in combination reduced the risk of prostate cancer. In 2011, updated trial data

showed that the men taking vitamin E had a 17% increased risk of prostate cancer compared to men taking the placebo. In 2014, an analysis showed that men who started the trial with high levels of selenium, as assessed by measures of selenium in their toenail clippings, doubled their risk of developing a high-grade prostate cancer by taking selenium supplements and men who had low levels of selenium at the start of the trial doubled their risk of high-grade prostate cancer by taking vitamin E. Trial sponsors recommended that men avoid supplementation with these agents.

Clinical Stage	Calculator Origin	Interactive Location (All Accessed April 22, 2014)
Pre-biopsy	Sunnybrook Health Sciences Center, Toronto	http://sunnybrook.ca/content/?page = occ-prostateriskca
Pre-/post-biopsy	PCPT (prostate cancer prevention trial)	http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp
Pre/post-biopsy	ERSPC (European Randomized Study of Screening for Prostate Cancer)	http://www.prostatecancer-riskcalculator.com/
Preoperative	Partin Tables	http://urology.jhu.edu/prostate/partintables.php
Pre-/post-operative	Kattan Nomograms MSKCC (Memorial Sloan Kettering Cancer Center)	http://www.mskcc.org/mskcc/html/10088.cfm
Postoperative	CPDR (Center for Prostate Disease Research and Treatment) Recurrence	http://www.cpdr.org/

In 2008, ASCO and the AUA 2008 issued the following Clinical Practice Guidelines:

- Asymptomatic men, PSA <3.0 ng/mL who are regularly screened or anticipate undergoing annual PSA screening may benefit from a discussion of risks and benefits of 5-ARIs for 7 yr for the prevention of prostate cancer.
- Men taking 5-ARIs for LUTS should also discuss risks and benefits.
- A reduction of PSA by 50% at 12 mo is expected in men on 5-ARIs; the panel did not recommend a specific cut-point to trigger a biopsy for men taking a 5-ARI.

However at the present time there is no approved agent to prevent the development of prostate cancer.

REFERENCES

Kramer BS, Hagerty KL, Justman S, et al. Use of 5α-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Urol*. 2009;181:1642–1657.

Parnes HL, Brawley OW, Minasian LM, et al. Phase III prostate cancer chemoprevention trials. *Recent Results Cancer Res*. 2014;202:73–77.

Selenium And Vitamin E Cancer Prevention Trial (SELECT) http://www.cancer.gov/newscenter/qa/2008/selectqa, Accessed March 6, 2014.

PROSTATE CANCER RISK CALCULATORS

DESCRIPTION Usually in the form of tables or nomograms, these are predictive instruments developed to aid clinicians and patients alike in objectively assessing different aspects of prostate disease throughout its various stages of diagnosis and treatment. Most calculators are available online, with interactive modules that facilitate their incorporation into clinical practice (see below).

REFERENCES

Caras RJ, Sterbis JR. Prostate cancer nomograms: a review of their use in cancer detection and treatment. *Curr Urol Rep.* 2014;15(3):391.
Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int.* 2013;111(1):22–29.

PROSTATE CANCER, RISK STRATIFICATION (D'AMICO CLASSIFICATION)

DESCRIPTION One challenge presented by prostate cancer is choosing the appropriate therapy based on the risk of disease progression. It is often useful to assign a relative risk to an individual. These risk groups were established from literature and based on known prognostic factors: PSA level, biopsy Gleason score, and 1992 AJCC T staging. 1 typical system, commonly referred to as the *D'Amico classification*, is described here. Note that this is risk of PSA progression posttherapy and not overall or disease-specific survival:

- Low risk: Stages T1c and T2a, PSA level of ≤ 10 ng/mL, and biopsy Gleason score of ≤ 6 ($< 25\%$ PSA progression at 5 yr post therapy)
- Intermediate risk: PSA levels ≤ 10–20 ng/mL, biopsy Gleason score of 7, or AJCC clinical stage T2b (25–50% PSA progression at 5 yr post therapy)
- High risk: T2c disease or a PSA level > 20 ng/mL or a biopsy Gleason score of ≥ 8 ($> 50\%$ PSA progression at 5-yr post therapy)

REFERENCE

D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969–974.

PROSTATE CANCER, SECONDARY HORMONAL THERAPY

DESCRIPTION In the setting of primary ADT failure (rising PSA with castrate level of testosterone considered to be a serum testosterone of < 50 ng/dL), is called castrate refractory prostate cancer (CRPC). A variety of strategies involving so-called "secondary hormonal therapy" can be applied. It should be noted that in all cases, castrate levels of testosterone should be maintained through the use of agents such as LHRH analogs while these additional therapies are applied. Common secondary hormonal therapies include:

- Antiandrogen withdrawal (See Section II: "Antiandrogen Withdrawal Syndrome [Flutamide Withdrawal Syndrome].")
- Administration of antiandrogens (eg, bicalutamide, nilutamide, flutamide)
- Administration of ketoconazole (ketoconazole has a weak and nonspecific inhibitory affect on several enzymes involved in androgen synthesis and has been widely used in combination with hydrocortisone for the treatment of CRPC)
- Estrogens, such as DES

To date, none of these agents have demonstrated a prolongation in overall survival in the prechemotherapy setting. The use of secondary hormonal manipulation is decreasing with the approval of multiple newer medications for CRPC. In the presence of metastasis (mCRPC) abiraterone acetate with low-dose prednisone and enzalutamide prolong overall survival

among men with metastatic CRPC who have been previously treated with docetaxel. Abiraterone acetate can be considered for men with metastatic CRPC the predocetaxel metastatic CRPC setting. Other new agents for mCRPC include sipuleucel-T, cabazitaxel and radium 223. (See also Section I: "Prostate Cancer, Rising PSA Following Androgen Ablation [Castrate Refractory Prostate Cancer, CRPC, mCRPC]".)

REFERENCES

Al-Asaaed S, Winquist E. Secondary hormonal manipulation in castration resistant prostate cancer. *Can J Urol.* 2014;21(Suppl 1):37–41.

NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer V.1.2014. Available at www.nccn.org, Acessed March 25, 2014.

PROSTATE CANCER, SMALL CELL (NEUROENDOCRINE)

DESCRIPTION A rare subtype of prostate malignancy that has a rapidly fatal course. Considered to be a variant of Gleason 5 adenocarcinoma of the prostate, it is identical to small cell carcinomas of the lung and has neuroendocrine (small cell, oat cell) differentiation. In 50% of the cases, the tumors are mixed small cell carcinoma with adenocarcinoma. Histologically, prostatic SCCs of the prostate are part of a spectrum of anaplastic tumors of the prostate and are similar to SCCs of the lungs. Neuroendocrine cells are identified by special staining (ie, neuron-specific enolase [NSE] or other markers). It should be noted that the normal prostate does have some neuroendocrine positivity, but it is limited and can only be detected by staining. About 10% of acinar adenocarcinomas of the prostate can have Paneth-like cells (large eosinophilic cells) that are neuroendocrine, and it is recognized that adenocarcinoma of the prostate that is not classified as neuroendocrine can have some patchy cells that stain as neuroendocrine cells. Large numbers of Gleason 5 cells in a prostate sample should prompt a neuroendocrine staining workup of the sample. Tumors can exhibit a spectrum of differentiation, with a carcinoid-like pattern (low-grade neuroendocrine carcinoma) to the small cell undifferentiated type (oat cell), the highest grade of neuroendocrine tumor. Immunohistochemically, these cells can stain for serotonin, calcitonin, ACTH, hCG, and other markers. Most of these small cell tumors do not produce detectable levels of hormones but sometimes can produce detectable levels in the serum. They may also express and stain for PSA and acid phosphatase, but pure small cell carcinoma usually does not stain for PSA. The clinical behavior of small cell prostate carcinomas is characterized by extensive local disease, visceral disease, and low PSA levels despite large metastatic burden. At diagnosis, 70% of patients have metastatic disease, and visceral metastases are common (ie, liver). The average survival is <1 yr. Androgen receptor–positive tumors have a worse prognosis than do tumors that do not express the receptor median survival (10 mo vs. 30 mo). Diagnosis is made by TRUS biopsy, symptoms associated with metastasis, and elevated LFTs and CEA.

SYNONYMS

- Small cell anaplastic carcinoma of the prostate (SCCP)
- Oat cell carcinoma of the prostate
- Neuroendocrine prostate cancer
- Carcinoid of the prostate

TREATMENT

- These tumors respond poorly to androgen ablation, but this should be attempted.
- Surgery and/or radiation therapy may provide local control.
- Chemotherapy with agents such as VP-16 and cisplatinum have some activity.

REFERENCE

Nadal R, Schweizer M1, Kryvenko ON, et al. Small cell carcinoma of the prostate. *Nat Rev Urol.* 2014;11(4):213–219.

PROSTATE CANCER, SQUAMOUS AND ADENOSQUAMOUS

DESCRIPTION A rare lesion that can arise in patients infected with *Schistosoma haematobium*. It can be confused with more common conditions, such as squamous metaplasia of the prostate due to infarction, radiation, and hormonal therapy. Pure primary SCC of the prostate does not respond to estrogen therapy, and it does not develop elevated serum PSA or PAP levels with metastatic disease. Bone metastases are osteolytic instead of osteoblastic. Median survival is about 14 mo.

REFERENCE

Bostwick DG, Meiers I. Neoplasms of the prostate (Chapter 9). In: Bostwick DG, ed. *Urologic Surgical Pathology.* 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008:512.

PROSTATE HEALTH INDEX (PHI) AND [–2] proPSA

DESCRIPTION The Beckman Coulter Prostate Health Index (phi) is a mathematical combination of total PSA (tPSA), free PSA (fPSA) and [–2] proPSA (an isoform of PSA). The mathematical equation is: ([–2] proPSA/fPSA) × (√tPSA). The phi has been shown to have a higher PCa predictive value than both total PSA and free PSA. The measurement of %[–2] proPSA improves the accuracy of prostate cancer detection in comparison with PSA or % of PSA, particularly in the group of patients with PSA between 2 µg/L and 10 µg/L. The phi may be able to reduce the number of unnecessary biopsies, maintaining a high cancer detection rate. Published results also showed that %[–2] proPSA and phi are related to the aggressiveness of the tumor.

REFERENCES

Lazzeri M, Haese A, de la Taille A, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2–10 ng/ml: A multicentric European study. *Eur Urol.* 2013;63(6):986–994.

Filella X, Giménez N. Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: A systematic review and meta-analysis. *Clin Chem Lab Med.* 2013;51(4):729–739.

PROSTATE URETHRAL ANGLE

DESCRIPTION The prostatic urethra runs through the prostate from the base to the apex, making an anterior angle of ~35° at the proximal verumontanum. In men with prostate hyperplasia this angle tends to be >35°. However, men without hyperplasia can also have an

increased prostatic urethral angle. On cystoscopic exam, an increased prostatic urethral angle (PUA) is often noted as a high bladder neck in men without prostatic enlargement. In preliminary clinical studies, the PUA was inversely associated with the urinary flow rate.

REFERENCE

Cho KS, Kim JH, Kim DJ, et al. Relationship between prostatic urethral angle and urinary flow rate: Its implication in benign prostatic hyperplasia pathogenesis. *Urology*. 2008;71:858–862.

PROSTATE, BASAL CELL HYPERPLASIA

DESCRIPTION Basal cell hyperplasia is important in that it is commonly associated with BPH and may sometimes be mistaken for prostate cancer. The prostatic epithelium consists of 3 major cell types: Epithelial, basal, and neuroendocrine cells. The basal cells are small and round with a scant cytoplasm and dark nuclei. These cells are less differentiated and almost devoid of secretory products; they are located between the secretory cells and rest on the basement membrane. Basal cells are negative for PSA and PAP. Typical basal cell hyperplasia consists of a proliferation of basal cells ≥ 2 cell layers thick at the periphery of prostate glands and acini. Basal cell proliferation in the prostate gland exhibits a spectrum from focal basal cell hyperplasia in the setting of nodular hyperplasia to a florid adenoid basal cell tumor. Many confusing names have been used in the literature fet alization of prostate, embryonal hyperplasia, basal cell tumor, basal cell adenoma, BC, adenoid cystic carcinoma. The differential diagnosis includes transitional cell hyperplasia, squamous metaplasia, urothelial carcinoma (TCC) of the prostate, and adenocarcinoma of prostate.

REFERENCE

Bhat S, Thomas A, Nazar M, et al. Basal cell hyperplasia of prostate-an entity a urologist must know. *Indian J Urol*. 2000;17:61–62.

PROSTATE, BENIGN ENLARGEMENT (BENIGN PROSTATE ENLARGEMENT [BPE])

DESCRIPTION Benign prostatic enlargement (BPE) is used when there is gland enlargement and is usually a presumptive diagnosis based on the size of the prostate. This term differs from BPH which is reserved for the histologic pattern it describes. A patient may have LUTS with or without BPE. (See also Section I: “Bladder Outlet Obstruction [BOO],” “Prostate, Benign Hyperplasia/ Hypertrophy [BPH]” and Section II: “Prostate, Benign Obstruction (Benign Prostatic Obstruction [BPO]).”)

REFERENCE

Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol*. 2009;181:1779–1778.

PROSTATE, BENIGN OBSTRUCTION (BENIGN PROSTATIC OBSTRUCTION [BPO])

DESCRIPTION BPO is used when obstruction has been proven by pressure–flow studies, or is highly suspected from flow rates and if the gland is enlarged. This is different from bladder outlet obstruction, the generic term for all forms of obstruction to the bladder outlet (eg, urethral stricture) including BPO. (See also Section I: "Bladder Outlet Obstruction [BOO]", "Prostate, Benign Hyperplasia/Hypertrophy [BPH]" and Section II: "Prostate, Benign Enlargement (Benign Prostate Enlargement [BPE]).")

REFERENCE

Abrams P, Chapple C, Khoury S, et al. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol.* 2009;181:1779–1787.

PROSTATE CALCULI

DESCRIPTION Calculi are more common in older males and are rarely found in children. They usually occur in clusters and are associated with other disease processes. Often found in a dilated prostatic utricle. They are generally asymptomatic but may cause symptoms such as decreased urinary stream, prostatism, and lower back pain; they are a rare source of chronic bacterial prostatitis. Calculi may form secondary to calcification of the corpora amylacea and simple precipitation of prostatic secretions.

TREATMENT

- Generally none
- Transurethral resection with laser lithotripsy as needed if markedly symptomatic

REFERENCE

Klimas R, Bennett B, Gardner WA Jr. Prostatic calculi: A review. *Prostate.* 1985;7(1):91–96.

PROSTATE, FEMALE

DESCRIPTION A coined radiologic expression that refers to an impression at the base of the female bladder seen on excretory urography or cystogram. The impression resembles an enlarged prostate in the male and can be caused by urethral diverticulum, benign and malignant tumors of the anterior vaginal wall, urethral neoplasm, and repair of SUI. Anatomically Skene paraurethral glands and ducts are considered homologous to the male prostate and immunohistochemical studies demonstrate expression of PSA and prostate-specific acid phosphatase (PSAP) in these paraurethral glands and ducts.

REFERENCES

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston: Little, Brown; 1991:289.

Zaviaĉiĉ M, Ablin R. The female prostate. *J Natl Cancer Inst.* 1998;90(9):713.

PROSTATE, HEMATURIA

DESCRIPTION Hematuria attributed to bleeding from the prostate is a diagnosis of exclusion. Patients should have an appropriate workup according to the guidelines provided by the AUA. Older patients with larger, more vascular prostates are more susceptible and can

be managed with 5α-reductase inhibitors or transurethral resection if bleeding is refractory to medical therapy. Most often idiopathic, bleeding can also be iatrogenic after prostate biopsy and endoscopic urologic procedures or due to locally advanced prostate cancer late manifestation.

TREATMENT

- 5α-reductase inhibitors (1st-line therapy for troublesome benign prostatic hypertrophy bleeding)
- Intravesical alum, silver nitrate, and formalin (2nd-line therapy)
- Transurethral resection or vaporization of the prostate

REFERENCE

Rastinehad AR, Ost MC, VanderBrink BA, et al. Persistent prostatic hematuria. *Nat Clin Pract Urol.* 2008;5(3):159–165.

PROSTATE, INFARCTION

DESCRIPTION The etiology of prostatic infarction is still unclear, although it has been linked to prostate hyperplasia. Histologic findings include infraction of prostatic epithelium, with hemorrhage and neutrophils in the intervening stroma. Recent infarcts generally do not have squamous metaplasia, whereas older ones do. Typically, the infarctions are multiple and located in the central and middle concentric zones of the middle 3rd of the prostate. Prostatic infarction may elevate PSA levels.

REFERENCE

Brawn PN, Foster DM, Jay DW, et al. Characteristics of prostatic infarcts and their effect on serum prostate-specific antigen and prostatic acid phosphatase. *Urology.* 1994;44(1):71–74.

PROSTATE, MASSAGE

DESCRIPTION Repetitive prostatic massage is not a new tool in the urologists' armamentarium. It can be used to localize lower UTIs or as a therapeutic modality. Once the most popular therapeutic maneuver used to treat prostatitis, it was abandoned as primary therapy almost 30 yr ago. Based on experience reported outside North America and anecdotal experiences of some patients and their physicians, some believe it has a role in certain forms of prostatitis, such as chronic non-bacterial prostatitis or chronic pelvic pain syndrome (CPPS). The prostate is massaged from the lateral border to the medial aspect on each side, from base to apex. Firm pressure is necessary to express prostatic fluid into the urethra. A sterile container should be held by the patient at the meatus to capture the expressed prostatic fluids. The test is contraindicated in acute bacterial prostatitis. (See also Section II: "Attentive Digital Rectal Exam [DRE]" "Expressed Prostatic Secretions [EPS]" and "Stamey Test [Three-glass test, Four-glass tests, Meares-Stamey Test].")

REFERENCE

Nickel JC, Alexander R, Anderson R, et al. Prostatitis unplugged? Prostatic massage revisited. *Techniques Urol.* 1999;5(1):1–7.

PROSTATE STENTS (UROLUME AND SPANNER)

DESCRIPTION The UroLume stent is a woven tubular mesh designed to treat obstructions secondary to BPH, recurrent bulbar urethral strictures (RBUS), or detrusor external sphincter dyssynergia (DSD or DESD) long-term. The cylinder is made of high strength, impact grade, super alloy wire. It has the potential to expand to a diameter of 14 mm (42F) and is available in lengths of 1.5, 2.0, 2.5, and 3.0 cm. UroLume is provided preloaded in a sterile, disposable delivery instrument. The outer diameter of the tool is 22F along the shaft and 24F at the tapered tip. Numerous problems have plagued the stent, including short-term problems with irritative voiding symptoms, painful ejaculation, and stent migration. Long-term problems include stent encrustation and ingrowth of epithelial tissue causing restenosis. It may have a role in patients who present with urinary retention and are considered at high risk for surgical intervention, but it should otherwise not be used for patients who can tolerate a surgical procedure.

The Spanner stent is similar to a Foley catheter in that it has a proximal port to drain urine, a balloon that resides at the bladder neck to prevent migration, and a stent that spans the prostatic urethra. Considered a temporary device, it may have a role in temporary management of bladder outlet obstruction following procedures such as brachytherapy or TUMT. Other stents such as the Memotherm (Angiomed Gmbh & Co.) are available outside the United States. EAU considers prostate stents are an alternative to catheterization for men unfit for surgery (Image ☼).

REFERENCES

Vanderbrink BA, Rastinehad AR, Badlani GH. Prostatic stents for the treatment of benign prostatic hyperplasia. *Curr Opin Urol*. 2007;17(1):1–6.

Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2013;64(1):118–140.

Goh MH, Kastner C, Khan S, et al. First experiences with the Spanner™ temporary prostatic stent for prostatic urethral obstruction. *Urol Int*. 2013;91(4):384–390.

PROSTATIC ACID PHOSPHATASE (PAP)

DESCRIPTION Human PAP is a glycoprotein dimer of 102,000 MW. Its activity is much greater in the prostate than in any other tissue. PAP is not prostate-specific, and can be found in other tissues. Historically, PAP was used as a serum marker for the staging and detection of prostate cancer before the discovery of prostate-specific antigen (PSA). Although enzymatic elevation of PAP is associated with advanced prostate cancer, other causes of an elevated PAP are possible, including liver, skelet al, and renal disease. PAP is the primary target for the prostate cancer immunotherapy sipuleucel-t.

REFERENCES

Romas M, Kwan DJ. Prostatic acid phosphatase. *Urol Clin N Am*. 1993;20:581–588.

Gomella LG, Gelpi-Hammerschmidt F, Kundavram C. Practical guide to immunotherapy in castration resistant prostate cancer: the use of sipuleucel-T immunotherapy. *Can J Urol*. 2014;21(Suppl 1):48–56.

PROSTATIC URETHRAL POLYPS

DESCRIPTION Urethral polyps are rare abnormalities in male children who present with hematuria or obstructive symptoms. Strangury (slow and painful urination) may be seen, with large lesions on a long stalk. The diagnosis is best confirmed by voiding cystourethrography. These polyps are nearly always in the prostatic fossa, although anterior urethral polyps have been reported. These are benign lesions and are not related to the polypoid masses of sarcoma botryoides.

TREATMENT

Transurethral excision of the polyps

REFERENCE

Raviv G, Leibovitch I, Hanani J, et al. Hematuria and voiding disorders in children caused by congenital urethral polyps. Principles of diagnosis and management. *Eur Urol.* 1993;23:382–385.

PROSTATIC UTRICLE ANOMALIES

DESCRIPTION The prostatic utricle is a small slitlike orifice found at the apex of the verumontanum. The utricle has been considered by most to be a remnant of the fused caudal ends of the müllerian ducts while others propose the origin is from the urogenital sinus. The most common anomaly associated with the prostatic utricle is a prostatic utricle cyst. Can be associated with unilateral renal agenesis, hypospadias, and cryptorchidism. Prostatic utricle cysts always arise from the level of the verumontanum and are always in the midline. Prostatic utricle cysts have been associated with LUTS, infertility, infection, stone formation, hypospadias, recurrent epididymitis, and neoplastic degeneration. However, prostatic utricle cysts are often asymptomatic (found in up to 4% of newborns and 1% of adults). The incidence of prostatic utricle cyst is 11–14% in association with hypospadias or intersex anomalies and up to 50% of perineal hypospadias. Rarely these may contain cancer (clear cell or squamous cell carcinoma). Differential diagnoses include müllerian duct cysts, bladder diverticulum, teratoma, seminal vesicle cyst, epididymal cyst, and wolffian duct cyst. Prostatic utricle cysts can be diagnosed on VCUG or trans rectal ultrasound.

Stones may also be found in the dilated prostatic utricle. These are considered to belong to the category of prostatic pseudocalculi (not caused by abnormal urine composition, but from deciduous epithelial cells of enlarged prostatic utricle). (See also Section II: “Müllerian Duct Remnants and Persistent Müllerian Duct Syndrome [PMDS] and Prostatic Utricle Calcification.”)

SYNONYMS

- Müllerian duct cyst (however müllerian duct cysts can be found anywhere along the path of müllerian duct regression, from the prostatic utricle into the scrotum whereas prostatic utricle cysts are always midline)
- Utricular cysts
- Utriculoceles
- Mega-utricles

TREATMENT

- Transurethral unroofing, endoscopic incision
- Surgical excision (suprapubic, transvesical, perineal, or laparoscopic)

REFERENCES

Priyadarshi V, Singh JP, Mishra S, et al. Prostatic utricle cyst: A clinical dilemma. *APSP J Case Rep*. 2013; 4(2):16.

Song NH, Wu HF, Xu NC, et al. The composition and structure of stones in enlarged prostatic utricles (EPU). *J Androl*. 2012;33(1):45–49.

PROSTATIC UTRICLE CALCIFICATION

DESCRIPTION The prostatic utricle is a remnant of the müllerian ducts. It is a small indentation located at the apex of the verumontanum. Enlargement of the prostatic utricle (EPU) is a rare abnormality which is associated with hypospadias and is the result of insufficient androgenic stimulation. The incidence of stones in EPU is unknown. 1 study found stones in 8 patients out of 44 (18.2%). Their size ranged from 3–18 mm and they were all composed of hydroxyapatite (HAP) crystal. Treatment includes transurethral utricle fenestration and stone removal. (See also Section II: “Prostatic Utricle Anomalies” and “Calcification, Prostate" (Image ☼).)

REFERENCE

Song NH, Wu HF, Xu NC, et al. The composition and structure of stones in enlarged prostatic utricles (EPU). *J Androl*. 2012;33(1):45–49.

PROSTATITIS, ASYMPTOMATIC INFLAMMATORY (NIH IV)

DESCRIPTION A type of nonbacterial prostatitis that is not associated with any specific symptom but is seen as inflammation on prostate biopsy. No specific treatment is necessary. (See Section II: “Prostatitis, NIH Classification.”)

REFERENCE

Habermacher GM, Chason JT, Schaeffer AJ. Prostatitis/chronic pelvic pain syndrome. *Annu Rev Med*. 2006;57:195–206.

PROSTATITIS, MYCOTIC (FUNGAL PROSTATITIS)

DESCRIPTION A type of granulomatous prostatitis caused by fungi and typically associated with systemic mycosis or immunocompromised hosts. Fungal infections can include blastomycosis, coccidiomycosis, cryptococcosis, histoplasmosis, and *Candida*. Diagnosis is based on prostatic histology and culture results. For systemic therapy, see the specific causative agent. (See Section I: “Fungal Infections, Genitourinary” and “Prostatitis, Granulomatous.”)

SYNONYM

Fungal prostatitis

REFERENCE

Schwartz J. Mycotic prostatitis. *Urology*. 1982;19:1–5.

PROSTATITIS, NIH CLASSIFICATION SYSTEM

DESCRIPTION A classification proposed by an NIH working group that clearly defines the different types of prostatitis in order to improve the diagnosis and management of the disease. (See Section I: "Prostatitis, Acute, Bacterial [NIH I]," "Prostatitis, Chronic, Bacterial [NIH II],", "Prostatitis, Chronic Nonbacterial, Inflammatory & Noninflammatory [NIH CP/CPPS III A and B]" and Section II: "Prostatitis, Asymptomatic Inflammatory [NIH IV].") For an explanation of EPS (expressed prostatoc secretions) and VB3 (voided bladder urine 3) see Section II: Stamey Test (Three-glass Test, Four-glass Tests, Meares-Stamey Test)

- Category I: Acute bacterial prostatitis; acute infection of the prostate gland
- Category II: Chronic bacterial prostatitis; recurrent infection of the prostate
- Category III: Chronic non-bacterial prostatitis/CPPS; no demonstrable infection
  - Category IIIA: Inflammatory CPPS; WBCs in semen/EPS VB3
  - Category IIIB: Noninflammatory CPPS; no WBCs in semen/EPS VB3
- Category IV: Asymptomatic inflammatory prostatitis; no symptoms

REFERENCE

Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236–237.

PROSTATITIS, STRESS

DESCRIPTION Classically defined as a subset of chronic abacterial noninflammatory prostatitis/prostatodynia in which a pattern of excessive tension could be identified as a trigger of the syndrome. Symptoms usually responded to anxiolytic agents or behavioral modifications. No longer considered an appropriate term in the NIH Prostatitis classification system.

REFERENCE

Miller HC. Stress prostatitis. *Urology* 1988;32:507.

PROSTATITIS, TUBERCULOUS

DESCRIPTION TB of the prostate is rare, and in many cases, it is diagnosed incidentally after a transurethral resection in the prostate chips. Tuberculous prostatitis results from hematogenous dissemination, with an incidence of 10% with men in TB. Symptoms are nonspecific. Irritative voiding may be the only complaints; other complaints include perineal pain and infertility. On exam, the prostate may be hard, irregular, and nodular. On labs, urine analysis can demonstrate microscopic hematuria or sterile pyuria. Acid-fast bacilli staining of urine and semen has a sensitivity of only 52%; however, culture can take up to 8 wk. A transrectal ultrasound can demonstrate collections or abscess, and an intravenous urogram (IVU) or CT Urogram (CTU) should be done because 72% of patients with prostatic TB have renal TB.

TREATMENT

- Hospitalization is usually unnecessary.
- Transurethral resection of the prostate in patients with obstructive symptomatology is reasonable.
- Medication includes a 3-drug regimen of isoniazid, pyrazinamide, and either ethambutol or streptomycin.
- In complicated cases, 9–12 mo therapy may be required. A negative prostatic biopsy to document successful treatment is recommended.

REFERENCE

Cek M, Lenk S, Naber KG, et al. EAU guidelines for the management of genitourinary TB. *Eur Urol*. 2005;48(3):353–362.

PROSTATODYNIA

DESCRIPTION Classically described as a symptom complex of multiple complaints including pain in the perineum, lower back, or upon ejaculation; slow stream; and hesitancy. Patients exhibit no evidence of prostatic inflammation. Dysuria, frequency, and systemic signs are usually absent. This term is not currently considered to be appropriate and has been replaced by the designation chronic pelvic pain syndrome or CPPS NIH Category III Chronic Abacterial Prostatitis. (See also Section I: "Prostatitis, Chronic Nonbacterial, Inflammatory & Noninflammatory [NIH CP/CPPS III A and B].")

REFERENCE

Orland SM, Hanno PM, Wein AJ. Prostatitis, prostatosis, and prostatodynia. *Urology*. 1985;25(5):439–459.

PROSTHESIS, INFECTED PENILE

DESCRIPTION A dreaded complication of penile prosthesis implantation. Rates of infection range from 1–8%; risk factors include spinal cord injury (SCI), diabetes mellitus especially (if poorly controlled with $HgbA_{1C} > 11.5\%$), history of UTI, and multiple prosthesis operations.

Infection usually occurs within 6 mo after implantation, but delayed infection is also reported. The most common symptom is persistent pain; patients also present with erythema, drainage, or fever. Causes of infection are *Staphylococcus epidermidis* (most common); gram-negative rods and yeast are also common. In the presence of an infection the implant and all foreign material should be removed. A salvage procedure, during which the wound is thoroughly washed with antiseptic solutions after device removal and placement of a new implant during the same procedure, has a high success rate and is becoming a popular approach. The alternative is device removal with return at a later date for placing a new implant, which entails a more difficult corporal dilation, and the resulting erection is noticeably shorter. (See also Section I: "Penile Prosthesis Problems [Infection/Extrusion/Malfunction] and Section II: "Mulcahy Protocol.")

TREATMENT

- Surgical removal

- Irrigation and antibiotic treatment
- Immediate salvage procedures with surgical removal
- Washout and immediate replacement have reported with good results: Vigorous intraoperative irrigation with 4 different solutions, including vancomycin; immediate reimplantation of a new inflatable penile prosthesis; and postoperative outpatient antibiotics, with oral ciprofloxacin or IV vancomycin or cefazolin.

REFERENCE

Mulcahy JJ. Current approach to the treatment of penile implant infections. *Ther Adv Urol.* 2010; 2(2): 69–75.

PRURITUS, EXTERNAL GENITALIA, MALE

DESCRIPTION The anogenital area is a common location for pruritic complaints in men and women. Itching can precede the appearance of a rash or other lesion. When the itching results in red, weeping skin with crusts, it is often called *eczematous dermatitis*. *Pruritus scroti* is a historic term for scrotal itching. The differential diagnosis of itching of the male external genitalia includes:

- Allergic reactions (allergic dermatitis)
- Cancer: Penile, scrotal, extra-mammary Paget disease (intraepidermal adenocarcinoma, found in areas with apocrine sweat glands).
- Candidal infection
- Chemical irritants: Detergents, fabric softeners, soaps, creams, ointments and sexual lubricants
- Dermatologic conditions: Seborrheic dermatitis, psoriasis, eczema (atopic dermatitis), lichen simplex chronicus (LSC)
- Fixed drug reaction
- HIV: Pruritus is 1 of the most frequent symptoms encountered in HIV infection and can even be the 1st clinical symptom
- Infestations: Pubic lice (“crabs”), scabies
- Nutritional deficiencies: Riboflavin, nicotinic acid
- Red scrotum syndrome possibly due to steroid abuse
- Sexually transmitted infections: Genital herpes
- Sunitinib toxicity
- Systemic illnesses: Diabetes mellitus, renal failure
- Tinea cruris: Also known as ringworm of the groin

Some patients manifest itching with or without a demonstrable local factor. The skin may appear normal or demonstrate excoriation (lichenification skin thickening) from rubbing, or both. These patients tend to have chronic illness (eg, diabetes) or depression with no pathogen identified. When treating anogenital pruritus, topic irritants and potential sensitizers must be eliminated and cleansing and toilet habits should be addressed. Treatment of the specific pathogen is essential. A short course of a high-potency topical steroid usually brings relief. Sedating antihistamines may limit nighttime symptoms. Some patients may require psychotropic agents for adequate sedation. Antidepressants may be required in patients refractory to standard treatment or those with underlying psychiatric disorders. (See

also Section II: “Scabies, Urologic Considerations.”)

REFERENCES

Johnston G, Sladden M. Scabies: diagnosis and treatment. *BMJ*. 2005;331(7517):619–622.

Krishnan A, Kar S. Scrotal Dermatitis - Can we consider it as a Separate Entity? *Oman Med J*. 2013;28(5):302–305.

PSA, AGE-ADJUSTED (SEE SECTION II “PSA, GENERAL CONSIDERATIONS”)

PSA BOUNCE (SEE SECTION II “PSA, GENERAL CONSIDERATIONS”)

PSA COMPLEXED (SEE SECTION II “PSA, GENERAL CONSIDERATIONS”)

PSA DENSITY (PSAD) (SEE SECTION II “PSA, GENERAL CONSIDERATIONS”)

PSA FAILURE, ASTRO AND PHOENIX DEFINITIONS (SEE SECTION II “PSA, GENERAL CONSIDERATIONS”)

PSA, FREE AND TOTAL (SEE SECTION II "PSA, GENERAL CONSIDERATIONS")

PSA, GENERAL CONSIDERATIONS AND PSA DERIVATIVES

DESCRIPTION

- **PSA Background:**
  - PSA was initially approved by the FDA as prostate cancer monitoring test in 1986 and as an aid for prostate cancer detection in 1994 in combination with DRE. PSA is a glycoprotein secreted by both malignant and benign prostate cells. PSA functions as a serine protease with the primary function to split the seminal vesicle proteins to liquefy the seminal coagulum. PSA is expressed in nearly all prostate cancers, although its level of expression on a per cell basis, especially in poorly differentiated prostate cancers, is actually lower than in normal prostate epithelium. The disruption of the basement membrane of prostate cancer allows more PSA to "leak" into the circulation.
- **PSA Physiology:**
  - PSA is a kallikrein that is also known as human glandular kallikrein 3 (hK3). The kallikreins are a type of enzymes (serine proteases), that cleave protein peptide bonds.
  - PSA is produced as a proenzyme (proPSA) by the secretory cells of the prostate acini and secreted into the lumen, where the proPSA is cleaved to enzymatically active PSA.
  - PSA circulates in serum in complexed forms (bound to protease inhibitors) or in un-complexed (free or unbound) forms
  - Active PSA undergoes proteolysis to form inactive PSA, of which a small portion enters the bloodstream in an unbound state (free PSA).
    - 10–30% of PSA is free in the serum and composed of various PSA isoforms. It is composed of 3 distinct isoforms: ProPSA, BPSA and iPSA (for "intact PSA" which decreases with cancer).
    - The precursor form of PSA (pro-PSA), especially its truncated (-2) form is significantly increased in PCa patients.
  - Active PSA can also enter the bloodstream where it is rapidly bound and inactivated (complexed) by protease inhibitors (alpha-1-antichymotrypsin [ACT] and alpha-2-macroglobulin). Most of the PSA in serum exists as a complex with ACT.
  - With prostate cancer the disrupted basal membrane allows proPSA and several truncated PSA isoforms direct access to the circulation. This PSA

"leaking" into the blood has a larger fraction of the PSA produced by malignant tissue escaping proteolytic processing (ie, activation of proPSA to active PSA and degradation of active PSA to inactive PSA).

  - In men with a normal prostate (no cancer or infection), the majority of free PSA in the serum reflects protein inactivated by internal proteolytic cleavage. In contrast, the cleaved fraction is relatively decreased in prostate cancer. Thus, the percentage of free or unbound PSA is lower in the serum of men with prostate cancer (and conversely, the amount of complexed PSA is higher) compared with those without cancer.
  - These observations have resulted in the use of the ratio of free to total PSA and complexed PSA (cPSA) as a means of distinguishing prostate cancer and BPH.
- **PSA Collection:** The PSA blood sample should be centrifuged, and the serum separated in

2–3 hr. If the assay is not performed within the next 2–3 hr, the serum should be frozen.

- **PSA Basic Clinical Considerations:** There is a vast amount of clinical data available to guide the clinicians in the use of PSA in patient care. This section highlights some of the published PSA clinical data in a highly annotated form.
  - Routine PSA blood testing refers to Total PSA and is reported in ng/mL; SI units mcg/L are identical.
  - Half-life: of PSA is 2.2 days.
  - PSA measured repeatedly can vary due to intrinsic biologic and assay variability (6–14%).
  - For serial PSA measurements using the same lab with the same analytic method is recommended.
  - No diurnal variation in PSA levels exists.
  - Increased BMI is associated with lower PSA.
  - Lower limits of PSA detection: 1st-generation assays 0.2 ng/mL; 2nd-generation assays <0.1 ng/mL; 3rd-generation "ultrasensitive assays" as low as 0.003 ng/mL. (Note: The utility of "ultrasensitive" PSA testing has not been clearly established in the post radical prostatectomy setting).
- **Normal PSA:** The exact definition of an "abnormal" PSA is subject to controversy. The historically defined level of 4.0 ng/mL was considered to be normal. PSA 4.0–10 ng/mL were considered to be mostly due to BPH.
  - **Age-specific PSA reference ranges**: Accounts for increases in prostate volume with age.
    - 40–49 yr: 0 to 2.5 ng/mL
    - 50–59 yr: 0 to 3.5 ng/mL
    - 60–69 yr: 0 to 4.5 ng/mL
    - 70–79 yr: 0 to 6.5 ng/mL
  - **Race-specific PSA normal ranges:** Different ethnic and racial groups are reported to have different average PSA.

Age Range	Whites	African Americans	Asians
40–49 yr:	0–2.5 ng/mL	0–2.0 ng/mL	0–2.0 ng/mL
50–59 yr:	0–3.5 ng/mL	0–4.0 ng/mL	0–3.0 ng/mL
60–69 yr:	0–3.5 ng/mL	0–4.5 ng/mL	0–4.0 ng/mL
70–79 yr:	0–3.5 ng/mL	0–5.5 ng/mL	0–5.0 ng/mL

  - **Common causes of elevated PSA:**
  - BPH, prostate cancer, acute prostatitis, prostate trauma (prostate biopsy, TURP, instrumentation, cystoscopy, perineal trauma), urinary retention, prostatic infarction
  - Wait at least 6 wk after biopsy or TURP before measuring PSA to avoid false elevation; less time after cystoscopy.
  - Following relief of urinary retention PSA levels decrease by 50% in 24–48 hr
  - A routine DRE will not clinically significantly increase PSA whereas formal prostate massage may elevate PSA.
  - In a small subset of men, sexual activity (ejaculation) and vigorous bicycle riding may elevate PSA. It is prudent to refrain from ejaculation and aggressive bicycle riding for 48 hr before PSA testing.
  - PSA levels tend to increase with age (related to prostate volume). Most PSA is made in the transition zone of the prostate, the region of the prostate that increases in volume in men

with BPH.
- **Medication effects on PSA:**
- 5-ARI (finasteride/dutasteride) regardless of dose will reduce PSA by 50% at 6 mo; "correct" PSA by doubling value.
- Any increase in PSA from baseline in men on 5-ARI should raise the concern for the development of prostate cancer.
- Statins, thiazides, NSAID's and acetaminophen all appear to lower PSA. Whether the relatively small changes in PSA with these drugs has clinical relevance is unknown.
- Lowering serum testosterone to castrate levels (<50 ng/dL using androgen deprivation using LHRH analogs/antagonists) will significantly decrease PSA initially. However, if the prostate cancer develops castration resistant features, the PSA usually rises.
- Increasing testosterone levels through supplementation can sometimes increase PSA.
- α1-adrenergic antagonists for BPH (tamsulosin, others) and herbals such as saw palmetto do not impact PSA.

• **PSA and Prostate Cancer Treatment:**
- Due to the half-life, wait a minimum 3 wk following RP for PSA nadir.
- A widely accepted definition of cancer recurrence following RP: A PSA >0.2 ng/mL that has risen on at least 2 separate occasions at least 2 wk apart and measured by the same lab.
- Persistently detectable PSA immediately following RP suggests systemic disease.
- A slowly rising PSA after being undetectable for >2 yr is most likely to be a prostate bed recurrence following RP.
- PSA >20 ng/mL with a diagnosis of prostate cancer is associated with extraprostatic disease and/or metastasis.
  - AUA guidelines suggest that bone scans and CT/MRI imaging is unnecessary with a PSA <20 ng/mL and no symptoms suggestive of advanced disease.
- Positive bone scan and PSA: 2.3% PSA <10.0 ng/mL; 5.3% PSA 10.1–19.9 ng/mL; 16.2% PSA >20.0 ng/mL
- PSA nadir of <1.0 ng/mL is associated with best long-term outcome following radiation therapy.
- If measured during external beam radiation therapy for prostate cancer, PSA shows a progressive decline.
- Since prostatic glandular tissue remains after radiation, PSA levels are unlikely to fall to undetectable following radiation therapy unless androgen ablation is also used.
- Optimum outcome for interstitial prostate brachytherapy is a PSA <0.7 ng/mL at 5 yr.
- Recurrence after radiation therapy for prostate cancer:
  - 3 consecutive rises in PSA (1996 ASTRO definition)
  - 2 point rise in PSA above posttreatment nadir (2005 Phoenix definition).
- **PSA bounce:** An initial decline in PSA followed by a transient rise (the so-called "bounce") 12–18 mo following radiation therapy (brachytherapy up to 40% of cases, also described for external beam radiation).This transient rise may not be a recurrence and should be followed. The PSA increases are generally small (<0.8 ng/mL) but can sometimes reach 10 ng/mL and may last 6–18 mo. Ironically bounces may predict a good outcome.

- PSA should fall to a low level after high intensity focused ultrasound (HIFU) and cryotherapy and should not rise on successive occasions. Data is limited using other.
- Salvage radiation following RP; especially those with positive surgical margins receiving treatment when the PSA is low (ie, 0.5–1.5 ng/mL) and slowly rising; appear to have best outcomes.
- With metastatic disease on androgen deprivation, failure to nadir PSA <4.0 ng/mL 7 mo after initiation of therapy is associated with a poor prognosis (median survival: 1 yr). With PSA nadir of <0.2 ng/mL median survival is 6 yr.
- PSA increase after RP or radiation with no radiologic evidence of metastases, a PSA nadir of >0.2 ng/mL within 8 mo of androgen suppression is associated with a 20-fold greater risk of prostate cancer-specific mortality vs. a nadir of <0.2 ng/mL.

• **PSA Derivatives:** There is recent conflict in the literature if PSA-V or PSADT add value to the screening and detection of prostate cancer. The following information is based on published data that provide support for these derivatives.

- **PSA density (PSAD):** PSAD is a ratio of PSA to prostate size, as measured by transrectal ultrasound. (PSAD = PSA divided by prostate volume). Proposed as a method to differentiate benign vs. malignant with an elevated PSA of 4–10 ng/mL without evidence of prostate cancer on digital rectal exam. May also prevent unnecessary prostate biopsies.
  - Higher PSA density values (>0.15 ng/mL/cc) are more suggestive of prostate cancer; lower values suggest BPH.
  - Potential role as predictor for Gleason score upgrade after RP in patients with clinically low-risk disease.
  - PSA transition zone density (PSAD-TZ) is a similar concept but not commonly used.
- **PSA velocity (PSA-V):** Rate of PSA change over time; the utility of PSA velocity is in part limited by intra-patient variability; at least 3 consecutive measurements should be performed.
  - **PSA-V** >0.75 ng/mL/yr distinguished patients with prostate cancer from BPH or no prostate disease in 1 study. Other studies suggest >0.4 ng/mL/yr is better for cancer detection.
  - **PSA-V** <0.35 ng/mL/yr is often associated with the development of BPH
  - **PSA-V** >0.35 ng/mL/yr and PSA <4.0 ng/mL associated with prostate cancer death at 15 yrs.
  - **PSA-V** >2 ng/mL/yr in the year prior to diagnosis: Associated with an increased risk of prostate cancer death after RP or radiation.
  - **Very high PSA-V** (>3.0 ng/mL/year) is often associated with prostatic inflammation as the cause of the elevated PSA
- **PSA doubling time (PSA-DT):** Another reported measure of PSA change over time. PSADT is defined as the time it takes for a patient's PSA value to double based on an exponential growth pattern. Pretreatment PSA-DT has little diagnostic value but it can predict tumor progression, therapeutic outcome, and tumor-specific mortality.
  - PSA-DT <3 mo, prostate cancer-specific mortality rates 5 yr. After biochemical failure were 35% (Gleason scores ≤ 7) and 75% (Gleason Score ≥ 8).
  - PSA-DT ≥ 3 mo, the 5-yr prostate cancer-specific mortality rates for 4% (Gleason scores ≤ 7) and 15% (Gleason score ≥ 8).

- **Other PSA Based Tests**
  - **Free vs. total f/t) PSA:**
    - Prostate cancer has a lower percent of free PSA in the serum relative to benign prostate conditions.
    - In the PSA range of 2–10 ng/mL the lower the ratio of free/total(f/t) PSA, the increased likelihood of prostate cancer. The probability of cancer f/t PSA $<10\%$ is 56%; f/t value $>25\%$, 8% have cancer.
  - **Complexed PSA:**
    - Complexed PSA (cPSA) relies on the level of anti-chymotrypsin (ACT) bound PSA. This should provide similar enhanced specificity as the f/t PSA but requires only the measurement of a single analyte.
    - Compared to a PSA cutoff ≥ 4.0 ng/mL, cPSA cutoff of 3.75 ng/mL provides higher specificity (48% vs. 33%) for cancer diagnosis with a small decrease in sensitivity.
    - Complexed PSA is approved for monitoring men with prostate cancer.
  - **[-2] proPSA Percent:**
    - [-2]proPSA is 1 of the PSA isoforms that can leak into the circulation that is unbound. The ratio of [-2]proPSA to free PSA (expressed as percent [-2]proPSA or %[-2]proPSA) is under study for prostate cancer screening and is approved in the EU.
  - **Prostate Health Index (*phi*)**: The *phi* is a composite test which incorporates: PSA, free PSA, and [–2]pro-PSA.
    - The calculation involves a formula: $phi = ([-2]\ proPSA/fPSA \times \sqrt{PSA})$
    - Use of *phi* level of >27 for prostate biopsy (with total PSA 2–10 ng/mL), may decrease unnecessary biopsies and reduce over-detection of indolent prostate cancer.
    - Prostate cancer risk increases with increasing *phi* values.
    - The probability of finding cancer on biopsy: *phi* 0–24.9 = 11%; *phi* 25.0–34.9 = 28.25; *phi* 35.0–54.9; 32.7%; *phi* >55 = 52.1%.
    - Correlation of *phi* and high-grade prostate cancer (Gleason score of >7): *phi* 0–24.9 = 26.1%; *phi* 25.0–34.9 = 28.2%; 35.0–54.9 = 30.1% *phi*; *phi* >55 = 42.1%.
- **4K score (4-kallikrein panel):** Consists of these 4 kallikreins: PSA, freePSA, intactPSA, and human kallikrein 2 (hK2) are combined with a patient's age and digital rectal exam using a proprietary algorithm to calculate the probability of a finding of aggressive prostate cancer. Ordered after an elevated PSA to determine the need for biopsy if an aggressive cancer is suspected. hK2 is a prostate-specific kallikrein produced by the prostatic epithelium with approximately 80% DNA sequence homology with PSA and $>20{,}000$ times the activity of the relatively weak protease PSA.
- **PSA Screening.** The use of PSA as a screening test is controversial but remains in place using PSA and DRE in appropriate patients based on various organizations guidelines. (See Section II: "Prostate Cancer Screening Guidelines.")
  - Challenges related to PSA based screening for prostate cancer:
    - About 15% of men with a "normal" PSA level (<4 ng/mL) may have prostate cancer.
    - The Prostate Cancer Prevention Trial: With a PSA cutoff of 1.1 ng/mL 17% of cancers would be missed, including 5% poorly differentiated cancers.
    - 2 out of 3 men with an elevated PSA level don't have prostate cancer.
    - 1 out of 3 men with an elevated PSA level will have cancer.

- 2 out of 3 men who have a biopsy do not have cancer.
- Biopsies in 1 in 5 men can miss prostate cancer.

– There is no clear cutpoint between "normal" and "abnormal" PSA levels.
– Historically PSA >4.0 ng/mL has been most accepted as abnormal. It is a balance between missing important cancers at a curable stage and avoiding detection and treatment of insignificant disease and avoiding unnecessary prostate biopsies

• "Normal" PSA levels must be interpreted on an individual basis.
– **Population-based PSA levels** in a random sample of men without regard to any specific prostate condition or race.

Age Range	Median	PSA Range
<40 yrs	0.52 ng/mL	0.19–1.3 ng/mL
40–49 yr:	0.65 ng/mL	0.22–1.6 ng/mL
50–59 yr:	0.8 ng/mL	0.25–2.6 ng/mL
60–69 yr:	1.2 ng/mL	0.29–5.6 ng/mL

• 13% of men >55 yr have a PSA level of ≥ 4 ng/mL
• Positive predictive value of PSA in detecting prostate cancer (US Studies):
– PSA > 4.0 ng/mL: 30%
– PSA 4–10 ng/mL: 25%
– PSA >10 ng/mL: 42–64%
• Negative predictive value for PSA <4.0 ng/mL: 85%
• Based on biopsies from European Randomized Study of Screening for Prostate Cancer (ERSPC) the risk of finding prostate cancer based on PSA:

– <2.0 ng/mL	7.1%
– 2.0–3.9 ng/mL	18.7%
– 4.0–5.9 ng/mL	21.3%
– 6.0–7.9 ng/mL	28.6%
– 8.0–9.9 ng/mL	31.7%
– >10.0 ng/mL	56.5%

• Based on the following data there is some support for 1.5 ng/mL being the new "normal" PSA in mid-life.
– In one longitudinal PSA biopsy study baseline PSA level >1.50 ng/mL, the risk of prostate cancer increased from 12.3–76.8% at 7.6 yr.
– PSA >1.5 ng/mL between the ages of 45 and 49 yr account for nearly 1/2 of the prostate cancer deaths over the next 30 yr.
– PSA level at age 44–50 was very strongly associated with the likelihood of developing prostate cancer up to 25 yr later. The odds ratio for a PCA diagnosis:
- PSA ≤0.50 ng/mL; (population average = Odds Ratio 1.0).
- PSA 0.51–1.0 ng/mL: Odds ratio 2.51
- PSA 1.0–1.5 ng/mL: Odds ratio 7.02
- PSA 2.01–3.0 ng/mL:Odds ratio 9.01

REFERENCES

PSA Testing for the Pretreatment staging and Post Treatment management of Prostate Cancer. http://www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Specific-Antigen.pdf, Accessed April 4, 2013.

Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2] Pro-PSA combined with PSA and free PSA for prostate cancer detection in the 2.0 to 10.0 ng/mL PSA range. *J Urol*. 2011;185:1650.

Gann PH, Hennekens CH, Stampfer MJ A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA*. 1995;273: 289–94.

Freedland, S. Measurement of prostate specific antigen. www.UpToDate.com, Accessed April 4, 2013.

Lughezzani G, Lazzeri M, Larcher A, et al. Development and internal validation of a prostate health index based nomogram for predicting prostate cancer at extended biopsy. *J Urol*. 2012;188:1144–1150.

Moul JW, Lee RW. Rising serum PSA following local therapy for prostate cancer: Definition, natural history, and risk stratification. www.UpToDate.com, Accessed April 4, 2013.

Shahrokh F. Shariat, Tumor markers in prostate cancer I: blood-based markers *Acta Oncol*. 2011;50(Suppl 1): 61–75.

Vickers AJ, Gupta A, Savage CJ, et al. A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening. *Cancer Epidemiol Biomarkers Prev*. 2011;20(2):255–261.

Vickers AJ, Thompson IM, Klein E, et al. Commentary on PSA velocity and doubling time for clinical decisions in prostate cancer. *Urology*. 2014;83(3):592–598.

PSA, RACE-ADJUSTED (SEE SECTION II “PSA, GENERAL CONSIDERATIONS AND PSA DERIVATIVES”)

PSA, RT-PCR

DESCRIPTION First clinically reported in 1992, RT-PCR is used to amplify mRNA transcripts of PSA. These PSA mRNA species should theoretically only be present in prostate tissues. Extraprostatic tissue of patients with biopsy-proven prostate cancer is tested, including peripheral blood, lymph nodes, and bone marrow, to detect PSA mRNA transcripts and presumably prostate cells in extraprostatic sites. It is being investigated as an assay to detect micrometa-stasis of prostate cancer before clinical presentation or evidence of disease spread (molecular staging). Its clinical utility as a diagnostic assay remains uncertain and is generally replaced by CTC assays.

REFERENCE

Gomella LG, Raj GV, Moreno JG. Reverse transcriptase polymerase chain reaction for prostate specific antigen in the management of prostate cancer. *J Urol.* 1997;158:326–337.

PSA VELOCITY (PSAV) AND PSA DOUBLING TIME (PSADT) (SEE SECTION II "PSA, GENERAL CONSIDERATIONS AND PSA DERIVATIVES")

PSEUDODYSSYNERGIA (HINMAN SYNDROME)

DESCRIPTION A form of detrusor-external sphincter dyssynergia in which voluntary contraction of external sphincter occurs during detrusor contraction. It produces the functional voiding dysfunction seen in children with intractable voiding symptoms, men with chronic prostatitis or prostatodynia, and women with urethral syndrome. It may sometimes be a cause of urinary incontinence. This condition is thought to be a learned behavioral abnormality, possibly an overcompensation of the continence mechanism. Diagnosis is based on urodynamic evidence of increased or vacillating external sphincter activity during detrusor contraction, usually with simultaneous elevation of intra-abdominal pressure indicating voluntary nature of contraction, without clinical evidence of neurologic deficit. (See also Section II: "Hinman Syndrome [Hinman–Allen Syndrome, Nonneurogenic Neurogenic Bladder, Occult Neuropathic Bladder].")

SYNONYMS

- Nonneurogenic neurogenic bladder
- Hinman syndrome/Hinman–Allen syndrome in children
- Dysfunctional voiding syndrome
- Occult Neuropathic Bladder

TREATMENT

- Children must be motivated to participate in the therapy.
- Teach how to void and defecate properly.
- Timed voiding, voiding diary, double voiding, psychotherapy, and biofeedback may all be appropriate in select children.
- Anticholinergics may control instability; α-adrenergics may improve outlet resistance.
- Psychotherapy, with a change in parental attitude, can greatly improve the situation.
- Intermittent catheterization may be necessary in more difficult cases (eg, with upper tract changes, failure to respond to less invasive measures).
- Biofeedback

REFERENCE

Kaplan SA, Santarosa RP, D'Alisera PM, et al. Pseudodyssynergia (contraction of the external sphincter during voiding) misdiagnosed as chronic nonbacterial prostatitis and the role of biofeedback as a therapeutic option. *J Urol.* 1997;157(6):2234–2237.

PSEUDOMYXOMA OVARII-LIKE POSTTHERAPEUTIC ALTERATION IN PROSTATE ADENOCARCINOMA

DESCRIPTION *Pseudomyxoma ovarii*-like posttherapeutic alteration in prostate adenocarcinoma refers to histologic alterations observed in prostate cancer foci after exposure to total androgen blockade. Changes in nontumoral glands exposed to total androgen blockade characteristically display acinar atrophy, basal cell hyperplasia, squamous or

transitional cell metaplasia, and stromal hypercellularity. Conversely, tumor glands may shrink in size and extravasate mucin. This extravasated mucin resembles pseudomyxoma ovarii. This is an important distinction, as this appearance can be easily confused with mucinous carcinoma. It is important to recognize these posttreatment effects, as it may be the sole histologic evidence of therapeutic response and may guide definitive treatment after neoadjuvant hormone deprivation.

REFERENCE

Tran TA, Jennings TA, Ross JS, et al. Pseudomyxoma ovarii-like post therapeutic alteration in prostatic adenocarcinoma: A distinctive pattern in patients receiving neoadjuvant androgen ablation therapy. *Am J Surg Pathol.* 1998;22:347–354.

PSMA (PROSTATE-SPECIFIC MEMBRANE ANTIGEN)

DESCRIPTION A protein with intracellular, transmemberane, and extracellular components of prostatic epithelial cells. PSMA levels are reported to be elevated in hormone-refractory prostate cancer and with metastatic disease. Its use as a tumor marker is not as useful in screening as PSA. PSMA is a highly sensitive and specific immunomarker for the detection of metastatic prostate carcinoma, however cells of the small intestine, proximal renal tubules, and salivary glands also can also express PSMA. PSMA is an in vivo target for imaging utilizing radiolabeled mAb 7E11 (CYT-356, capromab), the ProstaScint Scan. PSMA is currently being targeted as a therapeutic intervention for advanced prostate cancer including monoclonal Ab-directed therapy (PSMA Specific Membrane Antigen Antibody Drug Conjugate [PSMA ADC]), radionuclides and anti-PSMA vaccines and other immunotherapies.

REFERENCE

Eder M, Eisenhut M, Babich J, et al. PSMA as a target for radiolabelled small molecules. *Eur J Nucl Med Mol Imaging.* 2013;40(6):819–823.

PSOAS ABSCESS, UROLOGIC CONSIDERATIONS

DESCRIPTION A psoas abscess is a discrete abscess or phlegmon in the retroperitoneum, adjacent to the psoas muscle. Usually the consequence of direct spread of infection from an adjacent structure; primary psoas abscesses are rare and are a result of hematogenous spread. A wide variety of etiologies are reported in the literature, including perinephric abscess; pyelonephritis; postoperative infection following renal, ureteral, or bladder surgery; complications from ESWL; and urothelial carcinoma metastasis. Clinical presentation includes fever, lower abdominal or back pain, referred lower extremity pain, limp, flexion deformity of the hip from a reflex spasm, flank mass, and a psoas sign. Rarely, a psoas abscess can directly obstruct the ipsilateral ureter or cause a retroperitoneal inflammatory response. Treatment can initially be medical using antibiotic therapy; however, failure to resolve requires drainage. (See also Section I: “Retroperitoneal Abscess; Retroperitoneal Masses and Cysts.” (Image ☼))

REFERENCE

Hamano S, Kiyoshima K, Nakatsu H, et al. Pyogenic psoas abscess: Difficulty in early

diagnosis. *Urol Int.* 2003;71:178–183.

PSOAS HITCH PROCEDURE

DESCRIPTION A surgical procedure used to replace short segments of distal ureteral loss or in combination with a ureteral reimplantation to provide a fixed posterior bladder wall. The bladder is mobilized and stretched superiorly along the axis of the ureteral deficit. The stretched bladder is then sutured to the fascia of the ilio-psoas muscle (Image ☼).

REFERENCE

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston: Little, Brown; 1991:370.

PSORIASIS, EXTERNAL GENITALIA

DESCRIPTION A chronic papulosquamous skin disease frequently affecting external genitalia, more commonly in males. Genital involvement is reported in 25–40% of patients with psoriasis. The lesions characteristically are sharply demarcated plaques with silvery, scaly patches. Psoriasis most frequently involves the penis in males and the mons pubis, labia majora, and inguinal crease in females. It is reported to increase the risk of squamous cell carcinoma (SCC) genitalia. Treatment includes topical steroids, tar preparations and maintaining good hygiene. (See Also Section II: “Pruritus, External Genitalia, Male.”)

REFERENCES

Farber EM, Nall L. Genital psoriasis. *Cutis.* 1992;50(4):263–266.
Loughlin KR. Psoriasis: Association with two rare cutaneous urological malignancies. *J Urol.* 1997; 157(2):622–623.

PSYCHOGENIC POLYDIPSIA

DESCRIPTION Psychogenic polydipsia (PPD) is a clinical disorder characterized by polyuria and polydipsia, and is a common occurrence in inpatients with psychiatric disorders. The underlying pathophysiology of the syndrome is unclear, but multiple factors have been implicated, including a hypothalamic defect and adverse medication effects. Workup for PPD includes a comprehensive evaluation for other medical causes of polydipsia, polyuria, hyponatremia, and the syndrome of inappropriate secretion of antidiuretic hormone. Workup should include plasma and urine osmolality and plasma and urine sodium. Other tests may include a complete metabolic panel, urinalysis, urea, chest x-ray, and CT scan of the head.

TREATMENT

- Treatment for hyponatremia: Fluid restriction, furosemide (if hypervolemic), intravenous normal saline, or hypertonic saline
- Behavioral treatments: Fluid restriction, therapy including cognitive techniques
- Drug treatments: Atypical antipsychotics, clozapine, risperidone, olanzapine, β-blockers, demeclocycline, clonidine, ACE inhibitors, conivaptan

REFERENCE

Dundas B, Harris M, Narasimhan M. Psychogenic polydipsia review: Etiology, differential, and treatment. *Curr Psychiatry Rep*. 2007;9:236.

PUDENDAL NERVE ENTRAPMENT/PUDENDAL NEUROPATHY

DESCRIPTION Compression of the pudendal nerve or its branches causing chronic perineal numbness or pain. The pudendal nerve carries sensations from the external genitalia, distal rectum, and the perineum. Symptoms can be seen if these nerve branches are compressed during pelvic surgery, a finding commonly seen in male and female pelvic sling operations (tension-free vaginal tape or transobturator tape) for incontinence, or it can occur spontaneously. A validated set of simple diagnostic criteria (Nantes criteria) include: (1) Pain occurs in the anatomic territory of the pudendal nerve, (2) is worsened by sitting, (3) the patient is not awakened at night by the pain, (4) no objective sensory loss is found on clinical exam, and (5) a positive response is seen to anesthetic pudendal nerve block. Exclusion criteria include purely coccygeal, gluteal, or hypogastric pain; exclusively paroxysmal pain; exclusive pruritus; or the presence of imaging abnormalities able to explain the symptoms. The diagnosis of pudendal neuralgia by pudendal nerve entrapment syndrome is essentially clinical. There are no specific clinical signs or complementary test results for this disease. However, a combination of criteria can be suggestive of the diagnosis. Initial symptoms should be managed conservatively with anti-inflammatory medications and analgesics. Physical therapy, infiltration with steroids, or surgical decompression are treatment options. If applicable, sling removal should be considered if symptoms persist >6 wk.

REFERENCE

Labat JJ, Riant T, Robert R, et al. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). *Neurourol Urodyn.* 2008;27(4):306–310.

PULMONARY METASTASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION The lungs are the site of potential metastasis in all GU cancers. It is the most common site of metastasis in RCC and a common metastatic site in prostate, urothelial carcinoma, and testicular tumors. Chest CT is more sensitive at detecting pulmonary nodules as it can detect lesions <1 cm, the typical minimal size for plain film detection. Since a direct correlation exists between the likelihood of malignancy and size of pulmonary nodule, lesions <1 cm in size are usually nonclinical. Therefore, plain chest x-ray is the screening test of choice. Malignant nodules usually appear as noncalcified soft tissue densities. Suspicious nodules on chest x-ray warrant a chest CT. Tissue diagnosis of suspicious lesions should be performed if doing so will alter the intervention. Although metastatic disease requires systemic therapy, resection of pulmonary RCC metastases have been shown to improve survival when compared to immunotherapy alone.

REFERENCE

Hofmann HS, Neef H, Krohe K, et al. Prognostic factors and survival after pulmonary resection of metastatic renal cell carcinoma. *Eur Urol.* 2005;48:77–81.

PURPLE URINE BAG SYNDROME

DESCRIPTION Purple urine bag syndrome (PUBS) is an uncommon disorder in which the urine bags of catheterized patients turn purple or blue. Most patients are bedridden, cognitively impaired, and constipated. The discoloration is attributed to indigo and indirubin pigments, which appear purple when combined. The pigments are created when ingested tryptophan is exposed to intestinal flora in patients with altered gut motility. PUBS is usually associated with organisms that have indoxyl phosphatase/sulfatase activity (*Klebsiella pneumonia, Providencia stuartii, Enterobacter, Proteus mirabilis, Morganella morganii,* and *Escherichia coli*).

TREATMENT

- Antibiotics to treat urinary tract infection
- Catheter change

REFERENCE

Keenan CR, Thompson GR: Purple Urine Bag Syndrome. *J Gen Internal Medicine.* 2011;26:1506.

PYELITIS CYSTICA

DESCRIPTION Ingrowth of urothelial cells into the lamina propria with subsequent liquefaction, giving a cystlike appearance. Identical to cystitis cystica, this lesion occurs in the renal pelvis and calyces. It is a rare condition, usually associated with chronic infection, and is more common in females, usually >50 yr of age. Presenting symptoms are related to chronic infections, including fever, dysuria, hematuria, and flank pain. Identified on radiographic studies as multiple small cysts up to 10 mm in diameter in the renal pelvis and calyces, and confirmed by endoscopic biopsy. Not thought to be a premalignant condition, but urine cytology and biopsy are recommended to rule out other neoplastic conditions. (See also Section I: “Filling Defect, Upper Urinary Tract [Renal Pelvis and Ureter].”)

REFERENCE

Gronlund A, Glenthøj A, Kvist E. Pyelitis cystica. *Scand J Urol Nephrol.* 1997;31(5):509–511.

PYELITIS GLANDULARIS

DESCRIPTION In this condition, combined urothelial hyperplastic and metaplastic changes of the renal pelvis occur and characteristic glandular structures are seen haphazardly arranged within the lamina propria. These glands are lined by mucin-secreting columnar epithelial cells, which differentiate them from other forms of urothelial hyperplasia such as Vonbrunn nests and pyelitis cystica. It is not uncommon to see later hyperplastic changes and pyelitis glandularis in a single specimen. Intracellular and luminal mucin can be demonstrated by mucicarmine stain. Most commonly, the overlying surface epithelium remains of the transitional cell type, although metaplastic squamous epithelium or mucous-secreting columnar cells may be seen. Pyelitis glandularis is commonly focal. Extensive lesions with columnar cell metaplasia of the surface urothelium bear a high resemblance to colonic mucosa. However, the absence of muscularis mucosa helps distinguish these 2 entities. (See also Section I: “Filling Defect, Upper Urinary Tract [Renal Pelvis and Ureter].”)

REFERENCE
Dabbs DJ. Cytology of pyelitis glandularis cystica. A case report. *Acta Cytol.* 1992;36(6):943–945.

PYELOGENIC CYST

DESCRIPTION A pyelogenic cyst is a smooth intrarenal diverticulum that communicates directly with the renal pelvis. Conversely, a calyceal diverticulum communicates indirectly to the renal pelvis through a calyx or infundibulum. Pyelogenic cysts are lined with transitional cell epithelium. Diagnosis is best made by CT urogram or delayed-phase or retrograde pyelography showing contrast pooling in the cyst. Asymptomatic pyelogenic cysts do not require treatment. Pain, persistent or recurrent infections, stones, and milk of calcium warrant surgical intervention through ureteroscopic, percutaneous, laparoscopic, or open surgical techniques.

REFERENCE
Canales B, Monga M. Surgical management of the calyceal diverticulum. *Curr Opin Urol.* 2003; 13(3):255–260.

PYOCYSTIS

DESCRIPTION Pyocystis is a severe UTI of the bladder associated with a nonfunctioning bladder or in patients with chronic oligo-/anuria. Also called vesical empyema. Commonly seen (20–30%) in patients with a neurogenic bladder treated with urinary diversion. Pyocystis should be suspected in patients with a nonfunctioning bladder or in those who are oligo/anuric presenting with systemic signs of infection. Bladder catheterization should be performed and the pus cultured. A positive culture is diagnostic; however, imaging studies such as CT may reveal diagnostic signs such as bladder wall thickening. Conservative medical therapy is often adequate, comprised of culture-specific antibiotics and bladder drainage. Some advocate periodic bladder irrigations and instillations with antibiotic solutions therapy are directed by the specific organisms isolated. Bladder irrigation with either saline or an antibiotic solution benefit is not clear. Cystectomy is reserved for refractory pyocystis.

REFERENCE
Bibb JL, Servilla KS, Gibel LJ, et al. Pyocystis in patients on chronic dialysis. A potentially misdiagnosed syndrome. *Int Urol Nephrol.* 2002;34(3):415–418.

PYONEPHROSIS

DESCRIPTION Infected, obstructed collecting system with grossly purulent drainage and suppurative necrosis of renal parenchyma. This can be a chronic, indolent infection, but it usually presents acutely with sepsis, flank pain, and ipsilateral loss of renal function. Immediate aspiration with retrograde or percutaneous catheter drainage is essential.

REFERENCE
Baumgarten DA, Baumgartner BR. Imaging and radiologic management of upper urinary tract infections. *Urol Clin N Am.* 1997;24(3):545–569.

PYOSPERMIA

DESCRIPTION The World Health Organization defines pyospermia as $>1\times10^6$ WBCs/mL semen (either peroxidase or by immunohistologic methods). Pyospermia (also referred to as *leukocytospermia*) has multifactorial causes, including infection, inflammation, and autoimmunity, and is considered to be 1 of the causes of male infertility. The short half-life of polymorphonuclear neutrophils (PMNs) in semen makes them a major source for factors that can be harmful to sperm. The differential diagnosis of symptomatic pyospermia includes infection, autoimmune disease, and inflammation of the accessory sex glands and lower male urogenital tract. Urogenital infections include acute and chronic prostatitis, seminal vesiculitis, epididymo-orchitis, cystitis, urethritis, urethral stricture, stone disease, foreign bodies, upper UTI, retrograde ejaculation, localized sepsis of the adjacent lower GI tract, and asymptomatic bacteriuria. The chronic infections that may result in pyospermia include fungal, mycobacterial, and congenital lesions causing infection of the urogenital tract. Autoimmune diseases that afflict the urogenital tract include Behçet syndrome and Reiter syndrome (Reactive arthritis/reactive arthritis triad). There is no defined medical management of pyospermia since the specific cause cannot be reliably identified. Options include antibiotic treatment (doxycycline, trimethoprim-sulfamethoxazole, ofloxacin) and other medications such as calcium dobesilate, propofol, rebamipide, N-acetyl-L-cysteine, glutathione, and vitamins C and E. Removal of cause and primary predisposing factors include the correction of any congenital or acquired defect in the GU tract harboring infection and inflammation, vesicourethral reflux, prostatic obstruction and infection, retrograde ejaculation, and urethral valves. Although antibiotics are a commonly used empiric therapy, studies have not confirmed their benefit, and a high rate of spontaneous resolution occurs without specific therapy. (See also Section II: “Semen Analysis, Abnormal Findings and Terminology”; “Semen Leukocytes.”)

REFERENCE

Pentyala S, Lee J, Annam S, et al. Current perspectives on pyospermia: A review. *Asian J Androl.* 2007;9(5):593–600.

Q-TIP TEST

DESCRIPTION The Q-tip test is useful to evaluate the urethral axis and evidence of hypermobility in the evaluation of urinary incontinence in the female. A cotton-tipped applicator is advanced per urethra to the level of the bladder neck and observed for changes in angle during straining maneuvers. Hypermobility suggests that a bladder neck suspension may restore continence.

REFERENCE

Dupont MC, Albo ME, Raz S, et al. Diagnosis of stress urinary incontinence. *Urol Clin N Am.* 1996;23(3):407–415.

QUAKEL CORPORAL SHUNT

DESCRIPTION Used for the treatment of priapism. Through a scrotal-perineal approach, a longitudinal incision is made in the outer bulbar urethra (making sure not to completely traverse and injure the urethra), and a parallel incision is made in the corporal body. After irrigating stagnant corporal blood, these 2 incisions are anastomosed.

REFERENCE

Thomas AJ. Surgery for priapism. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:826–832.

RADIATION EXPOSURE GUIDELINES

DESCRIPTION The National Council on Radiation Protection and Measurements has recommended maximum permissible dose limits for occupational exposure to members of the public, which apply to the sum of the effective doses from external radiation and the committed effective doses from internal exposures.

Occupational exposure

- The individual worker's lifetime effective dose should not exceed age in years times 10 mSv
- An annual effective dose limit of 50 mSv
- An annual dose limit of 150 mSv for the lens of the eye
- An annual dose limit of 500 mSv for localized areas of the skin and the hands and feet
- A monthly dose limit of 0.5 mSv to the fetus once a pregnancy is declared
- No occupational exposure should be permitted until age 18 yr

Public exposure

- An annual effective dose limit of 1 mSv for continuous exposure and 5 mSv for infrequent exposure
- An annual dose limit of 50 mSv for the hands and feet and localized areas of the skin and 15 mSv for the lens of the eye
- For educational and training purposes involving people aged <18 yr, an annual effective dose limit of 1 mSv

REFERENCE

Cuaron JJ, Hirsch AE, Medich DC, et al. Introduction to Radiation Safety and Monitoring. *J Am Coll Radiol.* 2011;8:259.

RADIATION, PELVIC, UROLOGIC CONSIDERATIONS

DESCRIPTION Pelvic radiation is commonly used as both a primary treatment for localized prostate cancer and also as a treatment for local recurrence after surgery or nodal disease. Muscle-invasive bladder cancer is also treated with radiation. Urologists often encounter patients who have received previous pelvic radiation for gynecologic cancers such as cervical, ovarian, or rectal cancer. Radiation can cause several urologic complications, including cystitis, ureteral stricture, secondary bladder malignancy, fistula, and retroperitoneal fibrosis. Previous pelvic radiation is a contraindication for orthotopic neobladder reconstruction, and urinary diversion should be performed using bowel and with placement of the stoma outside the radiation field.

REFERENCE

Duggan B, Nambirajan T, Johnston SR. Radiation-induced haemorrhagic cystitis. *Eur Urol.* 2003;43:111–123.

RADIATION PROCTITIS, UROLOGIC CONSIDERATIONS

DESCRIPTION One potentially serious complication of radiation therapy for prostate and other pelvic malignancies is radiation proctitis. Radiation proctitis refers to radiation-induced

injury to the rectal mucosa beginning 3 mo after treatment has ended. The incidence varies from 5–20%. Predisposing factors include prior lower abdominal surgery, diabetes, hypertension and possibly chemotherapy. Symptoms of radiation proctitis include tenesmus, bleeding, low-volume diarrhea, rectal pain, and less commonly, low-grade obstruction or fistula. Diagnosis is made with sigmoidoscopy.

TREATMENT

- Corticosteroids
- Sucralfate enemas
- Argon laser
- Bipolar electrocoagulation
- Formalin-soaked gauze
- Hyperbaric oxygen
- Surgery

REFERENCE

Babb R: Radiation proctitis: A review. *Am J Gastroenterol.* 1996;91:1309.

RADIATION, RENAL AND RETROPERITONEAL, UROLOGIC CONSIDERATIONS

DESCRIPTION Radiation therapy (RT) for RCC as primary therapy is ineffective, but it is useful for palliation of bone metastases. It can be utilized for renal sarcomas or lymphoma. Retroperitoneal radiation is used for seminoma but not for nonseminomatous testis tumors. Nonseminomatous germ cell tumors (NSGCT) are generally less radiosensitive, and RT is typically not used. Side effects of renal and retroperitoneal RT include retroperitoneal fibrosis, ureteral stricture or obstruction, hematuria, enteritis, cardiovascular complications, and secondary malignancy.

REFERENCE

Garcia-Serra AM, Zlotecki RA, Morris CG, et al. Long-term results of radiotherapy for early-stage testicular seminoma. *Am J Clin Oncol.* 2005;28:119–124.

RADIOPHARMACEUTICALS, UROLOGIC CONSIDERATIONS (STRONTIUM^{89}, SAMARIUM^{153}, RADIUM^{223})

DESCRIPTION Strontium^{89} and Samarium^{153} ethylene diamine tetramethylene phosphonate (EDTMP) are FDA-approved radioisotopes approved for the treatment of bony metastatic pain. Phosphorus^{32} has been used for bony metastases but is infrequently employed today. All of these agents are β-*emitters* that can cause significant bone marrow suppression, although myelosuppression has limited its application. These radioisotopes are infused intravenously and taken up in bony areas of high metabolic activity. The radioactive decay has a toxic effect on tumor cells, and relief of symptoms generally begins 1–4 wk after initial infusion.

Radium 223 is a newly approved α-*emitting* radioisotope for metastatic castrate resistant prostate cancer without visceral disease. Can palliate boney disease and also extend survival.

Less likely to impact bone marrow due to larger particle size and limited field effect. (See also Section VI: "Urologic Drug Reference.")

- α-emitters: Consists of helium nuclei; high linear energy transfer, will not penetrate a sheet of paper; number of DNA hits to kill a cell:1–10; induces double strand breaks that are more lethal and difficult to repair
- β-emitters: Consists of electrons; relatively low linear energy transfer; may be halted by an aluminum plate; 100–1,000 hits to kill cells; single strand breaks that are more easily repaired

REFERENCES

Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: A systematic review. *Lancet Oncol.* 2005;6:392–400.

Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213–223.

Perez, et al. *Principles and Practice of Radiation Oncology*. 5th ed. Lippincott Williams & Wilkins; 2007.

RAPID PLASMA REAGIN (RPR) BLOOD TEST

DESCRIPTION The RPR test is a screening test for syphilis (*T. pallidum* infection). RPR detects serum antibodies to substances released by cells damaged by *T. pallidum*. It is 78%, 100%, and 95% sensitive in screening for primary, secondary, and tertiary syphilis, respectively. If a patient tests positive, a confirmatory treponemal particle agglutination or fluorescent treponemal antibody test should be ordered. False positives can be seen in some viral infections, and HIV can cause a false-negative reaction.

REFERENCE

Frenkl TL, Potts J. Sexually transmitted infections. *Urol Clin North Am.* 2008;35:233–246.

RAZ BLADDER NECK SUSPENSION (URETHROPEXY)

DESCRIPTION This is 1 of many surgical bladder neck suspension techniques aiming to fix the vesicourethral junction in a physiologic position to correct genuine stress incontinence in females. It is a modification of the Pereyra needle suspension. Through an inverted U-shaped incision in the anterior vaginal wall, the operator performs (1) retropubic urethrolysis, (2) fingertip guidance of a double-pronged suture carrier placed through a suprapubic opening, and (3) placement of helical nonabsorbable sutures through the urethropelvic ligament, otherwise known as the endopelvic fascia. Cystoscopy is performed after the sutures are placed. Best suited for patients with urethral and bladder neck hypermobility and no cystocele.

REFERENCE

Stothers L, Chopra A, Raz S. Surgery for female stress urinary incontinence. *Can J Urol.* 1995;2(Supp1):33–37.

RAZ VAGINAL WALL SLING

DESCRIPTION Technique to treat urinary incontinence due to intrinsic sphincter dysfunction or anatomic incontinence, this is a modification of the original Raz bladder neck suspension. This technique provides support for both the bladder neck and mid-urethra. In addition to the principal maneuvers described in the Raz urethropexy, the author incorporates a patch of anterior vaginal wall with the suspension sutures at the level of the bladder neck, which, in effect, creates a hammock that serves as a backboard to the bladder neck and mid-urethra.

REFERENCE

Raz S, Stothers L, Young GP, et al. Vaginal wall sling for anatomical incontinence and intrinsic sphincter dysfunction: Efficacy and outcome analysis. *J Urol.* 1996;156(1):166–170.

REACTIVE ARTHRITIS/REACTIVE ARTHRITIS TRIAD (FORMERLY REITER SYNDROME)

DESCRIPTION The preferred term today is *reactive arthritis*, a classic triad of polyarthritis, conjunctivitis, and nongonococcal urethritis; in women, cervicitis. Anterior uveitis and skin or genital rash may be seen. Thought to be a systematic inflammatory response triggered by microbial infection in the GU or GI tracts, the condition is a member of the spondyloarthritis family of disorders. The arthritis is usually asymmetric, with predominately lower extremity involvement. Joint aspiration is typically sterile. Association with HLA-B27 is noted, and may confer susceptibility. 2 forms exist: Sexually transmitted, in which symptoms emerge 10–14 days after exposure. Causes include *C. trachomatis*, *Salmonella* sp., *Shigella* sp., *Yersinia* sp., and *Ureaplasma urealyticum*. The overall prognosis is good, with spontaneous remission or remission following NSAID therapy within 6 mo of onset. A small proportion have chronic persistent arthritis; a few will develop ankylosing spondylitis more frequent (if HLA-B27 positive). Usual treatment includes supportive care NSAIDs, intra-articular or systemic steroids for polyarthritis. Antibiotic treatment is initiated for identified organisms, if possible, such as *C. trachomatis* doxycycline 100 mg PO BID for 7–14 days. (Note: The name change from Reiter syndrome to reactive arthritis is based in part on allegations that Dr. Reiter was an un-convicted war criminal.)

REFERENCE

Hannu T, Inman R, Granfors K, et al. Reactive arthritis or postinfectious arthritis? *Best Pract Res Clin Rheumatol.* 2006;20(3):419–433.

RECTOCELE, UROLOGIC CONSIDERATIONS

DESCRIPTION Rectocele generally presents as a posterior vaginal wall defect with varying degrees of prolapse. It can present with urologic symptoms including sexual dysfunction and voiding symptoms, as well as constipation. If a patient presents with voiding dysfunction, a urodynamic study should be performed with the rectocele reduced to unmask the patient's underlying urodynamic parameters. Prior to repair, it is important to determine if there is evidence of enterocele or cystocele, to determine the appropriate reconstructive procedure. Treatment can be conservative using a vaginal pessary or surgical using 1 of several

techniques, including open or laparoscopic, transvaginal, or endorectal. (See also Section I: "Pelvic Organ Prolapse [Cystocele and Enterocele].")

REFERENCE

Hall GM, Shanmugan S, Nobel T, et al. Symptomatic rectocele: What are the indications for repair? *Am J Surg*. 2014;207(3):375–379.

RED SCROTUM SYNDROME

DESCRIPTION The external genitalia can be affected by many inflammatory processes such as atopic and irritant dermatitis, psoriasis, or ichthyosis. A rare scrotal disease Red Scrotum Syndrome (RSS) affects males in their 2nd half of life and typically runs a chronic course. It may represent a localized phenotypical expression of erythromelalgia. RSS is characterized by persistent redness of the anterior 1/2 of the scrotum and may also involve the base of the penis. Symptoms include itching, burning, and pain sensations. It can develop after prolonged use of topical corticosteroids. It is often mistaken for eczema but itching is not common in RSS. Burning and hyperalgesia are typical in RSS and are not usual with eczema. The pain is aggravated by warmth, relieved by cold. Differential diagnosis includes atopic dermatitis, contact dermatitis, psoriasis, ichthyosis, mycosis such as tinea cruris, secondary syphilis and Langerhans cell histiocytosis among others. Oral doxycycline is used initially with gabapentin a 2nd-line therapy. (See also Section II: "Scrotal Skin Lesion.")

REFERENCE

Wollina U. Red scrotum syndrome. *J Dermatol Case Rep*. 2011;5(3): 38–41.

REED SYNDROME

DESCRIPTION Multiple cutaneous and uterine leiomyomatosis, also known as Reed syndrome, is an autosomal dominant condition. Individuals have an increased predisposition to develop benign smooth muscle tumors (leiomyomas) in the skin and uterus (fibroids). Subsets of these patients are at risk for renal cell cancer and have been determined to have mutations in the fumarate hydratase gene. The term hereditary leiomyomatosis and renal cell cancer refers to families with an increased prevalence of smooth muscle tumors and renal cell cancer as a result of the fumarate hydratase genetic defect. (See also Section II: "Leiomyomatosis, Hereditary" and "Renal Cell Carcinoma, Familial.")

REFERENCE

Emer JJ, Solomon S, Mercer SE. Reed's Syndrome A Case of multiple cutaneous and uterine leiomyomas. *J Clin Aesthet Dermatol*. 2011;4(12):37–42.

REFLUX NEPHROPATHY

DESCRIPTION Renal scarring secondary to reflux of sterile or infected urine from the bladder to the kidney. Girls are at increased risk of developing reflux nephropathy because of the increased incidence of UTI's. Most cases are associated with vesicoureteral reflux, and children are usually asymptomatic or may present with infection, hypertension, or renal failure in cases of severe scarring. Usually a radiographic diagnosis; US and voiding

cystourethrography identify the reflux, and renal scarring is detected radiographically by a cortical imaging agent such as DMSA technetium^{99m} (dimercaptosuccinic acid). Treatment is directed at the cause (such as vesicoureteral reflux antibiotic suppression or surgical correction). (See also Section I: "Vesicoureteral Reflux." and (Image ☼))

REFERENCE

Polito C, La Manna A, Rambaldi PF, et al. Long-term evolution of renal damage associated with unilateral vesicoureteral reflux. *J Urol.* 2007;178(3):1043–1047.

REIFENSTEIN SYNDROME

DESCRIPTION A form of incomplete male pseudohermaphroditism, usually presenting with perineoscrotal hypospadias and frequently cryptorchidism at birth, azoospermia and incomplete virilization at puberty, and infertility and gynecomastia at or after puberty. Caused by mutations in the DNA-binding domain of androgen receptor, with varying degrees of androgen receptor dysfunction. Patients are usually assigned to male sex at birth, and they exhibit elevated levels of testosterone and luteinizing hormone. Surgical repair of hypospadias and cryptorchidism as the treatment and supplemental testosterone is not beneficial. (See also Section II: "Androgen Insensitivity Syndrome [AIS or Androgen Resistance Syndrome], Complete and Partial.")

SYNONYMS

- Lubor Gilbert–Dreyfus Syndrome
- Type 1 incomplete male pseudohermaphroditism

REFERENCE

Androgen Insensitivity, Partial; PAIS: in Online Mendelian Inheritance in Man http://www.omim.org/entry/312300, Accessed March 6, 2014.

REINKE CRYSTALS

DESCRIPTION Cytoplasmic crystalloid inclusions found in human Leydig cells. The crystals are large, distinctive, and easily visible under light microscopy. It has been noted that their numbers increase with age; their function or significance is unknown.

REFERENCE

Kerr JB. Ultrastructure of the seminiferous epithelium and intertubular tissue of the human testis. *J Electron Microsc Technique.* 1991;19(2):215–240.

RENAL ADENOMA (PAPILLARY ADENOMA)

DESCRIPTION The most common renal epithelial neoplasm and found in 4–37% of autopsy specimens. Controversial if these are small adenocarcinomas. Strict diagnostic criterion include papillary, tubular, or tubulopapillary architecture, <5 mm and no resemblance to any renal malignancy.

REFERENCE

Grignon DJ, Eble JN. Papillary and metanephric adenomas of the kidney. *Semin Diagn Pathol.* 1998;15(1):41–53.

RENAL AGENESIS (BILATERAL AND UNILATERAL)

DESCRIPTION This condition is defined by the congenital absence of 1 or both kidneys:

- Bilateral renal agenesis: Incompatible with life as kidney function in utero is necessary in development of the lungs. Infants born with bilateral agenesis have hypoplastic lungs, oligohydramnios, anuria, and renal failure, as well as a well-described group of physical findings such as a flattened nose, low-set ears, bowed limbs, and a small chest collectively referred to as *Potter syndrome*. Bilateral agenesis is reported in 1 in 3,000 births but the actual incidence is unknown since many fetuses are believed to spontaneously abort without a diagnosis.
- Unilateral renal agenesis: In contrast, unilateral agenesis is usually asymptomatic and is often undetected throughout life. It occurs in 1 in 1,100 births, and is more common in males (1.8:1); the left kidney is more commonly missing. Commonly associated with müllerian duct, wolffian duct, and ureteric bud abnormalities and thus may involve the vas deferens, ureter, trigone, vagina, and seminal vesicles. 65% of patients have another urologic anomaly. Associated anomalies include reflux; contralateral UPJ obstruction including single umbilical artery; absence of ipsilateral ureter and hemi-trigone; vaginal atresia/agenesis (Mayer–Rokitansky syndrome); unilateral vas deferens agenesis/atresia; and seminal vesicle cysts. Unilateral renal agenesis is also associated with anomalies of other systems (such as cardiovascular in 30% valvular or septal cardiac anomalies); GI in 25%; imperforate anus or atresia of anus or esophagus; and vertebral or pharyngeal anomalies. If diagnosed, some clinicians propose yearly screening of BP and urinary protein levels because of the risk of hypertension, renal insufficiency, and proteinuria found in some adult studies. (See also Section II: “Potter Syndrome/Potter Facies.” and (Image ☼))

REFERENCE

Uetani N, Bouchard M. Plumbing in the embryo: Developmental defects of the urinary tracts. *Clin Genet.* 2009;75(4):307–317.

RENAL ANATOMY, NORMAL RADIOGRAPHIC FINDINGS (SIZES, CALYCES)

DESCRIPTION The kidney can be imaged by plain film, US, CT, MRI, radionuclide scanning, or pyelography, either IV excretory, antegrade, or retrograde. A normal adult kidney should measure 10–13 cm vertically, 5–7 cm transversely, and 3 cm anteroposteriorly. The right kidney tends to be shorter and wider than the left due to hepatic compression. The renal pedicle usually consists of a single renal artery and vein, although many normal anatomic variants exist. Typically each kidney has 2–3 major calyces and 8–14 minor calyces. Many normal variants of calyceal anatomy also exist, but pathologic findings include debris and filling defects; calyceal diverticulum, dilation of calyces or a single calyx suggests ureteral and infundibular obstruction, respectively (Image ☼).

REFERENCE

Singer A, Simmons MZ, Maldjian PD. Spectrum of congenital renal anomalies presenting in adulthood. *Clin Imaging*. 2008;32:183–191.

RENAL ARTERY ANEURYSM

DESCRIPTION A renal artery aneurysm is defined as a dilated segment of renal artery that exceeds twice the diameter of a normal renal artery. Although rare, the diagnosis and incidence of this entity have been steadily increasing due to the routine use of cross-sectional imaging. Incidence ranges from 0.3–1.0% on radiographic studies, accounting for 1% of all arterial aneurysms and 10% of visceral aneurysms. They are commonly bilateral or multiple 20% and 30%, respectively, and occur typically in the 5th–6th decades of life, slightly more frequently on the right. They are associated with hypertension (HTN), but a causal effect has not been shown. Spontaneous rupture is rare, but risk is increased during pregnancy. Presentation is usually secondary to HTN, flank pain, hematuria, or an incidental finding on radiographic study. Causes include atherosclerosis, congenital fibromuscular dysplasia, trauma, infectious disease (syphilis or TB), intrarenal aneurysms, collagen vascular diseases (PAN, Wegener granulomatosis).

TREATMENT

- Most studies recommend repair of renal artery aneurysms (RAAs) >2 cm, spontaneous rupture, or asymptomatic lesions in high-risk patients women of childbearing age or patients with a functional or anatomic solitary kidney. Recent data suggests that many of these patients with RAA >2 cm can be observed if symptomatic.
- Repair includes primary repair with excision of aneurysmal segment, or aortorenal bypass with vein. Extra-anatomic bypass (hepatorenal, gastroduodenal-renal, or splenorenal) is useful for a severely calcified aorta or when aortic cross-clamping is undesirable.
- Autotransplantation is useful for complex repairs with long ischemic time.
- Percutaneous treatment with embolization or occlusion of aneurysmal segments is reserved for high-risk surgical candidates.
- Intraluminal vascular stent: Investigational

REFERENCES

González J, Esteban M, Andrés G, et al. Renal artery aneurysms. *Curr Urol Rep*. 2014;15(1):376. doi: 10.1007/s11934-013-0376-z.

Klausner JQ, Harlander-Locke MP, Plotnik AN, et al. Current treatment of renal artery aneurysms may be too aggressive. *J Vasc Surg*. 2014 Jan 22. pii: S0741–5214(13)02157–5. doi: 10.1016/j.jvs.2013.11.062. [Epub ahead of print]

RENAL ARTERY FIBROMUSCULAR DYSPLASIA

DESCRIPTION Fibromuscular diseases of the renal artery account for 1/3 of cases of renovascular hypertension. Treatment consists of antiplatelet therapy for asymptomatic individuals and percutaneous balloon angioplasty for patients with indications for intervention. Patients with macroaneurysms should be treated with either a covered stent or surgery. BP control with ACE inhibitor or angiotensin II receptor blocker. 4 pathologic entities have been described.

- *Intimal fibroplasia* affects mainly children and young male adults. Angiographically, a smooth focal stenosis is typically seen at the mid renal artery or its branches. Prompt repair is advised because of the progressive nature of the disease.
- *Fibromuscular hyperplasia* of smooth muscle and fibrous tissue is rare, progressive, and affects mainly children and young adults.
- *Medial fibroplasia* is the most common (80%), affecting women in their 30s. On angiogram, it has the appearance of a string of beads. This lesion does not dissect, and complete occlusion has not been reported. Angioplasty is the treatment of choice.
- *Perimedial fibroplasia* is a tightly stenotic, progressive lesion, affecting women 15–30 yr of age. On angiography, extensive collateral vessels are commonly identified. Follow potassium and creatinine after initiation of therapy. Revascularization using percutaneous angioplasty is the definitive treatment of choice.

REFERENCE

Olin JW, Pierce M. Contemporary management of fibromuscular dysplasia. *Curr Opin Cardiol.* 2008;23(6):527.

RENAL CARCINOID TUMOR

DESCRIPTION Rare tumor derived from enterochromaffin or amine precursor uptake and decarboxylation (APUD) cells, occurring most commonly in the GI tract and lung, but also in ovaries, testes, thymus, pancreas, and hepatobiliary system. Primary renal lesions are extremely rare, with only 32 cases reported. The lesions are thought to originate in renal collecting cells undergoing intestinal metaplasia or from teratomatous epithelial cells within the kidney. Horseshoe kidneys are shown to have a markedly elevated risk of carcinoid tumor, although still very rare, and may have a more benign course.

REFERENCE

Krishnan B, Truong LD, Saleh G, et al. Horseshoe kidney is associated with an increased relative risk of primary renal carcinoid tumor. *J Urol.* 1997;(1576):2059–2066.

RENAL CELL CARCINOMA, CHROMOPHOBE

DESCRIPTION Chromophobe RCC is a subtype of RCC derived from the distal renal tubules, and it comprises about 3–5% of all RCCs. Tumor cells display a transparent cytoplasm with a plant cell appearance and a characteristic perinuclear halo. On electron microscopy, microvesicles are seen that stain positive for Hale's colloidal iron. There are 2 types. Type 1, or classic, is defined by loss of chromosomes 1, 2, 6, 10, 13, 17, or 21 and has a better prognosis than type 2, or eosinophilic variant. The eosinophilic variant is part of Birt–Hogg–Dubé syndrome. In general, chromophobe RCC has a better prognosis than other RCC histologies. Chromophobe RCC is difficult to distinguish from oncocytoma on biopsy, making definitive diagnosis difficult without a complete pathologic exam. CD82 and epithelial-related antigen (MOC31) may be helpful in the distinction between chromophobe RCC and renal oncocytoma. (See also Section I: "Renal Cell Carcinoma, General" and (Image ☼).)

REFERENCE

Klatte T, Han KR, Said JW, et al. Pathobiology and prognosis of chromophobe renal cell carcinoma. *Urol Oncol.* 2008;266:604–609.

RENAL CELL CARCINOMA, CLEAR CELL

DESCRIPTION This represents up to 85% of renal tumors. It is thought to arise from the proximal renal tubule and is characterized by a 3p deletion in over 90%. The Von Hippel–Lindau (VHL) gene is found on chromosome 3 (3p25–26) and is involved in the development of clear cell RCC in patients with VHL disease. In addition, VHL gene alterations are involved in the pathogenesis of sporadic RCC. The diffuse positivity for carbonic anhydrase 9 (CA9) is diagnostic for clear cell RCC. A worse prognosis is associated with higher nuclear grade or the presence of a sarcomatoid pattern. Tumors with predominant eosinophilic cells were classified as "granular cell" carcinoma but the 2004 WHO classification of renal tumors based on the presence of vasculature and genetic alterations included these under clear cell RCC. Treatment and staging are discussed elsewhere. (See also Section I: "Renal cell carcinoma, General" and "Von Hippel–Lindau Disease/Syndrome" and Section II: "Renal Cell Carcinoma, Familial." and (Image ☼))

SYNONYMS

- Hypernephroma (once thought to be adrenal origin)
- Grawitz tumor

REFERENCE

Delahunt B, Eble Jn. History of the development of the classification of renal cell neoplasia. *Clin Lab Med.* 2005;25(2):231–246.

RENAL CELL CARCINOMA, FAMILIAL

DESCRIPTION Approximately 2% of renal cell carcinomas (RCC's) can be inherited. Familial renal cancers are characterized by an early onset compared with sporadic cases and frequently comprise bilateral and multicentric tumors. Moreover, extrarenal features suggestive of a described familial renal cancer syndrome might be present. See table for common renal tumor familial syndromes. (See also Section I: "Renal Cell Carcinoma, General.")

Common Renal Tumor Familial Syndromes (All autosomal dominant inheritance)	Gene Protein (Chromosome)	Renal Tumor Type	Common Clinical Manifestations
Von Hippel–Lindau (VHL)	VHL (3p25)	Multiple bilateral clear cell renal cell carcinoma, renal cysts	Hemangioblastomas of the CNS; retinal angiomas; pheochromocytoma
Tuberous sclerosis	TSC1 (9q34) TSC2 (16p13)	Multiple bilateral angiomyolipomas; lymphangioleiomyomatosis	Cortical brain tubers and other lesions; mental retardation; epilepsy; facial angiofibromas; cardiac rhabdomyomas
Hereditary papillary renal cell carcinoma	c-MET (7q31)	Multiple bilateral papillary renal cell carcinoma type 1	
Birt–Hogg–Dubé (BHD)	BHD/Folliculin (17.p11.2)	Chromophobe; occasional clear cell renal cell carcinoma	Cutaneous fibrofolliculomas; lung cysts; spontaneous pneumothorax
Hereditary leiomyomatosis and renal cell carcinoma	Fumarate hydratase (FH) (1q42–43)	Papillary renal cell carcinoma type 2. Aggressive unilateral, early metastasizing with high fatality	Cutaneous leiomyomas; severely symptomatic uterine fibroids oncocytoma; transitional tumors

REFERENCES

Lopez-Beltran A, Scarpelli M, Montironi R, et al. 2004 WHO classification of the renal tumors

of the adults. *Eur Urol.* 2006;49(5):798–805.
Refae MA, Wong N, Patenaude F, et al. Hereditary leiomyomatosis and renal cell cancer: An unusual and aggressive form of hereditary renal carcinoma. *Nat Clin Pract Oncol.* 2007;4:256–261.

RENAL CELL CARCINOMA, PAPILLARY TYPES 1 AND 2

DESCRIPTION An uncommon variant of RCC, representing ~10–15% of cases. The lesions exhibit a tubulo-papillary growth pattern. A hereditary pattern is demonstrated in a small number of families, tending to be multifocal, bilateral, and associated with a loss of short arm of chromosome 3. Subtypes are cytologically classified as type 1 with small single-layer cells, and type 2 with large pseudostratified cells. Type 1 papillary RCC typically exhibits genetic alterations including gains of chromosome 7 and 17 and loss of Y, which has a better prognosis; type 2 has a more heterogeneous genetic alterations and a poorer prognosis. CK7 and AMACR are excellent markers for papillary RCC. (See also Section I: "Renal Cell Carcinoma, General" and (Image ☼).)

REFERENCE

Pignot G, Elie C, Conquy S, et al. Survival analysis of 130 patients with papillary renal cell carcinoma: Prognostic utility of type 1 and type 2 subclassification. *Urology*. 2007;69(2):230–235.

RENAL CELL CARCINOMA, SARCOMATOID

DESCRIPTION An uncommon histologic variant of RCC, with an approximate incidence of 5–10% of all cases. Histologically, the lesion is composed of clear cells and pleomorphic spindle cells resembling sarcoma. It tends to have a more malignant behavior and worse prognosis, with higher local recurrence, more frequent metastasis, and shorter survival. Sunitinib shows efficacy in advanced renal tumors with sarcomatoid differentiation particularly in patients with good performance status. (See also Section I: "Renal Cell Carcinoma, General" and "Renal Sarcoma, Adult and Pediatric." and (Image ☼))

REFERENCES

Kunene V, Miscoria M2, Pirrie S3, et al. Sarcomatoid renal cell carcinoma: Clinical outcome and survival after treatment with sunitinib. *Clin Genitourin Cancer*. 2013;pii: S1558–7673(13)00312–1. doi: 10.1016/j.clgc.2013.12.001. [Epub ahead of print]
Oda H, Machinami R. Sarcomatoid renal cell carcinoma. A study of its proliferative activity. *Cancer.* 1993;71(7):2292–2298.

RENAL CELL CARCINOMA, TUBULOCYSTIC

DESCRIPTION Tubulocystic carcinoma of the kidney (TCCK), a newly described entity, is well-demarcated multicystic lesions giving a "wrapped bubble" or "spongy" appearance. Microscopically, the tumors were composed of tubules and cysts lined by a single layer of eosinophilic, columnar, cuboidal, flat, or hobnail cells with large nuclei and prominent nucleoli separated by a thin fibrotic stroma. In all TCCKs, the majority of neoplastic cells

showed immunohi-stochemical (CD10(+), RCC(+), vimentin(+), and AMACR(+)) and ultrastructural (abundant long brush border microvilli) characteristics of proximal renal tubules, but the cell of origin is unclear. The major differential diagnostic considerations are oncocytoma, multilocular cystic RCC, and cystic nephroma/mixed epithelial and stromal tumor of the kidney. It generally pursues an indolent clinical course. Nephrectomy/ partial nephrectomy of involved renal unit is usually necessary (Image ☼).

REFERENCE

Alexiev BA, Drachenberg CB. Tubulocystic carcinoma of the kidney: a histologic, immunohistochemical, and ultrastructural study. *Virchows Arch.* 2013;462(5):575–581.

RENAL CELL CARCINOMA, UNCLASSIFIED

DESCRIPTION A diagnostic category to which renal carcinomas should be assigned when they do not fit into 1 of the other categories, even after genetic analysis. In some series, this group has amounted to 3–5% of cases. Features which might prompt the assignment of a carcinoma to this category include apparent composites of recognized types, sarcomatoid morphology without recognizable epithelial elements, mucin production, mixtures of epithelial and stromal elements, and unrecognizable cell types. Unclassified RCC is associated with distinct and highly aggressive biologic behavior with poor clinical outcomes. Whenever feasible, immunotherapy with nephrectomy is warranted.

REFERENCES

Kovacs G, Akhtar M, Beckwith BJ, et al. The Heidelberg classification of renal cell tumours. *J Pathol.* 1999;183:131–133.

Zisman A, Chao DH, Pantuck AJ, et al. Unclassified renal cell carcinoma: Clinical features and prognostic impact of a new histological subtype. *J Urol.* 2002;168:950.

RENAL CELL CARCINOMA, XP11.2;TFE3 TRANSLOCATIONS

DESCRIPTION A number of sporadic cases of RCC have chromosomal translocations involving the TFE3 gene at chromosome Xp11.2. Children and young adults are affected without predilection for gender however there appears to be a female predilection in the adult population. The histologic features of such cases have been variably described as papillary RCC, clear cell RCC, or a unique type of pathology. Papillary RCC is the most reported subtype associated with the translocation. The TFE3 gene encodes a transcription factor related to the proto-oncogene product c-myc. RCC is likely due to TFE3 overexpression. TFE3, TFEB, and ALK protein expression are crucial in establishing the diagnosis. This is an aggressive disease and targeted therapy (sorafenib, sunitinib, temsirolimus) and VEGF-targeted therapy demonstrate some activity in advanced disease (Image ☼).

REFERENCE

Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): A report from the Juvenile RCC Network. *Ann Oncol.* 2010;21(9):1834–1838.

RENAL CHOLESTEROL EMBOLISM SYNDROME

DESCRIPTION Cholesterol microembolism (also called cholesterol emboli and cholesterol crystal emboli) of the kidney is an uncommon cause of hypertensive emergencies, affecting mainly elderly men with atherosclerotic vascular disease. It is increasingly associated with thrombolytic therapy. Clinical findings include severe hypertension, digital gangrene, livedo reticularis, cerebrovascular accidents, GI hemorrhage or infarction, bowel perforation, retinal emboli, and eosinophilia. Dialysis for renal insufficiency might be necessary. Diagnosis is made from clinical history, physical exam, lab findings, and selective renal angiogram, and is confirmed by renal biopsy. In the kidneys, intralobular and arcuate arteries are most frequently affected. Treatment is supportive and preventative with management of hypertension and renal insufficiency through control of the underlying pathology.

CAUSES

- Angiographic manipulation
- Anticoagulant medications
- Cardiovascular surgery
- Iatrogenic
- Spontaneous

REFERENCE

Hitti WA, Anderson J. Cholesterol emboli-induced renal failure and gastric ulcer after thrombolytic therapy. *South Med J*. 2005;98(2):235–237.

RENAL CORTICAL ADENOMA

DESCRIPTION Also called *papillary adenoma of the kidney* this is a type of benign renal neoplasm. It falls under the general category of renal adenomas and is considered one of the most common of renal epithelial neoplasms. These small papillary tumors are characterized by scant cytoplasma (chromophilic cells), occasionally somewhat eosinophilic, with tubular-papillary patterns, limited but not encapsulated. Renal papillary adenoma defines papillary or tubular architecture of low nuclear grade with a maximum diameter of 5 mm. Based on autopsy series prevalence rate is 40% in patients older than 70. It has been postulated that papillary adenoma may progress to papillary RCC because of high coexistence, histopathologic similarity, and similar genetic alterations between papillary adenoma and papillary RCC. Cytogenetic changes of papillary adenomas include loss of the Y chromosome and combined trisomy of chromosomes 7 and 17. Histologic and genetic abnormalities of small renal adenomas are indistinguishable from larger papillary RCCs. Based on these findings it is now considered that these small benign lesions can increase in size and transform into papillary carcinomas. For this reason, the WHO 2004 renal cell tumors classification considered tumors with a maximum diameter of 5 mm as papillary adenomas. Renal papillary adenoma frequently develops in patients with acquired renal cystic disease and long-term hemodialysis and may have a different pathogenesis (Image ☼).

REFERENCES

Algaba F. Renal adenomas: pathological differential diagnosis with malignant tumors. *Adv*

Urol. 2008:974848. doi: 10.1155/2008/974848. Epub 2008 Oct 8.
Wang KL, Weinrach DM, Luan C, et al. Renal papillary adenoma–a putative precursor of papillary renal cell carcinoma. *Hum Pathol.* 2007;38(2):239–246.

RENAL HEMANGIOMA

DESCRIPTION These benign vascular neoplasms are usually diagnosed in the 3rd–5th decades, with no sex predilection. The most common presenting symptom is intermittent hematuria. Angiographic appearance varies markedly, with hypervascular, hypovascular, and normal lesions being reported. In the past, a clinical finding of unilateral hematuria and a suggestive angiographic pattern were the basis of preoperative diagnosis. Currently, hemangioma can be identified ureteroscopically, without the need for a biopsy, where they may appear as small, red or bluish spots on the tip or base of a papilla, or they may be large, bulbous, erythematous lesions on the papillary tips. Pathologically, hemangiomas have the gross appearance of a well-demarcated lesion that shows a cluster of blood-filled vascular channels. Microscopically, the majority of cases conform to the typical features of cavernous hemangioma, with variable, large, blood-filled vascular tributaries in a disorganized tangle. Variation in vascular wall thickness and structure indicates arterial and venous components. The benign cytologic feature of flat lining endothelial cells allows for differentiation of this lesion from angiosarcoma.

TREATMENT

- Ureteroscopic electrocauterization or laser ablation using holmium, ND:YAG, or a combination of both
- Surgical resection

REFERENCE

Waller JI, Throckmorton MA, Barbosa E. Renal hemangioma. *J Urol.* 1995;74:186.

RENAL HEMANGIOPERICYTOMA

DESCRIPTION A rare primary sarcoma of the kidney, accounting for 1–3% of renal malignancies. Solid hypervascular mass with calcifications, originating from pericytes, located external to endothelial cells of capillaries, and enveloped by basement membrane. It can be metabolically active, secreting renin. Common presenting signs include flank pain, flank mass, hypertension, hypoglycemia, and hematuria. It can be treated by radical nephrectomy, with reports of nephron-sparing surgery.

REFERENCE

Brescia A, Pinto F, Gardi M, et al. Renal hemangiopericytoma: Case report and review of the literature. *Urology.* 2008;71(4):755.e9–e12.

RENAL LEIOMYOMA

DESCRIPTION A rare benign renal tumor, with an incidence of 5% on autopsy series, it originates from smooth muscle, usually from renal capsule or vessels, and less commonly from the renal pelvis. Radiographically, it can appear as a solid or cystic mass, difficult to

differentiate from RCC, thus usually prompting radical nephrectomy. Imaging findings that can help to suggest the diagnosis of renal leiomyomas are tumors that are hyperdense before contrast, with density similar to that of muscles, and with lower enhancement than the adjacent renal parenchyma. Most are peripheral, without involvement of the renal cortex and with well-defined margins. (See also Section I: "Renal Mass.")

REFERENCE

Derchi LE, Grenier N, Heinz-Peer G, et al. Imaging of renal leiomyomas. *Acta Radiol.* 2008;49(7):833–838.

RENAL LEIOMYOSARCOMA

See Section I: "Renal Sarcomas, Adult and Pediatric."

RENAL LYMPHANGIECTASIA

DESCRIPTION A very uncommon benign disorder of renal lymphatics with unknown pathophysiology, the condition can present with perinephric collections, ascites, abdominal pain, and reversible hypertension. Imaging demonstrates enlarged kidneys with fluid collections seen to be abutting the surrounding structures. Perinephric fluid analysis usually demonstrates elevated protein levels with leucocytes (mostly lymphocytes). Management alternatives range from percutaneous drainage in symptomatic cases to medical therapy (antihypertensives and diuretics).

REFERENCE

Ashraf K, Raza SS, Ashraf O, et al. Renal lymphangiectasia. *Br J Radiol.* 2007;8095(4):e117–118.

RENAL MALROTATION

DESCRIPTION The abnormal orientation of the kidney, such that the position of the renal pelvis is not antero-medial, and the calyces are not pointing laterally. This condition may occur in cases of ectopia, fusion, and incomplete renal ascent; it has an incidence of 1 in 390. Three types of renal malrotation have been described

- Nonrotation: The renal pelvis is anterior.
- Reverse rotation: The renal pelvis is lateral.
- Hyper-rotation: The renal pelvis is posterior.

Symptoms are usually absent; occasionally, vague abdominal pain and/or vomiting due to renal obstruction may occur. Patients may develop ureteral obstruction, infections, or calculi. Diagnosis is made typically on excretory urography with altered orientation of the calyces and pelvices. Retrograde pyelography is often useful in defining the anatomy. No treatment is necessary unless symptoms, stones, or obstruction become problematic. Follow-up US to evaluate for stones or hydronephrosis is recommended. (See also Section I: "Renal Ectopia.")

REFERENCE

Kelalis P, et al., eds. *Clinical Pediatric Urology*. 3rd ed. Vol. 1. Informa Healthcare; 1992:505–

507.

RENAL MASS, INDETERMINATE

DESCRIPTION An indeterminate renal mass is one that cannot be diagnosed confidently as benign or malignant at the time it is discovered. The American College of Radiology has provided appropriateness criterion for the radiographic evaluation of the indeterminate renal mass. The utility of radiologic procedures in the evaluation of the indeterminate renal mass are summarized in the table on the next page.

Radiologic Procedure	Rating	Comments
CT abdomen without and with contrast	9	Either CT or MRI is appropriate. Thin-section CT.
MRI abdomen without and with contrast	8	Either CT or MRI is appropriate. See statement regarding contrast in text under "Anticipated Exceptions."
US kidney retroperitoneal with Doppler	8	To clarify mass that is probably a hyperdense or simple cyst.
Biopsy and aspiration kidney	5	Depends on clinical scenario—the appearance and size of mass. US, CT, or MRI may be used for image guidance.
MRI abdomen without contrast	3	Can be useful to characterize simple cysts.
Tc-99m DMSA scan kidney	1	May be useful to rule out pseudomass of functioning renal tissue.
Arteriography kidney	1	To rule out arteriovenous malformation, arteriovenous fistula, or renal artery aneurysm.
X-ray intravenous urography	1	May be helpful to differentiate parenchymal masses from collecting system masses.
CT abdomen without contrast	1	

Rating Scale: 1, 2, 3, usually not appropriate; 4, 5, 6, may be appropriate; 7, 8, 9, usually appropriate

REFERENCE

Israel GM, et al. ACR Appropriateness Criteria® indeterminate renal masses. Reston (VA): American College of Radiology (ACR); 2010. Online Publication Available at AHRQ (Agency for Healthcare Research and Quality) http://www.guideline.gov/content.aspx?id=32641&search=renal+masses (Accessed August 30, 2014)

RENAL MEDULLARY CARCINOMA

DESCRIPTION This is an aggressive renal malignancy limited almost exclusively to young black patients with sickle cell trait and, less commonly, sickle cell disease. Typical age of presentation is 21–24 yr of age with a male predominance. Over 75% occur in the right kidney. Genetic testing has suggested a potential association with various chromosomal anomalies. It is considered a variant of collecting duct carcinoma. Patients usually present with gross hematuria, UTI, flank pain, an abdominal mass, and/or weight loss. Metastasis in the cervical nodes or brain are often the initial finding. Hematuria in the target population should prompt evaluation for renal medullary carcinoma. Imaging typically demonstrates a centrally located infiltrative lesion invading the renal sinus with peripheral caliectasis. Size ranges from 4–12 cm (averaging 7 cm) and usually associated with hemorrhage and necrosis. Metastatic disease is commonly present at diagnosis. Surgical resection is not usually curative. There is limited experience in the treatment of metastatic disease. Survival after diagnosis is usually $<$6–12 mo (Image ☼).

REFERENCE

Dimashkieh H, Choe J, Mutema G, et al. Renal medullary carcinoma a report of 2 cases and review of the literature. *Arch Pathol Lab Med.* 2003;127:E135–E138.

RENAL OSTEODYSTROPHY

DESCRIPTION Renal osteodystrophy is defined by the National Kidney Foundation as bone morphology alterations observed in chronic kidney disease. Several changes can occur, including osteitis fibrosa cystica due to secondary hyperparathyroidism, osteomalacia, or low bone turnover. The most common presenting symptoms are bone fracture and pain, and usually occurring once a patient is on dialysis. Treatment may include treating hyperphosphatemia, Calcitrol, vitamin D analogs, calcimimetics, or parathyroidectomy.

REFERENCE

Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2006;69:1945–1953.

RENAL PSEUDOTUMOR

DESCRIPTION A benign condition of the kidney mimicking a renal neoplasm on radiographic studies. Most commonly is a *hypertrophied column of Bertin* (sometimes referred to as an *anomalous calyx*), a prominent medullary column usually located between the upper and middle pole calyceal infundibula that can appear as a renal mass but is homogeneous with surrounding renal parenchyma, with normal-appearing calyces. Other conditions giving appearance of renal tumor include persistent fet al lobulation, dromedary or splenic humps, arteriovenous malformation (AVM), extramedullary hematopoiesis, splenorenal fusion (extremely rare), lobar nephronia (focal glomerulonephritis), renal abscess, scarred kidney, regenerating nodule after reflux. xanthogranulomatous pyelonephritis (XGP), granulomatous diseases (sarcoidosis and malakoplakia) subepithelial renal pelvic hematoma (due to anticoagulant or vasculitis) and renal sinus lipomatosis. Contrast-enhanced ultrasound, CT, or MRI can all assist in characterization, but final diagnosis may require percutaneous biopsy or surgery. (See also Section I: “Renal Mass” and Section II: “Renal Mass Indeterminate.”)

REFERENCES

Bhatt S, MacLennan G, Dogra V. Renal Pseudotumors. *Am J Roentgenol.* 2007;188:1380–1387.
Mazziotti S, Zimbaro F, Pandolfo A, et al. Usefulness of contrast-enhanced ultrasonography in the diagnosis of renal pseudotumors. *Abdom Imaging.* 2010;35(2):241–245.

RENAL SINUS ABNORMALITIES

DESCRIPTION The renal sinus is a central spacious cavity in which major branches of the renal artery and vein, along with the major and minor calyces of the collecting system, are located. It is usually filled with adipose tissue, lymphatic channels, nerve fibers, and fibrous tissue. Lesions that may develop in the sinus could be benign, including parapelvic simple cysts, lipomatosis, cysts, urinomas, and vascular lesions such as renal artery aneurysm or AV fistula. Malignant tumors originating in renal pelvis or parenchyma, such as TCC and RCC, may also protrude or even invade and obliterate renal sinus fat. Primary tumors, such as hemangioma, fibroma, leiomyoma, and MFH are rare but may develop in the space.

REFERENCE

Rha SE, Byun JY, Jung SE, et al. The renal sinus: Pathologic spectrum and multimodality imaging approach. *Radiographics*. 2004;24(Suppl 1):S117–S131.

RENAL TRANSPLANT TYPES (STANDARD/EXTENDED/DONOR AFTER DEATH)

DESCRIPTION Renal transplant donors can be by living donors or deceased donors. Deceased donors are individuals who meet the criteria for brain death, but whose organs are being perfused by life-support methods, allowing adequate time for procurement. Donor after cardiac death is an expanded criteria donor. Nonheart beating donor (NHBD) death is characterized by irreversible absence of circulation. NHBDs are less than ideal because organs suffer ischemia during prolonged periods of circulatory dysfunction. Nearly /2 of all renal transplants are from deceased donors. Living donors can be either related or unrelated. On preoperative evaluation, normal renal function after donation is the goal. In line with this, the better functioning kidney is left with the donor. HLA-identical siblings have the highest graft survival rates followed by 1-haplotype siblings. In paired donor exchange, also known as kidney swap, 2 kidney recipients exchange willing donors whom they are incompatible with. This allows the donors to provide 2 recipients with grafts where previously no transplant would have been possible. Overall, living donor grafts have higher survival rates, with 80% surviving at the 5-yr mark compared to 67% of deceased donor grafts (Image ☼).

REFERENCE

Dunn D. Kidney Transplantation. In: Schwartz SI, et al. *Schwartz's Principles of Surgery*. 9th ed. New York, NY: McGraw-Hill; 2010.

RENAL TRANSPLANTATION AND NEOPLASIA

DESCRIPTION Transplant recipients have an elevated risk of cancer. There is a very small risk of primary malignancy harbored in the graft being transferred to the recipient. The most common malignancies that form after transplantation are de novo malignancies. They are thought to occur secondary to chronic use of immunosuppressive drugs. After 10 yr of immunosuppression, kidney transplant recipients have a cumulative incidence of cancer as high as 20%. The most common are Kaposi's sarcoma and non-Hodgkin lymphoma. Compared to age and sex matched general population, kidney cancer recipients are 3–5-fold increased risk of developing skin cancers and urologic malignancies. Recipients who have been on hemodialysis are also at a higher risk of acquired cystic disease and subsequent primary renal malignancy.

REFERENCE

Piselli P, Serraino D, Segoloni GP, et al. Risk of de novo cancers after transplantation: Results from a cohort of 7217 kidney transplant recipients, Italy 1997-2009. *Eur J Cancer*. 2013;49(2):336–344.

RENAL TUMORS, WHO 2004 CLASSIFICATION

DESCRIPTION The 2004 World Health Organization (WHO) classification of the adult renal

epithelial neoplasms replaced the previous 1998 WHO classification. It incorporates other classifications (Mainz, Heidelberg) and describes entities based on both pathologic and genetic analyses. (See table)

WHO (2004) Classification of All Renal Tumors

Renal cell tumors
- Clear cell renal cell carcinoma
- Multilocular clear cell renal cell carcinoma
- Papillary renal cell carcinoma
- Chromophobe renal cell carcinoma
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinomas
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

Metanephric tumors
- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumor

Nephroblastic tumors
- Nephrogenic rests
- Nephroblastoma
  - Cystic partially differentiated nephroblastoma

Mesenchymal tumors Occurring Mainly in Children
- Clear cell sarcoma
- Rhabdoid tumor
- Congenital mesoblastic nephroma
- Ossifying renal tumor of infants

Mesenchymal tumors Occurring Mainly in Adults
- Leiomyosarcoma (including renal vein)
- Angiosarcoma
- Rhabdomyosarcoma
- Malignant fibrous histiocytoma
- Hemangiopericytoma
- Osteosarcoma
- Angiomyolipoma
  - Epithelioid angiomyolipoma
- Leiomyoma
- Hemangioma
- Lymphangioma
- Juxtaglomerular cell tumor
- Renomedullary interstitial cell tumor
- Schwannoma
- Solitary fibrous tumor

Mixed mesenchymal and epithelial tumors
- Cystic nephroma
- Mixed epithelial and stromal tumor
- Synovial sarcoma

Neuroendocrine tumors
- Carcinoid
- Neuroendocrine carcinoma
- Primitive neuroectodermal tumor
- Neuroblastoma
- Pheochromocytoma

Hematopoietic and lymphoid tumors
- Lymphoma
- Leukemia
- Plasmacytoma

Germ cell tumors
- Teratoma
- Choriocarcinoma

Metastatic tumors

WHO Histologic Classification of Benign Renal Neoplasms

Renal Cell Tumors	Metanephric Tumors	Mesenchymal Tumors	Mixed Epithelial and Mesenchymal Tumors
Oncocytoma	Metanephric adenoma	Angiomyolipoma	Cystic nephroma
Papillary adenoma	Metanephric adenofibroma	Leiomyoma	Mixed epithelial and stromal tumor
	Metanephric stromal tumor	Hemangioma	
		Lymphangioma	
		Reninoma	
		Fibroma	
		Schwannoma	

REFERENCE

Eble JN, et al. *Pathology and Genetics. Tumors of the urinary system and male genital organs*. Lyon: IARC Press; 2004.

RENAL VEIN, LEIOMYOSARCOMA

DESCRIPTION A rare tumor arising from the smooth muscle element of the renal vein, occurring most commonly on the left side. The highest incidence is seen in 60–69 year olds and is twice as common in women. Only 32 cases of renal vein leiomyosarcoma have been reported in the literature. The renal vein is the most common site of venous leiomyosarcoma outside of the vena cava. Presenting symptoms include flank or abdominal pain, weight loss, and a palpable abdominal mass. 3-dimensional abdominal imaging imaging reveals a

homogeneous, well-circumscribed mass at or near the renal hilum, commonly encasing the renal vein. Mean survival is 28 mo, with an aggressive malignant pattern to distant sites, including lung, liver, bone, skin and soft tissue, and brain.

TREATMENT

- Aggressive surgical resection with nephrectomy and en-bloc resection
- Nonsurgical treatment with XRT and chemotherapy can be instituted but the efficacy is limited.

REFERENCE

Gage MJ, Patel AV, Koenig KL, et al. Non-vena cava venous leiomyosarcomas: a review of the literature. *Ann Surg Oncol.* 2012;19(11):3368–3374.

RENAL–RETINAL SYNDROME

DESCRIPTION Also called juvenile nephronophthisis with retinal disease or Senior-Loken syndrome (SLS) it is a subtype of juvenile nephronophthisis. (See Section II: "Juvenile Nephronophthisis.") It is an autosomal recessive disease characterized by development of retinitis pigmentosa- or Leber congenital amaurosis-like retinal dystrophy and a medullary cystic kidney disease. These patients have concomitant retinitis pigmentosa, which is slowly progressive and bilateral, with retinal degeneration. Rods are affected, leading to defective night vision that becomes symptomatic in early childhood. The disc may look yellow and waxy. Treatment is supportive, with renal replacement therapy as needed.

SYNONYMS

- Juvenile nephronophthisis with retinal disease
- Senior–Loken syndrome

REFERENCE

Ronguillo CC, Bernstein PS, Baehr W. Senior-Loken syndrome: A syndromic form of retinal dystrophy associated with nephronophthisis. *Vision Res.* 2012;75:88–97.

RENIN, PLASMA AND RENAL VEIN

DESCRIPTION In suspected renovascular hypertension, an elevated renin level of >50% in the renal vein compared to the renal artery plasma level (estimated from the IVC renin level) of the affected kidney is diagnostic. Individual renal veins can be sampled to isolate ischemic individual renal segments using this same technique. Normal, morning plasma renin activity for seated subjects ranges from about 1– 4 ng/mL/h (0.8–3.0 nmol/L/h). Corresponding active renin concentrations are 8–35 mU/L. Renin is increased with diuretics (including spironolactone), dihydropyridine calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. Levels are decreased by β-blockers, clonidine, or α-methyldopa (all of which reduce β-sympathetic stimulation of renin release), or nonsteroidal anti-inflammatory agents (which promote salt retention and also inhibit renal prostaglandin production).

- Normal renin: Secondary adrenal insufficiency (ie, hypopituitarism or isolated ACTH deficiency); Cushing syndrome, but they can be low when there is a marked degree of

hypercortisolism.
- Low renin: Primary aldosteronism; with 11β-hydroxylase or 17α-hydroxylase deficiency (due to mutations in CYP11B1 and CYP17, respectively), which are hypertensive forms of CAH; primary glucocorticoid resistance; DOC-producing adrenal tumors; ectopic ACTH syndrome.

REFERENCES

Rossi GP, Cesari M, Chiesura-Corona M, et al. Renal vein renin measurements accurately identify renovascular hypertension caused by total occlusion of the renal artery. *J Hypertens.* 2002;2:975–984.

Stowasser, M. Assays of the renin-angiotensin-aldosterone system in adrenal disease. In UpToDate.com, Accessed March 7, 2014.

RENINOMA (RENIN-SECRETING JUXTAGLOMERULAR CELL TUMOR)

DESCRIPTION A rare renin-secreting tumor of the juxtaglomerular apparatus. Its usual presentation is in a young female with severe, refractory, frequently paroxysmal hypertension with hypokalemia, hyperaldosteronism, and elevated plasma renin levels. Selective renal vein sampling for renin may help localize the lesion. It is generally a benign tumor, although untreated hypertension can be fatal. Surgical intervention (open or laparoscopic) may be curative and in high-risk patients, radiofrequency ablation may be a less invasive alternative to radical nephrectomy (Image ☼).

REFERENCE

Chao CT, Chang FC, Wu VC, et al. Reninoma. *Kidney Int.* 2011;79(2);260.

RENO-ALIMENTARY FISTULA

DESCRIPTION A broad group of nonanatomic communications between the upper urinary collecting system and the alimentary canal, with nephrocolic and right renal pelvis and duodenal fistulas being the most common presentations. Symptoms vary from GI symptoms, such as nausea, vomiting, and diarrhea, to recurrent UTIs with flank pain and fever. Retrograde ureterography is generally needed to visualize the fistula. (See also Section II: “Fistula, Enterovesical.”)

CAUSES
- Renal inflammatory disease acute/chronic)
- Malignancy of either intestinal or renal origin
- Iatrogenic (eg, percutaneous surgery)
- Trauma
- Ulcer disease

TREATMENT
- Conservative: Stenting or nephrostomy tube
- Nephrectomy with removal of fistula tract and bowel resection

REFERENCE

Bissada NK, Cole AT, Fried FA. Reno-alimentary fistula: An unusual urological problem. *J Urol*. 1973;110:273–276.

RENO-BRONCHIAL FISTULA

DESCRIPTION Fistulous communication between pleural cavity and kidney, associated with pyelonephritis and perinephric abscess. Usually presents with flank or abdominal pain with an ipsilateral pneumonia. Patients commonly have a history of pyelonephritis or abdominal abscess. Fistulas involving the kidney are most commonly caused by iatrogenic trauma. These may include percutaneous nephrostomy or nephrolithotomy tract placement. Reno-bronchial fistulas usually develop from an upper pole approach to the kidney, where the pleural cavity may be traversed. It can involve pleural space alone or erode into lung parenchyma and bronchial tree. Diagnosis is made with CT.

SYNONYMS
- Nephrobronchial fistula
- Renal, bronchopleural fistula

CAUSES
- Pyelonephritis with perinephric abscess
- Xanthogranulomatous pyelonephritis
- Most common pathogens: *E. coli* and *Proteus* sp account for 1/3 of cases
- Tubercular infections also reported
- Iatrogenic trauma: Percutaneous nephrostomy, nephrolithotomy tract placement

TREATMENT
- Percutaneous or open drainage and antibiotic therapy acutely
- Nephrectomy may ultimately be required

REFERENCE

Qazi H, Manikandan R, Holmes ME, et al. Nephrobronchial fistula- A case report. *Int Urol Nephrol*. 2007;39(1):31–32.

RENOMEDULLARY INTERSTITIAL CELL TUMOR (MEDULLARY FIBROMA, RENAL HAMARTOMA)

DESCRIPTION Also referred to as *medullary fibromas and renal hamartomas*, this is a benign renal mesenchymal neoplasm. Rarely they are large and symptomatic. It is a common incidental finding in as many as 50% of adults at autopsy. Renomedullary interstitial cell tumor arises from interstitial cells of the medulla. They do not appear to have any effect on blood pressure. At gross exam, medullary fibromas are white or gray nodules within the renal pyramid. At histologic exam, this tumor is characterized by stellate spindle cells in the background of a basophilic stroma. It can be seen on CT as a small nonenhancing noncalcified hypoattenuating solid mass within the renal medulla. Although it is a benign tumor, it is difficult to differentiate this lesion from other malignancies of the kidney on radiologic basis and hence many patients undergo radical nephrectomy (Image ☼).

REFERENCES
Katabathina V, Vikram R, Nagar AM, et al. Mesenchymal neoplasms of the kidney in Adults: Imaging spectrum with radiologic-pathologic correlation. *Radiographics*. 2010;30(6):1525–1540.
Kumar S, Choudhary GR, Nanjappa B, et al. Benign medullary fibroma of the kidney: A rare diagnostic dilemma. *J Clin Imaging Sci.* 2013;3:43.

REPERFUSION INJURY, RENAL (RENAL ISCHEMIA AND REPERFUSION INJURY)

DESCRIPTION Ischemic acute kidney injury (AKI) is a syndrome that develops following a transient drop in total or regional blood flow to the kidney. Although reperfusion is essential for the survival of ischemic tissue, there is evidence that reperfusion itself causes additional cellular injury after a period of ischemia. This can occur during renal transplantation and with vascular clamping during partial nephrectomy. Studies comparing partial nephrectomy with and without clamping show that ischemia is associated with an increased risk of ARF and advanced chronic kidney disease. Oncologic outcomes and complications in partial nephrectomy without clamping are similar to those with clamping. The clinical sequelae of warm ischemia reperfusion renal injury of approximately 30 min in one study of laparoscopic partial nephrectomy are minimal, however advanced age and pre-existing azotemia increase the risk of renal dysfunction after partial nephrectomy, especially when the warm ischemia time exceeds 30 min. No renoprotective drug therapy has proven clinical utility and renal cooling has not been proven uniformly beneficial. Attempting partial nephrectomy without vascular clamping is optimal. If renal vascular clamping is necessary, it seems that this should be for <30 min to limit renal reperfusion injury.

REFERENCES
Desai MM, Gill IS, Ramani AP, et al. The impact of warm ischaemia on renal function after laparoscopic partial nephrectomy. *BJU Int.* 2005;95(3):377–383.
Wszolek MF, Kenney PA, Libertino JA. Nonclamping partial nephrectomy: towards improved nephron sparing. *Nat Rev Urol.* 2011;8(9):523–527.

RESIDUAL URINE (POSTVOID RESIDUAL [PVR])

DESCRIPTION PVR is the amount of urine remaining immediately after a void. It can be measured by US (bladder scan) or directly by catheterization. Significant variability occurs between PVR measurements in any 1 individual, and several separate measurements should be performed. The absolute value of PVR has little significance but can indicate voiding dysfunction in symptomatic individuals. Therefore, PVR should be part of any assessment of patients with incontinence, LUTS, recurrent UTI, suspected bladder outlet obstruction, or neurogenic bladder.

REFERENCE
Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and postvoid residual urine in men: Separating truth from tradition. *J Urol.* 2008;180:47–54.

RESISTIVE INDICES (RI)

DESCRIPTION The RI is a measurement of renal blood flow using Doppler ultrasound (US). It is defined as the PSV minus the end-diastolic velocity divided by PSV. It used to evaluate upper tract urinary obstruction as well as graft function in transplanted kidneys. Although there are no accepted parameters of normal RI, values >0.7 suggest obstruction or graft hypoperfusion.

REFERENCE

Nezami N, Tarzamni MK, Argani H, et al. Doppler ultrasonographic indices after renal transplantation as renal function predictors. *Transplant Proc.* 2008;40:94–99.

RETE TESTIS, ADENOCARCINOMA

DESCRIPTION A rare, highly malignant tumor arising from rete testis that usually occurs in older men, but has been reported in men as young as 17. It commonly presents with a painless scrotal mass or symptoms related to metastasis. Pathology reveals papillary adenocarcinoma in the rete testis, commonly with local invasion. May be associated with maldescended testis or adenomatous hyperplasia of the rete testis. Prognosis is poor, with $<50\%$ survival at 1 yr. Metastatic sites include retroperitoneal lymph nodes, lungs, bone, and liver. The diagnostic criteria include:

- Tumor in mediastinum separate from the body of testis
- Transition in rete testis from normal epithelium to neoplastic cells
- No evidence of teratoma
- No primary tumor elsewhere
- Intact pariet al tunica

TREATMENT

- Radical orchiectomy is the mainstay of treatment.
- XRT and chemotherapy have limited efficacy for metastatic disease.
- Retroperitoneal lymph node dissection may have a role in the absence of metastasis.

REFERENCE

Sogni F. Primary adenocarcinoma of the rete testis: Diagnostic problems and therapeutic dilemmas. *Scand J Urol Nephrol.* 2008;(421):83–85.

RETE TESTIS, TUBULAR ECTASIA AND CYSTIC DYSPLASIA

DESCRIPTION Tubular ectasia of the rete testis is a benign condition (sometime called cystic ectasia of the rete testes) seen mostly in older men, which involves cystic dilatation of the rete testis often detected on ultrasound. Ovoid cluster of anechoic cystic spaces located peripherally in the mediastinum testis (without any solid component) and no flow within the lesion on Doppler imaging and normal adjacent testicular parenchyma are pathognomic for tubular ectasia of the rete testis. It is believed that this is secondary to obstruction of the epididymis as 85% of cases have coexisting epididymal abnormalities like epididymal cysts. Vasectomy, spermatoceles or epididymitis, may also be associated with dilatation of the rete testis. It must be differentiated from testicular neoplasm and MRI is potentially helpful. It is

unclear whether this lesion is a cause of infertility.

Cystic dysplasia of the rete testis is similar sonographically and histologically, but it is a congenital lesion that occurs in children. It is associated with ipsilateral renal or urogenital excretory duct malformations.

Both of these lesions (tubular ectasia and cystic dysplasia) must be differentiated from benign intratesticular varicocele and tumors such as adenocarcinoma of the rete testis.

REFERENCES

Gadodia A, Goyal A, Thulkar S. Ectasia of the rete testis: Beware of this masquerader. *Indian J Urol.* 2010;26(4):593–594.

Jequier AM, Phillips N. Cystic dilatation of the rete testis: a hidden diagnosis among infertile men. *Reprod Biomed Online.* 2009;18(2):190–194.

RETROCAVAL/CIRCUMCAVAL URETER

DESCRIPTION A rare congenital anomaly in which the infrarenal vena cava (IVC) is derived from the right subcardinal or postcardinal vein, anterior to the ureter. The term*circumcaval ureter* refers to the ureter emerging medial to IVC after running behind it, whereas the term *retrocaval* applies to those ureters that only knuckle behind the IVC but re-emerge laterally. Males are affected 3 times more often than are females. Not all retrocaval/circumcaval ureters are obstructed, but if obstruction exists, surgical repair is typically warranted. CT is the best imaging modality for identification. Despite its congenital origin, symptoms are usually absent in childhood and present later in life. Less commonly, patients present with hematuria or UTI.

REFERENCE

Qian ZY, Yang MF, Zuo KQ, et al. Computed tomography manifestations of common inferior vena cava dysplasia and its clinical significance. *Exp Ther Med.* 2013;5(2):631–635.

RETROGRADE URETHROGRAM (RUG), TECHNIQUE

DESCRIPTION RUG is used to radiographically evaluate the urethra. It is most commonly used to evaluate urethral stricture disease or trauma. It is commonly performed by inserting a Foley catheter or Brodney clamp into the Fossa Navicularis. The balloon is inflated with a few milliliters of water to create a seal. Then 50 cc of contrast solution is injected into the urethra under low pressures while obtaining a series of x-rays. An oblique view allows best visualization of the entire urethra (Image ☼).

REFERENCE

Berná JD, Berná JD Jr, Aparicio Meson M. Urethrography in the male: The clamp method. *Acta Radiol.* 2009;50(2):233–237.

RETROPERITONEAL HEMATOMA

DESCRIPTION A retroperitoneal hematoma is hemorrhage contained within the retroperitoneum. Etiologies include disruption of the kidney or renal pedicle from trauma, postoperative hemorrhage, spontaneous hemorrhage of a renal mass typically

angiomyolipoma (or RCC), or abdominal vessel hemorrhage. Ecchymosis may be observed around the umbilicus (*Cullen sign*) or flank (*Grey–Turner sign*). Management is primarily conservative, including frequent hemoglobin levels, resuscitation, and transfusion, as necessary. However, if the patient is hemodynamically unstable and the bleeding is from a renal source, and they have an expanding pulsatile hematoma, or renal hemorrhage cannot be stopped with selective embolization, then surgical exploration is indicated. Further evaluation of the underlying pathology and follow-up imaging for resolution is warranted. (See also Section I: "Renal Angiomyolipoma"; "Retroperitoneal Abscess"; "Retroperitoneal Masses and Cysts" and (Image ☼).)

REFERENCE

Heyns CF. Renal trauma: Indications for imaging and surgical exploration. *BJU Int.* 2004;93:1165–1170.

RETROPERITONEAL LIPOSARCOMA

DESCRIPTION Retroperitoneal liposarcoma is the most common retroperitoneal sarcoma arising from adipose tissue. However retroperitoneal sarcomas are rare, with just 2.7 new cases per 1 million persons reported annually. They are usually identified incidentally or at a locally advanced stage when they cause symptoms from adjacent tissue invasion or compression. Compression of ureters can cause obstruction, but other symptoms can include early satiety, obstruction, or retroperitoneal bleeding. Contrast-enhanced CT or MRI should be used for diagnosis, staging, and surgical planning. On CT it appears as a large encapsulated mass containing variable amount of fatty (<–20 Hounsfield units) and soft tissue components. A germ cell tumor (GCT) must be ruled out by tumor markers, and a biopsy is necessary if there is diagnostic uncertainty. Complete resection is the only curative treatment. Radiotherapy can be used preoperatively for local control. (See also Section I: "Retroperitoneal Masses and Cysts." and (Image ☼))

REFERENCE

Chang IY, Herts BR. Retroperitoneal liposarcoma. *J Urol.* 2013;189(3):1093–1094.

RETROPERITONEAL LYMPHOMA

DESCRIPTION Lymphoma involving retroperitoneal lymph nodes; it can be the primary site of involvement or a site of metastasis. The lesion can cause extrinsic compression of ureters with obstructive uropathy. Positive diagnosis is made when a mass is visualized on CT or a ureteral obstruction is visualized with US or IVP. Differential diagnosis may include retroperitoneal fibrosis, retroperitoneal fat necrosis, lymphangiomas, ganglioneuroma, sarcomas, metastasis form other tumors such as prostate, or bladder or germ cell tumor metastasis. (See also Section I: "Retroperitoneal Masses and Cysts" and (Image ☼).)

TREATMENT

- CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine, prednisolone) and radiation therapy
- Obstructive uropathy may require ureteral stenting or percutaneous decompression prior to

chemotherapy.

REFERENCE

Terao T, Fujii Y, Ikeda I, et al. Retroperitoneal malignant lymphoma showing follicular type: Report of a case. *Hinyokika Kiyo.* 1992;38(10):1151–1155.

RETROPERITONEAL RHEUMATOID NODULES

DESCRIPTION Rheumatoid nodules (*necrobiotic granulomas*) are a common extra-articular manifestation of rheumatoid arthritis, usually found in subcutaneous tissue. They have been reported in numerous other locations, including blood vessels, larynx, pharynx, sclera, and extradural space. GU involvement is rare and includes renal cortex and bladder. Retroperitoneal occurrence has been reported and can cause ureteral compression and obstruction requiring ureterolysis and repair. (See also Section I: “Retroperitoneal Masses and Cysts.”)

REFERENCE

Adelson GL, Saypol DC, Walker AN. Ureteral stenosis secondary to retroperitoneal rheumatoid nodules. *J Urol.* 1982;127(1):124–125.

RETROPERITONEAL SARCOMA

DESCRIPTION Retroperitoneal sarcomas are mesenchymal neoplasms. Approximately ½ of retroperitoneal sarcomas are high-grade tumors, with the most common type being liposarcoma, followed by leiomyosarcoma. Median age at presentation is, although they can occur at any age. At the time of presentation, more than 50% are >20 cm in size. They are typically incidentally diagnosed but when patients do present with symptoms they are abdominal or back pain and increased abdominal girth. Differential diagnosis of a retroperitoneal mass includes neoplasm from a retroperitoneal visceral structure, lymphoma, or a metastatic lesion. Retroperitoneal sarcomas carry a worse prognosis than extremity sarcomas due to the difficulty of complete resection, involvement of critical structures, and delay of diagnosis. Contrast-enchanced CT is the imaging modality of choice. In patients whom systemic therapy or radiation is deemed to be potentially beneficial, a biopsy is mandatory. Complete surgical resection is considered the only curative modality. Neoadjuvant chemotherapy or radiation should be based on optimizing the patient for surgical resection. (See also Section I: “Retroperitoneal Masses and Cysts.”)

REFERENCE

Mullinax JE, Zager JS, Gonzalez RJ. Current diagnosis and management of retroperitoneal sarcoma. *Cancer Control.* 2011;18(3):177–187.

RETROPERITONEUM, FAT NECROSIS

DESCRIPTION Retroperitoneal fat necrosis is a pathologic syndrome characterized by the histologic hallmarks of coalescence of fat cells into fat cysts bordered by foreign-body giant cell granulomas. Local injury to fat cells from trauma appears to be the initiating event of fat necrosis in the retroperitoneum. In addition, an inflammatory trigger such as acute

pancreatitis may also be an initiating event. Its presentation is similar to that of retroperitoneal fibrosis with insidious onset of abdominal or flank pain with the possibility of extrinsic ureteral obstruction.

REFERENCES

Ross JS, Prout GR Jr. Retroperitoneal fat necrosis producing ureteral obstruction. *J Urol.* 1976;115(5):524–529.

Howard JM. Studies of acute pancreatitis with retroperitoneal necrosis: "The suet syndrome". Improvements in patient survival *Journal of Hepato-Biliary-Pancreatic Surgery* 1996, Volume 3, Issue 3, pp. 195–202.

RHABDOID TUMOR, MALIGNANT

DESCRIPTION The most lethal renal neoplasm, formerly believed to be a form of Wilms tumor. It comprises 2% of all renal tumors and primarily affects children and 85% are diagnosed before the age of 5. The incidence has increased from <0.1 per million in 1986 to 0.6 per million in 2005. It has a tendency to early metastatic spread. The most common presentation is an abdominal mass detected in these young patients. Extrarenal sites include central nervous system (35%), liver, and gastrointestinal tract. Presence of mutations in the hSNF5/INI1 gene on chromosome 22 is the hallmark. The lack of staining of the INI1 gene product is diagnostic. Younger patients have a worse prognosis compared with older patients. Radiotherapy is an essential part of multimodality therapy.

REFERENCE

Zhuge Y, Cheung MC, Yang R, et al. Pediatric non-Wilms renal tumors: subtypes, survival, and prognostic indicators. *J Surg Res.* 2010;163(2):257–263.

RIEGER SYNDROME

DESCRIPTION Also known as the *Axenfeld–Rieger Syndrome*, this is an autosomal dominant syndrome affecting multiple organ systems. It is manifested by ocular anomalies such as glaucoma; cardiovascular outflow tract malformations, craniofacial abnormalities and pituitary abnormalities which can result in severe endocrinologic sequelae. Genitourinary anomalies occur in the form of hypospadias. 2 major genes have been identified, PITX2 and FOXC1 on chromosome 25.

REFERENCE

Chang TC, Summers CG, Schimmenti LA, et al. Axenfeld-Rieger syndrome: New perspectives. *Br J Ophthalmol.* 2012;96(3):318–322.

RIFLE CRITERION FOR ACUTE RENAL INJURY

DESCRIPTION Also referred to as the RIFLE Classification System for AKI, it assesses levels of renal injury (**R**isk, **I**njury, and **F**ailure) based on the degree of elevation in serum creatinine or urine output, and 2 outcome measures (**L**oss and **E**nd-stage renal disease):

- Risk: $1.5\times$ increase in creatinine or 25% GFR decrease by 25% or urine output <0.5 mL/kg/h for 6 hr

- Injury: 2× increase in creatinine or 50% GFR decrease or urine output <0.5 mL/kg/h for 12 hr
- Failure: 3× increase in creatinine or 75% GFR decrease or urine output of <0.5 mL/kg/h for 24 hr, or anuria for 12 hr
- Loss: Complete loss of kidney function (eg, renal replacement therapy necessary) for >4 wk
- End stage renal disease (ESRD): Complete loss of kidney function (eg, renal replacement therapy necessary) for >3 mo

The RIFLE criteria correlates with prognosis, with a stepwise increase in the risk of death in patients who met the RIFLE criteria for various stages of AKI. Compared to patients without AKI, patients in the RIFLE stages of risk, injury, and failure had increased mortality risks of 2.4, 4.15, and 6.37, respectively. (See also Section I: "Acute Kidney Injury, Adult [Renal Failure, Acute].")

REFERENCE

Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8(4):R204.

RIM SIGN (RIM NEPHROGRAM)

DESCRIPTION A radiographic appearance in which only a thin peripheral rind of renal tissue is visible. This condition occurs as a result of marked thinning of the parenchyma due to end-stage obstructive atrophy, and it usually denotes irretrievable renal function.

REFERENCE

Bedon WE, Levitt SB, Baker DH, et al. Hydronephrosis in infants and children: Value of high dosage excretory urography in predicting renal salvageability. *AJR Am J Roentgenol Radium Ther Nucl Med.* 1970;109:380–389.

ROBINOW SYNDROME

DESCRIPTION A skelet al dysplasia with both autosomal dominant and recessive inheritance pattern. It is characterized by short stature, limb shortening, genital hypoplasia (micropenis), and craniofacial abnormalities. The more phenotypically severe autosomal recessive form has been associated with mutations in the ROR2 gene on the long arm of chromosome 9.

REFERENCE

Person AD, Beiraghi S, Sieben CM, et al. WNT5A mutations in patients with autosomal dominant Robinow syndrome. *Dev Dyn.* 2010;239(1):327–337.

ROBSON STAGING SYSTEM

DESCRIPTION Robson's modification of Flocks and Kadesky's staging system for renal cell carcinoma (RCC) was the most commonly used in the United States. The fact that long-term

evaluation of patients with stage IIIA lesions, without disease extension into perinephric fat and lymph nodes, has shown survivals comparable to those of stages I and II, has currently led many investigators to prefer the TNM system prosed by IUAC. (See Section I: "Renal Cell Carcinoma, General"; Section VII: "TNM Kidney.")

- Stage I: Tumor is confined within the kidney parenchyma (no involvement of perinephric fat, renal vein, or regional nodes).
- Stage II: Tumor involves the perinephric fat but is confined within Gerota fascia (including adrenal).
- Stage IIIA: Tumor involves the renal vein or inferior vena cava.
- Stage IIIB: Tumor involves regional lymph nodes.
- Stage IIIC: Tumor involves both local vessels and regional lymph nodes.
- Stage IVA: Tumor involves adjacent organs other than the adrenals (colon, pancreas, etc.).
- Stage IVB: Distant metastases.

REFERENCE

Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *Trans Am Assoc Genitourin Surg*. 1968;60:122–129.

ROKITANSKY–KUSTER–HAUSER SYNDROME

DESCRIPTION Pathologic condition characterized by primary amenorrhea and infertility and by congenital aplasia of the uterus and upper 2/3 of the vagina. Also referred to in the literature as *Mayer–Rokitansky–Kuster–Hauser Syndrome*. The condition is usually discovered during evaluation of a normal-appearing girl who presents with failure of menstruation at the time of expected puberty. They have a normal female karyotype 46, XX and do develop normal secondary sexual characteristics. The syndrome may be caused by the lack of development of the müllerian ducts between the 5th and 6th wk of gestation. In some patients, cyclic abdominal pain suggestive of some functional endometrium is noted. Vaginal reconstruction with bowel or skin grafting is performed. It can also be associated with renal and skelet al abnormalities.

REFERENCE

Pizzo A, Laganà AS, Sturlese E, et al. Mayer-Rokitansky-Kuster-Hauser Syndrome: Embryology, genetics and clinical and surgical treatment. *ISRN Obstet Gynecol*. 2013;628717.

ROSEWATER SYNDROME

DESCRIPTION Rosewater syndrome is an infertility disorder associated with germ cell aplasia. On testicular biopsy, the seminiferous tubules contain only Sertoli cells. This is considered irreversible and precludes germ cell restoration. Not infrequently, tubular and peritubular fibrosis is associated with germ cell aplasia.

REFERENCE

Craig JM. The pathology of infertility. *Pathol Ann*. 1975;10:299.

ROVSING POLYCYSTIC KIDNEY OPERATION

DESCRIPTION A historically important surgical procedure that entails unroofing multiple renal cysts. This procedure does not prevent deterioration of renal function but may improve flank pain if the cysts cause obstruction of the collecting system.

REFERENCE

Yates-Bell JG. *Rovsing's Operation For Polycystic Kidney The Lancet* , Volume 269, Issue 6960, pp. 126–128; 1957.

ROVSING SYNDROME

DESCRIPTION This is a symptom complex associated with horseshoe kidney, in which the patient experiences pain (often periumbilical), nausea, and vomiting on hyperextension of the spine. It is due to compression of the isthmus of the fused kidney on the vena cava and aorta, accentuated by hypertension and accompanied by a sensation of fullness.

REFERENCE

Glenn JF. Analysis of 51 patients with horseshoe kidney. *N Engl J Med.* 1959;261:684.

SACRAL NEUROMODULATION

DESCRIPTION Sacral neuromodulation (SNM) is a 2nd-line treatment for lower urinary tract dysfunction, such as nonobstructive chronic urinary retention, urgency–frequency syndrome (overactive bladder), and urgency incontinence refractory to conservative and pharmacologic treatment. A continuous or cycling mode of electrical pulses are generated by an implanted device to activate or inhibit neural reflexes associated with lower urinary tract function via stimulation of the sacral nerves, which innervate the lower urinary tract and pelvic floor. The mechanism of action is unclear. 1 theory is that indirect stimulation of the pudendal nerve and direct inhibition of the preganglionic neurons suppresses detrusor over activity and therefore improves symptoms. An alternate theory is that stimulation may inhibit involuntary reflex voiding by altering the transmission of sensory input from the bladder to the pontine micturition center, inhibiting ascending afferent pathways but not the descending pathways. In the patient with nonobstructive urinary retention, SNM most likely causes an inhibition of the guarding reflex, with a reduction in sphincteric over activity that may reduce bladder outlet and urethral resistance.

Patients should have failed conservative management with medications and or behavioral therapies and should undergo extensive evaluation including UDS. The procedure of implantation occurs in usually 2 stages. Stage I consists of percutaneous placement of temporary wire leads into the S3 foramina. It can either be performed in the office or in the operating room. A 1–2-wk trial period occurs with the leads in place and voiding symptoms are reevaluated. If >50% improvement in symptoms occur, the patients moves on to Stage II which is always performed in the operating room. Permanent leads are placed as well as an implantable pulse generator. The most commonly used device is the InterStim™ (Medtronic, Minneapolis, Minnesota) (FDA-approved since 1997 for urge incontinence and since 1999 for urinary retention and significant symptoms of urgency–frequency) (Image ☼).

REFERENCE

Hubsher CP, Jansen R, Riggs DR, et al. Sacral nerve stimulation for neuromodulation of the lower urinary tract. *Can J Urol.* 2012;19(5):6480–6484.

SANI SCORE

DESCRIPTION The SANI (Survival after Nephrectomy and Immunotherapy) score is a tool for predicting survival for patients with metastatic RCC in response to the multimodality treatment of aggressive surgical resection and systemic immunotherapy. The regional lymph node status, the presence or absence of constitutional symptoms, the location of metastases, the presence or absence of sarcomatoid pathologic features, and TSH levels are incorporated into the scoring algorithm. Patients are stratified based on predicted survival into low-risk, intermediate-risk and high-risk groups for appropriate treatment regimens and for prospective trials of new therapies.

REFERENCE

Leibovich BC, Han KR, Bui MH, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma. *Cancer.*

2003;98:2566–2575.

SARCOMA, CLEAR CELL OF THE KIDNEY

DESCRIPTION Clear cell sarcoma of the kidney (CCSK) is a renal tumor that comprises ~5% of all primary renal tumors in children. It is the 2nd most common pediatric renal tumor after Wilms tumor (WT). The mean age of presentation is 36 mo. It is unique from WT in its potential for bone and brain metastases. Clinical presenting symptoms of patients with CCSK are similar to those of patients with WT including abdominal distension or mass, abdominal pain, and gross hematuria. The genetics and cell of origin remain poorly understood. Several histologic subtypes are described, the classic pattern, which is present in over 90% of tumors, is characterized by round/oval cells with clear cytoplasm with uniform nuclei.

TREATMENT

- Radical nephrectomy followed by treatment with multi-agent chemotherapy and radiation
- In most recent NWTS-5 trial, vincristine, doxorubicin, and cyclophosphamide, alternating with cyclophosphamide and etoposide for 24 wk, and postoperative radiotherapy the 5-yr overall survival (OS) 89%. 5-yr and recurrence free survival (RFS) was 100% for stage I.

REFERENCE

Gooskens SL, Furtwängler R, Vujanic GM, et al. Clear cell sarcoma of the kidney: A review. *Eur J Cancer.* 2012;48:2219–226.

SAW PALMETTO

DESCRIPTION The extract of the dried ripe fruit from the American dwarf saw palmetto plant *Serenoa repens* (also known as *Sabal serrulata*) is the most widely used phytotherapeutic compound for the treatment of BPH. Berries from saw palmetto were 1st used by Native Americans in the early 1700s to treat testicular atrophy, erectile dysfunction (ED), and prostate swelling or inflammation. The mechanism of action is not completely understood, but may include alteration of cholesterol metabolism, anti-inflammatory, antiestrogenic, and anti-androgenic effects, and decrease in available sex hormone-binding globulin. In a systematic review of 32 randomized, controlled trials which included 5,666 men, *Serenoa repens*, at double and triple the usual dose compared to placebo provides no improvement for nocturia, peak urine flow, and symptom scores for men with BPH. (See also Section V: “Alternative and Complementary Urologic Therapies.”)

SYNONYM

Serenoa Repens, Sabal serrulata, Saw Palmetto Berry

REFERENCE

Tacklind J, Macdonald R, Rutks I, et al. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev.* 2012;12:CD001423.

SCABIES, UROLOGIC CONSIDERATIONS

DESCRIPTION An intensely pruritic parasitic infection that affects simultaneous areas of the

body, including the genitalia, anus, legs, hands, umbilicus, and axillae. Diagnosis can be made by identifying the mite (*Sarcoptes scabiei*), expressed from the papular or linear burrow-like lesion. Transmission occurs from fomites or by direct contact with infected individuals, including sexual contact.

TREATMENT

- Lindane 1% cream, washed off after 8 hr. Do not use in pregnant or lactating women or in children <2 yr.
- Permethrin 5% cream, washed off after 8–14 hr.
- Crotamiton 10% cream for 2 consecutive nights; wash off 24 hr after the 2nd application.
- Treat sexual partners and close contacts.

REFERENCE

Peterson CM, Eichenfeld LF. Scabies. *Pediatr Ann.* 1996;(252):97–100.

SCARDINO-PRINCE PYELOPLASTY

DESCRIPTION Used to treat UPJ obstruction. An inverted J-configured incision is started on the anterior surface of the pelvis and brought down across the UPJ obstruction to a –2-cm point beyond the obstruction. The upper apex of the flap is then flipped down to the apex of the ureterotomy, where a 5-0 chromic stay suture is placed. The medial aspect of the flap is sutured to the lateral edge of the ureterotomy. The lateral edge of the flap is sutured to the lateral aspect of the ureterotomy, and the pelvis is closed.

REFERENCE

Kay R. Procedures for ureteropelvic junction obstruction. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:220–233.

SCHAEFER OBSTRUCTION GRADING SYSTEM

DESCRIPTION Schaefer's obstruction grading system (also called *Schaefer Nomogram*) allows the use of urodynamic evaluation in patients with BPH to determine the effectiveness of a TURP of alleviating their symptoms. Using the urodynamic parameters of pressure (p) and flow rate (Q), a ratio is plotted and every data point reflects bladder contractility outflow conditions. Using a linear approximation to the p/Q data, an assessment can be made of outflow conditions. By comparing urodynamic data before and after surgery for patients with BPH, obstruction is defined as those outflow conditions that improve after surgery. They are graded (Grade 0–Grade VI) with grade 0/I outflow conditions not improving after TURP and Grade VI being severely obstructed and seeing the most improvement after TURP.

REFERENCE

Schaefer W. Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grade obstruction: From complex to simple. *World J Uro.* 1995;13:47–58.

SCHILLER-DUVAL BODIES

DESCRIPTION Perivascular papillary structures seen in histologic specimens of yolk sac tumors, similar to the endodermal sinuses of Duval in the placenta of the rat (histo image).

REFERENCE

Moran CA, Suster S. Hepatoid yolk sac tumors of the mediastinum: A clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol.* 1997;21(10):1210–1214.

SCHISTOSOMIASIS, UROLOGIC CONSIDERATIONS

DESCRIPTION A parasitic infection by the blood fluke *Schistosoma haematobium*. This condition has a broad spectrum of urologic manifestations due to the parasite's life cycle: Infection across the skin, hematogenous migration to perivesical venous plexus, transmural migration into bladder, and shedding into urine. Typically, patients will exhibit polypoid urothelial mucosal lesions (active infection) or "sandy patch" flat, tan lesions (inactive infection). Significant upper urinary tract obstruction is possible with chronic disease. Classic symptoms are hematuria and terminal dysuria. Infection has been linked to bladder cancer, occurring earlier in life (40–50 yo); this is most commonly squamous cell carcinoma (SCC) (60–90%) and adenocarcinoma (5–15%). The presence of fluke eggs in urinary sediment is diagnostic of schistosomiasis. (See also Section I: "Bladder Cancer, Squamous Cell Carcinoma" and (Image ☼).)

TREATMENT

- Medical management: Metrifonate and praziquantel
- Surgical management: Infection refractory to medical management; ureteral or bladder outlet obstruction; persistent or refractory hematuria; or malignancy

REFERENCE

Michaud DS. Chronic inflammation and bladder cancer. *Urol Oncol.* 2007;(253):260–268. Review.

SCHWANNOMA, RENAL

DESCRIPTION Also called *neurinoma* or *neurilemmoma*, a tumor arising from Schwann cell neural elements of the kidney. Schwannomas of renal origin are very rare with only 20 reported cases in the literature. They present in middle-aged patients with a male-to-female ratio of 1:2. They typically appear as spherical, solid, and well-circumscribed encapsulated lesions. The vast majority are benign, and the malignant degeneration is very rare. Partial or radical nephrectomy (open or laparoscopic technique) is the treatment of choice as there are no reliable preoperative diagnostic methods.

REFERENCE

Sfoungaristos S, Kavouras A, Geronatsiou K, et al. Schwannoma of the kidney with magnetic resonance images of non-homogenous renal mass-a case presentation. *Prague Med Rep.* 2011;112(2):137–143.

SCLERODERMA, UROLOGIC CONSIDERATIONS

DESCRIPTION Scleroderma (systemic sclerosis) is a systemic, acquired disorder of connective tissue, including cutaneous sclerosis, visceral organ fibrosis, and vascular lesions. The condition commonly affects kidneys, with renal disease affecting 10–50% of patients. Lower urinary tract manifestations are also reported, including bladder fibrosis, microscopic hematuria, urodynamic abnormalities, such as poor compliance and obstructive uropathy. LUTS include urinary urgency, frequency, and incontinence.

REFERENCE

Lally EV, Kaplan SR, Susset JG, et al. Pathologic involvement of the urinary bladder in progressive systemic sclerosis. *J Rheumatol.* 1985;12:778–781.

SCLEROSING ADENOSIS OF THE PROSTATE

DESCRIPTION A rare benign lesion arising in the transition zone of the prostate. It is a part of the histologic differential diagnosis of prostate cancer. It is characterized by a cellular proliferation of variably sized glands and solid nests surrounded by basement membrane material in a cellular stroma. The contours of the lesion can be well circumscribed or infiltrative, raising concern for carcinoma. The specimen will be immunoreactive with S-100 and smooth muscle actin, indicating a myoepithelial differentiation. Other features differentiating this condition from cancer are that cells have bland nuclei and are sometimes surrounded by a hyaline-like sheath. (See also Section II: “Atypical Adenomatous Hyperplasia of the Prostate” and “Postatrophic Hyperplasia of the Prostate.”)

REFERENCE

Harik LR, O’Toole KM. Non-neoplastic lesions of the prostate and bladder. *Arch Pathol Lab Med.* 2012;136(7):721–734.

SCROTAL PAIN SYNDROME (CHRONIC SCROTAL PAIN SYNDROME [CSPS])

DESCRIPTION CSPS is not well documented in the literature and may have overlap with CPPS. CPPS is defined as pain and discomfort in the pelvic area, perineum, scrotum, penis, and pelvis. CSPS is described as chronic or recurrent pain located in the scrotum. There is little evidence for the widely held belief that CSPS is predominantly the result of a chronic bacterial infection.

REFERENCE

Strebel RT, Schmidt C, Beatrice J, et al. Chronic scrotal pain syndrome (CSPS): The widespread use of antibiotics is not justified. *Andrology*. 2013;1(1):155–159.

SCROTAL PEARLS (SCROTOLITHS)

DESCRIPTION Benign calcifications within the scrotum, usually free floating. Usually diagnosed by ultrasound, these are described as a hyperechoic density in the scrotal wall that demonstrates acoustic shadowing. Scrotal pearls can occur from infection or trauma and themselves are rarely symptomatic. They may also be noticed as artifacts after torsion of the

appendix testis or epididymis.

REFERENCE

Chen P, John S. Ultrasound of the acute scrotum. *Appl Radiol.* 2006;353:8–17.

SCROTAL SKIN LESIONS

DESCRIPTION Scrotal skin lesions may be localized or a manifestation of more systemic diseases.

- Benign
  - Amyloidosis (rare)
  - Angiokeratoma of Fordyce: Small, 1–2-mm red, vascular papules seen predominantly in older men
  - Atopic/neurodermatitis: Itch/scratch cycle with lichenification with or without excoriation. The posterior scrotum is a common site.
  - Calcinosis, idiopathic scrotal
  - Contact dermatitis: Allergic or irritant: Pruritis, burning, and stinging
  - Crohn disease: "Metastatic." Crohn disease may have associated scrotal ulcers and edema.
  - Eczema frequently affects the genital region, particularly the scrotum. Patients present with lichenified erythematous plaques on the lateral scrotum. The eruption may develop into Lichen simplex chronicus (LSC) (also referred to as "Neurodermatitis") characterized by extensive lichenification and hypertrophy of the affected skin due to excessive scratching and rubbing
  - Epitheloid hemangioma, penis and scrotum
  - Fixed drug eruption: Erythematous, well-demarcated "burn-like" area, may evolve from erythema to vesicles or blebs
  - Folliculitis: Usually caused by *Staphylococcus aureus*
  - Genital lentiginoses: Hyperpigmented macules that may be confused with melanoma
  - Genital warts (condyloma): Uncommon on the scrotum
  - Ichthyosis: excessive amounts of dry surface scales; inherited or acquired
  - Insect bite
  - Juvenile gangrenous vasculitis, scrotal (pyoderma gangrenosum)
  - Langerhans cell histiocytosis
  - Lichen simplex chronicus (LSC): Reaction to chronic scratching (See Eczema above)
  - Lymphangioma
  - Molluscum contagiosum: Pearly white papular, smooth-surfaced umbilicated papules
  - Psoriasis: Well-demarcated papulosquamous plaques with silver scale; usually bleeds if scale removed
  - Red Scrotum Syndrome (RSS): Persistent redness of the anterior 1/2 of the scrotum and may involve the base of the penis as well. Treated with oral doxycycline PO and tacrolimus 0.1% ointment twice daily. Gabapentin can be used as 2nd-line therapy
  - Scabies: Red, linear, excoriated areas, often with papules, pustules, and burrows
  - Sebaceous cysts/epidermal inclusion cyst
  - Seborrhic dermatitis: Red scaling eruption ("inflammatory dandruff")
  - Secondary syphilis: Condyloma lata (moist, red, raised wheal-like lesions) or mucous

patches (reddish ulcers with a violaceous border)
  – Tinea cruris or jock itch: Involvement of the scrotum is uncommon
  – Vitiligo may appear similar to lichen sclerosis: Hypopigmented or depigmented areas
- Malignant
  – Basal cell carcinoma: Ulcerated lesion
  – Kaposi sarcoma: A purple, papular, plaque-like, or ulcerated lesion
  – Marjolin ulcer: Cancer arising from site of prior inflammation
  – Melanoma (uncommon)
  – Metastatic lesion: The scrotum is a rare site of cutaneous metastasis and associated with dermal and angiolymphatic invasion. The colon/rectum (34%), prostate (28%), and lung (14%) are the most frequent tumor origins.
  – Paget disease: Primary extramammary from apocrine ducts or sweat gland carcinoma; secondary is intraepithelial spread from underlying malignancy
  – Sarcoma: Leiomyosarcoma from the Dartos layer of the scrotum is most common, though still very rare
  – Squamous Cell carcinoma (SCC): Papule or plaque that enlarges and ulcerates in older men

REFERENCES

Hoyt BS, Cohen PR. Cutaneous scrotal metastasis: origins and clinical characteristics of visceral malignancies that metastasize to the scrotum. *Int J Dermatol.* 2013;52(4):398–403.
Practitioners Handbook for the management of Sexually Transmitted diseases. http://depts.washington.edu/handbook/syndromesboth/ch10_lesions.html, Accessed April 6, 2014.

SCROTAL TONGUE

DESCRIPTION Scrotal tongue is not a urologic condition. It refers to a deeply fissured tongue. Sometimes called a *geographic tongue*.

REFERENCE

Reamy BV, Derby R, Bunt CW. Common tongue conditions in primary care. *Am Fam Physician.* 2010;81(5):627–34. Review.

SCROTAL VARICES

DESCRIPTION Scrotal varices or varicocele is an abnormal dilation of the internal spermatic veins which drain the testis that can be palpated through the scrotal skin. Overall, they are present in 15% of the male population. Varicocele is the most common etiology of male factor infertility, being present in 35% of males with primary infertility and 81% with secondary infertility. They most commonly occur on the left secondary to drainage of the left internal spermatic vein into the left renal vein. Varicocele can impair testicular function with the likely mechanism being through thermal injury. Diagnosis is made through physical exam of the scrotum. Grade I varicocele is palpable with Valsalva only, grade II is palpable in the standing position, and grade III is visually apparent through the scrotal skin as a “bag of worms.” Scrotal ultrasound is not necessary unless the physical exam is unclear.

TREATMENT

- If a varicocele is not associated with infertility, decreased testicular volume or pain, it is considered subclinical and surgical correction is not indicated.
- Nonsurgical approach includes percutaneous radiographic occlusion and sclerotherapy.
- Surgical options include retroperitoneal, inguinal or subinguinal ligation, laparoscopic and microsurgical varicocelectomy.

REFERENCE

Hopps CV, et al. Varicocele: General considerations. In: Graham S, et al. *Glenn's Urologic Surgery*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

SCROTUM, ACCESSORY AND ECTOPIC

DESCRIPTION *Accessory scrotum* is a rare condition in which a small empty pouch of scrotal tissue is attached to the scrotum or the perineum. *Ectopic scrotum* is an anomalously positioned hemiscrotum usually found near the external inguinal ring. The testis generally accompanies the hemiscrotum to its abnormal position and may be normal or dysplastic. These lesions are often accompanied by other GU anomalies (upper tract). Surgical repair involves an attempt to bring down the scrotum and the testis. If the gonad is dysplastic and the ectopic scrotum is rudimentary, removal of 1 or both structures is reasonable.

REFERENCE

Kumar V, Marulaiah M, Chattopadhyay A, et al. Unilateral inguinal ectopic scrotum with covered exstrophy. *Pediatr Surg Int*. 2002;18(5–6):511–513.

SCROTUM, BIFID

DESCRIPTION A disorder characterized by separation of the labioscrotal folds, seen with mid scrotal or perineal hypospadias and intersex disorders. Embryologically, it is a failure of the genital swellings to fuse at the midline. The condition represents a spectrum of penoscrotal transposition abnormalities. Surgical realignment at the midline and hypospadias repair is recommended management. (See Section II: "Scrotum, Engulfment [Penoscrotal Transposition]." and (Image ☼))

REFERENCE

Sule JD, Skoog SJ, Tank ES, et al. Perineal lipoma and the accessory labioscrotal fold: An etiological relationship. *J Urol*. 1994;151(2):475–477.

SCROTUM, ENGULFMENT (PENOSCROTAL TRANSPOSITION)

DESCRIPTION The most extreme form of penoscrotal transposition, in which the scrotum is located in a cephalad position with respect to the penis. A milder form is bifid scrotum. Major renal anomalies include complete agenesis of the urinary system, unilateral or bilateral renal agenesis, polycystic or dysplastic kidneys, horseshoe kidney, ectopic pelvic kidney, and obstructive uropathy. Abnormalities of the external genitalia include a disproportionately long flaccid penis, complete urethral atresia, and hypospadias. Treated by hypospadias repair with scrotoplasty using an inverted omega skin incision around the scrotal skin and the base

of the penis. This allows placement of the scrotal flaps beneath the penis.

REFERENCE

Parida SK, Hall BD, Barton L, et al. Penoscrotal transposition and associated anomalies: Report of five new cases and review of the literature. *Am J Med Genet.* 1995;59(1):68–75.

SCROTUM, EPIDERMAL INCLUSION CYST

DESCRIPTION Epidermal (epidermoid) inclusion cysts are benign tumors. They result from the implantation of epidermal tissue into the dermis or subcutis, from trauma or abnormal embryologic closure of the median raphe and urethral groove. These lesions appear solid on imaging and often contain a material that is a combination of keratin and cholesterol, often in a laminated configuration arising from a stratified squamous epithelial wall. They can be asymptomatic or more commonly rupture or become infected. Local excision is the treatment, since epidermoid inclusion cysts can mimic rare malignant tumors such as liposarcoma, fibrosarcoma, and even metastatic disease.

REFERENCE

Yang WT, Whitman GJ, Tse GM, et al. Extratesticular epidermal cyst of the scrotum. *AJR Am J Roentgenol.* 2004;183:1084.

SCROTUM, FAT NECROSIS

DESCRIPTION An uncommon lesion that is seen in prepubertal boys and can be a cause of acute scrotal pain. Typical presentation is an obese prepubertal child with recent exposure to cold, such as during swimming. Bilateral intrascrotal masses are present inferior to the testis. If the diagnosis is made with US and shows the classic presentation, conservative management can be employed.

REFERENCE

Donohue A, Utley WLF. Idiopathic fat necrosis in the scrotum. *Br J Urology.* 2008;47(3):331–333.

SCROTUM, GIANT NEUROLEMMOMA

DESCRIPTION Well-encapsulated tumors of neural elements (also called neurinoma or Schwannoma) within the scrotum. Most such tumors are benign, with malignant transformation as an extremely rare occurrence. Surgical removal of the lesion is the definitive treatment.

REFERENCE

Fernandez MJ, Martino A, Khan H, et al. Giant neurilemmoma: Unusual scrotal mass. *Urology.* 1987;30(1):74–76.

SCROTUM, HEMANGIOMA

DESCRIPTION These lesions should be differentiated from angiokeratoma of Fordyce that

appear in older men (see Section II: "Angiokeratoma of Fordyce [Penile and Scrotal Angiokeratomas]"). Hemangiomas represent 7% of all nonmalignant tumors and are the most common benign tumor of infancy; however, they involve the penis and scrotum only 1% of the time. Cutaneous hemangiomas also called (*strawberry angiomas*) may grow for up to 6–12 mo and then undergo involution. By age 7, complete regression will be seen in approximately 75–90% such that most do not need therapy. Subcutaneous hemangiomas are even more infrequent but tend to expand gradually and may clinically resemble a varicocele.

TREATMENT

- Large cutaneous lesions can be excised surgically or ablated with a laser.
- Subcutaneous lesions usually require surgical excision.

REFERENCE

Leavitt DA, Hottinger DG, Reed RC, et al. A case series of genital vascular anomalies in children and their management: Lessons learned. *Urology*. 2012;80(4):914–918.

SCROTUM, HYPOPLASIA

DESCRIPTION The unilateral or bilateral underdevelopment of the scrotum, which simulates labia majora, is most commonly associated with cryptorchid testes and ambiguous genitalia. Some syndromes associated include: Prader–Willi syndrome (PWS), Genitopatellar syndrome, many others. For a complete listing see: http://monarch.monarchinitiative.org/phenotype/HP:0000046, Accessed March 8, 2014.

TREATMENT

- A testicular prosthesis can improve the cosmetic appearance of the scrotum.
- Testosterone cream can also be applied for an improved cosmetic result on the affected side.

REFERENCE

Maat-Kievit A, Brunner HG, Maaswinkel-Mooij P. Two additional cases of the Ohdo-blepharophimosis syndrome. *Am J Med Genet*. 1993;47(6):901–906.

SCROTUM, IDIOPATHIC CALCINOSIS

DESCRIPTION Patients with this condition are typically young men who present with multiple hard nodules throughout the scrotal wall. Although the skin is usually intact, lesions may ulcerate. Thought to be caused by calcification of the scrotal dermal connective tissue (eccrine sweat glands) for unknown reasons. No therapy is necessary unless recurrent episodes of infection occur; then surgical excision may help.

REFERENCE

Tela UM, Ibrahim MB. Scrotal calcinosis: a case report and review of pathogenesis and surgical management. *Case Rep Urol*. 2012;2012:475246.

SEAPI INCONTINENCE CLASSIFICATION SYSTEM

DESCRIPTION SEAPI is an acronym for **s**tress incontinence, **e**mptying ability, **a**natomy, **p**rotection, and **i**nstability. Is useful as a reliable and uniform method of following the short-

and long-term outcome of stress urinary incontinence (SUI) surgery. This system is similar to the TNM tumor staging classification system in that each component is graded with a score from 0 (no symptoms) to 3 (severe symptoms). After completion of the evaluation of the incontinent patient, a preoperative subjective and objective SEAPI score is determined. These scores are then compared with postoperative SEAPI scores to access treatment outcome. It has been found to have a high degree of reliability and internal consistency across a wife age range in both genders.

REFERENCE

Stothers L. Reliability, validity, gender differences in the quality of life index of the SEAPI-QMM incontinence classification system. *Neurourol Urodyn.* 2004;(233):223–228.

SEBORRHEIC DERMATITIS

DESCRIPTION Commonly referred to as *dandruff*, this condition can be seen on the penis, anus, or pubic hair. Pruritus is the rule, with the lesions in hair-bearing areas having a red base and waxy yellow crust. While the organism *Pityrosporon orbiculare* is suspected, the exact agent is unknown. Standard antidandruff shampoos are usually effective. Shampoo containing ketoconazole may be needed. Steroids should be used with caution, if at all, because this tends to be a lifelong problem. (See also Section II: “Pruritus, External Genitalia, Male.”)

REFERENCE

Margolis DJ. Cutaneous diseases of the male external genitalia. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell’s Urology*. 7th ed. Philadelphia, PA: Saunders; 1998.

SEMEN ANALYSIS, ABNORMAL FINDINGS AND TERMINOLOGY

DESCRIPTION A significant overlap exists between fertile, subfertile, and infertile populations, therefore, absolute parameters for infertility (except for aspermia or azoospermia) are difficult to measure precisely. In general, fertile populations demonstrate mean sperm densities of 70–80 million/mL. Assisted reproduction techniques (ART’s) are now able to overcome many of these abnormalities. (See also Section I: “Infertility”; Section II: “Semen Analysis, Technique, and Normal Values.” and “Semen Analysis, Abnormal Findings and Terminology.”)

- Aspermia: No semen ejaculated
- Asthenospermia: $<50\%$ of spermatozoa with forward progression of 3–4
- Asthenozoospermia: Poor motility and/or poor forward progression
- Azoospermia: No spermatozoa found in semen
- Globozoospermia: Round-headed sperm devoid of acrosome
- Hematospermia: Blood present in an ejaculate/semen
- Hyperspermia: Volume of ejaculate >6.5 mL
- Hypospermia: Volume of ejaculate <1.5 mL
- Leukocytospermia/pyospermia: Excess white cells >1 WBC $\times$ 10^6/mL) in semen
- Necrozoospermia: No live sperm in ejaculated semen
- Normozoospermia/normospermia: Refer to a normal semen analysis
- Oligoasthenoteratospermia: Very generalized abnormalities in sperm concentration, motility,

and morphology; often associated with varicocele
- Oligoasthenoteratozoospermia: Signifies disturbance of all 3 variables (combinations of 2 prefixes may also be used)
- Oligozoospermia: Low concentration of sperm $<20 \times 10^6$/mL
- Polyspermia: Abnormally high sperm density $>250 \times 10^6$/mL
- Polyzoospermia: Excessive number of sperm in ejaculate sample
- Pyospermia/leukocytospermia: Excess white cells >1 WBC $\times 10^6$/mL in semen
- Teratozoospermia: Reduced percentage of morphologically normal sperm, usually $<50\%$ spermatozoa with normal morphology

REFERENCES

Gilbert BR, Cooper GW, Goldstein M. Semen analysis in the evaluation of male factor subfertility. *AUA Update Series.* Vol. XI, Lesson 32; 1992.

Grimes DA. Oligozoospermia, azoospermia, and other semen-analysis terminology: The need for better science. *Fertil Steril.* 2007;(886):1491–149.

Rowe PJ, et al., eds. WHO manual for the standardized investigation, diagnosis and management of the infertile male. New York, NY: Cambridge University Press; 2000.

SEMEN ANALYSIS, TECHNIQUE, NORMAL VALUES

DESCRIPTION *Normozoospermia/normospermia* are terms sometimes used to refer to a normal semen analysis. After 48–72 hr of abstinence, a semen specimen is collected in a wide-mouth polypropylene container with a screw top through masturbation without the use of any lubricants that could contaminate the sample. Care must be taken to capture all of the ejaculate. The sample is kept as close to body temperature as possible and delivered to the lab within 1.5 hr. Analysis includes (may vary slightly by lab) total seminal volume, sperm concentration, sperm motility, sperm morphology, fructose content, coagulation time, liquefaction time, viscosity, and leukocyte count. Newer computer-assisted systems (CASA) can also evaluate curvilinear velocity, straight-line velocity, linearity, and amplitude of lateral head displacements. Antisperm antibodies may be considered a secondary test. Normal parameters are established by most labs. The following are general reference parameters and are typically determined on at least 2 specimens. (See also Section I: “Infertility”; and Section II: “Semen Analysis, Abnormal”; also see Section II for topics on specific semen abnormalities.)

Typical Reference Lab Values for Routine Semen Analysis

Volume	1.5–5.0 mL
Appearance	White, viscid, opaque
pH	7.2–7.8
Sperm density	$>20 \times 10^5$/mL
Total sperm count	$>40 \times 10^6$/mL
Motility	>60%
Forward progression	>50% or >2 + on a scale of 0–4 (0, no movement; 4, excellent forward progression)
Morphology	>60% normal
Viability	>50% (by dye exclusion)
Fructose, quantitative	>13 μmol per ejaculate
Liquefaction	10–20 min (measured on a scale of 0–4)
Agglutination	Minimal dumping (increased clumping suggests inflammatory/immunologic process)

Normal Semen Analysis Parameters Published by the WHO

Parameter	Minimum Value
Volume	2.0 mL
Sperm concentration	20 million/mL
Motility	50%
Forward progression	3.0–4
Normal morphology (WHO)	30%
Normal morphology (Strict)	14%
Total sperm count	40 million
Total motile sperm	20 million
Total functional sperm	6 million

Based on data from Rowe PJ, et al., eds. WHO manual for the standardized investigation, diagnosis and management of the infertile male. New York: Cambridge University Press, 2000.

REFERENCE

McLachlan RI, Baker HW, Clarke GN, et al. Semen analysis: Its place in modern reproductive medical practice. *Pathology*. 2003;(351):25–33.

SEMEN LEUKOCYTES

DESCRIPTION The leukocyte is the most common nonsperm cell seen in semen analysis, and it may be confused with immature spermatozoa on microscopy. *Leukocytospermia* and *pyospermia* are terms used to describe excess white cells in the semen sample >1 WBC $\times$ 10^6/mL. Elevations usually are associated with infection, but may be linked to reactive oxygen species and may be present when there is no finding of infection or immune response. Leukocytospermia is often found in patients with unexplained infertility. Semen cultures are prone to contamination, and the use of antibiotics to treat pyospermia is controversial. (See also Section I: “Infertility”; Section II: “Semen Analysis, Abnormal Findings and Terminology”; “Semen Analysis, Technique, Normal Values” and “Pyospermia.”)

REFERENCE

Agarwal A, Bragais FM, Sabanegh E. Assessing sperm function. *Urol Clin N Am.* 2008;35:157–171.

SEMINAL PLASMA HYPERSENSITIVITY (SEMINAL PLASMA ALLERGY) AND HYPERSENSITIVITY TO HUMAN SEMEN (HHS)

DESCRIPTION An allergic reaction to human semen that presents as a systemic reaction (ranging from mild to anaphylaxis) or a localized vaginal symptoms shortly after ejaculation into the vagina. 2 types described in the literature the more common reaction to human seminal plasma (allergic reactions to human seminal plasma [HSP] proteins) or a response to spermatozoa (hypersensitivity to human semen [HHS]). These conditions are likely underreported and may not be discussed or ascribed to dyspareunia or vulvovaginitis. These are seen exclusively in women (usually from 20–30 yr of age) and can be avoided through the use of condoms or less commonly through anti-allergy medications or allergen desensitization. Once established, it usually occurs with other male partners. In addition to the potential symptoms infertility is an issue.

REFERENCES

Carroll M, Horne G, Antrobus R, et al. Testing for hypersensitivity to seminal fluid-free spermatozoa. *Hum Fertil (Camb)*. 2013;16(2):128–131.

Shah A, Panjabi C. Human seminal plasma allergy: A review of a rare phenomenon. *Clin Exp Allergy*. 2004;34:827.

SEMINAL VESICLE AGENESIS

DESCRIPTION Can be unilateral or bilateral (very rare). Unilateral agenesis results from an embryologic insult before separation of the ureteral bud from the mesonephric ducts. Unilateral agenesis is associated with ipsilateral agenesis of the ductus deferens and with renal agenesis in 79%, ipsilateral renal abnormalities in 12%, and only 9% had normal kidneys bilaterally. The contralateral seminal vesicle is often hypoplastic.

REFERENCE

Trigaux JP, Van Beers B, Delchambre F. Male genital tract malformations associated with ipsilateral renal agenesis: Sonographic findings. *J Clin Ultrasound.* 1991;19:3–10.

SEMINAL VESICLE, AMYLOIDOSIS

DESCRIPTION A benign localized condition characterized by subepithelial deposition of amyloid in the seminal vesicles. Amyloids are low–molecular-weight fibrils found in extracellular tissues; they consist of a variety of proteins. Its incidence increases with increased age and can often be misinterpreted as regional spread of bladder or prostate cancer. No treatment is necessary if asymptomatic.

REFERENCE

Erbersdobler A. Seminal vesicle amyloidosis does not provide any protection from invasion by prostate cancer. *BJU Int.* 2009;103(3):324–326.

SEMINAL VESICLE CALCULI AND CALCIFICATIONS

DESCRIPTION Calcification of vas deferens seems to be specific to diabetes melitus and may

be associated with calcification of the seminal vesicles. Other causes include: TB, schistosomiasis, gonorrhea, chlamydia, gonadal dysgenesis, and uremia with secondary hyperparathyroidism. Intraluminal seminal vesicle calcifications can be seen (Image ☼).

REFERENCE

Yadav R, Goel A, Sankhwar SN, et al. Incidentally detected bilaterally symmetrical seminal and vas calcification in young infertile male: A case report, literature review and algorithm for diagnosis. *Can Urol Assoc J.* 2012;6(5):E206–E208.

SEMINAL VESICLE, CARCINOMA

DESCRIPTION Primary tumors of the seminal vesicles are extremely rare as there are no more than 60 histologically confirmed reported cases. The seminal vesicles are often secondarily involved by cancer of surrounding structures such as prostate, bladder, or rectal carcinoma. Lymphoma of the seminal vesicles has been reported. Primary adenocarcinoma of the seminal vesicle (the most common primary type) occurs in patients >50. Immunohistochemistry is helpful in diagnosis. They are PSA and PSAP negative. RP and/or cystoprostatectomy including pelvic lymph node dissection, offers curative treatment. Adjuvant or neoadjuvant chemotherapy is of unproven worth, but a combination of hormonal deprivation and radiotherapy seems to be more effective than any chemotherapy.

REFERENCE

Campobasso D, Fornia S, Ferretti S, et al. Primary bilateral seminal vesicle carcinoma: Description of a case and literature review. *Int J Surg Pathol.* 2012;20(6):633–635.

SEMINAL VESICLE, CYSTS

DESCRIPTION Cysts, of either congenital or acquired origin, located in the seminal vesicles. Many studies in the past have linked such cysts to other GU issues, including renal agenesis, infertility, hematospermia, GU infection, and adult polycystic kidney disease. Causes are congenital, ejaculatory duct obstruction (EDO), or a basement membrane defect, especially in cysts associated with adult polycystic kidney disease. (See also Section I: “Seminal Vesicle Masses and Cysts" and Image ☼)

TREATMENT

- No treatment is necessary if asymptomatic.
- Aspiration, marsupialization, or excision, if symptomatic

REFERENCE

Labanaris AP, Zugor V, Meyer B, et al. A case of a large seminal vesicle cyst associated with ipsilateral renal agenesis. *Sci World J.* 2008;8:400–404.

SEMINAL VESICULITIS

DESCRIPTION Inflammation of the seminal vesicles that often occurs secondary to bacterial infection, causing prostatitis or epididymitis. Older literature referred to this condition as *pyospermia*. Symptoms are often vague and may include penile, scrotal, or perineal pain;

painful ejaculation; hematospermia; lower abdominal or back pain; and LUTS. Diagnosis is often 1 of exclusion of other more common causes made with positive cultures from the ejaculate as well as imaging via transrectal US, CT, or MRI. Pyospermia/leukocytospermia is prominent on semen analysis. Abscess formation is a complication of seminal vesiculitis and can be an initial presentation of the disease. Treatment includes culture-sensitive antibiotics, transrectal aspiration, or excision (open or laparoscopic seminal vesiculectomy) for severe cases. Transurethral seminal vesiculoscopy with irrigation has been described. (See also Section II: "Pyospermia.")

REFERENCES

Zeitlin SI, et al. Seminal vesiculitis. In: Nickel JC, ed. *Textbook of Prostatitis*. 1st ed. Informa HealthCare; 1999.

Liu B, Li J, Li P, et al. Transurethral seminal vesiculoscopy in the diagnosis and treatment of intractable seminal vesiculitis. *J Int Med Res*. 2014;42(1):236–242.

SEMINOMA WITH HIGH MITOTIC RATE (SEMINOMA, ANAPLASTIC)

DESCRIPTION Histologic subtype of seminoma, seen in up to 10% of all seminomas. Anaplastic seminoma is typically more aggressive and invasive compared to classic and spermatocytic seminoma, demonstrating increased mitotic activity and more β-hCG production than its counterparts. It is associated with increased local invasion and rate of metastatic growth as well. Patients usually present at a higher stage. Despite these findings, no survival difference after treatment has been reported when compared to classic seminoma, stage for stage. Treatment depends on tumor stage. Radical orchiectomy followed by either surveillance, radiation therapy, and/or chemotherapy are performed, depending on the extent of disease. (See also Section I: "Testis Cancer, Seminoma.")

REFERENCE

Neill M, Warde P, Fleshner N. Management of low-stage testicular seminoma. *Urol Clin N Am*. 2007;34(2):127–136.

SEMINOMA, CLASSIC

DESCRIPTION The most common histologic subtype of seminomatous germ cell tumor (GCT), it accounts for ~85% of cases. Typically presents in males in the 3rd–5th decades of life. Syncytiotrophoblastic elements are seen in 10% of lesions. These elements produce β-hCG, which can be used as a tumor marker to help assess resolution or recurrence of disease after treatment. Like all testicular tumors, treatment depends on tumor stage. Radical orchiectomy followed by either surveillance, radiation therapy, and/or chemotherapy are performed, depending on the extent of disease. (See also Section I: "Testis, Seminoma.")

REFERENCE

Neill M, Warde P, Fleshner N. Management of low-stage testicular seminoma. *Urol Clin N Am*. 2007;34(2):127–136.

SEMINOMA, SPERMATOCYTIC

DESCRIPTION Accounts for ~2% of all seminomatous germ cell tumor (GCT). Patients present later in life, usually in their 5th–6th decades. Unlike classic and anaplastic subtypes, spermatocytic seminoma rarely metastasizes. It is believed that this subtype arises from a different, more mature germ cell line, which likely contributes to its more favorable presentation. Due to its low metastatic potential, no further treatment is often recommended after radical orchiectomy. (See also Section I: "Testis cancer, Seminoma.")

REFERENCE

Neill M, Warde P, Fleshner N. Management of low-stage testicular seminoma. *Urol Clin N Am.* 2007;34(2):127–136.

SEX REVERSAL SYNDROME (XX MALE)

DESCRIPTION These patients demonstrate small, firm testes; frequent gynecomastia; a small to normal penis; and azoospermia. Testicular biopsy may demonstrate seminiferous tubule sclerosis, causing elevated gonadotropins and decreased testosterone levels. Individuals are shorter than average height. There is no increase in the incidence of mental retardation, but there is an increase in hypospadias. Although karyotyping demonstrates 46, XX, molecular biologic mapping suggests that portions of the Y chromosome are present. It has been hypothesized that the portion of the Y chromosome containing the testes-determining factor has been translocated. Diagnosis is based on karyotype, molecular biologic mapping, and PCR using Y-specific probes. If necessary, phenotypic gender assignment is done very early, and appropriate surgical correction is performed. After puberty, management is more difficult because of androlgic problems such as hypogonadism, micropenis, undescended testes, lack of secondary sex characteristics, and impotence. Treatment plans must address these issues.

REFERENCE

Yamamoto M, Yokoi K, Katsuno S, et al. A case of sex reversal syndrome with sex-determining region. *Nagoya J Med Sci.* 1995;58(3–4):111–115.

SEX-HORMONE BINDING GLOBULIN (SHBG)

DEFINITION

Testosterone (T) circulates bound to either SHBG, albumin or corticosteroid binding globulin (CBG), or in an unbound form (free). SHBG-bound T is about 44% of the total T and is unavailable to cells. Albumin-bound T is about 50% of the total. Conditions that increase SHBG, include aging, hyperthyroidism, estrogens, HIV disease, anticonvulsants, hepatitis and hepatic cirrhosis. Conditions that decrease SHBG, include obesity, diabetes mellitus, hypothyroidism, androgenic steroids, nephrotic syndrome, acromegaly and glucocorticoids. The age-related SHBG increase means that older men may have a normal T levels even if they are hypogonadal, as they will have low levels of free or bioavailable T. Obesity, on the other hand, decreases SHBG and T, even when the available T may be normal.

REFERENCE

Paduch D, et al. The Laboratory Diagnosis of Testosterone Deficiency: AUA White Paper

available at http://www.auanet.org/common/pdf/education/clinical-guidance/Testosterone-Deficiency-WhitePaper.pdf, Accessed March 27, 2014.

SEXSOMNIA

DESCRIPTION Sexsomnia, also known as *somnambulistic sexual behavior* or *sleep sex* is a particular form of parasomnia (disruptive sleep disorders) characterized by atypical sexual behavior during sleep. The repertoire of sexual behavior during sleep can vary from explicit vocalizations with sexual content, violent masturbation, and complex sexual activities including oral sex, and vaginal or anal intercourse.

The exact etiology is unknown, but precipitating factors are stress, sleep deprivation/fragmentation, alcohol or drug consumption, excessive fatigue and physical overactivity in the evening

TREATMENT

- Benzodiazepines are 1st-line therapy
- Sleep hygiene and safety precautions should be implemented

REFERENCE

Andersen, ML, Poyares D, Alves RS, et al. Sexsomnia: Abnormal sexual behavior during sleep. *Brain Res Rev.* 2007;56:271–282.

SEXUAL ANHEDONIA/EJACULATORY ANHEDONIA

DESCRIPTION Lack of appropriate pleasure from sexual activity. Patients typically elicit a failure of genital response. Men have difficulty initiating or sustaining an erection; pre-menopausal women have difficulty with lubrication. Ejaculatory anhedonia describes lack of pleasure during ejaculation. Although a psychogenic etiology is often present, the clinician must rule out hormonal influences. Medications such as selective serotonin reuptake inhibitors have been reported to cause this phenomenon as well.

REFERENCES

Hatzimouratidis K, Hatzichristou D. Sexual definitions: Classifications and definitions. *J Sex Med.* 2007;(41):241–250.

Ralph DJ, Wylie KR. Ejaculatory disorders and sexual function. *BJU Int.* 2005;(959):1181–1186.

SEXUAL FUNCTION SURVEY (SFS) (INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

DESCRIPTION The IIEF is a 15-item, self-administered questionnaire scale for the assessment of erectile function that has been linguistically validated in 10 languages. It addresses the relevant domains of male sexual function: Erectile function (EF), orgasmic function (OF), sexual desire (SD), intercourse satisfaction (IS), and overall satisfaction. EF is represented in items 1(5 and 15 of the questionnaire, with a score range of 0 or 1) to 5, a minimum score of 1, and a maximum score of 30. OF is represented in items 9 and 10, with a score range of 0–5, a minimum score of 0, and a maximum score of 10. SD is represented in

items 11 and 12, with a score range of –5, a minimum score of 2, and a maximum score of 10. IS is covered in items 6, 7, and 8, with a score range of 0–5, a minimum score of 0, and a maximum score of 15. OS is covered in items 13 and 14, with a score range of 1–5, a minimum score of 2, and a maximum score of 10. In general, the lower the score, the worse the erectile function. (See Section VII: "Reference Tables: International Index of Erectile Function [IIEF] [Sexual Function Survey].")

REFERENCE

Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997;49:822–830.

SEXUAL HEALTH INVENTORY FOR MEN (SHIM) SCORE

DESCRIPTION The SHIM, sometimes called IIEF-5 (International Index of Erectile Function), is a validated questionnaire that assesses male sexual function and can be used as an adjunct for the assessment and treatment of ED. This is an abridged version of the original 15-question IIEF questionnaire. The SHIM questionnaire consists of 5 questions pertaining to the quality of the patient's erections and sexual satisfaction over the last 6 mo. Each question is graded on a scale from 1–5. ED is then assessed based on the cumulative value of the SHIM score: 22–25, no ED; 17–21, mild ED; 12–16, mild to moderate ED; 8–11, moderate ED; 5–7, severe ED. (See Section VII for the SHIM Instrument.)

REFERENCE

Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res.* 1999;(116):319–326.

SHY DRAGER SYNDROME, UROLOGIC CONSIDERATIONS

DESCRIPTION Shy Drager syndrome, also known as *multiple system atrophy*, is a progressive neurodegenerative disease in which the etiology is unknown. Bladder dysfunction causing urinary incontinence and erectile dysfunction (ED) are early features. Urinary urgency, frequency, incomplete bladder emptying as well as urinary retention or any combination are seen as urologic manifestations of Shy Drager syndrome. In addition, weakness of the striated urethral sphincter contributes to incontinence. DO is seen on urodynamic evaluation.

REFERENCE

Fowler CJ, Dalton C, Panicker JN. Review of Neurologic Diseases for the Urologist. *Urol Clin North Am.* 2010;37(4):517–526.

SIGNET RING CARCINOMA, PROSTATE

DESCRIPTION A rare, high-grade neoplasm that carries a poor prognosis. A GI primary tumor should be considered with this pathology. Immunohistochemical exam demonstrates cytoplasmic immunoreactivity to PSA in signet-ring cancer cells, with intracytoplasmic vacuoles in the signet-ring cells staining positively for mucus with periodic acid-Schiff. This malignancy is more aggressive than other cell types; >50% of these patients die within a

year of diagnosis.

REFERENCE

Matsuoka Y, Arai G, Ishimaru H, et al. Primary signet-ring cell carcinoma of the prostate. *Can J Urol.* 2007;14(6):3764–3766.

SILBER VASOEPIDIDYMOSTOMY

DESCRIPTION In 1978, Silber was the 1st to report the use of the microscope to perform a vasoepididymostomy. The distal epididymis is cut and, with aid of the microscope, the tubule exuding semen is identified. The freshly cut mucosal lumen of the vas deferens is anastomosed to this tubule, and the adventitia of the vas is then anchored to the epididymal tunic. The procedure is used in selected cases of obstructive infertility.

REFERENCE

Thomas AJ. Vasovasostomy. In: Novick AC, Streem SB, Pontes JE., eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:767–773.

SKENE (PARAURETHRAL) GLAND ADENOCARCINOMA

DESCRIPTION An extremely rare primary urethral carcinoma occurring in approximately 1.5 women per million and constituting $<1\%$ of all female malignancies. Presence of PSA in tissue and/or serum confirms a Skene gland origin, due to its homology to the male prostate. PSA levels normalize after treatment. Complete excision, using a technique similar to repair of urethral diverticulum, is curative. Decision for radiotherapy is based on tumor size and location, with smaller, distal lesions generally undergoing surgical excision and RT, and large or proximal lesions treated with radiation therapy (RT) in an effort to preserve organ function.

REFERENCE

Champ CE, Hegarty SE, Shen X, et al. Prognostic factors and outcomes after definitive treatment of female urethral cancer: A population-based analysis. *Urology*. 2012;80(2):374–381.

SKENE (PARAURETHRAL) GLAND, INFLAMMATION/ADENITIS

DESCRIPTION Skene glands are homologous to the male prostate gland and are located along the anterior vaginal wall, adjacent to the urethral meatus. These glands may become infected and present as a tender, fluctuant periurethral nodule. Infection or inflammation of the Skene glands can cause exquisite tenderness and may be associated with dyspareunia and vulvar vestibulitis. The most common pathogen is *Neisseria gonorrhoeae*. Treatment includes culture of infected area along with surgical incision and drainage if abscess formation is present. Appropriate antibiotic therapy is administered. Other causes of vestibulitis or vulvodynia should be assessed and evaluated.

REFERENCE

Metts JF. Vulvodynia and vulvar vestibulitis: Challenges in diagnosis and management. *Am*

Fam Physician. 1999;(596):1547–1556.

SKIN TAGS, EXTERNAL GENITALIA (ACROCHORDON, PEDUNCULATED PAPILLOMA)

DESCRIPTION Benign, flesh-colored, soft pedunculated benign lesions that may occur anywhere on the body and generally are < 5 mm, although larger lesions can be seen. They may be pinkish, skin-colored, or hyperpigmented and are more common on obese individuals. Usually asymptomatic, these lesions are often found in skin folds (neck, axillae, groin) and rarely involve the external genitalia. They may accompany hamartomatous skin lesions (fibrofolliculomas and trichodiscomas) associated with Birt–Hogg–Dubé syndrome. Irritation and possibly HPV types 6/11 are possible causes. No treatment is necessary, and they are usually considered clinically insignificant. If treatment is desired for cosmesis or irritation, then the tags may be treated by electrocautery, simple scissor excision, suture ligation of the base, or cryotherapy.

REFERENCE

Emir L, Ak H, Karabulut A, et al. A huge unusual mass on the penile skin: Acrochordon. *Int Urol Nephrol.* 2004;36(4):563–565.

SLEEP APNEA, UROLOGIC CONSIDERATIONS

DESCRIPTION Patients with obstructive sleep apnea may have their condition exacerbated by testosterone replacement therapy (TRT); their sleep apnea status should be monitored closely and treated if possible. Sleep apnea also may cause nocturnal hypoxia and may be a factor for erectile dysfunction (ED). Obstructive sleep apnea may also be involved with nocturia and daytime overactive bladder in women.

REFERENCES

Hanafy HM. Testosterone therapy and obstructive sleep apnea: Is there a real connection? *J Sex Med.* 2007;(45):1241–1246.

Lowenstein L, Kenton K, Brubaker L, et al. The relationship between obstructive sleep apnea, nocturia, and daytime overactive bladder syndrome in women. *Am J Obstet Gynecol.* 2008;198(5):598.e1–e5.

SLING MATERIALS

DESCRIPTION Slings, usually mid-urethral, are a common option for the treatment of intrinsic sphincteric deficiency. Sling materials are either autologous, allografts, xenografts, or synthetic. (See also Section I: “Incontinence, Female”; “Incontinence, Male”; Section II: “Urethral Sling.”)

- Autologous grafts (harvested at the time of surgery):
  - Rectus fascia
  - Fascia lata
  - Vaginal wall
  - Round ligament

  – Dermis
- Allografts (processed by freeze-drying or solvent dehydration):
  – Cadaveric fascia
  – Cadaveric dermis
- Xenografts:
  – Porcine dermis
  – Porcine small intestinal submucosa
- Synthetic slings:
  – Marlex
  – Gore-Tex
  – Silicone
  – Transvaginal tape (polypropropylene mesh)

REFERENCE

Wilson TS, Lemack GE, Zimmern PE. Management of intrinsic sphincteric deficiency. *J Urol.* 2003;169(5):1662–1669.

SMEGMA

DESCRIPTION A substance composed of desquamated cells that originate from the epithelium of the glans penis and on the inner surface of the foreskin. Smegma is composed of 26% fat and 13% protein. It remains unclear whether smegma is only desquamated epithelial cells or whether secretions from preputial glands at the coronal sulcus contribute to smegma. The issue of smegma carcinogenicity is still controversial. Some believe that phimosis allows for retention of smegma, which is an irritant that produces malignant transformation of the epithelium by direct contact. 50% of men harbor *Mycobacterium smegmatis* in the preputial sac; this organism has been implicated in the conversion of sterols in smegma into carcinogenic compounds. Good puerperal hygiene is recommended if uncircumcised.

REFERENCE

Maden C, Sherman KJ, Beckmann AM, et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst.* 1993;85(1):19–24.

SMITH–LEMLI–OPITZ SYNDROME

DESCRIPTION An autosomal recessive multisystemic disease found in newborns that present with hypospadias and cryptorchidism. Anomalies in other systems include pernicious anemia, mental retardation, syndactyly, renal abnormalities, and microcephaly. These patients have an inborn error of cholesterol (biosynthesis defect of δ5,7-sterol, δ7-reductase), which results in deficiency of cholesterol and elevation of 7-dehydrocholesterol, a cholesterol precursor. Patients can take cholesterol with or without bile acids.

REFERENCE

Irons M, Elias ER, Abuelo D, et al. Treatment of Smith-Lemli-Opitz syndrome. *Am J Med Genet.* 1997;68(3):311–314.

SMOKING, UROLOGIC CONSIDERATIONS

DESCRIPTION Smoking is a modifiable behavioral risk factor with an array of impact on urologic disorders. The smoking population attributable risk of bladder cancer is 50% in men and 52% in women. The relative risk of developing both renal parenchymal cancer as well as upper tract carcinoma ranged in men from 27–37% and 10–24% in women. In addition, there is a dose-response relationship as the risk of developing RCC is increased in lifelong smokers who smoke >20 cigarettes a day compared those who smoke less. Smoking may cause irreversible damage to neuromuscular and vaso-endothelial mechanisms of erectile function as though only 20% of the population are smokers, 40% of men with ED are currently smokers. Smoking has also been associated with increased risk of acquiring HIV and HPV (both high and low-risk strains). The semen parameters in men who smoke have been found to be significantly decreased, especially sperm motility.

REFERENCE

Watson RA, Sadeghi-Nejad H. Tobacco abuse and the urologist: Time for a more proactive role. *Urology*. 2011;(786):1219–1223.

SNODGRASS HYPOSPADIAS REPAIR

DESCRIPTION Snodgrass hypospadias repair, also known as *tubularized incised-plate urethroplasty*, is the most commonly performed operation to repair distal hypospadias. The key step in the procedure is a midline incision of the urethral plate. The urethral plate is then tubularized beginning at the neomeatus, turning all epithelium into the neo-urethral lumen.

REFERENCE

Snodgrass WT. Snodgrass technique for hypospadias repair. *BJU Int.* 2005;95:683–689.

SOAP-BUBBLE NEPHROGRAM

DESCRIPTION The Soap-bubble nephrogram seen on IVP is caused by end-stage obstruction atrophy, this is a radiographic appearance of the dilated pyelocalyceal system in which overlapping curved, white densities several millimeters in thickness appear after IV or intra-arterial injection of contrast material. Dilated calyces are represented by bubbles, and remnants of Bertin columns appear as thin opacities between adjacent calyces.

REFERENCE

Ransley PG. Opacification of the renal parenchyma in obstruction and reflux. *Pediatr Radiol.* 1976;4:226.

SODIUM CYANIDE NITROPRUSSIDE TEST

DESCRIPTION A qualitative test for cystinuria. The assay involves the conversion by cyanide of cystine to cysteine. Nitroprusside binds cysteine resulting in a purple color in 2–10 min. The test detects cystine levels above 75 mg/g creatinine. If positive a quantitative 24-hr collections should be performed. (See also Section I: “Urolithiasis, Cystine and Cystinuria (Hypercystinuria)” and Section II: “Metabolic Stone Evaluation [24-hr Urine Studies].”)

REFERENCE
Eggermann T, Venghaus A, Zerres K. Cystinuria: An inborn cause of urolithiasis. *Orphanet J Rare Dis*. 2012;7:19–29.

SOLITARY FIBROUS TUMOR, RENAL

DESCRIPTION Solitary fibrous tumors (SFTs) are mesenchymal tumors arising at any site. When involving the kidney, they arise from the capsule, renal pelvis, or hilar fatty tissue. They present similar to patients with RCC. On gross appearance, the tumor is solid with a pseudocapsule. Microscopically, it shows a spindle cell proliferation. Controversy exists concerning the diagnosis of SFT and hemangiopericytoma because of overlapping immunohistochemical features. No cases of metastasis from renal SFTs has been described.

TREATMENT
Radical nephrectomy with complete resection including negative margins is needed for a favorable prognosis.

REFERENCE
Makris A, Tabaza R, Brehmer B, et al. Solitary fibrous tumor of the kidney: A case report. *Can J Urol*. 2009;(165):4854–4856.

SPERM GRANULOMA

DESCRIPTION Sperm granulomas form from the testicular end of the vas deferens after vasectomy. Because sperm is highly antigenic, the inflammatory reaction creates a granuloma, which is usually asymptomatic. Some studies have shown that men who undergo vasectomy reversal have higher success rates if they have a sperm granuloma at the vasectomy site. A mass in the scrotum, often tender postvasectomy, is diagnostic.

TREATMENT
- When chronic post-vasectomy pain is localized to the sperm granuloma, the lesion should be excised and occluded with electrocautery.
- Post-vasectomy congestive epididymitis may be relieved with open-ended vasectomy, which will produce a pressure-relieving sperm granuloma.

REFERENCE
Awsare NS, Krishnan J, Boustead GB, et al. Complications of vasectomy. *Ann R Coll Surg Engl*. 2005;87(6):406–410.

SPERM PENETRATION ASSAY (SPA, HAMSTER TEST)

DESCRIPTION Also called *hamster oocyte penetration test* and in some publications (*Humster test*), a test for infertility that assesses the ability of sperm to penetrate the ovum. The zona pellucida from hamster oocytes is removed, which allows capacitated human sperm to penetrate it. This assay requires the sperm to be able to undergo capacitation, the acrosome reaction, fusion with the oolemma, and incorporation into the ooplasm. If sperm penetration is 10–30%, the sample is considered normal, but this bioassay is not standardized. Some studies have shown that IVF success is correlated with a positive SPA, while others have not.

These inconsistencies require that the physician become familiar with the lab performing this test. Although there are controversies surrounding SPA, it is a test that should be performed for unexplained infertility.

REFERENCE

Aitken RJ. Sperm function tests and fertility. *Int J Androl.* 2006;29(1):69–75.

SPERM VITALITY

DESCRIPTION Also referred to as *sperm viability or sperm motility*, this is 1 parameter in semen analysis during workup of male infertility. Determination of the percentage of viable and motile sperm in semen samples is helpful to determine if the sperm could be of therapeutic use for various fertilization techniques. (See also Section I: "Infertility"; Section II: "Semen Analysis, Technique, and Normal Values.")

REFERENCE

Cooper TG, Hellenkemper B. Method-related estimates of sperm viability. *J Androl.* 2009;30(3):214–218.

SPERMATIC CORD, LIPOSARCOMA

DESCRIPTION A rare soft tissue malignancy derived from mesenchymal tissue. It is often mistaken for hydrocele, cord lipoma, or incarcerated hernia and preoperative diagnosis is rare. Most malignant paratesticular tumors are sarcomas, but 5–7% are liposarcomas. High-resolution ultrasound, CT, and MRI have become imaging of choice. Tumors in the literature have been reported to range from 0.4 cm to as large as 50 cm. The majority of tumors are low grade and well differentiated. Late recurrences and metastases may be seen, particularly with high-grade lesions. Radical orchiectomy with wide local excision and high ligation of the spermatic cord, is the treatment. Liposarcoma is radiosensitive and radiotherapy can be used to prevent local recurrence. (See also Section I: "Spermatic Cord Mass and Tumors.")

REFERENCE

Li F, Tian R, Yin C, et al. Liposarcoma of the spermatic cord mimicking a left inguinal hernia: a case report and literature review. *World J Surg Oncol.* 2013;11:18.

SPINA BIFIDA/SPINA BIFIDA OCCULTA, UROLOGIC CONSIDERATIONS

DESCRIPTION Spina bifida is a birth defect that results in the incomplete closure of the embryologic neural tube, leading to incomplete development of the spinal cord and vertebrae. This usually involves the lumbar and sacral areas. As a result, many patients develop a neurogenic bladder dysfunction requiring long-term urologic care. Although 90% of patients born with spina bifida have normal upper urinary tracts, over 1/2 of these patients will show signs of renal deterioration if no urologic intervention is performed. Spina bifida occulta is the mildest form of spina bifida. The vertebrae may not fuse together, although the spinal cord and nerves are intact. Patients with spina bifida occulta may have no neurologic deficits at birth. Neurologic deficits that are present are usually mild compared to patients with spina bifida, and may develop later in life. Treatment involves aggressive urologic surveillance to

preserve renal and bladder function. A neonatal renal US and voiding cystourethrography are obtained to assess for hydronephrosis and vesicoureteral reflux. Up to 20% of patients with spina bifida will have reflux. A urodynamic study (UDS) is also performed during this period to evaluate bladder compliance, detrusor pressures, capacity, leak pressures, contractions, and sphincter dyssynergia. Some institutions recommend prophylactic antibiotics and CIC until the neonate's 1st UDS. Patients with poorly compliant bladders with elevated filling pressures (typically above 40 cm H_2O) are in danger of upper tract deterioration and are typically started on clean intermittent catheterization (CIC) and anticholinergic therapy. If a patient fails conservative medical therapy, surgical procedures such as intravesical botulinum toxin injection, vesicostomy, augmentation cystoplasty, or urinary diversion (continent or incontinent) may be appropriate treatment options. It should be stressed to patients and their families to have strict routine follow-up visits to evaluate bladder or upper tract deterioration. (See also Section I: "Myelodysplasia Spinal Dysraphism, Urologic Considerations" and (Image ☼).)

REFERENCE

Joseph DB. Current approaches to the urologic care of children with spina bifida. *Curr Urol Rep.* 2008;(92):151–157.

SPINAL CORD COMPRESSION, UROLOGIC CONSIDERATIONS

DESCRIPTION Epidural spinal cord compression, if due to a urologic etiology, is most likely bone metastasis from prostate cancer. Other types of cancer (eg, breast, lung, kidney, GI) must also be kept in mind. Vertebral body metastases are present in the majority of patients dying from metastatic prostate cancer. Compression of the cord causes edema, venous congestion, and demyelination. Symptoms include back pain, progressive weakness, sensory loss, and paralysis. Bowel and bladder dysfunction are late findings. Neurologic impairment can progress overnight, so patients must be followed carefully. Survival of patients with spinal cord compression due to metastasis is relatively poor: 46% of patients survive <6 mo, and 20% <2 mo. Diagnosis is based on findings of CT and MRI. (See also Section I: "Spinal Cord Injury, Urologic Considerations.")

TREATMENT

- Glucocorticoids, high-dose steroids 100 mg IV then 24 mg IV every 6 hr for 3 days, then taper
- Orchiectomy, high-dose ketoconazole (200–400 mg PO TID) or LHRH antagonist degarelix) to rapidly reduce serum testosterone if hormone naïve
- External radiation therapy with or without vertebrectomy note decompressive laminectomy has not been as successful as vertebrectomy with spinal stabilization, as most disease is located anterior to the spinal cord.

REFERENCES

Kuban DA, el-Mahdi AM, Sigfred SV, et al. Characteristics of spinal cord compression in adenocarcinoma of prostate. *Urology*. 1986;28(5):364–369.

Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial.

Lancet. 2005;366(9486):643–648.

SPINAL SHOCK

DESCRIPTION After acute spinal cord injury (SCI), a period of areflexia and flaccid paralysis usually occurs below the level of injury. This period of spinal shock is variable; reflex detrusor activity usually returns after 2–12 wk, although it may take up to 1 yr. Urodynamic studies assessing bladder function are postponed until spinal shock resolves. Treatment is supportive during this period of detrusor areflexia. CIC is the recommended means of emptying the bladder, although an indwelling Foley catheter may be another alternative. (See also Section I: “Spinal Cord Injury, Urologic Considerations.”)

REFERENCE

Watanabe T, Rivas DA, Chancellor MB. Urodynamics of spinal cord injury. *Urol Clin N Am.* 1996;23(3):459–473.

SPINDLE CELL NEOPLASM, UROLOGIC CONSIDERATIONS

DESCRIPTION Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare neoplasm of the kidney and is classified by the WHO as a variant of RCC. It is considered a low-grade carcinoma with a favorable prognosis. It typically presents in adult women in a 4:1 ratio. It is believed to be derived from the epithelial cells of the loop of Henle or possibly the collecting duct. There are also rare case reports of spindle cell neoplasm of the bladder and penis. The histologic features are characterized by elongated tubules and cord arrangements, which are separated by mucinous stroma. The parallel tubular arrays have a spindle cell configuration. There are also rare case reports of spindle cell neoplasm involving the bladder and penis.

TREATMENT

- Complete surgical excision appears to be adequate treatment
- Those with true sarcomatoid changes have increased risk of recurrence, regional adenopathy, or distant metastases

REFERENCE

Lima, MS, Barros-Silva GE, Pereira RA, et al. The imaging and pathological features of a mucinous tubular and spindle cell carcinoma of the kidney: a case report. *World J Surg Oncol.* 2013;11:34.

SPINNING TOP URETHRA

DESCRIPTION Spinning top urethra (STU) is a widened posterior urethra seen mainly in girls that is seen on videourodynamics. The most common mechanism for dilatation of the posterior urethra is unstable bladder contractions are resisted by a voluntary increase in the tension of the external urinary sphincter. The increased pressure results in a dilation of the posterior urethra. It is seen in patients with voiding dysfunction.

REFERENCE

Saxton HM, Borzyskowski M, Mundy AR, et al. Spinning top urethra: not a normal variant.

Radiology. 1988;168(1):147–150.

SPLENIC INJURY DURING RADICAL NEPHRECTOMY

DESCRIPTION Of cases involving iatrogenic injury to the spleen, up to 12% have been reported to occur during nephrectomy. Splenic injuries usually tend to occur from excessive traction rather than direct injury or scalpel laceration; adequate exposure starting from an appropriate incision is essential. Capsular tears are the most common encountered event. The inferior portion of the spleen is typically involved, since the spleen has ligamentous associations (splenocolic, splenorenal, splenophrenic) with the kidney and other nearby organs and structures. The splenic artery can be found crossing the upper pole of the left kidney, dividing into segmental branches. Optimal treatment 1st involves recognizing splenic injury in a timely fashion intraoperatively. Depending on the extent of injury and condition of the patient, the decision is made to proceed with either salvage of the spleen or splenectomy. Splenic salvage techniques depend on severity of injury and includes the use of topical hemostatic agents, primary suture repair, partial segmental resection, or mesh repair. Complications associated with splenic injury repair or splenectomy include subphrenic abscess; injury to the stomach, colon, or tail of the pancreas; pancreatitis or pancreatic fistula formation; and pleural effusion.

REFERENCE

Merchant A, et al. Management of intraoperative splenic injury. *Operative Techniques Gen Surg.* 2008;(101):4–10.

SPLENOGONADAL FUSION

DESCRIPTION A rare congenital malformation in which an abnormal fusion exists between the spleen and the gonad or mesonephros derivatives. This fusion occurs in both sexes, but it is more common in males. Half of the cases are reported in children. The 2 types are continuous and discontinuous. In the continuous splenogonadal fusion, the main spleen is connected to the left gonad by a strand of tissue. This cord may be fibrous or splenic or contain beads of splenic tissue. The discontinuous type has no cord between the spleen and left gonad. 1/3 of all reported cases are associated with other congenital abnormalities, especially peromelia. The majority of cases present with scrotal mass or scrotal tenderness. Some are found incidentally during herniorrhaphy or orchidopexy. Although evaluation is usually done in the operating room, a technetium^{99} colloid liver spleen scan can easily identify splenic tissue in the scrotum if splenogonadal fusion is suspected preoperatively. Scrotal US does not help to diagnosis this entity.

TREATMENT

- Usually involves removing both the testis and adjoining mass.
- If the diagnosis of discontinuous splenogonadal fusion is made before surgery, the splenic nodule can simply be excised.
- For the continuous variety, exploratory laparotomy is necessary to identify the anatomy involved and deal with the continuous cord.

REFERENCE

Gouw AS, Elema JD, Bink-Boelkens MT, et al. The spectrum of splenogonadal fusion. Case report and review of 84 reported cases. *Eur J Pediatr.* 1985;144(4):316–323.

SPLENULE/SPLENOSIS, UROLOGIC CONSIDERATIONS

DESCRIPTION A benign condition associated with splenic rupture, typically during splenic surgery or trauma. Autotransplantation of splenic tissue occurs via seeding of splenic pulp in the abdominal or thoracic cavities. Hematogenous spread has also been reported. Patients are asymptomatic, and the discovery of splenosis is usually incidental on imaging studies. Splenosis in the abdominal cavity has been mistaken for primary malignancies, such as primary RCC. Similarly, thoracic splenosis can mimic metastatic urologic malignancies as well. The diagnostic modality of choice is nuclear scintigraphy. Once splenosis is confirmed and malignancy is ruled out, no treatment is necessary due to the benign nature of the condition.

REFERENCE

Fremont RD, Rice TW. Splenosis, a review. *South Med J.* 2007;(1006):589–593.

SPORTS HERNIA (ATHLETIC PUBALGIA, SPORTSMAN'S HERNIA)

DESCRIPTION A sports hernia is a painful, soft tissue injury that occurs in the groin area. It most often occurs during sports that require sudden changes of direction or intense twisting movements and is considered an "overuse" injury. It is a musculo-tendinous injury that involves the insertion of abdominal muscles on the pubis and the upper aponeurotic insertion of the adductor muscles. The pain develops during exercise, is generally unilateral but occasionally bilateral, and is typically located in the supra-inguinal portion of lower abdomen lateral to rectus abdominis, sometimes radiating to the testis. Although a sports hernia may lead to a traditional, abdominal wall hernia, it is a different injury. A sports hernia is a strain or tear of any soft tissue (muscle, tendon, ligament) in the lower abdomen or groin area. Because different tissues may be affected and a traditional hernia may not exist, the medical community prefers the term *athletic pubalgia* to refer to this type of injury. The existence, significance and diagnosis of sports hernia are all controversial. The condition needs to be differentiated from a direct, indirect, or femoral groin hernia, adductor longus origin "tendonitis," or osteitis pubis based on history and physical exam. The symptoms are nonspecific and can include tenderness on palpation of the medial inguinal floor, tenderness on palpation over the pubic ramus, and exacerbated pain with resisted hip adduction. MRI may be useful in the differential. Rest, anti-inflammatory medications (NSAIDs) and physical therapy are beneficial. Rarely surgery may be necessary to repair the torn ligament or tendon.

REFERENCES

Litwin DE, Sneider EB, McEnaney PM, et al. Athletic pubalgia (sports hernia). *Clin Sports Med.* 2011;30(2):417–434.

Goel A, et al. Athletic Pubalgia http://radiopaedia.org/articles/athletic-pubalgia-1, Accessed April 6, 2014.

SQUAMOUS METAPLASIA, GENITOURINARY

DESCRIPTION The replacement of normal urothelium by mature squamous epithelium. Nonkeratinizing squamous metaplasia is thought to be a normal variant in premenopausal women, occurring under hormonal influence. This form is commonly found in the trigone; cystoscopically, it appears as a white patch. Keratinizing squamous metaplasia, also known as vesical leukoplakia, is a response to chronic irritation and infection. Some patients go on to develop squamous carcinoma. Keratinizing squamous metaplasia often occurs with long-term urinary catheters, a bladder stone, vesical schistosomiasis; long-term observation is warranted for the development of squamous carcinoma of the bladder.

SYNONYMS

- Pseudomembranous trigonitis
- Vesical leukoplakia

TREATMENT

Transurethral resection ablation and biopsy in cases of keratinizing squamous metaplasia

REFERENCE

Ahmad I, Barnetson RJ, Krishna NS. Keratinizing squamous metaplasia of the bladder: A review. *Urol Int.* 2008;(813):247–251.

STAMEY PROCEDURE (URETHROPEXY)

DESCRIPTION Stamey was the 1st to report the use of the cystoscope to aid in the performance of a transvaginal urethropexy. In addition, the nonabsorbable sutures that are placed with a needle carrier incorporate a Dacron pledget to buttress the suture at the level of the bladder neck. Used to treat stress incontinence in women; of the patients who have undergone this procedure, 82% of 192 were improved, and 65% of the 192 would be willing to undergo the procedure again. Another study showed that although the Stamey procedure has a high early success rate, the long-term results were poor. After 5 yr, only 18% of 28 women remained dry. Concomitant abdominal hysterectomy, respiratory disease, and obesity were likely to point to a lower long-term cure rate. Possible complications include long-term erosion of sutures into the urinary tract and long-term urinary retention if sutures are tied too tightly.

REFERENCE

O'Sullivan DC, Chilton CP, Munson KW. Should Stamey colposuspension be our primary surgery for stress incontinence? *Br J Urol.* 1995;(754):457–460.

STAMEY TEST (3-GLASS TEST, 4-GLASS TEST, MEARES–STAMEY TEST)

DESCRIPTION The 3-glass test described by Meares and Stamey is a method of collecting urine, which can provide information on the site of the urinary tract origin of RBCs or bacteria. Although this method is effective in localizing the cause of hematuria, it is more commonly used in diagnosing prostatitis. A specimen is collected from the urethra, midstream urine, and prostatic secretions. The 1st-voided 10 mL of urine is the urethral specimen (VB1). The midstream urine of 10 mL (VB2) is collected after the patient has voided about 200 mL.

The patient is then instructed to stop voiding, at which time the physician massages the prostate and collects the prostatic fluid expressed prostatic secretions (EPS). Afterward, the patient voids again, and a 10-mL specimen (VB3) is collected. Cultures are sent on the 4 specimens hence the 3-glass or 4-glass test (nomenclature). When the bladder urine is sterile, urethral, and prostatic infection can be differentiated by comparing the bacterial colony counts of VB1 and prostatic EPS and VB3 counts. In urethral infections, the VB1 count is much higher than the EPS or VB3 count. The EPS and VB3 counts in prostatic infections significantly exceed the VB1 count. When interpreting bacterial colony counts, the clinician must take into account that the VB3 specimen is a 100× dilution of prostatic fluid. When the bladder urine is infected, the infection cannot be localized, because all specimens will show heavy growth of organisms. Note that this test is often replaced by the*2-glass test,* which collects a more convenient pre-/postprostatic massage urine sample. The premassage and postmassage 2-glass test has strong concordance with the 4-glass test and is a reasonable alternative when EPS are not obtained. The technique and diagnosis algorithm are discussed in Section I: “Prostatitis, General” and “Prostatitis, Chronic, Bacterial [NIH II].”

REFERENCES

Meares EM, Stamey TA. The diagnosis and management of bacterial prostatitis. *Br J Urol.* 1972;(442):175–179.

Nickel JC, Shoskes D, Wang Y, et al. How does the premassage and postmassage 2-glass test compare to the Meares-Stamey 4–glass test in men with chronic prostatitis/chronic pelvic pain syndrome? *J Urol.* 2006;176(1):119–124.

STAUFFER SYNDROME

DESCRIPTION A syndrome associated with nonmetastatic hepatic dysfunction commonly seen in cases of RCC. Symptoms include fever, fatigue, and weight loss. The patient has unusual liver function tests, WBC loss, and areas of hepatic necrosis without hepatic metastasis. The presence of hepatic dysfunction should not be a contraindication to surgery. Hepatic function usually returns to normal after nephrectomy. If the syndrome persists, it is a sign of recurrent tumor. Diagnostic indicators are elevation of alkaline phosphatase and bilirubin, hypoalbuminemia, prolonged PTT, and hypergammaglobulinemia.

REFERENCE

Jacobi GH, Philipp T. Stauffer’s syndrome: Diagnostic help in hypernephroma. *Clin Nephrol.* 1975;(43):113–115.

STEINSTRASSE

DESCRIPTION A German expression for “street of stones,” referring to multiple stone fragments in the ureter after extracorporeal shock wave lithotripsy. Characteristically, stone fragments are found in a line within the ureter, which may or may not be obstructed. The condition occasionally presents with renal colic, nausea, or vomiting. Observation is sufficient if symptoms are tolerable or absent; with severe colic or obstruction, treatment is ureteral stent placement, percutaneous nephrostomy, or ureteroscopic lithotripsy (Image ☼).

REFERENCE

Weinerth JL, Flatt JA, Carson CC 3rd. Lessons learned in patients with large Steinstrasse. *J Urol.* 1989;142:1425.

STING PROCEDURE

DESCRIPTION This refers to subureteral transurethral injection (“STING”) of bulking agents to correct vesicoureteral reflux. The original coined term was subureteric Teflon injection (STING) using pyrolyzed Teflon (PTFE) particles suspended in glycerin. Due to concern over migration of the Teflon to the brain and lung it was abandoned in favor of other agents. Silicone was also used as a bulking agent (Macroplastique) and while effective was also abandoned due to safety concerns. Other materials such as glutahaldehyde crosss-linked bovine collagen [Contigen] and calcium hydroxyapatite (Coaptite) are also no longer used a bulking agents. Bulking agents such as Deflux (cross-linked dextranomer/hyaluronic acid copolymer) has been accepted and is currently in widespread use. The basic technique involves the periureteral injection at the 6 o’clock position of the ureteral orifice. A modification is the hydrodistention implantation technique (HIT) where the agent is injected inside the ureteral hiatus. Overall the success rate is inferior to that of open surgery. About 70% have reflux resolution after 1 procedure. With repeat STING procedures, the success rate increases to 90–95%. (See also Section I: “Vesicoureteral Reflux, Pediatric"; and Section II: “Bulking Agents, Injectable.”)

REFERENCES

Aubert D, Zoupanos G, Destuynder O, et al. Sting procedure in the treatment of secondary reflux in children. *Eur Urol.* 1990;(174):307–309.

Watters ST, Sung J, Skoog SJ. Endoscopic treatment for vesicoureteral reflux: how important is technique? *J Pediatr Urol.* 2013;9(6 Pt B):1192–1197.

STRANGURIA

DESCRIPTION Slow, painful, spasmodic expulsion of urine in a drop-wise fashion, usually occurring at the end of micturition due to spasm of the bladder and urethra. Associated with an irritative process in the GU system, it often refers pain to the urethral meatus. Historically, the pathophysiology has been attributed to a significant inflammatory component. The term is not commonly used in human medicine, but is firmly entrenched in veterinary medicine.

SYNONYMS

- Strangury
- Terminal dysuria

REFERENCE

Wright B, Husbands E. Strangury: the case of a symptom with ancient origins. *BMJ Support Palliat Care.* 2011;1:49–50.

STREAK GONAD

DESCRIPTION Streak gonads are hypoplastic and dysfunctioning gonads mainly consisting

of fibrous tissue. Patients with streak gonad usually present with female phenotype, primary amenorrhea, infantile breast status, sparse pubic and axillary hair, infantile external genitalia and vagina, atrophic vaginal smear, immature uterus, high serum FSH, low urinary estrogen, and osteoporosis, as well as the streak gonad. Diagnosis is made by measuring FSH and urinary estrogen, and determining karyotype. (See Section II: "Gonadal Dysgenesis, Mixed and Pure.")

TREATMENT

- Management includes laparotomy with excision of any intra-abdominal testis or streak gonads. These masses progress to malignancies, which may develop before puberty.
- Female sex assignment and reconstructive surgery are advised in cases with severely deficient virilization of the genitalia.

REFERENCE

Calabrese F, Valente M. Mixed gonadal dysgenesis: Histological and ultrastructural findings in two cases. *Int J Gynecol Pathol.* 1996:(153):270–275.

STRICKLER URETERAL ANASTOMOSIS

DESCRIPTION Through an extracolonic approach, a small linear incision is made in the taenia, and a small clamp is used to create a submucosal 3–4-cm tunnel exiting out of the colon laterally. The ureter is delivered through the tunnel, the spatulated end is anastomosed to the mucosa, and the taenia is closed while incorporating ureter adventitia.

REFERENCE

McDougal WS. Use of intestinal segments and urinary diversion. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders; 1998:3137–3144.

STRUVITE

DESCRIPTION The mineral name for magnesium ammonium phosphate hexahydrate ($NH_4MgPO_4{\cdot}6H_2O$) stones. Struvite stones (also sometimes known as triple phosphate stones) are composed of calcium magnesium ammonium phosphate and form only in urine infected by urea-splitting bacteria, such as Proteus, Providencia, and sometimes Klebsiella, Pseudomonas, and enterococci. Because of their potential for rapid growth and substantial morbidity, early detection and eradication are essential (See also Section I: "Urolithiasis, Staghorn") and (Image ☼).

REFERENCES

Healy KA, Ogan K. Pathophysiology and management of infectious staghorn calculi. *Urol Clin N Am.* 2007;343:363–374.

Xu H, Zisman AL, Coe FL, et al. Kidney stones: an update on current pharmacological management and future directions. *Expert Opin Pharmacother*. 2013;14(4):435–447.

STUDER POUCH

DESCRIPTION An orthotopic neobladder is made, based on 60 cm of marsupialized ileum, which is configured and sutured into a W to create a broad intestinal plate. In addition, a nontubularized segment of ileum extends from a limb of the W, simulating a chimney. The ureters are implanted into the chimney. The intestinal plate is anastomosed to the urethra and then closed into a sphere and connected to the urethra.

REFERENCE

Colombel M, Chopin DK, Studer UE. A procedure for bladder replacement using a low-pressure ileal reservoir. *Ann Urol (Paris)*. 1993;(271):36–41.

SUPERFICIAL INGUINAL POUCH OF DENIS-BROWNE

DESCRIPTION A superficial inguinal pouch is defined as the space distal to the internal inguinal ring, but above the inguinal canal, between the external oblique fascia and Scarpa fascia. Studies suggest that a testis in the superficial inguinal pouch is, in reality, a cryptorchid testis.

REFERENCE

Herzog B, Steigert M, Hadziselimovic F. Is a testis located at the superficial inguinal pouch (Denis-Browne pouch) comparable to a true cryptorchid testis? *J Urol.* 1992;(1482 Pt 2):622–623.

SUPERNUMERARY KIDNEY

DESCRIPTION A supernumerary kidney is a rare condition in which a free accessory renal organ exists as a distinct entity, with its own blood supply, with presence of 2 normal kidneys. It is distinguished by its small size and/or abnormal position. The kidney is either a component of a bifid ureteral system or a completely duplicated system. When diagnosed, treatment for a supernumerary kidney should be based on pathologic processes affecting the kidney rather than its redundant appearance or abnormal position. Association of a normal kidney with a 2nd or 3rd ipsilateral smaller kidney is an extremely rare anomaly with only a total of 81 cases reported through 2013.

REFERENCE

Afrouzian M, Sonstein J, Dadfarnia T, et al. Four miniature kidneys: supernumerary kidney and multiple organ system anomalies. *Hum Pathol.* 2013. pii: S0046–8177(13)00522-4. doi: 10.1016/j.humpath.2013.11.015. [Epub ahead of print]

SUPINE STRESS TEST

DESCRIPTION Nonurodynamic method to test for intrinsic sphincteric deficiency, it is performed by placing the patient in lithotomy position and filling the empty bladder with 200 cc saline under gravity. The patient is then asked to cough and perform a Valsalva maneuver. A test is deemed positive if fluid is seen leaking from the meatus at time of cough or Valsalva. Studies have shown that it is a relatively quick and inexpensive test that has a sensitivity of 93.5% and specificity of 90.0%.

REFERENCE

Hsu TH, Rackley RR, Appell RA. The supine stress test: A simple method to detect intrinsic urethral sphincter dysfunction. *J Urol.* 1999;(1622):460–463.

SWYER SYNDROME (XY SEX REVERSAL)

DESCRIPTION A sex reversal disorder with a female phenotype and 46, XY genotype with pure gonadal dysgenesis. Patients have bilateral streak gonads and often present in adolescence as phenotypic females with delayed puberty. A 46, XY genotype may develop rapid breast or clitoral enlargement due to hormonally active gonadoblastomas within the streak gonads. The presence of the Y chromosome increases the risk of gonadal tumors and therefore a prophylactic bilateral salpino-gonadenectomy is often advised. (See also Section II: “Gonadal Dysgenesis [Mixed and Pure].”)

REFERENCES

Moreira-Filho CA, Toledo SP, Bagnolli VR, et al. H-Y antigen in Swyer syndrome and the genetics of XY gonadal dysgenesis. *Hum Genet.* 1979;53(1):51–56.

Zhu J, Liu X, Jin H, et al. Swyer Syndrome, 46, XY gonadal dysgenesis, a sex reversal disorder with dysgerminoma: A case report and literature review. *Clinical & Experimental Obstetrics & Gynecology*. 2011;38(4):414–418.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

DESCRIPTION SIADH is the most frequent cause of hyponatremia. The condition usually results when plasma levels of antidiuretic hormone or arginine vasopressin are elevated when normal physiologic secretion of vasopressin from the posterior pituitary should be suppressed, causing a euvolemic hypo-osmolar hyponatremia. There are many causes of this syndrome of inappropriate diuresis, which include malignancies (such as small cell lung cancer, cancers of the GI tract, lymphoma), pulmonary diseases (pneumonia, TB, cystic fibrosis, asthma), disorders of the CNS (neurologic diseases as well as infection, bleeding, or trauma-related), and drugs. Intranasal desmopressin (DDAVP) to treat nocturnal enuresis can be associated with this condition. Acute management requires evaluation of the clinical status of the patient, assessment of the type of hyponatremia, and treatment based on the degree of hyponatremia. After the patient is stabilized, treatment can then be focused on determining the underlying cause of SIADH. If possible, removal or treatment of the underlying cause can result in full resolution. Long-term treatment consists of fluid restriction and possible use of pharmacologic agents such as demeclocycline (causes a nephrogenic DI) or vasopressin receptor antagonists.

REFERENCE

Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med.* 2007;356(20):2064–2072.

SYSTEMIC LUPUS, UROLOGIC CONSIDERATIONS

DESCRIPTION The kidney (*lupus nephritis*) is the organ most commonly affected by systemic

lupus erythematosus (SLE), a chronic, multisystem autoimmune disease with no known cause. A variety of diseases related to SLE can affect the kidney, with renal biopsy usually necessary to identify the specific type. The renal manifestations of SLE vary from patient to patient. Proteinuria with or without an elevated creatinine is the most common manifestation of renal disease in SLE. Urine sediment typically shows >5 red and white blood cells per high power field and/or ≥ 1 cellular cast in more severe forms of disease. Immune complexes result in injury to the glomerulus, and the specific lesion is determined by renal biopsy. International Society of Nephrology classification divides the SLE glomerular disorders into different classes: Classes I and II (minimal mesangial lupus nephritis and mesangial proliferative lupus nephritis) are the mildest forms; classes III and IV (focal proliferative lupus nephritis and diffuse proliferative lupus nephritis) more severe forms; and classes V and VI (membranous lupus nephritis and advanced sclerosing lupus nephritis) are the most severe forms. These more severe forms of lupus nephritis can cause impaired renal function, proteinuria, and the nephrotic syndrome. In addition to these glomerulopathies, SLE can also result in interstitial nephritis and renal vascular disease. Rarely, certain medications (eg, anti-TNFα therapy [infliximab and etanercept], chlorpromazine, diltiazem, hydralazine, interferon-α, isoniazid [INH], minocycline, penicillamine, quinidine, methyldopa, procainamide) can cause drug-induced SLE. Mild forms are not treated, but more severe forms are treated with cytotoxic agents (cyclophosphamide therapy) and prednisone. Renal replacement may be needed in the most severe forms.

REFERENCE

Waldman M, Appel GB. Update on the treatment of lupus nephritis. *Kidney Int.* 2006;70(8):1403–1412.

TABES DORSALIS

DESCRIPTION Tertiary syphilis involving the dorsal spinal roots and posterior spinal column. This condition can present with voiding dysfunction, presumably due to loss of bladder sensation, with high residual volumes and urinary retention. Urodynamic evaluation reveals detrusor atony and detrusor areflexia. (See Section I: "Syphilis.")

SYNONYMS
- Neurosyphilis
- Tabetic bladder
- Tertiary syphilis

TREATMENT
- Penicillin for syphilis
- Clean intermittent catheterization (CIC) for bladder atony

REFERENCE
Erturk E, Sheinfeld J, Davis RS. Voiding dysfunction in tertiary syphilis. *Urology*. 1987;30(3):284–286.

TAGHAANDAN

DESCRIPTION The practice of forcibly snapping or cracking an erect penis to achieve rapid detumescence. This is a common cause of penile fracture in Middle Eastern countries. In Iran, 69% of penile fractures are due to this mechanism and were encountered at an average of one per wk. Treated as described in Section I: "Penis, Trauma."

REFERENCE
Zargooshi J. Penile fracture in Kermanshah, Iran: Report of 172 cases. *J Urol*. 2000;164(2):364–366.

TAKAYASU ARTERITIS, UROLOGIC CONSIDERATIONS

DESCRIPTION A vasculitis of unknown origin involving mainly major vessels, which results in stenosis and aneurysmal dilatation. Involvement of renal arteries might lead to renovascular hypertension. The disease is progressive and difficult to manage and is often treated and diagnosed with angiography and surgery.

REFERENCES
Di Luccio GM, Lopes de Souza SA, Lopes FP, et al. Self-kidney transplantation in Takayasu arteritis. *Transplantation*. 2012;94(7):e47–e49.
Kumar S, Mandalam KR, Rao VR, et al. Percutaneous transluminal angioplasty in non-specific aortoarteritis (Takayasu's disease): Experience in 16 cases. *Cardiovasc Intervent Radiol*. 1990;12:321.

TANNER STAGES/CLASSIFICATION OF SEXUAL MATURITY

DESCRIPTION The Tanner scale defines physical measurements of the onset and development of pubertal changes based on external primary and secondary sex characteristics, such as breast and genitalia development and the growth of pubic hair. It is useful in the evaluation of delayed or precocious puberty.

- **Pubic hair (boys and girls)**
  - Stage 1: Prepubertal (none or vellus hair similar to abdominal wall)
  - Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
  - Stage 3: Darker, coarser, and more curled hair, spreading sparsely over junction of pubes
  - Stage 4: Hair is adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
  - Stage 5: Adult in type and quantity, with horizontal distribution (feminine type)
- **External genitalia (boys)**
  - Stage 1: Prepubertal
  - Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
  - Stage 3: Enlargement of penis (length at 1st); further growth of testes
  - Stage 4: Increased size of penis, with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker
  - Stage 5: Adult genitalia
- **Breast development (girls)**
  - Stage 1: Prepubertal
  - Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
  - Stage 3: Further enlargement of breast and areola; no separation of their contour
  - Stage 4: Areola and papilla form a secondary mound above level of breast
  - Stage 5: Mature stage: Projection of papilla only, related to recession of areola

REFERENCES

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;4423(5):291–303.

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;4523(9):13–23.

TERATOMA, SACROCOCCYGEAL, UROLOGIC CONSIDERATIONS

DESCRIPTION Sacrococcygeal tumors are usually diagnosed in the neonate (1 in 40,000 births) and less frequently in infants or adults. Females are more affected than males. Clinical presentation is usually in the form of palpable mass, skin discoloration, or hairy nevus. Related diseases include bilateral hydronephrosis, neurologic deficit, bladder or bowel dysfunction (obstruction or incontinence), high-output cardiac failure, or fet al hydrops. Sacrococcygeal tumors of the newborn are generally benign, whereas those discovered later have a 50% chance of being malignant. Wide, local excision of the tumor is primary management.

REFERENCE

Okada T, Sasaki F, Cho K, et al. Management and outcome in prenatally diagnosed

sacrococcygeal teratomas. *Pediatr Int.* 2008;50(4):576–580.

TESTICULAR FEMINIZATION SYNDROME

DESCRIPTION Now commonly described as *complete androgen insensitivity syndrome*, this syndrome involves phenotypic women with a 46, XY karyotype and normal development of testes in utero, but with a genetic defect in the androgen receptor that leads to insensitivity to androgens. (See also Section II: "Androgen Insensitivity Syndrome [AIS or Androgen Resistance Syndrome], Complete and Partial.")

REFERENCE

Conn J, Gillam L, Conway GS. Revealing the diagnosis of androgen insensitivity syndrome in adulthood. *BMJ.* 2005;331(7517):628–630.

TESTICULAR PROSTHESIS

DESCRIPTION Prosthetic device implanted in the scrotum to help cope with the psychological distress of losing a testicle from torsion, malignancy, trauma, or agenesis. Studies have shown that the improved cosmetic result increases patient self-esteem, body image, and sexual function. Implants were typically made of silicone rubber filled with silicone gel until 1995, when they were taken off the US market due to concerns about the association of silicone and connective tissue disease. Currently, in the United States, the testicular prosthetic of choice is comprised of a silicone rubber shell filled with saline to achieve desired size and consistency. Implantation is fairly simple and well tolerated. It is most commonly placed in a subdartos, subcapsular, or subtunical position. The most common major complication reported was extrusion of the implant, occurring in 2% and the most common minor complication was postoperative discomfort or pain, occurring in 9% of patients (Image ☼).

REFERENCES

Bush NC, Bagrodia A. Initial results for combined orchiectomy and prosthesis exchange for unsalvageable testicular torsion in adolescents: Description of intravaginal prosthesis placement at orchiectomy. *J Urol.* 2012;188(4):1424–1428.

Turek PJ, Master VA, and the Testicular Prosthesis Study Group. Safety and effectiveness of a new saline filled testicular prosthesis. *J Urol.* 2004;172(4):1427–1430.

TESTIS BIOPSY, INDICATIONS

DESCRIPTION Testicular biopsy was once considered a cornerstone in the diagnosis of unexplained male infertility and azoospermia, but its current indications are now limited to a specific subgroup of patients. Current practice guidelines limit biopsy to those with obstructive azoospermia, those who require TESE (testicular sperm extraction), and to confirm the diagnosis of carcinoma in situ (CIS) of the testis. In men with obstructive azoospermia confirmation of the presence of normal spermatogenesis is usually helpful before surgical correction of the obstruction. TESE often requires multiple testicular biopsies for sperm harvesting with part of the specimen to be used for histologic exam. In special

situations where ultrasonographic abnormalities indicate the potential presence of CIS, namely testicular microlithiasis, inhomogeneity, or a solid testicular mass, a testicular biopsy may prove to be helpful before orchiectomy.

REFERENCE

Dohle GR, Elzanaty S, van Casteren NJ. Testicular biopsy: clinical practice and interpretation. *Asian J Androl.* 2012:14:88–93.

TESTIS, CARCINOID

DESCRIPTION Carcinoid tumors of the testis are rare neoplasms that originate from neuroendocrine cells. Most carcinoid tumors are found in the GI tract, particularly in the ileum or appendix. Because of their neuroendocrine precursors, some tumors elicit endocrine activity; 88% secrete 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin. Carcinoid syndrome results from the vasoactive substances secreted from the tumor and can cause symptoms such as flushing, sweating, wheezing, diarrhea, abdominal pain, and fibrosis of cardiac valves. Carcinoid tumors of the testis can be divided into 3 groups: Primary, metastasis from a primary site, or carcinoid tumor originating from a testicular teratoma. Most patients present with a painless scrotal mass; unlike germ cell tumor (GCT), there is no predilection for a particular age group. ~16% of patients have carcinoid syndrome. Tumors localized to the testis have an excellent prognosis; however long-term follow-up is needed, due to risk of late metastases.

As with all testicular neoplasms, treatment begins with radical orchiectomy, with high ligation of the spermatic cord. Chemotherapy or radiation therapy has been reported, but these treatment modalities have poor efficacy. Octreotide analogs have been reported to stabilize disease progression, as well as help relieve symptoms of carcinoid syndrome. Once discovered, other extratesticular sources of carcinoid tumor should be determined. 5-HIAA can be measured in the urine and can be a useful adjunct. GI endoscopy, CT scan, MIBG scintigraphy, or somatostatin receptor scintigraphy can be used to search for GI sources of carcinoid tumor.

REFERENCE

Stroosma OB, Delaere KP. Carcinoid tumours of the testis. *BJU Int.* 2008;101(9):1101–1105.

TESTIS, CARCINOMA IN SITU (CIS)/INTRATUBULAR GERM CELL NEOPLASIA (ITGCN)

DESCRIPTION Testicular CIS is considered to be the precursor to all GCT, except for yolk sac tumors and spermatocytic seminoma. CIS may be present during infancy; however, lesions do not proliferate until adolescence, when hormonal influences come into play. Studies have shown that 50% of males with CIS developed invasive tumor growth within 5 yr; virtually all patients with CIS will progress to testicular cancer. Risk factors for testicular CIS are cryptorchidism, contralateral testis cancer, extragonadal GCT, infertility, and intersex patients with a Y chromosome. There is controversy concerning the screening, management, and treatment of testicular CIS. Diagnosis is made through testis biopsy. Treatment options involve surveillance, radiation, and orchiectomy. Cisplatin-based chemotherapy has been

associated with incomplete treatment and recurrence. High-risk patients may be offered testicular biopsy and subsequent treatment, although some physicians would advocate surveillance alone. Surveillance is a viable treatment option due to the long, protracted nature of CIS, the morbidity of treatment options, and the fact that effective treatment of GCT exist. Radiation (14–20 Gy) may be performed in the patient with a testicular tumor and contralateral CIS, or in the patient with bilateral CIS. Orchiectomy is offered to the patient with unilateral CIS and a normal contralateral testis. Extensive counseling regarding the risks and benefits of surveillance vs. biopsy and subsequent treatment is needed. The option to cryopreserve sperm should be offered as well. (See also Section II: “Testis, Microlithiasis” and (Image ☼).)

REFERENCE

Hoei-Hansen CE, Rajpert-De Meyts E, Daugaard G, et al. Carcinoma in situ testis, the progenitor of testicular germ cell tumours: A clinical review. *Ann Oncol.* 2005;16(6):863–868.

TESTIS, CYSTIC LYMPHANGIOMAS

DESCRIPTION Testicular cystic lymphangiomas, benign tumors of unknown etiology, are often misdiagnosed as other conditions like hernia, hydrocele, hematocele, varicocele, or possible torsion in children. Lymphangiomas are characterized by an extensive overgrowth of lymphatic vessels; 50% are present at birth, 90% are evident by the age of 2 yr. Gradual painless scrotal swelling is the common symptom. On palpation, the mass may be soft and spongy or firm and tense, usually not separable from the scrotal skin. Skin showing bluish/purplish discoloration or erythematous changes is often present. The ultrasound exam usually shows a complex multilocular septated cystic mass without perfusion. Often, these lesions are more extensive than expected according the preoperative investigations, with deep perineal, inguinal, pelvic, or retroperitoneal involvement. Complete excision is mandatory to prevent recurrence.

REFERENCE

Liniger B, Fleischmann A, Zachariou Z. Benign cystic lesions in the testis of children. *J Pediatr Urol.* 2012;8(3):226–233.

TESTIS, CYSTS

DESCRIPTION Intratesticular cysts, once considered rare, are being reported with an increasing prevalence as a result of the wider use of scrotal ultrasound (8–9.8% incidence in men undergoing ultrasound). Nonneoplastic testicular cysts include hydatid, epidermoid, simple, and cystic dysplasia. Hydatid cysts are rarely seen, except in the Middle East. These are very rare lesions and are generally clinically interpreted as neoplastic, until proven otherwise at the time of postorchiectomy pathology. Treatment has included enucleation and even radical orchiectomy over concern for malignancy. A more conservative approach with serial ultrasound scanning has been advocated if a clear distinction can be made between neoplastic and nonneoplastic testicular cysts. Selected cases can potentially be managed by intraoperative frozen section to demonstrate no malignancy and enucleation of the tumor

performed.

In children, testicular tumors are rare and the majority are benign, especially before puberty. Pediatric simple testicular cysts are very rare, as most cysts occur in men >40 yr. Most can be treated with testicle-sparing surgery. The differential diagnosis of testis cysts in the pediatric population:

- Infancy: Juvenile granulosa cell tumor, simple testicular cyst.
- Early childhood: Prepubertal teratoma, cystic lymphangioma, cystic dysplasia of the rete testis. Teratomas can present as solid, cystic, or mixed solid and cystic lesions and are always almost benign in children.
- In the older child/young adult epidermoid and dermoid cysts predominate (Image ☼).

REFERENCES

Kang SM, Hwang DS, Lee JW, et al. Multiple Intratesticular Cysts. *World J Mens Health.* 2013;31(1):79–82.

Liniger B, Fleischmann A, Zachariou Z. Benign cystic lesions in the testis of children. *J Pediatr Urol.* 2012;8(3):226–233.

Mahdavi-Zafarghandi R, Shakiba B, Ameli M. Testis-sparing surgery in testicular mass: Testicular epidermoid cysts. *Can Urol Assoc J.* 2014;8(1–2):E101–E103

TESTIS, DERMOID CYST

DESCRIPTION A primary non-germ cell tumor (GCT) representing 1% of testis tumors, with 1/2 of the patients presenting in their 20s. Grossly, the lesions present as encapsulated intratesticular nodules, which are round and sharply circumscribed, with firm consistency. The cut surface reveals a grayish white, cheesy, amorphous mass. The microscopic picture is that of dense fibrous tissue lined by keratinized stratified squamous epithelium with degeneration and macrocalcification. The benign behavior of these tumors is the rule. These are categorized separately from a mature testicular teratoma because of the malignant nature of the latter in postpubertal patients. Testicular ultrasound may aid in this tumor's differentiation from GCT. Most cases have been managed by radical orchiectomy, although local excision has been equally successful in a small number of patients.

REFERENCE

Ulbright TM, Srigley JR. Dermoid cyst of the testis: A study of five postpubertal cases, including a pilomatrixoma-like variant, with evidence supporting its separate classification from mature testicular teratoma. *Am J Surg Pathol.* 2001;25(6):788–793.

TESTIS, HEMANGIOMA

DESCRIPTION Testicular hemangioma is a very rare neoplasm; only 25 cases are in the English literature. Intratesticular tumors of vascular origin are extremely rare. Intratesticular hemangioma can mimic malignant testicular tumors on presentation and imaging. Testicular hemangiomas histologically comprise 3 types: Cavernous, capillary, and epithelioid. Patients usually present with testicular enlargement with or without tenderness. Although it is impossible to differentiate a hemangioma from a seminoma preoperatively, intraoperative frozen study may be helpful in the differential diagnosis. Frozen section must be performed if

the neoplasm has significant vascular proliferation identified by Doppler sonography. Since the lesion is benign, conservative surgical treatment by means of tumor enucleation with preservation of the testis is possible if intraoperative frozen section exam can be performed.

REFERENCE

Kryvenko ON, Epstein JI. Testicular hemangioma: A series of 8 cases. *Am J Surg Pathol.* 2013;37(6):860–866.

TESTIS, LEUKEMIA

DESCRIPTION Of children with acute lymphocytic leukemia (ALL), 5% will develop testicular disease at initial presentation or at 1st relapse. The testis is a common site of primary relapse (8%) after treatment of ALL. Children with T-cell lymphoblastic leukemia and/or a high initial leukemia cell burden are at higher risk of initial testicular involvement, as well as of testicular relapse. The condition commonly presents as either unilateral or bilateral testicular painless mass or swelling. Diagnosis is made with testicular biopsy.

Irradiation of both testes with 18–24 Gy plus systemic chemotherapy is the standard recommended treatment. Orchiectomy may be considered, depending on the extent of infiltration.

REFERENCE

Gutjahr P, Humpl T. Testicular lymphoblastic leukemia/lymphoma. *World J Urol.* 1995;13(4):230–232.

TESTIS, LYMPHOMA

DESCRIPTION Most common testicular malignancy in men >60, and the most common secondary neoplasms of the testis. Initial presentation is usually painless testicular swelling. Diagnosis is made through orchiectomy. Bilateral involvement occurs in ~50% of cases (10% are synchronous). Treatment is multimodal; orchiectomy is performed, followed by systemic chemotherapy (doxorubicin), CNS prophylaxis, and local radiation. (See also Section II: “Lymphoma, Urologic Considerations" and (Image ☼).)

REFERENCE

Vitolo U, Ferreri AJ, Zucca E. Primary testicular lymphoma. *Crit Rev Oncol Hematol.* 2008;65(2):183–189.

TESTIS, METASTASIS TO

DESCRIPTION Due to the nature of the disease, this metastasis usually presents in men >50. Spread to the testis may be hematogenous, lymphatic, or by direct extension. Most common primary malignancies are prostate, lung, GI tract, melanoma, and kidney cancers (Image ☼).

REFERENCE

Rosevear HM, Mishail A, Sheynkin Y, et al. Unusual Scrotal pathology: An overview. *Nat Rev Urol.* 2009;6(9):491–500.

TESTIS, MICROLITHIASIS

DESCRIPTION Numerous and diffuse calcifications throughout the entire testicle seen on transscrotal ultrasound. Advances in ultrasound technology have led to an increased detection of testicular microlithiasis. It is reported in undescended testicles (0.3% incidence), prepubertal Klinefelter syndrome, and male pseudohermaphroditism, and is slightly more common in prepubertal males. Infertility and malignancy have been reported to be associated with the condition, and some consider it possibly premalignant. Both seminomas and nonsemino-matous GCT have been described in association with microlithiasis. Others suggest an association with carcinoma in situ of the testicle, but this is not settled. Recent studies have a prevalence of 2% in boys who undergo scrotal US, most commonly bilateral, with increased risk of malignancy. Most advocate close surveillance of patients with testicular microlithiasis, such as yearly testicular ultrasound, physical exam, and judicious tumor marker determinations (Image ☼).

REFERENCES

Cooper ML, Kaefer M, Fan R, et al. Testicular microlithiasis in children and associated testicular cancer. *Radiology*. 2014;270(3):857–863.

Heller HT, Oliff MC, Doubilet PM, et al. Testicular microlithiasis: Prevalence and association with primary testicular neoplasm. *J Clin Ultrasound*. 2014 Feb 28. [Epub ahead of print]

TESTIS, NORMAL SIZE

DESCRIPTION Testis size measurements can be made by ultrasound (US) (most accurate) or Prader orchidometer. At birth, testicular length is ~1.5 cm with a volume of 1.1 cm^3. In prepubertal boys, testicular length is usually <2 cm and volume <2 cm^3. Normal testicular size after puberty in an adult is about 4.5–5.5 cm with a volume ranging from 15–30 cm^3.

REFERENCES

Keefer JR. Endocrinology. In: Siberry GK, Iannone R, eds. *Harriet Lane Handbook*. 15th ed. St. Louis, MO: Mosby; 2000.

Krone KD, Carroll BA. Scrotal ultrasound. *Radiol Clin North Am.* 1985;23:121–139.

TESTIS, RETRACTILE

DESCRIPTION A testicle that can ride high in the scrotum or near the external inguinal ring; caused by a brisk cremasteric reflex. The testicle is able to be gently manipulated into the scrotum. Usually considered a variant of normally descended testes, 32% of retractile testes may ultimately become undescended (ascending or acquired undescended), and this is seen more frequently in boys <7 yo. Boys with retractile testes should be followed annually until the outcome of descent or nondescent is clear, which in many cases won't be until puberty.

REFERENCE

Agarwal PK, Diaz M, Elder JS. Retractile testis: Is it really a normal variant? *J Urol.* 2006;175(4):1496–1499.

TESTIS, SEX CORD STROMAL TUMORS

DESCRIPTION These tumors arise from the supporting structures of the testis and not the germ cells. They usually present as a mass, are rarely hormonally active, and do not produce tumor markers such as hCG. Leydig cell tumors comprise about 3% of testicular neoplasms. They occur in both adults (80% of cases) and children. Sertoli cell tumors (<1% of testicular tumors) can be found in children and middle-aged adults, and ~10% can be malignant. Granulosa cell tumor is usually found in older men and can present with gynecomastia. The testicular juvenile granulosa cell tumor is the most common neoplasm of the testis in the 1st 6 mo of life (yolk sac tumors peak after 6 mo). Other tumors sometimes placed in this category include malignant mesothelioma of the tunica vaginalis, paratesticular rhabdomyosarcoma, and adenocarcinoma of the rete testis.

REFERENCE

Young RH. Sex cord-stromal tumors of the ovary and testis: Their similarities and differences with consideration of selected problems. *Mod Pathol.* 2005;18:S81–S98.

TESTIS, TERATOMA, EXTRAGONADAL

DESCRIPTION Primary tumors of extragonadal origin are rare. In a decreasing order of frequency, the most common sites are the mediastinum, retroperitoneum, sacrococcygeal region, and pineal gland. Theories include a displacement of primitive germ cells that takes place during early embryonic migration from the yolk sac endoderm, and pluripotential cells that persist in sequestered primitive rests during early somatic development. Histologically, all types of GCT are represented, with pure seminoma accounting for 1/2 of mediastinal and retroperitoneal tumors. Clinically, males are affected more often than females, with the exception of sacrococcygeal tumors, where females predominate. The majority of adults present with advanced local disease and distant metastasis. Patients with mediastinal extragonadal tumors are usually diagnosed in their 20s, with or without symptoms of chest pain, cough, or dyspnea. Patients with primary retroperitoneal tumors may present with abdominal or back pain, a palpable mass, or vascular obstruction. Tumors of the pineal gland usually present in children and young adults, with symptoms of increased intracranial pressure, oculomotor dysfunction, hearing loss, hypopituitarism, or hypothalamic disturbances. Fine needle aspiration (FNA) can be used to assist in the diagnosis, but carries the risk of insufficient cellular return. When suspicion for teratoma exists, it is important to differentiate between mature and immature teratoma as immature carries the risk of malignant transformation.

TREATMENT

- Intensive chemotherapy regimens have shown some success in primary retroperitoneal seminoma.
- The nonseminomatous version has done poorly despite surgery, radiotherapy, and chemotherapy.
- Primary radiation therapy has been much favored for pineal tumors (a CSF shunt may be required).

REFERENCES
Garnick MB, Canellos GP, Richie JP, et al. Treatment and surgical staging of testicular and primary extragonadal germ cell cancer. *JAMA*. 1983; 250:1733–1741.
Gupta R, Mathur SR, Arora VK, et al. Cytologic features of extragonadal germ cell tumors. *Cancer*. 2008;114(6):504–511.

TESTIS, VASOCONGESTION FROM SEXUAL AROUSAL WITHOUT EJACULATION ("BLUE BALLS")

DESCRIPTION "Blue balls" is a colloquialism describing scrotal pain after sustained sexual arousal unrelieved because of lack of orgasm and ejaculation. This term has only been referred to in the pediatric literature. It is likely due to vasocongestion of the external genitalia associated with the physiology of sexual arousal but no formal studies are available in the peer-reviewed literature. As noted by Chalett and Neremberg "The medical literature completely lacks acknowledgment of condition." This is suspected to be more common among young male adults and should be considered in the differential diagnosis of acute testicular/scrotal pain in such patients.

REFERENCES
Chalett JM, Nerenberg LT. Blue balls: A diagnostic consideration in testiculoscrotal pain in young adults: A case report and discussion. *Pediatrics*. 2000;106:843–844.
Rockney R, Alario AJ. Blue Balls. *Pediatrics*. 2001;108(5):1233–1234.

TESTOSTERONE (FREE AND TOTAL) SERUM

DESCRIPTION Measurement of serum testosterone is most commonly used as the initial test for hypogonadism in males; it is less commonly used in the evaluation of virilism and hirsutism in females. Testosterone assays should be collected from 8–11 AM, due to higher morning plasma levels from the typical male circadian rhythm. In males, increased testosterone levels can be found in complete androgen resistance (testicular feminization syndromes). Decreased levels occur in hypogonadism, surgical orchiectomy, estrogen or LHRH analog or antagonist therapy, Klinefelter syndrome, hypopituitarism, and hepatic cirrhosis:

- Generally accepted normal ranges total testosterone (may vary by lab):
  - Prepubertal children: 5–20 ng/dL (0.17–0.7 nmol/L)
  - Men (≥17 yr): 300–1,000 ng/dL (10.4–34.7 nmol/L)
  - Women: 20–70 ng/dL (0.7–2.6 nmol/L)
- A total testosterone level (free plus protein bound) of <200 ng/dL (or 6.9 nmol/L) (American Association of Clinical Endocrinologists) or <300 ng/dL (or 10 nmol/L) (FDA) is associated with hypogonadism and warrants further workup in an adult.
- Free testosterone (adult male range 8.8–27 pg/mL) is a useful diagnostic test as well, as elevated or decreased sex hormone binding globulin (SHBG) changes the bioavailability of testosterone. It can be used as an adjunct to the patient with low total testosterone levels. For example, obesity is characterized by reduced total testosterone and normal free testosterone due to reduced protein binding.

- Serum SHBG concentrations increase with age. With increasing age, less of the total testosterone is free or biologically active, as SHBG binds testosterone with high affinity.
- Serum T peaks early morning and then declines over the course of the day until the nadir in the evening (15% lower than morning values, but may vary up to 50% in younger men).
- Testosterone replacement monitoring: For men on transdermal T preparations measure at any time; for men on injectable T measure T midway between injections. Target T should generally be in the range of 400–700 ng/dL (13.9–27.7 nmol/L). If higher, the dose should be reduced.
- Methods used to measure T: Radioimmunoassay (RIA), Enzyme-linked Immunoassay (EIA) and Liquid Chromatography-Mass Spectroscopy (LC-MS) with the AUA and other organizations working to establish standardization of assay methods.

REFERENCES

Miner MM, Sadovsky R. Evolving issues in male hypogonadism: Evaluation, management, and related comorbidities. *Cleve Clin J Med*. 2007;74(Suppl 3):S38–S46.

Paduch D, et al. The Laboratory Diagnosis of Testosterone Deficiency: AUA White Paper available at http://www.auanet.org/common/pdf/education/clinical-guidance/Testosterone-Deficiency-WhitePaper.pdf Accessed March 27, 2014.

TESTOSTERONE REPLACEMENT FOLLOWING LOCALIZED PROSTATE CANCER THERAPY

DESCRIPTION Both prostate cancer and hypogonadism become more prevalent as men age; up to 20% of men who undergo radical prostatectomy (RP) are found to be hypogonadal and many men who receive combined hormonal ablation and radiation may not recover testosterone to pre treatment levels. Patients with hypogonadism may have decreased muscle mass, ED, osteopenia, decreased libido, depression, and possibly increase cardiovascular risk. Studies have shown that TRT does not increase the risk of prostate cancer development in men with both normal and increased risk. In addition, in limited series, postprostatectomy testosterone replacement does not correlate with biochemical recurrence or increases in PSA. TRT may help to preserve erectile function and improve quality of life, but the supplementation of testosterone in hypogonadal men after treatment for prostate cancer remains controversial. All testosterone replacements in the United States contain warnings concern the use with a history of prostate cancer. The 2012 European Association of Urology (EAU) Guidelines are as follows:

- Following RP and without evidence of disease with symptoms of testosterone deficiency man can be cautiously considered for TRT
- Approach is considered “off label”
- Restrict to low risk: Preop Gleason <8; pT1-2; PSA <10 ng/mL
- Wait 1 yr postop
- With radiation therapy for prostate cancer if low-risk and hypogonadism, use TRT cautiously with monitoring (See also Section I: “Testosterone Replacement Therapy, General Principles.”)

REFERENCES

Dohle GR, et al. Guidelines on Male Hypogonadism http://www.uroweb.org/gls/pdf/16_Male_Hypogonadism_LR%20II.pdf
Khera M, Lipshultz LI. The role of testosterone replacement therapy following radical prostatectomy. *Urol Clin N Am.* 2007;34(4):549–553.

TESTOSTERONE REPLACEMENT THERAPY, PROSTATE CANCER RISK

DESCRIPTION Multiple published review articles have shown that testosterone replacement therapy (TRT) does not cause prostate cancer or place patients at increased risk for the development of prostate cancer. A recent audit of the UK Androgen Study showed that initiating testosterone treatment had no statistically significant effect on the incidence of prostate cancer. These findings from this study show that, with careful monitoring, men with symptoms of testosterone deficiency can be treated safely with TRT without an increased risk of developing or progressing already present prostate cancer. (See also Section I: "Testosterone Replacement Therapy, General Principles.")

REFERENCE

Feneley MR, Carruthers M. Is testosterone treatment good for the prostate? Study of safety during long- term treatment. *J Sex Med.* 2012;9:2138–2149.

TETHERED CORD

DESCRIPTION Tethered cord is an acquired or congenital occurrence that results from tissue attachments causing restriction of the normal movement of the spinal cord. It is most often seen in patients with spina bifida or meningomyelocele who have undergone surgical closure of the spine. This may result in scar tissue formation that adheres to the spinal cord. Patients may also present with a congenital tethered cord, mostly seen in patients with spina bifida occulta. As the child moves or grows, the tethered spinal cord is stretched, causing direct trauma to the cord, as well as compromising blood flow by stretching blood vessels. Tethering may also occur after spinal cord injury (SCI) when scar tissue prevents fluid flow around the cord. This causes pressure to build up, as well as cyst formation. The degree of tethering and strain placed on the spinal cord is correlated to severity and time of presentation of symptoms. The constellation of symptoms caused by a tethered cord is called *tethered cord syndrome*. (See also Section I: "Myelodysplasia [Spinal Dysraphism], Urologic Considerations" and Section II: "Tethered Cord Syndrome" and "Spina Bifida/Spina Bifida Occulta, Urologic Considerations.")

REFERENCE

Agawalla PK, Dunn IF, Scott RM, et al. Tethered cord syndrome. *Neurosurg Clin N Am.* 2007;18(3):531–547.

TETHERED CORD SYNDROME

DESCRIPTION Late sequelae of spinal dysraphism, in which fixation or scarring of the spinal cord and conus medullaris, due to prior spinal surgery, prevents normal cephalad migration of spinal cord with childhood growth and causes spinal cord ischemia. Usually

manifests with changes in voiding pattern, or with neurologic or musculoskelet al deficits. Urodynamic evaluation typically reveals detrusor hyperreflexia or detrusor areflexia. Detrusor-external sphincter dyssynergia or poor detrusor compliance with elevated bladder pressure can also be seen and warrant aggressive intervention. MRI is usually diagnostic. (See also Section I: "Myelodysplasia [Spinal Dysraphism], Urologic Considerations" and Section II: "Tethered Cord" and "Spina Bifida/Spina Bifida Occulta, Urologic Considerations.")

TREATMENT

- Surgery to untether spinal cord
- Urologic intervention, based on urodynamic findings

REFERENCE

Palmer LS, Richards I, Kaplan WE. Subclinical changes in bladder function in children presenting with nonurologic symptoms of the tethered cord syndrome. *J Urol.* 1998;159(1):231–234.

THIERSCH-DUPLAY HYPOSPADIAS REPAIR

DESCRIPTION The distal urethral plate is tubularized to advance the meatus. The glans is reapproximated over the repair. Thiersch urethroplasty is the most commonly performed technique after surgical correction of penoscrotal transposition.

REFERENCE

Sunay M, Emir L, Karabulut A, et al. Our 21-year experience with the Thiersch-Duplay technique following surgical correction of penoscrotal transposition. *Urol Int.* 2009;82(1):28–31.

THOMPSON PYELOPLASTY

DESCRIPTION A surgical procedure initially introduced in 1969 that is used when insufficient renal pelvis is available to close lesions due to trauma or scarring. A triangular flap of renal capsule is sharply developed, then flipped over onto the renal pelvic opening and closed with 5-0 chromic sutures.

REFERENCES

Kay R. Procedures for ureteropelvic junction obstruction. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:220–233.

Thompson IM, Baker J, Robards VL Jr, et al. Clinical experience with renal capsule flap pyeloplasty. *J Urology*. 1969:101:487–490.

THORACIC KIDNEY

DESCRIPTION A type of renal ectopia in which the kidney is found in the posterior mediastinum, partially or completely above the level of the diaphragm. The diaphragm is thin, yet envelops the protruding kidney, keeping it separate from the pleural cavity. Aside from the ectopic location, the renal anatomy is essentially normal; the kidney is usually not malrotated. The ureter may be longer due to its higher position, however it inserts into the

bladder orthotopically. Similarly, the renal vessels usually arise from their normal origins, although in some cases they may insert in a position more cranially. The vast majority of patients are asymptomatic. (See also Section I: "Renal Ectopia.")

REFERENCE

Donat SM, Donat PE. Intrathoracic kidney: A case report with a review of the world literature. *J Urol.* 1988;140(1):131–133.

TINEA CRURIS (JOCK ITCH)

DESCRIPTION Dermatophytic infection of the crural areas of the genitalia. Caused by dermatophytes *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum.* Clinically, reddish brown lesions with an elevated red border can be identified in the crural area, inner thigh, and scrotum. Penis involvement is rare. Postinflammatory hyperpigmentation may occur as a result of chronic or recurrent disease. Culture or KOH exam is necessary to confirm diagnosis. Scraping should be performed on the active border of the lesion and reveals branching septate hyphae. Differential diagnosis includes erythrasma, psoriasis, and seborrheic dermatitis. Recurrent disease is not unusual, and treatment should be aimed toward active disease rather than postinflammatory hyperpigmentation. (See also Section II: "Pruritus, External Genitalia, Male.")

TREATMENT

- Prevent skin maceration by keeping skin dry.
- Apply antifungal agents on overt lesions. Agents include Lotrimin, Mycelex, Loprox, Spectazole, Lamisil, and others for up to 14 days.
- Rarely, oral agents may be needed if topical agents fail: Ketoconazole (Nizoral) for 14 days (requires baseline lab monitoring CBC, LFTs).

REFERENCE

Geer DL. An overview of common dermatophytes. *J Am Acad Dermatol.* 1994;31:S112.

TMPRSS2-ERG GENE FUSION, PROSTATE CANCER

DESCRIPTION Fusion of the transmembrane protease, serine 2 (TMPRESS2) and erythroblastosis virus E26 (ERG) genes is known as the TMPRSS2-ERG gene fusion. It is present in up to 80% of human prostate cancers. This gene fusion contributes to development of androgen-independence in prostate cancer through disruption of androgen receptor signaling. TMPRSS2:ERG, in combination with urine prostate cancer antigen 3 (PCA3), improved the performance of Prostate Cancer Prevention Trial risk calculator in predicting cancer on biopsy. The men were stratified into 3 groups based upon the levels of TMPRSS2:ERG and PCA3 in their urine: low, intermediate and high. Prostate cancer was diagnosed in each of the groups, respectively: 21%, 43%, and 69%. High-grade prostate cancer (>Gleason score), was diagnosed 7%, 20%, and 40% in each group, respectively. TMPRSS2:ERG and PCA3 urine analysis appears to enhance the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy. (See also Section II: "PCA3 [Prostate Cancer Gene 3] Urine Assay.")

REFERENCE

Tomlins SA, et al. Urine TMPRSS2:ERG Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA *Sci Transl Med* 3 August 2011: Vol. 3, Issue 94, p. 94.

TOILETING PROGRAMS

DESCRIPTION Type of behavioral training to treat urinary incontinence. The patient is instructed to establish a routine voiding schedule regardless of the sensation to void. Initially, the patient is told to void at frequent intervals (eg, every 1 hr); the time between voids is then slowly increased, usually until he or she establishes an acceptable period (usually 2–4 hr) of continence.

REFERENCE

Wallace SA, Roe B, Williams K, et al. Bladder training for urinary incontinence in adults. *Cochrane Database Syst Rev*. 2004;(1):CD001308.

TRANSESOPHAGEAL ECHOCARDIOGRAM (TEE), UROLOGIC CONSIDERATIONS

DESCRIPTION A useful diagnostic tool in the management of renal tumors with tumor thrombus; the TEE is used to identify the extent of tumor thrombus involvement in the inferior vena cava. This may be used for preoperative surgical planning or may be used intraoperatively as well.

REFERENCE

Zini L, Haulon S, Decoene C, et al. Renal cell carcinoma associated with tumor thrombus in the inferior vena cava: Surgical strategies. *Ann Vasc Surg.* 2005;19(4):522–528.

TRANSURETEROURETEROSTOMY, TECHNIQUE AND INDICATIONS

DESCRIPTION Transureteroureterostomy (TUU) is an alternative surgical technique used to treat distal ureteral strictures that are not amenable to more conventional reconstruction techniques. It is useful in patients with a history of prior pelvic radiation or in those with an obstructing pelvic malignancy. There must be adequate length of diseased ureter proximal to the strictured segment to allow a tension free anastomosis. Relative contraindications include patients with upper tract urothelial carcinoma, nephrolithiasis, retroperitoneal fibrosis, chronic pyelonephritis, and bladder pathology—including reduced bladder capacity, thickened bladder wall, or invasion carcinoma. In addition, reflux to the recipient ureter needs to be identified preoperatively with a voiding cystourethrogram and treated, if present.

TUU is performed through a midline incision where the diseased ureter is mobilized and divided just proximal to the strictured segment. A tunnel is then created under the mesentery of the sigmoid colon and the recipient ureter is incised anteriomedially. The spatulated donor ureter is then anastomosed to the recipient in a tension free end-to-side fashion over an indwelling double J ureteral stent.

REFERENCES

Iwaszko MR, Krambeck AE, Chow GK, et al. Transureteroureterostomy Revisited: Long-term surgical outcomes. *J Urol*. 2010;183(3):1055–1059.
Nakada SY, Hsu THS. Management of upper urinary tract obstruction. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011.

TRANSSEXUALISM, UROLOGIC CONSIDERATIONS

DESCRIPTION Transsexualism, also known as *gender identity disorder*, is the strong desire to be and also identify with the opposite sex, which includes the desire to change the body hormonally and/or surgically to be similar to the aspired sex. This disorder causes severe impairment and distress. Treatment is multidisciplinary, and starts with an evaluation with an experienced mental health professional to discuss initiating hormonal and/or surgical procedures that are long-term and irreversible. Consultation with plastic surgeons, urologists, and gynecologists in high-volume centers is essential. Genital sex reassignment surgeries are available for male-to-female patients, and involve clitoroplasty, vulvuloplasty, and vaginoplasty. However, no consensus operative standard has been agreed upon regarding female-to-male reassignments, particularly regarding neophallus creation.

REFERENCE

Sohn M, Bosinski HA. Gender identity disorders: Diagnosis and surgical aspects. *J Sex Med*. 2007;4(5):1193–1207.

TRI-MIX

DESCRIPTION A custom-compounded formulation for intracorporal injection therapy of erectile dysfunction (ED). Typically consists of prostaglandin E1 (5.88 g/mL), papaverine (18 mg/mL), and phentolamine (0.6 mg/mL), but no dosage is considered standardized. It is usually administered to patients who cannot receive prostaglandin E1 injection alone due to lack of response.

REFERENCE

Seyam R, Mohamed K, Akhras AA, et al. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. *Int J Impot Res*. 2005;17:246–353.

TRICHOMONIASIS

DESCRIPTION Sexually transmitted infection caused by the protozoan *Trichomonas vaginalis*. It is a rare cause of nongonococcal urethritis in men, common cause of vaginitis in women (from 4–35%). It is associated with a high prevalence of coinfection with other STDs. Signs and symptoms include urethral discharge, dysuria, and the presence of neutrophils in urethral secretions. Some women have symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. However, many women have minimal or no symptoms. Because of the high prevalence of trichomoniasis in clinical and non-clinical settings, testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge. *T. vaginalis* has, if any, only minor influence on male fertility. In women, it can

cause premature rupture of the membranes and preterm delivery, as well as tubal infertility and cervical neoplasia. Females may have an elevated vaginal pH of >4.5. A positive diagnosis is made by identification of the protozoan on wet mount (must be examined in <10–20 min). Culture on Diamond's medium may take up to 7 days; a more rapid commercial culture method is available (InPouch*T. vaginalis* culture system, with results in 3 days). FDA-cleared tests for trichomoniasis in women include OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), an immunochromatographic capillary flow dipstick technology, and the Affirm VP III (Becton Dickenson, San Jose, California), a nucleic acid probe test that evaluates for*T. vaginalis, G. vaginalis, and C. albicans*. Each of these tests, which are performed on vaginal secretions, have a sensitivity of >83% and a specificity of >97%. Both tests are considered point-of-care diagnostics. Treatment is metronidazole 2 g PO or Tinidazole 2 g orally in a single dose for patient and sexual partners. It is not considered mandatory to identify the organism in partners before treating (CDC Expedited partner therapy). Metronidazole gel is considerably less efficacious for the treatment of trichomoniasis (<50%) than oral preparations of metronidazole. Topically applied antimicrobials (eg, metronidazole gel) are unlikely to achieve therapeutic levels in the urethra or perivaginal glands; therefore, use of this gel is not recommended. (See also Section I: "Sexually Transmitted Infections [STIs]; Sexually Transmitted Diseases [STDs], General"; Section II: "Vaginal Discharge, Urologic Considerations" and "Vaginosis" and (Image ☼).)

REFERENCE

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR Recomm Rep*. 2010;59(No. RR-12):1–110.

TRICHOTEMNOMANIA, PUBIC

DESCRIPTION Trichotemnomania is the obsessive compulsive habit of cutting or shaving hair that often includes the pubic area. It is considered a willful self-induced type of isolated alopecia. It is a distinct disorder that should not be confused with trichotillomania (pulling hair). Behavioral counseling is indicated. (See also Section II: "Trichotillomania, Pubic.")

REFERENCE

Happle R. Trichotemnomania: Obsessive-compulsive habit of cutting or shaving the hair. *J Am Acad Dermatol*. 2005;52(1):157–159.

TRICHOTILLOMANIA, PUBIC

DESCRIPTION Trichotillomania is defined by the Diagnostics and Statistic Manual of Mental Disorders, 4th edition (DSM-IV) as hair loss from a patient's repetitive self-pulling of hair leading to a noticeable loss of hair. Any body area, including the pubic region, can be involved. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Most individuals start pulling their hair during childhood or adolescence and may also consume the hair. Anxiety, depression and obsessive–compulsive disorders are frequently encountered in patients with trichotillomania. Treatment is a combination of education, behavior therapy and if necessary medication such as antidepressants. (See also Section II: "Trichotemnomania, Pubic.")

REFERENCE

Sah DE, Koo J, Price VH. Trichotillomania. *Dermatol Ther.* 2008;21(1):13–21.

TRIGONITIS

DESCRIPTION Sometimes referred to as *Pseudomembranous trigonitis,* this is a common cause of microscopic hematuria in women. Nonkeratinized squamous epithelium is commonly seen on the trigone and bladder neck in up to 86% of women of reproductive age and in up to 75% after menopause. Considered a normal finding and distinct from squamous metaplasia, which is considered a premalignant lesion. Cystoscopically, these are pale white-gray areas with irregular borders. This condition is not seen in men, except for some reports in men receiving estrogens for prostate cancer. Treatment is not necessary. (See also Section II: "Squamous Metaplasia, Genitourinary.")

REFERENCE

Stephenson TJ, Henry L, Harris SC, et al. Pseudomembranous trigonitis of the bladder: Hormonal aetiology. *J Clin Pathol.* 1989;42(9):922–926.

TRISOMY 4 P

DESCRIPTION This trisomy features hypertelorism and GU anomalies in the form of hydronephrosis, hypospadias, and undescended testes.

REFERENCE

Barakat AY, Seikaly MG, Der Kaloustian VM. Urogenital abnormalities in genetic disease. *J Urol.* 1986;136:778–785.

TRISOMY 8

DESCRIPTION A trisomy associated with a large, square head; a prominent forehead; widely spaced eyes; a slender body; and GU anomalies in the form of hydronephrosis, horseshoe kidney, reflux, hypospadias, and undescended testis. Males are more frequently affected than females. In the absence of serious problems, life expectancy is normal. Complete trisomy 8 is lethal and often results in miscarriage during the 1st trimester.

REFERENCE

Hale NE, Keane JF Jr. Piecing together a picture of trisomy 8 mosaicism syndrome. *J Am Osteopath Assoc.* 2010;110(1):21–23.

TRISOMY 9

DESCRIPTION This trisomy is characterized by a small cranium and GU anomalies in the form of renal hypoplasia and hypospadias.

REFERENCE

Barakat AY, Seikaly MG, Derkaloustian VM. Urogenital abnormalities in genetic disease. *J Urol.* 1986;136:778.

TRISOMY 9 P

DESCRIPTION This trisomy produces strabismus and GU anomalies in the form of a pancake kidney and undescended testis.

REFERENCE

Barakat AY, Seikaly MG, Der Kaloustian VM. Urogenital abnormalities in genetic disease. *J Urol*. 1986;136:778–785.

TRISOMY 10 Q

DESCRIPTION A trisomy characterized by oval, flat face and GU anomalies in the form of hydronephrosis and small penis.

REFERENCE

Mininberg D. The genetic basis of urologic disease. *AUA Update Series*. 1992;9:218.

TRISOMY 11 Q

DESCRIPTION A trisomy producing flat nose, wide glabella, cleft lip/palate, and micropenis.

REFERENCE

Mininberg D. The genetic basis of urologic disease. *AUA Update Series*. 1992;9:218.

TRISOMY 13

DESCRIPTION This trisomy is associated with polydactyly, congenital heart disease, and cystic kidney.

REFERENCE

Barakat AY, Seikaly MG, Der Kaloustian VM. Urogenital abnormalities in genetic disease. *J Urol*. 1986;136:778–785.

TRISOMY 18 (EDWARDS SYNDROME)

DESCRIPTION A trisomy producing hypertonia and GU anomalies in the form of hydronephrosis and small penis. Hypoplasia of the labia majora may cause a false impression of a large clitoris.

REFERENCE

Barakat AY, Seikaly MG, Der Kaloustian VM. Urogenital abnormalities in genetic disease. *J Urol*. 1986;136:778–785.

TRISOMY 20 P

DESCRIPTION A trisomy characterized by short nose, dental abnormalities, vertebral abnormalities, and polycystic kidney.

REFERENCE
Mininberg D. The genetic basis of urologic disease. *AUA Update Series.* 1992;9:218.

TRISOMY 21

DESCRIPTION See Section II: "Down Syndrome, Urologic Considerations."

TRISOMY 22

DESCRIPTION A trisomy producing microcephaly, low-set ears, cleft palate, beaked nose, and microphallus.

REFERENCE
Mininberg D. The genetic basis of urologic disease. *AUA Update Series.* 1992;9:218.

TRISOMY SYNDROME

DESCRIPTION A congenital condition characterized by the presence of 3 instead of the normal pair of homologous or sex chromosomes; these disorders often result in a wide range of phenotypical expressions, including GU anomalies. Examples include trisomy 13 and 18, which produce cryptorchidism; trisomy 4p and 9p, which produce micropenis; and trisomy 7, which is associated with sporadic papillary RCC.

REFERENCE
Kliegman RM. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA: Saunders; 2007.

TRUE HERMAPHRODITISM (OVO-TESTICULAR DISORDER OF SEXUAL DIFFERENTIATION [OVO-DSD])

DESCRIPTION True hermaphrodite or ovo-testicular disorder of sexual differentiation (OVO-DSD) is 1 of the rarest variety of all disorders of sexual differentiation. Up to 90% have 46, XX karyotype with infrequent 46, XY/46, XX mosaicism and 46, XY. The gonads are asymmetrical having both ovarian and testicular differentiation on either sides separately or combined as ovotestis. In ovotestis, testis is always central and ovary polar in location. Testosterone and müllerian inhibitory substance (MIS) are either normal or low. However, for final diagnosis there must be histologic documentation of both types of gonadal epithelium. On the basis of location of gonads and histology these patients are classified as:

- Lateral: Testis and contralateral ovary (30%).
- Bilateral: Testicular and ovarian tissue identified on both sides, usually as ovotestis (50%).
- Unilateral: Ovotestis on 1 side and testis or ovary on other side (20%).

The commonest presentation is an abnormal external genitalia ranging from normal male to normal female. In many of these cases such distinction may not be present and chordee, hypospadias and cryptorchidism may be noted. Proper gender assignment to a neonate born with DSD is a social emergency of the newborn period. A few cases of malignancies like dysgerminoma and gonadoblastoma have been reported. (See also Section I: "Disorders of Sexual Development [DSD].")

REFERENCE
Iqbal MZ, Jam MR, Saleem M, et al. True Hermaphrodite: A Case Report. *APSP J Case Rep*. 2011;2(2):16.

TUBERCULOSIS, BLADDER AND URETHRA

DESCRIPTION The hematogenous dissemination of TB can affect the entire urinary system. Bladder TB is caused by a descending infection from renal TB. Urethral TB is rare and can present as periurethral fistulas and abscess. Symptoms include urinary frequency, urgency, and dysuria, with mucosal ulcerations and thickening, and diminished bladder capacity. (See also Section I: "Tuberculosis, Genitourinary.")

DIAGNOSIS

- Urine culture of acid-fast bacilli: Typically 1st morning void, requires multiple sequential cultures.
- Urethral TB is typically diagnosed on biopsy.
- Imaging such as IVU and CT may be normal, but can aid in diagnosis.

TREATMENT

- Combination antituberculous treatment: Typical regimen: 6 mo of rifampicin, isoniazid, pyrazinamide, and ethambutol
- Urethral TB may require suprapubic cystostomy tube drainage and urethral dilation for stricture.

REFERENCE
Raghavaiah NV. Tuberculosis of the male urethra. *J Urol*. 1979;122(3):417–418.

TUBERCULOSIS, MALE EXTERNAL GENITALIA

DESCRIPTION Rare manifestation of TB that may present as a papulonecrotic ulcer, tubercular cavernositis, or a solid nodule, which may be clinically indistinguishable from malignant disease. Diagnosis is confirmed on biopsy. Treatment is systemic antituberculous medication. (See also Section I: "Tuberculosis, Genitourinary.")

REFERENCE
Wu WC, Chen SC, Hsieh JT, et al. Penile tuberculosis associated with monoclonal gammopathy of undetermined significance. *J Formos Med Assoc*. 2006;105(9):753–755.

TUBERCULOSIS, PROSTATE AND EPIDIDYMIS

DESCRIPTION A recent case study of an HIV and tuberculosis (TB) population noted that 10% of genitourinary tuberculosis involves the testicle or prostate. Tuberculous prostatitis can present with an elevated PSA, irritative voiding symptoms, and a hard, nodular prostate. Tissue exam can distinguish it from carcinoma. Prostate involvement is thought to spread hematogenously. Another case report of post mortem tuberculosis patients showed that 10–14% of patients who died from TB had asymptomatic tuberculous prostatitis. Tuberculous epididymitis can be diagnosed with a urine culture positive for acid fast bacilli, a swollen, painful epididymis, and/or ultrasound findings showing edema predominantly in the tail of

the epididymis with marked heterogeneity. The presence of pulmonary or renal disease provides indirect evidence for the diagnosis. Spread of TB to the epididymis is controversial but is thought to occur either hematogenously, through lymphatics, retrograde from the urethra, or by direct extension. Conjugal transmission has been reported as well. (See also Section I: "Tuberculosis, Genitourinary, General Considerations.")

REFERENCE

Wise GJ, Shteynshlyuger A. An update on lower urinary tract tuberculosis. *Current Urology Reports.* 2008(9):305–313.

TUBEROUS SCLEROSIS

DESCRIPTION An autosomal dominant disease mapped to chromosome 16 or 9 that clinically presents with a classic triad of epilepsy, mental retardation, and adenoma sebaceum. Named for the tubers or periventricular calcifications seen on CT scan. Adenoma sebaceum describes the facial angiofibromas around nasolabial regions and cheeks. The renal system may be free of anomalies or may display cysts (10%), angiomyolipomas (AML) in (40–80%), or both. AML can bleed, with increasing risk at 3.5 cm. Renal failure is a result of parenchymal compression by expanding cysts. Hypertension may also occur. Renal cell carcinoma (RCC) is present in 2% of patients. (See also Section I: "Renal Angiomyolipoma.")

SYNONYMS

- Tuberous sclerosis complex
- Bourneville disease

TREATMENT

- Absolute indications for intervention include suspicion of malignancy, hemorrhage with significant hypotension or symptoms, persistent hematuria.
- Symptomatic AML or lesion >4 cm: Selective arterial embolization or nephron-sparing surgery.
- Surveillance best for lesions <4 cm.
- Embolization is 1st-line treatment for acute hemorrhage from AML.
- mTOR inhibitors are under study.

REFERENCE

Wong IY, Shortliffe LD. The management of renal angiomyolipomas in a patient with tuberous sclerosis. *Nat Clin Pract Urol.* 2009;6(3):168–172.

TUMOR LYSIS SYNDROME (TLS)

DESCRIPTION A syndrome associated with chemotherapy, radiation, and other treatments in which massive tumor lysis occurs, with subsequent release of large amounts of potassium, phosphate, and nucleic acids that are converted to massive amounts of uric acid. More commonly associated with chemotherapy of lymphomas and leukemias, it can be seen with any tumor type. Extensive metastatic tumor, pretreatment renal impairment, and markedly elevated LDH concentrations have been reported to be serious risk factors in developing TLS. Lab investigations would reveal hyperkalemia, hypocalcemia, hyperphosphatemia, and

concurrent metabolic acidosis, as well as severe hyperuricemia with eventual renal failure. If these patients are being treated with allopurinol, they are at risk of ARF and xanthine stone formation (See also Section II: "Nephropathy, Urate and Xanthine"; "Urolithiasis [Xanthinuria]."")

TREATMENT

- Prevention with adequate hydration (urine output of $>80–100$ mL/m^2/h).
- Cautious use of rasburicase; some recommend allopurinol.
- Urinary alkalinization should not be done, as it may cause further precipitation of calcium phosphate in the kidney and other tissues.

REFERENCE

Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review. *J Clin Oncol.* 2008;26(16):2767–2778.

TUNICA VAGINALIS TUMORS

DESCRIPTION Malignant mesothelioma of the tunica vaginalis is rare (0.3–5% of all malignant mesotheliomas) and often fatal. However, increased frequency has been reported since 1980. Most of the patients are 40–79 yr of age, with prior exposure to asbestos being reported in some. Microscopically, mesothelioma may be epithelial, fibrous, or a combination of both. The malignant nature of the disease is indicated by its frequent mitosis, nuclear atypia with prominent nucleoli, and invasion of adjacent structures or lymphatics. Positive staining with keratin and failure to stain with CEA indicate mesothelioma. In addition, an immunoperoxidase stain has been reported to be specific for the tumor. CT and aspiration cytology may aid in preoperative diagnosis. The most important differential diagnostic considerations include mesothelial hyperplasia, adenomatoid tumor, carcinoma of the rete testis, and serous papillary tumors. The prognosis for this entity is grave, with a median survival of 23 mo and aggressive therapy with radical orchiectomy remains the mainstay of treatment. Adjunct chemotherapy may be tried. However, its value has not been established. (See also Section I:"Paratesticular Tumors" and "Scrotum and Testicle, Mass.")

REFERENCE

Chekol SS, Sun CC. Malignant mesothelioma of the tunica vaginalis testis: Diagnostic studies and differential diagnosis. *Arch Pathol Lab Med.* 2012;136(1):113–117.

TURNER SYNDROME (XO SYNDROME)

DESCRIPTION A sex chromosome abnormality with a 46, XO karyotype. It is the most common sex chromosome abnormality with an incidence of 1:10,000 newborn females. Neonates may have lymphedema. Clinically, patients present with short stature, primary amenorrhea, webbed neck, shield-like chest, streak gonads, hypertension, and coarctation of the aorta. GU anomalies include horseshoe kidney, anomalous blood supply to the kidney, and infantile genitalia. The external genitalia are female but immature, and most women with Turner syndrome are infertile. Karyotype analysis should be performed to confirm the diagnosis. Any patient with Turner syndrome who presents with virilization should also be

evaluated for Y-chromosome mosaicism, as these individuals are at increased risk of gonadoblastoma or germ cell tumor.

TREATMENT

- Echocardiography at diagnosis to detect cardiovascular anomalies (coarctation of the aorta or a bicuspid aortic valve are most common causes of morbidity and mortality)
- Renal US to determine if GU abnormalities are present
- Hormonal therapy in the form of growth hormone, estrogen, and medroxyprogesterone, aimed toward maximizing final height, induction of secondary sexual characteristics, and menarche

REFERENCE

Stochholm K, Juul S, Juel K, et al. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91(10):3897–3902.

TURNER–WARWICK INLAY URETHROPLASTY

DESCRIPTION Through a midline scrotal incision, the urethral stricture is opened and scarred tissue is removed, leaving a strip of urethra in place. The edges of the scrotal incision are sutured to the urethral strip. In a 2nd stage, the mature marsupialized urethra is tubularized with the surrounding scrotal skin and closed.

REFERENCE

Devine CJ, Devine PC. Operations for urethral stricture. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's Operative Urology*. Baltimore, MD: Williams & Wilkins; 1989:550–680.

UISS-UCLA INTERNATIONAL KIDNEY CANCER STAGING SYSTEM

DESCRIPTION A prognostic system for renal cell carcinima (RCC) to differentiate survival; the system integrates the 3 most commonly used prognostic factors: Cancer TNM stage, Furman grade, and patient performance status. Patients are categorized after nephrectomy into 3 risk groups: Low-, intermediate-, and high-risk for localized and metastatic disease.

REFERENCE

Escudier B, Eisen T, Porta C, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(Suppl 7):vii65-vii71.

UNDERVIRILIZED MALE SYNDROME (MILD ANDROGEN INSENSITIVITY)

DESCRIPTION A disorder of androgen receptor function caused by androgen receptor gene mutation. Patients with androgen receptor mutations have a 46, XY karyotype and present with a spectrum of phenotypes from complete external feminization, to ambiguous genitalia, to phenotypically infertile male, which is also known as undervirilized male syndrome. These patients present with gynecomastia at puberty, and may have scarce body hair, small penis, and complaints of impotence. Spermatogenesis may or may not be impaired. Patients may have elevated luteinizing hormone, normal to slightly elevated testosterone, and high estradiol. Treatment may not be necessary, however, breast reduction surgery at puberty is sometimes necessary. Infertile men may benefit from assisted reproductive techniques (ART's). (See also Section II: "Androgen Insensitivity Syndrome [AIS or Androgen Resistance Syndrome], Complete and Partial.")

REFERENCE

Gottlieb B, Lombroso R, Beitel LK, et al. Molecular pathology of the androgen receptor in male (in)fertility. *Reprod Biomed Online*. 2005:42–48.

UNINHIBITED DETRUSOR CONTRACTION

DESCRIPTION Uninhibited detrusor contraction leads to an overactive bladder. Bladder overactivity can result from damage to central inhibitory pathways, sensitization of peripheral afferent terminals in the bladder that unmask primitive voiding reflexes, or changes in bladder smooth muscle cells. Cystometry is essential if a definitive diagnosis is required. (See Section I: "Overactive Bladder.")

SYNONYMS

- Overactive bladder
- Unstable bladder

TREATMENT

- Traditionally centers on the use of anticholinergic medications (oxybutynin, tolterodine, others)
- Estrogens may help in the postmenopausal woman.

REFERENCE
Anonymous. The overactive bladder: From basic science to clinical management consensus conference. *Urology*. 1997;50(Suppl 6A):1–114.

URACHAL ABNORMALITIES

DESCRIPTION The urachus is a tubular connection between the allantoic stalk and the dome of the bladder. Faulty embryologic resolution of this connection results in urachal abnormalities. Microscopic urachal remnants are common, appearing in 3% of autopsy specimens, and are almost always asymptomatic. Except for the asymptomatic urachal diverticulum, the treatment of all urachal abnormalities is surgical; ie, complete excision of the abnormal structure, including a cuff of bladder. Congenital urachal abnormalities can be divided into 4 types:

- Urachal sinus: The most common urachal abnormality. The urachal sinus arises from a persistent patent urachus that drains to the umbilicus; may present with wetness, purulence, or malodorous discharge.
- Urachal cyst: Persistence of part of this channel between the bladder and umbilicus, lacking communication to either structure. The 2nd most common urachal anomaly. Most commonly presents in an older child with signs of suppuration (Latin “calor, rubor, dolor”) in the lower abdominal wall. Occasionally, a urachal cyst will present as an asymptomatic midline lower abdominal mass or tenderness.
- Patent urachus: Persistence of the urachal channel between the bladder and umbilicus; an uncommon type of urachal abnormality.
- Urachal diverticulum of the bladder: May result from drainage of a urachal cyst to the bladder; presents with UTI

Urachal carcinoma is a malignant adenocarcinoma that presents later in life. (See also Section I: “Urachal Carcinoma” and “Umbilical Abnormalities, Urologic Considerations” and (Image ☼).)

REFERENCE
Mesrobian H, Zacharias A, Balcom AH, et al. Ten years of experience with isolated urachal anomalies in children. *J Urol*. 1997;158:1316–1318.

URACHAL CARCINOMA STAGING SYSTEMS

DEFINITION
Two staging systems have been reported by Sheldon and Ashley. No formal TNM classification exists specifically for urachal carcinoma. (See also Section I: “Urachal carcinoma.”)

Stage	Sheldon et al. (1984)	Ashley et al. (2006)
I	Confined to urachal mucosa	Confined to urachus and bladder
II	Invasion confined to urachus	Extension beyond muscularis of urachus or bladder
III	—	Metastatic to regional lymph nodes
IIIA	Extension to bladder	—
IIIB	Extension to abdominal wall	—
IIIC	Extension to peritoneum	—
IIID	Extension to other viscera	—
IV	—	Metastatic to nonregional lymph nodes or distant sites
IVA	Metastatic to lymph nodes	—
IVB	Metastatic to distant sites	—

Reproduced with permission from Mohile SG, et al. (2008).

REFERENCE

Mohile SG, Schleicher L, Petrylak DP. Treatment of metastatic urachal carcinoma in an elderly woman. *Nat Clin Pract Oncol.* 2008;5:55–58.

URATE, DIETARY

DESCRIPTION Foods rich in urate should be restricted in patients with hyperuricosuric calcium oxalate stone disease and in patients with uric acid stone disease. The intake of urate should not exceed 500 mg/day. Urate rich foods include:

- Calf thymus, 900 mg urate/100 g
- Liver, 260–360 mg urate/100 g
- Kidneys, 210–255 mg urate/100 g
- Poultry skin, 300 mg urate/100 g
- Herring with skin, sardines, anchovies, sprats, 260–500 mg urate/100 g.

REFERENCE

Tiselius HG, et al. EAU Guidelines on Urolithiasis. http://www.uroweb.org/fileadmin/user_upload/Guidelines/Urolithiasis.pdf, Accessed April 6, 2014.

UREAPLASMA UREALYTICUM

DESCRIPTION Common bacterial inhabitant of the lower GU tract in adult men and women who are sexually active. As an STI/STD it can also be transmitted venereally and from mother to offspring. It is the most common cause of nongonococcal and nonchlamydial urethritis, and can cause chorioamnionitis, pyelonephritis, and septic arthritis. It is implicated in chronic prostatitis in men and urgency–frequency symptoms in women and in HIV-related acute epididymitis. It is also sometimes associated with decreased fertility. Diagnosis is by culture, but specific media and growth conditions are necessary. Treatment is doxycycline 100 mg/d

for 2 wk or a single dose of azithromycin 1 g PO. (See also Section I: “Sexually Transmitted Infections [STIs] (Sexually Transmitted Diseases [STDs]), General.”)

REFERENCE

Frenkl TL. Sexually transmitted infections. *Urol Clin N Am.* 2008;35(1):33–46.

URETER, AGENESIS/ATRESIA

DESCRIPTION Bilateral ureteral agenesis is incompatible with life. Unilateral ureteral agenesis indicates failure of ureteral bud development and is often accompanied by ipsilateral renal agenesis or multicystic kidney. Ureteral atresia is caused by varying degrees of failure in ureteral bud development. When either atresia or agenesis is unilateral, it is usually asymptomatic and of no clinical significance. However, it can be associated with infection (UTI) on occasion.

REFERENCE

Morozumi M, Ogawa Y, Fujime M, et al. Distal ureteral atresia associated with crossed renal ectopia with fusion: Recovery of renal function after release of a 10 yr ureteral obstruction. *Int J Urol.* 1997;4(5):512–515.

URETER, DEVIATION

DEFINITION

The ureter is a retroperitoneal structure in adults and is typically 25–30 cm in length. The ureters are in close proximity to abdominal and pelvic viscera, lymph nodes, and vessels. The course of the ureter can be altered by extrinsic pathologic processes as well as congenital and normal anatomic variation. Normal course of ureters: Proximally lateral to the lumbar vertebral pedicles and distally medial to pelvic brim in the true pelvis. Lateral ureteral deviation is more common than medial deviation.

- Medial deviation:
  - Normal anatomic variant in up to 15%
  - Retroperitoneal fibrosis; usually involving the lower lumbar and sacral regions
  - Retrocaval ureter: “shepherd’s crook” configuration; the right ureter passes behind the IVC at approximately the level of L4 (most common location). The distal ureter lies medial to the dilated proximal ureteral segment
  - Retroiliac ureter (very rare)
  - Pelvic lipomatosis; associated with elevation and elongation of the bladder, rectum, and sigmoid and increased pelvic wall lucency
  - After abdominal perineal resection
  - Iliac lymphadenopathy
  - Aneurysmal dilation of the iliac vessels
  - Perianeurysmal fibrosis due to chronic leakage associated with aortoiliac aneurysms
  - Lower pole renal mass; usually medial deviation of proximal ureter
- Lateral deviation
  - Psoas muscle hypertrophy; more common in young men; lateral and/or anterior deviation of the middle 3rd of 1 or both ureters

– Retroperitoneal adenopathy (paracaval/paraaortic lymphadenopathy): Metastatic disease, lymphoma, testicular cancer
– Pelvic mass (fibroids, ovarian tumor and cysts)
– Aortic aneurysm
– Malrotated and horseshoe kidney
– Patent umbilical artery (children)
– Retroperitoneal tumors
– Neurogenic tumors
– Fluid collection (abscess, urinoma, lymphocele, hematoma)

REFERENCES

Bamberger MH. Ureteral Deviation: A sign of retroperitoneal anatomy and pathology. Available at http://www.medscape.com/viewarticle/410210_4, Accessed March 29, 2014.
Chapter 8.39 *Deviated Ureters.* In: Davies, SG ed. Chapman & Nakielny's Aids to Radiological Differential Diagnosis. 6th ed. Philadelphia, PA: Saunders Elsevier; 2013.

URETER, DIVERTICULUM

DESCRIPTION Diverticula can be congenital or acquired, although most have been discovered in adults. Most diverticula are solitary outpouchings involving the distal ureters and upper portions of the pelvis. They are true diverticula composed of a muscular wall, which is lined by transitional cell epithelium. Renal pelvic diverticula tend to be larger than those found in the ureter. Diverticula may be associated with other pathology, such as Ask-Upmark kidney. The most common complications are infection and/or stone formation. Unlike diverticula found in the bladder and urethra, major complications and development of urothelial carcinoma (TCC) are rare (Image ☼).

REFERENCE

McLoughlin LC, Davis NF, Dowling C, et al. Ureteral diverticulum: A review of the current literature. *Can J Urol.* 2013;20(5):6893–6896.

URETER, DUPLICATED AND BIFID

DESCRIPTION Duplication of ureters is a common anomaly. Duplication may be either complete or incomplete. Complete duplication is most often associated with vesicoureteral reflux, ectopic ureteral insertion, and ectopic ureterocele, all of which are more commonly found in females than in males. Incomplete duplication is most often associated with UPJ obstruction of the lower pole of the kidney. Common clinical presentations include UTIs and urinary incontinence. Diagnosis is made usually in childhood by US, excretory urography, and voiding cystourethrography.

Also known as *bifid ureter* (if partial duplication) or *double ureters* (if complete duplication). Treatment is ureteroneocystostomy in the presence of persistent reflux or ureteropyelostomy if obstructed without reflux (Image ☼).

REFERENCE

Fernbach SK, Feinstein KA, Spencer K, et al. Ureteral duplication and its complications.

Radiographics. 1997;17(1):109–127.

URETER, ECTOPIC (URETERAL ECTOPIA)

DESCRIPTION Ectopic ureters open in a position other than on the trigone and can be associated with both reflux and obstruction and with ureteroceles. They predispose to UTI and may cause hematuria or abdominal/flank pain. Up to 80% are associated with a duplicated collecting system in females and ~20% are nonduplicated ureters usually in males with an absent hemi-trigone. In females, the ureter typically inserts in the urethra or vagina (distal to the sphincter) and cause incontinence or constant dribbling. In males the sites include the posterior urethra or seminal vesicles (no incontinence is seen) and often present later in life. Treatment is usually partial nephroure-terectomy of the nonfunctioning upper pole moiety with nephrectomy often necessary for single ureter systems.

REFERENCE

Hanson GR, Gatti JM, Gittes KG. Diagnosis of ectopic ureter as a cause of urinary incontinence. *J Ped Urol*. 2007;3(1):53–57.

URETER, FIBROEPITHELIAL POLYPS

DESCRIPTION Fibroepithelial polyps are rare benign neoplasms. The majority of these polyps are found at the UPJ. Signs and symptoms usually associated with ureteral obstruction include flank pain and hematuria. In addition, varying degrees of hydroureteronephrosis and ureteral intussusception have been described. Grossly, ureteral polyps are intraluminal lesions, most commonly covered with transitional epithelium. The bulk of the polyp is composed of vascularized collagenous fibrous tissue, with or without areas of chronic inflammation and edema. Ureteroscopy is often necessary to confirm the diagnosis.

SYNONYMS

- Fibromyxoma
- Myxoma
- Fibroma
- Vascular fibrous polyps

TREATMENT

- Ureteroscopic resection
- Open ureterotomy with polypectomy or partial ureterectomy is a viable conservative treatment option if the diagnosis can be confirmed preoperatively
- Many patients undergo nephroureterectomy for suspected malignancy

REFERENCE

Wang ZJ, et al. Ureteral Fibroepithelial Polyp. *J Ultrasound Med.* 2008;27(11):1647–1649.

URETER, FISH HOOK (REVERSE J)

DESCRIPTION A radiographic appearance of the type I (low-loop) circumcaval ureter, in which the dilated proximal part of the ureter takes a characteristic fish hook or reverse J course. Ureteral dilation usually ends 1–2 cm lateral to the inferior vena cava, where the

ureter turns upward at the border of the psoas muscle.

REFERENCE

Kenawi MM, Williams DI. Circumcaval ureter: A report of four cases in children with a review of the literature and a new classification. *Br J Urol*. 1976;48:183.

URETER, HEMANGIOMA

DESCRIPTION Hemangiomas are benign ureteral tumors. They may be the most common cause of chronic unilateral hematuria. Symptomatology may include hematuria, pain, hydronephrosis, bladder irritations, and palpable tumor. Varicoceles have also been found, but less frequently. Like other ureteral tumors, hemangiomas usually cause incomplete obstruction and may eventually cause complete obstruction with dilation of the urinary tract. They present as red, slightly elevated structures, fairly diffusely, and demarcated from their surroundings. Urothelial malignancies must be excluded, especially in the elderly. Flexible ureteropyeloscopy is considered a good diagnostic and therapeutic option in selected patients with unilateral hematuria of uncertain etiology.

REFERENCE

Biyani CS, Mackay AM, Sissions G, et al. An unusual filling defect in the ureter. *Urol Int*. 1998;61(2):124–125.

URETER, J HOOKING

DESCRIPTION With progressive benign prostatic hypertrophy, elevation of the trigone occurs, resulting in a characteristic J hooking of the distal ureters. This is a reliable sign on IVP of significant prostatic hypertrophy.

REFERENCE

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston, MA: Little Brown, 1991:320.

URETER, LEIOMYOMA

DESCRIPTION Leiomyomas of the urinary tract are rare (neoplasms of mesenchymal origin comprise $<3\%$ of all primary ureteral tumors). These benign tumors are seen predominantly in the 4th–5th decades of life. The left ureter is more frequently affected. Immunohistochemical studies confirm the diagnosis. Conservative management (urethroscopic or partial ureterectomy) is the treatment of choice.

REFERENCE

Naruse K, Yamada Y, Aoki S, et al. A case of primary leiomyoma of the ureter. *Int J Urol*. 2007;14(3):248–250.

URETER, LEIOMYOSARCOMA

DESCRIPTION Leiomyosarcoma originating from the ureters is exceedingly rare, with only

13 reported cases of primary leiomyosarcoma of the ureter. It is a disease that is very difficult to diagnose, and furthermore, it has a poor 5-yr disease-specific survival. Patients present with flank pain, hematuria, and/or UTI. Radiographic exam includes IVP, retrograde pyelogram, and CT. Light microscopy immunohistochemical staining and electron microscopy should be used to confirm the diagnosis of leiomyosarcoma.

TREATMENT

- Tumor resection
- Possible nephroureterectomy, depending on tumor grade and stage
- Adjuvant radiation therapy may be helpful.

REFERENCE

Griffin JH, Waters WB. Primary leiomyosarcoma of the ureter. *J Surg Oncol.* 1996;62(2):148–152.

URETER, METASTASIS TO

DESCRIPTION Metastatic tumors of the ureter are uncommon, and 1 of the rarest causes of ureteric obstruction. Since their 1st mention in the literature in 1909 only ~400 cases are reported. Among 1/2 of the cases, the breast or gastrointestinal tract (colorectum) is the site for primary cancer. Prostate cancer and uterine cervical cancer are responsible for 30–40% of cases, with stomach and lung cancer being reported in the remaining case. A predilection exists for the lower 1/3 of the ureter. Many are asymptomatic with the majority autopsy reports.

REFERENCE

Arvind NK, Singh O, Gupta S, et al. Ureteral Metastasis as the presenting manifestation of pancreatic carcinoma. *Rev Urol.* 2013;15(3):124–130.

URETER, NEPHROGENIC ADENOMA (NA)

DESCRIPTION Nephrogenic adenoma (NA) is a rare metaplastic lesion of the ureter and assumed to be secondary to chronic irritation of the urothelium. It is a benign papillary and tubular proliferation in response to trauma, infection, or ionizing radiation. Although it can be seen anywhere in the urinary tract, it is most commonly observed in the bladder (55%). The incidence in ureter is ~4%. Biopsy and fulgeration are appropriate, as it is treated as a low-grade urothelial malignancy. Malignant transformation has not been described.

REFERENCE

Doluoglu OG, Acarer EY, Yavuz A, et al. Nephrogenic adenoma of the ureter. *Rare Tumors.* 2012;4(2):e28.

URETER, NEUROFIBROMA

DESCRIPTION Grossly, neurofibromas may be single or multiple and comprise different sized nodules. Histologically, they are composed of fascicles of elongated, spindle-shaped cells with thin, wavy nuclei in a collagenized background. Neurofibromas in the ureter are very

rare but have an increased incidence in von Recklinghausen disease. Neurofibromas frequently recur and can cause death by urinary obstruction and renal failure. Endoscopic or open excision is the treatment of choice.

REFERENCE

Bostwick DG, ed. *Urologic Surgical Pathology*. 1st ed. St. Louis, MO: Mosby; 1997.

URETER, PIPE-STEM

DESCRIPTION A radiographic appearance seen in late stages of tuberculous involvement of the ureter. On IVP, the ureter appears straight with a narrow lumen, due to diffuse fibrotic changes of the wall.

REFERENCE

Murphy DM, Fallon B, Lane V, et al. Tuberculous stricture of ureter. *Urology*. 1982;20:382–384.

URETER, RADIATION INJURY TO

DESCRIPTION Clinically, radiation injury to the ureter will present as obstruction. Upper urinary tract obstruction secondary to the effects of radiation is generally reported to occur in ~5% of patients with ureteral encroachment, and in <1% of all treated patients. The ureters are relatively resistant to the effects of radiation, although some factors are postulated to increase the chance of injury after radiation exposure, such as infection of the ureter, necrosis of the tumor invading the ureteral wall, and direct radiation injury to the ureteral wall. Radiation therapy of ≥8,000 Gy results in a 40% urologic complication rate. A dose of ≤6,000 Gy results in a <2% complication rate. (See also Section I: “Ureter, Obstruction.”)

REFERENCE

Resnick MI, Kursh ED. Extrinsic obstruction of the ureter. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell’s Urology*. 7th ed. Philadelphia, PA: Saunders; 1998:409–410.

URETER, RETROCAVAL (CIRCUMCAVAL, POSTCAVAL)

DESCRIPTION A retrocaval ureter is a congenital anomaly in which the problem arises from the inferior vena cava rather than the ureter. Normally, the vena cava derives from the supracardinal vein, which lies posterior to the ureter. If it derives from either the persistent right subcardinal or postcardinal vein, both of which lie anterior to the ureter, a portion of the lumbar ureter becomes trapped behind the vena cava. Clinically, a retrocaval ureter may present as ureteral obstruction with a Shepards crook deformity. Males are affected more than females and the presentation usually relates to the ureteral obstruction (pain infection, stones).

Two types have been described. Type 1 is the more common where the ureter crosses behind IVC at the level of 3rd lumbar vertebra assuming the appearance of a shephards crook or sickle shaped at the point of obstruction. Marked hydronephrosis usually present. Type 2 retrocaval ureter is less common and the ureter tends to cross at a much higher level relative to the renal pelvis and the degree of hydronephrosis is usually mild. Treatment is surgery

with transection of the ureter and reanastomosis in front of the inferior vena cava. (See "Ureter, Shepherd's Crook.")

REFERENCE

Chung BI, Gill IS. Laparoscopic dismembered pyeloplasty of a retrocaval ureter: Case report and review of the literature. *Eur Urol.* 2008;54(6):1433–1436.

URETER, SHEPHERD'S CROOK

DESCRIPTION Characteristic S-shaped appearance of the circumcaval/retrocaval ureter on excretory urography or retrograde ureterography. A normal-caliber ureter emerging at the medial aspect of the inferior vena cava runs inferiorly between it and the aorta. The elongation and dilatation of ureter above the site of the obstruction along with the course around the inferior vena cava cause a "shepherd's crook" or "sickle-shaped deformity." On frontal projection, the ureter is medial to the lower lumbar pedicles, where it crosses anterior to the right iliac vessels to enter the pelvis. Clinically, a retrocaval ureter may present as ureteral obstruction with pain, stones, or infection. Males are affected more than females. Treatment is surgery with transection of the ureter and reanastomosis in front of the inferior vena cava (See also Section II: "Ureter, Retrocaval [Circumcaval, Postcaval].")

REFERENCE

Kenawi MM, Williams DI. Circumcaval ureter: A report of four cases in children, with a review of the literature and a new classification. *Br J Urol.* 1976;48:183.

URETER, SPIRAL (CORKSCREW)

DEFINITION

A spirally twisted or "corkscrew" ureter is a very rare anomaly beyond the neonatal age. A spirally twisted ureter is not considered clinically significant, unless it causes obstruction and secondary hydronephrosis. Infants frequently have a "corkscrew" appearance of the proximal segment of the ureter seen on intravenous urography, but this has been considered an imaging finding of no postnatal clinical significance. It may represent persistence of normal fet al developmental structures, such as congenital folds. Corkscrew configuration of the ureter may also be the result of ureteric varicosities or extrinsic ureteric obstruction when seen later in life. Obstruction secondary to spiral deformity of the ureter may be due to involvement of the ureter by dense fibrous bands (Image ☼).

REFERENCE

Prodromos P, Payne D, Keeley F. Let's get it straight: the story of the spiral ureter. *Can J Urol.* 2012;19:6118–6120.

URETER, STONE PASSAGE STATISTICS

DEFINITION

The ureter is the smallest diameter structure of the urinary tract. It is also the area most likely to be obstructed by a stone. Most stones <5 mm in diameter are likely to pass spontaneously with the likelihood of spontaneous stone passage decreasing with increased stone size. It is

estimated that 2/3 of ureteral stones that pass spontaneously pass within 4 wk of the onset of symptoms.

Stone Size (mm)	Number of Days to Pass Stone (Mean)	Likelihood of Eventual Need for Intervention
2 or less	8	3%
3	12	14%
4–6	22	50%
>6	–	99%

REFERENCE

Kidney Stones. http://www.auanet.org/education/kidney-stones.cfm, Accessed April 5, 2014.

URETER, STRICTURE

DESCRIPTION Strictures are 1 of the main causes for ureteral obstruction that might lead to hydronephrosis and renal function impairment. Ureteral strictures may present with an insidious onset of irreversibly damaged renal parenchymal due to slow development of silent hydronephrosis. Common signs of symptomatic stricture are flank pain, elevated creatinine level, or decreased urine output. Imaging studies with contrast are an essential part of the diagnostic workup. The location and length of obstruction are important parameters for treatment planning. (See also Section I: “Ureter, Obstruction.” and (Image ☼))

CAUSES

- Congenital
- Extrinsic trauma
- Iatrogenic (gynecologic or other pelvic surgeries)
- Inflammatory and infectious factors (Crohn disease)
- Instrumentation (ureteroscopy)
- Malignant (intrinsic or extrinsic)
- Postchemotherapy and radiation therapy
- Sclerosing retroperitoneal fibrosis

TREATMENT

- Relieve the obstruction with concomitant antibiotic coverage, if needed.
- Surgical correction with endoscopic, laparoscopic, robotic, or open surgery.
- Reimplantation with excision for distal strictures.

REFERENCE

Ogan K, Abbott JT, Wilmot C, et al. Laparoscopic ureteral reimplant for distal ureteral strictures. *JSLS*. 2008;12(1):13–17.

URETER, VALVES

DESCRIPTION Ureteral valves obstruct the forward flow of fluid, causing a proximal hydronephrosis. About 35% of ureteral valves occur at the UPJ; 60% occur near the ureterovesical junction, and 5% in the upper ureter. Valves are 3 times more common in males. They are usually unilateral, although they may be bilateral, and, if so, usually lead to

renal failure. 75% of valves occur on the left side. Treatment depends on the location of the valve and may include ureteral reimplantation (distal ureter), endoscopic ablation (midproximal ureter), or UPJ repair.

REFERENCE

Amis ES, Newhouse JH, eds. *Essentials of Uroradiology*. 1st ed. Boston, MA: Little Brown; 1991:63.

URETERAL JETS

DESCRIPTION Ureteral jets have been studied to diagnose urinary tract obstruction. Ureteral jets are visualized on color Doppler ultrasound as ureteral urine passes into the bladder. Sensitivity of 100% and specificity of 90.9% in detecting ureteral obstruction has been reported based on the absence of the ureteral jet on a given side. Patients must be well hydrated and often a prolonged imaging interval is needed to document the presence or absence of the ureteral jet (Image ☼).

REFERENCE

Deyoe LA, Cronan JJ, Breslaw BH, et al: New techniques of ultrasound and color doppler in the prospective evaluation of acute renal obstruction: Do they replace the intravenous urogram? *Abdom Imaging*. 1995;20:58–63.

URETERAL STRICTURE FOLLOWING URINARY DIVERSION

DESCRIPTION Ureteral strictures are seen in 2–10% of patients who receive a cystectomy and urinary diversion for bladder cancer. The stricture is most commonly located at the ureteroenteric anastomosis and more commonly involves the left ureter. Considered a late complication, strictures usually present in the 6–12 mo postoperative time period. Ureteral recurrence of urothelial carcinoma should be ruled out. Treatment includes percutaneous nephrostomy, indwelling ureteral stent, balloon dilatation, or reanastomosis.

REFERENCE

Tal R, Sivan B, Kedar D, et al. Management of benign ureteral strictures following radical cystectomy and urinary diversion for bladder cancer. *J Urol*. 2007;178:538–542.

URETERITIS

DESCRIPTION A generic characterization given to describe inflammation of the ureter which can be further qualified into subtype descriptions based loosely on its etiologic factors. For example, postoperative ureteritis, infective ureteritis, and noninfective ureteritis. Noninfective causes of ureteritis include ureteral amyloidosis, eosinophilic ureteritis, IgG-4 associated ureteral inflammation, and idiopathic segmental ureteritis.

REFERENCE

Atsuta T, Shimizu Y, Masuda N, et al. First report of idiopathic segmental ureteritis successfully treated by steroid therapy. *Int J Urol*. 2012;19:583–586.

URETERITIS CYSTICA

DESCRIPTION A benign and rare condition, ureteritis cystica is characterized by multiple cysts and space-filling defects in urothelium. Usually asymptomatic, it may present with hematuria, and if obstruction occurs, may lead to stone formation, UTIs, and renal compromise. The etiology is unknown, but associated with chronic UTI. Space-filling defects seen on retrograde pyelography or excretory urography may appears as smooth, round or oval filling defects of varying sizes that protrude into the lumen. It can mimic other conditions such as bladder cancer, blood clots, air bubbles, radiolucent stones, fibroepithelial polyps, and sloughed renal papillae. It manifests as cystic areas of glandular metaplasia associated with chronic urothelial inflammation; this is more commonly seen in the bladder, called cystitis cystica. Treatment is ureteroscopy and the mechanical disruption of cysts or instillation of chemicals such as silver nitrate to relieve obstruction.

REFERENCE

Rothschild JG, Wu G. Ureteritis Cystica: A Radiologic Pathologic Correlation. *J Clin Imaging Sci.* 2011;1:23.

URETERONEOCYSTOSTOMY, TECHNIQUES AND INDICATIONS

DESCRIPTION Ureteral reimplantation, or ureteroneocystostomy, is used when there is an abnormality at the ureterovesical junction. Abnormalities include an obstructing ureterocele, megaureter, ureteral reflux, distal ureteral stricture, or iatrogenic injuries. The surgical treatment options can be classified on the basis of the ureteral approach to the bladder as intravesical, extravesical, or combined or on the relationship of the submucosal tunnel to the site of the original ureteral hiatus as suprahiatal or infrahiatal.

REFERENCE

Khoury AE, Bägli DJ. Vesicoureteral reflux. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia, PA: Saunders; 2011.

URETHRA, ADENOCARCINOMA OF ACCESSORY GLANDS

DESCRIPTION In males, the urethral accessory glands can develop rare, aggressive neoplasms that are difficult to diagnose because of the local destructive nature of the lesions (Cowper and Littré glands). Cowper gland cancers are found in the bulbous urethra, while Littré gland lesions can arise along the entire urethra, but tend to arise distally. In females, the Skene glands can develop adenocarcinoma as well. Patients typically present with hematuria, dysuria, and progressive urinary obstruction. Management is similar to that for urethral adenocarcinoma. (See also Section II: “Cowper Gland Carcinoma”, “Skene (Paraurethral) Gland, Adenocarcinoma.”)

SYNONYMS

- Adenocarcinoma of Cowper gland
- Adenocarcinoma of Littré glands
- Adenocarcinoma of Skene (periurethral) glands

REFERENCE
Reuter VE. Urethra, Chapter 11. In: Bostwick DG, ed. *Urologic Surgical Pathology*. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2008:608.

URETHRA, ADENOMATOUS POLYPS

DESCRIPTION Congenital, benign papillary-appearing lesions that occur most frequently in the prostatic urethra and contain benign prostatic epithelium. These have been reported in the anterior urethra. Cores of the papillary projections contain prostatic stroma and glands. The lesions typically present in the 1st decade of life, but can appear at any age. Hematuria, enuresis, and obstruction are common. Cystourethroscopy is usually diagnostic.

SYNONYMS
- Villous polyp of the urethra
- Ectopic prostatic tissue in the urethra

TREATMENT
Transurethral or suprapubic resection is curative.

REFERENCE
Chan JK, Chow TC, Tsui MS. Prostatic-type polyps of the lower urinary tract: Three histogenetic types? *Histopathology*. 2007;11(8):789–801.

URETHRA, BLEEDING (BLOOD AT MEATUS)

DESCRIPTION Usually associated with GU trauma, blood at the urethral meatus is the single most important sign of urethral injury. Patients often complain of abdominal pain or inability to urinate, and report a history of crush injury to the pelvis. Clinically, this finding is an absolute contraindication to immediate urethral catheter placement. Instead, urethrography should be performed (see below). This is distinct from idiopathic urethrorrhagia, which is bleeding from the urethra or blood spotting on the undergarments in preadolescents. Urethrorrhagia is a benign lesion and self-limited in most cases. (See also Section I: “Urethra, Trauma [Anterior and Posterior]”; Section II: “Urethrorrhagia, Idiopathic.”)

CAUSES
- Posterior urethral injury (prostatic and membranous urethra, proximal to urogenital diaphragm) associated with pelvic fracture and deceleration/shear injury
- Anterior urethral injury (bulbous and pendulous urethra, distal to urogenital diaphragm) associated with straddle injury and iatrogenic laceration
- Traumatic urethral catheterization; more common in men
- Nontraumatic causes: Idiopathic urethrorrhagia, malignancy (urethral, prostate, bladder), urolithiasis, urethral condyloma, urethral diverticulum, urethral stricture, benign prostatic bleeding, urethral hemangioma

TREATMENT
- In cases of urethral trauma, standard trauma management; shock and hemorrhage control
- Avoid urethral catheterization

- Retrograde urethrogram (12-Fr catheter in fossa navicularis with 3 cc in balloon; retrograde injection of 20–30 cc of water-soluble dye) to evaluate for extravasation beyond the urethra:
  - Positive extravasation: Immediate open bladder exploration with placement of suprapubic cystostomy tube; delayed urethral repair (3 mo after injury) with silicone urethral catheter placement concomitant with primary anastomosis
  - Negative extravasation: Careful urethral catheter placement; cystography

REFERENCE

Smith DR, et al. *Smith's General Urology*. New York, NY: McGraw-Hill; 2004:291–304.

URETHRA, CALCULI

DESCRIPTION Urethral calculi comprise <2% of all urinary stone disease in the Western world, with a greater incidence in men than women, given increased urethral length. They are classified as *migrant*, from the proximal GU system, or *native*, developing in the urethra itself. Stones <10 mm should pass spontaneously. Although native stones tend to be asymptomatic, urethral calculi may present with irritative voiding symptoms, hematuria, a palpable mass, and/or urethral discharge.

CAUSES

- Migrant calculi: See Section I: "Urolithiasis, Adult, General and Bladder Calculi"
- Native calculi: Urinary stasis (urethral strictures, diverticula, foreign-body entrapment, hair-bearing graft following urethroplasty), chronic infections (UTIs, schistosomiasis)

TREATMENT

- Depends on location and size of stone
- Acute retention: Suprapubic tube placement (allows for definitive planning)
- Trial of spontaneous expulsion with 2% intraurethral lidocaine
- Forceps extraction with or without meatotomy
- Antegrade massage/milking of calculus
- Retrograde manipulation with intravesical lithotripsy
- Intraurethral/endoscopic lithotripsy and fragment extraction
- Open urethrotomy (2-layer closure)

REFERENCE

Koga S, Arakaki Y, Matsuoka M, et al. Urethral calculi. *Br J Urol*. 1990;65(3):288–289.

URETHRA, CONDYLOMA (WARTS)

DESCRIPTION Condyloma (condylomata acuminatum, venereal warts) are a common finding in the lower genital tract, but a rare finding in the urinary tract. Condyloma of the urethra or bladder is often associated with immunosuppression. It is estimated that 0.5–5.0% of patients with condylomata of the genitalia may also have urethral involvement. Clinically, urethral involvement is suspected when pyuria or urethral discharge appears in a patient with genital verrucae. The cause is human papilloma virus (HPV), and primary treatment is ablative with cryotherapy, laser, or surgical excision. Urethral instillation via urethral syringe of fluorouracil injection mixed with lidocaine gel has also been reported. (See also Section I:

“Condylomata Acuminata [Venereal Warts]”) and (Image ☼).

REFERENCES

Frenkl TL. Sexually transmitted infections. *Urol Clin N Am.* 2008;35(1):33–46.
Gammon DC, Reed KA, Patel M, et al. Intraurethral fluorouracil and lidocaine for intraurethral condyloma acuminata. *Am J Health Syst Pharm.* 2008;65(19):1830–1833.

URETHRA, DIVERTICULAR CARCINOMA

DESCRIPTION Carcinoma of the urethral diverticulum is a rare pathologic entity commonly found in females, with an average age at presentation of 52. Reported symptoms include urethral bleeding (most common), dysuria, vaginal mass, and urethral obstruction. Adenocarcinoma occurs more frequently than transitional and squamous cell cancers combined and carries a more favorable diagnosis. Female urethral diverticula can be diagnosed through MR imaging with a high index of suspicion in patients with recurrent UTIs, dysuria, urgency, and postvoid dribbling. (See Section I: “Urethra Diverticula, Female”; “Urethra, Carcinoma, General.”)

TREATMENT

- Surgical: Radical cystourethrectomy with pelvic node dissection is recommended by most authors.
- Diverticulectomy has been suggested for low-stage adenocarcinoma, if close follow-up is assured.

REFERENCES

Clayton M, Siami P, Guinan P. Urethral diverticular carcinoma. *Cancer.* 1992;70:665.
Pathi SD, Rahn DD, Sailors JL, et al. Utility of clinical parameters, cystourethroscopy, and magnetic resonance imaging in the preoperative diagnosis of urethral diverticula. *Int Urogynecol J.* 2013;24:319–323.

URETHRA, DIVERTICULUM, MALE

DESCRIPTION Urethral diverticulum are usually found in the ventral anterior urethra but have been reported from the bulbous to the mid pendulous. These can be acquired (often iatrogenic from the treatment of urethral pathology) and very rarely, congenital. Congenital urethral diverticula may be either saccular or tubular. The saccular type has a true neck and may cause urinary obstruction when the cavity fills at the beginning of micturition. The tubular or diffuse type is located proximal to the urethral bulb, where urinary stasis can cause infection and/or calculous formation. Most are asymptomatic unless infection or obstruction develops. A mass can be palpated in the ventral aspect of the anterior urethra, which empties with compression. The diagnosis is made by cystoscopy, urethrography, and voiding urethrography. Management can be endoscopic unroofing for small diverticulum with open repair reserved for larger lesions.

REFERENCE

Ballesteros Sampol JJ, Cortadellas Angel R, Juanpere Rodero N. Acquired male urethra diverticula. Report of seven cases. Bibliographic review. *Arch Esp Urol.* 2008;61(1):1–6.

URETHRA, DUPLICATION

DESCRIPTION Duplication of the urethra is rare and afflicts mainly boys. Duplication of the urethra may be complete, extending from the bladder to the dorsum of the penis, or partial, extending from the dorsal surface or, less commonly, the ventral surface of the penis and ending blindly. In only 15% of cases of duplicated urethra, whether complete or partial, is there a connection with the functional urethra. Urethral duplication is often associated with GU and GI abnormalities that maybe be severe. Most cases are asymptomatic, but the most common complication is infection. Patients may have urinary obstruction caused by compression of the functional urethra by a mass of material in the blind, accessory urethra. In other cases, patients may complain of incontinence or double urinary streams. Complete resection of the nonfunctioning urethra, if symptomatic, is curative.

REFERENCE

Arena S, Arena C, Scuderi MG, et al. Urethral duplication in males: Our experience in ten cases. *Pediatr Surg Int.* 2007;23(8):789–794.

URETHRA, FOREIGN BODY

DESCRIPTION Cases of self-inflicted foreign bodies in male urethra have been reported, including objects such as fishhooks, bones, screws, safety pins, and light bulbs. Cause for inserting foreign bodies varies, including psychiatric disorder, intoxication, and erotic stimulation. Endoscopic retrieval is usually successful using modern instruments. Open surgery may also be considered. IV perioperative antibiotics followed by PO antibiotics for 1 wk has been recommended. Delayed complications include stricture disease, therefore close urologic follow-up is recommended (Image ☼).

REFERENCE

Rahman NU, Elliott SP, McAninch JW. Self-inflicted male urethral foreign body insertion: Endoscopic management and complications. *BJU Int.* 2004;94(7):1051–1053.

URETHRA, HEMANGIOMA

DESCRIPTION Urethral hemangiomas are extremely rare tumors. The lesion is believed to be congenital, arising from the embryonic rest of unipotent angioblastic cells that fail to develop into normal blood vessels. The clinical presentation is bloody urethral discharge or frank urethral bleeding. These lesions are benign in nature. They are treated by local resection or ablation with electrocoagulation or laser. (See also Section II: “Urethra, Bleeding [Blood at Meatus].”)

REFERENCE

Parshad S, Yadav SP, Arora B, et al. Urethral hemangioma. An unusual cause of hematuria. *Urol Int.* 2001;66(1):43–45.

URETHRA, LEIOMYOMA

DESCRIPTION Rare benign neoplasm arising from smooth muscle. The majority occur in

females, with a peak age of 30–40 yr. It usually presents as an asymptomatic mass, or with dysuria, UTI or obstruction, and dyspareunia. The proximal urethra is most commonly involved. No etiology is known, but it is hormonally associated and many of these tumors enlarge in pregnancy. Treatment is local excision, and prognosis is excellent as no malignant transformation or local recurrence has been reported in the literature. (See also Section I: "Urethral Mass.")

REFERENCE

Pahwa M, Saifee Y, Pahwa AR, et al. Leiomyoma of the female urethra – a rare tumor: Case report and review of the literature. *Case Rep Urology*. 2012:1–2.

URETHRA, LEIOMYOSARCOMA

DESCRIPTION Leiomyosarcoma is a smooth muscle tumor that often exhibits necrosis, hemorrhage, and cystic degeneration. Leiomyosarcomas are extremely rare tumors that are more common in females than in males. Patients present with hematuria, pain, or mass. The prognosis is poor, and the treatment is radical excision with consideration of adjuvant radiation. (See also Section I: "Urethral Mass.")

REFERENCE

Ahalla Y, Tazi MF, Khallouk A, et al. Primary leiomyosarcoma of the male urethra: a case report. *Cases J*. 2009;2:207.

URETHRA, LEUKOPLAKIA

DESCRIPTION The term leukoplakia (also called *squamous metaplasia*) refers to the presence of grossly discernible white patches commonly seen on the mucosal surfaces of areas of squamous metaplasia. There seems to be an increased incidence in patients with diabetes, as well as in those with chronic irritation or infection. Generally believed to be a premalignant lesion caused by chronic infection or irritation, it may progress to squamous cell carcinoma (SCC). It is treated by biopsy and ablation.

REFERENCE

Benson RC, et al. Relationship of urethral leukoplakia to urothelial malignancy. *J Urol*. 1984;13:507–511.

URETHRA, LYMPHOMA

DESCRIPTION Primary malignant lymphoma rarely affects the lower urinary tract. When it does, it generally affects the bladder. Initial presentation within the urethra is extremely rare. Concurrent or subsequent regional or systemic lymphoma is generally the rule. Only 11 cases of lymphoma presenting in the urethra have been documented, and 10 were in women. (See Section II: "Lymphoma, Urologic Considerations.")

TREATMENT

- The high probability of regional or systemic extension is an argument against radiotherapy as a primary treatment.

• Chemotherapy is an excellent treatment, and the prognosis is good.

REFERENCE

Hatcher PA, Wilson DD. Primary lymphoma of the male urethra. *Urology*. 1997;49(1):142–144.

URETHRA, MALACOPLAKIA

DESCRIPTION This designation refers to a peculiar pattern of inflammatory reaction, characterized macroscopically by soft, yellow, slightly raised mucosal plaques (classic intracytoplasmic Michaelis–Gutmann bodies and von Hansemann cells). The disease shows a predilection for involving the bladder, ureter, renal pelvis, UPJ, and urethra. The disease predominates in females by a 4:1 ratio, and the peak age is in the 6th decade. Apart from symptoms associated with UTIs, the clinical manifestations are usually unremarkable. Most often, the bladder is involved, and symptoms of bladder irritability or hematuria may be present. Malacoplakia occurs with increased frequency in immunosuppressed transplant recipients. Pathogenesis is unknown, but an altered host response is suspected. There is an association with diabetes mellitus, alcoholic liver disease, sarcoidosis, and mycobacterial infection. When the lower urinary tract is involved, long-term antibiotics are successful.

REFERENCE

Karaiossifidi H, Kouri E. Malacoplakia of the urethra: A case of unique localization with follow-up. *J Urol*. 1992;148(6):1903–1904.

URETHRA, MALIGNANT MELANOMA

DESCRIPTION Primary urethral malignant melanoma is rare, with <100 cases reported in the literature. 90% of patients are diagnosed in the 6th–7th decades. 80% of cases were reported to be in the fossa navicularis and the meatus. The most common presentations are dysuria, hematuria, deviated urinary stream, or urinary obstruction. Endoscopically, a pigmented nodular mucosal mass or masses, which may be ulcerated, may be seen. Local recurrence is common. Metastasis is usually to inguinal and pelvic lymph nodes. Hematogenous spread to liver, lung, and brain is also common. Staging for urethral melanoma has not yet been standardized. Prognosis depends on the thickness of the lesion.

TREATMENT

• Surgical: Urethrectomy or penectomy with regional lymph node dissection
• The role of radiotherapy, immunotherapy, or chemotherapy is yet to be defined

REFERENCES

Kokatas NS, Kallis EG, Fokitis PJ. Primary malignant melanoma of male urethra. *Urology*. 1982;18:392.
Ramos JA, et al. Melanoma of the female urethra. *Indian J Urol*. 2011;27(4):448–450.

URETHRA, MEATUS, NORMAL CALIBER

DESCRIPTION Normal limits of male urethral calibration are as follows:

- 6 wk–3 yr: 15% <8 Fr; 85% 10 Fr
- 4–10 yr: 8% tight at 8 Fr; 76% 12 Fr
- 11–12 yr: 5% <10 Fr; 75% 14 Fr

Normal limits for female urethra are as follows:
- 2–4 yr: 14 Fr
- 6–10 yr: 16 Fr
- 12 yr: 20 Fr
- >14 yr: 24 Fr

REFERENCE

Elder JS. Congenital abnormalities of the genitalia. In: Walsh PC, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders; 1998:2128, 2137.

URETHRA, METASTASIS TO

DESCRIPTION Primary urethral tumors are rare, accounting for <1% of urologic cancers in the United States with metastatic urethral involvement even more uncommon. This involvement is mainly a result of local spread from the surrounding organs. Metastatic lesions to the urethra usually originate from the prostate, bladder, and rectum, although origin from more distant sites such as testicle has been reported. In a patient with a known malignancy, pain, hematuria, and/or urethral obstruction may suggest the diagnosis.

REFERENCES

Roberts TW, Melicow MM. Pathology and natural history of urethral tumors in females. *Urology*. 1977;10:583.

Ararwal V, Wah T, Chilka S, et al. Urethral metastasis from nonseminomatous germ cell tumor: A case report. *J Med Case Rep*. 2011;5:12.

URETHRA, NEPHROGENIC METAPLASIA (ADENOMA)

DESCRIPTION Nephrogenic metaplasia is a rare metaplastic lesion of urethral epithelium, with a classic triad of tubular, cystic, and papillary–polypoid patterns microscopically. Occurs at all ages, with a 3:1 male predominance. 15% of nephrogenic metaplasia is found in the urethra. Etiology is unknown, but resembles distal renal tubules and is associated with surgical trauma, calculi, indwelling catheter, chronic infections, and immunosuppression. This condition must be differentiated from prostatic carcinoma. Presenting symptoms include irritative voiding symptoms and hematuria, or the patient may be asymptomatic. Diagnosed by cystoscopy and biopsy, the clinical course is usually benign, although the problem may persist or recur. Rarely, a metaplastic lesion can cause carcinoma.

SYNONYMS
- Adenomatoid metaplasia
- Adenomatoid tumor
- Adenomatous metaplasia
- Hamartoma
- Tubular metaplasia

- Nephrogenic adenoma

TREATMENT
- Regular cystoscopic exam
- Removal of underlying cause
- Transurethral excision

REFERENCE
Xiao GQ, Burstein DE, Miller LK, et al. Nephrogenic adenoma: Immunohistochemical evaluation for its etiology and differentiation from prostatic adenocarcinoma. *Arch Pathol Lab Med.* 2006;130(6):805–810.

URETHRA, OBSTRUCTION

DESCRIPTION Urethral obstruction can occur anywhere from the meatus to bladder neck, and can be congenital or acquired. Posterior urethral valves are the most common cause of obstructive uropathy in boys. The incidence of posterior urethral valves is 0.25–0.5:10,000 births and anterior urethral valves occur 10 times less frequently than posterior valves. Other causes of urethral obstruction in both sexes include meatal stenosis, stricture, foreign body, phimosis (males), urethral calculus, urethral abscess, urethral diverticulum (acquired or congenital), or urethral neoplasm. (See also Section I: “Urethra, Mass.”)

REFERENCE
Narasimhan KL, Choudhary SK, Kaur B. Anterior urethral valves. *Indian Pediatr.* 2005;42:708–710.

URETHRA, POLYPS (FIBROEPITHELIAL, ADENOMATOUS, INFLAMMATORY)

DESCRIPTION Uncommon benign polypoid of papillary lesions of the urethra, these are usually limited to male patients and occur most often in children. Polyps vary in microscopic features, which result in their classification into fibroepithelial, adenomatous, or inflammatory. *Adenomatous polyps* are thought to represent prostatic glandular material from a congenital developmental error. *Fibroepithelial polyps* consist of stromal elements. *Inflammatory polyps* have a distinct inflammatory infiltrate. Presenting symptoms can include hematuria, hematospermia, obstruction, or UTI. Cystourethroscopy with biopsy is the test of choice. Transurethral resection with fulguration is the treatment of choice, along with removal of the source of inflammation (eg, catheter or stone removal) if present. (See Section II: “Cystitis, Polypoid and Papillary;” “Urethritis, Polypoid.”)

REFERENCE
Walsh IP, et al. Benign urethral polyps. *Br J Urol.* 1993;72:937–938.

URETHRA, PROLAPSE (FEMALE)

DESCRIPTION Prolapse of the urethra is a rare condition, described as complete eversion of urethral mucosa through the external urethral orifice; the etiology is unknown. It is primarily

associated with prepubertal girls and postmenopausal women with African American girls more commonly afflicted. Vaginal bleeding is often the presenting symptom, followed by urinary complications such as dysuria. Associated factors involve increased abdominal pressure, such as coughing or constipation, and trauma or infections of the vagina or urinary tract. Management ranges from conservative medical treatment to a variety of surgical corrective procedures, such as excision and urethroplasty. Medical treatment includes local hygiene, sitz bath, topical antibiotics, steroid, or topical estrogen creams (adults). Surgical intervention is indicated for more severe cases: significant bleeding, thrombosis, or gangrenous changes or if topical estrogen is contraindicated. Surgical treatment is usually accomplished with the modified Kelly–Burnam operation. The prolapsed mucosa is excised, and the mucocutaneous junction is reapproximated with absorbable sutures.

REFERENCES

Fernandes ET, Dekermacher S, Sabadin MA, et al. Urethral prolapse in children. *Urology.* 1993;41(3):240–242.

Olumide A, Kayode Olusegun A, Babatola B. Urethral mucosa prolapse in an 18-year-old adolescent. *Case Rep Obstet Gynecol.* 2013;2013:231709.

URETHRA, VILLOUS ADENOMA

DESCRIPTION An adenomatous lesion of the urethra, usually polypoid in nature, covered by mucinous material. Masses as large as 2–4 cm in the urinary tract have been described. Etiology is possibly due to an embryologic origin similar to that of the rectosigmoid. Urinary obstruction and/or hematuria can be presenting symptoms. Best treated by complete removal, due to the premalignant changes seen in some lesions and malignant potential seen in adenomas of the colon. These lesions are most commonly encountered in the male prostatic urethra. Histogenesis has been suggested to be secondary to residual cloacal epithelium in the prostatic urethra.

REFERENCES

Ulgaba F, Matias-Guiu X, Badia F, et al. Villous adenoma of the prostatic urethra. *Eur Urol.* 1988;14:255–257.

Zarineh A, et al. Recurrent villous adenoma with high grade dysplasia arising in a urethral diverticulum. *Case Rep Med.* 2009;1–3.

URETHRAL HYPERMOBILITY

DESCRIPTION Also called type II stress urinary incontinence (SUI), urethral hypermobility is caused by weak support of pelvic floor supporting structures, in which increased intra-abdominal pressure causes the descent of the bladder neck and proximal urethra. Women with hypermobility present with SUI, although some continent women have it as well. The degree of hypermobility is measured by the Q-tip test, in which a well-lubricated sterile cotton-tipped applicator is placed into the bladder and then withdrawn to the point of resistance. The patient is then asked to strain and the motion of the Q-tip is observed. Hypermobility is defined as a resting or straining angle 30% from horizontal. Treatment is periurethral collagen injection or pubovaginal sling procedure.

REFERENCE

Bakas P, Liapis A, Creatsas G. Q-tip test and tension free vaginal tape in management of female patients with genuine stress incontinence. *Gynecol Obstet Invest.* 2002;53(3):170–173.

URETHRAL PRESSURE PROFILE (UPP)

DESCRIPTION The UPP is a graphic representation of the intraluminal pressure along the length of the urethra. This static study provides no assessment of physiologic urethral function during voiding. The micturitional urethral pressure profile, however, is a dynamic study that can be performed by withdrawing a catheter from the urethra during micturition. The study can define the site of urethral obstruction by demonstrating a drop in urethral pressure immediately distal to the obstructive lesion in the urethra. Controversy exists on its use in clinical practice due to the variability in the reproduction of measurements and lack of standardization.

REFERENCES

Sullivan MP, Comiter CV, Yalla SV. Micturitional urethral pressure profilometry. *Urol Clin N Am.* 1996;23(2):263–278.

Valentini FA, Robain G, Marti BG. Is a sequence of tests during urethral pressure profilometry correlated with symptoms assessment in women? *Int Brazil J Urol.* 2012;38(6):809–817.

URETHRAL SLING, INDICATIONS AND ANATOMIC POSITIONS

DESCRIPTION A urethral sling is a surgically placed to support pelvic structures or lift the urethra to enhance the bladder and pelvic floor's ability to retain urine in patients with stress urinary incontinence (SUI). Slings can be made from autologous, allograft, xenograft, or synthetic tissues that provide strength. They can be placed at the proximal urethra (pubovaginal slings) or mid urethra (tension-free transvaginal tape [TVT] and transobturator [TOT] and other mid urethral slings). The urethral sling is a very effective treatment for SUI, with cure rates of 80–90% vs. other options such as the periurethral injection of bulking agents. Complications include erosion into surrounding structures such as vagina, urethra, and bladder, as well as bladder perforation, urinary tract infection, and new onset irritative voiding symptoms. (See also Section I: "Incontinence, Urinary, Adult Female"; Section II: "Sling Materials.")

REFERENCES

Schulz JA. Midurethral minimally invasive sling procedures for stress urinary incontinence. *J Obstet Gynaecol Can.* 2008;30(8):728–740.

Rehman H, Bezerra CC, Bruschini H, et al. Traditional suburethral sling operations for urinary incontinence in women. *Cochrane Database Syst Rev.* 2011;(1):CD001754.

URETHRA, STENOSIS/STRICTURE, FEMALE

DESCRIPTION A decrease in the caliber of the urethra, uncommon in females compared with males. Causes can include recurrent UTIs, previous endoscopic instrumentation, surgical

management of urethral pathology or diverticular repair, trauma (including childbirth), neoplasia, or pelvic radiation, or it can be idiopathic. The patient usually presents with recurrent UTI or obstructive urinary symptoms (weak stream, straining to urinate, incomplete emptying). Female urethral stricture has been formally defined as a fixed anatomic narrowing between the bladder neck and distal urethra of <14 Fr preventing catheterization, with the diagnosis confirmed by cystourethroscopy, and/or videourodynamics. Intermittent catheterization has been used successfully, with internal urethrotomy or urethroplasty also as options.

REFERENCES

Smith AL, Ferlise VJ, Rovner ES. Female urethral strictures: Successful management with long-term clean intermittent catheterization after urethral dilatation. *BJU Int.* 2006;98(1):96–99.

Tsivian A. Dorsal graft urethroplasty for female urethral stricture. *J Urol.* 2008;176(2):8-611–613.

URETHRAL SYNDROME

DESCRIPTION A nonspecific term used in the past to describe symptoms such as urinary frequency, urgency, dysuria, and pelvic/perineal discomfort having no obvious cause. Because this term is so nonspecific, it is not meaningful for diagnosis or treatment planning. A more effective approach is to delineate each of the patient's specific symptoms (eg, frequent voiding), then pursue the differential diagnosis and treatment options for each symptom. The concept of chronic or acute urethral syndrome is now essentially historical, and is no longer used in modern medical literature.

REFERENCE

Hanno PM. Painful bladder syndrome/interstitial cystitis and related disorders. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*, 9th ed. Philadelphia, PA: Saunders; 2007.

URETHRITIS, ACUTE

DESCRIPTION Syndrome of urethral inflammation marked by painful urination, urethral pruritus, and discharge. Usually caused by a STD/STI, but other causes are not uncommon. Untreated cases may gradually resolve, but complications, such as urethral stricture in males or pelvic inflammatory disease (PID) in women, may ensue. Cause is predominantly *N. gonorrhoeae* and *C. trachomatis* infection; often together. Less common infectious agents include *Ureaplasma urealyticum, Trichomonas vaginalis,* herpesvirus, and *Mycoplasma genitalium.* Rare noninfectious causes include foreign bodies, soaps, shampoos, douches, spermicides, and urethral instrumentation. Gram stain of discharge with >5 WBC/HPF strongly suggests urethritis. Intracellular gram-negative diplococci are strongly indicative of gonorrhea. Cultures may be difficult to obtain, but are important for antimicrobial sensitivity testing and should be performed in all symptomatic patients. Routine urine analysis may be normal in simple urethritis. st-void urine is often positive for leukocyte esterase and should show ≥ 10 WBC/HPF in acute urethritis. NAAT utilizing PCR assay on urine is very sensitive and specific, but costly. Wet prep of discharge may reveal *Trichomonas*; this is usually

reserved in males who fail adequate treatment for gonorrhea and chlamydia. Syphilis, HIV, and hepatitis B serology is performed as indicated to rule out concomitant STDs.

TREATMENT

- The United States Preventative Services Task Force recommends screening all sexually active women ≤25 yo and all other women at increased risk of infection.
- All sexual partners who came in contact with the patient within 60 days should be evaluated, tested, and treated for gonorrhea and chlamydia.
- Gonorrhea: Ceftriaxone 250 mg in a single IM PLUS Azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days
- Chlamydia: Azithromycin: 1 g PO single dose or doxycycline: 100 mg PO BID for 7 days
- Trichomoniasis: Metronidazole 2 g PO single dose or 250 mg TID for 7 days or tinidazole 2 g PO in a single dose

REFERENCE

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR*. 2010;59(No. RR-12).

URETHRITIS, CHRONIC, FEMALE

DESCRIPTION Chronic urethritis is a common urologic problems of females, as the distal urethra normally harbors pathogens. Infection may be increased by wearing contaminated diapers, by insertion of an indwelling catheter, by spread from cervical or vaginal infections, or by intercourse with an infected partner. Urethral inflammation may also occur from the trauma of intercourse or childbirth, particularly if urethral stenosis, either congenital or following childbirth, is present. The urethral mucosa is reddened, sensitive, and often stenotic. Granular areas are often seen, and polypoid masses are common. The symptoms resemble those of cystitis, although the urine is not infected. Complaints include dysuria, frequency, and nocturia. Discomfort in the urethra may be felt, particularly when walking. Urethral dilations may help if stenosis is found (dilate to 36 Fr). Empiric doxycycline or azithromycin can be tried.

REFERENCE

Tanagho EA, et al. Disorders of the female urethra. In: Tanagho EA, McAninch JW, eds., *Smith's General Urology*. 17 ed. New York, NY: McGraw-Hill; 2008.

URETHRITIS, POLYPOID

DESCRIPTION A urethral counterpart of polypoid cystitis, it occurs as single or multiple polypoid/papillary lesions. A nonneoplastic inflammatory lesion that is usually found in the prostatic urethra near the verumontanum. The lesions are edematous stroma with distended blood vessels and chronic inflammatory infiltrate. Usually resolves after removal of the inflammatory stimulus; if necessary, resection of the lesions usually leads to a cure. If the lesions persist, malignancy should be ruled out.

REFERENCE

Reuter VE. Urethra Chapter 11 in Bostwick DG, ed *Urologic Surgical Pathology*. 2nd ed

Philadelphia, PA: Mosby Elsevier, 2008:598.

URETHRITIS, SENILE

DESCRIPTION After physiologic (or surgical) menopause, hypoestrogenism occurs and retrogressive (senile) changes take place in the vaginal (atrophy) and the urethral walls. Some eversion of the mucosa at the urethral orifice, from atrophy of the vaginal wall, is usually seen and can be misdiagnosed as a caruncle. Many postmenopausal women have symptoms of vesical irritability (burning, frequency, urgency) and stress incontinence. Dysuria may occur due to urine contact with the inflamed atrophic tissues themselves or because of the increased incidence of UTIs in these women. Best treated symptomatically or with DES vaginal suppositories 0.1 mg nightly for 3 wk. The patient may also benefit from other topical agents such as estradiol vaginal tablets or from conjugated estrogen cream or slow release intravaginal therapy such as the Estring.

REFERENCES

Manonai J, Theppisai U, Suthutvoravut S, et al. The effect of estradiol vaginal tablet and conjugated estrogen cream on urogenital symptoms in postmenopausal women: A comparative study 2001:27:255–269.

Tanagho EA, et al. Disorders of the female urethra. In: Tanagho EA, McAninch JW, eds., *Smith's General Urology*. 17 ed. New York, NY: McGraw-Hill; 2008.

URETHROCELE

DESCRIPTION Urethrocele is a form of pelvic prolapse in which the urethra protrudes into the anterior wall of the vagina, due to loss of the normal urethral support from damage such as childbirth. Cystocele is also commonly present. In women, a urethrocele can cause voiding difficulty, some degree of incontinence, UTI, and dyspareunia. The condition can also develop in children after urethroplasty, with distal obstruction causing proximal dilation of the neourethra; it is very rarely congenital. (See also Section I: "Pelvic Prolapse [Cystocele and Enterocele].")

REFERENCE

Lentz G. Anatomic defects of the abdominal wall and pelvic floor: abdominal and inguinal hernias, cystocele, urthrocele, enterocele, rectocele, uterine and vaginal prolapse: diagnosis and management. In: Lentz GM, Lobo RA, Gershenson DM, Katz VL, eds., *Lentz: Comprehensive Gynecology*. 6th ed. Philadelphia, PA: Mosby; 2012.

URETHRORRHAGIA, IDIOPATHIC

DESCRIPTION Bleeding from the urethra or blood spotting on the undergarments in preadolescents average age (around 10 yr); this is a benign condition, self-limited in most cases. The etiology is unknown. Routine radiographic, lab, and endoscopic evaluation is unnecessary for evaluating urethrorrhagia. Watchful waiting is indicated, as the condition resolves in 71% and 91.7% of patients at 1 and 2 yr, respectively. Evaluation should be considered in patients with prolonged urethrorrhagia because urethral stricture may be

identified. (See also Section II: “Urethral, Bleeding [Blood at Meatus].”)

REFERENCE

Walker BR, Ellison ED, Snow BW, et al. The natural history of idiopathic urethrorrhagia in boys. *J Urol.* 2001;166(1):231–232.

URGE INCONTINENCE/URGE URINARY INCONTINENCE (UUI)

DESCRIPTION Urge urinary incontinence (UUI) is the involuntary leakage of urine immediately preceded by a sense of urgency; it is caused by detrusor muscle overactivity. Etiology is categorized into idiopathic; neurogenic, as from stroke or multiple sclerosis (MS); or nonneurogenic, including infection, bladder stones, and cancer. Initial workup includes a good history and physical, evaluation for other associated urinary symptoms, check of postvoid residual, urine analysis. Cystoscopy should be performed in the setting of simultaneous hematuria. Urodynamic evaluation can be considered in medically refractory patients. (See also Section I: “Incontinence, Female”; and “Incontinence, Male.”)

TREATMENT

- Symptomatic control mainstay of treatment.
- Dietary and behavioral modifications: Limiting caffeinated substances fluid intake, artificial sweeteners, and timed voiding should be the initial treatment.
- Biofeedback-assisted pelvic muscle training
- 1st-line medical therapy: Anticholinergics, β3-agonists
- 2nd-line therapy: Intravesical Botulinum toxin, sacral neuromodulation, and augmentation cystoplasty.

REFERENCES

Greer JA, Smith AL, Arya LA, et al. Pelvic floor muscle training for urgency urinary incontinence in women: a systematic review. *Int Urogyneol J.* 2012;23(6):687–697.

Holroyd-Leduc JM. What type of urinary incontinence does this woman have? *JAMA.* 2008;299(12):1446–1456.

URGENCY PERCEPTION SCORE (UPS)

DESCRIPTION The UPS is a system based on the grade of sensation of bladder fullness at each micturition. This system proposes that urgency is always abnormal, that it lies on a continuum, and that it can be graded on a scale of 0–4 where 0 is no urge; 1, mild urge; 2, moderate can hold (>10–60 min); 3 severe can hold (<10 min); and 4, desperate urge must go (immediately). The UPS can be a useful tool in a bladder diary, and it becomes a treatment outcome tool because improvements can be shown as decreases in grade, and in number or urgency of voids.

REFERENCE

Blaivas JG, Panagopoulos G, Weiss JP, et al. The Urgency Perception Score. *J Urol.* 2007;177(1):199–202.

URIC ACID NEPHROPATHY

DESCRIPTION Uric acid nephropathy can be both acute and chronic. Acute uric acid nephropathy is caused by intrarenal precipitation of uric acid crystals in the distal nephron (collecting tubules) due to its acidic environment. This can lead to obstruction of nephrons and development of ARF. Acute acid nephropathy more likely occurs in patients with leukemia and lymphomas undergoing chemotherapy (plasma urate concentration generally above 15 mg/dL or 893 μmol/L). Chronic uric acid nephropathy or gouty nephropathy occurs in individuals with more protracted forms of hyperuricemia. Monosodium urate crystals deposit in distal tubules, collecting ducts and the renal interstitium. Deposits induce a tophus from a fibrotic reaction. Tubular obstruction leads to cortical atrophy and scarring. Typically this form is a subtle disease with slow progression.

REFERENCES

Conger JD. Acute uric acid nephropathy. *Med Clin North Am*. 1990;74(4):859–871.
Alpers CE. Urate Nephropathy. In: Kumar V, Abbas AK, Fausto N, Aster JC, eds, *Kumar: Robbins and Cotran Pathologic Basis of Disease, Professional Edition*. 8th ed. Philadelphia, PA: Saunders; 2010.

URINARY ASCITES (UROPERITONEUM)

DESCRIPTION Urinary ascites is usually seen in infants, because of the relative lack of dilation of the newborn collecting system, when compared to that in adults. The condition most often occurs in neonates due to intraperitoneal bladder or upper tract perforation as a result of distal urinary obstruction. It is rare in adults. The most common cause is posterior urethral valves, accounting for 70% of cases. Persistent cloaca may allow the reflux of urine into the peritoneal cavity without perforation. Mortality rate is as high as 70%. Signs and symptoms may include abdominal distention, acidosis, electrolyte abnormalities, and respiratory compromise from increased abdominal pressure. In older patients, hyponatremia and increased serum creatinine can be observed. Diagnosis includes imaging (CT or US), voiding cystourethrography, and paracentesis to check creatinine levels in ascitic fluid.

A newer cause of urinary ascites relates to urinary extravasation following laparoscopic or robotically assisted radical prostatectomy (RP). Since the peritoneum is opened as part of the procedure urinary extravasation becomes urinary ascites. It can lead to ileus.

TREATMENT

- Relieve obstruction (ie, ablation of posterior urethral valves).
- Catheter bladder drainage in posterior urethral valves and upper tract drainage may be necessary.
- Correct fluid balance and electrolyte abnormalities.
- Direct repair at the perforation site is usually not indicated (Image ☼).

REFERENCES

Adams MC, Ludlow J, Brock JW, et al. Prenatal urinary ascites and persistent cloaca: Risk factors for poor drainage of urine or meconium. *J Urol*. 1998;(1606 Pt 1):2179–2181.
Hu JC, Nelson RA, Wilson TG, et al. Perioperative complications of laparoscopic and robotic

assisted laparoscopic radical prostatectomy. *J Urol.* 2006;175(2):541–546; discussion 546.

URINARY DIVERSION, ELECTROLYTE, AND OTHER ABNORMALITIES

DESCRIPTION Fluid and electrolyte complications can arise from solute transfer from urine across a bowel segment used for urinary diversion. The specific segment of bowel used, the amount and time of contact of urine with bowel mucosa, the age of the conduit, and renal function are all factors that can affect fluid and electrolyte balances. In addition to the metabolic disturbances listed below, bowel segment absorption can be associated with abnormal drug metabolism. For example, methotrexate toxicity in patients with ileal conduits is well recognized, and patients with continent diversion who receive chemotherapy should be monitored closely and stay well hydrated; the reservoir is drained during treatment. Other drugs reported to be absorbed from intestinal segments in the urinary tract include phenytoin, theophylline, and antibiotics. Diabetics have enhanced ability to absorb glucose from intestinal reservoirs so screening with urine tests may be inaccurate. Glucose blood testing is recommended.

- Ileal and colonic conduits can produce hyperchloremic metabolic acidosis. The mechanism is the absorption of ammonium chloride (a weak acid) in exchange for carbonic acid (CO_2 and water). Treatment, if necessary, consists of urinary alkalinization (sodium bicarbonate, Bicitra, Polycitra) or blockade of chloride transport (chlorpromazine 25–50 mg TID or nicotinic acid 400 mg TID)
- Jejunum is least attractive for use in urinary diversions, due to its high absorptive capacity, and it is associated with hyponatremic, hyperkalemic metabolic acidosis with azotemia.
- Gastric segments cause a hypochloremic, hypokalemic metabolic alkalosis. This is not normally a significant problem unless renal failure develops and the segment needs to be taken down.
- Distal ileum resection may result in macrocytic anemia due to B12 deficiency over long periods and may require supplementation.

REFERENCE

Gerharz EW, Hautmann RE, et al. Urinary diversion. *Urology.* 2007;69(Suppl 1A):17–49.

URINARY DIVERSION, RISK OF MALIGNANCY

DESCRIPTION Segments of bowel used for urinary diversion have an increased risk of malignant transformation. Some studies have shown an increase from 5% up to as high as 40% 10–20 yr after a urinary diversion. The etiology is unknown; adenocarcinomas, adenomatous polyps, sarcomas, TCCs, signet ring carcinomas, and SCCs have been identified. Many investigators now recommend annual screening in patients who have intestinal segments in contact with urine beginning 10 yr after the initial surgery. Patients who have previously undergone a ureterosigmoidostomy are at particularly increased risk for development of adenocarcinoma of the sigmoid colon along the anastamotic line. It is recommended that these patients undergo periodic colonoscopy to accurately define any morbidities from their previous diversion.

REFERENCES

North AC, Lakshmanan Y. Malignancy associated with the use of intestinal segments in the urinary tract. *Urol Oncol.* 2007;25(2):165–167.
Kalble T, Hofmann I, Riedmiller H, et al. Tumor growth in urinary diversion: A multicenter analysis. *Eur Urol.* 2011;60(5):1081–1086.

URINARY FLOW RATE (UROFLOWMETRY)

DESCRIPTION *Uroflowmetry* is the study of urinary flow rate. Urinary flow rate is defined as the product of detrusor contractility against bladder outlet resistance. Deviations from normal urinary flow rate may represent abnormalities of either process. It should not be used alone, but in combination with a determination of bladder residual volume and symptoms to determine the presence of bladder outlet obstruction. To interpret a uroflow, a voided volume of at least 125–150 mL is required for an adequate study. Some normal values are listed here, although clinical scenarios vary widely, with no given cutoff value to document the appropriateness of therapy:

- Males: <40 yr: >22 mL/s; 40–60 yr: >18 mL/s; >60 yr: >13 mL/s
- Female: <50 yr: >25 mL/s; >50 yr: >18 mL/s

A Q_{max} of <15 mL/s does not differentiate between obstruction and bladder hypocontractility. Men with >15 mL/s Q_{max} seem to have a poorer outcome with bladder outlet procedures such as prostatectomy. The study consists of a graphical flow rate pattern, along with values for maximum flow rate, also called peak flow rate (Q_{max}), average flow rate (Q_{ave}), maximum flow time, and total flow time. Various nomograms have been published to aid in the interpretation of uroflow data (Siroky, Abrhams, and Griffiths). A normal graphical flow rate pattern represents a bell-shaped curve. (See also Section II: “Pressure–Flow Studies.”)

REFERENCE

Smith JC. The measurement and significance of the urinary flow rate. *BJUI.* 2008;38(6):701–706.

URINARY RESIDUAL VOLUME (POSTVOID RESIDUAL)

DESCRIPTION Urinary residual volume is the amount of urine present in the urinary bladder immediately after a complete voiding. Also known as postvoid residual, it can assist in differentiating between disorders of emptying and disorders of storage in urinary incontinence. It provides clinical quantitative information on the degree of obstruction in certain conditions, such as BPH, or efficiency of bladder emptying in neurogenic bladder, for example. Chronic high urinary residual volumes can predispose a patient to bladder hypertrophy, ureterovesical reflux, increased intravesical pressure, incontinence, or loss of detrusor muscle tone. Residual volume is measured by US or catheterization and is usually interpreted in the context of uroflowmetry. Treatment of high urinary residual volumes is to treat the underlying cause and to provide bladder drainage.

REFERENCE

Simforoosh N, Dadkhah F, Hosseini SY, et al. Accuracy of residual urine measurement in men: Comparison between real-time US and catheterization. *J Urol.* 1997;158:59–61.

URINARY RETENTION FOLLOWING BRACHYTHERAPY

DESCRIPTION Urinary retention occurs in up to 22% of patients who undergo brachytherapy. Risk factors for postbrachytherapy retention include a large prostate (>36 g) and elevated I-PSS scores prior to treatment. Medical therapy that may aid with retention include corticosteroids, celecoxib, and α-blockers. Clean intermittent catheterization (CIC) is done to allow drainage of urine. Patients who fail medical therapy can safely undergo a cautious transurethral resection of the prostate. A temporary Spanner urethral stent has also ben used.

REFERENCE

Mabjeesh NJ, Chen J, Stenger A, et al. Preimplant predictive factors of urinary retention after iodine 125 prostate brachytherapy. *Urology.* 2007;(703):548–553.

URINARY RETENTION, POSTOPERATIVE

DESCRIPTION Postoperative urinary retention occurs in 4% of surgical patients, although abnormal voiding is seen up to 80% of postop patients. Subclinical obstructive uropathy, overdistention of bladder during operation, sympathomimetic and anticholinergic medication use, and inability to stand after surgery are common causes. Treatment with decompression of the bladder using an indwelling Foley catheter or with clean intermittent catherization should also include early ambulation and a bowel regimen to prevent constipation, as well as limited use of narcotic pain meds.

REFERENCE

Burchko BL, Robison LE. An evidence-based approach to decrease early post-operative urinary retention following urogynecologic surgery. *Urol Nurs.* 2012;(325):260–264, 273.

URINARY TRACT INFECTION (UTI), CATHETER-RELATED (CAUTI, CA-UTI)

DESCRIPTION UTI is the most common hospital-acquired infection in the United States and a major focus to improve patient outcomes. Any passage of a urethral catheter can introduce bacteria into the bladder. Once the catheter is in place, bacteria enter the bladder around the catheter (extraluminal infection) and from intraluminal infection failure of closed drainage or contamination of the urine collection bag. The incidence of bacteriuria in patients with indwelling bladder catheters is directly related to the duration of catheterization. Even with optimal bladder care, 3–10% develop significant bacteriuria daily. Of these patients, 10–25% develop symptomatic UTI (catheter associated UTI or abbreviated CAUTI), and 4% may develop bacteremia. Avoiding unnecessary catheterization, removing the catheter as soon as possible, and appropriate catheter management (closed catheter drainage) are the most effective methods to reduce these infections. Silver-coated urinary catheters have been shown to reduce infections. Patients who require long-term bladder drainage should be managed

with intermittent catheterization, if possible. This approach is associated with a lower rate of bacteriuria and symptomatic UTI than management with long-term indwelling catheterization. Prophylactic antibiotics are not consistently of proven benefit. Catheter-associated urinary tract infection definitions by the CDC have recently been narrowed to exclude asymptomatic bacteriuria. (See alco Section I: "Urinary Tract Infection [UTI], Catheter Associated [CAUTI, CA-UTI].")

REFERENCES

Press MJ, Metlay JP. Catheter-associated urinary tract infection: does changing the definition change quality? *Infect Control Hosp Ediomiol.* 2013;34(3):313–315.

Saint S, Kowalski CP, Kaufman SR, et al. Preventing hospital-acquired urinary tract infection in the US: A national study. *Clin Infect Dis*. 2008;46(2):243–250.

URINE, ABNORMAL COLOR

DESCRIPTION Normal urine is clear and pale to dark yellow due to the presence of urochrome. Foods, medications, metabolic products, and infection can cause abnormal urine colors. (See also Section IV: "Urine Studies."):

- Cloudy: Phosphaturia precipitated phosphate crystals in alkaline (urine), pyuria (UTI), fungal infection, chyluria, lipiduria, hyperoxaluria, diet high in purine-rich foods (hyperuricosuria)
- Colorless: Diabetes insipidus (DI), diuretics, excess fluid intake
- Brown: Nitrofurantoin, metronidazole, aloe, porphyria, bile pigments, myoglobin
- Brown-black: Bile pigments, melanin, acute intermittent porphyria, methemoglobin, medications: Cascara, chloroquine, ferrous salts/ iron dextran, levodopa, methocarbamol, methyldopa, metronidazole, nitrates, nitrofurantoin, quinine, senna, sulfonamides
- Deep yellow: Very concentrated urine, carrots, cascara
- Green-blue: Pseudomonal UTI; Medications: Indigo carmine, methylene blue, amitriptyline , indomethacin , doxorubicin, triamterene, methcarbamol
- Muddy: Pyuria, phosphaturia, chyluria
- Yellow-brown: Medications: Bismuth, chloroquine, cascara, metronidazole, nitrofurantoin, primaquine, senna, sulfonamides
- Orange-yellow: Bile pigments. Medications: Phenothiazines, phenazopyridine, laxatives, vitamin B, rifampin, warfarin, heparin, chlorzoxazone, sulfasalazine
- Pink or red: Hematuria, hemoglobinuria, myoglobinuria, porphyria, anthocyanin in beets, blackberries, rhubarb. Medications: phenolphthalein, rifampin, daunorubicin, doxorubicin, heparin, ibuprofen, methyldopa, phenothiazines, phenytoin, phenylbutazone, rifampin, salicylates, senna
- Tea-colored: Old blood

REFERENCES

Hanno PM, et al. *Clinical Manual of Urology*. 3d ed. New York, NY: McGraw-Hill; 2001:75.

Simerville JA, Maxted WC, Pahira JJ. Urinalysis: A comprehensive review. *Am Fam Physician*. 2006;74(7):1096.

URINE, CYTOLOGY

DESCRIPTION Urine cytology is the microscopic evaluation of shed urothelial cells in the urine. A positive reading suggests the existence of urothelial malignancy. It is highly specific (94% for high-grade tumors), but has low sensitivity (40–60%) especially for low-grade tumors (11%). It is combined with cystoscopy and upper tract imaging for workup of urothelial malignancy. The urine is stained by a multichromatic staining process called Papanicolaou stain (Pap stain). It is used to differentiate different cell types.

REFERENCES

Brown FM. Urine Cytology. It is still the gold standard for screening? *Urol Clin North Am.* 2000;27(1):25–37.

Jones JS. DNA-based molecular cytology for bladder cancer surveillance. *Urology*. 2006;673(Suppl 1):35–45.

URINE, FOAMING

DESCRIPTION Foaming urine is a clinical finding often associated with proteinuria and kidney disease and its observation dates back to Hippocrates. Increasing degrees of proteinuria produce decreasing degrees of surface tension. In addition, the ellipsoid shape of protein molecules at the air–water interface produces increased surface activity. These factors establish an environment in which molecules are unable to reorient in a monolayer due to electrostatic repulsion; this produces foam. Occasionally, foaming is transient and caused by a forceful urination into water in a toilet. (See also Section IV: “Urinalysis and Urine Studies.”)

TREATMENT

- Treat the underlying cause of proteinuria
- Qualitative dipstick analysis, 24-hr urine collection, renal workup

REFERENCE

Diskin CJ, Stokes TJ, Dansby LM, et al. Surface tension, proteinuria, and the urine bubbles of Hippocrates. *Lancet.* 2000;355:901–902.

URINE, ODOR

DESCRIPTION Urine odor is related to the volume, concentration, and composition of a variety of excreted chemicals and physiologic contributions from the urinary system. Normally, dilute urine ranges from odorless to mildly aromatic, often described as nutty or “urinous.” Changes in odor are often temporary and carry little prognostic indication; however, medical conditions can occasionally present with distinct urinary odors, as described below. (See also Section IV: “Urine Studies.”)

Condition	Urine Odor
Diseases	
Cystine decomposition, cystinuria	Sulfured
Dehydration	Strong
Diabetic ketoacidosis	Sweet, fruity odor
Enterovesicular fistula	Feculent
Retained urine	Ammonia-like
Stagnant urine, room temperature urine	Ammonia like
UTI	Pungent
Food and medications	
Asparagus	Pungent, rotten cabbage
Fish oils	Fishy
Vitamin B6	Pungent, vitamin-like
Inborn errors of metabolism	
Glutaric and isovaleric acidemia	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
Hypermethioninemia	Boiled cabbage
Maple syrup urine disease	Maple syrup
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Musty, mousey
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter

REFERENCES

Rezvani I. Metabolic diseases. In: Kliegman R, et al., eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA: Saunders; 2007.

Robertson J, Shikofski N. Inborn errors of metabolism. In: Gunn VL, et al., eds. *The Harriet Lane Handbook*. 17th ed. Elsevier Mosby. Philadelphia, PA: Elsevier Mosby; 2005.

URINE, PARTICLES IN

DESCRIPTION In the gross observation of particulate matter in the urine, differential diagnoses include infection (bacterial, fungal), enterovesical fistula (mucus, feces, or undigested food particles), blood clots from hematuria of any cause, papillary necrosis, ATN, chyluria, urolithiasis, crystalluria, bilharzia (schistosomiasis), urothelial or other carcinoma with sloughing tissue, clumping of excessive urinary cast or protein, postoperative (eg, suture material), or vaginal contamination. The condition can be a normal finding with any form of urinary diversion that uses a bowel segment (usually mucous or sloughed epithelium). Note that a urine sample left standing at room temperature may cause precipitation of phosphate salts. Urine samples that will not be analyzed immediately (in <2 hr) should be refrigerated. Clearing of the specimen after addition of a small amount of acid indicates that precipitation of salts is the probable cause. (See also Section II: “Fecaluria.”)

REFERENCE

McPherson RA, et al. Chapter 28: Basic Examination of Urine. In: McPherson, Pincus, eds. *Henry’s Clinical Diagnosis and Management by Laboratory Methods.* Philadelphia, PA: Elsevier; 2012.

URINOMA (PERINEPHRIC PSEUDOCYST)

DESCRIPTION A collection of urine outside the urinary tract (extravasation), commonly

seen from rupture of the collecting system (usually calyceal rupture) due to high pressures from obstruction (stones, posterior urethral valves, strictures, others), postoperative surgical leak (ureteral anastomosis, collecting system closure, urethral anastomosis, etc.), or traumatic disruption of the urinary tract (iatrogenic, penetrating, or blunt). Leakage of urine into the perirenal or periureteral tissues in excess of an amount that can be absorbed results in urinoma formation. The urine causes lipolysis of surrounding fat, creating a fibrous sac around the extravasated urine.*Perinephric pseudocyst* is the term sometimes used for an urinoma that surrounds the kidney. The urinoma fluid's creatinine level is typically elevated, indicating urine as the source. Urinoma must be distinguished from hematoma, abscess, or lymphocele. Classically, the urinoma is thin-walled and smooth, and the walls tend to enhance secondary to inflammatory neovascularity. In contrast, the walls of abscesses and hematomas tend to be thick and more irregular with even more prominent vascularity. Typically, urinomas demonstrate homogeneous Hounsfield units between –10 and +30 HU, and hematomas and abscesses demonstrate heterogeneous Hounsfield units. Treatment is directed at correcting the cause (relief of obstruction, stenting, or repair of leak). Small urinomas will reabsorb spontaneously, and drainage is not necessary. If the urinoma is large, CT- or US-guided drainage or aspiration can be performed. In perirenal urinomas due to trauma to the kidney, viability of the parenchyma must be assessed by contrast-enhanced CT. If nonviable tissue components extend to the collecting system (suggestive of necrosis), there is an increased risk for continued urine leak and debridement is necessary. (See also Section I: "Renal Trauma, Adult" and (Image ☼).)

REFERENCE

Heikkilä J, Taskinen S, Rintala R. Urinomas associated with posterior urethral valves. *Urology*. 2008;180(4):1476–1478.

URINOTHORAX

DESCRIPTION Urinothorax is rare and refers to the presence of urine in the pleural space. It usually occurs secondary to obstructive uropathy, from the leakage of urine into a retroperitoneal urinoma and then its passage into the pleural space directly or via lymphatics. Cases have been reported in the setting of interventions including percutaneous nephrolithotomy, ESWL, and others. It is classified as a transudate. The diagnosis can be confirmed by finding a pleural fluid-to-serum creatinine ratio >1 (often >10). Relief of obstruction causing the persistent urine leak and thoracentesis or chest tube placement is therapeutic.

REFERENCE

Mora, Silvente CM, Nieto JM, et al. Urinothorax: presentation of a new case as pleural exudate. *South M J*. 2010;103(9):931–933.

URODYNAMICS, INDICATIONS AND NORMAL VALUES

DESCRIPTION A series of investigational tests to assess lower urinary tract function. Usual components include uroflowmetry, cystometry, abdominal pressure monitoring, electromyography, and voiding pressure–flow studies. Through simultaneous measurement of

bladder and abdominal pressures, the detrusor pressure can be inferred and used to interpret neuromuscular events during voiding. UDS can be used to identify contributing factors to voiding dysfunction and assess their relevance, predict consequences of that dysfunction on the upper tracts, to predict the consequences and outcomes of therapeutic intervention, to confirm or understand the effects of interventional techniques, and to investigate the reasons for treatment failure. See table for Normal UDS values in Adults (Image ☼)

Common Urodynamic Indications Include:

- Failure of empiric treatments
- Symptomatic voiding dysfunction prior to beginning incontinence therapy
- Inability to demonstrate incontinence clinically despite subjective patient complaints
- Significant morbidity of proposed incontinence treatment course:
- Following prior surgical therapy for incontinence, following pelvic radiation or radical pelvic surgery
- Known or suspected neurologic disorder that may influence bladder function (ie, Spinal Cord Injury)
- Simpler diagnostic tests have been inconclusive

Normal Urodynamic Values in Adults:

- Volume Voided (mL): 338 ± 234
- Voiding Time (sec): 28 ± 22
- Max Flow (mL/sec): M 24 ± 10, W 30 ± 10
- Average Flow (mL/sec): M 14 ± 5, W 22 ± 14
- Maximum Capacity (mL): M 552 ± 132, W 453 ± 146
- Compliance (mL/cm water): M 56 ± 37, W 71 ± 40
- Postvoid Residual (mL): 20 ± 50

M: men; W: women.

REFERENCES

Lenherr SM, Clemens JQ Urodynamics : with a focus on appropriate indications. *Urol Clin North Am.* 2013;40(4):545–557.

Wyndaele JJ. Normality in urodynamics studied in healthy adults. *J Urol.* 1999;161:899–902.

Winters JC, Dmochowski RR, Goldman HB, et al. Urodynamic studies in adults: AUA/SUFU guideline. *J Urol.* 2012;188(6 Suppl):2464–2472.

UROGENITAL DISTRESS INVENTORY (UDI-6)

DESCRIPTION The UDI-6 is a 6-item questionnaire that assesses LUTS, including incontinence, in women. It is a short form of an original 19-question inventory. All questions are relatively easily understood by patients, and individual responses have been shown to correlate with different types of urinary incontinence (#3 >2 = SUI; #1, #2 >2 = detrusor overactivity; #5 > all other scores = bladder outlet obstruction) (see table on previous page).

Urogenital Distress Inventory–Short Form					
Do you experience and, if so, how much are you bothered by:		Not at All	A Little Bit	Moderately	Greatly
UDI#1	Frequent urination	0	1	2	3
UDI#2	Urine leakage related to urgency	0	1	2	3
UDI#3	Urine leakage related to physical activity	0	1	2	3
UDI#4	Small amounts of urine leakage (drops)	0	1	2	3
UDI#5	Difficulty emptying your bladder	0	1	2	3
UDI#6	Pain or discomfort in the lower abdomen/genitalia	0	1	2	3

REFERENCE

Lemack GE, Zimmern PE. Predictability of urodynamic findings based on the Urogenital Distress Inventory-6 Questionnaire. *Urology*. 1999;533:461–466.

UROLITHIASIS, DRUG INDUCED

DEFINITION

Drug-induced renal calculi represent about 1–2% of all renal calculi. Drugs used for the treatment of HIV have become the most frequent cause of drug-containing urinary calculi. Protease inhibitors used in the management of HIV are documented to induce kidney stones, especially indinavir and atazanavir, and more recently darunavir. Triamterene, topiramate and zonisamide (anticonvulsants), methotrexate, guaifenesin/ephedrine, ceftriaxone, trimethoprim-sulfamethoxazole, vitamin D, and calcium supplements are also responsible for some cases of drug-induced urolithiasis. Patients with triamterene-containing stones are more likely to have a prior history of stone disease, suggesting that metabolic predisposition is an important risk factor. Renal calculi have been noted in up to 64% of low–birth-weight infants receiving furosemide loop diuretic therapy. Laxative abuse should be suspected in patients who form ammonium acid urate stones in the absence of bowel disease or urinary tract infection. Loop diuretics, carbonic anhydrase inhibitors, and abused laxatives can cause metabolic abnormalities that facilitate the formation of stones.

REFERENCES

Izzedine H, et al. HIV medication-based urolithiasis. *Clin Kidney J*. 2014;7(2):121–126.
Matlaga BR, Shah OD, Assimos DG. Drug-induced urinary calculi. *Rev Urol*. 2003;5(4):227–231.

UROLITHIASIS, INDINAVIR AND OTHER PROTEASE INHIBITORS

DESCRIPTION Drug-induced renal calculi represent 1–2% of all renal calculi. In the last decade, drugs used for the treatment of HIV-infected patients have become the most frequent cause of drug-containing urinary calculi. Among these agents, protease inhibitors (PIs) are well known to induce kidney stones, especially indinavir and atazanavir, and more recently darunavir. A spectrum of asymptomatic crystalluria and renal colic secondary to urolithiasis, with or without dysuria or urgency, seen in patients who are HIV infected and being treated with indinavir and other PI's. Indinavir stones are not radiopaque nor are they always identified on unenhanced CT imaging. A high index of suspicion is necessary to make the diagnosis and stones may appear as a filling defect on contrast enhanced imaging. (See Section I: "HIV/AIDS, urologic considerations" and Section II: "HIV nephropathy.")

REFERENCE
Izzedine H, et al. HIV medication-based urolithiasis *Clin Kidney J*. 2014;7(2):121–126.

UROLITHIASIS, INFECTIOUS (STRUVITE)

DESCRIPTION Composed of magnesium, ammonium, and phophate mixed with carbonate; struvite stones directly correlate with the presence of urease-producing bacteria and active UTI. Associated with a urinary pH of >7.2, which causes struvite crystallization. They usually undergo rapid growth and may result in replacement of the entire pelvis with a stone. (See also Section I: "Urolithiasis, Staghorn" and Section II: "Struvite.")

CAUSES
- Foreign body in the urinary tract
- Neurogenic bladder
- Urinary diversion
- LUTS
- Indwelling catheter

REFERENCE
Vella M, Karydi M, Coraci G, et al. Pathophysiology and clinical aspects of urinary lithiasis. *Urol Int*. 2007;79(Suppl I):26–31.

UROLITHIASIS, MATRIX

DESCRIPTION Also called *matrix stone, matrix nephrolithiasis,* or *matrix calculus* in the literature, this rare renal calculus has been described as being composed of coagulated mucoids with little crystalline component. Found mostly in individuals with infection due to urease-producing organisms such as *Proteus*, matrix calculi can be confused with uric acid calculi because they are radiolucent. Matrix calculi, however, are usually associated with alkaline urine from a UTI, whereas uric acid calculi usually form in acidic sterile urine. Standard treatment techniques such as ureteroscopic lithotripsy are used. (See also Section I: "Urolithiasis, Adult, General.")

REFERENCE
Kim SH, Lee SE, Park IA. CT and ultrasound features of renal matrix stones with calcified center. *J Comput Assist Tomogr*. 1996;20(3):404–406.

UROLITHIASIS, MELAMINE

DESCRIPTION An increased incidence of kidney stones and renal failure recently reported in China are believed to be associated with ingestion of infant formula contaminated with melamine. Melamine (cyanuric acid, ammelide, ammeline) has industrial use as a resin or adhesive, and has been deliberately added to raw milk to boost its protein content. Although the mechanism is not clear, melamine is almost completely excreted by the kidney and appears to interact with cyanuric acid (a by-product or associated impurity) to form crystals. Low solubility promotes precipitation in renal tubules and causes progressive blockage and significant renal degeneration.

TREATMENT

- Immediately discontinue use of melamine-containing food products.
- Medically monitor renal function, fluid balance, and electrolyte status.
- Alkalize the urine.
- Treat acute kideny injury (AKI) if indicated; use blood or peritoneal dialysis.
- Consider surgical pyelolithotomy in refractory cases.

REFERENCES

World Health Organization. Melamine and cyanuric acid: Toxicity, preliminary risk assessment and guidance on levels in food 25 Sept 2008). Available online at: www.who.int/foodsafety/fs_management/melamine.pdf.

Yang L, Wen JG, Wen JJ, et al. Four years follow-up of 101 children with melamine-related urinary stones. *Urolithiasis*. 2013;41(3):265–266.

UROLITHIASIS, METHOTREXATE

DESCRIPTION Methotrexate is an anti-folate used to treat a wide variety of diseases including: Cancer, rheumatoid arthritis, lupus, ectopic pregnancy, and psoriasis. More than 90% of the drug is cleared in the urine. Drug and its metabolites are poorly soluble in acidic pH and can precipitate crystalline formation and subsequent tubular obstruction. Medication can also lead to an increase in uric acid levels in the body. Extremely rare with only a few reports of renal calculus to the FDA from using this medication. (See also Section I: "Urolithiasis, Adult, General" and Section II: "Urolithiasis, Drug Induced.")

TREATMENT

- Urine alkalinization
- Hydration to induce high urine flow rates

REFERENCE

Yarlagada SG, Perazella MA. Drug-Induced Crystal Nephropathy: an Update. *Expert Opin Drug Saf*. 2008;7(2):147–158.

UROLITHIASIS, TRIAMTERENE

DESCRIPTION Renal calculus consisting either completely or partially of triamterene, a potassium-sparing diuretic often used with hydrochlorothiazide in the treatment of hypertension. Promotion of nucleation and growth of renal calculi, especially calcium oxalate monohydrate, has been shown to occur from triamterene and its metabolites. They are usually radiopaque. Although rare, they usually occur in a patient with a history of urolithiasis. (See also Section II: "Urolithiasis, Adult, General.")

TREATMENT

- Avoid use of triamterene in patients with a history of urolithiasis.
- Discontinue use of triamterene in patients with triamterene urolithiasis.

REFERENCE

Carr MC, Prien EL Jr, Babayan RK. Triamterene nephrolithiasis: Renewed attention is

warranted. *J Urol*. 1990;1446:1339–1440.

UROLITHIASIS, XANTHINE

DESCRIPTION Renal calculus composed of xanthine are usually associated with hereditary xanthinuria, an autosomal recessively inherited inborn error of metabolism characterized by a deficiency of xanthine oxidase. Other causes include allopurinol use in patients with Lesch–Nyhan syndrome, APRT deficiency, or endogenous uric acid overproduction. Xanthine calculi can be confused with uric acid calculi because they are both radiolucent. Xanthine calculi, however, are associated with low serum uric acid levels. Treat with high fluid intake and standard lithotripsy or stone removal techniques. (See also Section II: "Urolithiasis, Adult, General.")

REFERENCE

Cameron JS, Moro F, Simmonds HA. Gout, uric acid, and purine metabolism in paediatric nephrology. *Pediatr Nephrol*. 1993;7:105–118.

URORADIOLOGY SIGNS

DESCRIPTION Uroradiology is rich with descriptions of imaging findings, often metaphorical, which have found common usage in the day-to-day practice of genitourinary radiology. (See Section VII: "Reference Tables: Uroradiology Signs.")

REFERENCE

Dyer RB, Chen MY, Zagoria RJ. Classic Signs in Uroradiology. *RadioGraphics*. 2004;24:S247–S280.

UROTHELIAL DYSPLASIA

DESCRIPTION Urothelial dysplasia represents an early morphologic manifestation of progressive alterations between normal urothelium and carcinoma in situ (CIS). Changes in cellular architecture restricted to the intermediate and basal cell layers. A flat lesion with changes including: Loss of nuclear polarity, nuclear enlargement, nucleolar prominence, nuclear membrane irregularity, and nuclear hyperchromasia. Should only be diagnosed when changes cannot be attributed to inflammation and there is not marked cytologic atypia of CIS. Urothelial dysplasia has the possibility of progressing to carcinoma.

REFERENCE

Hodges KB, Lopez-Beltran A, Davidson DD, et al. Urothelial dysplasia and other flat lesions of the urinary bladder: Clinicopathologic and molecular features. *Human Pathology*. 2010;41:155–162.

VACTERL/VATER ASSOCIATION

DESCRIPTION Also called VATER syndrome, a congenital abnormality involving defects in ≥3 of the following: Vertebral defects, anal atresia, cardiac defects, esophageal atresia and/or tracheo-esophageal fistula, renal dysplasia, and limb defects, especially radial limb defects.

REFERENCE

Botto LD, Khoury MJ, Mastroiacovo P, et al. The spectrum of congenital anomalies of the ATER association: An international study. *Am J Med Genet.* 1997;71:8–15.

VAGINAL AGENESIS

DESCRIPTION Absence or failure of formation of the vagina. Occurs in 1 in 4,000 to 1 in 5,000 female births. 50% of the time, vaginal agenesis is associated with renal abnormalities, such agenesis or ectopia. Uterine abnormalities are commonly associated as well. Etiology has been theorized to be a defect in the embryologic development of a single mesonephric duct. The patient usually comes to attention due to primary amenorrhea. Surgical reconstruction with the use of grafts or flaps is the treatment of choice.

REFERENCE

Marshall FF. Vaginal abnormalities. *Urol Clin North Am.* 1978;(51):155–159.

VAGINAL ATROPHY/VULVOVAGINAL ATROPHY, UROLOGIC CONSIDERATIONS

DESCRIPTION Vaginal atrophy/vulvovaginal atrophy (VVA) is thinning and inflammation of the vaginal walls secondary to lack of estrogen. Most common following menopause, the condition affects 50% of that population, but may also occur with breast-feeding and other low estrogen states. The condition presents as vaginal burning and itching with or without discharge; often linked with dyspareunia. It is often associated with increased urinary frequency, urgency, and/or dysuria. Increased number of UTIs and urinary incontinence have also been reported.

SYNONYMS

- Atrophic vaginitis
- Genitourinary atrophy

TREATMENT

- 1st-line therapy for symptomatic VVA: Nonhormonal lubricants during intercourse and, as indicated, regular use of long-acting vaginal moisturizers.
- Estrogen therapy is appropriate for moderate or severe symptomatic VVA and for milder symptoms unresponsive to initial treatment, including low-dose vaginal or systemic estrogen. Multiple factors figure into decision making for women with a history of breast or endometrial cancer: Patient preference, need, and understanding of potential risks, as well as consultation with the patient's oncologist if estrogens are to be used.
- Systemic estrogen therapy: Pill, patch, gel (note must use with progestin to avoid uterine

lining dysplasia). In general, a progestogen is not indicated for use with low-dose vaginal estrogen.
- Ospemifene is an option for dyspareunia.

REFERENCES

Gass MLS, et al. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause.* 2013;20:888–902.
Harms RW, et al. Vaginal atrophy. *MFMER*. 2006;(95):1–10.

VAGINAL DISCHARGE, UROLOGIC CONSIDERATIONS

DESCRIPTION Fluid flowing from the vaginal opening, which can be physiologic or pathologic. Timing, color, consistency, odor, and associated symptoms are all important aspects of the evaluation. (See also Section I: "Vaginitis/vulvovaginitis" and Section III: "Vaginal Discharge Algorithm.")

CAUSES
- Noninfective: Physiologic uterine sloughing, cervical ectopy, retained foreign bodies (eg, tampon), vulval dermatitis, urethral diverticulum, sexual abuse
- Nonsexually transmitted infective: Bacterial vaginosis, candidal infections
- Sexually transmitted infective: *C. trachomatis, N. gonorrhoeae, Trichomonas vaginalis* (Image)

REFERENCES

Elder JS. This month in pediatric urology. *J Urol.* 2006;1766):2333–2334.
Spence D. Vaginal discharge. *BMJ*. 2007;335:1147–1151.

VAGINAL DUPLICATION

DESCRIPTION A rare abnormality in embryologic development that results in duplication of the vagina. It is caused by failure of a primitive septum in the uterovaginal canal to regress or by abnormalities in the fusion of paramesonephric ducts during wk 8–9 of embryologic development of the upper vagina. The lower vagina develops from the urogenital sinus when the sinovaginal bulbs fuse. Abnormalities in the fusion can result in different vaginal abnormalities, including duplication. Presenting symptoms can include dysmenorrhea at menarche or a lower abdominal mass. Surgical correction of the septum is the treatment of choice for vaginal duplication.

REFERENCE

Burbige KA, Hensle TW. Uterus didelphys and vaginal duplication with unilateral obstruction presenting as a newborn abdominal mass. *J Urol.* 1984;132(6):1195–1198.

VAGINAL FUSION

DESCRIPTION Sometimes referred to as *vulvar fusion*, *vulvar atresia*, or *labial agglutination,* this is a complete or partial adherence of the labia minora. Usually presents between 3 mo and 4 yr of age with an incidence of 3.3%. The condition predisposes patients to

asymptomatic bacteriuria and recurrent UTIs. Rarely, near-complete fusion can cause urinary outlet obstruction with resultant bladder distention and/or hydronephrosis. Causes include diaper rash, infections, vulvovaginitis, irritants, mechanical trauma, and sexual abuse.

Treatment is initially observation, as spontaneous resolution can be seen. Medical treatment is topical estrogen cream for 4–8 wk, followed by 1–3 mo of topical petroleum jelly application to minimize recurrence.

REFERENCE

Leung AK, Robson WL, Kao CP, et al. Treatment of labial fusion with topical estrogen therapy. *Clin Pediatr*. 2005;44:245–247.

VAGINAL MASS, NEWBORN

DESCRIPTION Rare interlabial or periurethral lesions are found in young girls, each with strikingly similar gross appearances among the different etiologies listed below. Clinical exam should note exact location of lesion, urethral location, and urine flow. Workup depends on exam, although voiding cystourethrogram is usually warranted.

CAUSES

- Hydrocolpos (imperforate hymen)
- Paraurethral cyst
- Prolapsed ectopic ureterocele
- Rhabdomyosarcoma of the vagina
- Urethral polyp
- Urethral prolapse

REFERENCE

Nussbaum AR, Lebowitz RL. Interlabial masses in little girls. *Am J Roentgenol*. 1983;141(1):65–71.

VAGINAL PESSARIES, UROLOGIC CONSIDERATIONS

DESCRIPTION A passive intravaginal device used to maintain the correct anatomic position of the pelvic organs and aid in urinary continence. The overall prevalence of incontinence in individuals >65 is ~30%. Pessaries provide a noninvasive management option for that subset of patients with stress urinary incontinence (SUI). Despite a wide range in published results, when combined with pelvic floor muscle rehabilitation (ie, Kegel exercise, biofeedback), patients using a pessary should expect complete resolution in <20% of cases, but vast improvement of symptoms 50–75% of the time. This may be used as a final treatment mechanism in patients at high operative risk, or as a bridge to surgical correction of laxity in the pelvic anatomy.

REFERENCE

Junemann KP. The management of female stress urinary incontinence: II. The use of devices. *BJU Int*. 2001;87:449–455.

VAGINAL PROLAPSE

DESCRIPTION Disruption of the neuromuscular, ligamentous, or fascial components involved in normal vaginal support, resulting in the externalization of a portion of the vaginal canal. Despite a complex anatomic framework, implicated causative etiologies include the uterosacral and cardinal ligaments, as well as the endopelvic fascia. Urologically notable is the association with intraoperative ureteral injury during surgical correction (11%) and postoperative association with SUI once the pelvic anatomy is restored. (See also Section I: "Pelvic Prolapse [Cystocele and Enterocele].")

- Cystocele (bladder into vagina)
- Enterocele (small intestine into vagina)
- Rectocele (rectum into vagina)
- Urethrocele (urethra into vagina)
- Uterine prolapse (uterus into vagina)
- Vaginal vault prolapse (vaginal roof through vagina)

TREATMENT

- Abdominal sacrocolpopexy: Anterior and posterior grafts bridging vaginal wall to the sacral promontory via an abdominal incision
- Vaginal vault suspension: Apogee system (artificial recreation of the cardinal ligaments)
- Intravaginal sling plasty: Polypropylene sling recreation of the suspensory ligament
- Sacrospinous fixation: Elevation and fixation of vaginal apex to sacrospinous ligaments
- Iliococcygeal or uterosacral suspension: Via vaginal incision and fixation to surrounding structures

REFERENCE

Biller DH, Davila GW. Vaginal vault prolapse. *Clev Clin J Med.* 2005;72(4):S12–S19.

VAGINOSIS

DESCRIPTION The most common type of vaginal infection, resulting from an imbalance between the standard vaginal flora (*Lactobacillus* sp.) and potentially harmful organisms (typically *Gardnerella vaginalis, Mobiluncus, Bacteroides*, and *Mycoplasma*). Symptoms include a foul or "fishy" odor, milky white or gray discharge, and vaginal irritation especially prominent after sex. Diagnosis can be confirmed by elevated vaginal pH (typically pH >4.5), a positive "whiff test" malodorous/fishy odor when secretions are combined with 10% (KOH), or by the presence of "clue cells" epithelial cells (coated with bacteria) on microscopic normal saline wet mount. (See also Section I: "Vaginitis/vulvovaginitis" and Section II: "Trichomonas." (Image ☼))

TREATMENT

- Oral metronidazole 500 mg PO BID for 7 days
- Vaginal metronidazole (MetroGel) 1 applicatorful BID for 7 days
- Tinidazole (Tindamax) 2 g PO once a day for 2 days *OR* 1 g PO once a day for 5 days
- Avoid douches, feminine hygiene sprays

REFERENCE

Austin NM, Meyn LA, Hillier SL. Susceptibility of vaginal bacteria and tinidazole. *Anaerobe.* 2006;12:227–230.

VALSALVA MANEUVER

DESCRIPTION A maneuver affected by a forced expiratory effort against a voluntarily closed airway, which causes increased intrathoracic and intra-abdominal pressure and impedes venous return to the right atrium. The maneuver may increase the degree of varicocele dilatation, thus aiding in diagnosis. It can also be used to measure the pressure required to cause leakage in the absence of a bladder contraction, which correlates with the degree of urinary incontinence (called the "leak point pressure"). The Valsalva maneuver can also be used to aid in micturition in those with hypotonic bladders by increasing intravesical pressure. (See also Section II: "Leak Point Pressure.")

REFERENCE

Desautel MG, Kapoor R, Badlani GH. Sphincteric incontinence: The primary cause of post-prostatectomy incontinence in patients with prostate cancer. *Neurourol Urodyn.* 1997;16(3):153–160.

VANDERBILT CYSTECTOMY INDEX (VCI)

DESCRIPTION VCI is a health-related quality-of-life questionnaire for patients following radical cystectomy and urinary diversion. It consists of the 45 questions from the Functional Assessment of Cancer Therapy-General (FACT-G) as the core questionnaire. An additional 17 items were added from 3 other validated questionnaires designed to measure disease and treatment specific health outcomes. 4 from FACT-Bladder Cancer, 6 from FACT – Colorectal and 7 from the Functional Assessment of Incontinence Therapy-Urinary.

REFERENCE

Cookson MS, Dutta SC, Chang SS, et al. Health related quality of life in patients treated with radical cystectomy and urinary diversion for urothelial carcinoma of the bladder: Development and validation of a new disease specific questionnaire. *J Urol.* 2003;170(5):1926–1930.

VANISHING TESTIS SYNDROME

DESCRIPTION A condition in which a normal genotypic 46, XY male has absent or rudimentary testes with otherwise normal differentiation of internal and external structures. Etiology is vascular compromise in utero, infection in utero, or testicular torsion in utero. Infertility is inevitable, despite aggressive testosterone replacement therapy to induce virilization.

SYNONYMS

- Bilateral anorchia
- Gonadal agenesis
- Testicular regression syndrome
- XY agonadism

TREATMENT
TRT to induce virilization

REFERENCE
Gong M, et al. Testicular torsion with contralateral vanishing testis. *Urology*. 1996;(482):306–307.

VAS DEFERENS, CALCIFICATION (CVD)

DESCRIPTION CVD is a rare finding primarily detected through radiologic exams. It usually presents asymptomatically. A majority of the patients with calcification of the vas deferens are diabetics in their 5th–6th decades. For these diabetic patients, CVD has a bilateral and symmetrical presentation. In addition, a minority of patients will present with post-inflammatory CVD, which usually has a unilateral and segmental presentation (Image ☼).

REFERENCE
Banerji S, Devasia A. Calcified Vasa Deferentia. *N Engl J Med.* 2011;364:2043

VAS DEFERENS, OBSTRUCTION

DESCRIPTION Genital duct obstruction is a potentially curable cause of male infertility that may be bilateral or unilateral and may occur at multiple locations (epididymal, vasal, or ejaculatory duct). The prevalence is 7–12% of infertile men. Unilateral obstruction should not adversely affect fertility, although it has been identified as a risk factor for developing antisperm antibodies. Complete obstruction yields the pathognomonic clinical findings of acidic, fructose-negative, low-volume ejaculate azoospermia. Diagnostic modalities include static imaging (TRUS, MRI, seminal vesicle aspiration) and dynamic imaging with vasography, seminal vesiculography testing. (See also Section I: “Infertility” and “Vas Deferens, Congenital Absence.”)

CAUSES
- Congenital: Malformations, congenital bilateral absence of the vas deferens (CBAVD), wolffian duct anomalies/agenesis
- Acquired: Infection, iatrogenic injury, vasectomy

TREATMENT
- Varies with etiology and location of obstruction
- Ejaculatory duct: Transurethral resection, balloon dilation, antegrade seminal vesicle lavage, laser incision, vasoepididymostomy
- Vasectomy (reversal vasovasostomy)
- Sperm retrieval (aspiration vs. open biopsy) with IVF/ICSI

REFERENCE
Jarow JP. Male infertility. In: Wein AJ, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia, PA: Saunders; 2007.

VASCULITIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Vasculitis is a common reaction to injury caused by a multitude of different processes, including autoimmunity, infection, and hypersensitivity. Various types include Henoch–Schönlein purpura, PAN, hypersensitivity angiitis, Wegener granulomatosis, and lymphomatoid granulomatosis. A very strong correlation exists between the presence of anti-neutrophil cytoplasmic antibodies (ANCA) and the various types of systemic vasculitis that cause crescentic glomerulonephritis and/or focal necrotizing glomerulonephritis. Depending on the type of vasculitis, patients present with different signs and symptoms. Furthermore, some types can progress to chronic renal failure. However, upon renal biopsy, similar pathologic presentations are demonstrated. Can also result in renal hemorrhage. (See also Section II: "Henoch-Schönlein Purpura.")

TREATMENT

- ANCA titers have proved to be extremely useful in the management of these patients. They are a help in diagnosis, and even more important as a guide to maintenance immunosuppressive therapy.
- Cytotoxic agents and corticosteroids are effective, depending on the type of vasculitis.

REFERENCE

Rees AJ. Vasculitis and the kidney. *Curr Opin Hephrol Hypertens*. 1996;(53):273–281.

VASECTOMY REVERSAL, GENERAL CONSIDERATIONS (VASOVASOSTOMY)

DESCRIPTION Usually accomplished with a 2-layer microsurgical vasovasotomy (8 10-0 nylon mucosal sutures, 10 9-0 nylon muscular sutures). Although surgical reversal of vasectomy can be technically performed on most patients, operative decision-making requires workup. Gynecologic and fertility evaluation of the female partner should be performed. Epididymal or testicular sperm aspiration combined with IVF/ICSI should be discussed. Results with microsurgical repair reach 85–90% success sperm (appearing in semen), with postprocedural conception rates at 50–70%.

TREATMENT

- Vasovasostomy (when some component of sperm are present, grade I–IV vas fluid)
- Vasoepididymostomy (when no sperm are present in vas fluid)
- Postoperative scrotal support with abstinence for 2 wk

REFERENCE

ASRM Practice Committee. Vasectomy Reversal. *Fertil Steril.* 2006;86(4):S268–S271.

VASOGRAPHY, TECHNIQUE AND INDICATIONS

DESCRIPTION Vasography is the radiologic procedure used to evaluate patency of the vas deferens and ejaculatory ducts. The procedure involves injection of the contrast material into the vas deferens. Recently, seminal vesicle aspiration and vesiculography mainly replaced vasography for the diagnosis of EDO. Therefore, the primary indication for vasography is the assessment of vasal obstruction within the inguinal vas deferens. Inguinal obstruction of the vas deferens should be suspected in patients with azoospermia and previous surgeries,

including orchiopexies, hernias repair, ureteral surgery, and even appendectomy (iatrogenic injuries to the vas deferens). 4 techniques for vasography have been described: Vasopuncture, vasotomy, retrograde catheterization via cystoscopy and transrectal puncture. Isolated vasography (by vas puncture) is rarely performed because of the risk of subsequent vasal scarring; it is usually a part of microsurgical reconstructive procedure. For this reason, it is not indicated to perform vasography at the time of testicular biopsy with the findings of normal spermatogenesis. If open vasography is planned, the bladder should be catheterized with a Foley catheter and balloon inflated with air to outline the bladder neck area. After scrotal exploration, the vas deferens is identified and isolated at the junction of the straight and convoluted portions. Under the operating microscope, the vasal sheath is incised vertically and vasal vessels preserved. A short segment of the vas is cleaned and hemitransected using a 15.0 ultrasharp knife until the lumen is revealed. The sheath of 25-gauge angiocatheter is inserted into the abdominal portion of the vas deferens. The vas is then flushed with normal saline (the term *vasogram* at this point is a misnomer, since no contrast is injected and no x-rays are taken). If injection is easily achieved with minimal pressure, the vas deferens is patent. In case of resistance to the injection, the formal vasogram is performed with 1:2 diluted nonionic contrast, while gentle pressure is applied to the Foley catheter to prevent reflux of the contrast into the bladder and the table is put in the slightly reversed Trendelenburg position. If obstruction is confirmed at the level of ejaculatory duct, methylene blue may be added to the contrast since it enables the control of the depth and efficacy of transurethral resection of the ejaculatory duct.

The application of a 32-gauge soft radiopaque epidural catheter has been described for the vasography. The catheter is advanced down the vas deferens, and the vasogram is performed. Because the catheter is radiopaque, its position in the vas can be confirmed prior to injection. If needed, the catheter could be advanced further to obtain better details. If no further microsurgical reconstruction is performed, the vasotomy site is closed with a microsurgical technique using 10-0 monofilament Prolene or nylon for mucosa, 9-0 nylon for muscularis, and 6-0 Prolene for the adventitial layer.

The puncture technique employs a 30-gauge lymphangiogram needle placed through the wall of the vas deferens in the direction of the prostate. This technique, also less invasive, may be associated with a higher risk of creating submucosal false passages, with subsequent scarring and obstruction. Complications include stricture of the vas deferens, hematoma, injury to the vasal blood supply, and sperm granuloma.

REFERENCES

Kolettis PN, et al. Prediction of vasography outcomes based on clinical and laboratory data. *Fertil Steril*. 2005;84(1):S219–S220.

Turek PJ. Vasography, seminal vesicle aspiration and testicular biopsy. *Diagn Surg*. 2008;1–16.

VENOUS LEAK SYNDROME

DESCRIPTION Venous leakage is a common cause of vascular impotence due to veno-occlusive dysfunction. Possible leak sites are the superficial and deep dorsal veins, cavernosal venous system, and glans or corpus spongiosum. The majority of patients have >1 leak site.

Diagnosis can be demonstrated by pharmacocavernosography (caversonography performed after the intracorporal injection of papaverine or phentolamine).

CAUSES

- Congenital
- Iatrogenic
- Neovascularity associated with inflammatory reactions secondary to stricture disease or Peyronie disease

TREATMENT

- Surgical correction
- Combination of pharmacologic injection therapy with a venous constriction system or a vacuum device

REFERENCE

Shabsigh R, Fishman IJ, Toombs BD, et al. Venous leaks: Anatomical and physiological observations. *J Urol.* 1991;146:1260.

VESICULOBULLOUS LESIONS, EXTERNAL GENITALIA

DESCRIPTION Dermatologic lesions on the external genitalia mandate screening for STI/STDs. They may be painful or painless, single or multiple, exophytic or ulcerated, confined to the genitalia or occurring elsewhere on the body. Treatments vary widely based on etiology, and may require partner treatment in the case of STDs. (See also Section I: "Penis, Lesion, General"; "Sexually Transmitted Disease.")

Vesiculobullous Lesions, External Genitalia

Etiology	Examples
Infective, Nonsexually transmitted	**Balanitis/posthitis:** Ulcerated lesion preceded by 2–3 days of irritation, usually associated with foul discharge and edema. **Folliculitis/furunculosis:** Hair follicle infection marked by pointed lesions with central pustules; usually enlarge and rupture leaving edema/erythema for days to weeks. **Pediculosis pubis:** Parasitic infestation (lice) with red, itchy papules and white/gray eggs visible attached to hair. **Scabies:** Mite infestation. Organisms burrow under skin causing crusted papules 1–10 cm at the genitalia with satellite lesions on the extremities. **Tinea cruris:** Superficial fungal infection (jock itch) with raised, scaling patches on the inner thigh or groin with severe pruritus.
Infective, Sexually transmitted	**Chancroid:** *H. ducreyi* infection (with 1 or more) painful, deep, ulcerated lesions on the genitalia; bleeds easily with marked lymphadenopathy. **Genital herpes:** HSV (usually 1 or 2) produces fluid-filled vesicles on genitals and/or mouth or anus, which may rupture leaving shallow painful ulcers. Associated with prodrome of numbness and tingling. **Genital warts:** HPV causes painless pink/red pedunculated lesions varying in size; may have cauliflower appearance and become malodorous. **Syphilis:** 2–4 wk following *T. pallidum* infection, ≥1 small, red, fluid-filled papules erupt to form a painless deep ulcer with a clear base; may become systemic and is associated with unilateral lymphadenopathy.
Noninfective	**Bowen disease:** Brownish red, raised, scaly plaque with well-defined borders; possible ulceration; premalignant. **Leukoplakia:** White, scaly patches on glans/prepuce with skin thickening and fissures; premalignant. **Penile cancer:** Painless, enlarging wartlike lesion on glans or foreskin; occasionally associated with pain and malodorous discharge. **Urticaria:** Systemic allergic reactions may present with genital hives; erythematous, intensely pruritic with systemic eruption. **Drug eruption:** Similar in appearance to urticaria; associated with phenolphthalein, barbiturates, tetracyclines, and sulfonamides.

REFERENCE

Springhouse. *Handbook of Signs and Symptoms*. 3rd ed. Philadelphia, PA: Lippincott; 2005.

VIDEOURODYNAMICS

DESCRIPTION A technique in which urodynamic studies are performed at the same time as fluoroscopy of the lower urinary tract. The cystometry and pressure–flow studies are conducted in the same manner as regular urodynamics. The only difference is the addition of contrast and fluoroscopy. Radiation exposure is usually limited to <20 s. Adding simultaneous video enhances the evaluation of all patients, especially for more complex urodynamic problems. Videourodynamics is helpful when results from simple urodynamics do not agree with the clinical scenario. In complex bladder outlet obstruction, this technique can identify whether it occurs at the bladder neck, prostatic urethra, or distal sphincter. It is also helpful in the identification of bladder neck dysfunction in young men with voiding problems and in neurogenic patients with dyssynergia of the distal sphincter. In incontinence evaluation, videourodynamics can help identify the presence and degree of vesical neck hypermobility, degree of proximal urethral weakness, and degree and type of cystocele present. In neurogenic bladders, simultaneous video screening aids in diagnosing proximal and distal sphincter dyssynergia and demonstrates the presence of reflux and bladder diverticula. The presence of reflux, bladder and urethral diverticula, fistula, and stones can be identified and characterized. (See also Section II: “Urodynamics.”)

REFERENCE

McGuire EJ, Cespedes RD, Cross CA, et al. Video-urodynamic studies. *Urol Clin N Am*. 1996;23(2):309–321.

VILLOUS ADENOMA, BLADDER/URETHRA

DESCRIPTION Villous adenomas of the bladder and urethra are rare and histologically identical to those found in the colon. These tumors are more frequently found in the urachus at the dome of the bladder. On cystoscopy, these villous adenomas appear as exophytic papillary masses. Histologically, villous adenomas are complex branching papillary structures lined by a pseudostratified epithelium containing goblet cells. Often, this tumor is associated with cystitis glandularis. Villous adenoma of the urethra has been reported in both males and females. In males, villous adenoma may be associated with urinary retention, hematuria, and difficulty in micturition. In females, it may be less symptomatic and present with a slowly growing mass in the urethra. When villous adenomas are found, a primary intestinal tumor must be ruled out. After resection of the adenoma, the patient must be followed for recurrence or malignancy because their behavior is unpredictable. Diagnosis is made with urine cytology, cystogram, cystoscopy, or biopsy. Treatment is transurethral resection with selective cystectomy.

REFERENCE

Channer JL, Williams JL, Henry L. Villous adenoma of the bladder. *J Clin Pathol*. 1993;46(5):450–452.

VIMENTIN, STAINING

DESCRIPTION Monoclonal antibodies can be used to identify cell products or surface markers by directing antibodies against intermediate filaments. This facilitates the classification of otherwise poorly differentiated tumors. Vimentin is the predominant intermediate filament in mesenchymal cells, and it is found in all fibroblasts. Vimentin is less specific than the other intermediate filaments in immunocyto-chemistry because certain epithelial tumors (eg, RCC) may coexpress keratin and vimentin. (See also Section II: "Immunohistochemical Staining, Urologic Considerations.")

REFERENCE

Cotran R, et al., eds. *Pathologic Basis of Disease*. 5th ed. Philadelphia, PA: Saunders; 1995:299.

VINCENT CURTSY

DESCRIPTION Holding maneuver used by children to postpone voiding or suppress urinary urgency. Vincent curtsy is performed by squatting with a hand or heel pressed firmly into the perineum. Other common holding maneuvers including standing on tiptoe or forceful crossing of the legs (Image ☼).

REFERENCE

Vincent SA. Postural control of urinary incontinence. The curtsy sign. *Lancet*. 1966;2:631.

VITILIGO, UROLOGIC CONSIDERATIONS

DESCRIPTION A depigmentation of the skin in which sharply bordered patches become white. This is distinct from postinflammatory skin depigmentation in that there is no preceding inflammatory process. The etiology is probably autoimmune, and it is estimated to involve the external genitalia only in 0.3% of the adult male population. Treatment is optional and can include steroids, UV light, skin grafting, and cosmetic covering.

REFERENCES

Falabella R, Barona MI. Update on skin repigmentation therapies in vitiligo. *Pigment Cell Melanoma Res*. 2009;22(1):42–65.

Margolis DJ. Cutaneous diseases of the male external genitalia. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders; 1998.

VOIDING DIARY FREQUENCY VOLUME CHART (FVC)

DESCRIPTION A tool often used in association with pad testing to document the nature and severity of incontinence. A data sheet, maintained by the patient over a representative 24-hr period, typically documents the following:

- Time of urge to void
- Strength of urge or pain
- Time of actual void
- Voided volume
- Incontinence stress, urge, or unaware

- Amount of leakage small, medium, large

(See Section VII: "Voiding Diary.")

REFERENCE

Stav K, Dwyer PL, Rosamilia A. Women overestimate daytime urinary frequency: The importance of the bladder diary. *Urology*. 2009;18(15):2176–2180.

VOIDING SYMPTOMS, DEFINITIONS (ICS DEFINITIONS)

DESCRIPTION The ICS in 2002 published updated guidelines to define and categorize LUTS into 3 main groups including storage, voiding, and postmicturition, as defined and subdivided here:

- **Storage symptoms** are experienced during storage phase of bladder:
  - Increased day-time frequency
  - Nocturia: Complaint that individual wakes up more than once to void
  - Urgency: Complaint of sudden compelling desire to void that is difficult to defer
  - Urinary incontinence: Complaint of any involuntary loss of urine
- **Voiding symptoms** are experienced during voiding phase:
  - Slow stream
  - Splitting or spraying of urine stream
  - Intermittency during micturition
  - Hesitancy: Term used when individual has difficulty initiating micturition, resulting in a delay in the onset of voiding
  - Terminal dribble: Term used when an individual describes prolonged final part of micturition
- **Postmicturition symptoms** are experienced immediately after micturition:
  - Feeling of incomplete emptying
  - Postmicturition dribble describes the involuntary loss of urine after the patient finishes passing urine.

REFERENCE

Abrams P, Cardozo L, Fall M, et al. The standardization of terminology in lower urinary tract function. *Neurourol Urodyn*. 2002;21:167–178.

VULVAR MALIGNANCY, UROLOGIC CONSIDERATIONS

DESCRIPTION Vulvar carcinoma encompasses any malignancy that arises in the skin, glands, or underlying stroma of the perineum, including the mons pubis, labia minora, labia majora, Bartholin glands, or clitoris. Early detection lesions (<2 cm) allow for local resection without node dissection. Cases presenting late in the course of disease may require radical en-bloc resection of the tumor and surrounding organs, known as *pelvic exenteration*. Total exenteration refers to removal of the uterus, tubes, ovaries, parametrium, bladder, rectum or rectal segment, vagina, urethra, and a portion of the levator muscles. In an anterior exenteration, the rectum is spared, whereas in a posterior exenteration, the bladder and urethra are preserved. Urinary diversion (usually a continent catheterizable pouch) will be

provided by the urologist as a portion of the pelvic reconstruction.

REFERENCE

Gershenson DM, Miller B, Morris M, et al. Pelvic exenteration for primary and recurrent vulvar cancer. *Gynecol Oncol*. 1995;58:202–205.

VULVODYNIA

DESCRIPTION Vulvar discomfort, most often described as burning pain, occurring in the absence of relevant or visible findings or specific, clinically identifiable, neurologic disorder. Lifetime prevalence reported at 16%. The condition is often reported with dyspareunia, but not associated with urinary complaints. However, 11% of women with vulvodynia will concomitantly be diagnosed with interstitial cystitis.

REFERENCE

Clemens JQ, Bogart JM. Symptoms of interstitial cystitis, painful bladder syndrome and similar diseases in women: A systematic review. *J Urol*. 2007;177:450–456.

VURD SYNDROME

DESCRIPTION VURD stands for *vesicoureteral reflux associated with renal dysplasia*. This term applies to children with posterior urethral valves in which there is massive reflux into a dysplastic nonfunctioning kidney; ~15% of the patients with posterior urethral valves have this syndrome. Some believe that severe unilateral vesicoureteral reflux is protective of the contralateral nonrefluxing kidney. Diagnosis is made using kidney US, voiding cystourethrogram, nuclear imaging of kidneys, and serum creatinine levels. The patient should be observed 1st to see if kidney function returns. If function does not return, then nephrectomy is considered.

REFERENCE

Donnelly LF, Gylys-Morin VM, Wacksman J, et al. Unilateral vesicoureteral reflux: Association with protected renal function in patients with posterior urethral valves. *AJR*. 1997;168(3):823–826.

WAGR SYNDROME (WILMS TUMOR-ANIRIDIA-GENITAL ANOMALY RETARDATION)

DESCRIPTION WAGR is one of the Wilms tumor–associated syndromes, presenting in children <3 yr. It causes mental retardation and GU manifestations in the form of renal hypoplasia, ectopia, fusions, duplications, cystic disease, hypospadias, cryptorchidism, and pseudoher-maphroditism. Physical exam may also reveal ear deformities, umbilical/inguinal hernias, and aniridia.

REFERENCE

Kirsch AJ, Snyder HM III. What's new and important in pediatric urologic oncology. *AUA Update Series*. 1998;17:83.

WALLACE URETERAL ANASTOMOSIS

DESCRIPTION A surgical procedure used in urinary diversion in which the spatulated ureters are laid adjacent and the apex of each is sutured to the other. The medial and lateral walls of the ureters are then sutured together in either an interrupted or running fashion. The Y configured ureters are then anastomosed to the end of the small bowel segment used for the reservoir.

REFERENCE

McDougal WS. Use of intestinal segments and urinary diversion. In: Walsh PC, Retik AB, Vaughan ED, et al., eds. *Campbell's Urology*. 7th ed. Philadelphia, PA: Saunders; 1998:3137–3144.

WALTER REED STAGING SYSTEM, TESTIS CANCER

DESCRIPTION Lymphangiographic criteria used to evaluate the presence and location of testicular neoplasm metastases. The following lymphangiographic patterns were found to be useful in assessing metastatic disease: Filling defects, lymph node enlargement and masses, lymphatic obstruction and collateral vessel formation, and an increase or decrease in the number of lymph nodes.

REFERENCE

Maier JG, Schamter DT. The role of lymphangiography in the diagnosis and treatment of malignant testicular tumors. *AJR*. 1972;114:482.

WATERHOUSE URETHRAL STRICTURE REPAIR

DESCRIPTION Through a combined abdominal and perineal approach, a wedge of pubis is resected with a Gigli saw. The membranous stricture is identified and excised. The distal urethra is mobilized off the corporal bodies, and the spatulated urethral edges are reanastomosed.

REFERENCE

Devine CJ, Devine PC. Operations for urethral stricture. In: Novick AC, Streem SB, Pontes JE, eds. *Stewarts Operative Urology.* Baltimore, MD: Williams & Wilkins; 1989:650–680.

WATERHOUSE–FRIDERICHSEN SYNDROME

DESCRIPTION Acute adrenocortical insufficiency in children suffering from septicemia with *Pseudomonas* or meningococcemia, leading to acute hemorrhagic destruction of both adrenal glands.

REFERENCE

Rao RH, Vagnucci AH, Amico JA, et al. Bilateral massive adrenal hemorrhage: Early recognition and treatment. *Ann Intern Med.* 1989;116:227.

WEDDELLITE

DESCRIPTION Mineralogic name for renal calculi composed of calcium oxalate dihydrate. (See Section I: "Urolithiasis, Calcium Oxylate/Phosphate.")

WEGENER GRANULOMATOSIS, UROLOGIC CONSIDERATIONS

DESCRIPTION Systemic granulomatous vasculitis, most commonly affecting the upper and lower respiratory tracts and the kidneys, involving small arteries and venules. Respiratory infiltrates or sinusitis are commonly the presenting symptoms, as well as constitutional symptoms (weight loss, fever, etc.). Renal involvement is usually vasculitis-induced chronic renal failure, but acute fulminant glomerulonephritis and occasional interstitial nephritis can be present. Red cells, red cell and other casts, and proteinuria are noted. Other urologic manifestations include granulomatous necrotizing prostatitis, urethritis, or epididymoorchitis. Hemorrhagic cystitis is common, but usually iatrogenic secondary to cyclophosphamide treatment. Progressive renal insufficiency with ESRD occurs in up to 25% of patients.

DIAGNOSIS

- Granulomatous necrotizing vasculitis: Lung biopsy
- Focal necrotizing glomerulonephritis: Renal biopsy
- Red cell casts in voided urine: Glomerulonephritis
- Antineutrophil cytoplasmic antibodies: Useful for follow-up

TREATMENT

- Cyclophosphamide
- Corticosteroids
- Other cytotoxic and immunosuppressive agents: Methotrexate, cyclosporine, FK-506
- Surveillance cystoscopy when cyclophosphamide used

REFERENCE

Aasarød K, Iversen BM, Hammerstrøm J, et al. Wegener's granulomatosis: Clinical course in 108 patients with renal involvement. *Nephrol Dial Transplant.* 2000;(155):611–618.

WEISS CRITERION

DESCRIPTION Most commonly used histopathologic system to provide diagnostic criteria for malignant adrenocortical tumors. Originally proposed in 1984, it has since undergone 1 revision. Original Weiss Criteria requires ≥3 of the following:

- Fuhrman nuclear grade III or IV
- 5+ mitotic figures/HPF on 10+ fields
- Atypical mitotic figures (spindles)
- Clear or vacuolated cells <25% or tumor
- Diffuse architecture >1/3 of tumor (patternless organization)
- Microscopic necrosis
- Venous invasion
- Sinusoidal invasion
- Capsular invasion

Modified Weiss Criteria using "1" if factor is present in tumor, 0 otherwise:

- 2× mitotic rate + 2× clear cytoplasm + abnormal mitoses + necrosis + capsular invasion
- Score total of ≥3 suggests malignancy

REFERENCE

Aubert S, Wacrenier A, Leroy X, et al. Weiss system revisited: A clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. *Am J Surg Pathol.* 2002;26(12):1612–1619.

WHEWELLITE

DESCRIPTION Mineralogic name for renal calculi composed of calcium oxalate monohydrate. (See also Section I: "Urolithiasis, Calcium Oxylate/Phosphate.")

WHITAKER TEST

DESCRIPTION An antegrade pressure–flow study to assess for renal obstruction. It is used to determine if pelvocaliectasis or hydronephroureterosis seen radiographically represents functional obstruction or anatomic dilation. This is a technically difficult, invasive test, requiring placement of a percutaneous antegrade catheter into the renal pelvis, with simultaneous monitoring of bladder and renal pelvic pressures during set flow rate of 10 mL/min. Elevation of renal pelvic pressure over bladder pressure indicates some degree of renal obstruction. A Foley catheter must be in the bladder.

Renal Pelvis, Bladder Pressure Differential	Degree of Obstruction
<13 cm H_2O	Normal
14–20 cm H_2O	Mild obstruction
21–34 cm H_2O	Moderate obstruction
>35 cm H_2O	Severe obstruction

SYNONYMS

- Urodynamic antegrade pyelogram
- Ureteral perfusion test

• Pressure–flow Whitaker exam

REFERENCE

Whitaker RH. The Whitaker test. *Urol Clin N Am.* 1979;6(3):529–539.

WHITLOCKITE

DESCRIPTION Mineralogic name for renal calculi composed of tricalcium phosphate. (See Section II: "Urolithiasis, Calcium Oxylate/Phosphate.")

WHO 2004 HISTOLOGIC CLASSIFICATION OF TUMORS OF THE URINARY TRACT

DESCRIPTION This is the 2004 World Health Organization classification of tumors of the urinary tract. It primarily covers the renal pelvis, ureter, bladder and urethra. See Section II: WHO/ISUP classification of urothelial neoplasms (1998 and 2004) for an analysis of the changes in the specific bladder/urothelial classification.

WHO 2004 Histologic Classification of Tumors of the Urinary Tract

Urothelial Tumors
Infiltrating urothelial carcinoma
- with squamous differentiation
- with glandular differentiation
- with trophoblastic differentiation

Nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Lymphoma-like
Plasmacytoid
Sarcomatoid
Giant cell
Undifferentiated
Noninvasive urothelial neoplasias
Urothelial carcinoma in situ
Noninvasive papillary urothelial carcinoma, high grade
Noninvasive papillary urothelial carcinoma, low grade
Noninvasive papillary urothelial neoplasm of low malignant potential (PUNLMP)
Urothelial papilloma
Inverted urothelial papilloma

Squamous neoplasms
Squamous cell carcinoma
Verrucous carcinoma
Squamous cell papilloma

Glandular neoplasms
Adenocarcinoma
Enteric
Mucinous
Signet-ring cell
Clear cell
Villous adenoma

Neuroendocrine tumors
Small-cell carcinoma
Carcinoid
Paraganglioma

Melanocytic tumors
Malignant melanoma
Nevus

Mesenchymal tumors
Rhabdomyosarcoma
Leiomyosarcoma
Angiosarcoma
Osteosarcoma
Malignant fibrous histiocytoma
Leiomyoma
Hemangioma
Other

Hematopoietic and lymphoid tumors
Lymphoma
Plasmacytoma

Miscellaneous tumors
Carcinoma of Skene, Cowper and Littre glands
Metastatic tumors and tumors extending from other organs

REFERENCE

Eble JN, et al. *Pathology and Genetics. Tumors of the Urinary System and Male Genital Organs.*

Lyon: IARC Press; 2004.

WHO/ISUP CONSENSUS CLASSIFICATION OF UROTHELIAL NEOPLASMS (1998, 2004, AND 2010)

DESCRIPTION At a consensus conference of the World Health Organization (WHO) and the International Society of Urologic Pathologists (ISUP) in 1998, the WHO/ISUP classification of urothelial neoplasms of the bladder was developed. The innovations of this consensus included the elimination of grades of dysplasia, with high-grade dysplasia equated with carcinoma in situ, as well as a condensation of cytologic grading of urothelial carcinoma (ie, grades 1–3) into low- and high-grade carcinoma. In addition, a new entity was recommended for low-grade papillary lesions, entitled papillary urothelial neoplasm of low malignant potential (PUNLMP) in 2004. The most recent update adopted the use of the term urothelial instead of transitional to describe urothelium. The WHO/ISUP classification:

- Normal urothelium
- Flat urothelial hyperplasia
- Papillary urothelial hyperplasia
- Dysplasia (low-grade intraurothelial neoplasia)
- Carcinoma in situ (high-grade intraurothelial neoplasia)
- Reactive urothelial atypia
- Papilloma
- PUNLMP
- Papillary carcinoma, low-grade
- Papillary carcinoma, high-grade
- Invasive neoplasms
- Lamina propria invasion
- Muscularis propria (detrusor muscle) invasion

REFERENCE

Epstein JI. Diagnosis and classification of flat, paillary, and invasive urothelial carcinoma: The WHO/ISUP consensus. *Int J Surg Pathol.* 2010;18(3):106S–111S.

WILMS TUMOR STAGING SYSTEM, INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP)

DESCRIPTION Developed by the International Society of Pediatric Oncology, this staging system is based on postchemotherapy surgical evaluation. It is used extensively in Europe. The National Wilms Tumor Staging System is based upon surgical evaluation before chemotherapy. It is used throughout the United States and Canada (see table below). (See also Section I: “Wilms Tumor”; Section II: “Wilms Tumor Staging System, National NWTS”; “Wilms Tumor Staging System, International Society of Pediatric Oncology SIOP.”)

REFERENCES

Ahmed HU. An update on the management of Wilms’ tumour. *J Surg Oncol.* 2007;33(7):824–831.

Metzger ML, Dome JS. Current therapy for Wilms’ tumor. *Oncologist.* 2005;10(10):815–826.

WILMS TUMOR STAGING SYSTEM, NATIONAL (NWTS)

DESCRIPTION A unified system developed to aid in the conduct of clinical trials now widely used for clinical staging treatment decisions (see table). The National Wilms Tumor Study (NWTS) system is based upon surgical evaluation prior to the administration of chemotherapy. It is used throughout the United States and Canada. The SIOP system is based upon postchemotherapy surgical evaluation and is used extensively in Europe. (See also Section I: "Wilms Tumor"; Section II: "Wilms Tumor Staging System, International Society of Pediatric Oncology [SIOP].")

REFERENCES

D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor: Results of the Third National Wilms' Tumor Study. *Cancer.* 1989;64:349–360.

Metzger ML, Dome JS. Current therapy for Wilms' tumor. *Oncologist.* 2005;10(10):815–826.

WINTER CORPORAL SHUNT

DESCRIPTION A shunt between the corpora and glans penis created to treat priapism. A Tru-Cut biopsy needle is inserted through the tip of the glans and into the corpora, and a core of tissue is removed. Through the same glans puncture site, the Tru-Cut can be reinserted in order to create 2 fistulas at the end of both corpora. It is also referred to as a *percutaneous glanducavernous shunt.*

REFERENCE

Thomas AJ. Surgery for priapism. In: Novick AC, Streem SB, Pontes JE, eds. *Stewarts Operative Urology.* Baltimore, MD: Williams & Wilkins; 1989:826–832.

Wilms Tumor Staging System, International Society of Pediatric Oncology (SIOP)

Stage	Following Chemotherapy
I	Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and is completely resected (resection margins clear) The tumor may be protruding into the pelvic system and dipping into the ureter (but it is not infiltrating their walls) The vessels of the renal sinus are not involved Intrarenal vessel involvement may be present
II	The tumor extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins clear) The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected The tumor infiltrates adjacent organs or vena cava but is completely resected
III Residual tumor confined to the abdomen	Incomplete excision of the tumor, which extends beyond resection (margins gross or microscopical tumor remains postoperatively) Any abdominal lymph nodes are involved Tumor ruptures (before or intraoperatively irrespective of other criteria for staging) The tumor has penetrated through the peritoneal surface Tumor thrombi are present at resected margins of vessels or ureter, transected or removed piecemeal by surgeon The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery Regional lymph node involvement was considered stage II in the previous SIOP staging system
IV	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region
V	Bilateral renal tumors at diagnosis

Wilms Tumor Staging System, International Society of Pediatric Oncology (SIOP)	
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WOLFFIAN DUCT REMNANTS

DESCRIPTION Normally, an embryo develops 2 sets of paired (müllerian and wolffian mesonephric) ducts. In females, virilization of the molffian system fails to occur, and wolffian vestiges may persist as the epoophoron, Gartner duct, or the appendix vesiculosa, commonly forming paraovarian cysts. In males, virilization of the wolffian duct gives rise to the epididymis, vas deferens, ejaculatory duct and seminal vesicles. The rostral end of the wolffian duct occasionally persists as a vestigial remnant, the appendix epididymis. Remnants of the mesonephric tubules may persist as a cystic structure, the *paradidymis.* (See also Section I: "Torsion, Testis; Testicular Appendages.")

SYNONYMS

- Paradidymis
- Appendix epididymis

REFERENCE

Wilson JD, Griffin JE, George FW, et al. The role of gonadal steroids in sexual differentiation. *Recent Prog Horm Res.* 1981;37:1–39.

WOUND DEHISCENCE, UROLOGIC CONSIDERATIONS

DESCRIPTION Development of a postoperative gap or defect in the peritoneal suture line, with or without evisceration. Prevalence is in 1–3% of patients and carries a risk of mortality as high as 44%. Risk factors include anemia, hypoalbuminemia, advanced age, male gender, chronic lung disease, malnutrition, wound infection, and emergent procedure. Surgical variables include suture type, use of prosthetic material, incision location, hypothermia, perfusion, and oxygenation. Primary repair of initial dehiscence carries a 56% success rate with sutures and/or retentions, whereas the use of an interposition mesh confers an initial 100% success rate.

REFERENCE

Abbott DE, Dumanian GA, Halverson AL. Manage-ment of laparotomy wound dehiscence. *Am Surg.* 2007;73(12):1224–1227.

WOUND INFECTION, POSTOPERATIVE, UROLOGIC CONSIDERATIONS

DESCRIPTION Surgical site infections and postoperative UTIs are common causes of patient morbidity, complicating 5% and 20% of clean cases, respectively. Patient-related risk factors include advanced age, anatomic urinary anomalies, poor nutrition, tobacco use, corticosteroid use, immunodeficiency, external/indwelling catheters, distant infection, and prolonged hospitalization. The need for periprocedural antimicrobial prophylaxis has been well documented. Antibiotics should be given within 60 min of procedure start time, and selected based on patient history, as well as anticipated procedure. (See Section II: "Prophylactic Antibiotics, AUA Guidelines"; Section VII: "Antibiotic Prophylaxis: AUA Guidelines.")

TREATMENT

- Cellulitis: Antimicrobial therapy and local wound care
- Superficial abscesses: Opening of the surgical wound, drainage and local wound care

REFERENCE

Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol.* 2008;179:1379–1390.

WUNDERLICH SYNDROME

DESCRIPTION Clinical condition classically described as spontaneous renal bleeding of nontraumatic origin, confined to the subcapsular and perirenal space. Presentation may be insidious, but the *Lenk triad* (flank pain, palpable mass, and deterioration with hypovolemic shock) has been described in the event of an acute onset.

CAUSES

- Angiomyolipoma
- Cysts (pancreatic, etc.)
- Idiopathic
- Tumor urothelial carcinoma, renal cell carcinoma
- Vasculitis and/or inflammation

REFERENCE

Albi G, del Campo L, Tagarro D. Wunderlich syndrome: Causes, diagnosis and radiologic management. *Clin Radiol.* 2002;57:840–845.

XANTHOGRANULOMATOSIS (ERDHEIM–CHESTER DISEASE)

DESCRIPTION Erdheim–Chester disease is a rare non-Langerhans form of histiocytosis with a poor prognosis. This disease occurs most commonly in patients older than 50 presenting with xanthoma-like skin nodules and bilateral lower limb bone pain. More disseminated forms of the disease can have renal failure caused by retroperitoneal and perinephric infiltrative or constrictive changes. These patients can also have cardiopulmonary insufficiency and CNS involvement and may have a progressive and fatal disease. The pathophysiology is unknown with limited treatments.

REFERENCE

Jordan MD, Filipovich AH. Histiocytic Disorders. In: Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, eds. *Hoffman: Hematology: Basic Principles and Practice*. 6th ed. Philadelphia, PA: Saunders; 2013.

XANTHOMA, BLADDER

DESCRIPTION Collection of foamy histocytes found in the lamina propria in patients with disorders of lipid metabolism.

REFERENCE

Nishimura K, Nozawa M, Hara T, et al. Xanthoma of the bladder. *J Urol.* 1995;153:1912–1913.

X-LINKED SPINAL AND BULBAR ATROPHY SYNDROME (KENNEDY SYNDROME)

DESCRIPTION Kennedy syndrome is a late-onset, bulbar–spinal type of muscular atrophy. There is an X-linked recessive inheritance genetic marker CAG repeat sequences in the androgen receptor gene (on chromosome X). The majority of evidence of altered androgen sensitivity is restricted to exaggerated or persistent adolescent gynecomastia, and the mildly high LH, testosterone, and estradiol levels characteristic of other forms of androgen insensitivity. The condition becomes prominent in the 4th–5th decades, with proximal muscle wasting and weakness; bulbar signs; fasciculations in skelet al muscles; subtle signs of endocrine dysfunction, such as diabetes, gynecomastia, or testicular atrophy; and oligospermia. The progression is very slow, and these patients can expect a normal lifespan; it is essential to distinguish this syndrome from other, often more severe neurologic diseases.

REFERENCE

Jordan CL, Lieberman AP. Spinal and bulbar muscular atrophy: A motoneuron or muscle disease? *Curr Opin Pharmacol.* 2008;8(6):752–758.

XX GONADAL DYSGENESIS (46, XX)

DESCRIPTION Clinically, patients present with primary amenorrhea and lack of secondary sexual characteristics. This presentation is consistent with ovarian failure and may be

associated with a host of X-chromosome aberrations. Specifically, 46, XX gonadal dysgenesis is marked by normal female chromosome constitution and hypergonadotropic hypergonadism with concurrent ovarian failure. Etiologies may be sporadic or inherited, but the condition is rarely linked to other somatic abnormalities. Other clinical manifestations include short stature, episodic metabolic acidosis, and normal intelligence.

SYNONYMS
- Ovarian failure
- Ovarian dysgenesis
- Streak ovaries

REFERENCE
Hisama FM, Zemel S, Cherniske EM, et al. 46, XX gonadal dysgenesis, short stature and recurrent metabolic acidosis in two sisters. *Am J Med Genetics.* 2001;98:121–124.

XX MALE REVERSAL SYNDROME (XX MALE)

DESCRIPTION A rare disorder of phenotypic males who have a 46, XX karyotype. Physical exam may reveal short stature; small, firm testes; a small- to normal-sized penis; hypospadias; and gynecomastia. Azoospermia is typical. Seminiferous tubule sclerosis can be shown on testicular biopsy. Lab investigation reveals high gonadotropin levels and decreased testosterone levels. In most cases, DNA fragments from the short arm of the Y chromosome can be detected in the distal end of the short arm of the X chromosome.

REFERENCE
Petit C, de la Chapelle A, Levilliers J, et al. An abnormal terminal X-Y interchange accounts for most but not all cases of human XX maleness. *Cell.* 1987;49:595.

XXX SYNDROME (TRIPLE X SYNDROME, TRIPLO-X)

DESCRIPTION Triple X chromosome abnormality occurs in ~1.2 in 1,000 liveborn females. There are no specific diagnostic features. Menstrual irregularities and mental retardation have been reported. Fertility is usually preserved, and many XXX females have normal offspring.

REFERENCE
Sills JA, Brown JK, Grace E, et al. XXX syndrome associated with immunoglobulin deficiency and epilepsy. *J Pediatr.* 1978;93:469.

XXXY SYNDROME

DESCRIPTION Rare variant of Klinefelter syndrome (47, XXY), with an additional X chromosome (48, XXXY). Phenotype is similar to 47, XXY, with more pronounced features; these patients frequently exhibit microphallus, hypoplastic testicles, cryptorchidism, hypospadias, and gynecomastia. They are infertile (azoospermia), usually are mentally retarded, and have characteristic facies.

TREATMENT
Supplemental testosterone may be beneficial for virilization at puberty.

REFERENCE

Linden MG, Bender BG, Robinson A. Sex chromosome tetrasomy and pentasomy. *Pediatrics.* 1995;96(4 Pt 1):672–682.

XXY SYNDROME (KLINEFELTER SYNDROME)

DESCRIPTION A syndrome characterized by the presence of an extra X chromosome (usually 47 XXY), resulting in a hypogonadal male. It is the most common chromosomal aberration among men, with an estimated frequency of 1:500 among newborns. Caused by a nondisjunction of the meiotic chromosomes of the gametes from either parent, affected individuals are tall, with a eunuchoid habitus, small firm testes, and gynecomastia. Mental retardation and psychiatric disturbances have also been identified. Elevated gonadotropins and azoospermia are typically present. Seminiferous tubular sclerosis is a common finding on testicular biopsy. The diagnosis may be made with a chromatin-positive buccal smear, indicating the presence of an extra X chromosome. Karyotypes usually demonstrate 47, XXY or the milder mosaic pattern, 46, XY, 47, XXY.

TREATMENT

- No therapy improves spermatogenesis in Klinefelter syndrome.
- In mosaic Klinefelter syndrome with severe oligospermia, intracytoplasmic injection with IVF is technically possible.

REFERENCES

Klinefelter HG Jr., et al. Syndrome characterized by gynecomastia, aspermatogenesis without aleydigism and increased secretion of follicle stimulating hormone. *J Clin Endocrinol.* 1942;2:615.

Paduch DA, Fine RG, Bolyakov A, et al. New concepts in Klinefelter syndrome. *Curr Opin Urol.* 2008;18(6):621–627.

YOLK SAC TUMOR, BLADDER

DESCRIPTION Yolk sac tumor of the bladder is very rare and appears to have a predilection for the urachal remnant. It has the same pathologic characteristics as its counterparts in any other part of the body, and it is managed in the same way. (See Section II: "Yolk Sac Tumor, Prostate.")

REFERENCE

Huang HY, Ko SF, Chuang JH, et al. Primary yolk sac tumor of the urachus. *Arch Pathol Lab Med.* 2002;126(9):1106–1109.

YOLK SAC TUMOR, PROSTATE

DESCRIPTION Extragonadal GCT located in the prostate, similar to yolk sac tumor also called *endodermal sinus tumor*) found in the testis. A primary site of presentation in the prostate is extremely rare, with only a few reported cases. An increased incidence of extragonadal GCT is reported with Klinefelter syndrome. α-fetoprotein levels are commonly elevated, and are used as a tumor marker; human chorionic gonadotropin is not elevated. Schiller–Duval bodies are evident on histology. Treatment is multimodal, using cisplatinum-based combination chemotherapy and radical surgery.

REFERENCE

Tay HP, Bidair M, Shabaik A, et al. Primary yolk sac tumor of the prostate in a patient with Klinefelter's syndrome. *J Urol.* 1995;153(3):1066–1069.

YOUNG CLASSIFICATION OF POSTERIOR URETHRAL VALVES

DESCRIPTION Young described 3 general types of posterior urethral valves:

- Type I: The valves are continuous with the verumontanum and take an anterior course, dividing into 2 fork-like processes in the region of the bulbomembranous junction. Usually, anterior fusion of the valves is not complete; however, some cases exhibit complete anterior fusion and cleft between the folds posteriorly. A subdivision of type I consists of a single, instead of double, valve. Type I valves are the most common.
- Type II: Same as type I, but the valve, rather than taking an anterior course, tends to pass from the upper aspect of the verumontanum toward the internal sphincter, where it divides into 2 forklike processes. (Note: Type II valves are now thought to be nonexistent.)
- Type III: The valves have no relation to the verumontanum; instead, they are attached to the entire circumference of the urethra at any level, with a small opening in the center; they have been called *iris valves* due to their resemblance to the iris of the eye. Incomplete varieties of this type (crescentic or semilunar) have been described. Type III valves are a more distal diaphragmatic obstruction, similar to a urethral membrane.

REFERENCE

Young HH, et al. Congenital obstruction of the posterior urethra. *J Urol.* 1919;3:289.

YOUNG-DEES-LEADBETTER BLADDER RECONSTRUCTION

DESCRIPTION This procedure is used to achieve a functional bladder neck closure (ie, establish continence) in children with exstrophy; and also for urinary incontinence in nonexstrophy conditions, although the technique is generally no longer widely used. Through an anterior cystotomy, a rectangular area between the distal urethra and trigone is demarcated. Flaps lateral to this are developed and used to tubularize a neourethra over a 10-Fr catheter.

REFERENCE

Ouckett JW, Caldamone AA. Bladder and urachus. In: Kelalis P, King L, Belman B, eds. *Clinical Pediatric Urology*. 2nd ed. Philadelphia, PA: Saunders; 1985:735.

YOUNG SYNDROME

DESCRIPTION Obstructive azoospermia in patients with frequent respiratory infections or bronchiectasis. Motile sperm, with normal cilia and vas deferens are present. The condition is caused by inspissated secretions, causing epididymal obstruction, and treated by vasoepididymostomy; fertility rates remain poor.

REFERENCE

Hughes TM 3rd, Skolnick JL, Belker AM. Young's syndrome: An often unrecognized correctable cause of obstructive azoospermia. *J Urol.* 1987;137(6):1238–1240.

ZELLWEGER SYNDROME (CEREBROHEPATORENAL SYNDROME)

DESCRIPTION A family of diseases of inborn errors of metabolism caused by agenesis or disruption of peroxisomes (subcellular organelles). It follows an autosomal recessive inheritance pattern, with an incidence of 1 in 25,000 to 1 in 50,000 live births. Characteristics include severe developmental delay, sensorineural deafness, renal cortical cysts, retinal dysfunction, hepatomegaly, and characteristic facies (thus, cerebrohepatorenal syndrome). Usually lethal in childhood, rare patients survive into adolescence and adulthood. Positive diagnosis is made by serum assay of very long-chain fatty acids and dihydroxyacetone phosphate acyl transferase. Hyperoxaluria and nephrocalcinosis may also be present. No known treatment exists.

REFERENCE

van Woerden CS, Groothoff JW, Wijburg FA, et al. High incidence of hyperoxaluria in generalized peroxisomal disorders. *Mol Genet Metab.* 2006;88(4):346–350.

ZINNER SYNDROME

DESCRIPTION Ejaculatory duct obstruction (EDO) resulting from a unilateral seminal vesicle cyst with associated ipsilateral kidney agenesis, the condition is caused by a congenital müllerian/wolffian/utricular abnormality. Although EDO accounts for <1% of infertility, it is a treatable entity, using transurethral resection of ejaculatory duct.

REFERENCE

Pace G, Galatioto GP, Gualà L, et al. Ejaculatory duct obstruction caused by a right giant seminal vesicle with an ipsilateral upper urinary tract agenesia: An embryologic malformation. *Fertil Steril.* 2008;89(2):390–394.

ZIPPER ENTRAPMENT

DESCRIPTION Usually an emergency department presentation, this penile problem usually results from the entrapment of the foreskin between the fastener device and zipper teeth as a result of the caudal motion of the zipper. Often occurs in children 3–6 yr of age. Treatment should not include extraction of the foreskin or urgent circumcision, but instead should involve the release of the zipper median bar using orthopedic bone pliers (see below). An alternate method of release involves cutting the closed portion of the actuator (zipper teeth) with trauma shears to release the closed portion of the zipper from around the tissue.

- To remove a zipper, local anesthetic is injected into the area. Mineral oil is used to lubricate the zipper, and then 1 attempt is made to unzip the zipper. If this attempt is unsuccessful, a sturdy wire cutter (diagonal cutter) is used to cut the median bar on the top of the zipper slider, which connects its front and back plates. Then the slider falls off in 2 pieces, and the zipper teeth come apart readily (Image ☼).

REFERENCES

Inoue N, Crook SC, Yamamoto LG. Comparing two methods of emergency zipper release. *Am J Emer Med.* 2005;23:480–482.

Porter R, ed. Merck Manual of Diagnosis and Therapy. Copyright 2013 by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Whitehouse Station, NJ. Available at http://www.merckmanuals.com/professional/, Accessed April 5, 2014.

ZONA PELLUCIDA BINDING ASSAY

DESCRIPTION An assay used to counsel patients about their chances of success with IVF. Being species-specific, the human sperm-zona pelllucida binding requires human oocytes. Different sources of oocytes can be used, such as postmortem, IVF surplus, or surgical specimens. Oocytes are bisected, and 1/2 of the zona acts as the control. Different preservation methods are available, such as salt storage, dimethyl sulfoxide freezing, or ultra-low-temperature freezing. The assay is essentially composed of 2 steps: Initial attachment, followed by irreversible binding. After repeated rinsing, the number of tightly bound spermatozoa to ZP is counted using phase contrast microscopy. This can be expressed as the hemizona index, which is the number of the patient's bound spermatozoa divided by the bound spermatozoa from the fertile control donor, multiplied by 1,003. Using a cut off of 35%, the hemizona index has been used by some to predict IVF success rate. (See also Section II: "Sperm Penetration Assay [Hamster Test].")

REFERENCE

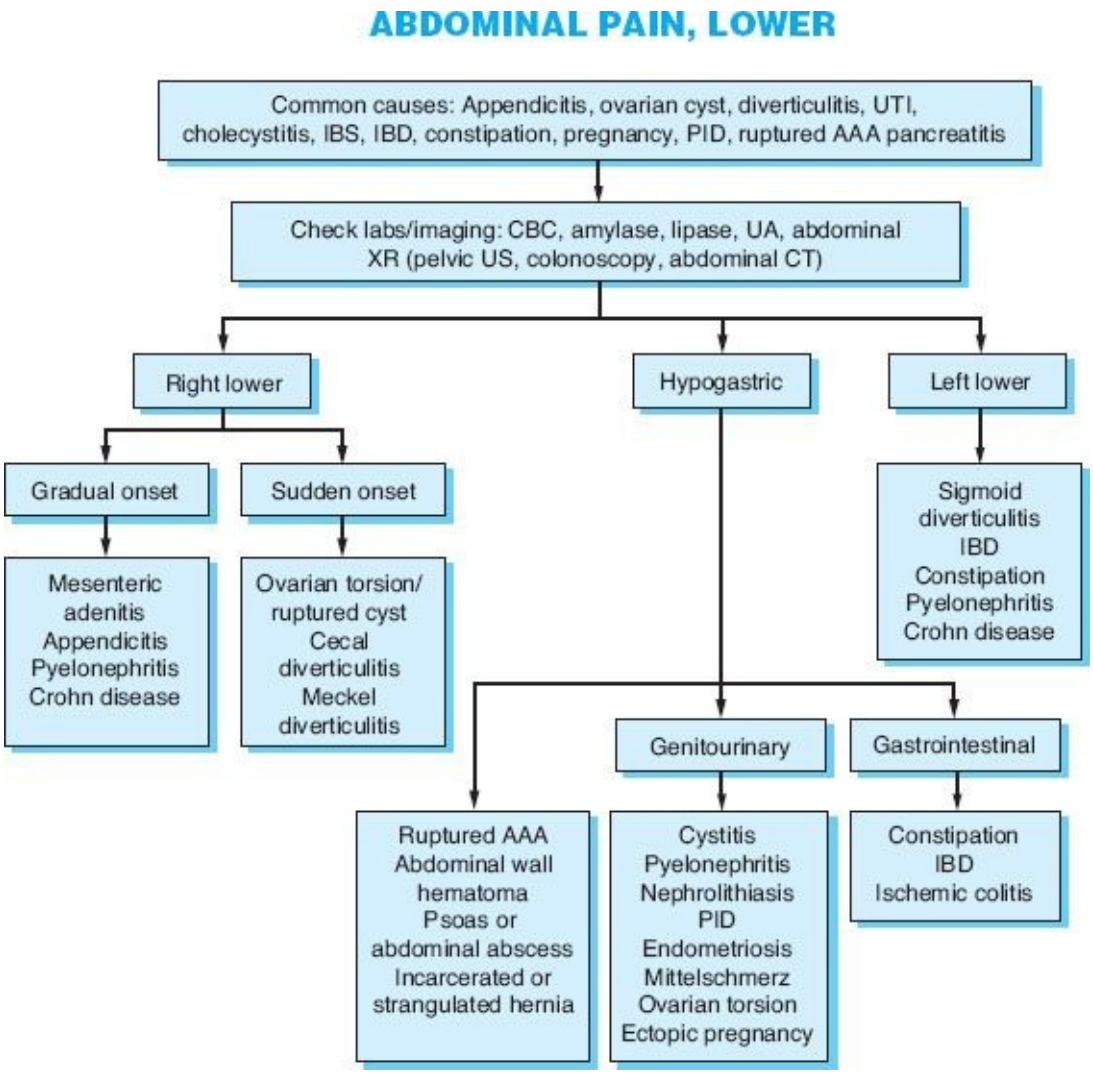
Oehninger S, Franken D, Alexander N, et al. Hemizona assay and its impact on the identification and treatment of human sperm dysfunctions. *Andrologia.* 1992;24:307–321.

SECTION III

Algorithms

Section Editor: Stanley Zaslau, MD, MBA, FACS

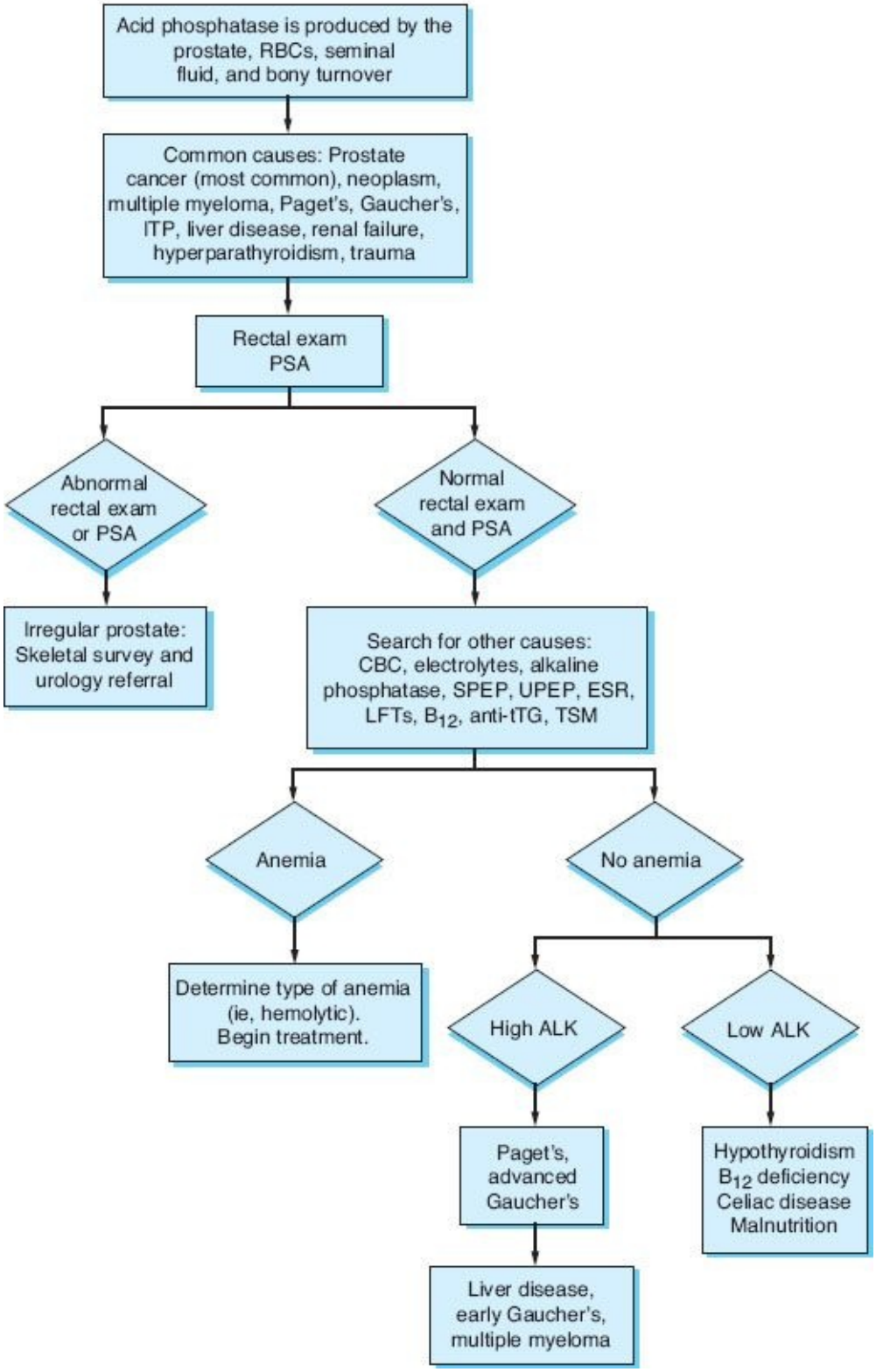
Abdominal Pain, Lower



Heading RC. Prevalence of upper gastrointestinal symptoms in the general population: A systematic review. *Scand J Gastroenterol Suppl.* 1999;231:3–8.

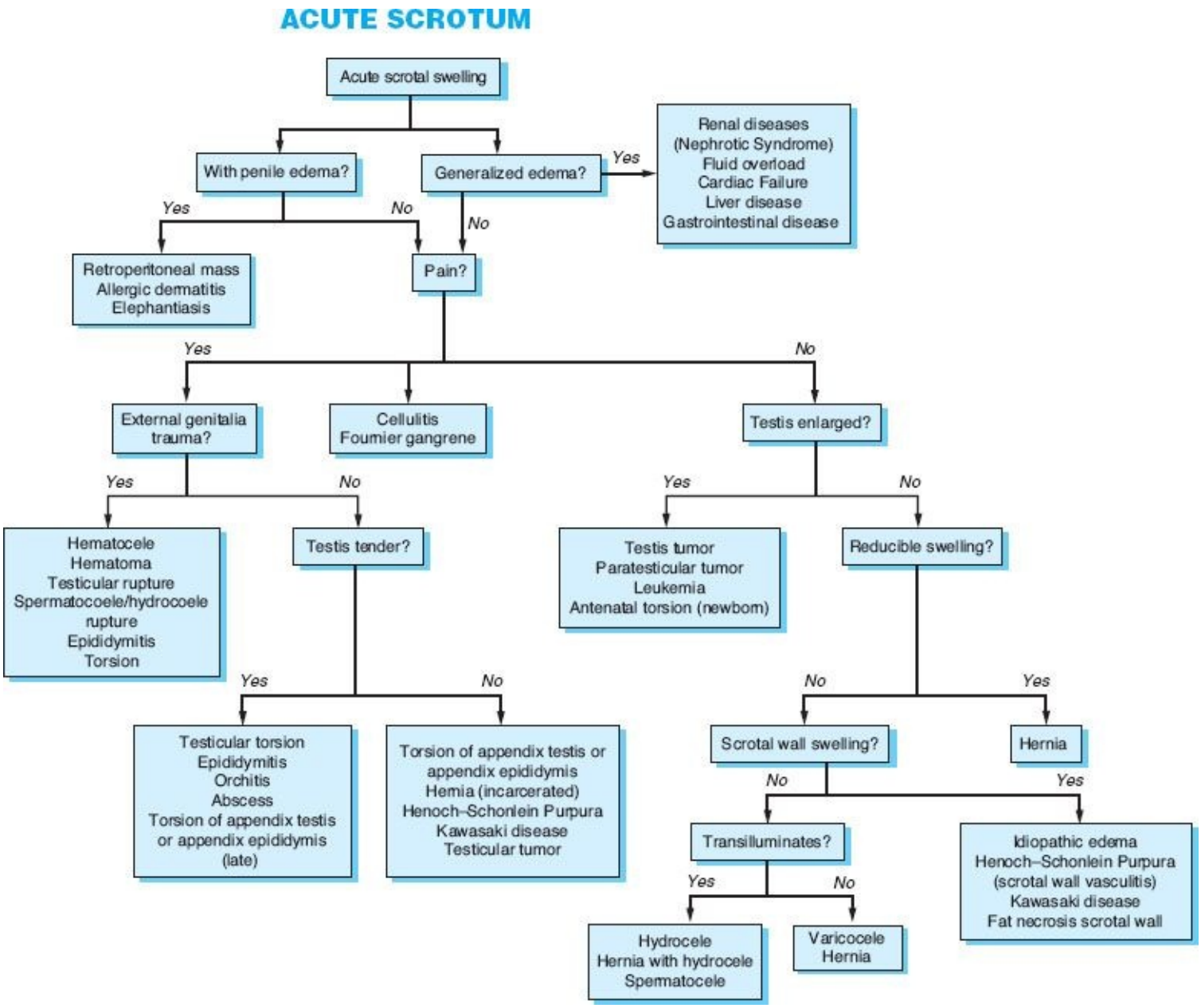
Acid Phosphatase Elevation

ACID PHOSPHATASE ELEVATION



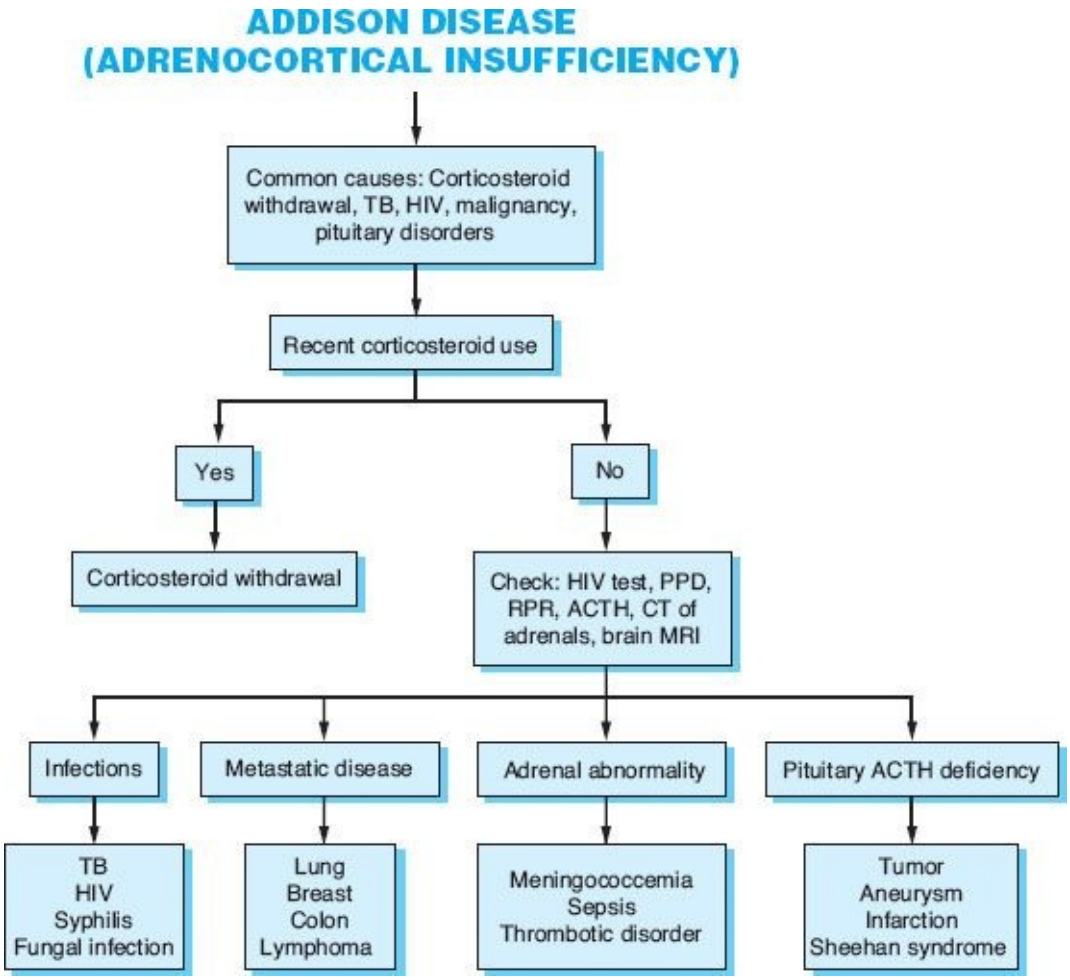
Scarnecchia L, Minisola S, Pacitti MT, et al. Clinical usefulness of serum tartrate-resistant acid phosphatase activity determination to evaluate bone turnover. *Scand J Clin Lab Invest.* 1991;51(6):517–524.

Acute Scrotum



Adapted from AUA University: Acute Scrotum (http://www.auanet.org/education/acute-scrotum.cfm) and The Royal Children's Hospital Melbourne Clinical Practice Guidelines (http://www.rch.org.au/clinicalguide/guideline_index/Acute_Scrotal_Pain_or_Swelling/)

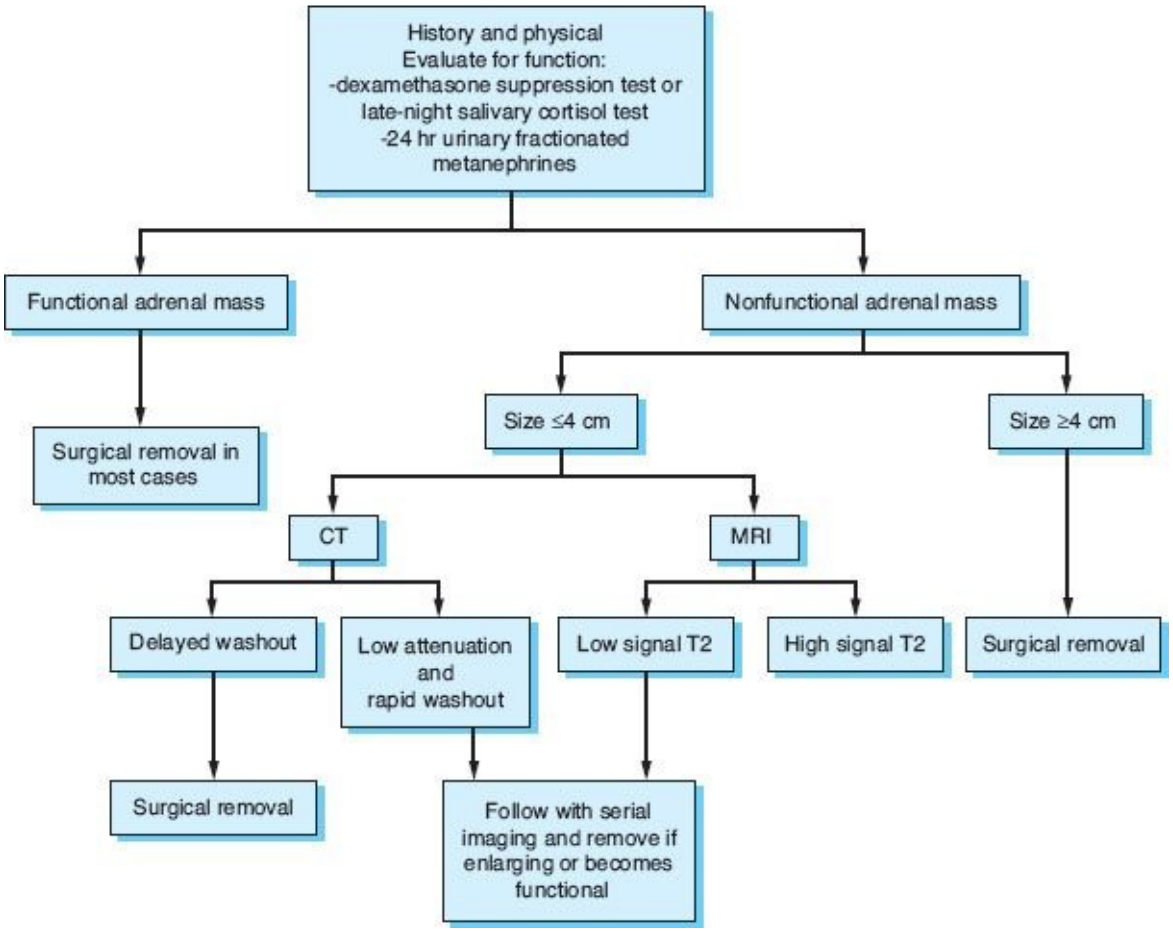
Addison Disease (Adrenocortical Insufficiency)



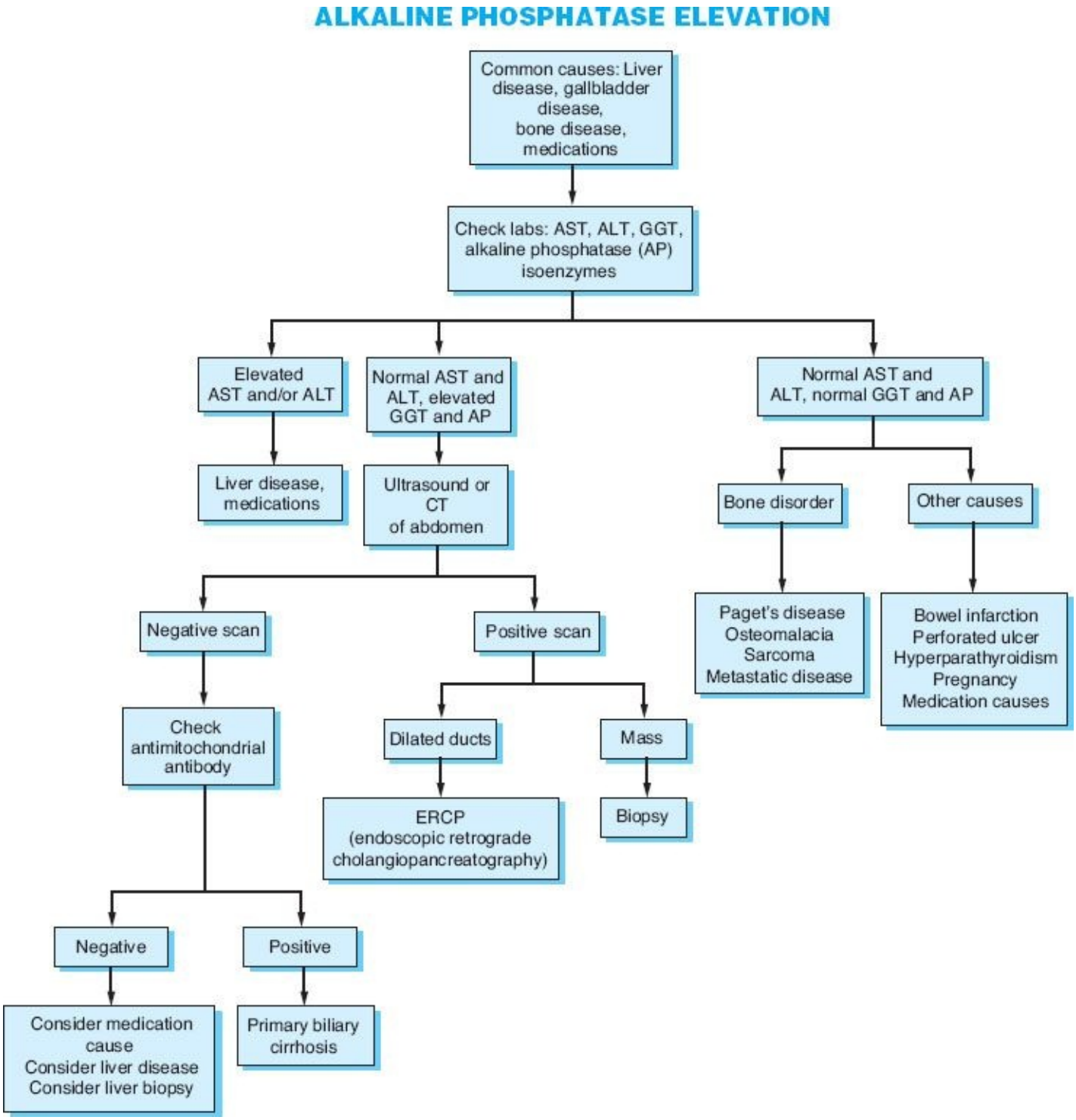
Reproduced with permission from Domino FJ, ed. *The 5-Minute Clinical Consult 2009*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

Adrenal Mass, Solid

ADRENAL MASS, SOLID

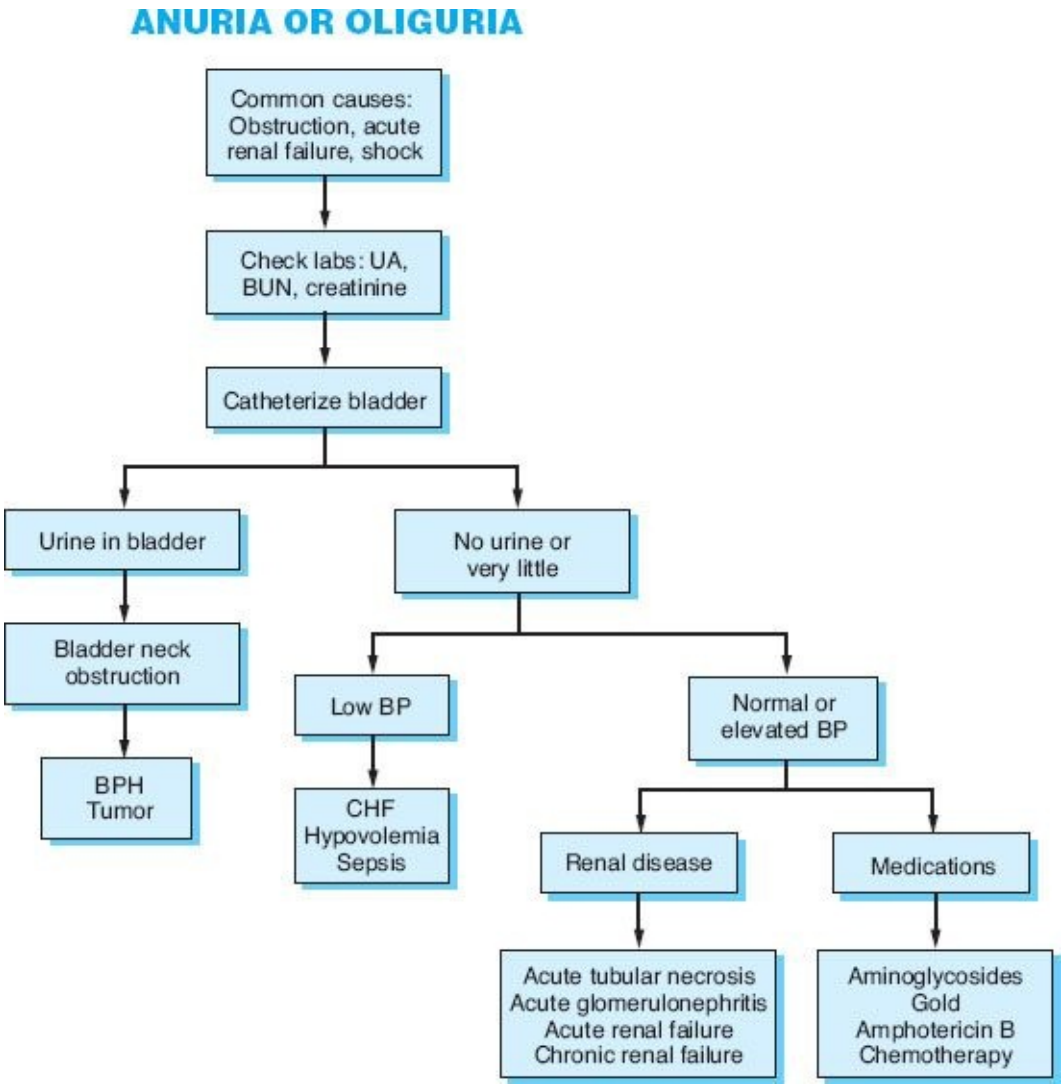


Alkaline Phosphatase Elevation



Reust CE, Hall L. Clinical inquiries. What is the differential diagnosis of an elevated alkaline phosphatase (AP) level in an otherwise asymptomatic patient? *J Fam Pract.* 2001;50:496–497.

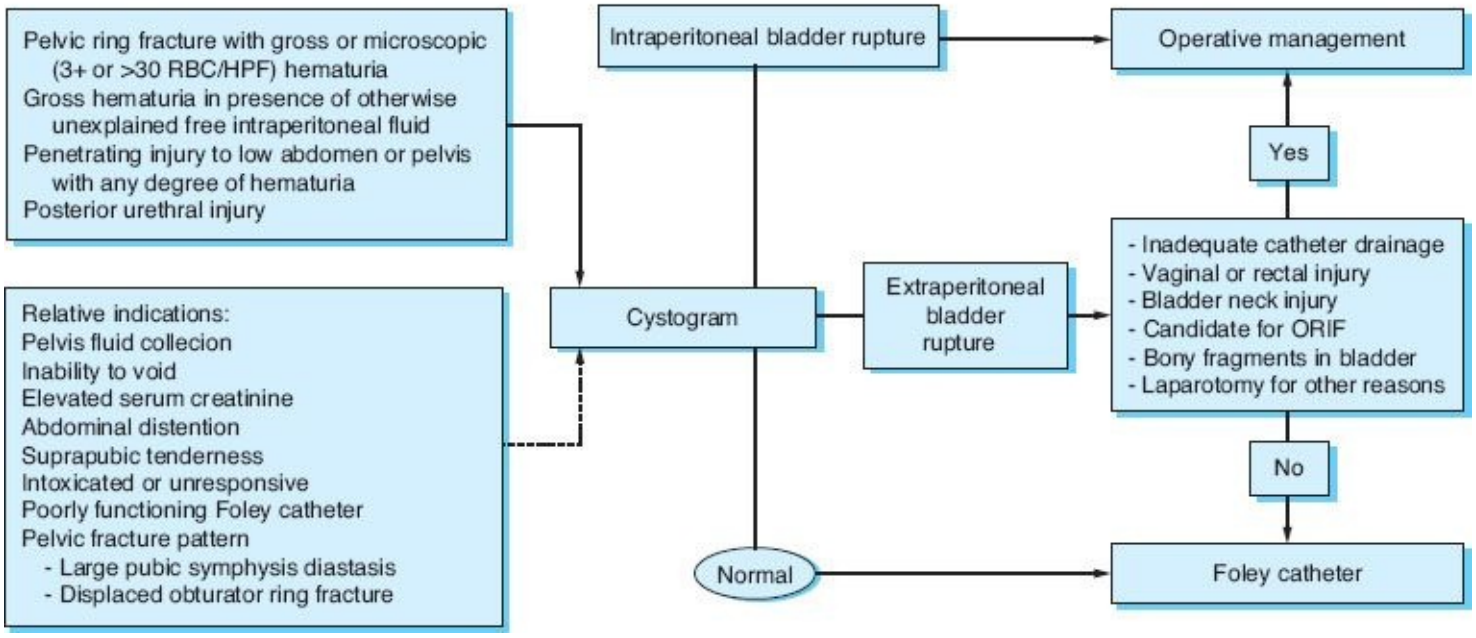
Anuria or Oliguria



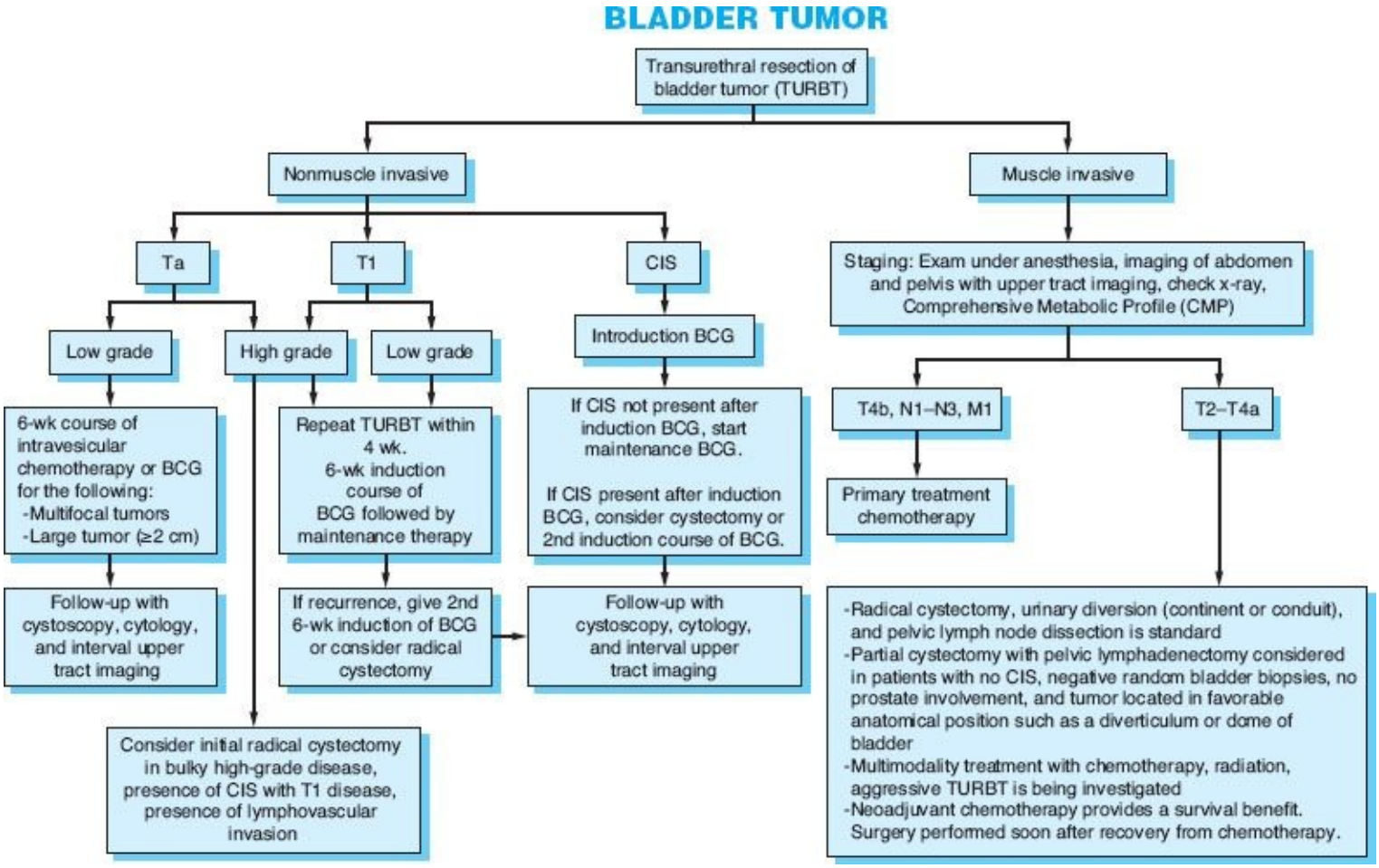
Agrawal M, Swartz R. Acute renal failure. *Am Fam Physician.* 2000;61:2077–2088.

Bladder Trauma

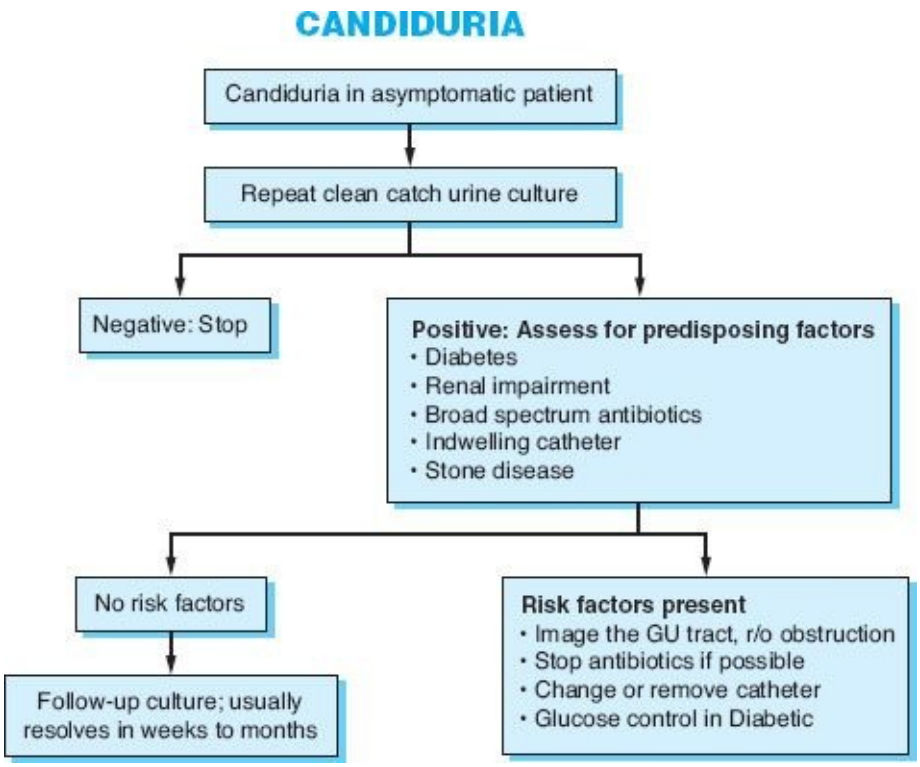
BLADDER TRAUMA



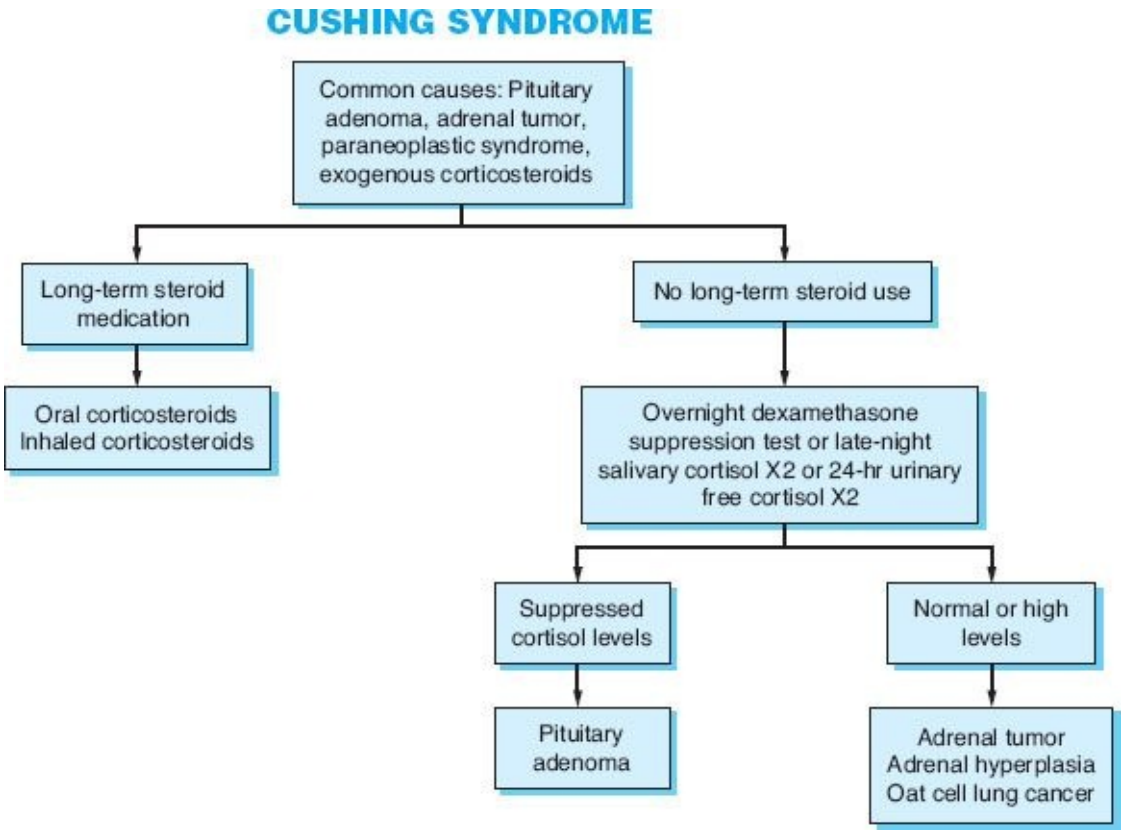
Bladder Tumor


BLADDER TUMOR
Transurethral resection of bladder tumor (TURBT)
Nonmuscle invasive
Muscle invasive
Ta
T1
CIS
Staging: Exam under anesthesia, imaging of abdomen and pelvis with upper tract imaging, check x-ray, Comprehensive Metabolic Profile (CMP)
Low grade
High grade
Low grade
Introduction BCG
T4b, N1–N3, M1
T2–T4a
6-wk course of intravesicular chemotherapy or BCG for the following:
-Multifocal tumors
-Large tumor (≥2 cm)
Repeat TURBT within 4 wk.
6-wk induction course of BCG followed by maintenance therapy
If CIS not present after induction BCG, start maintenance BCG.
If CIS present after induction BCG, consider cystectomy or 2nd induction course of BCG.
Primary treatment chemotherapy
Follow-up with cystoscopy, cytology, and interval upper tract imaging
If recurrence, give 2nd 6-wk induction of BCG or consider radical cystectomy
Follow-up with cystoscopy, cytology, and interval upper tract imaging
-Radical cystectomy, urinary diversion (continent or conduit), and pelvic lymph node dissection is standard
-Partial cystectomy with pelvic lymphadenectomy considered in patients with no CIS, negative random bladder biopsies, no prostate involvement, and tumor located in favorable anatomical position such as a diverticulum or dome of bladder
-Multimodality treatment with chemotherapy, radiation, aggressive TURBT is being investigated
-Neoadjuvant chemotherapy provides a survival benefit. Surgery performed soon after recovery from chemotherapy.
Consider initial radical cystectomy in bulky high-grade disease, presence of CIS with T1 disease, presence of lymphovascular invasion

Candiduria



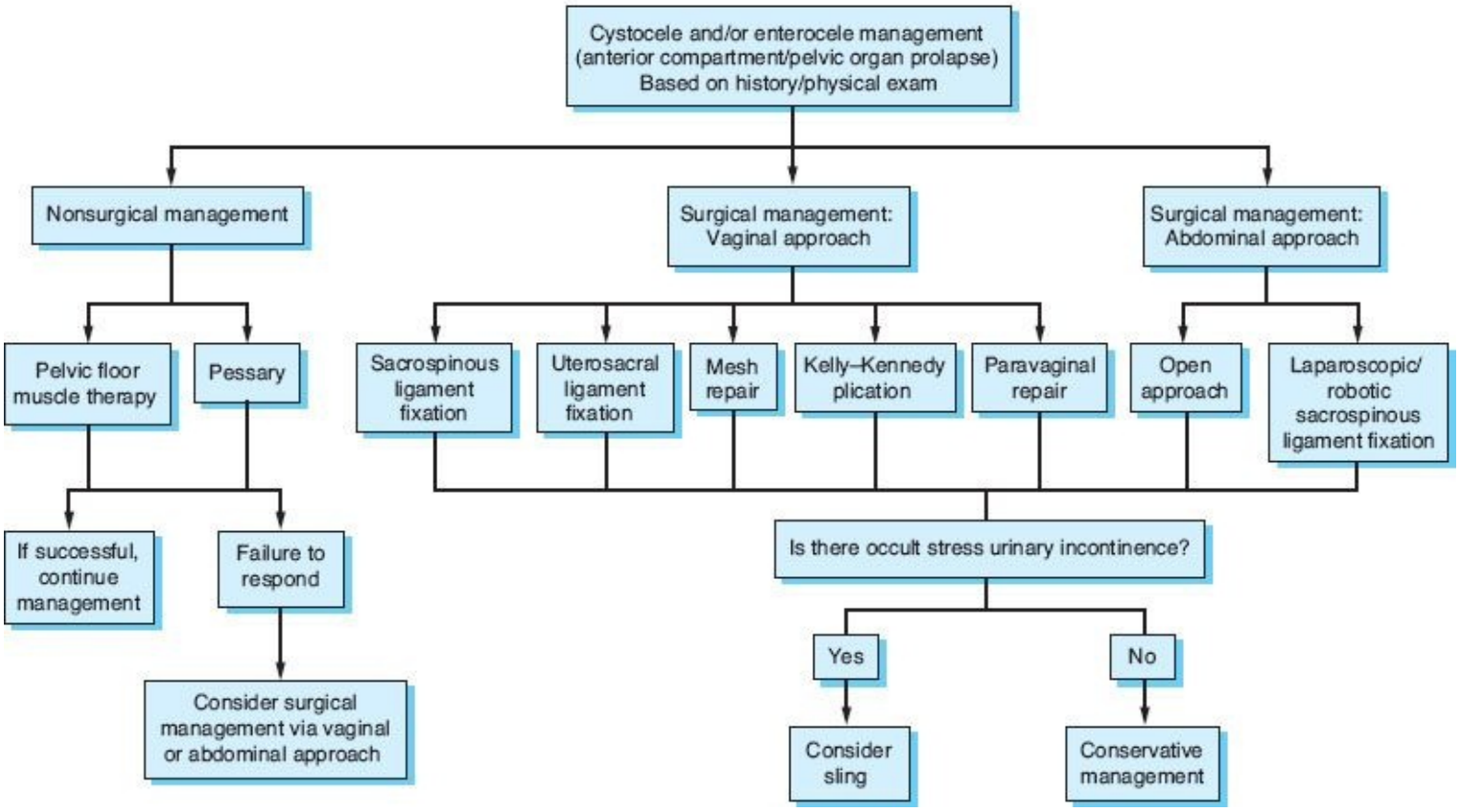
Cushing Syndrome



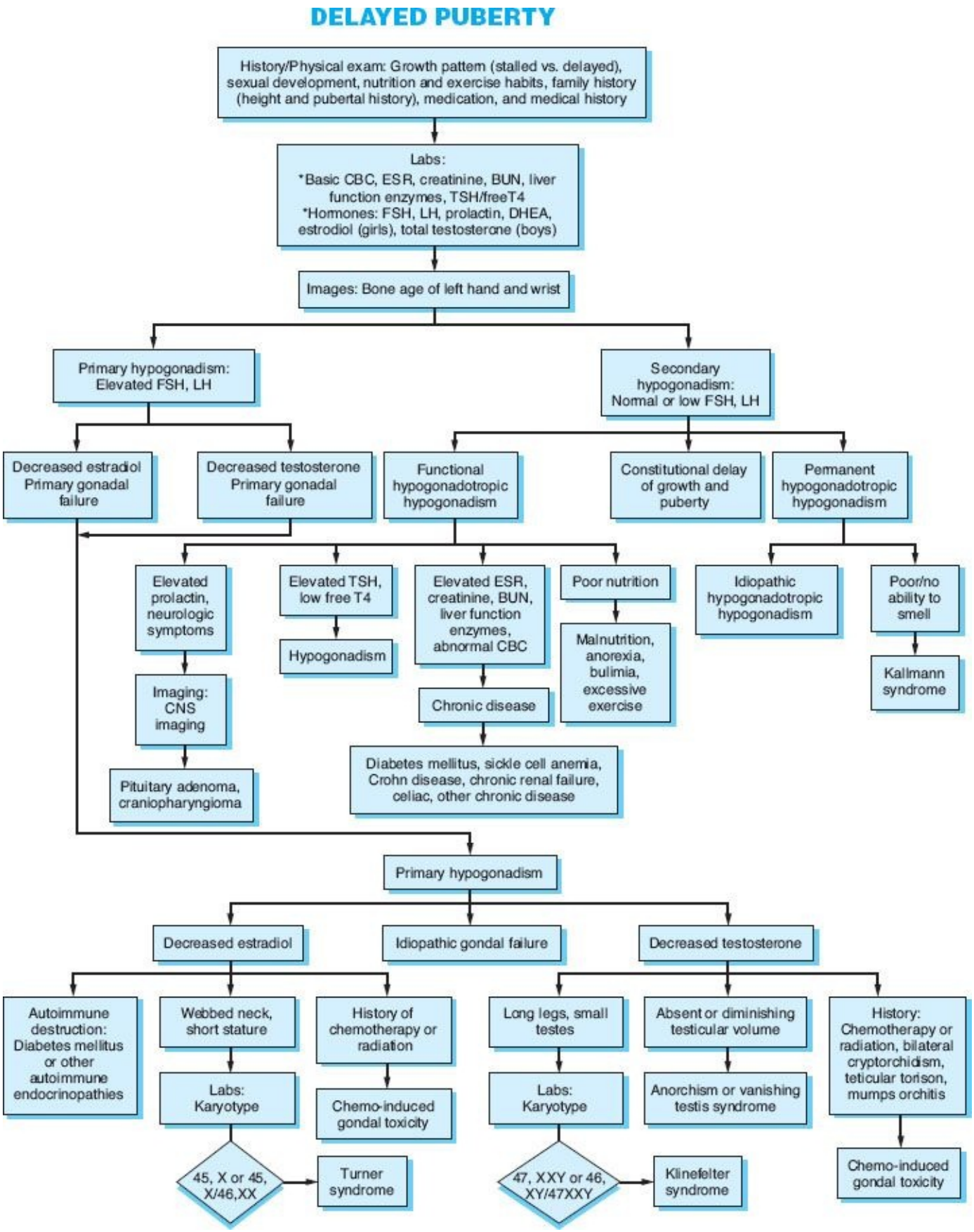
Adapted from Domino FJ, ed. *The 5-Minute Clinical Consult 2009*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

Cystocele and/or Enterocele

CYSTOCELE AND/OR ENTEROCELE



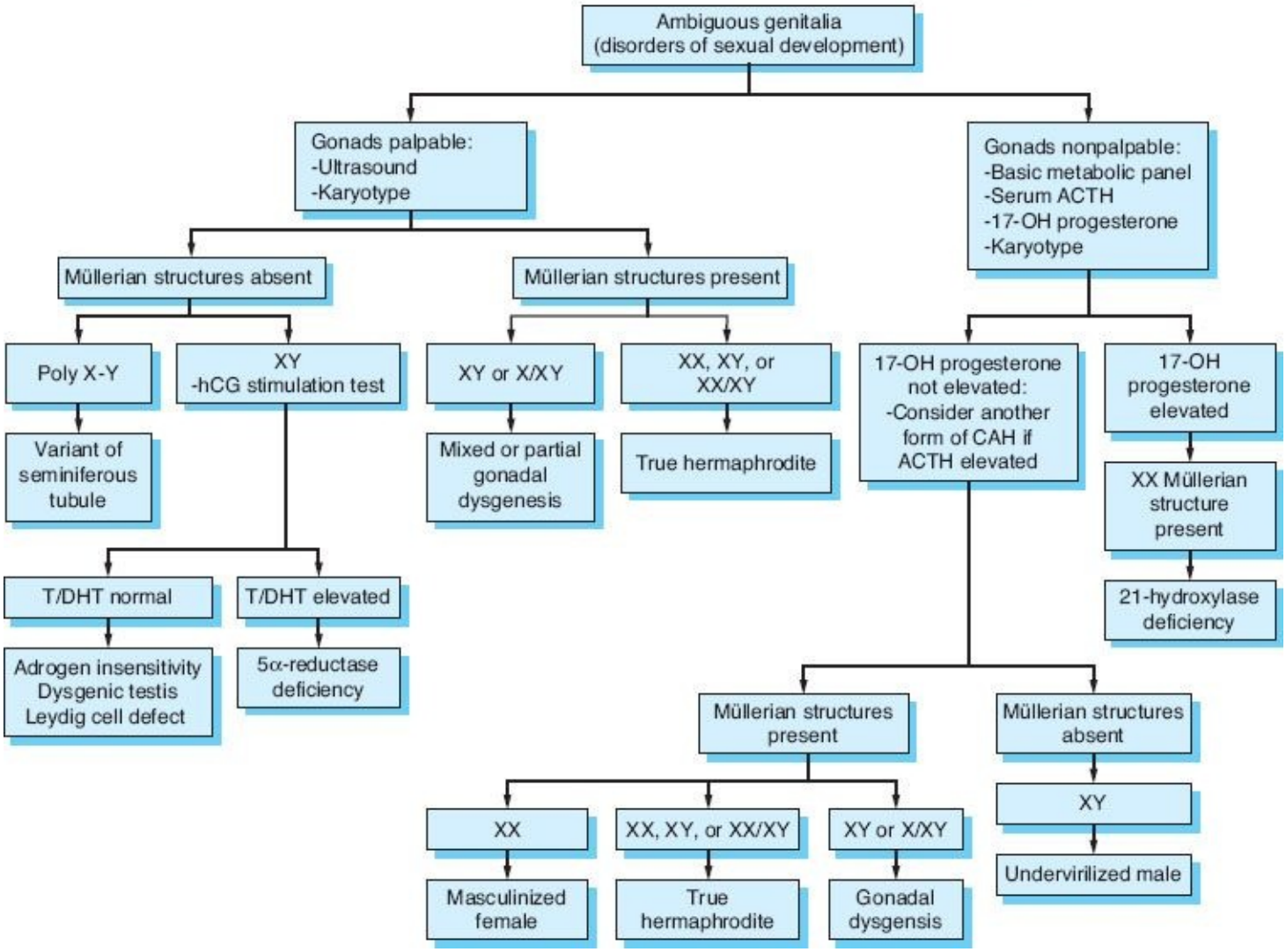
Delayed Puberty



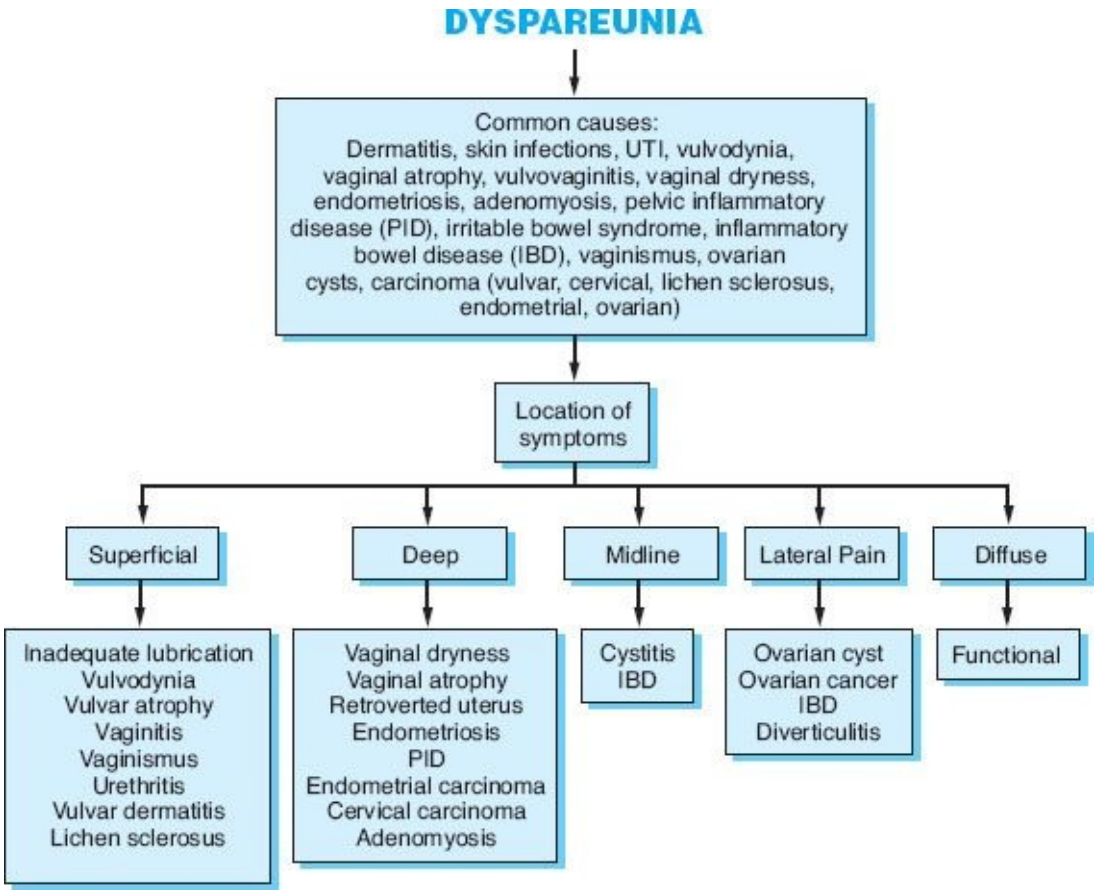
Master-Hunter T, Heiman DL. Amenorrhea: Evaluation and treatment. *Am Fam Physician.* 2006;73(8):1374–1382.

Disorders of Sexual Development (DSD)

DISORDERS OF SEXUAL DEVELOPMENT (DSD)

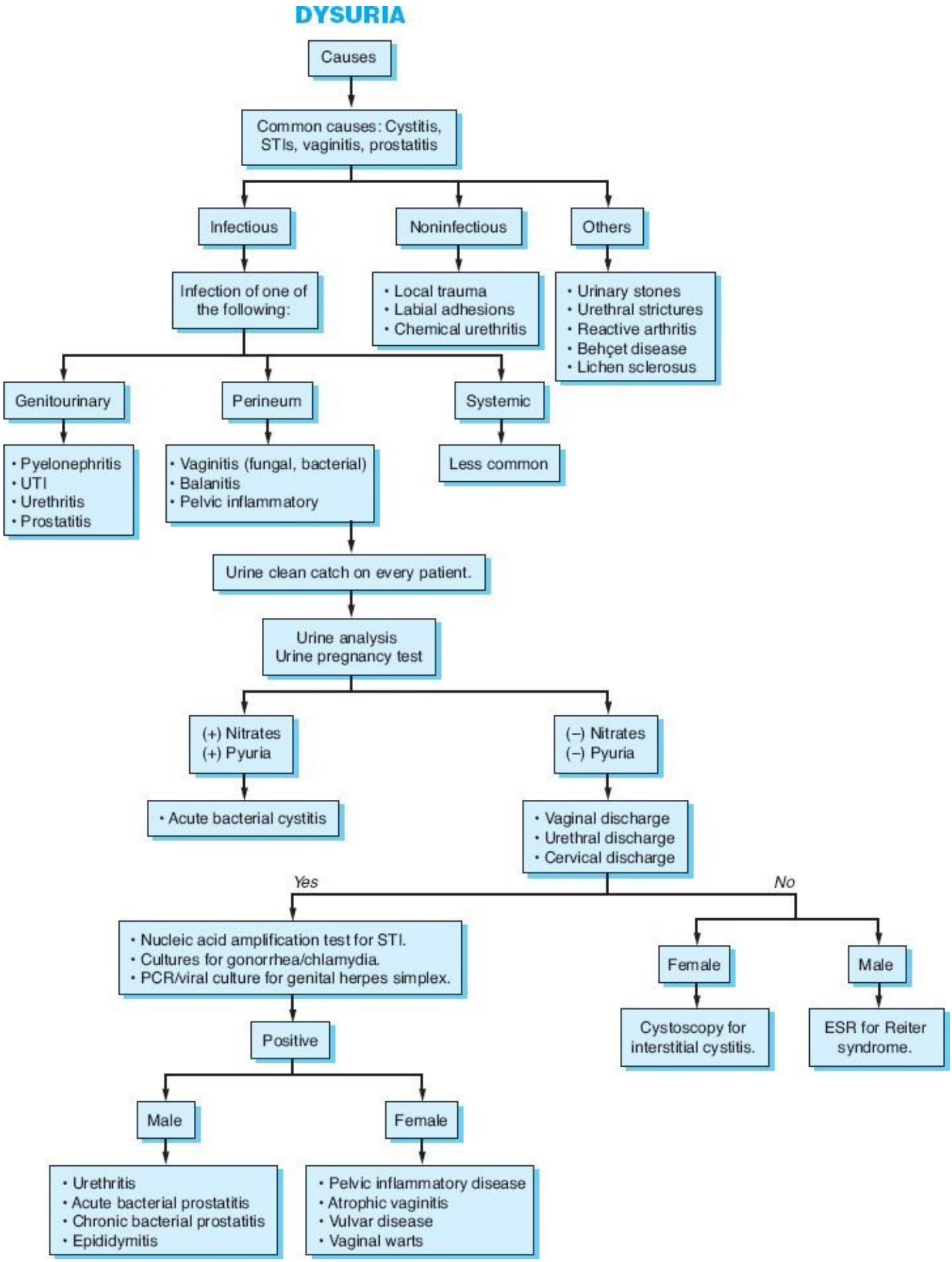


Dyspareunia



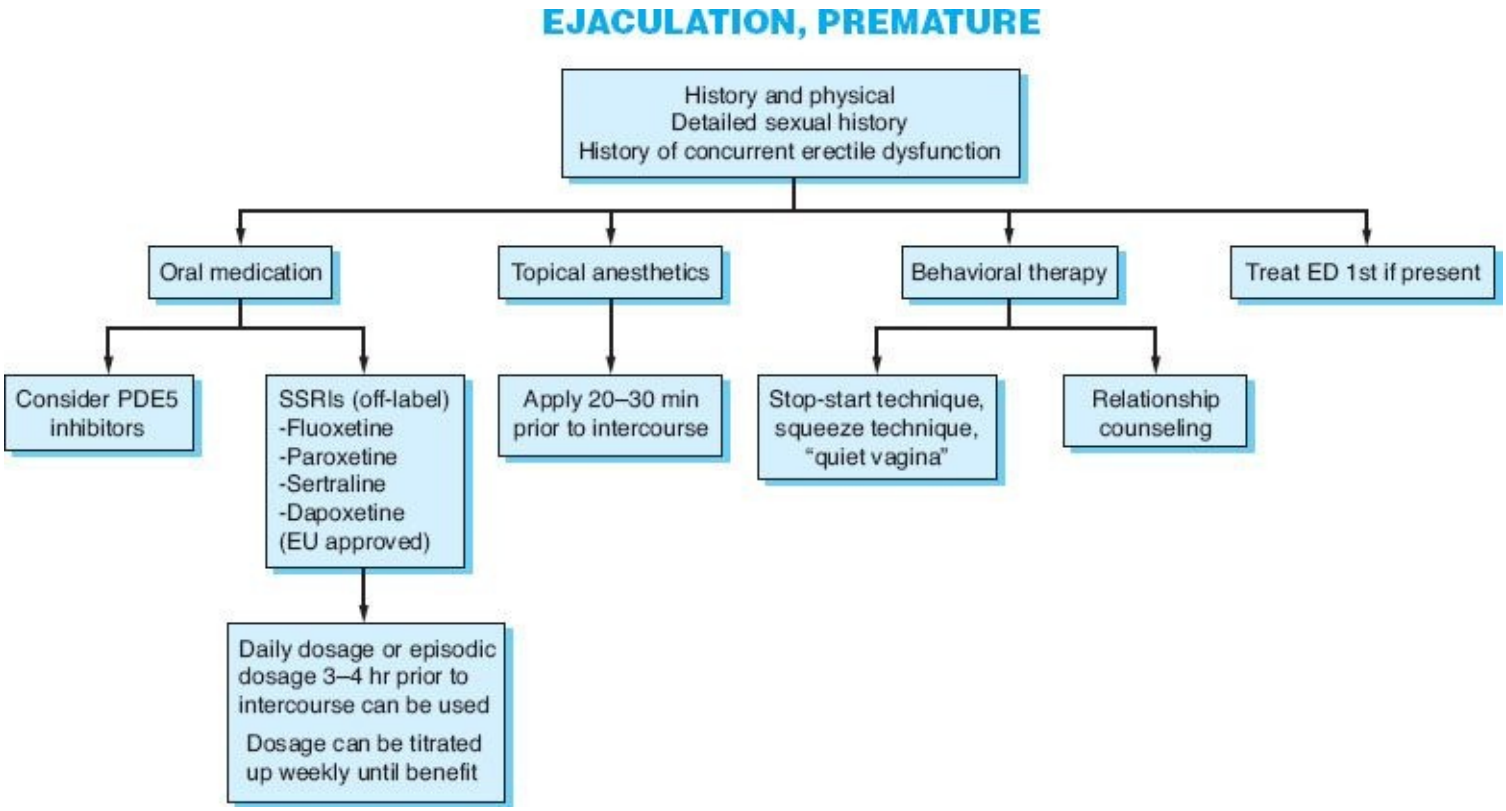
MacNeill C. Dyspareunia. *Obstet Gynecol Clin North Am.* 2006;33(4):565–577, viii.

Dysuria



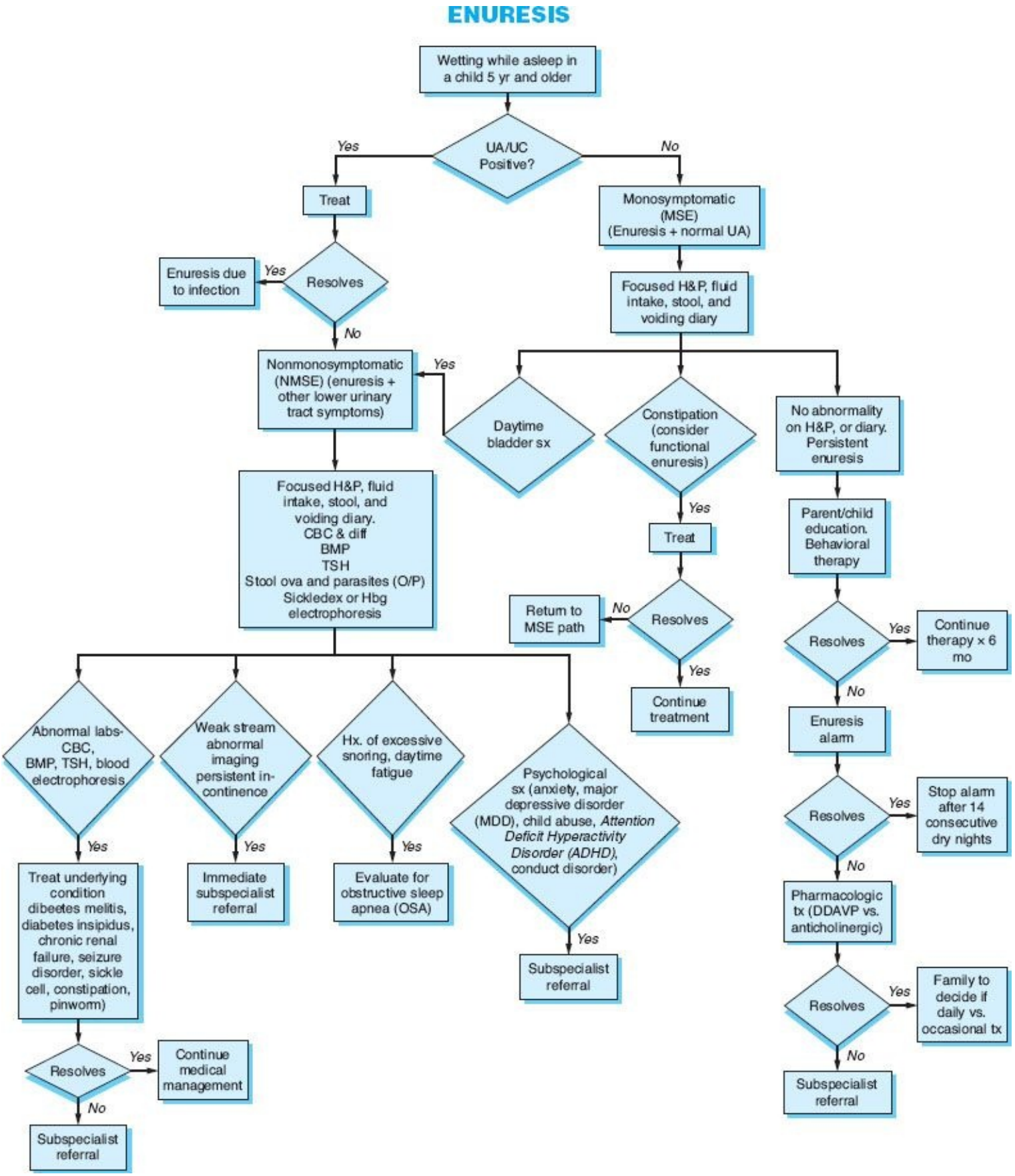
Mehnert-Kay SA. Diagnosis and management of uncomplicated urinary tract infections. *Am Fam Physician.* 2005;72(3):451–456.

Ejaculation, Premature



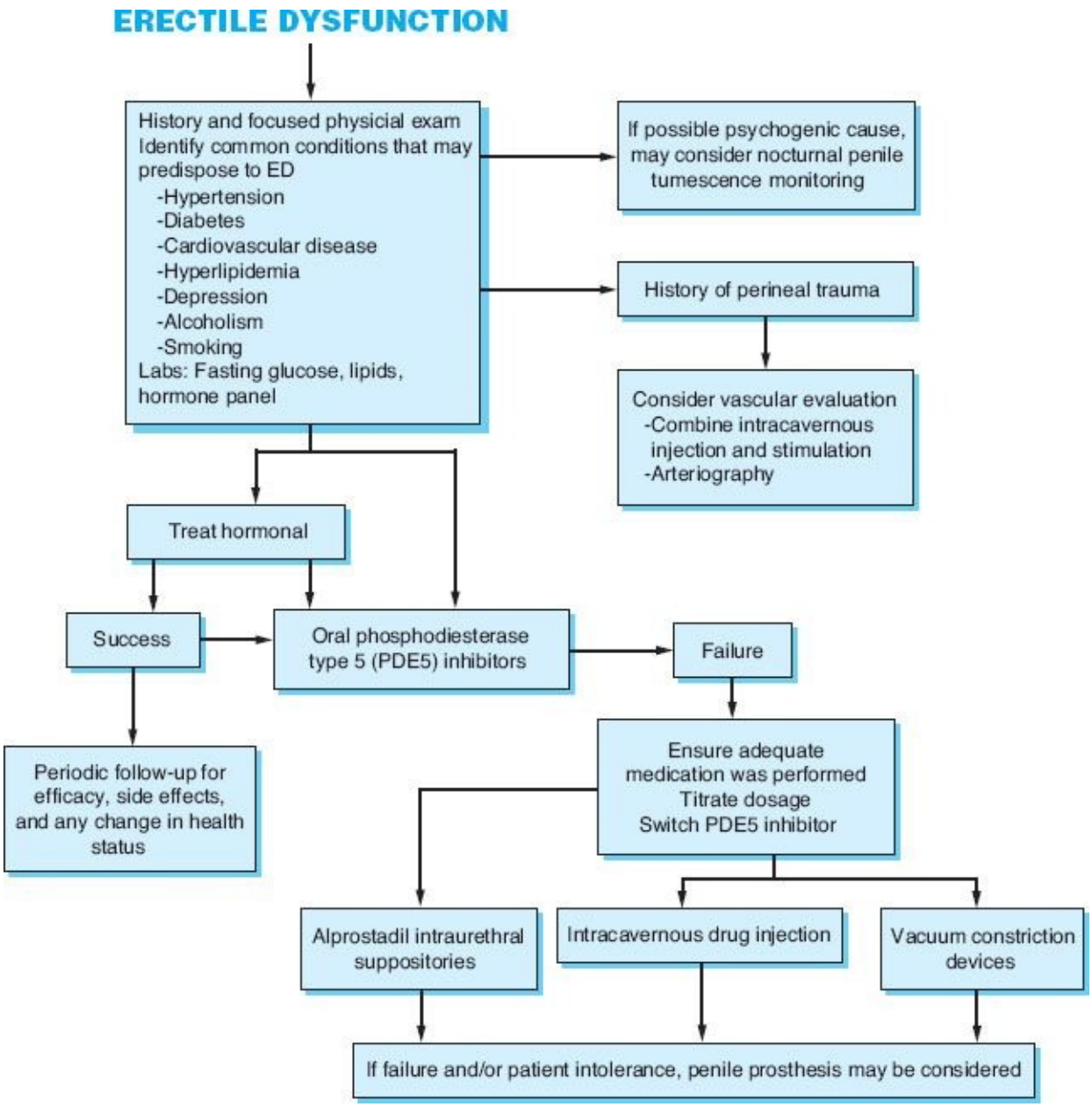
Adapted in part from Montague DK, Jarow J, Broderick GA, et al. AUA guideline on the pharmacologic management of premature ejaculation. *J Urol*. 2004;172(1):290–294; Wespes E, Eardly I, Guliano F, et al. EAU 2013 Guidelines on Male Sexual Dysfunction available at http://www.uroweb.org/guidelines/ (acessed May 26, 2014).

Enuresis



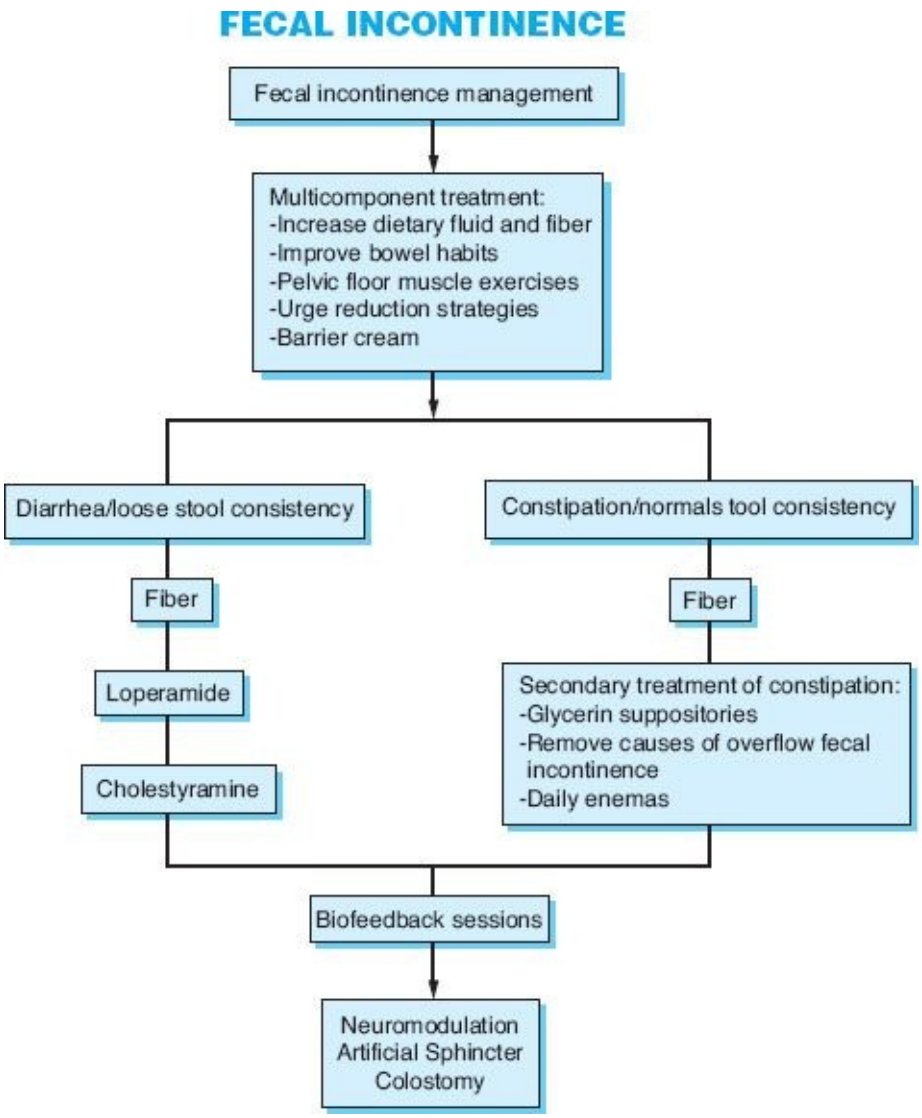
Franco I, von Gontard A, De Gennaro M, et al. Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: A standardization document from the International Children's Continence Society. *J Pediatr Urol.* 2013;9:234–243; Neveus T, Eggert P, Evans J, et al. Evaluation and treatment for monosymptomatic enuresis: A standardization document from the International Children's Continence Society. *J Urol.* 2010;183:441–447.

Erectile Dysfunction

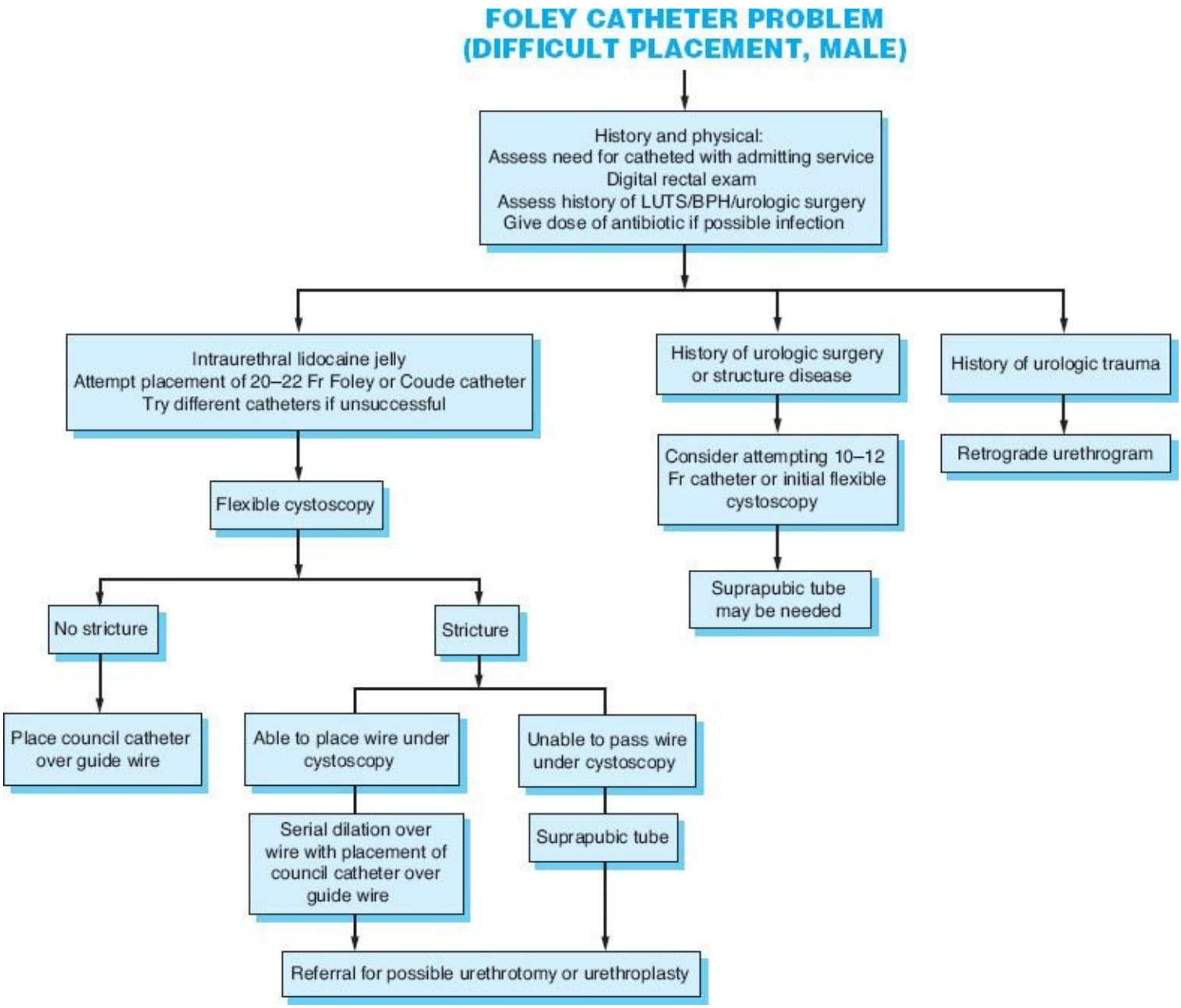


Adapted from Montague DK, Jarow J, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: An AUA update. *J Urol.* 2005;174(1):230–239.

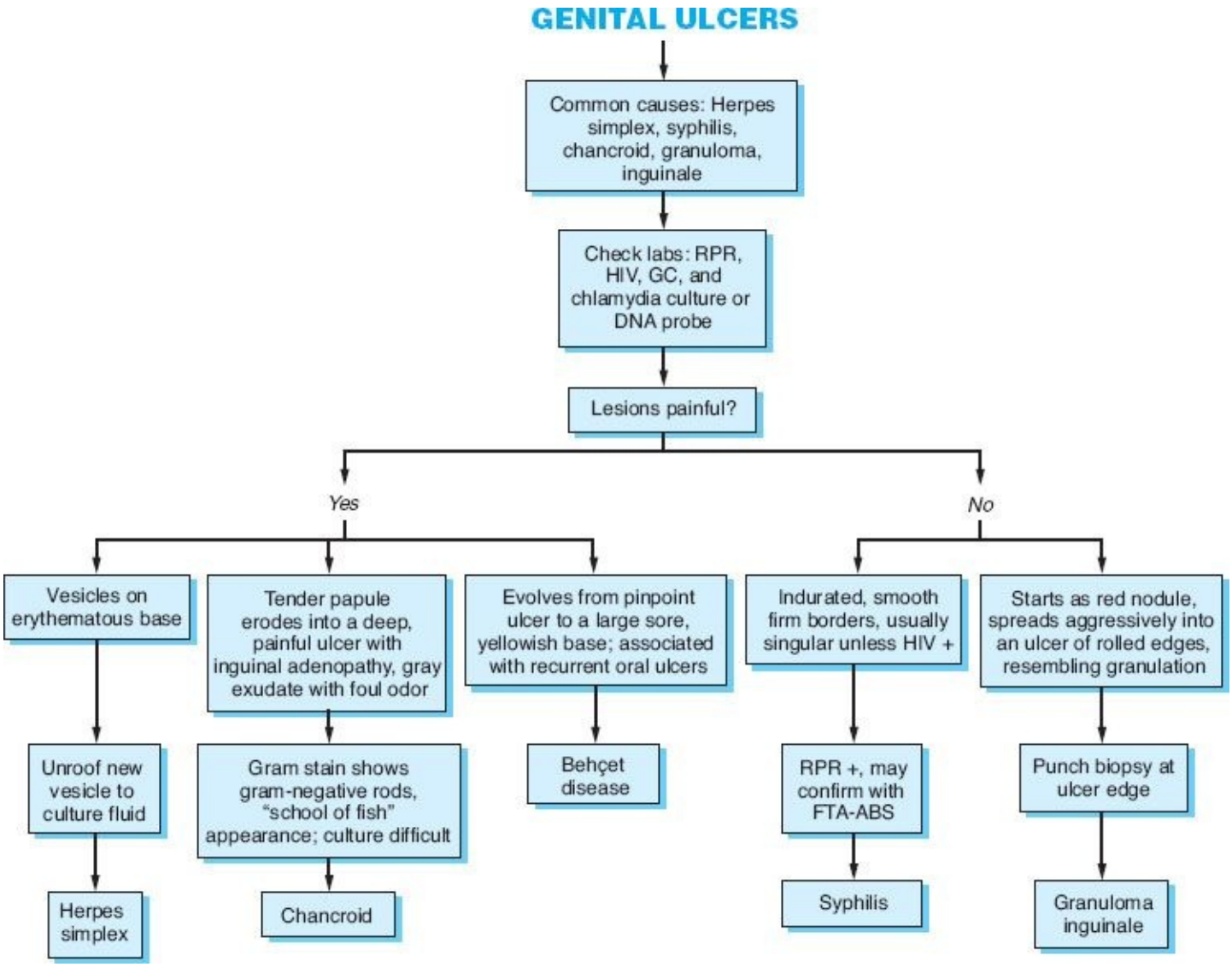
Fecal Incontinence



Foley Catheter Problem (Difficult Placement, Male)

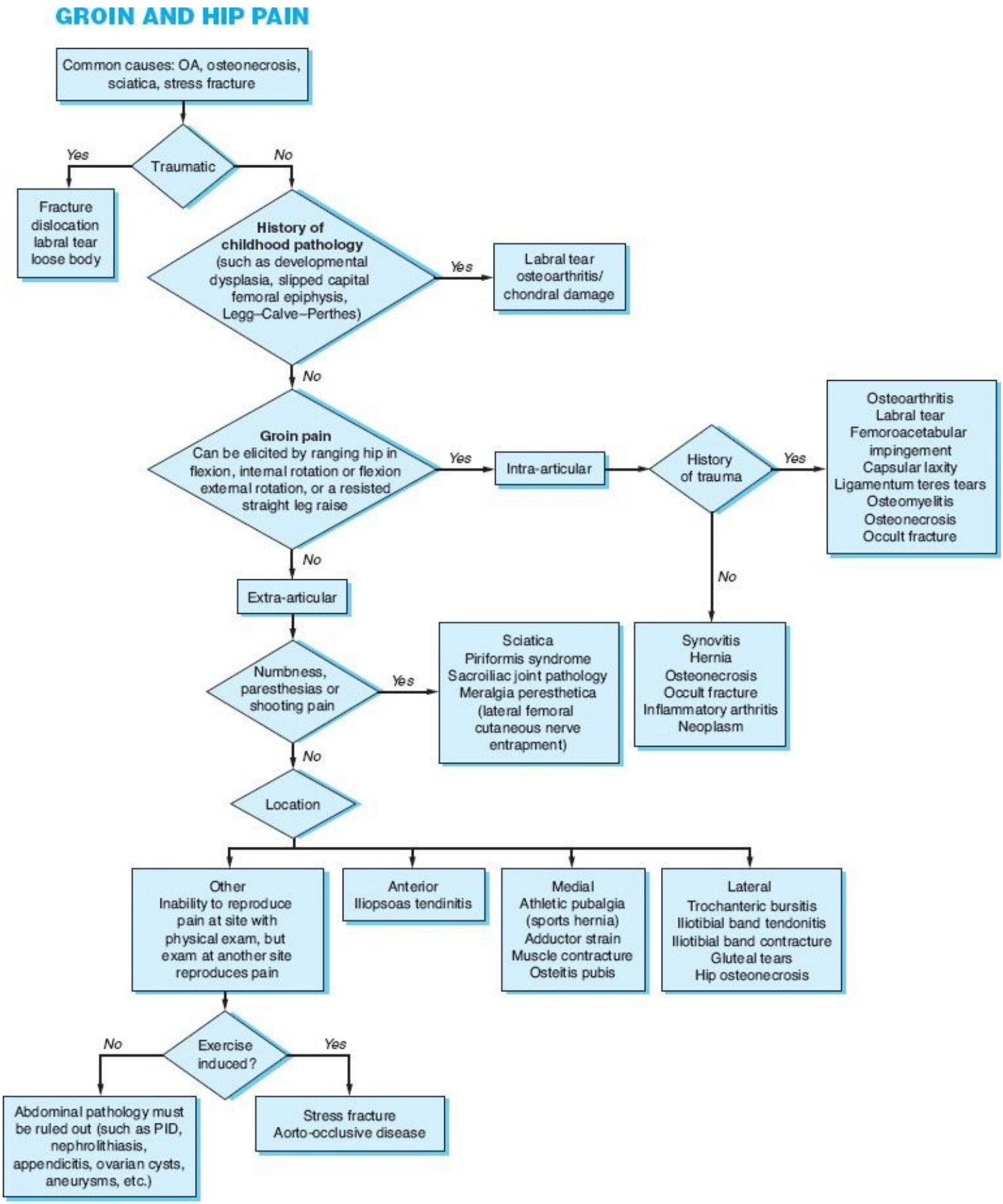


Genital Ulcers



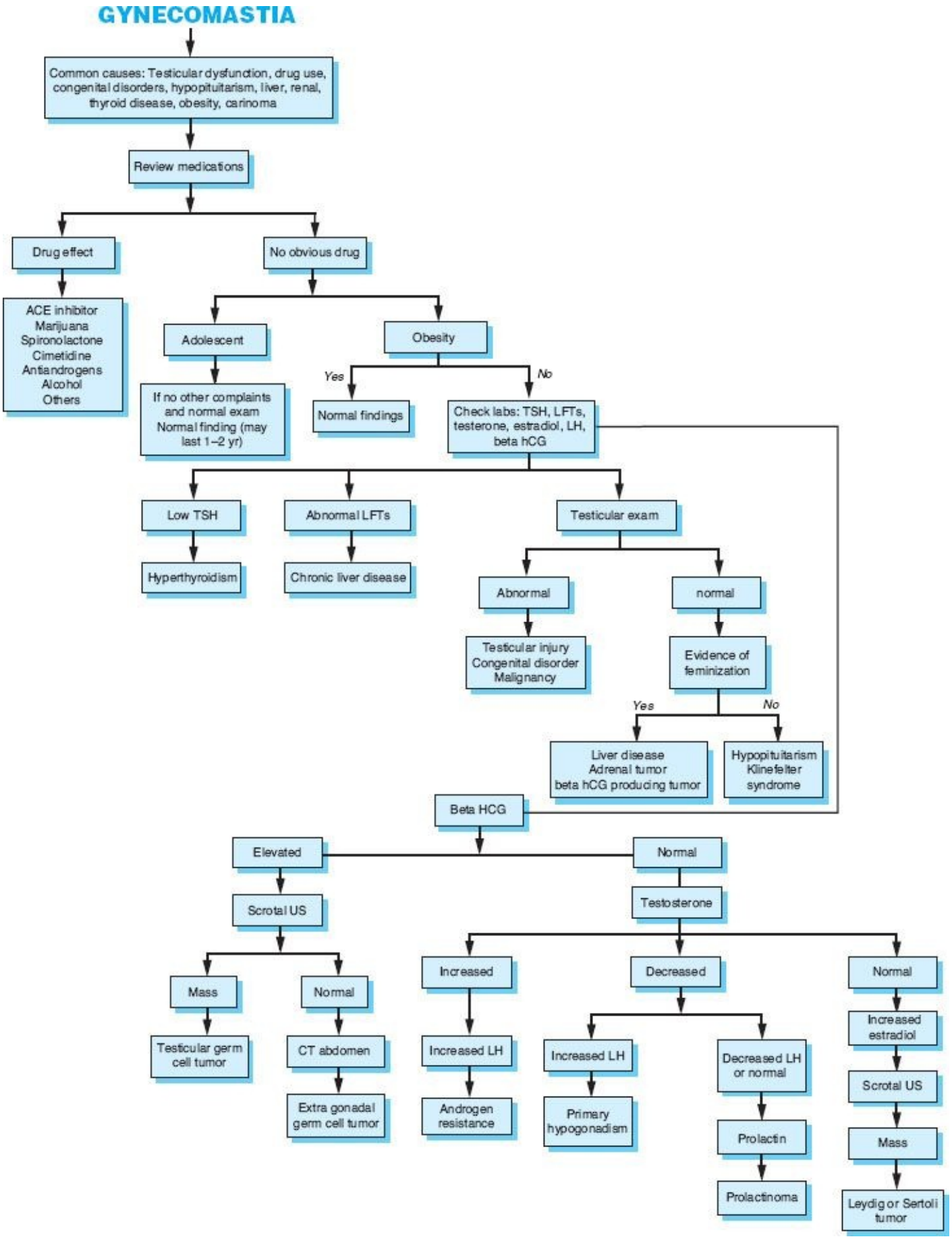
O'Farrell N, Morison L, Moodley P, et al. Genital ulcers and concomitant complaints in men attending a sexually transmitted infections clinic: Implications for sexually transmitted infections management. *Sex Transm Dis.* 2008;35(6):545–549.

Groin and Hip Pain



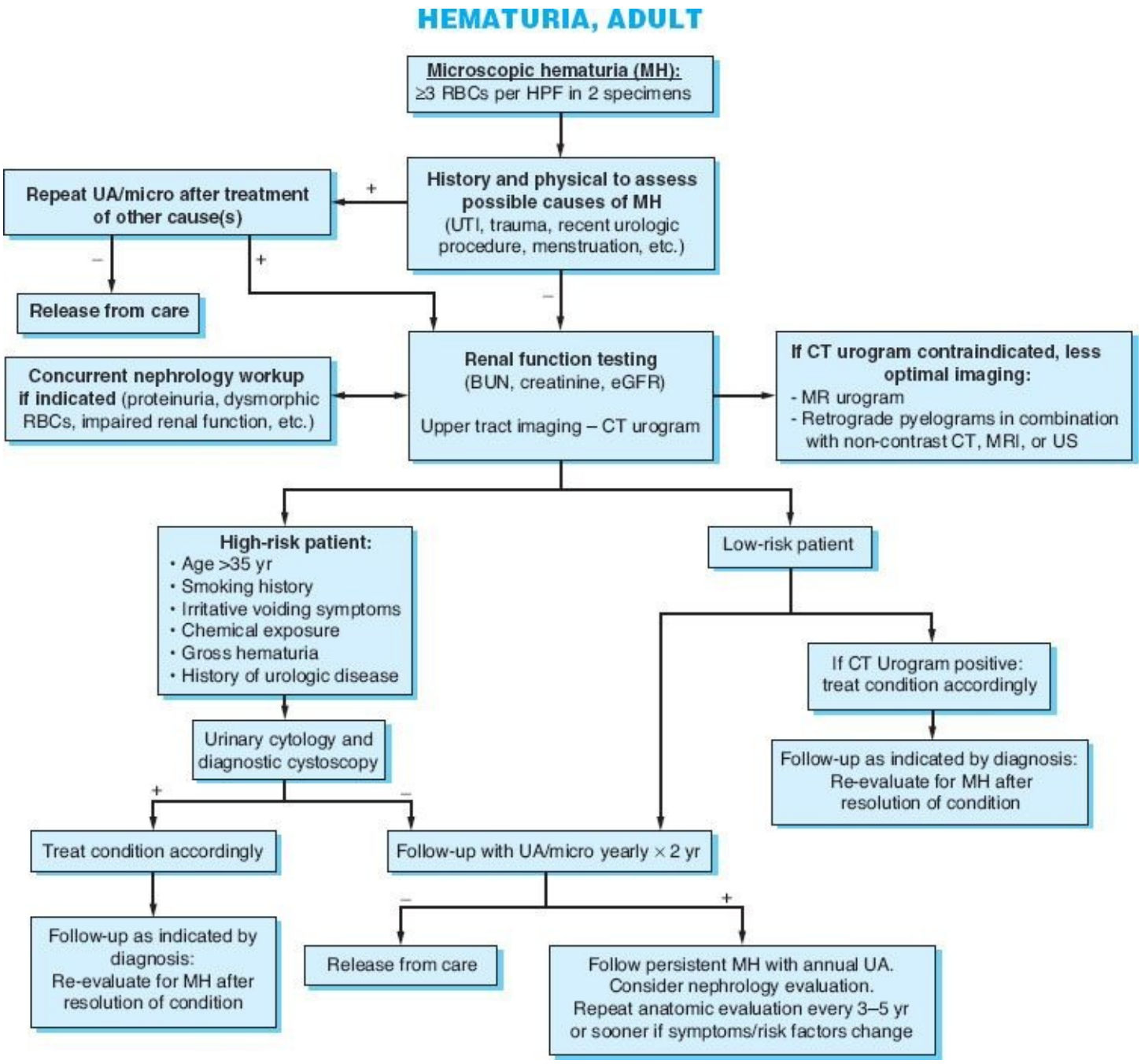
Kuhlman GS, Domb BG. Hip impingement: Identifying and treating a common cause of hip pain. *Am Fam Physician.* 2009;80:1429–1434.

Gynecomastia



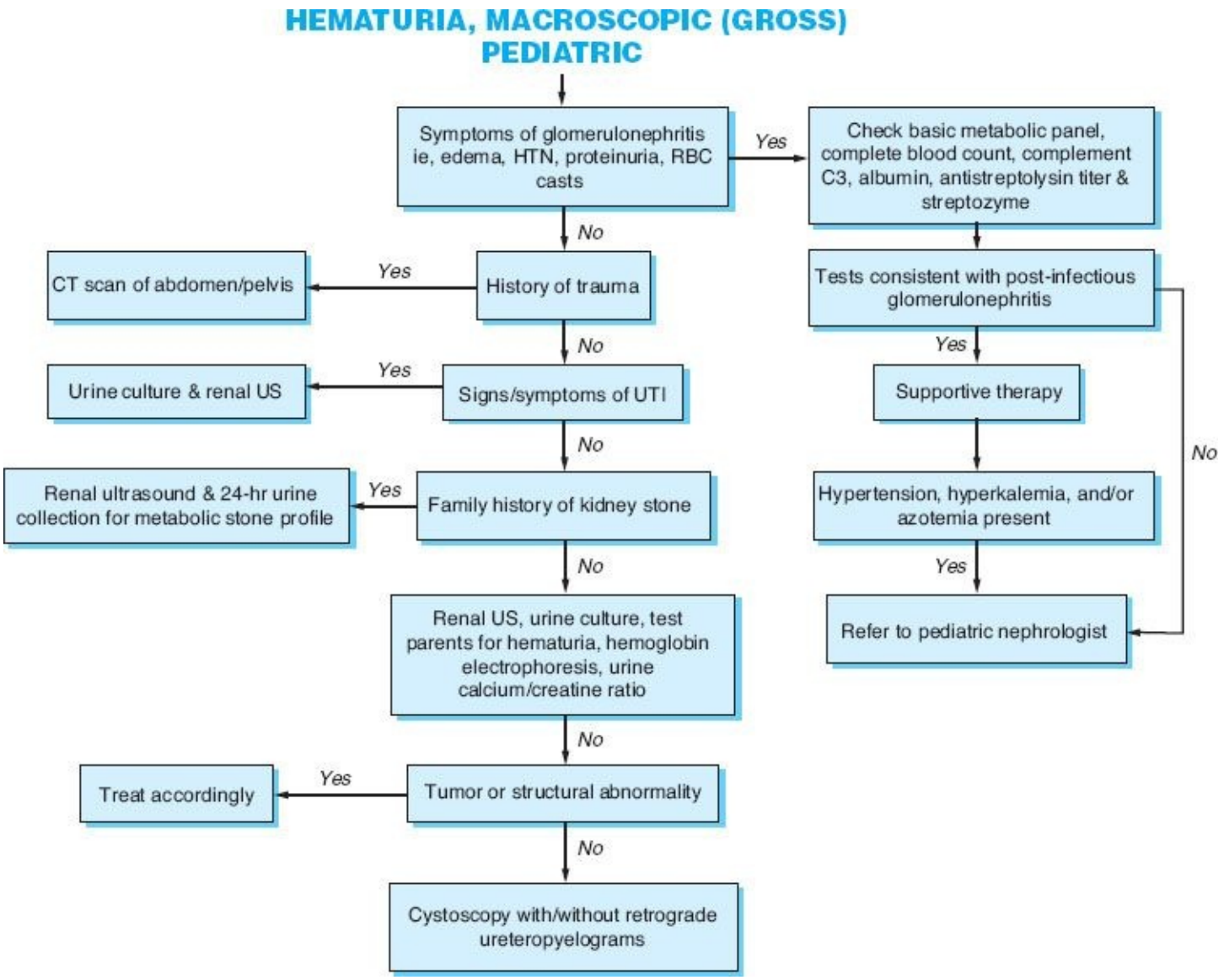
Adapted from Domino FJ, ed. *The 5-Minute Clinical Consult 2009*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

Hematuria, Adult

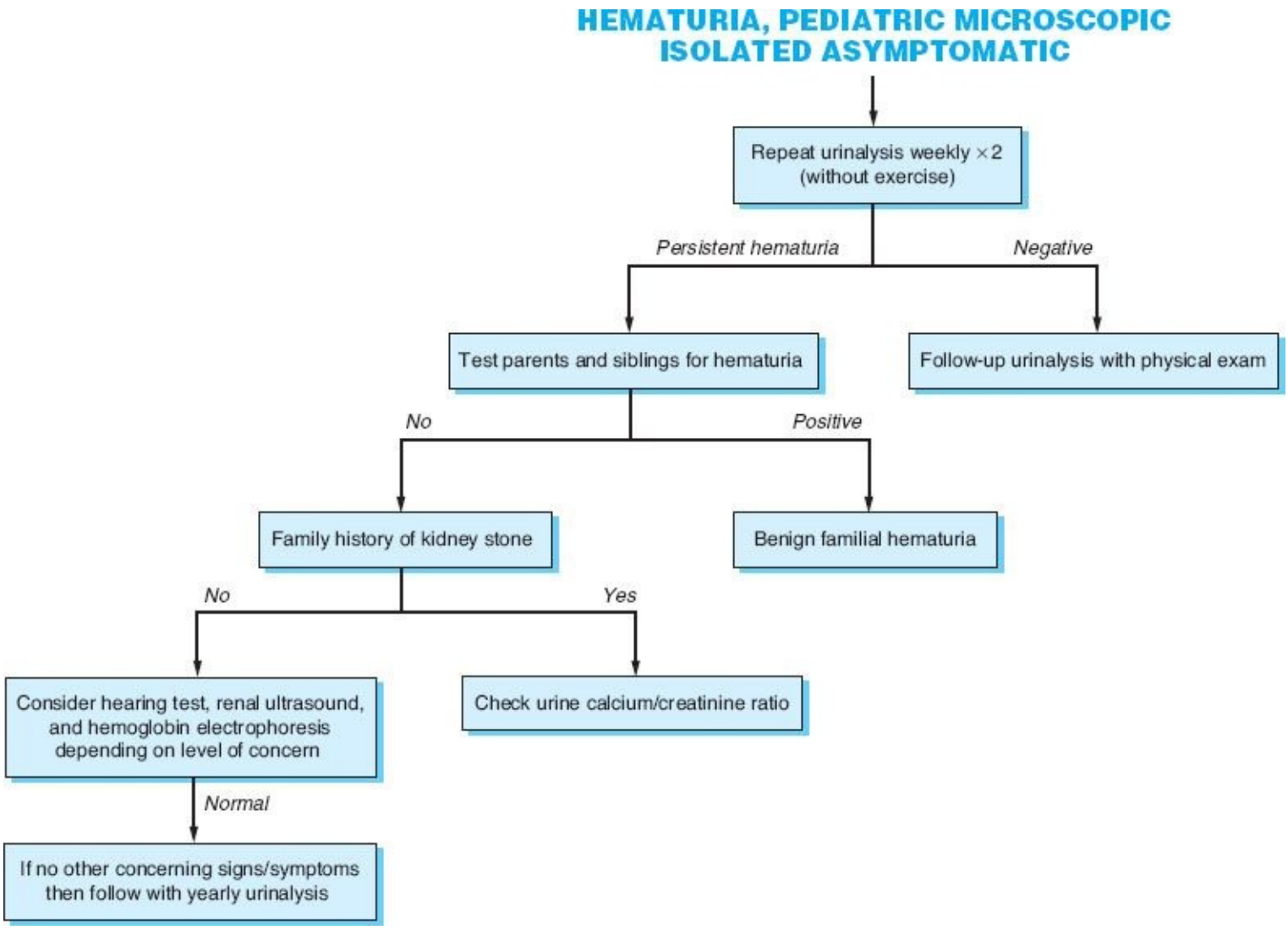


Adapted from Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol.* 2012;188:2473–2481.

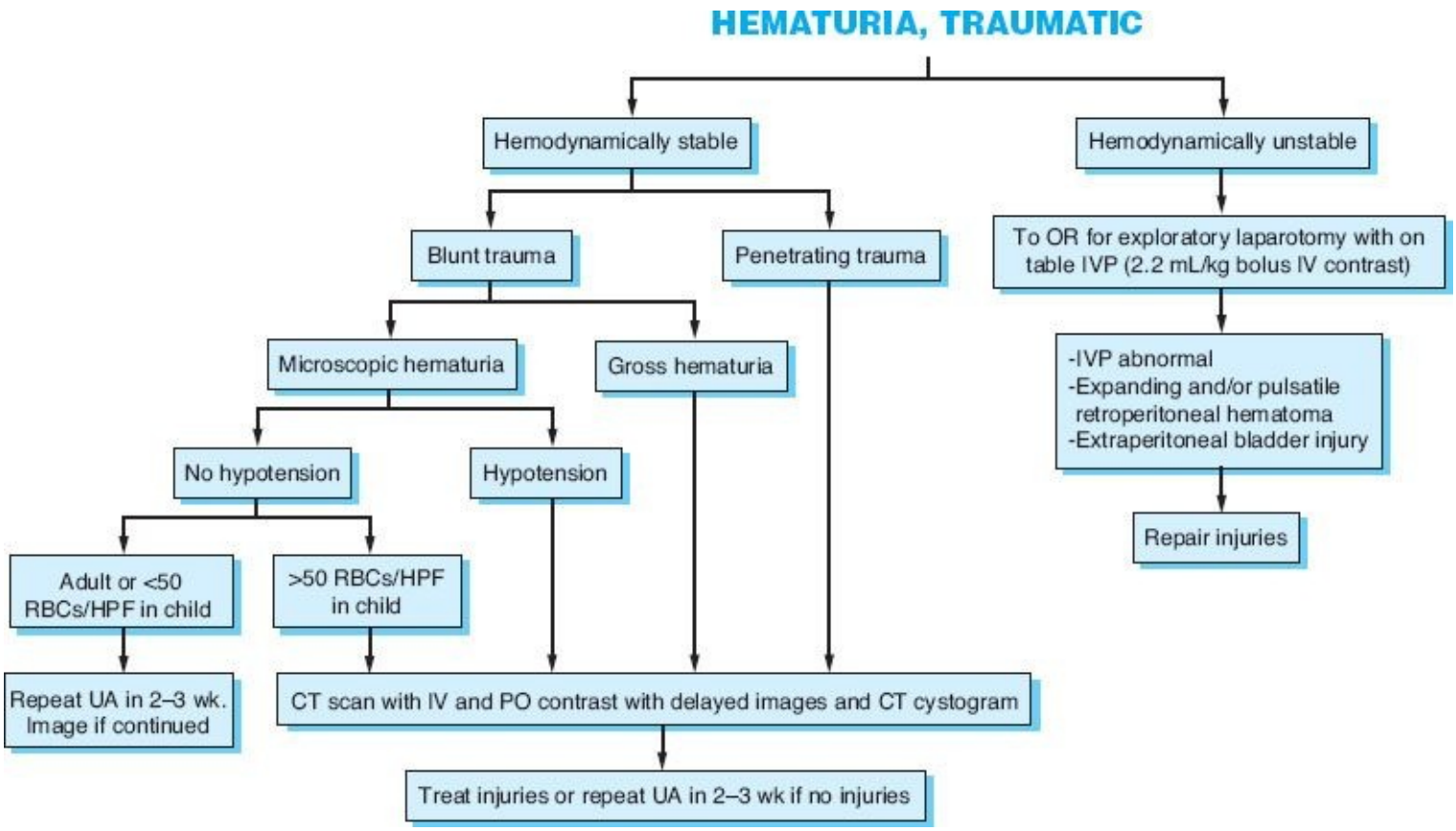
Hematuria, Macroscopic (Gross) Pediatric



Hematuria, Pediatric Microscopic Isolated Asymptomatic

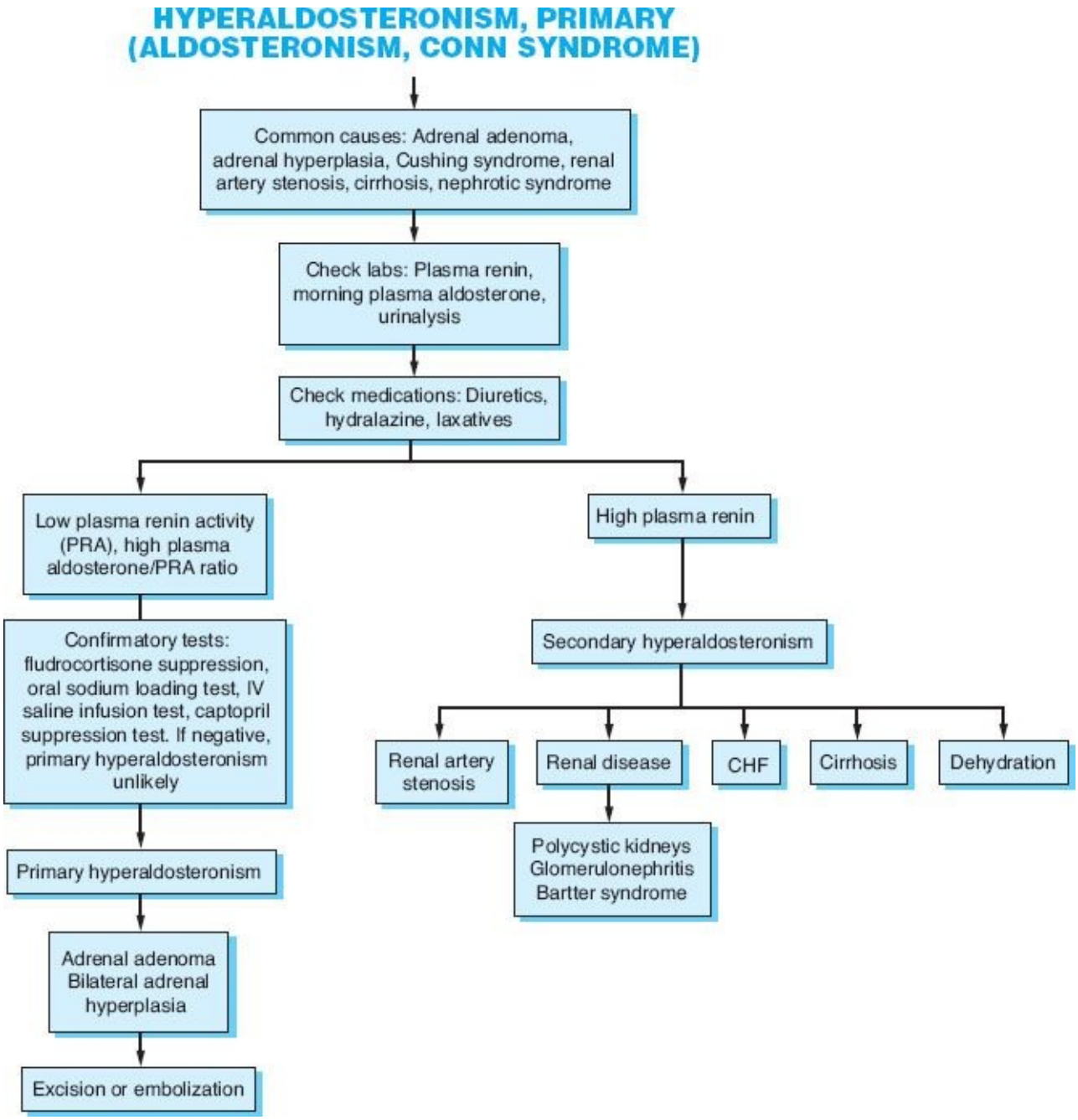


Hematuria, Traumatic



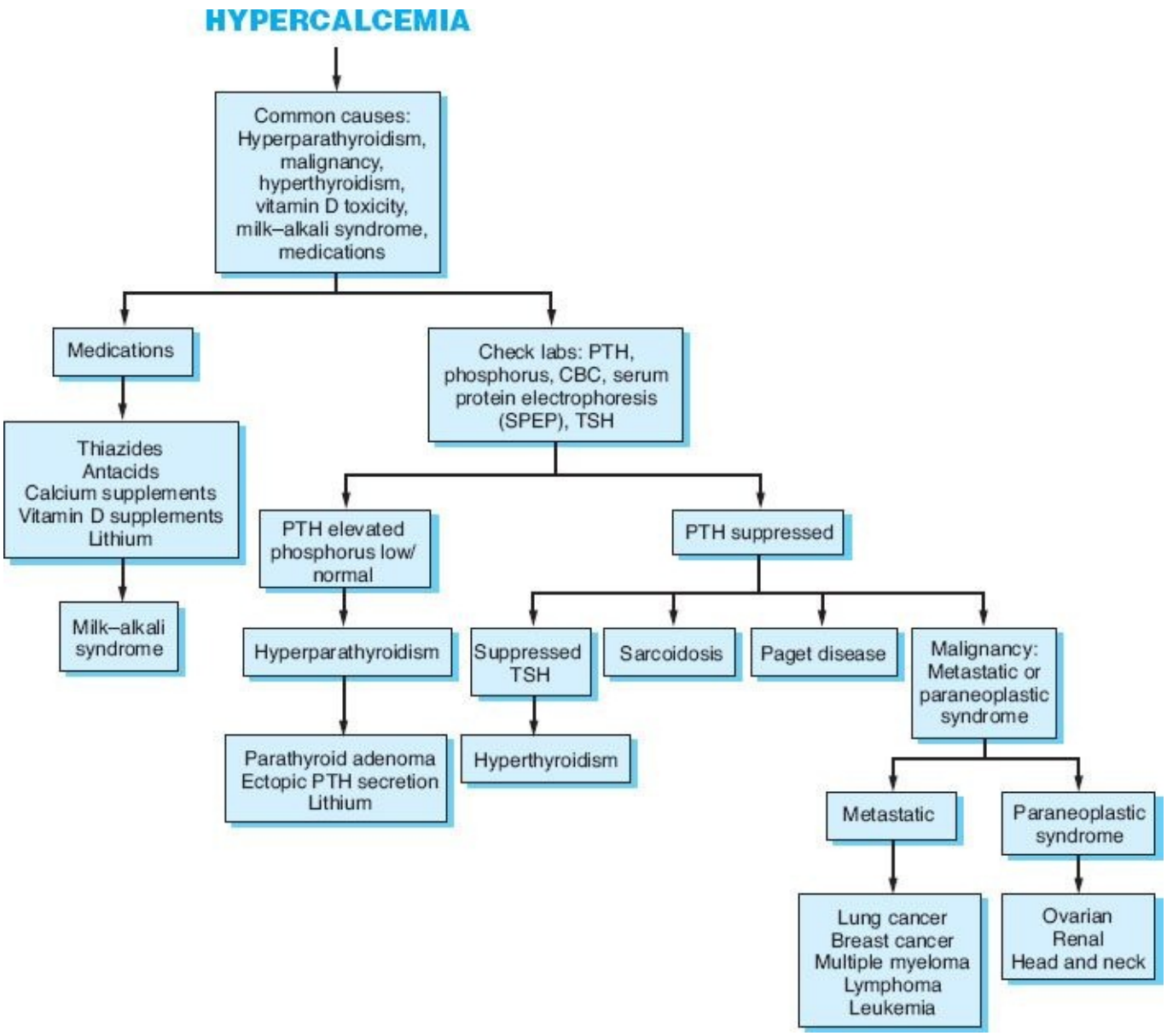
Adapted from Miller KS, McAninch JW. Radiographic assessment of renal trauma: Our 15 year experience. *J Urol.* 1995;154:352–355; Perez-Brayfield, Gatti JM, Smith EA. Blunt traumatic hematuria in children. Is a simplified algorithm justified? *J Urol.* 2002;167(6):2543–2546.

Hyperaldosteronism, Primary (Aldosteronism, Conn Syndrome)



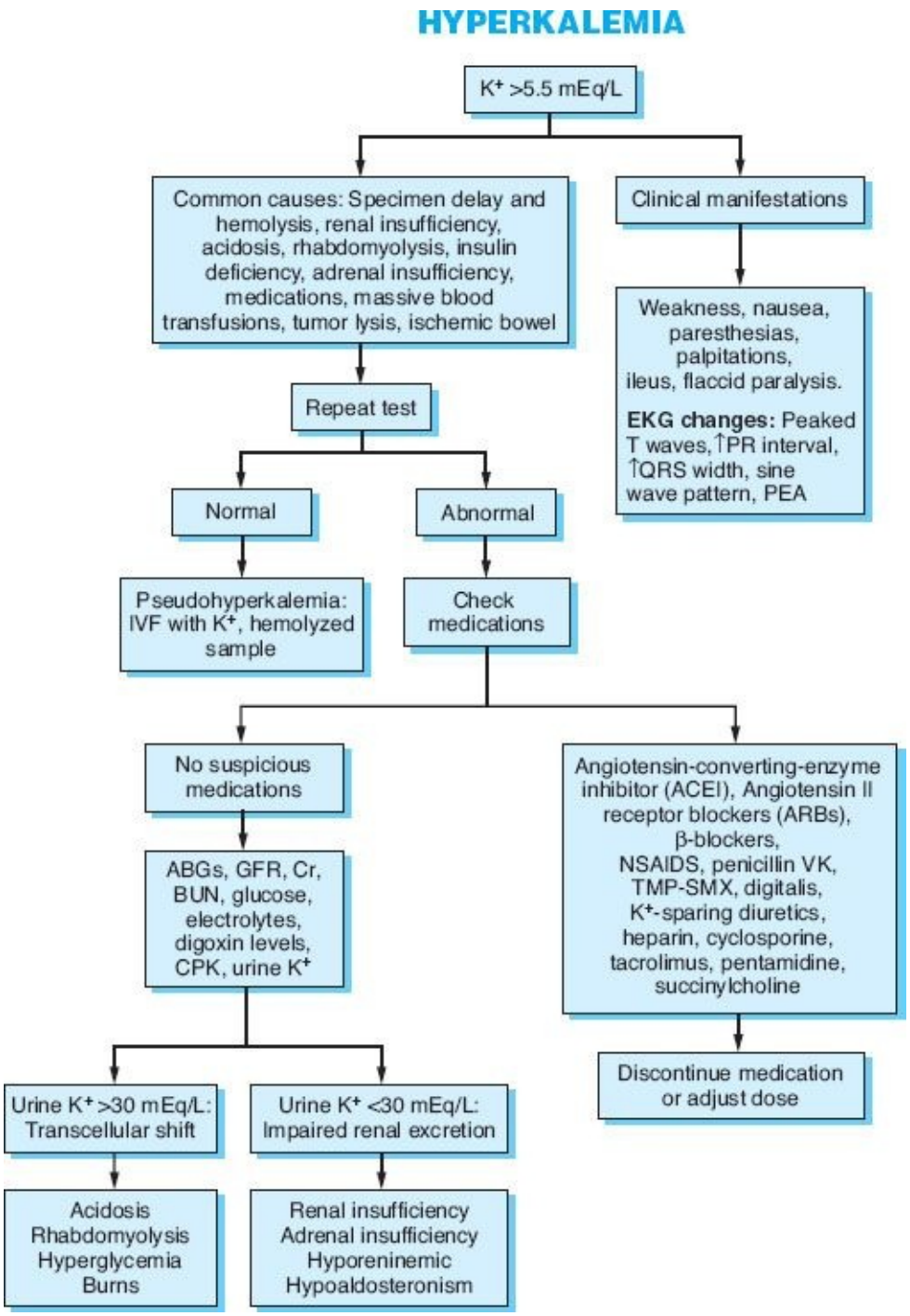
Modified from Domino FJ, ed. *The 5-Minute Clinical Consult 2009*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.

Hypercalcemia



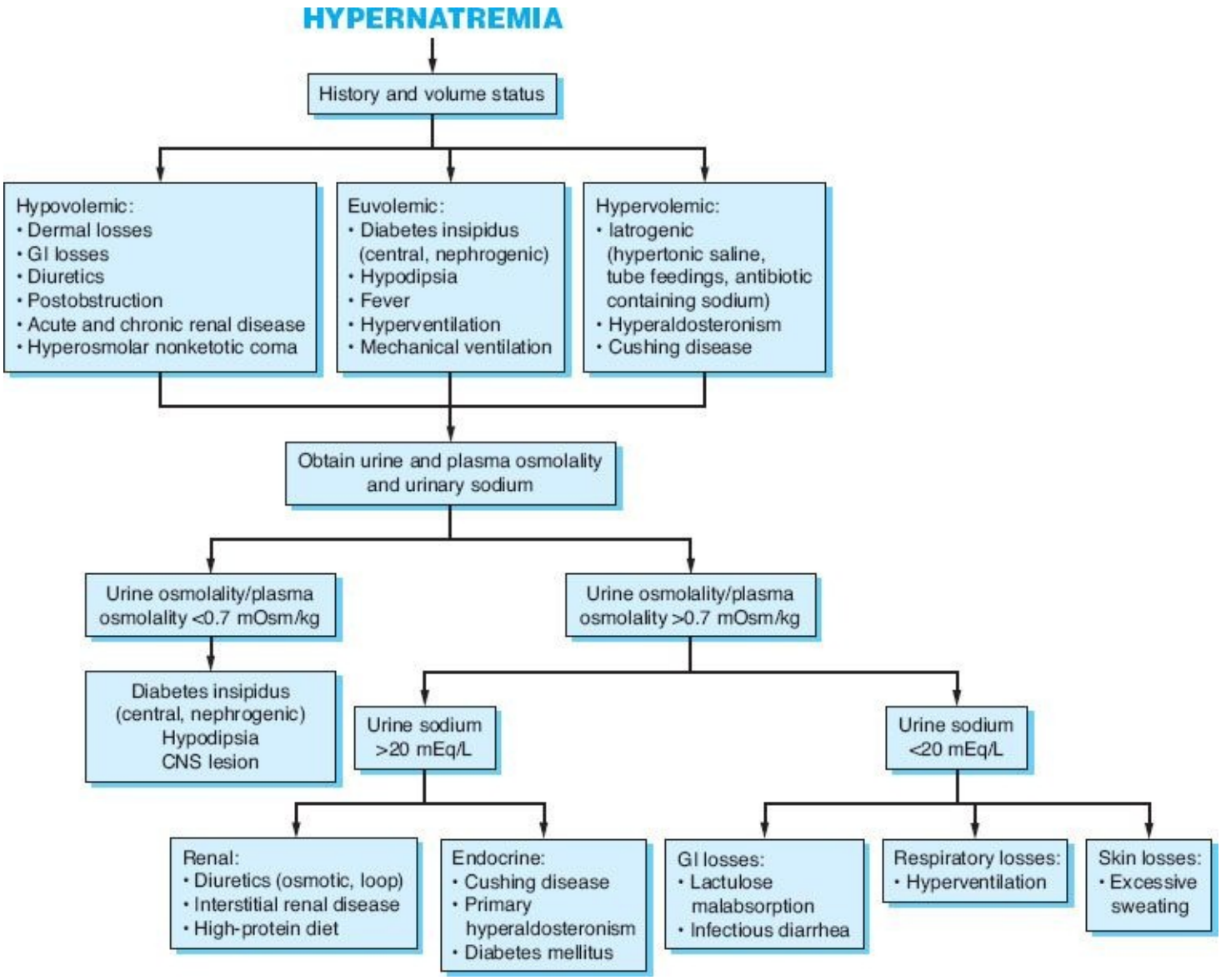
Carroll MF, Schade DS. A practical approach to hypercalcemia. *Am Fam Physician.* 2003;67(9):1959–1966.

Hyperkalemia



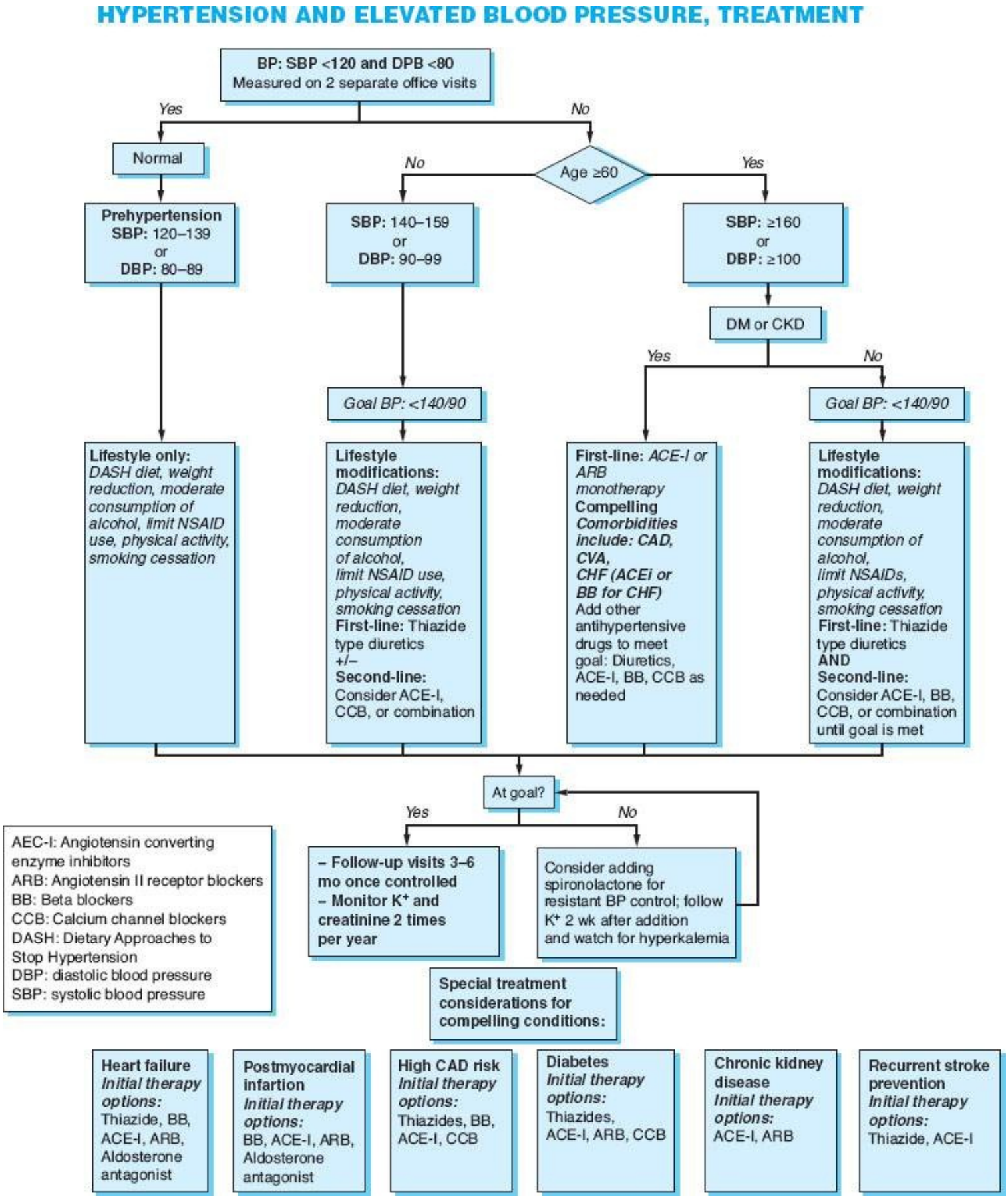
Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. *Am J Kidney Dis.* 2010;56(2):387–393.

Hypernatremia



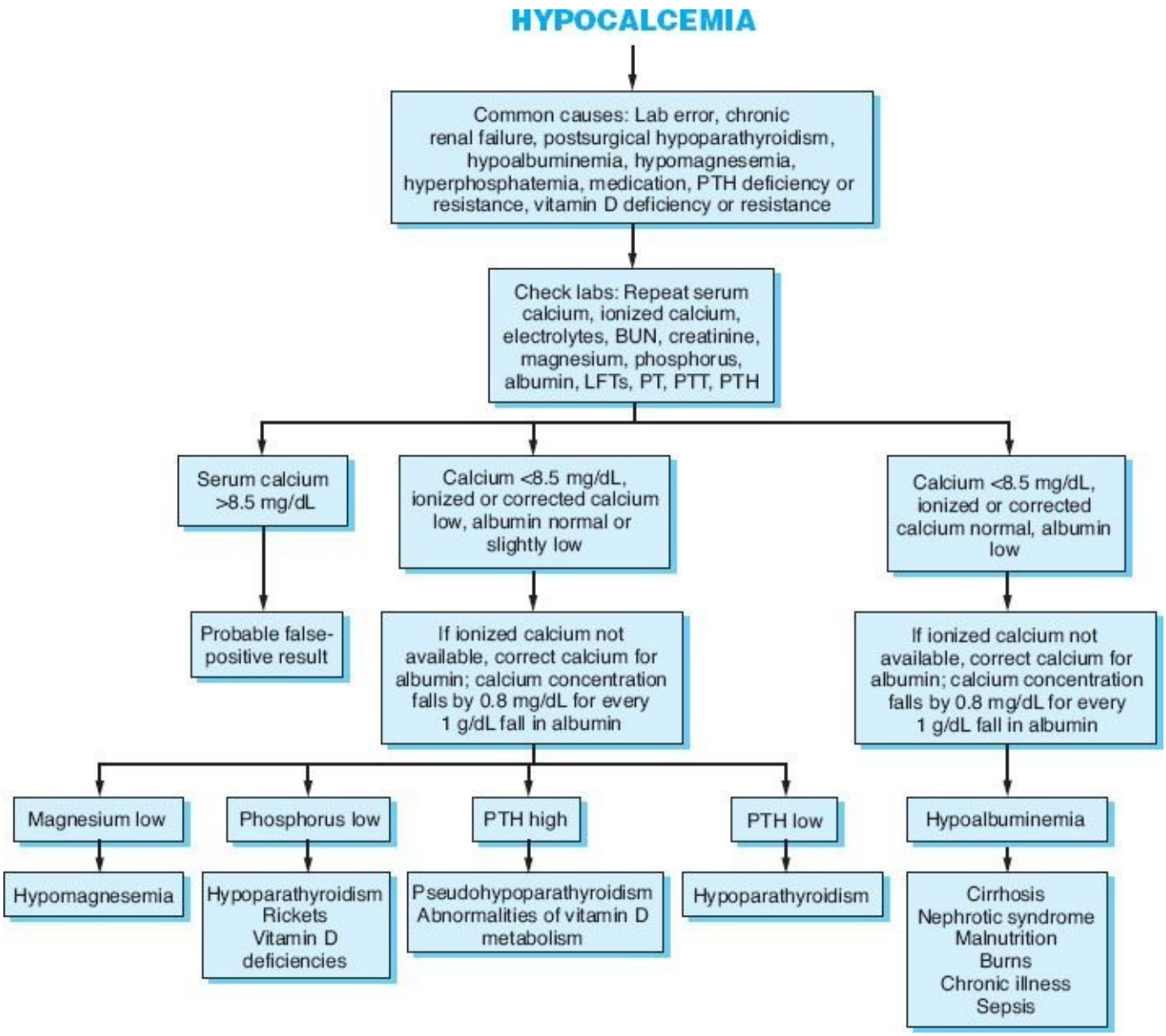
Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ.* 2006;332:702–705.

Hypertension and Elevated Blood Pressure, Treatment



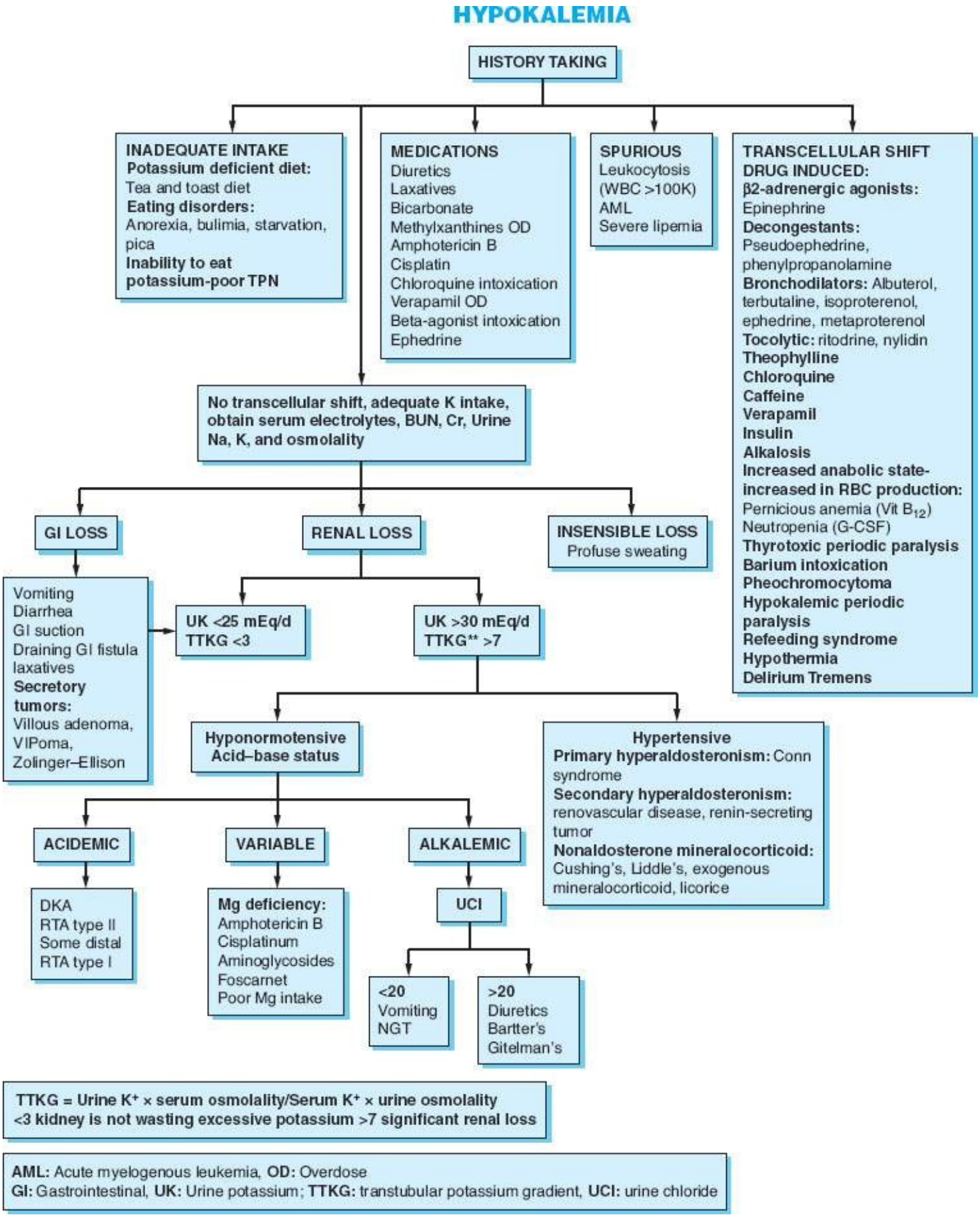
National Heart, Lung, and Blood Institute. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)*. Bethesda, MD: National Heart, Lung, and Blood Institute. 2004.

Hypocalcemia



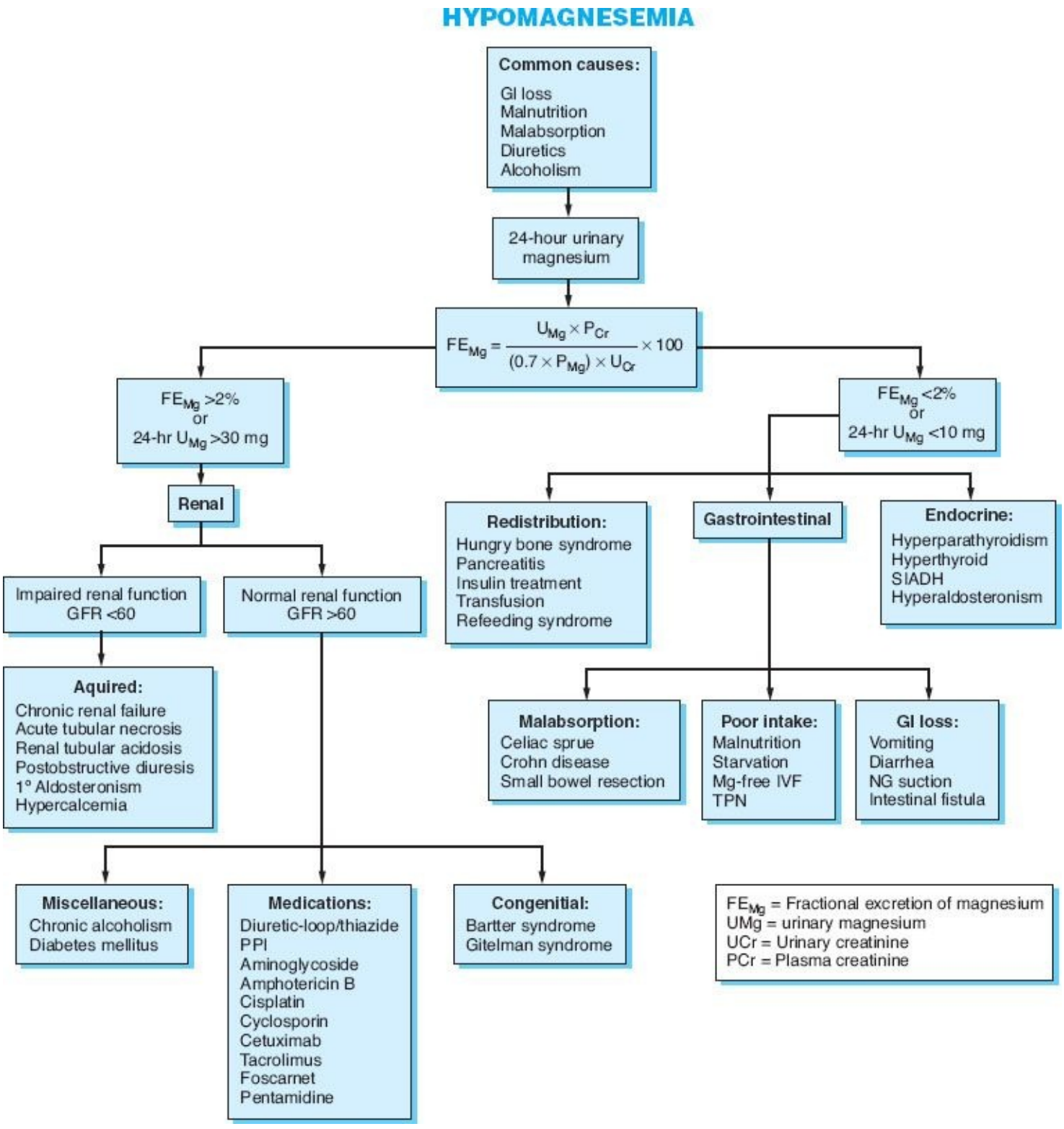
Michels TC, Kelly KM. Parathyroid disorders. *Am Fam Physician.* 2013;88:249–257.

Hypokalemia



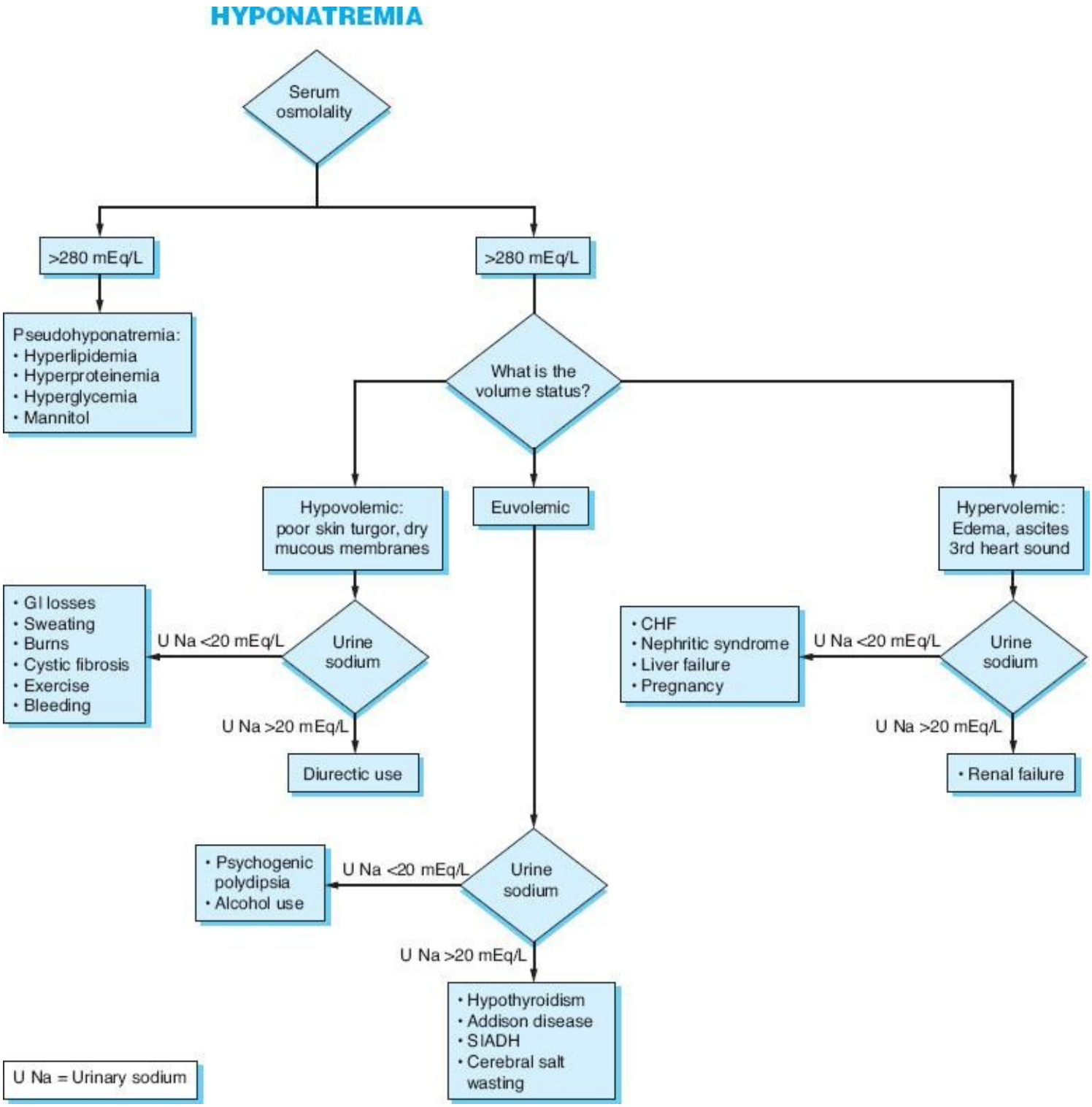
Unwin RJ, Luft FC, Shirley DG. Pathophysiology and management of hypokalemia: A clinical perspective. *Nat Rev Nephrol.* 2011;7(2):75–84.

Hypomagnesemia



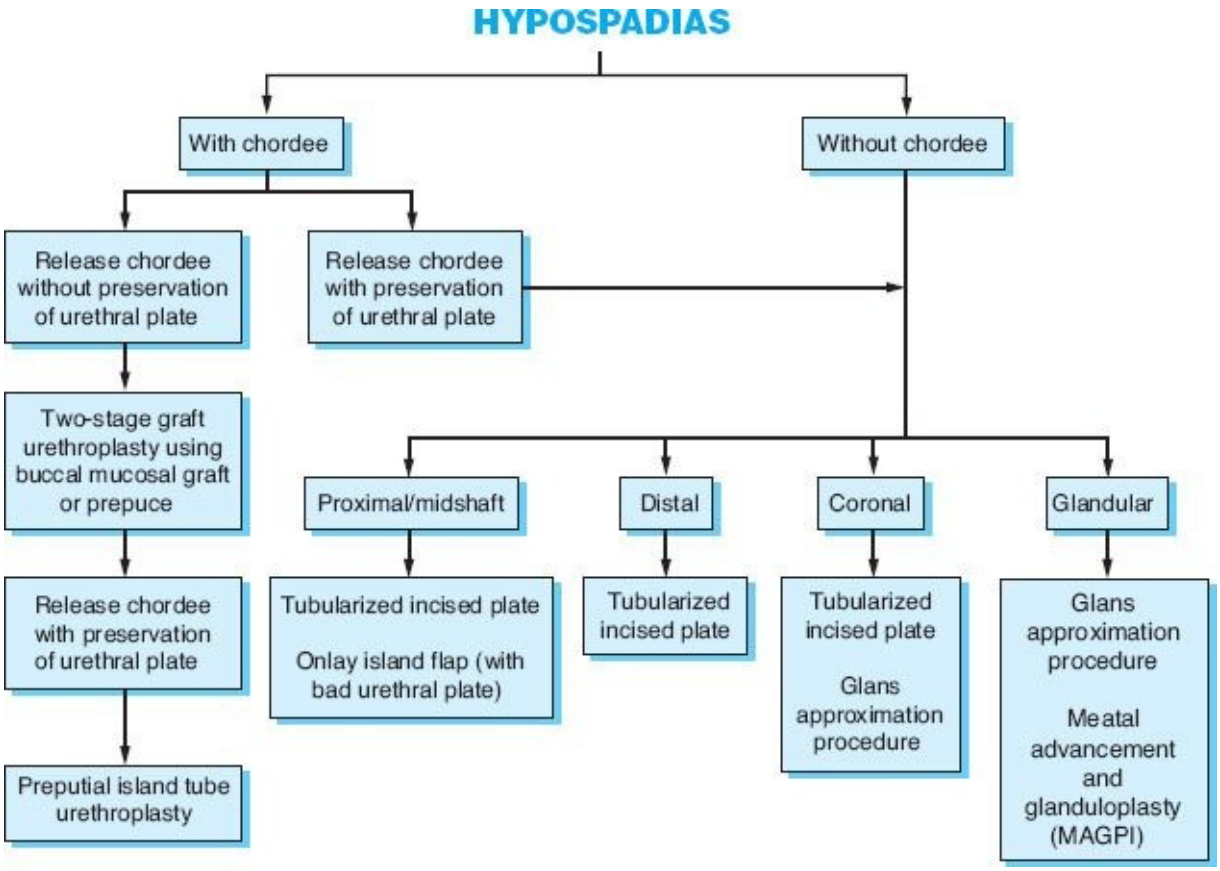
Martin KJ, Gonzalez EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol.* 2009;20:2291–2295.

Hyponatremia

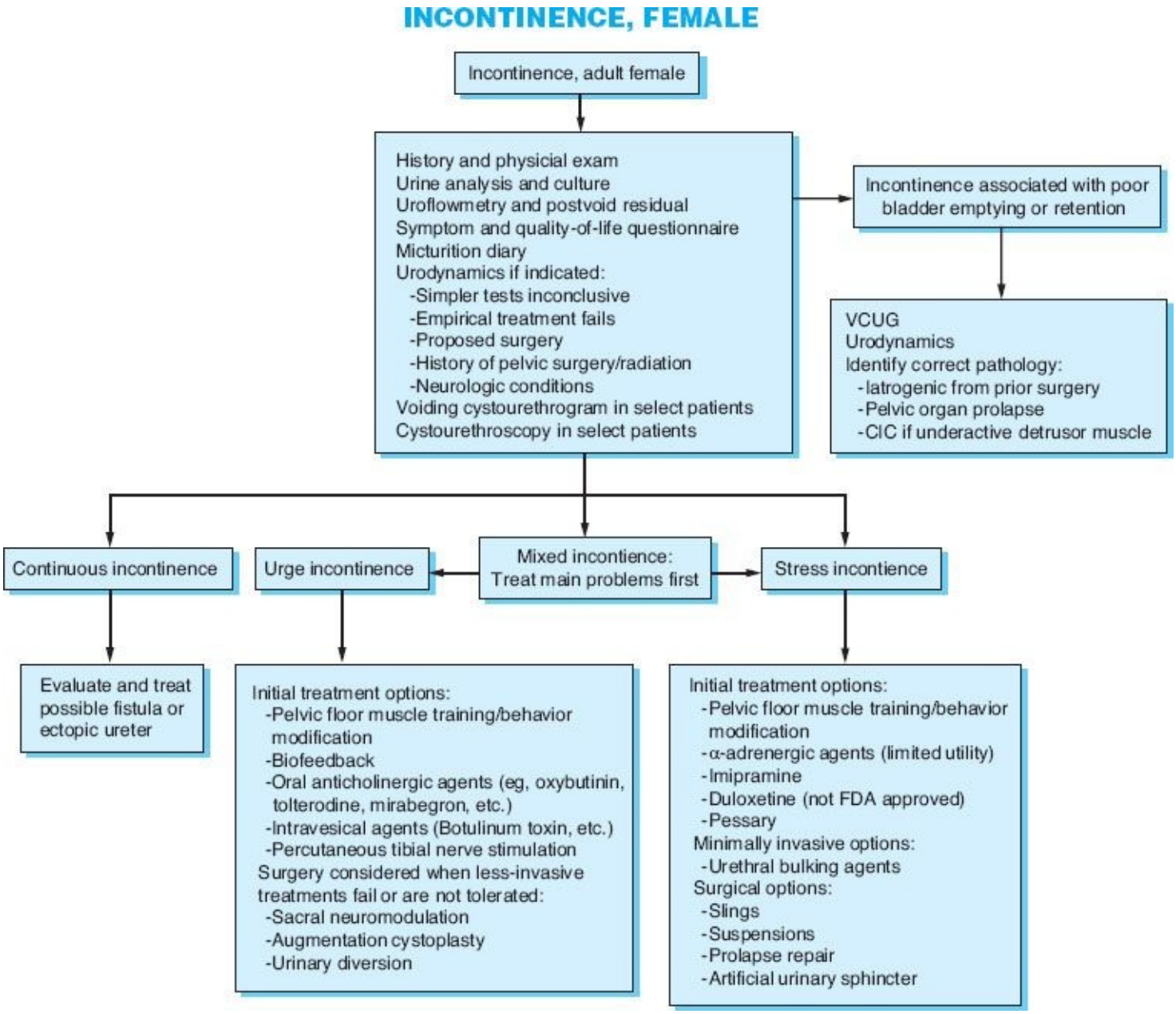


Lien YH, Shapiro JI. Hyponatremia: Clinical diagnosis and management. *Am J Med.* 2007;120(8):653–658.

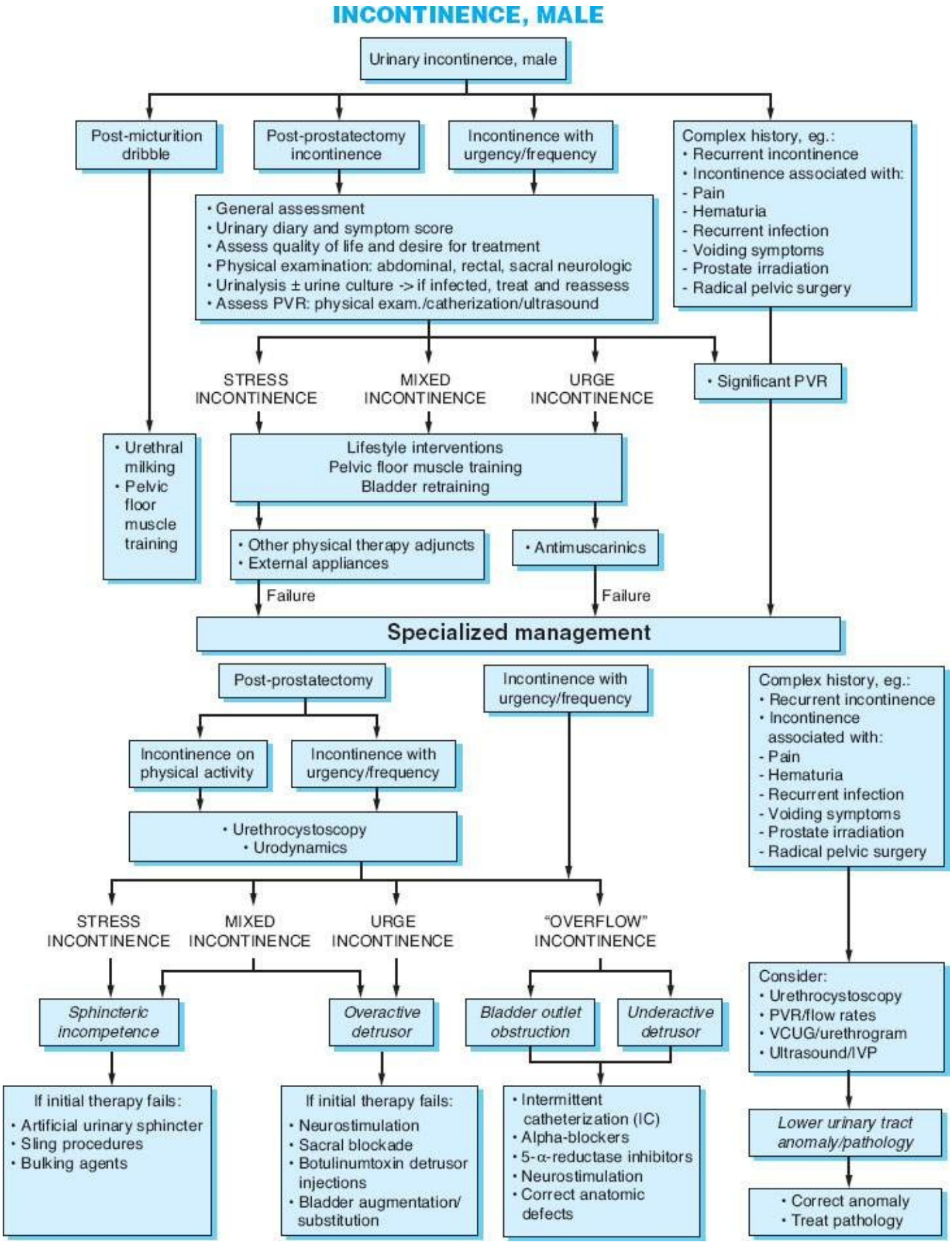
Hypospadias



Incontinence, Female

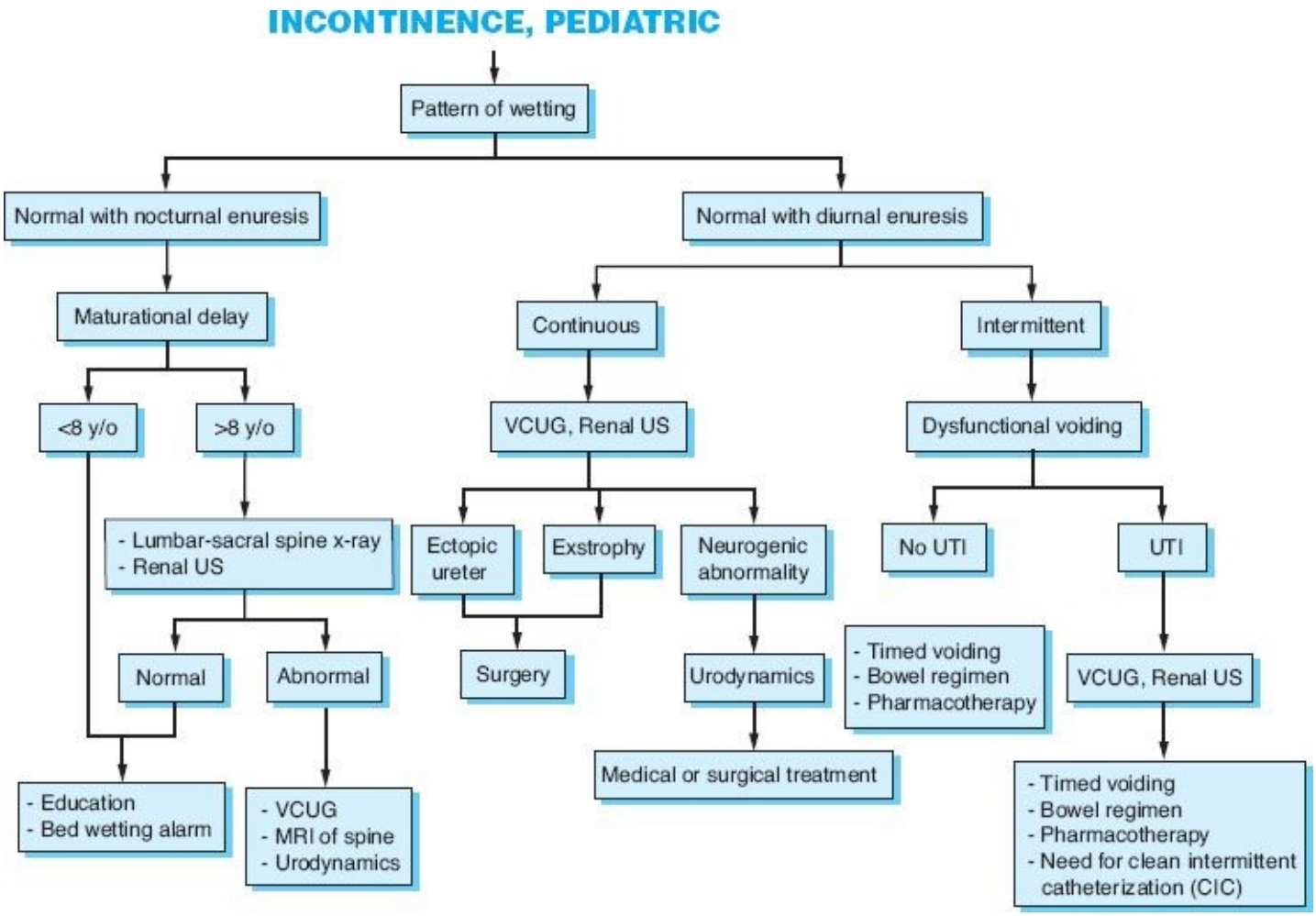


Incontinence, Male

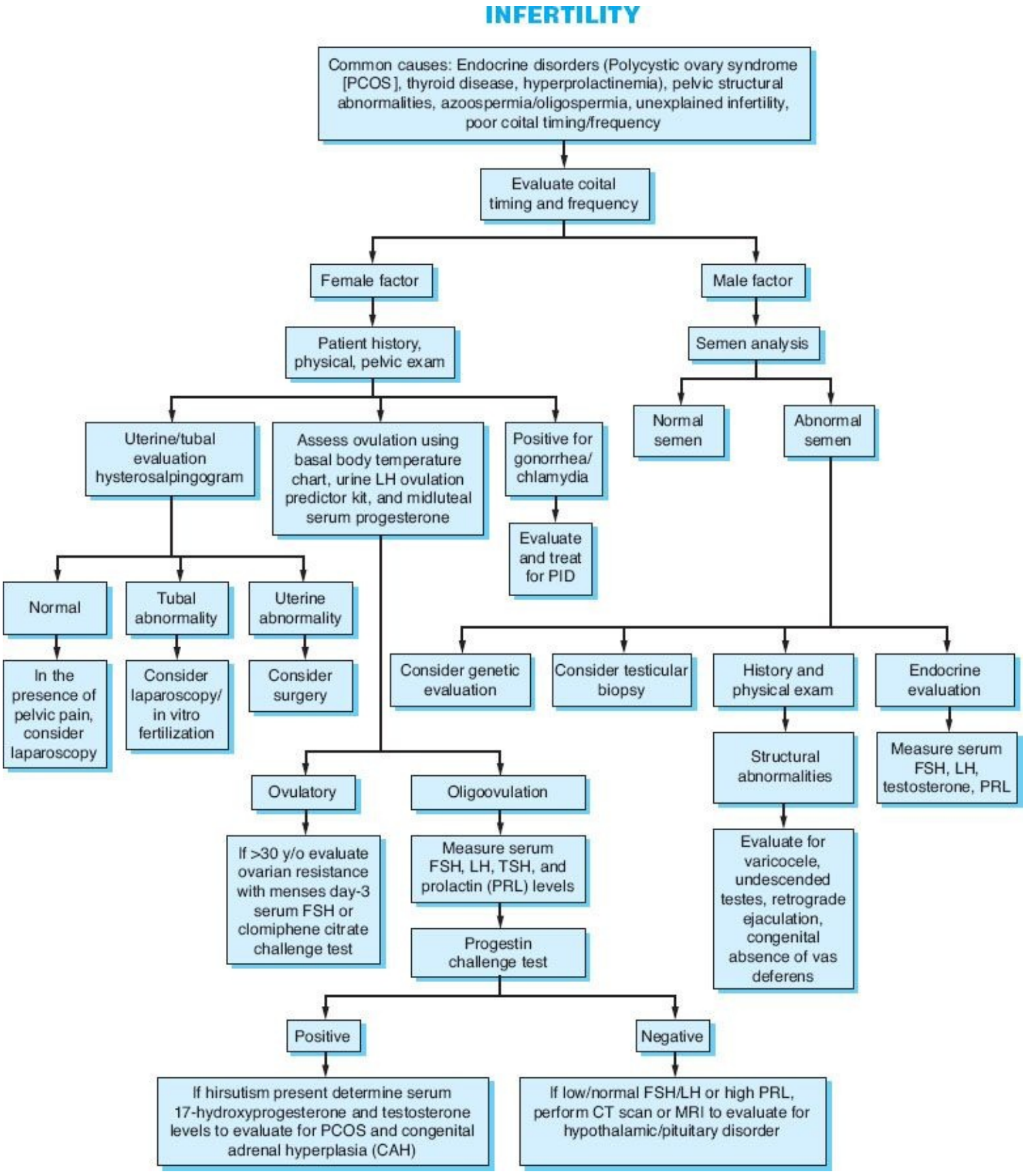


Adapted from: Schröder A, Abrams P, Andersson KE, et al. EAU Guidelines on Urinary Incontinence. http://www.uroweb.org/gls/pdf/Urinary%20Incontinence%202010.pdf

Incontinence, Pediatric



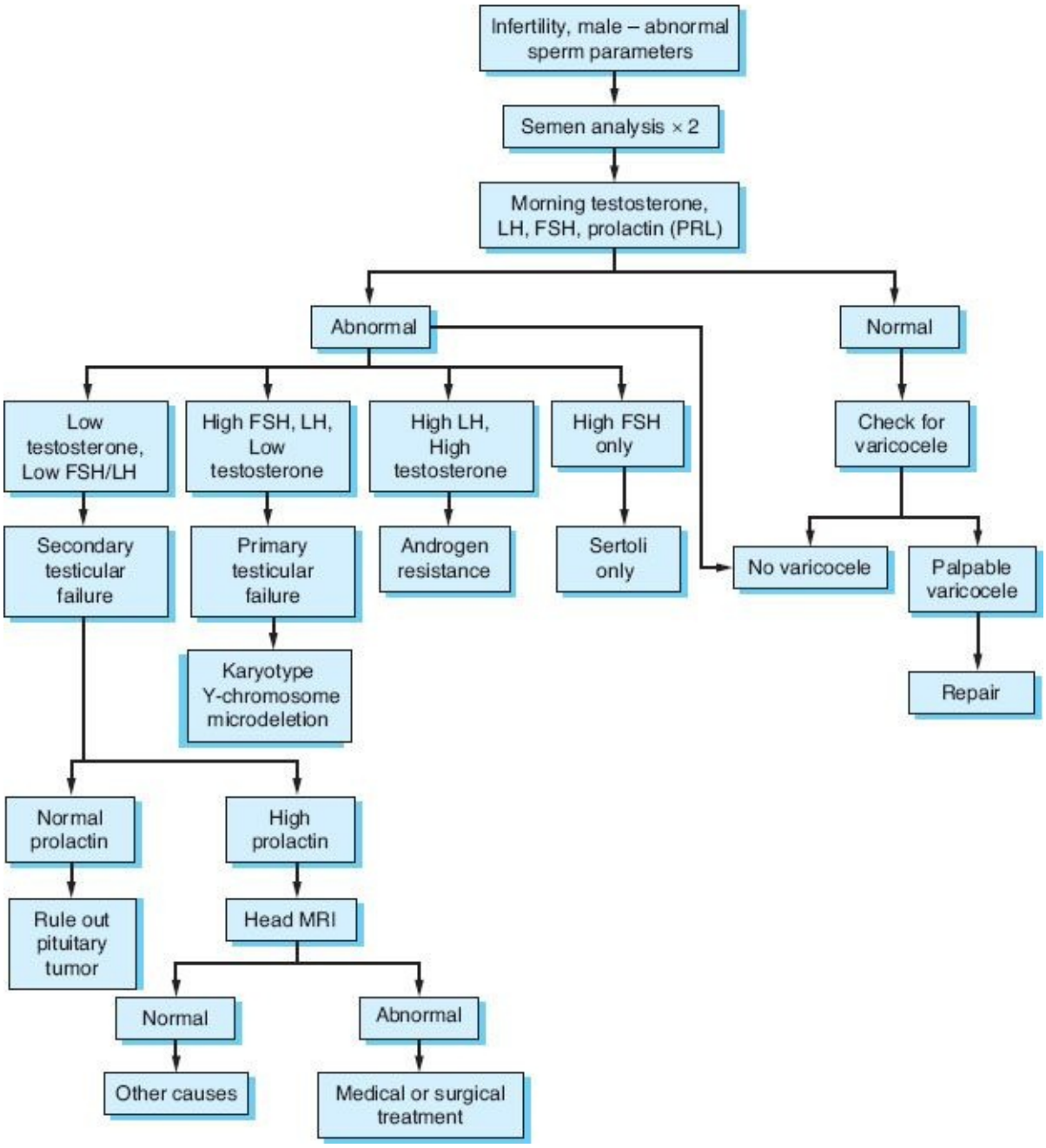
Infertility



Jose-Miller AB, Boyden JW, Frey KA. Infertility. *Am Fam Physician.* 2007;75(6):849–856.

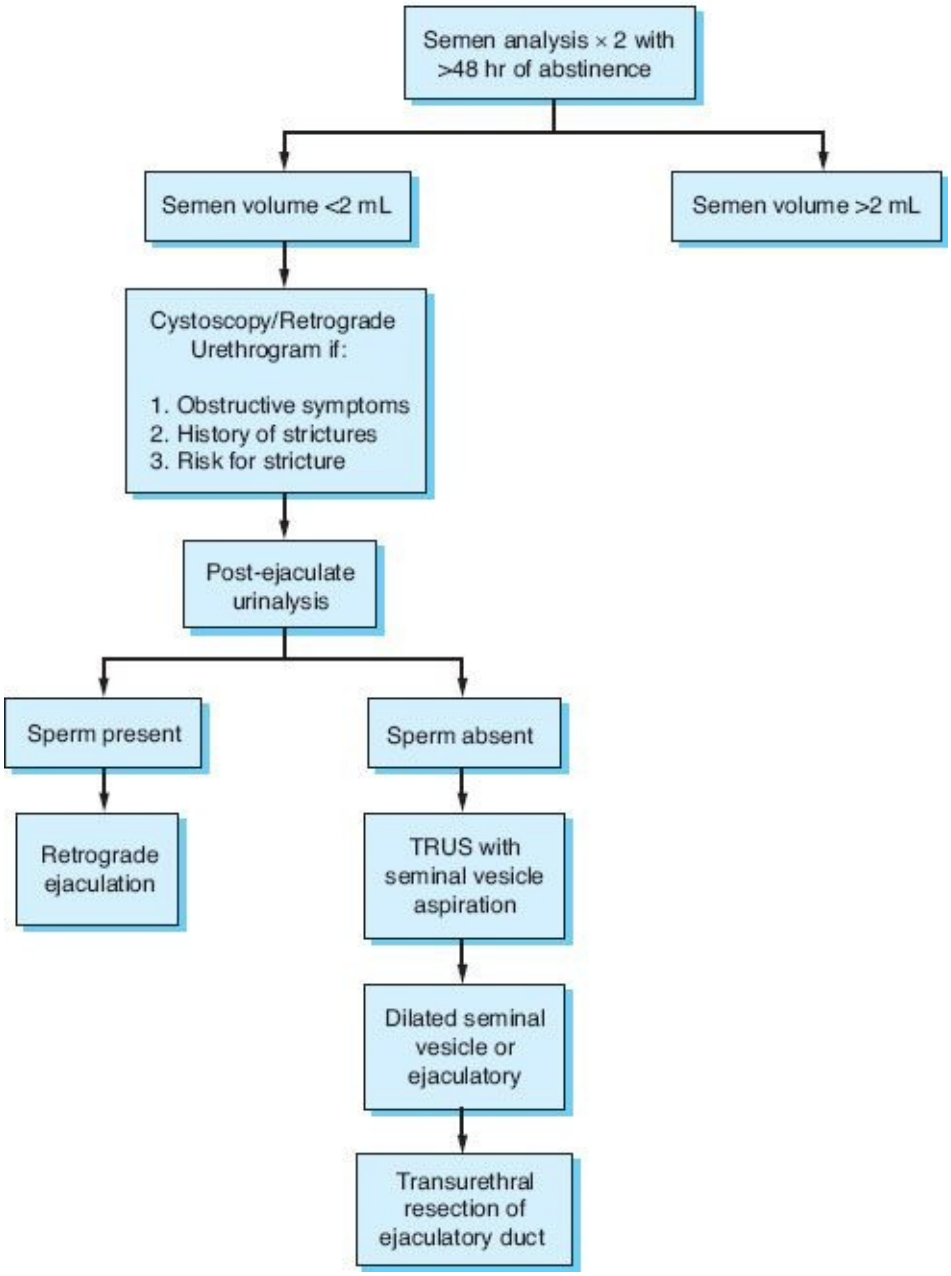
Infertility, Male Abnormal Semen

INFERTILITY, MALE ABNORMAL SEMEN

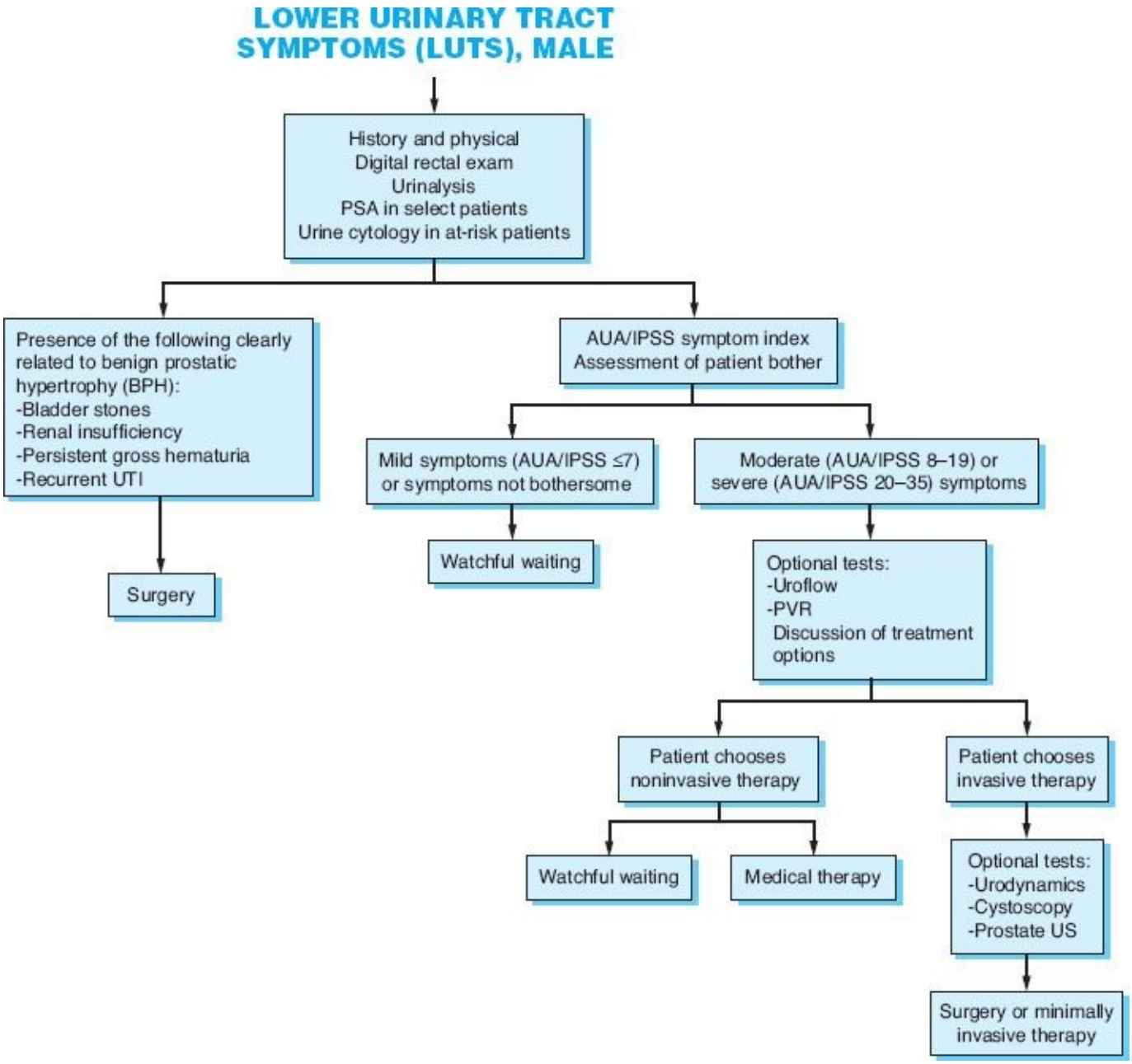


Infertility, Male, Low Semen Volume

INFERTILITY, MALE, LOW SEMEN VOLUME



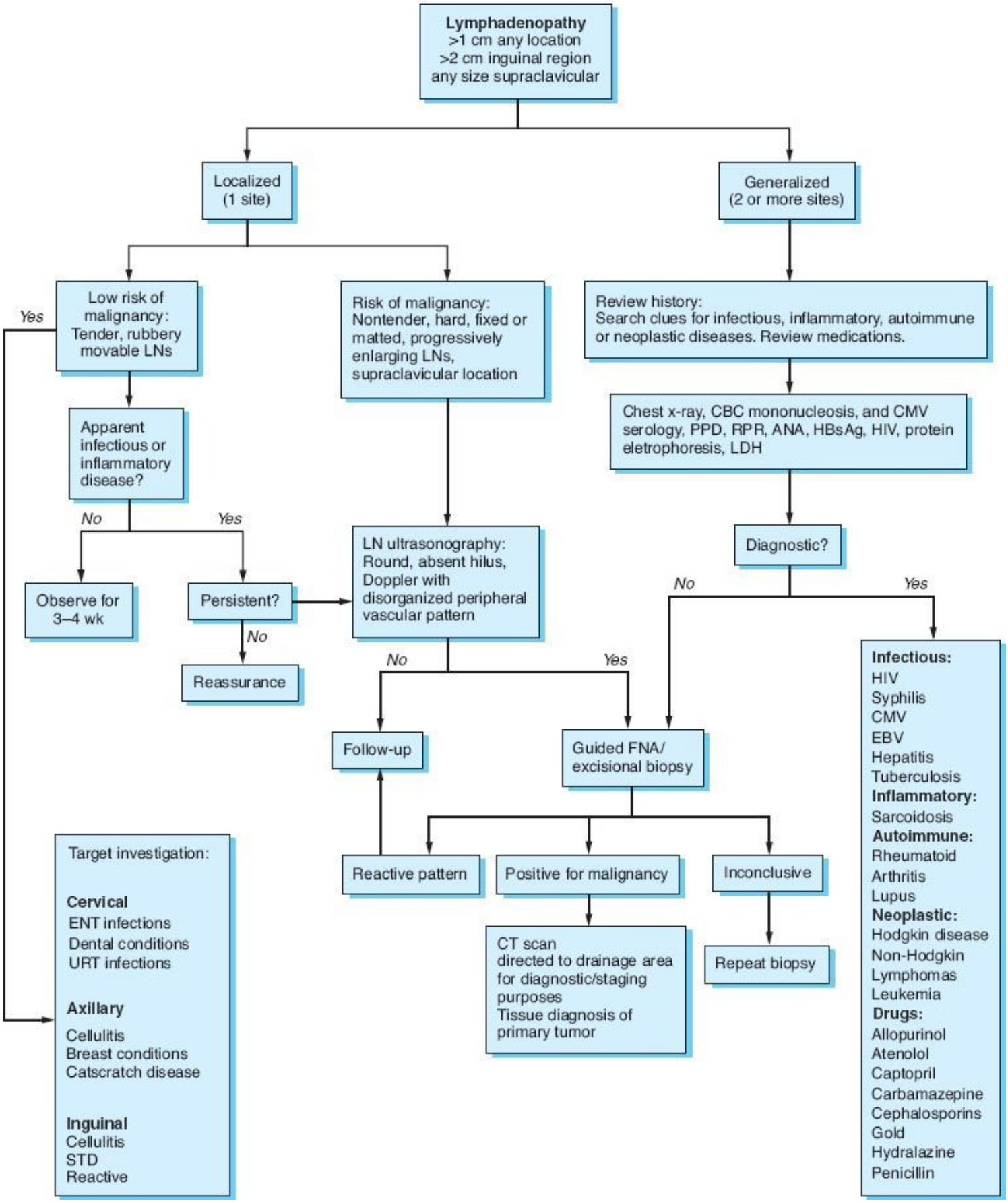
Lower Urinary Tract Symptoms (LUTS), Male



Adapted from Roehrborn C, McConnell JD, Barry MJ, et al. 2003 AUA Guidelines on the Management of Benign Prostatic Hyperplasia. Baltimore, MD: American Urological Association Education and Research; 2003.

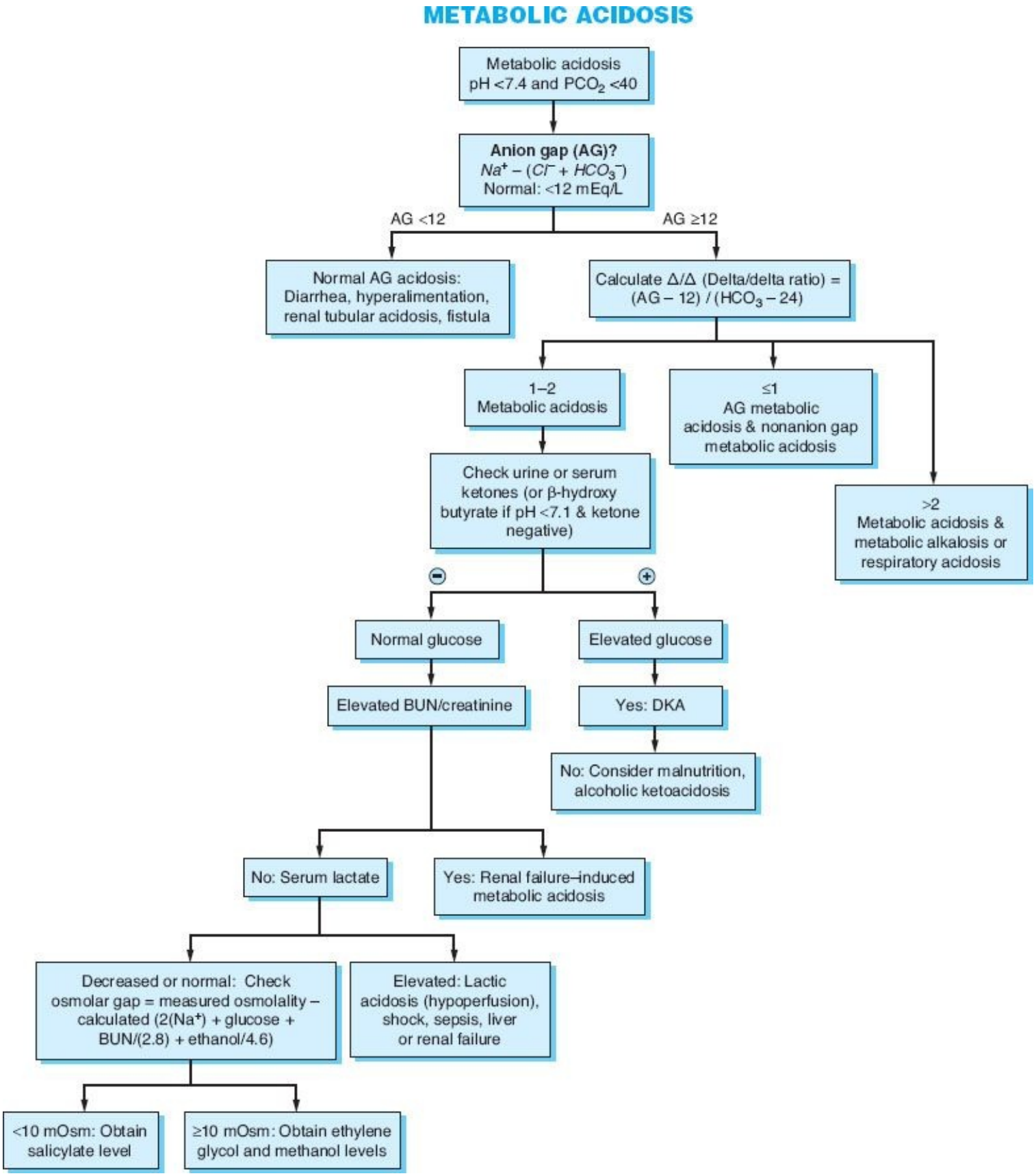
Lymphadenopathy

LYMPHADENOPATHY



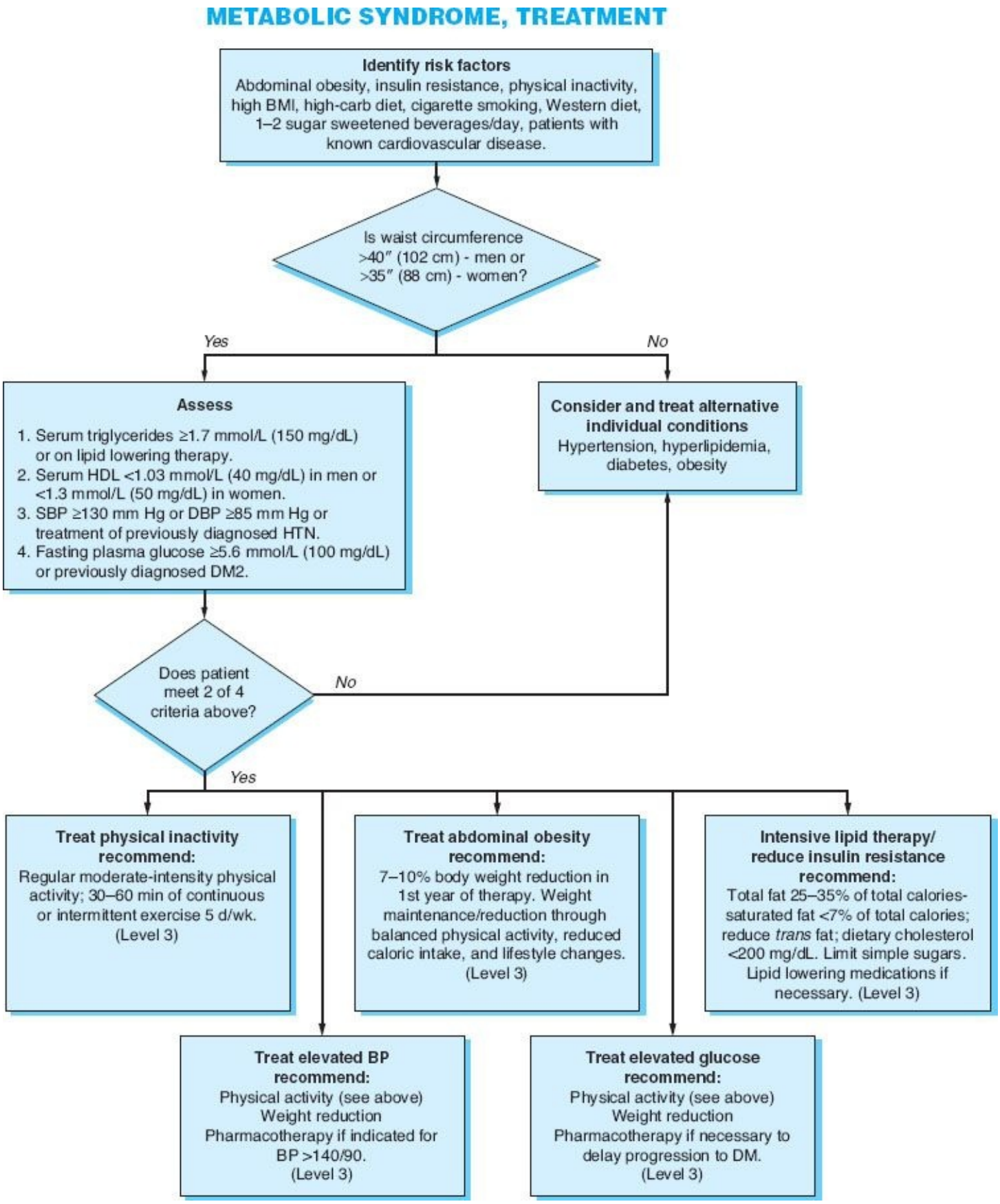
Motyckova G, Steensma DP. Why does my patient have lymphadenopathy or splenomegaly? *Hematol Oncol Clin North Am.* 2012;26(2):395–408.

Metabolic Acidosis



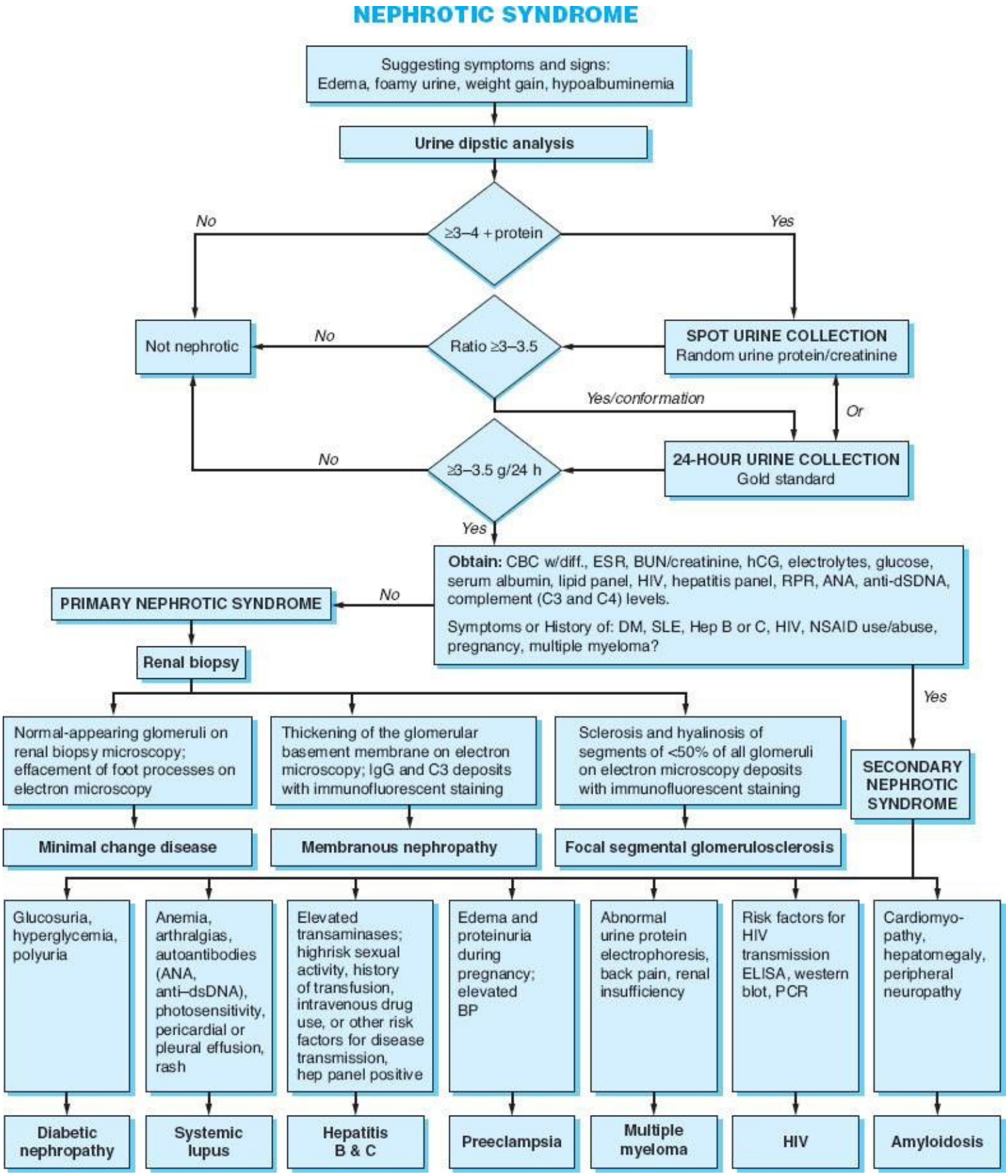
Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis, and management. *Nat Rev Nephrol.* 2010;6:274–285.

Metabolic Syndrome, Treatment



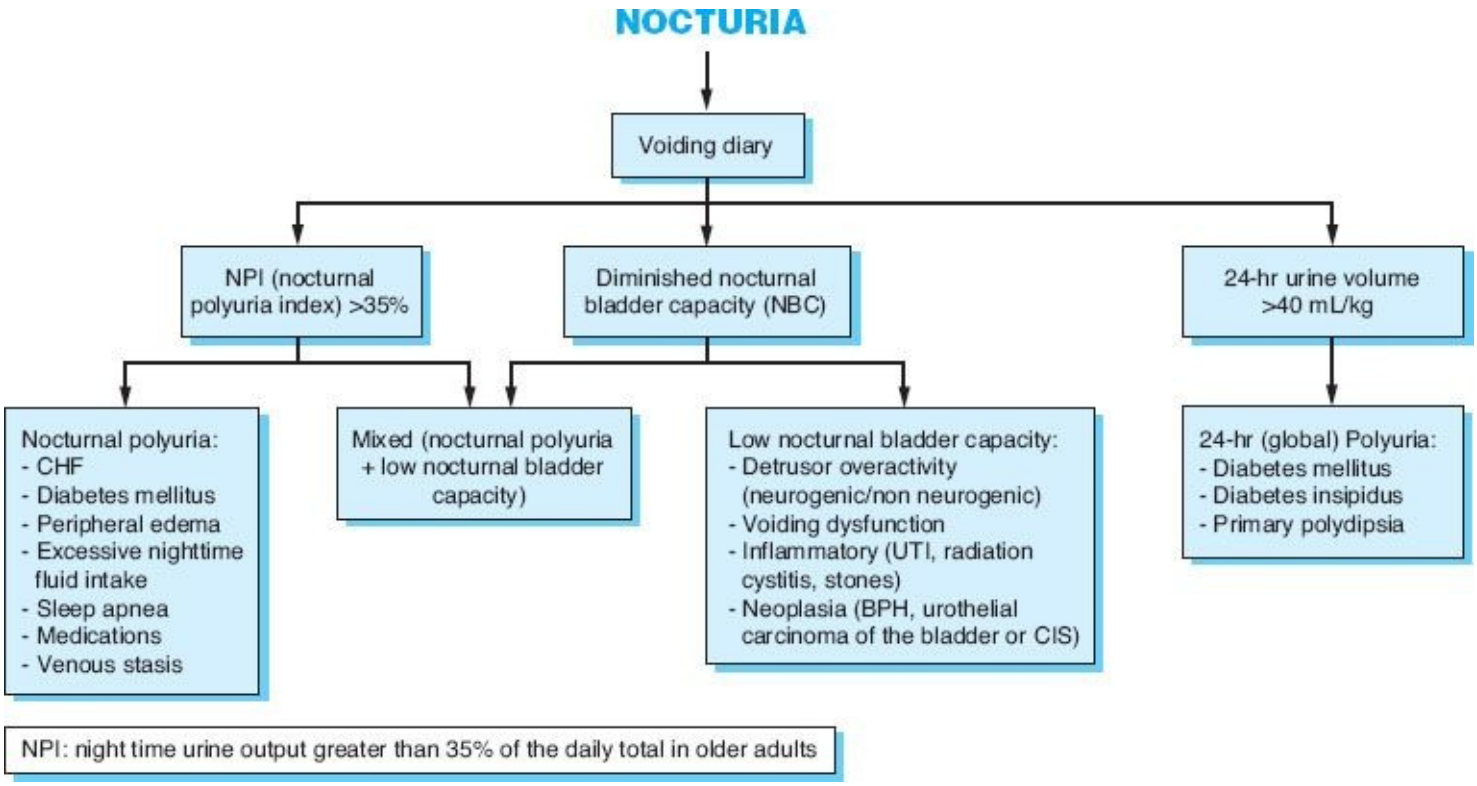
Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735–2752.

Nephrotic Syndrome



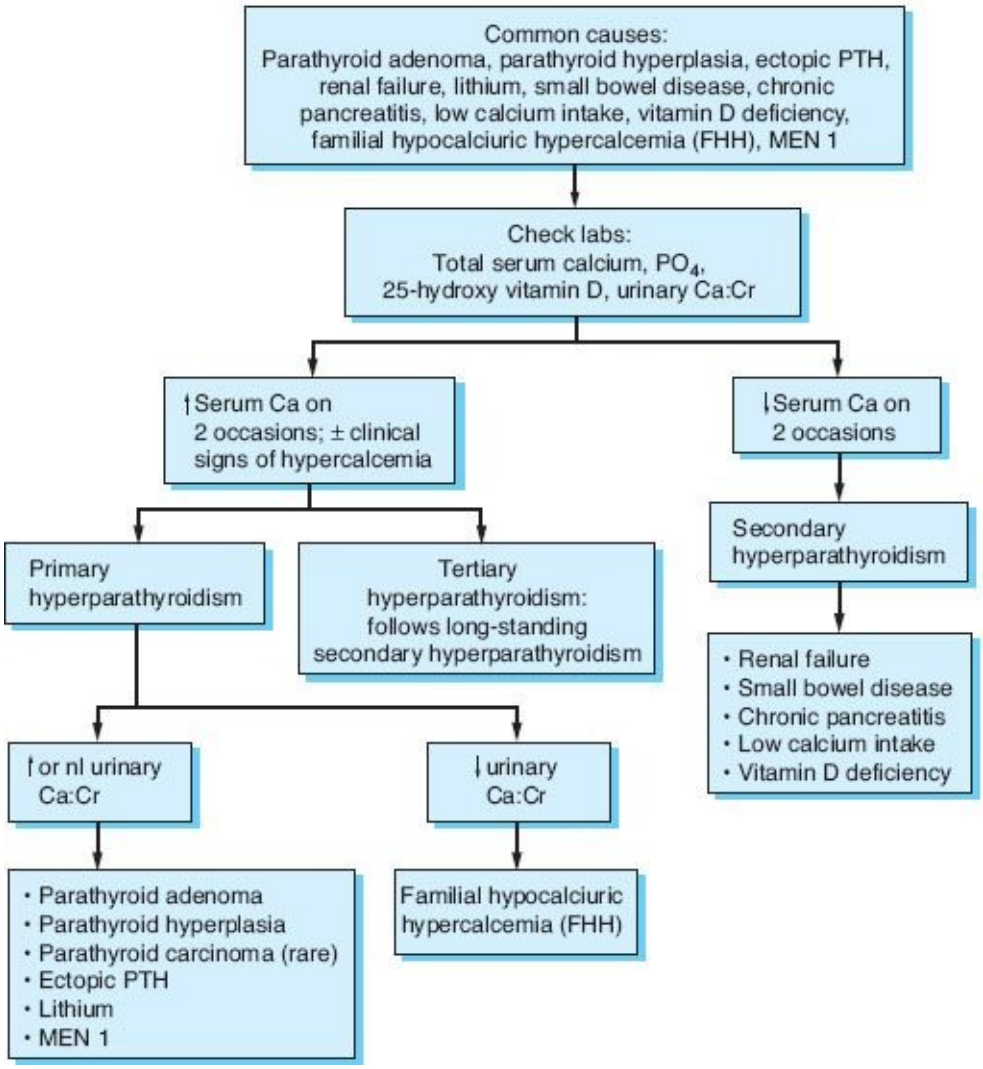
Kodner C. Nephrotic Syndrome in adults: Diagnosis and management. *Am Fam Physician.* 2009;80(10):1129–1134.

Nocturia



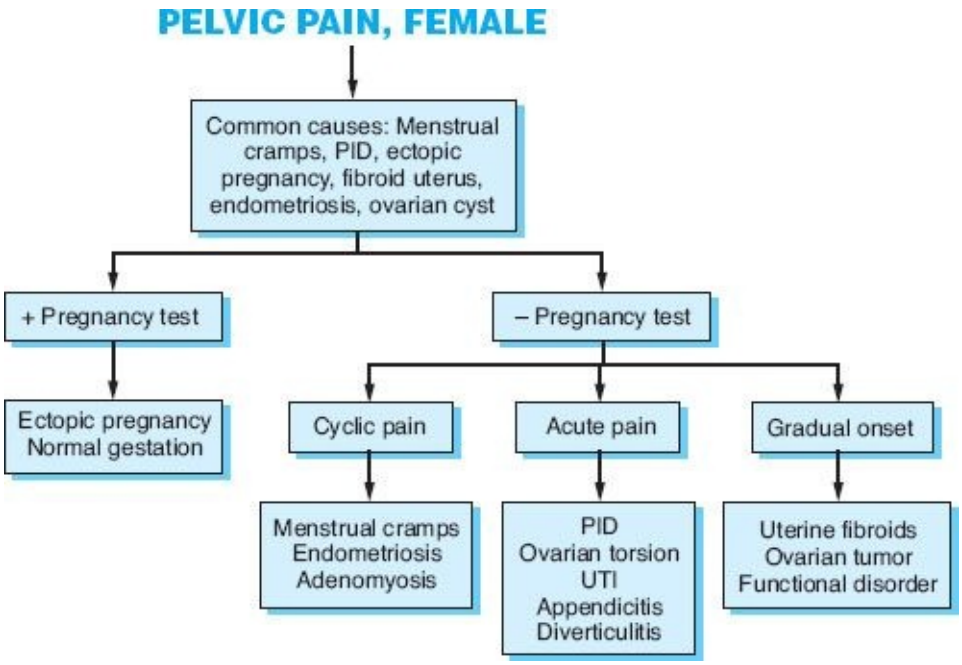
Parathyroid Hormone, Elevated Serum

PARATHYROID HORMONE, ELEVATED SERUM



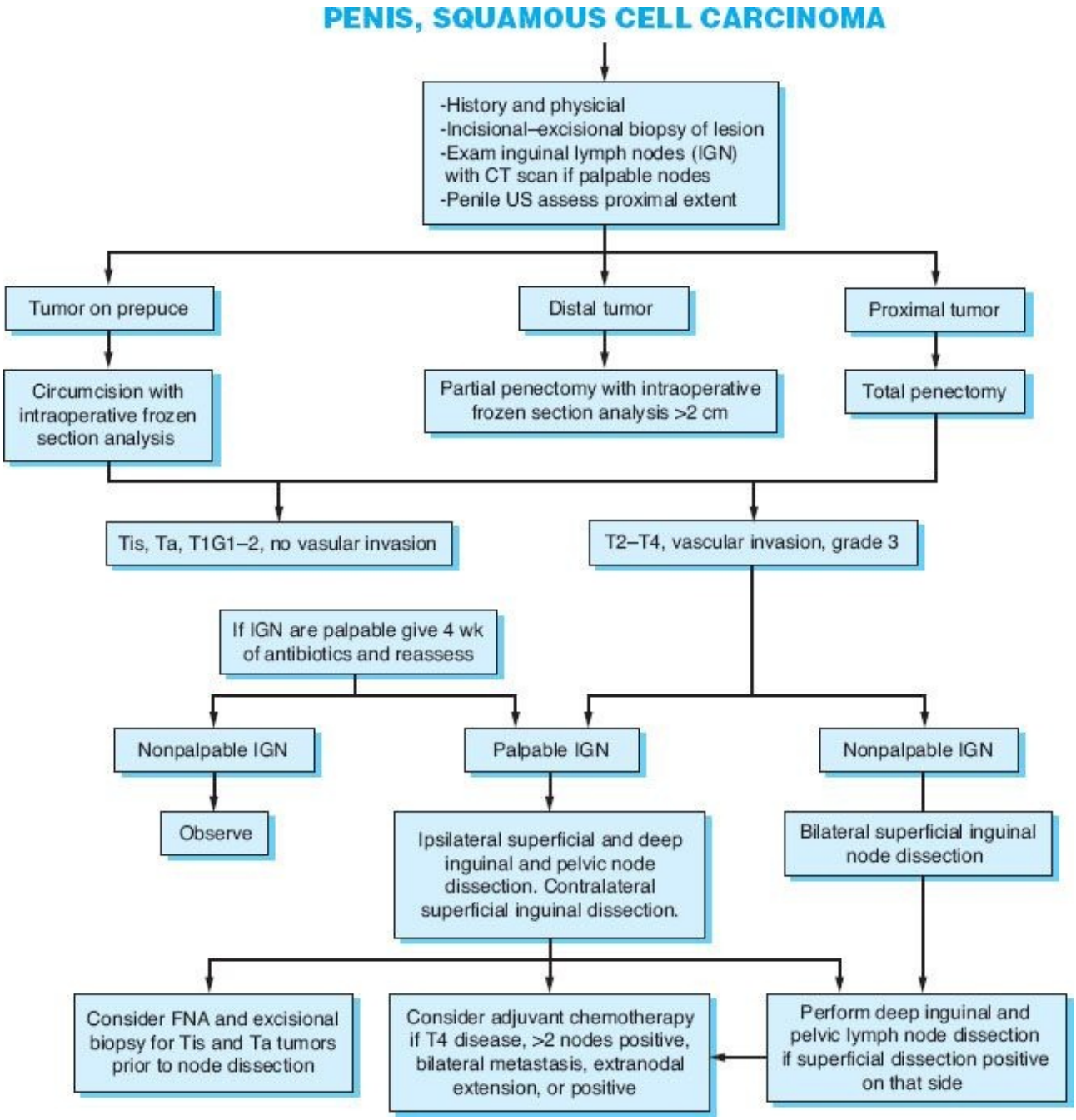
Mikhail N, Cope D. Evaluation and treatment of primary hyperparathyroidism. *JAMA*. 2005;294(21):2700.

Pelvic Pain, Female

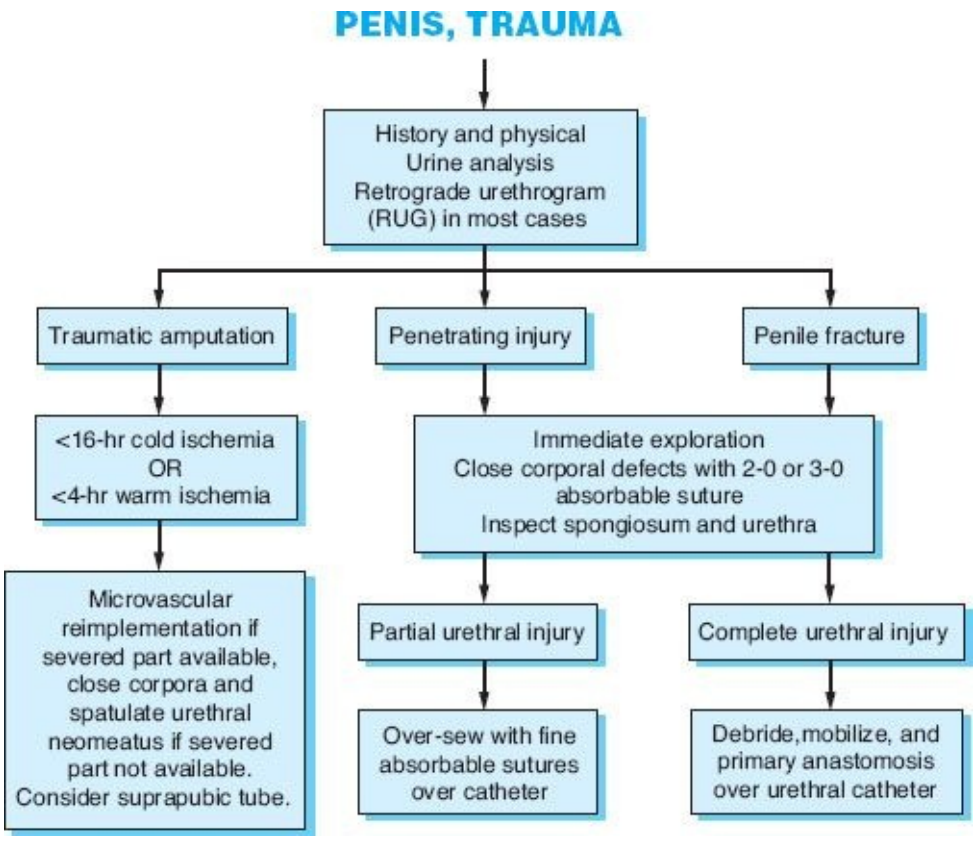


Ortiz DD. Chronic pelvic pain in women. *Am Fam Physician.* 2008;77(11):1535–1542.

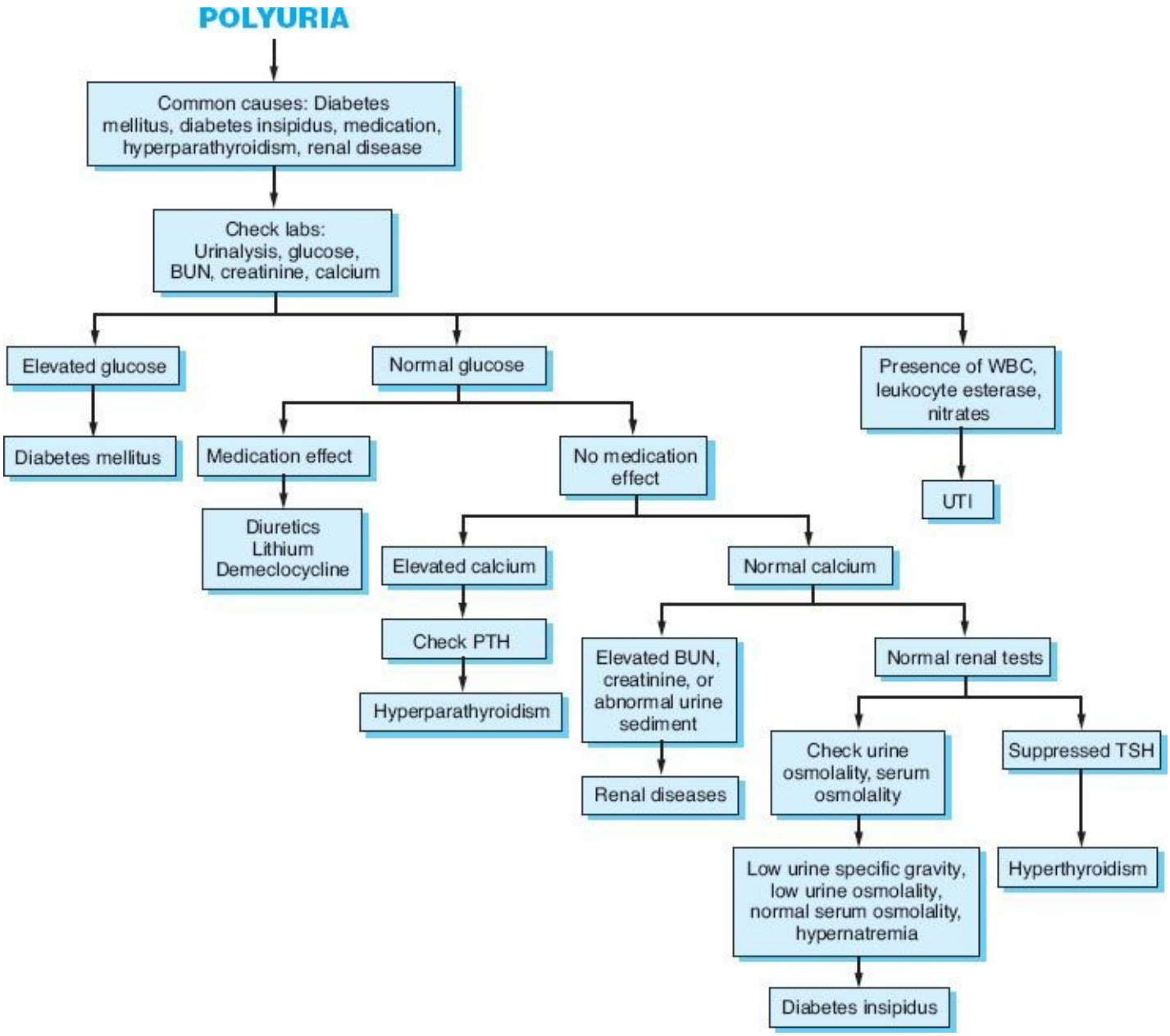
Penis, Squamous Cell Carcinoma



Penis, Trauma

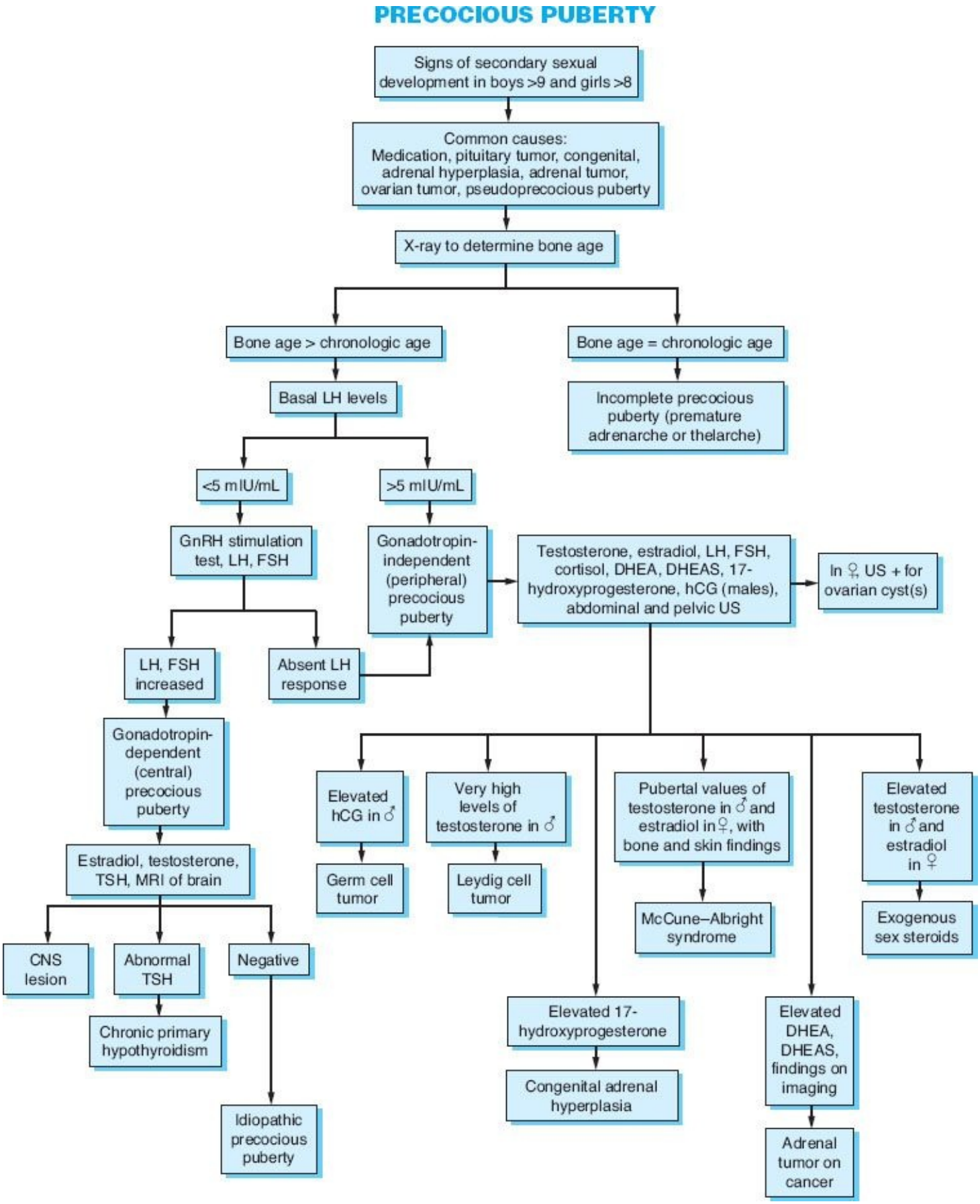

PENIS, TRAUMA
History and physical
Urine analysis
Retrograde urethrogram (RUG) in most cases
Traumatic amputation
Penetrating injury
Penile fracture
<16-hr cold ischemia
OR
<4-hr warm ischemia
Immediate exploration
Close corporal defects with 2-0 or 3-0 absorbable suture
Inspect spongiosum and urethra
Microvascular reimplementation if severed part available, close corpora and spatulate urethral neomeatus if severed part not available. Consider suprapubic tube.
Partial urethral injury
Complete urethral injury
Over-sew with fine absorbable sutures over catheter
Debride, mobilize, and primary anastomosis over urethral catheter

Polyuria



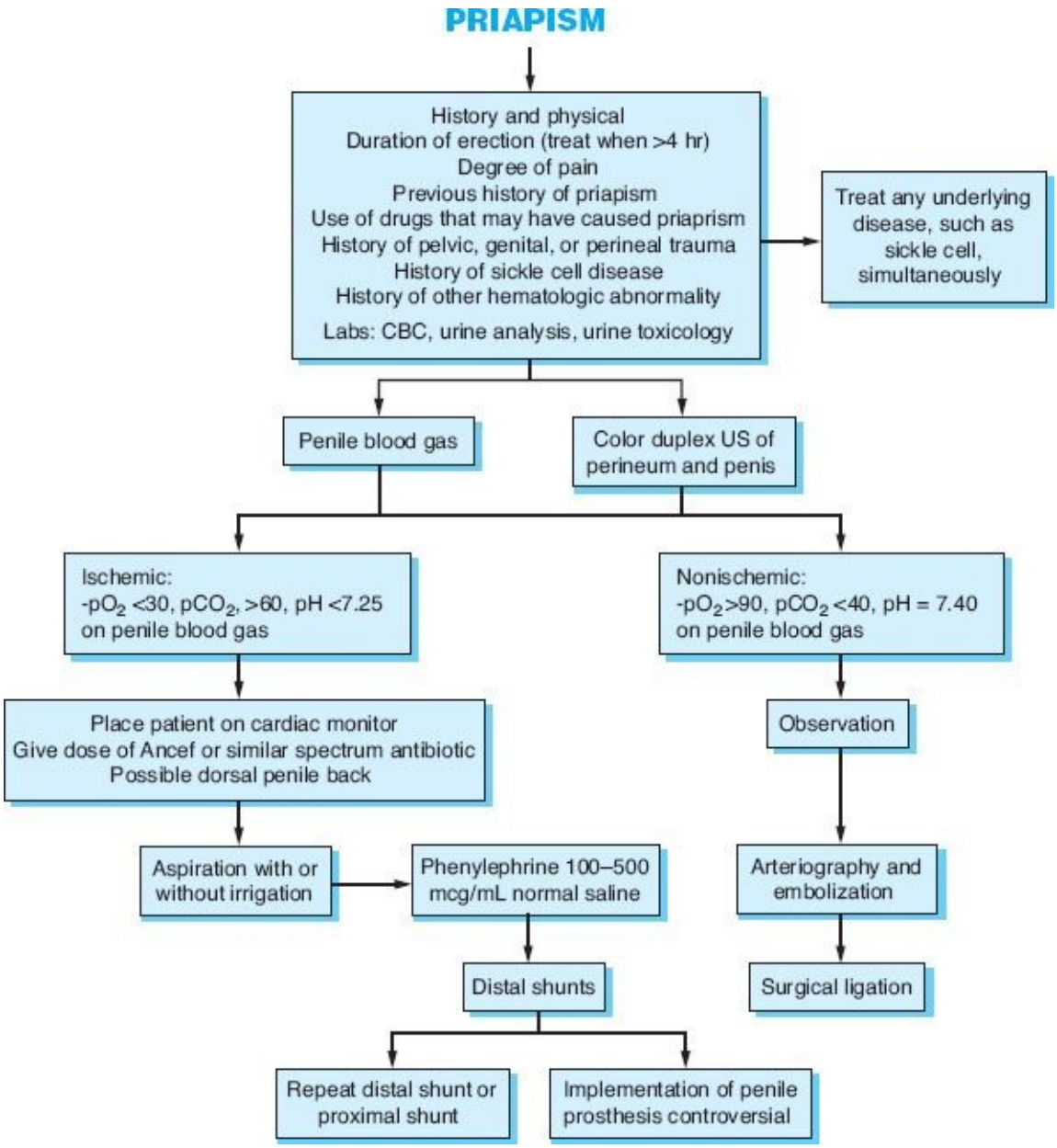
Kujubu DA, Aboseif SR. An overview of nocturia and the syndrome of nocturnal polyuria in the elderly. *Nat Clin Pract Nephrol.* 2008;4(8):426–435.

Precocious Puberty



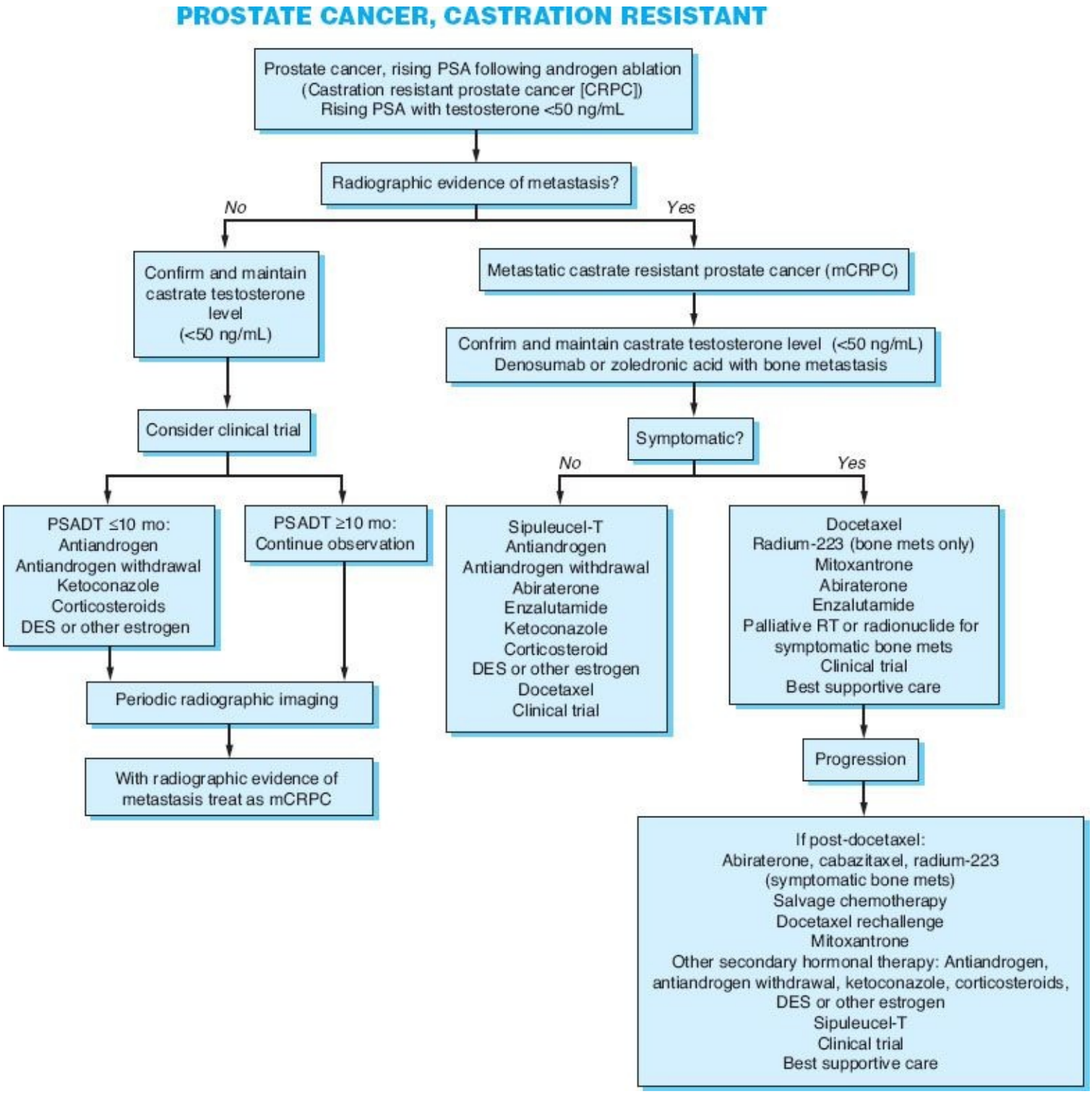
Nwosu BU, Lee MM. Evaluation of short and tall stature in children. *Am Fam Physician.* 2008;78(5):597–604.

Priapism



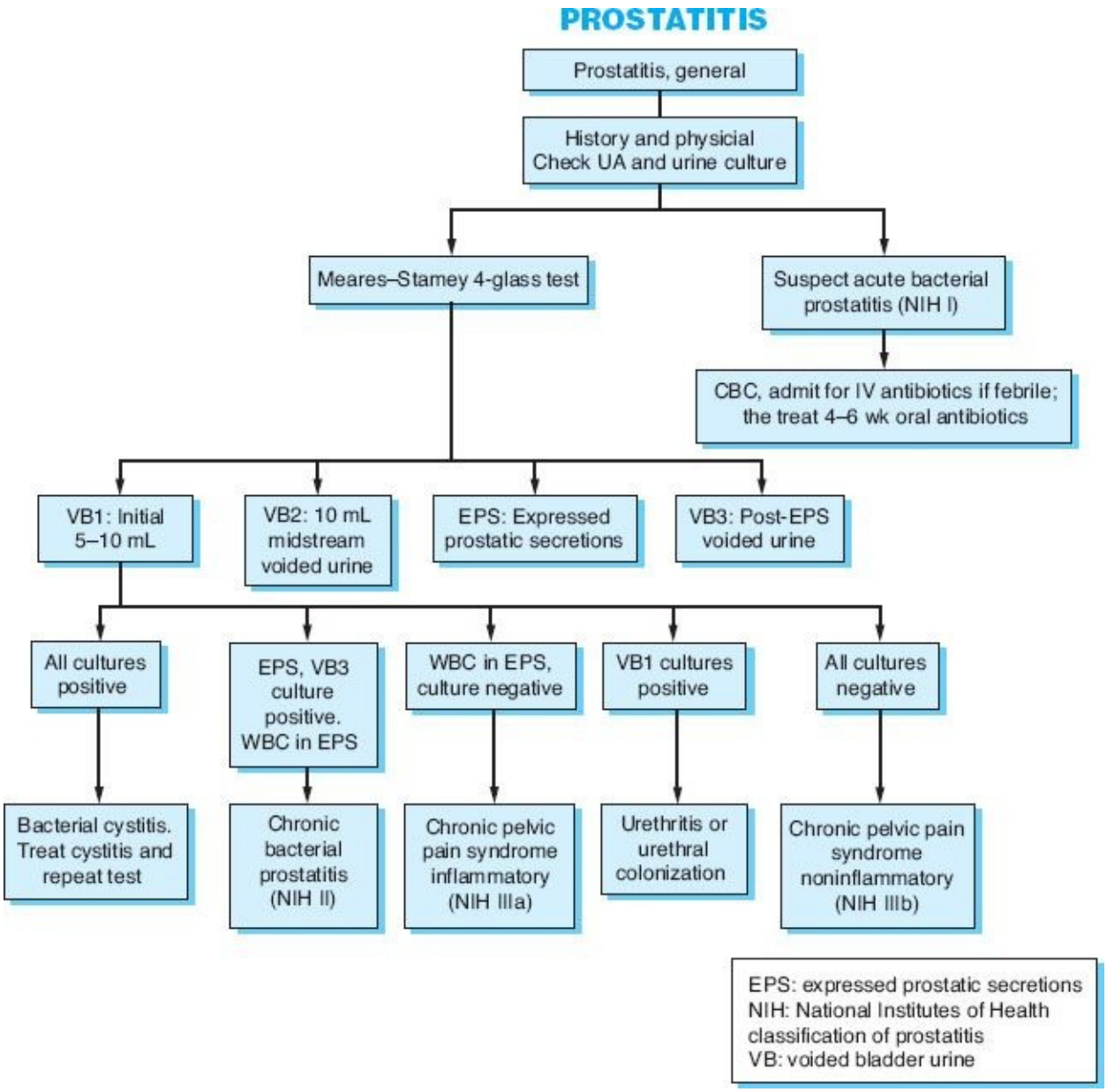
Adapted from Montague DK, Jarow J, Broderick GA, et al. American Urologic Association guideline on the management of priapism. *J Urol.* 2003;170(4 Pt 1):1318–1324.

Prostate Cancer, Castration Resistant

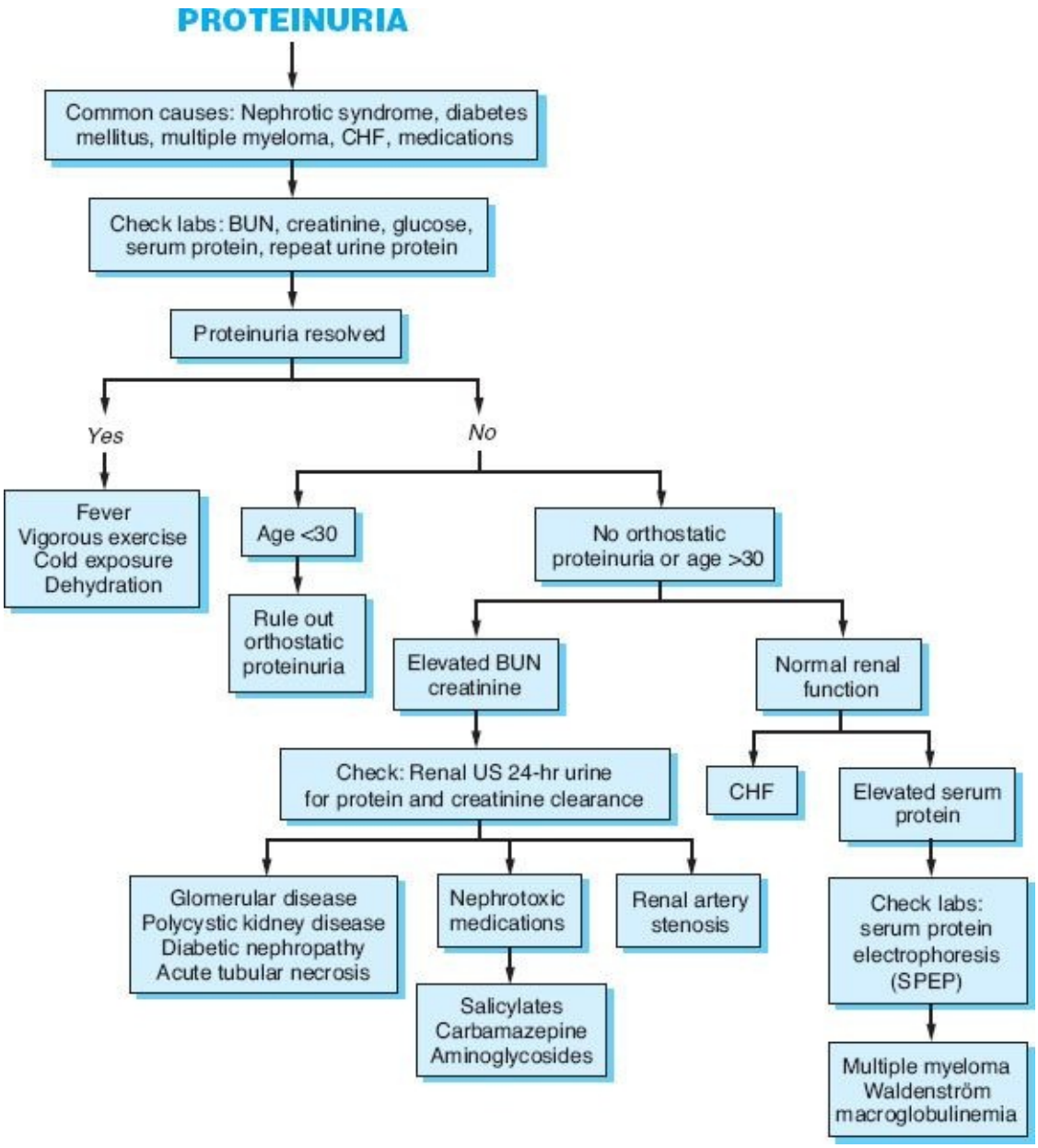


Based on prostate cancer guidelines from NCCN Version 2.2014 http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (Accessed June 1, 2014) and Gomella LG, Petrylak DP, Shayegan B. Current management of advanced and castration resistant prostate cancer. *Can J Urol.* 2014;21(2 Supp 1):1–6.

Prostatitis

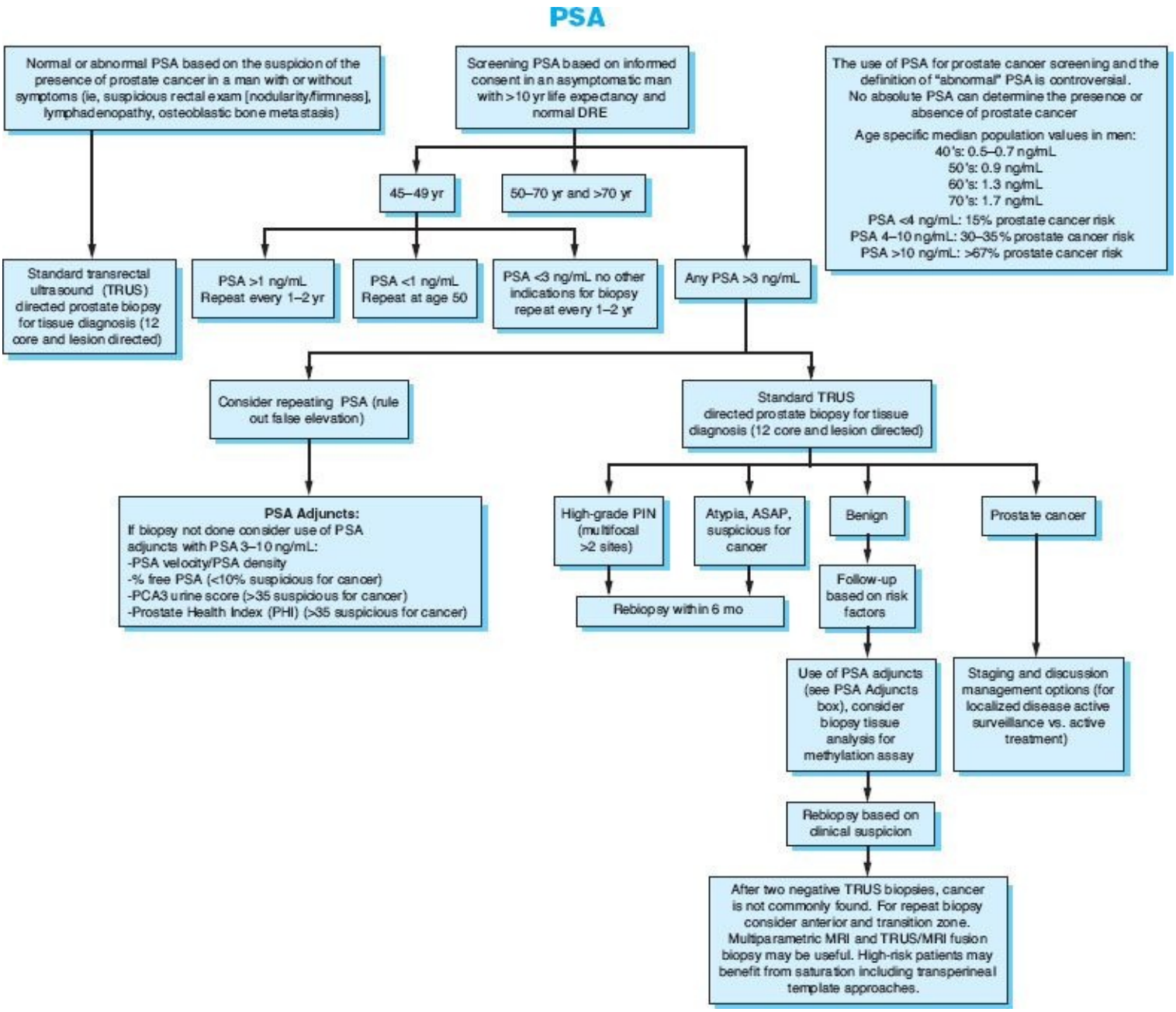


Proteinuria



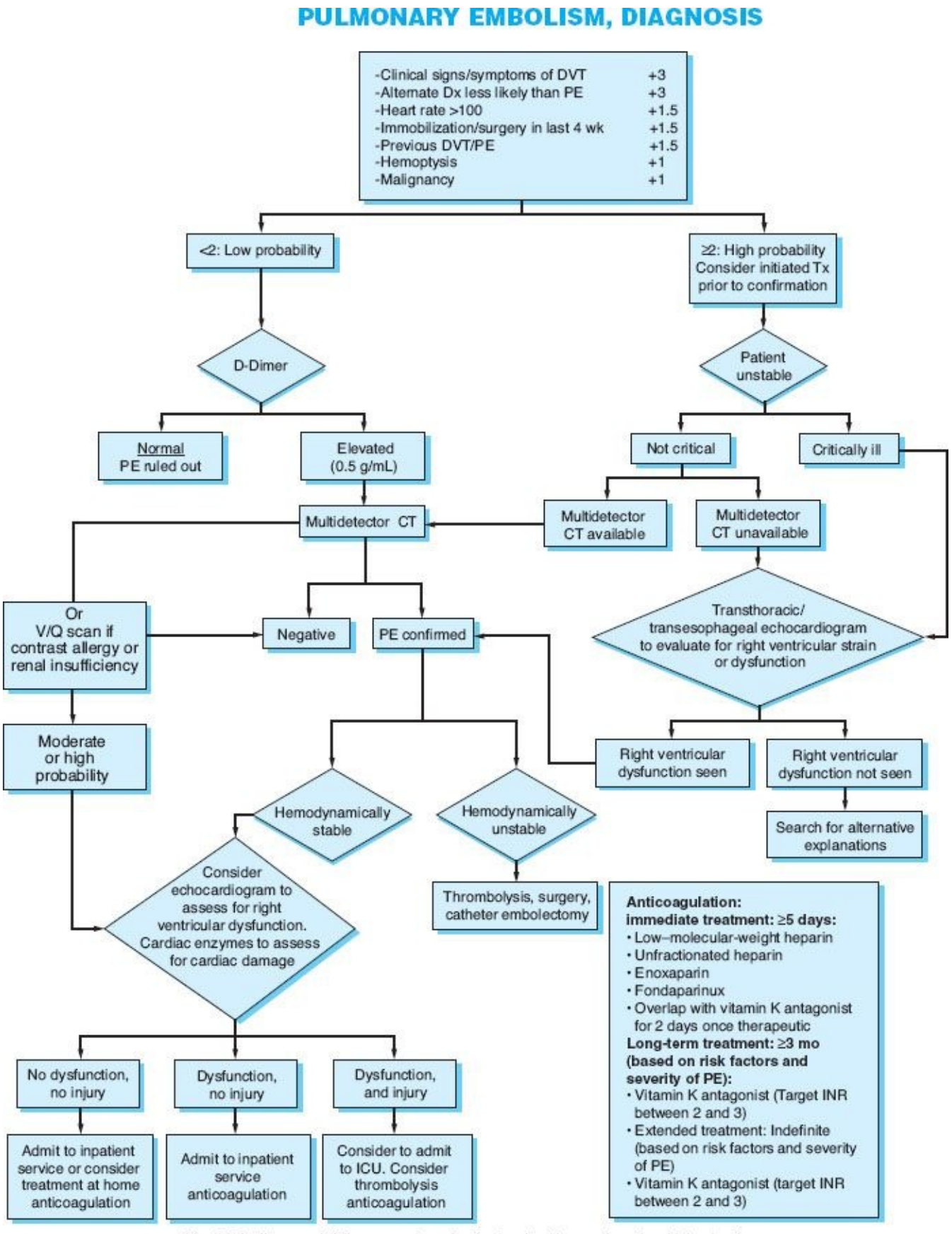
Carroll MF, Temte JL. Proteinuria in adults: A diagnostic approach. *Am Fam Physician.* 2000;62:1333–1340.

PSA



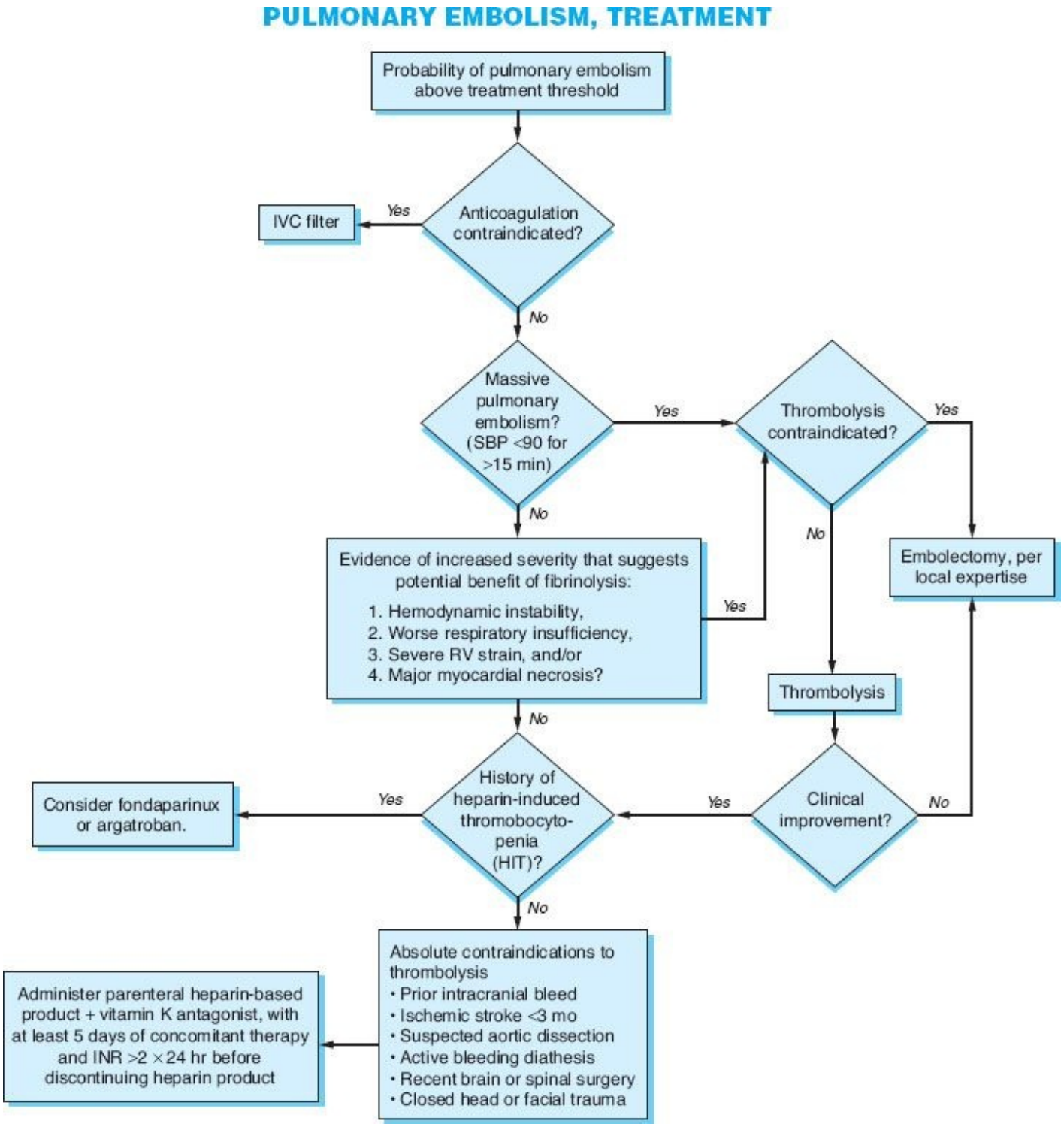
Courtesy Jefferson Kimmel Cancer Center GU Multidisciplinary Clinic; Based on guidelines from NCCN Prostate Cancer Early Detection Version 1.2014 (www.nccn.org, Accessed June 1, 2014); Loeb S, Catalona WJ. *The Oncologist*. 2008;13:299–305; Crawford ED, Ventii K, Shore ND. New biomarkers in prostate cancer. *Oncology (Williston Park)*. 2014;28(2):135–142. Review

Pulmonary Embolism, Diagnosis



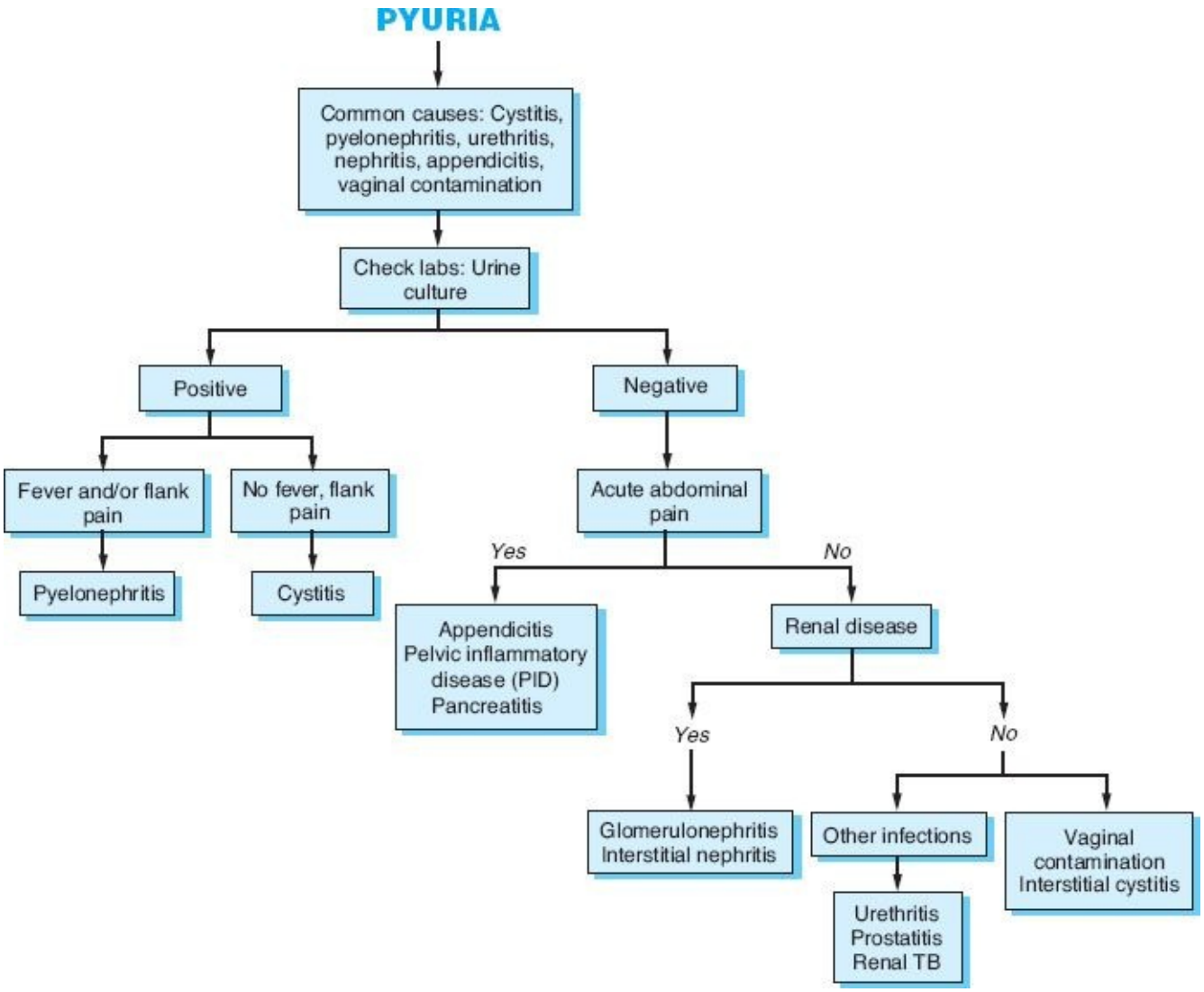
Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133(6 Suppl):454S–545S.

Pulmonary Embolism, Treatment



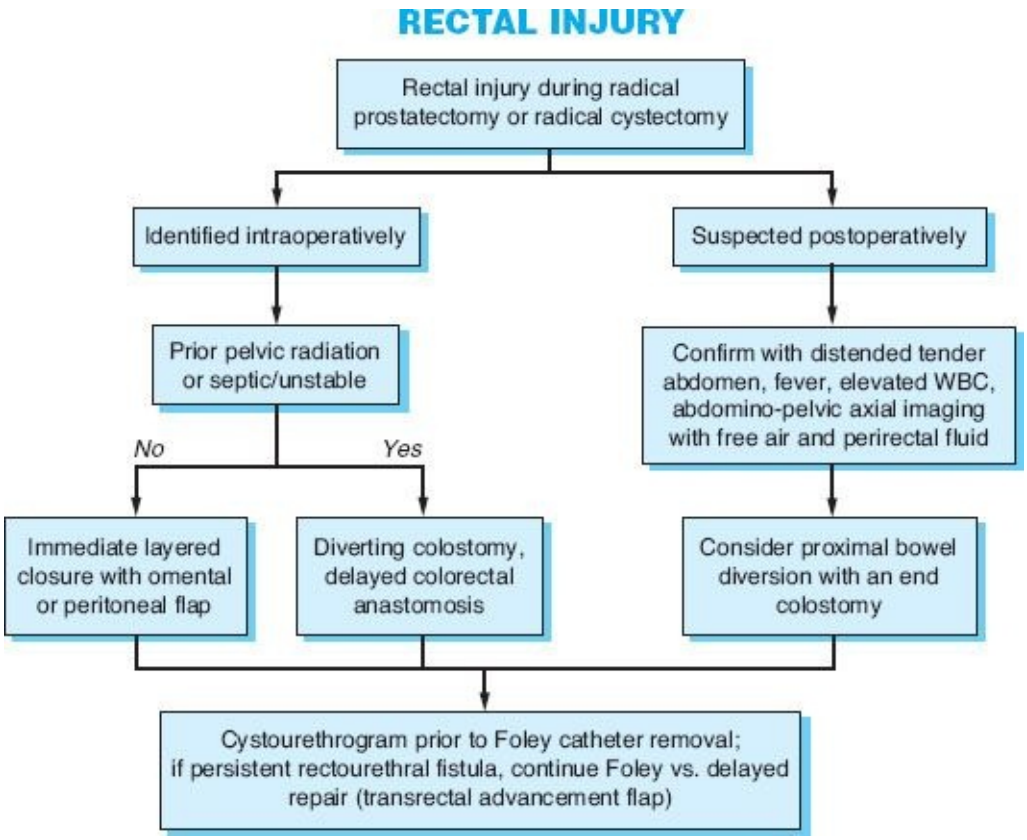
Updates and modified from: Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation.* 2011;123:1788–1830.

Pyuria



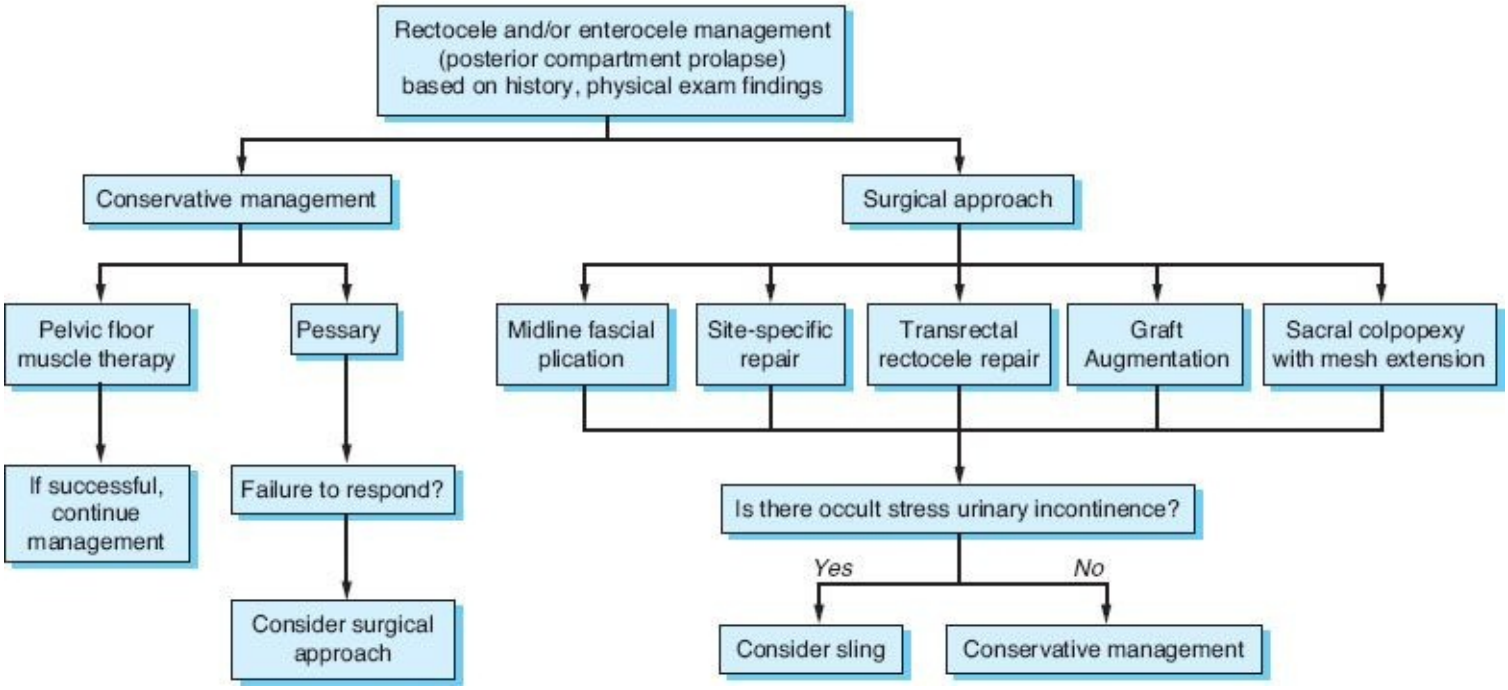
Simerville JA, Maxted WC, Pahira JJ. Urinalysis: A comprehensive review. *Am Fam Physician.* 2005;71:1153–1162.

Rectal Injury

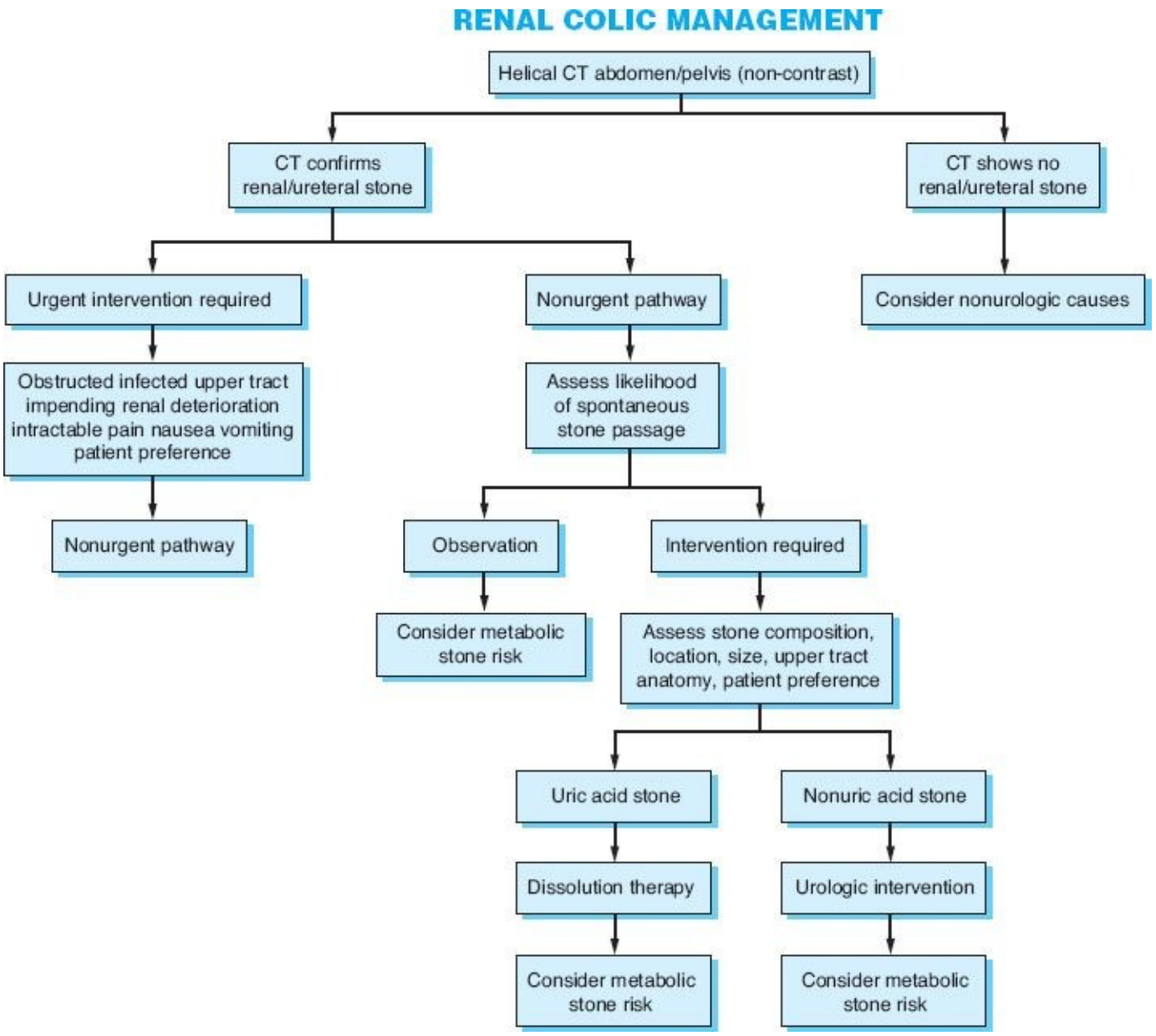


Rectocele and Enterocele

RECTOCELE AND ENTEROCELE



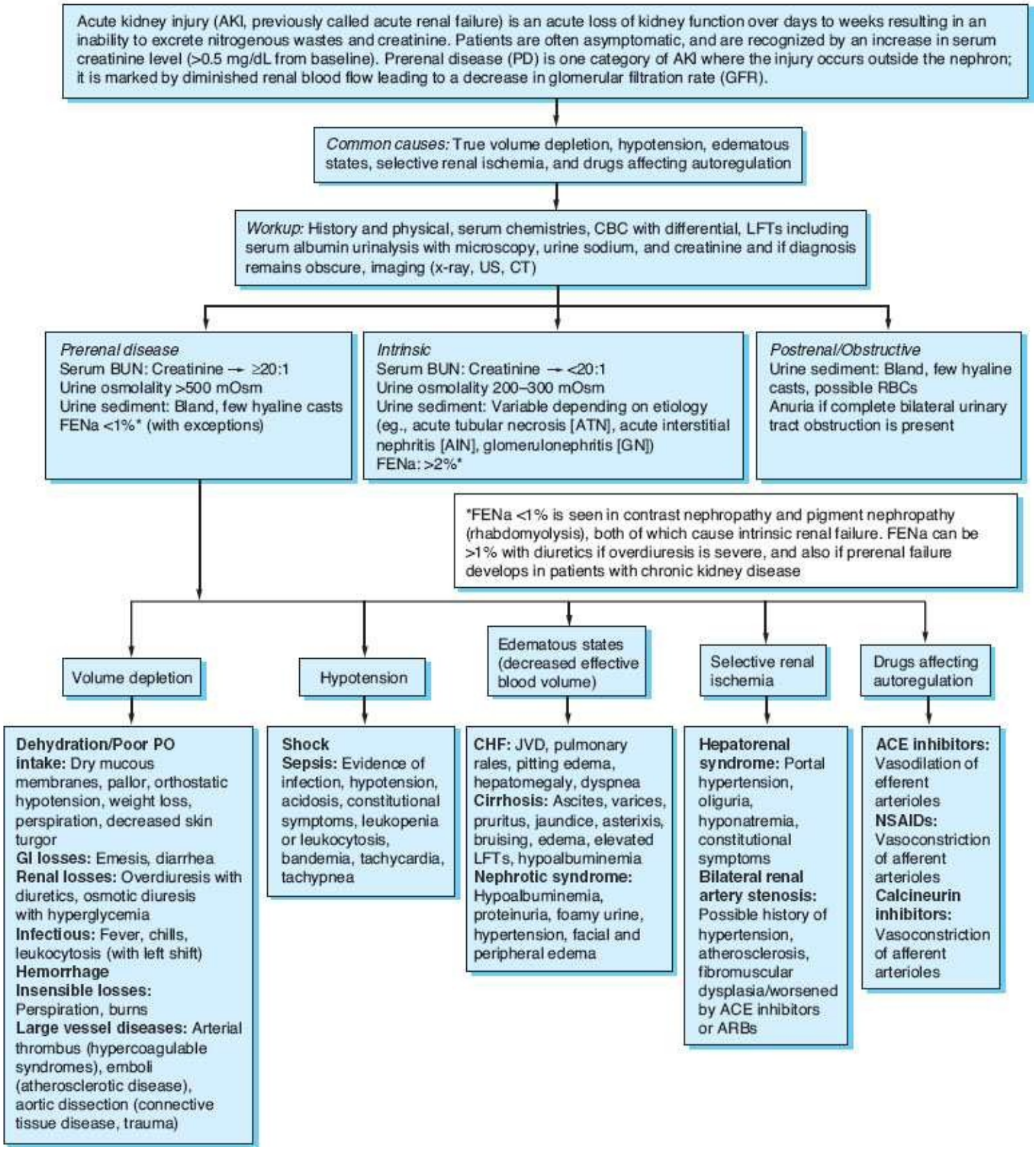
Renal Colic Management



Reproduced with permission from: AUA University: Kidney Stones. http://www.auanet.org/education/kidney-stones.cfm.

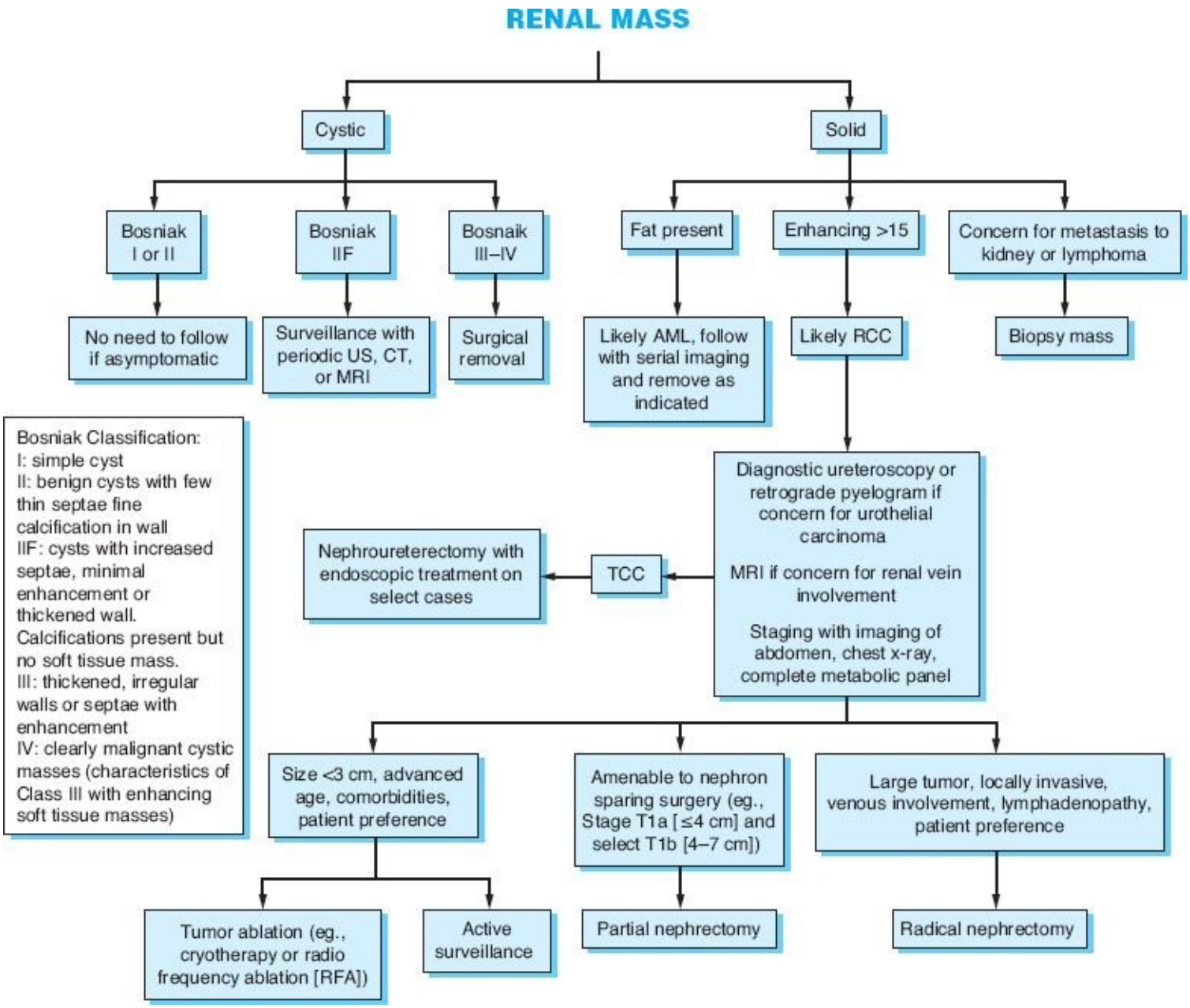
Renal Failure, Acute

RENAL FAILURE, ACUTE

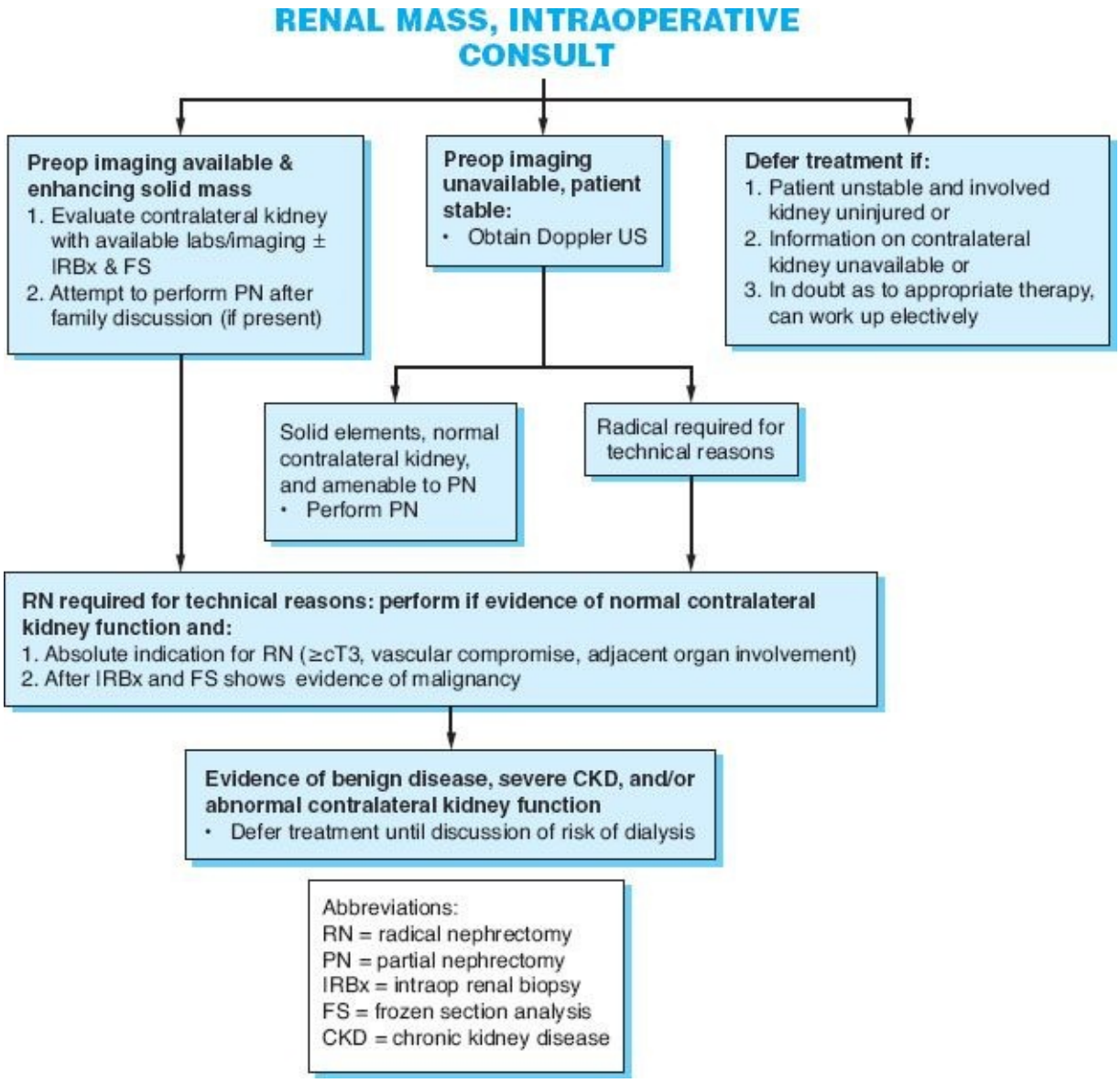


Needham E. Management of acute renal failure. *Am Fam Physician.* 2005;72:1739–1746.

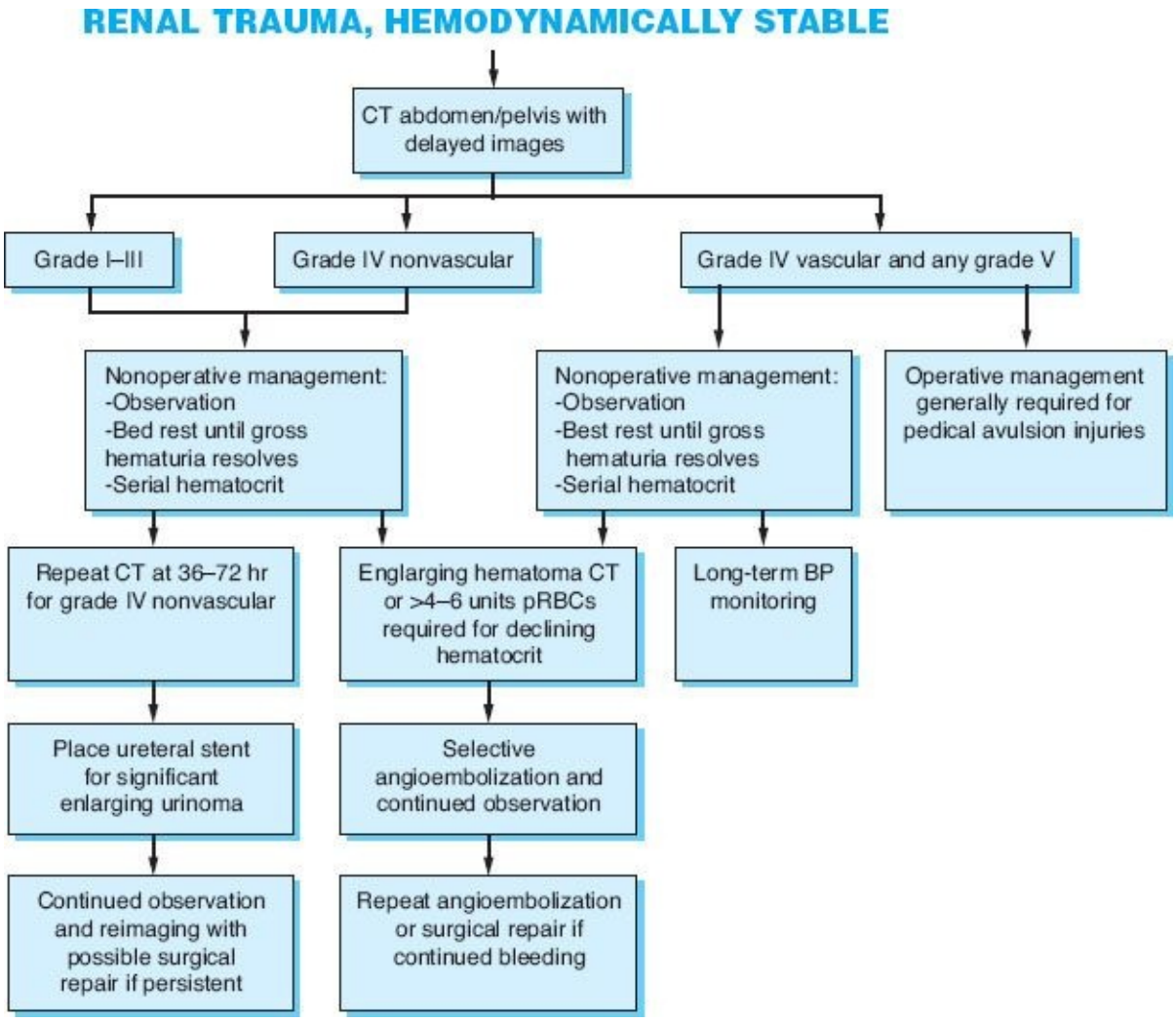
Renal Mass



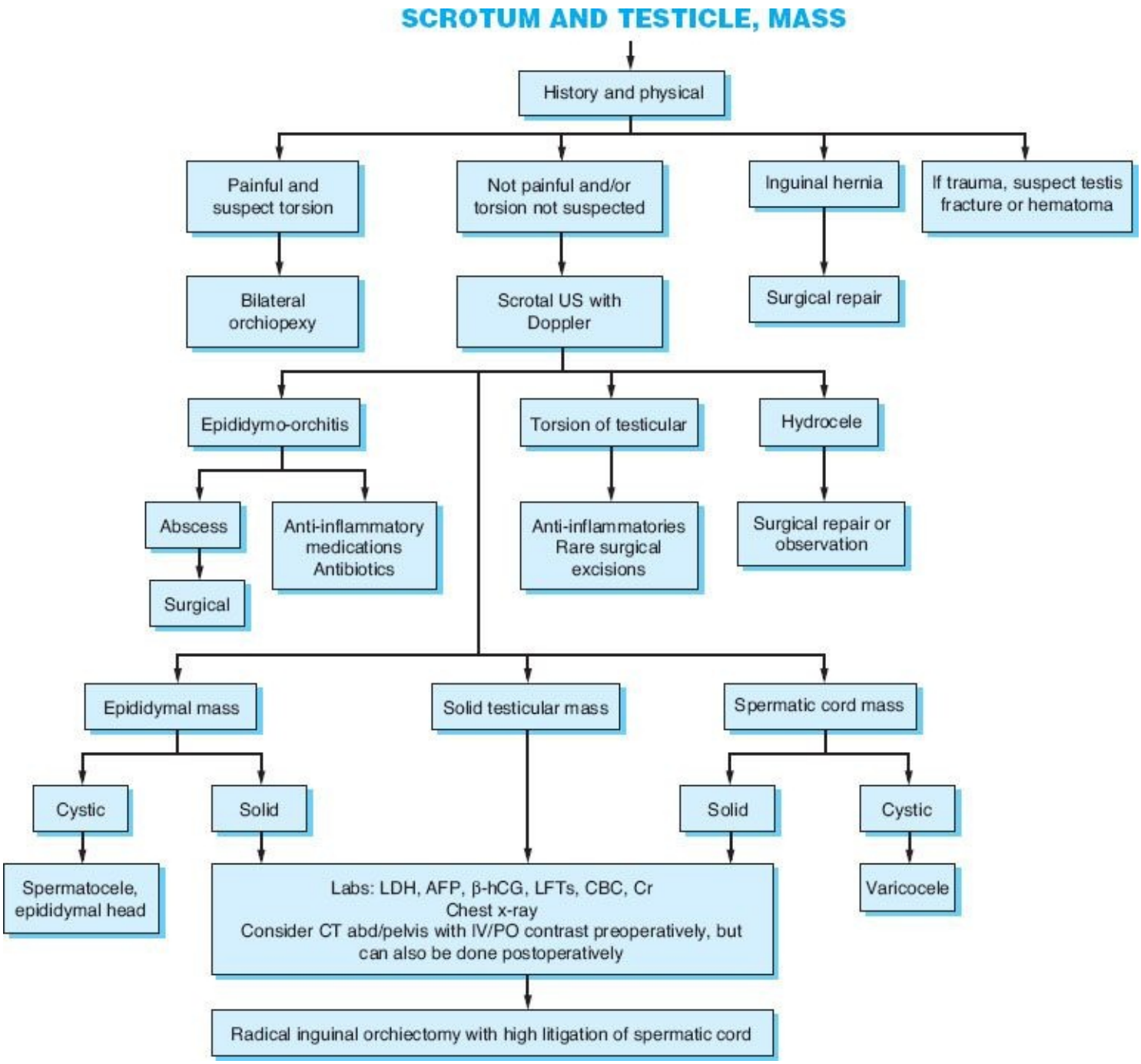
Renal Mass, Intraoperative Consult



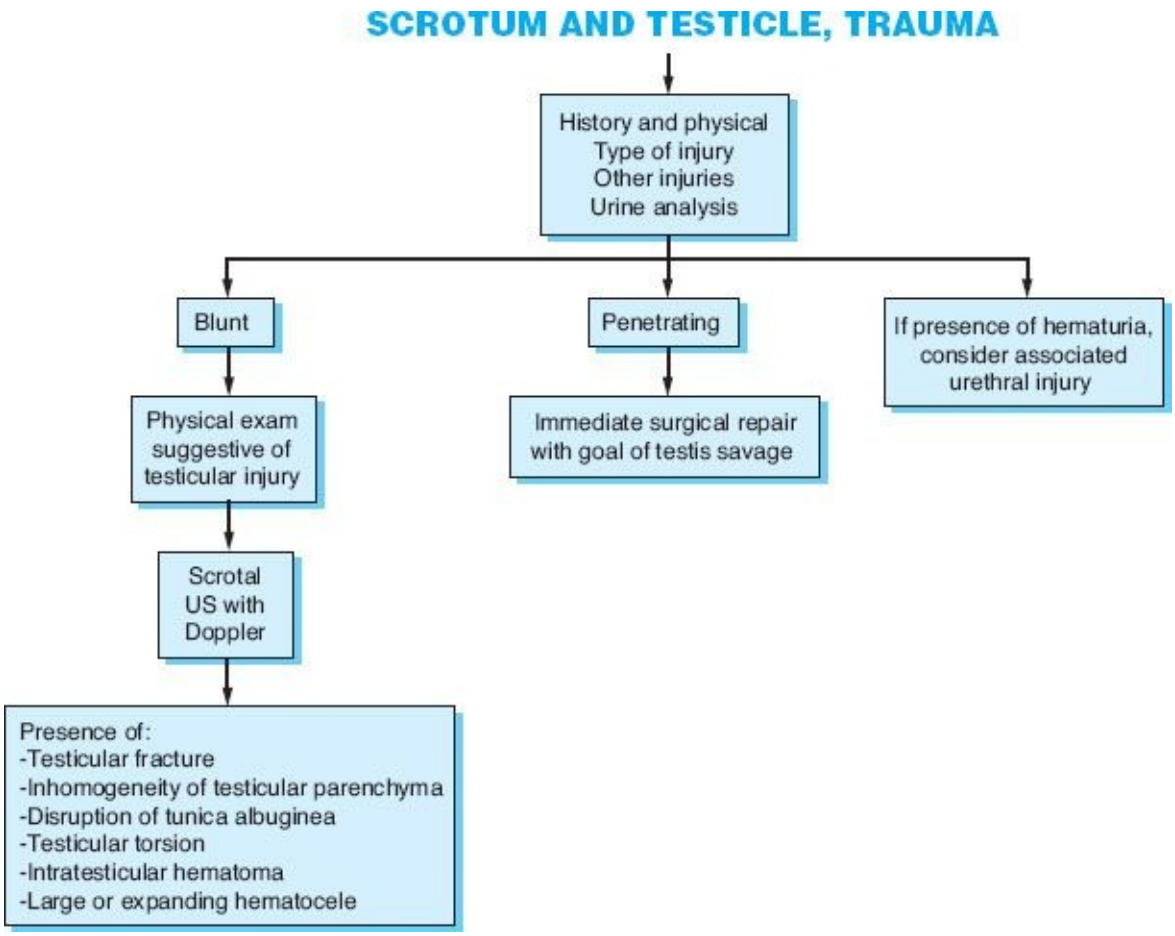
Renal Trauma, Hemodynamically Stable



Scrotum and Testicle, Mass

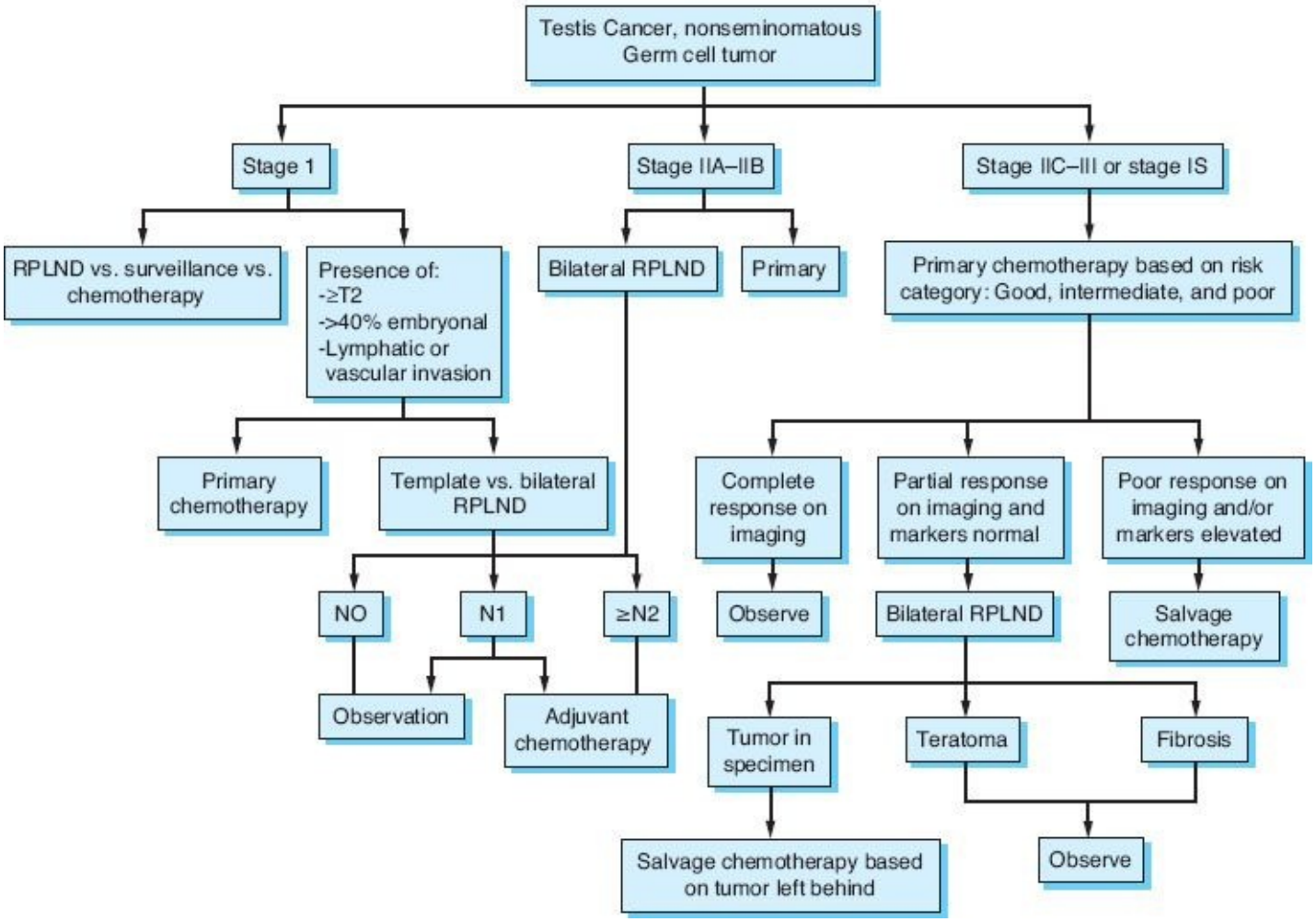


Scrotum and Testicle, Trauma

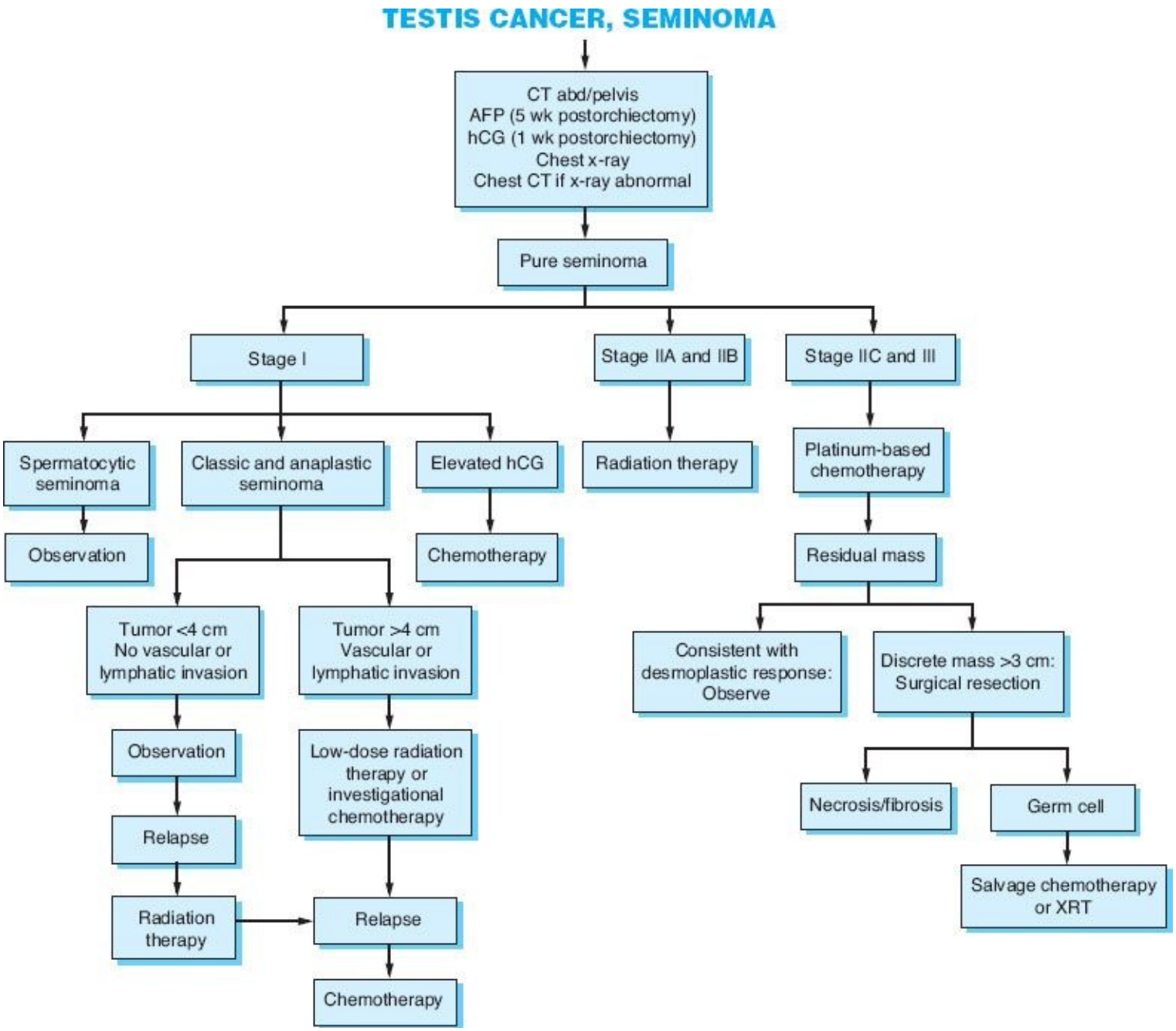


Testis Cancer, Nonseminoma

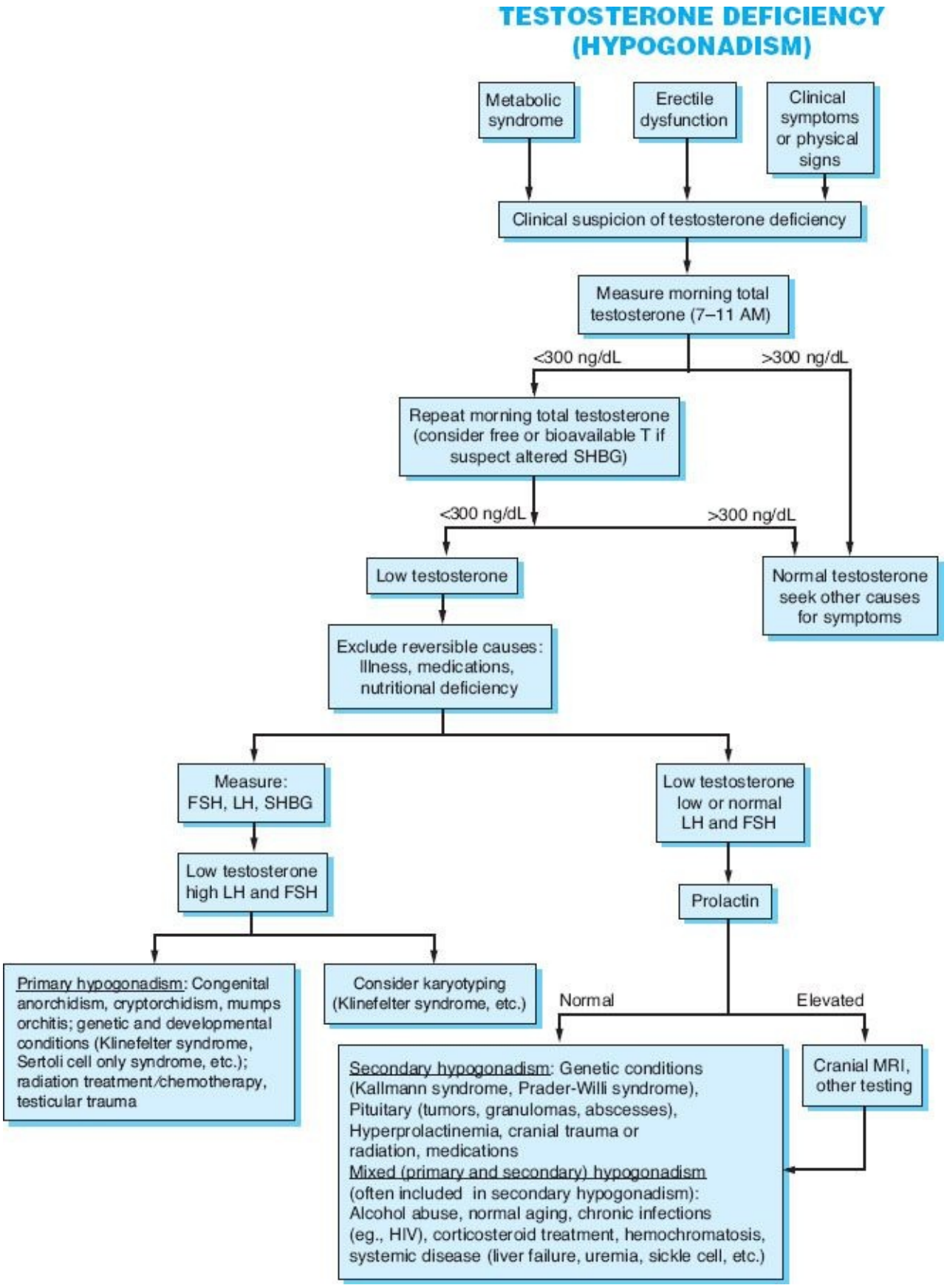
TESTIS CANCER, NONSEMINOMA



Testis Cancer, Seminoma

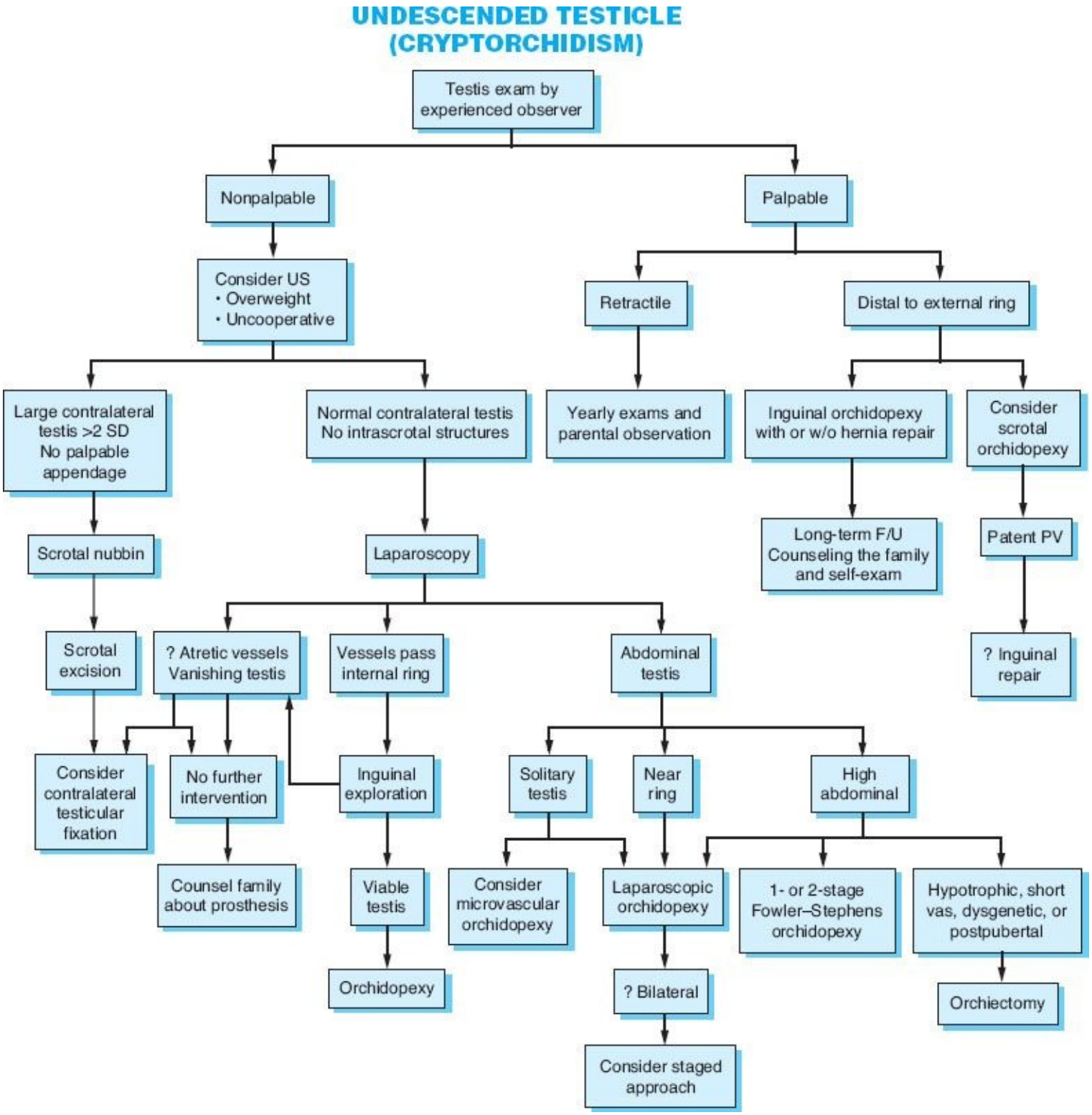


Testosterone Deficiency (Hypogonadism)



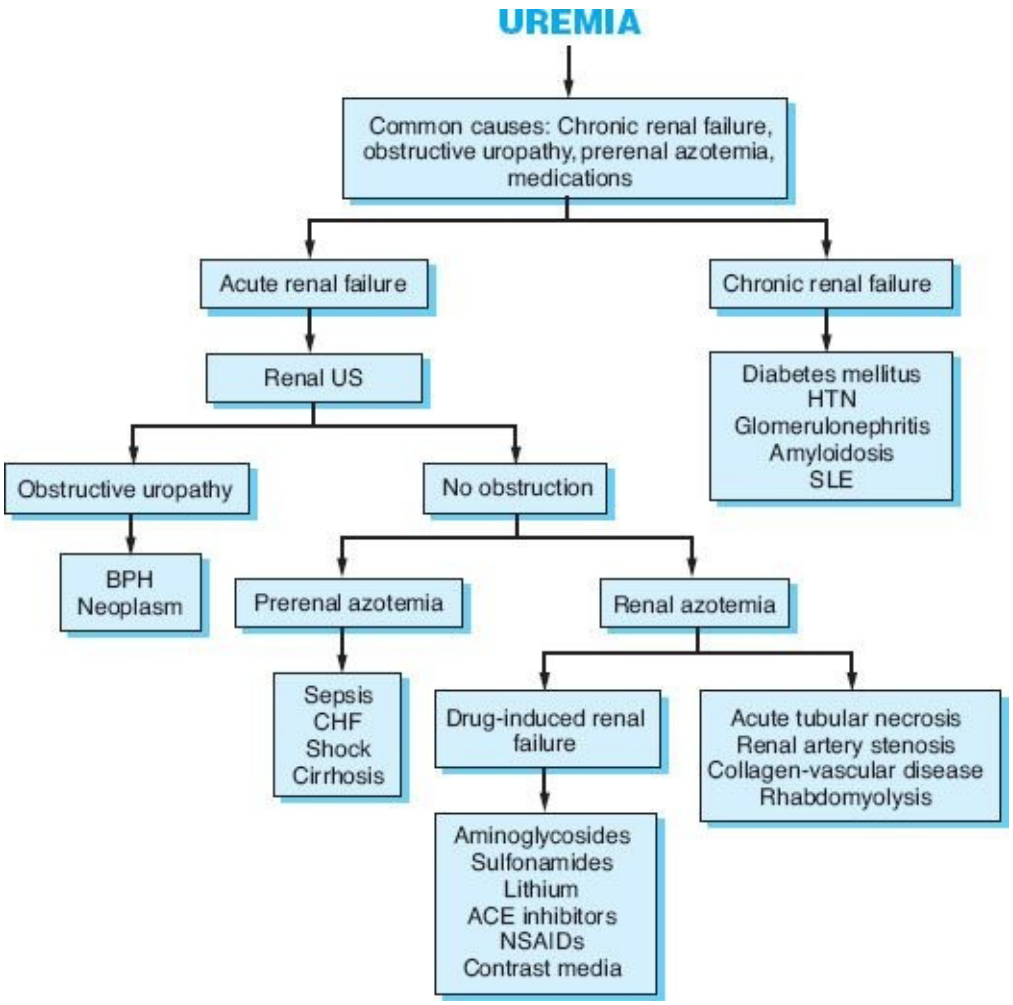
Based on data from: Miner MM, Morgentaler A, et al Testosterone deficinecy. *Am J Med.* 2011;124:578–587; Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract.* 2010;64(6):682–696.

Undescended Testicle (Cryptorchidism)



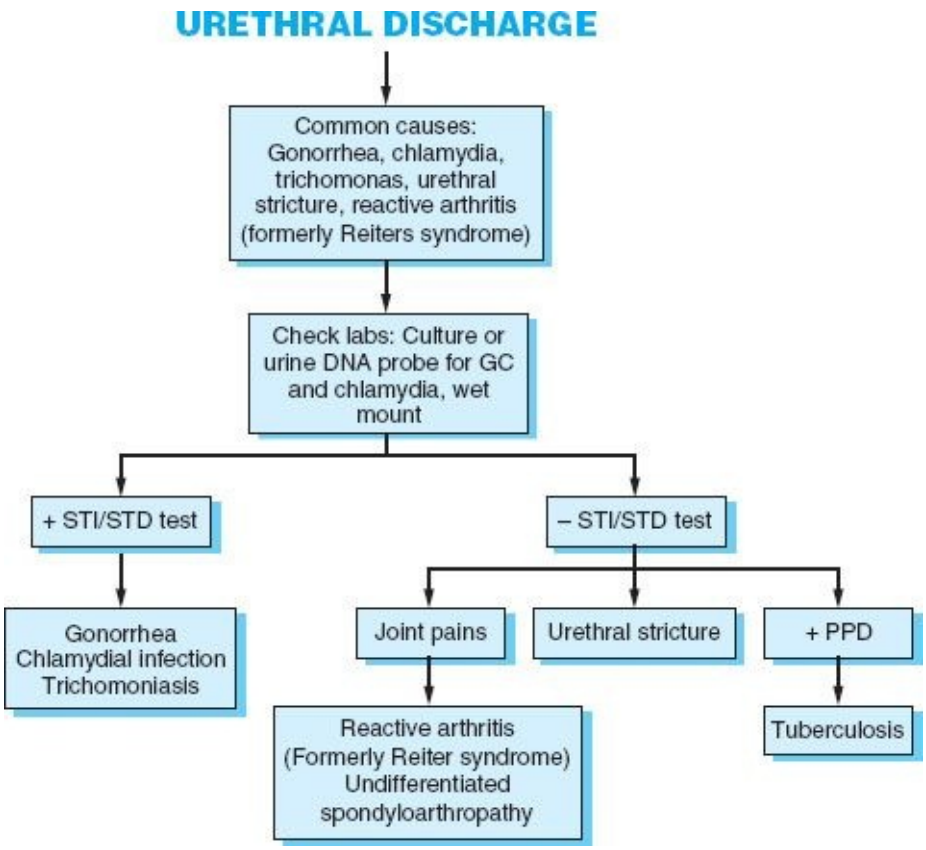
Reproduced with permission from Barthold JS. Abnormalities of the testis and scrotum and their management. Chapter 132. In: Wein AJ, Kavoussi LR, Novick AC, et al., eds. Campbells-Wash Urology. 10th ed. Philadelphia, PA: Elsevier Saunders; 2012:3568.

Uremia



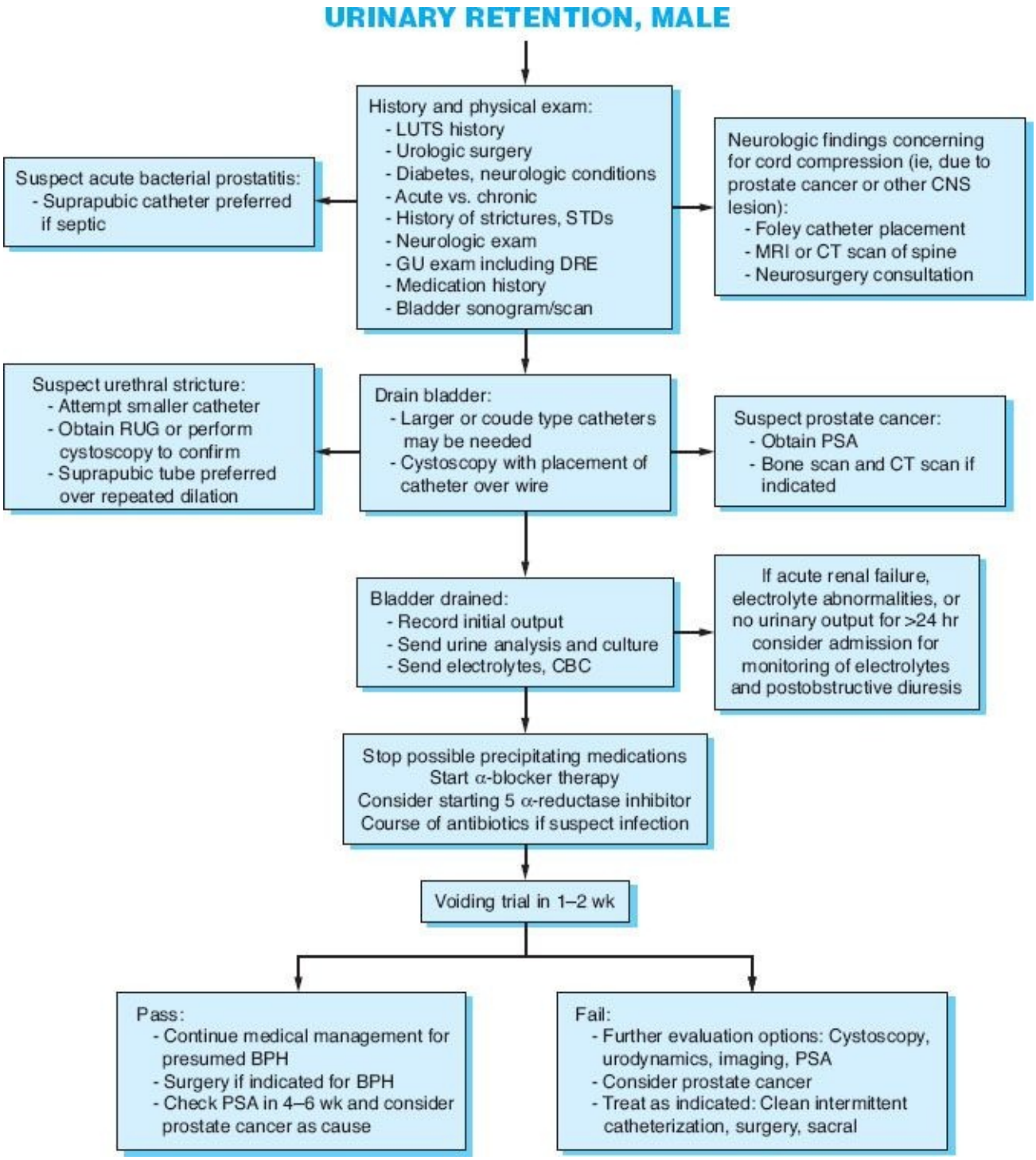
Diagnosis and management of adults with chronic kidney disease. Michigan Quality Improvement Consortium - Professional Association. 2006 Nov (revised 2008 Nov). 1 page. NGC:007054.

Urethral Discharge



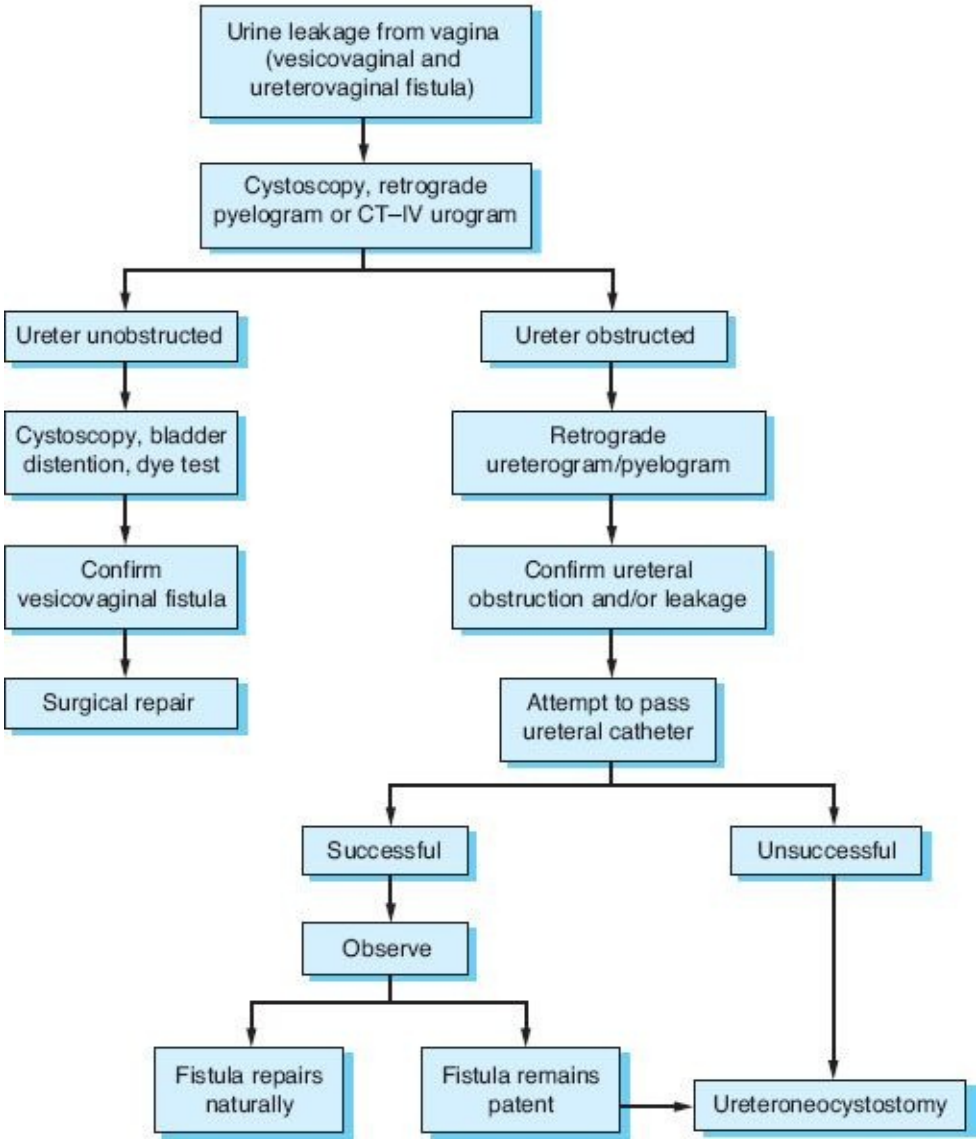
Djajakusumah T, Sudigdoadi S, Keersmaekers K, et al. Evaluation of syndromic patient management algorithm for urethral discharge. *Sex Transm Infect.* 1998;74(Suppl 1):S29–S33.

Urinary Retention, Male

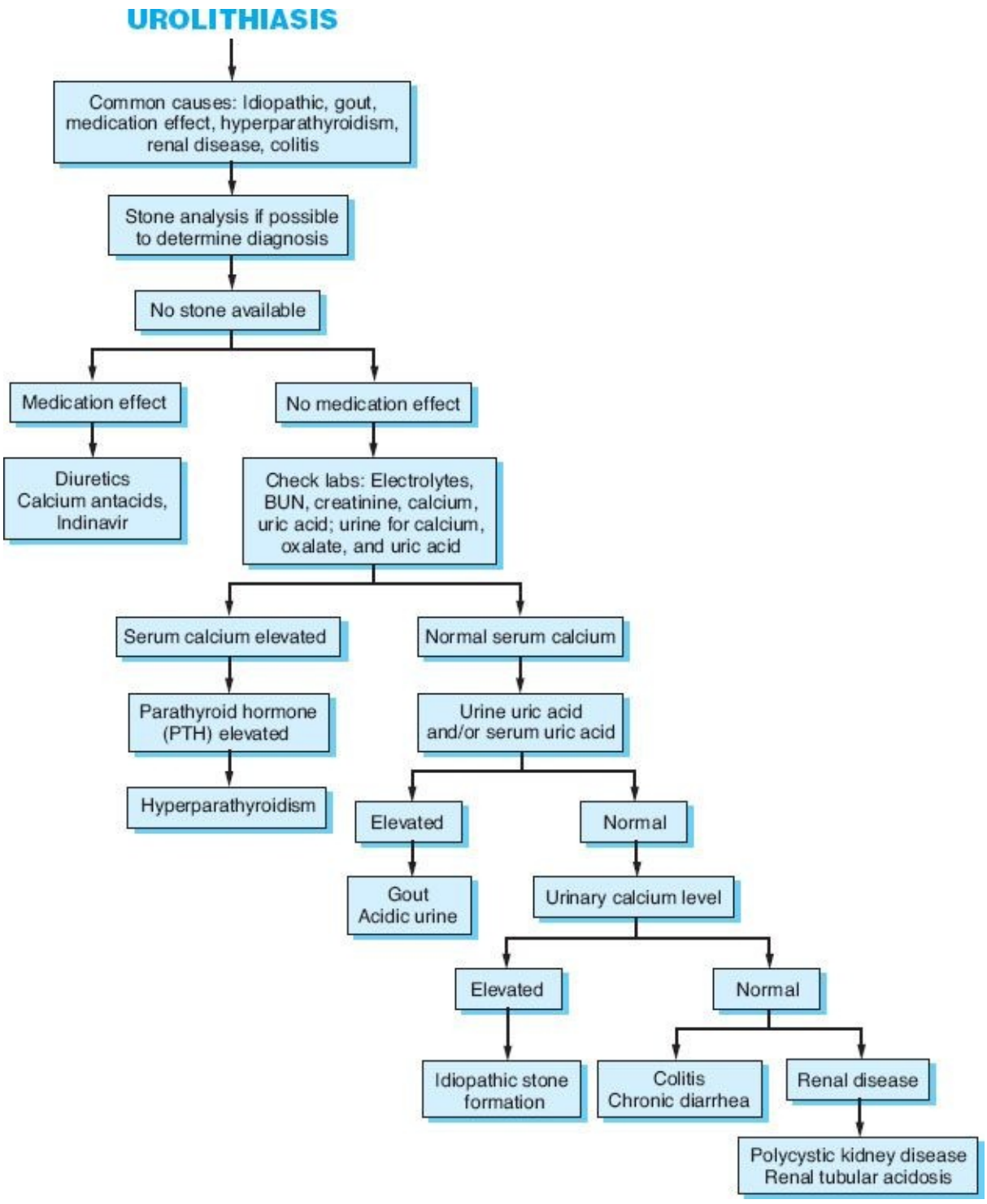


Urine Leak From Vagina

URINE LEAK FROM VAGINA

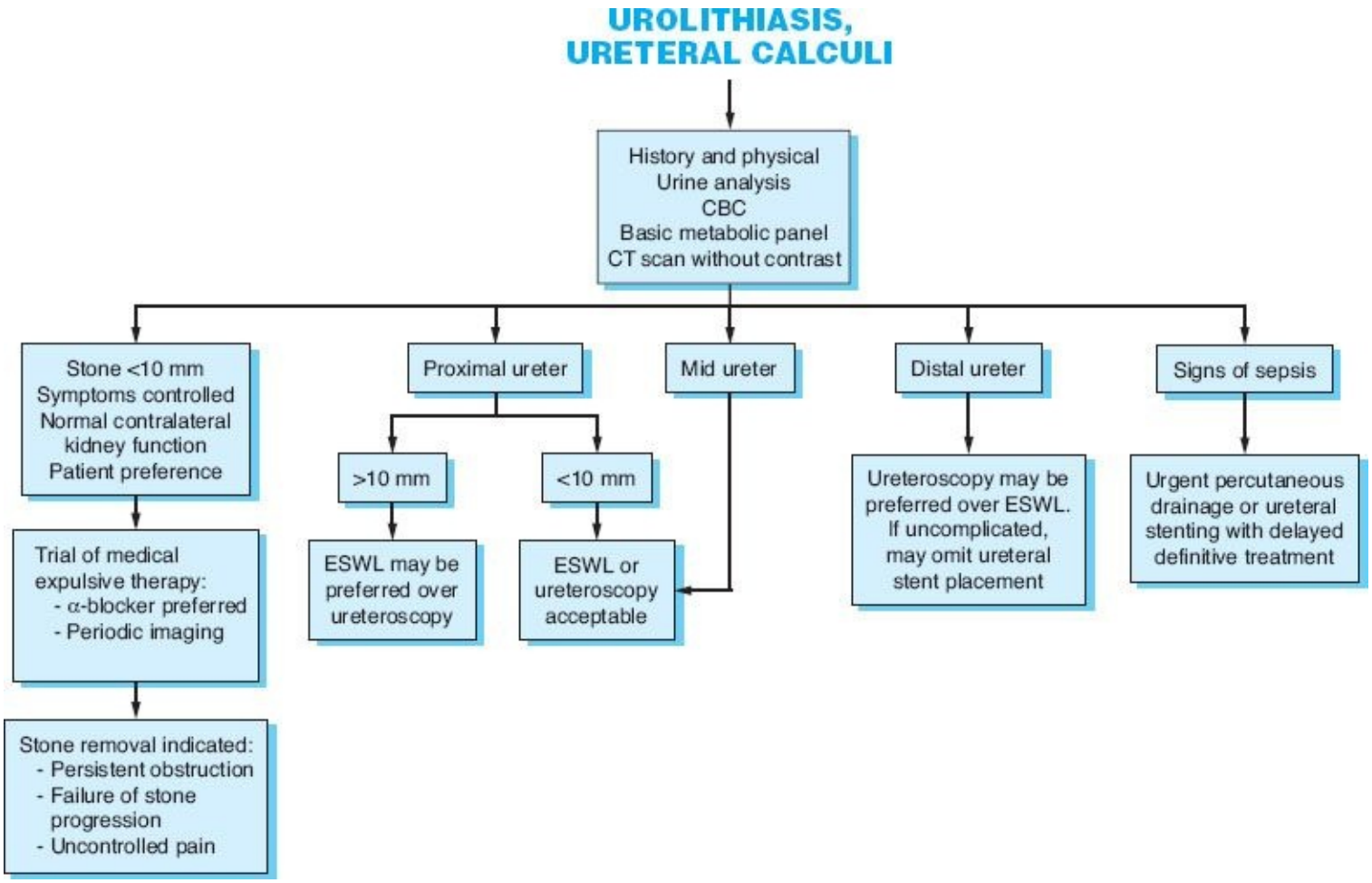


Urolithiasis



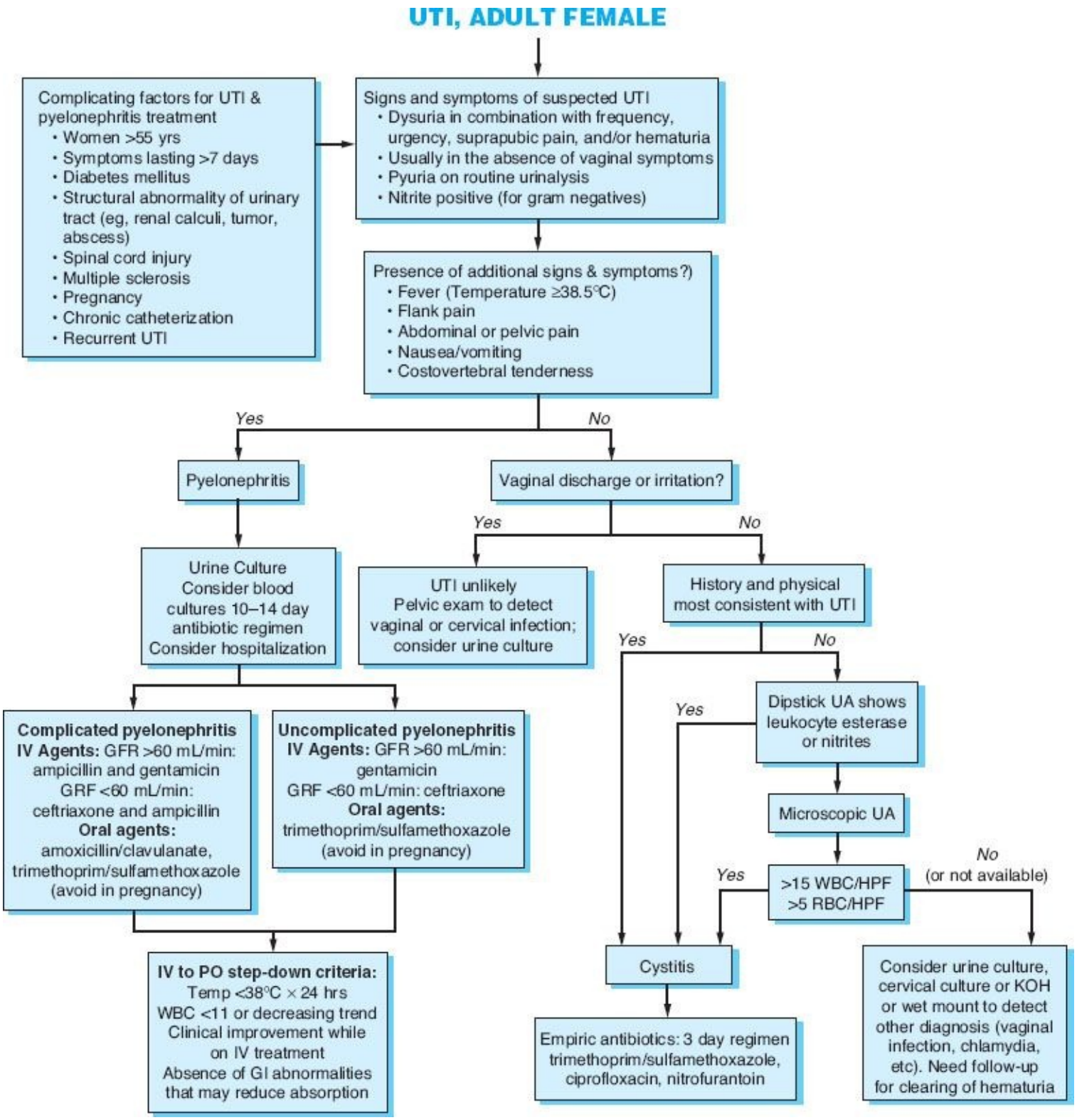
Worcester EM, Coe FL. Nephrolithiasis. *Prim Care.* 2008;35(2):369–391.

Urolithiasis, Ureteral Calculi



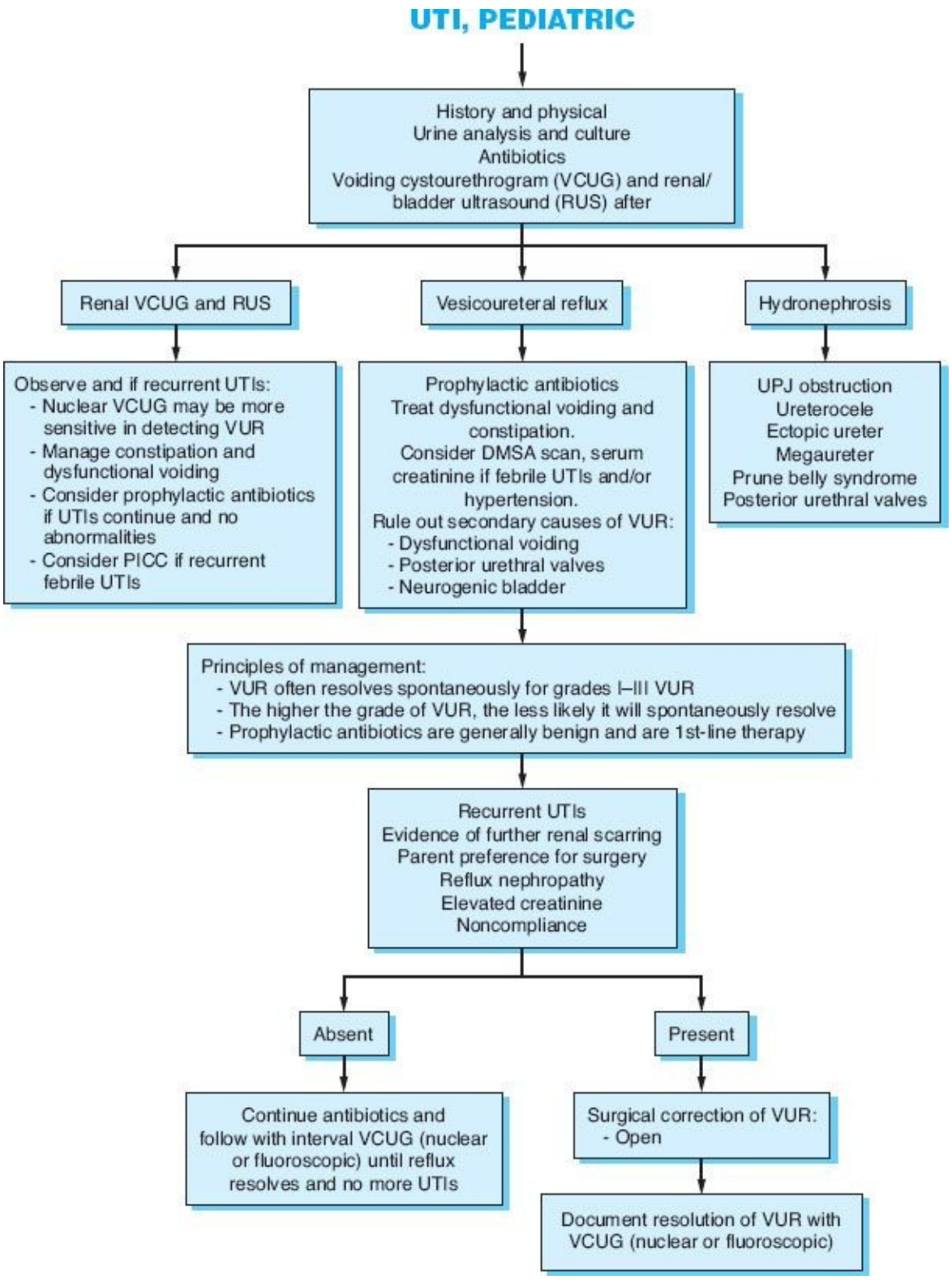
Adapted from Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. *J Urol.* 2007;178(6):2418–2434.

UTI, Adult Female

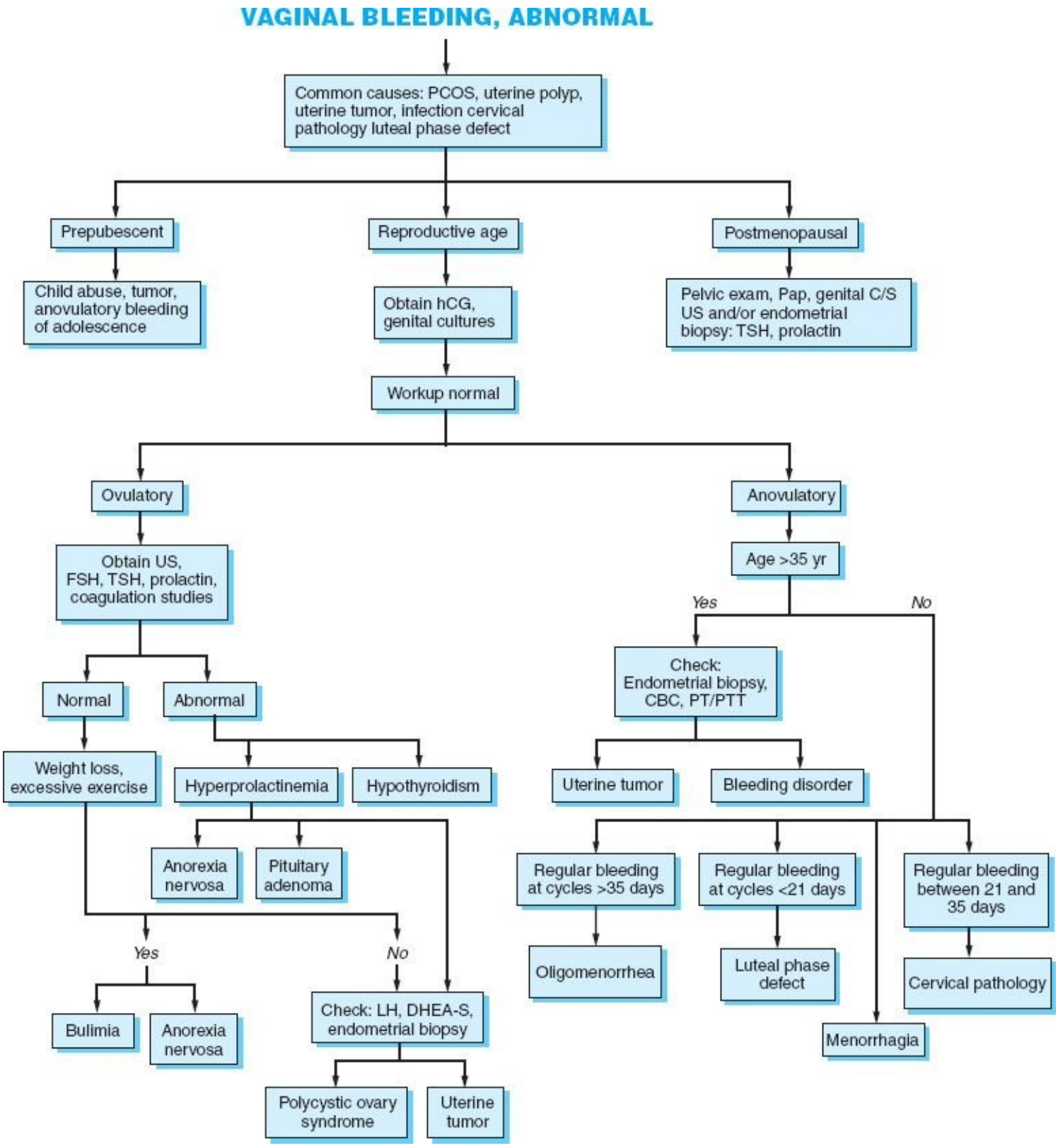


Based on data from Ebell MH. Treating adult women with suspected UTI. *Am Fam Physician.* 2006;73(2):293–296; British Columbia Center for Disease Control VIHA algorithim for Urinary Tract Infection (www.BCCDC.ca, Accessed June 1, 2014)

UTI, Pediatric

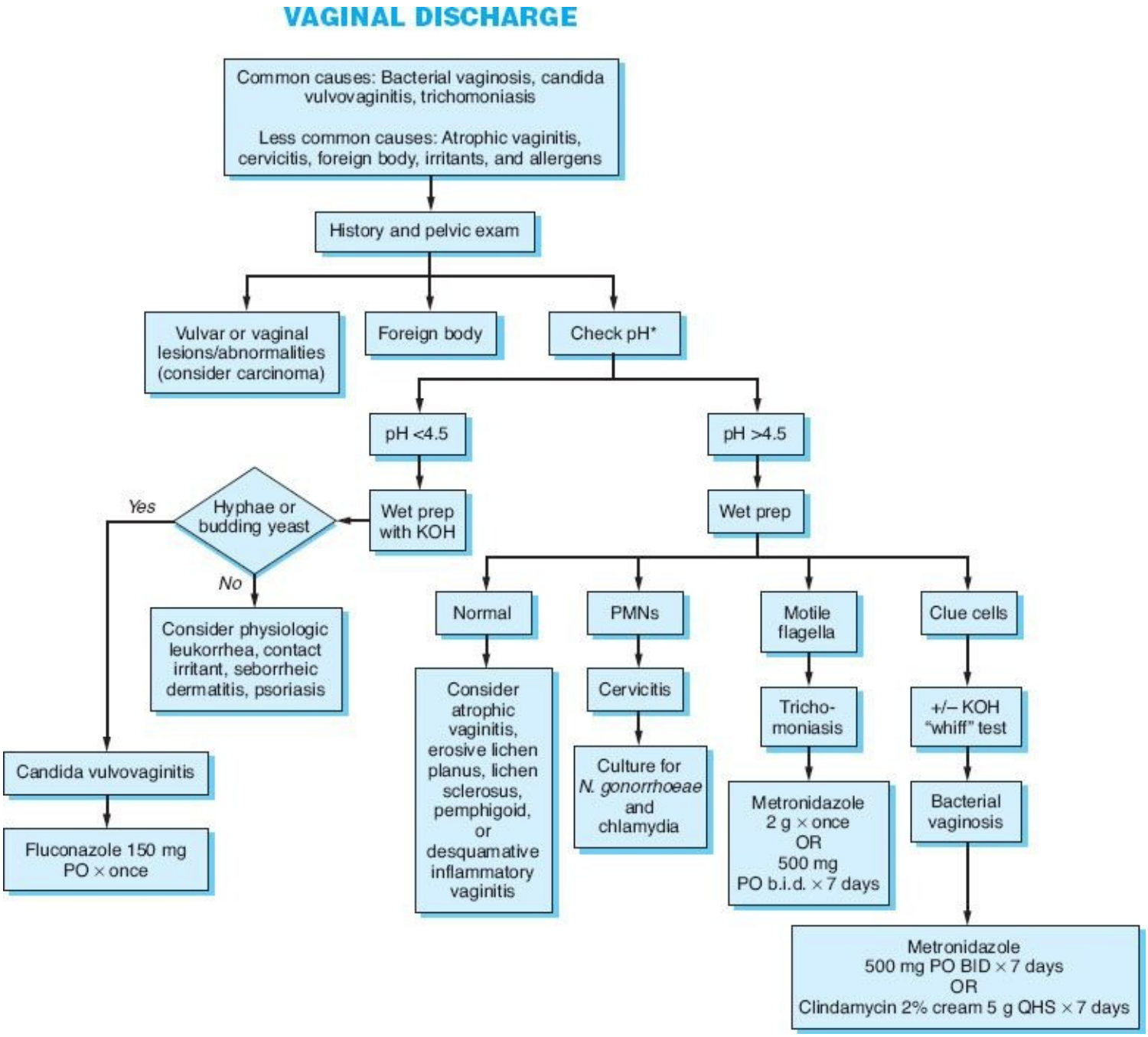


Vaginal Bleeding, Abnormal



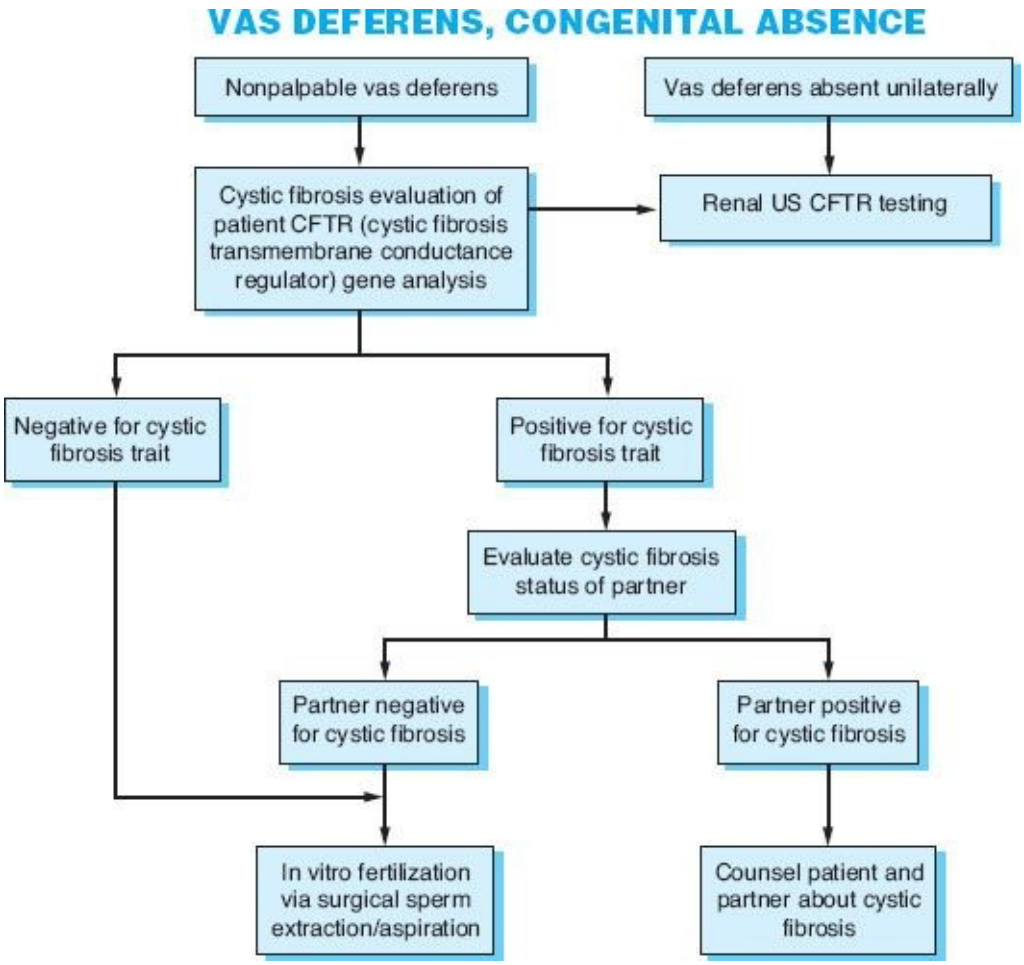
Keehbauch J, Nystrom J. Diagnosis and management of abnormal uterine bleeding. *Female Patient.* 2007;32(7):38–40.

Vaginal Discharge



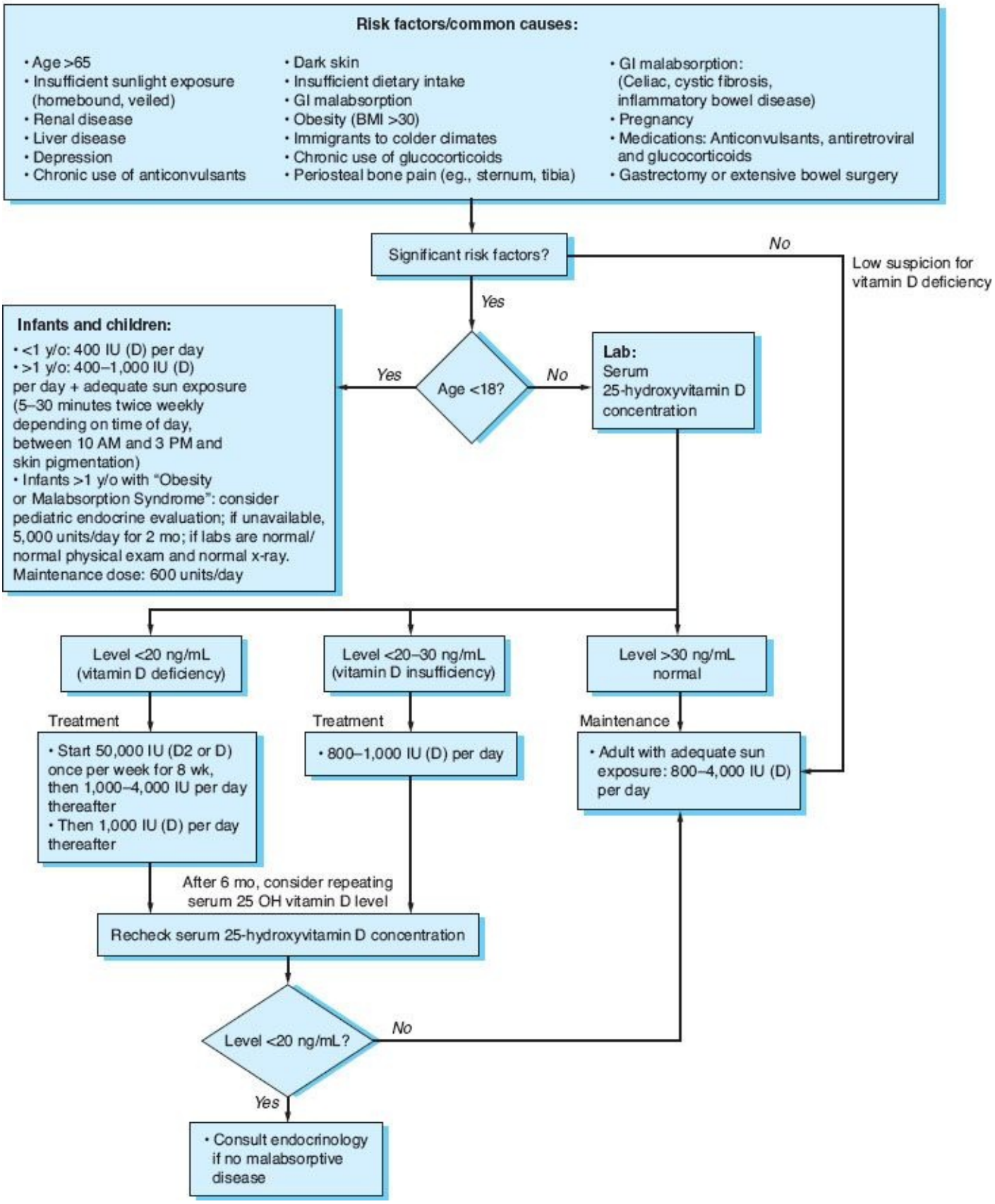
Hainer BL, Gibson MV. Vaginitis. *Am Fam Physician.* 2011;83:807–815.

Vas Deferens, Congenital Absence



Vitamin D Deficiency

VITAMIN D DEFICIENCY



Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. *Am Fam Physician.* 2009;80(8):841–846.

SECTION IV

Urinalysis and Urine Studies

Section Editor: Leonard Gomella, MD, FACS

URINALYSIS AND URINE STUDIES

I. URINE ANALYSIS

URINE ANALYSIS PROCEDURE

For a routine urine analysis, a fresh (<1 hr old), clean-catch urine sample is acceptable. If the analysis cannot be performed immediately, refrigerate the sample. (When urine stands at room temperature for a long period, casts and red blood cells undergo lysis, and the urine becomes alkalinized with precipitation of salts.)

1. Pour 5–10 mL of well-mixed urine into a centrifuge tube.
2. Check for appearance (color, turbidity, odor). If a urine sample looks grossly cloudy, it is sometimes advisable to examine an unspun sample. If an unspun sample is used, make note that you have done so. In general, for routine urine analysis, a spun sample is more desirable.
3. Spin a capped sample at 3,000 rpm for 3–5 min.
4. While the sample is in the centrifuge, use the dipstick (Chemstrip, etc.) to perform the dipstick evaluation on the remaining sample. Read the results according to the color chart on the bottle. Allow the correct amount of time before reading the test (usually 1–2 min) to avoid false results. Chemstrip 10 provides 10 tests (specific gravity, pH, leukocytes, nitrite, protein, glucose, ketone, urobilinogen, bilirubin, and blood). Other strips may provide less. Agents that color the urine (eg, phenazopyridine [Pyridium]) may interfere with the reading. Dipstick specific gravity is also available on some assay strips.
5. Decant and discard the supernatant. Mix the remaining sediment by flicking it with your finger and pouring or pipetting 1 or 2 drops onto a microscope slide. Cover with a coverslip.
6. Examine 10 low-power fields (LPFs; 10× objective) for epithelial cells, casts, crystals, and mucus. Casts are usually reported as number per low-power field and tend to collect around the periphery of the coverslip.
7. Examine several high-power fields (HPFs; 40× objective) for epithelial cells, crystals, RBCs, WBCs, bacteria, and parasites (trichomonads). RBCs, WBCs, and bacteria are usually reported as number per high-power field.

Normal Urine Analysis Values

- Appearance: Yellow, clear, or straw-colored
- Specific gravity:
  - Neonate: 1.012
  - Infant: 1.002–1.006
  - Child and adult: 1.001–1.035 (with normal fluid intake 1.016–1.022)
- pH:
  - Newborn/neonate: 5–7
  - Child and adult: 4.6–8.0
- Negative for bilirubin, blood, acetone, glucose, protein, nitrite, leukocyte esterase, reducing substances
- Trace: Urobilinogen
- RBC: The exact definition of microscopic hematuria is debated, but is generally defined as

>3 RBC/HPF (40×).
- WBC: 0–4/HPF
- Epithelial cells: Occasional
- Hyaline casts: Occasional
- Bacteria: None
- Crystals: Some limited crystals, based on urine pH (see below)

Differential Diagnosis for Routine Urine Analysis

- **Appearance** (see Section II Urine, Abnormal Color; Section II Urine, Foaming; Urine, Odor; and Urine, Particles in)
- **pH:**
  - Acidic: High-protein (meat) diet, ammonium chloride, mandelic acid and other medications, acidosis (due to ketoacidosis [starvation, diabetes], chronic obstructive pulmonary disease [COPD])
  - Basic: Urinary tract infections (UTIs), renal tubular acidosis, diet (high-vegetable, milk, immediately after meals), sodium bicarbonate therapy, vomiting, metabolic alkalosis, diuretic therapy
- **Specific gravity:**
  - Usually corresponds to osmolarity, except with osmotic diuresis. A value >1.023 indicates normal renal concentrating ability:
    - Increased: Volume depletion, congestive heart failure (CHF), adrenal insufficiency, diabetes mellitus, inappropriate antidiuretic hormone (ADH), increased proteins (nephrosis); if markedly increased (1.040–1.050), suspect artifact or excretion of radiographic contrast media.
    - Decreased: Diabetes insipidus, pyelonephritis, glomerulonephritis, water load with normal renal function
- **Bilirubin:**
  - Positive: Obstructive jaundice (intrahepatic and extrahepatic), hepatitis (Note: False positive with stool contamination)
- **Blood:**
  - Positive: See Section I Hematuria, gross and microscopic, adult and Hematuria, gross and microscopic, pediatric
  - Note: If the dipstick is positive for blood, but no RBCs are seen, free hemoglobin may be present from trauma, from a transfusion reaction, or from lysis of RBCs (RBCs will lyse if the pH is <5 or >8), or there may be myoglobin present because of a crush injury, burn, or tissue ischemia.
- **Glucose:**
  - Positive: Diabetes mellitus, pancreatitis, pancreatic carcinoma, pheochromocytoma, Cushing syndrome, shock, burns, pain, steroids, hyperthyroidism, renal tubular disease, iatrogenic causes

(Note: The glucose oxidase technique in many kits is specific for glucose and will not react with lactose, fructose, or galactose.)

- **Ketones:**
  - Detects primarily acetone and acetoacetic acid and not β-hydroxybutyric acid:
  - Positive: Starvation, high-fat/low-carbohydrate diet, diabetic ketoacidosis, vomiting,

diarrhea, hyperthyroidism, pregnancy, febrile states (especially in children)

- **Nitrite:**
  - Many bacteria will convert nitrates to nitrite. (See also the section on Leukocyte Esterase, below.)
    - Positive: Infection (A negative test does not rule out infection, because some organisms, such as *Streptococcus faecalis* and other gram-positive cocci, will not produce nitrite, and the urine must also be retained in the bladder for several hours to allow the reaction to take place.)
- **Protein:**
  - Indication by dipstick of persistent proteinuria should be quantified by 24-hr urine studies:
    - Positive: Pyelonephritis, glomerulonephritis, Kimmelstiel-Wilson syndrome (diabetes), nephrotic syndrome, myeloma, postural causes, preeclampsia, inflammation, and malignancies of the lower tract, functional causes (fever, stress, heavy exercise), malignant hypertension, congestive heart failure
- **Leukocyte esterase** (see Section I Pyuria.):
  - This test detects ≥5 WBCs/HPF or lysed WBCs. When combined with the nitrite test, it has a predictive value for UTI of 74% if both tests are positive, and >97% if both tests are negative:
    - Positive: Infection (false-positive with vaginal contamination)
- **Reducing substance:**
  - Positive: Glucose, fructose, galactose, false-positives (vitamin C, salicylates, antibiotics, etc.)
- **Urobilinogen:**
  - Positive: Cirrhosis, CHF with hepatic congestion, hepatitis, hyperthyroidism, suppression of gut flora with antibiotics (Note: With obstructive jaundice, urobilinogen is usually normal, but bilirubin is elevated.)

Urine Sediment

Many labs no longer do microscopic examinations unless specifically requested or if the dipstick test shows evidence of an abnormal finding (such as positive leukocyte esterase):

- **RBCs:** Trauma, pyelonephritis, genitourinary tuberculosis (TB), cystitis, prostatitis, stones, tumors (malignant and benign), coagulopathy, and any cause of blood on dipstick test (see above on hemoglobin)
- **WBCs:** Infection anywhere in the urinary tract, TB, renal tumors, acute glomerulonephritis, radiation, interstitial nephritis (analgesic abuse)
- **Epithelial cells:** Acute tubular necrosis (ATN), necrotizing papillitis (most epithelial cells are from an otherwise unremarkable urethra)
- **Parasites:** *Trichomonas vaginalis, Schistosoma haematobium* infections
- **Yeast:** *Candida albicans* infection (especially in diabetics, immunosuppressed patients, or if a vaginal yeast infection is present)
- **Spermatozoa:** Normal in males immediately after intercourse or nocturnal emission
- **Crystals:** Note that urine should be examined fresh and warm because clouding due to phosphate precipitation may be observed when urine cools:
  - Abnormal: Cystine, sulfonamide, leucine, tyrosine, cholesterol

- Normal in acidic urine: Oxalate (small square crystals with a central cross), uric acid
- Normal in alkaline urine: Calcium carbonate, triple phosphate (resemble coffin lids)

• **Contaminants:** Cotton threads, hair, wood fibers, amorphous substances (all usually unimportant)
• **Mucus:** Large amounts suggest urethral disease (normal from ileal conduit or other forms of urinary diversion).
• **Glitter cells:** WBCs are lysed in hypotonic solution.
• **Casts:** The presence of casts in a urine sample localizes some or all of the disease process to the kidney itself:
  - Hyaline casts (occasionally acceptable, unless they are numerous), benign hypertension, nephrotic syndrome, after exercise
  - RBC casts: Acute glomerulonephritis, lupus nephritis, subacute bacterial endocarditis (SBE), Goodpasture disease, after a streptococcal infection, vasculitis, malignant hypertension
  - WBC casts: Pyelonephritis
  - Epithelial (tubular) casts: Tubular damage, nephrotoxin, virus
  - Granular casts: Breakdown of cellular casts leads to waxy casts; dirty brown granular casts typical for ATN
  - Waxy casts (end stage of granular casts): Severe, chronic renal disease; amyloidosis
  - Fatty casts: Nephrotic syndrome, diabetes mellitus, damaged renal tubular epithelial cells
  - Broad casts: Chronic renal disease

II. SPOT OR RANDOM URINE STUDIES

The so-called spot urine is often ordered to aid in diagnosing various conditions. It relies on only a small sample (10–20 mL) of urine:

• **Spot urine for β_2 microglobulin** (< 0.3 mg/L):
  - A marker for renal tubular injury:
    - Increased: Diseases of the proximal tubule (ATN, interstitial nephritis, pyelonephritis), drug-induced nephropathy (aminoglycosides), diabetes, trauma, sepsis

• **Spot urine for electrolytes:**
  - The usefulness of this assay is limited because of large variations in daily fluid and salt intake, and the results are usually indeterminate if a diuretic has been given. (See also Section I Anuria and oliguria, adult and Anuria and oliguria, pediatric.)
    - Sodium < 10 mEq/L (mmol/L): Volume depletion, hyponatremic states, prerenal azotemia (CHF, shock, etc.), hepatorenal syndrome, glucocorticoid excess
    - Sodium > 20 mEq/L (mmol/L): Syndrome of inappropriate antidiuretic hormone (SIADH), ATN (usually > 40 mEq/L), postobstructive diuresis, high salt intake, Addison disease, hypothyroidism, interstitial nephritis
    - Chloride < 10 mEq/L (mmol/L): Chloride-sensitive metabolic alkalosis (vomiting, excessive diuretic use), volume depletion
    - Potassium < 10 mEq/L (mmol/L): Hypokalemia, potassium depletion, extrarenal loss

• **Spot urine for protein** (normal: < 10 mg/dL [0.1 g/L] or < 20 mg/dL [0.2 g/L] for a sample taken in the early morning)
  - See Section I Proteinuria for the differential diagnosis of protein in the urine.

- **Spot urine for eosinophils** (present with Hansel/Wright staining and white light microscopy):
  - Associated with acute interstitial nephritis (especially nephritis associated with drug hypersensitivity) or acute cystitis
  - Present with interstitial nephritis; absent with tubular disorders (ATN).
- **Spot urine for erythrocyte morphology:**
  - The morphology of RBCs in a sample of urine that tests positive for blood may give some indication of the nature of the hematuria. Eumorphic red cells are typically seen in cases of postrenal, nonglomerular bleeding. Dysmorphic red cells are more likely associated with glomerular causes of bleeding. Each reference lab has standards, but as a general rule, the presence of >90% dysmorphic erythrocytes in patients with asymptomatic hematuria indicates a renal glomerular source of bleeding, especially if associated with proteinuria and/or casts (ie, IgA nephropathy, poststreptococcal GN, sickle cell disease or trait, etc.). If <90% eumorphic erythrocytes or even mixed results (10–90% eumorphic erythrocytes), this indicates a post-renal cause of hematuria, requiring a complete urologic evaluation (ie, hypercalcuria, urolithiasis, cystitis, trauma, tumors, hemangioma, exercise-induced, benign prostatic hypertrophy [BPH], etc.).
- **Spot urine for osmolality** (ranges from 40–1,400 mOsm/kg water [mmol/kg]; varies with water intake):
  - Patients with normal renal function should concentrate >400–800 mOsmol/kg (mmol/kg) after a 14-hr fluid restriction; <200–400 mOsmol/kg (mmol/kg) is a sign of renal impairment:
    - Increased: Dehydration, CHF, hypercalcemia, SIADH, adrenal insufficiency, glycosuria, high-protein diet
    - Decreased: Excessive fluid intake, diabetes insipidus, acute renal failure, medications (acetohexamide, glyburide, lithium)
- **Spot urine for myoglobin** (qualitative negative):
  - Positive: Skelet al muscle conditions (crush injury, electrical burns, carbon monoxide poisoning, delirium tremens, surgical procedures, malignant hyperthermia), polymyositis

III. CREATININE CLEARANCE AND GLOMERULAR FILTRATION RATE

CREATININE CLEARANCE

- **Normal:**
  - **Adult male:** Total creatinine 1–2 g/24 h (8.8–17.7 mmol/d); clearance 85–125 mL/min/1.73 m^2
  - **Adult female:** Total creatinine 0.8–1.8 g/24 h (7.1–15.9 mmol/d); clearance 75–115 mL/min 1.73 m^2 (1.25–1.92 mL/s/1.73 m^2)
  - **Child:** Total creatinine (>3 yr) 12–30 mg/kg/ 24 h; clearance 70–140 mL/min/1.73 m^2 (1.17–2.33 mL/s/1.73 m^2)
  - **Decreased:** A decreased creatinine clearance results in an increase in serum creatinine, usually secondary to renal insufficiency. See Section I Renal Failure, Acute, and Renal Failure, Chronic for the differential diagnosis of increased serum creatinine.
  - **Increased:** Early diabetes mellitus, pregnancy

DETERMINATION OF CREATININE CLEARANCE

Creatinine clearance (CrCl) is a sensitive indicator of early renal insufficiency and is a measure of glomerular filtration rate (GFR); however, the GFR does not provide information on the etiology of the renal disease. CrCl decreases with age, with a CrCl of 10–20 mL/min indicating severe renal failure, and usually the need for dialysis. The National Kidney Disease Education Program (NKDEP) recommends using an estimation of GFR (eGFR) from serum creatinine in adults (>18yr) with chronic kidney disease (CKD) and those at risk for CKD (diabetes, hypertension, and family history of kidney failure).

Methods

1. Formal 24-hr Urinary Collection for Creatinine Clearance

Order a concurrent serum creatinine (SCr) and a 24-hr urine creatinine. A shorter time interval can be used (eg, 12 hr), but the formula must be corrected for this change; a 24-hr sample is less prone to collection error.

$$\text{Clearance} = \frac{(\text{Urine creatinine} \times \text{total urine volume})}{(\text{plasma creatinine} \times \text{time})}$$

Where time = 1,440 min if 24-hr collection is used

Example: The following are calculations of (a) CrCl from a 24-hr urine sample with a volume of 1,000 mL, (b) a urine creatinine of 108 mg/100 mL, and (c) a SCr of 1 mg/100 mL (1 mg/dL), where time = 1,440 min if 24-hr collection is used.

$$\text{Clearance} = \frac{(108\ \text{mg}/100\ \text{mL})\ (1{,}000\ \text{mL})}{(1\ \text{mg}/100\ \text{mL})\ (1{,}440\ \text{min})} = 75\ \text{mL/min}$$

To determine if there is a valid, full 24-hr collection, the sample should contain 18–25 mg/kg/24 h of creatinine for adult males or 12–20 mg/kg/24 h for adult females. If the patient is an adult (150 lb = body surface area of 1.73 m^2), adjustment of the clearance for body size is not routinely done. Adjustment for pediatric patients is a necessity.

If the values in the previous example were for a 10-yr-old boy who weighed 70 lb (1.1 m^2), the clearance would be:

$$75\ \text{mL/min}\ (1.73\ m^2 \div 1.1\ m^2) = 118\ \text{mL/min}$$

2. Estimated Creatinine Clearance (eGFR)

Estimated glomerular filtration rate (eGFR) is based on SCr combined with other factors such as age, sex, and race and has generally replaced 24-hr urinary CrCl determinations. Online calculators for adults and children are found at: http://nkdep.nih.gov/lab-evaluation/gfr-calculators.shtml (Accessed April 19, 2014)

Reference Table for Population Mean eGFRs from National Health and Nutrition Examination Survey (NHANES) III*

Age (Yr)	Mean eGFR* (mL/min/1.73 m^2)
20–29	116
30–39	107
40–49	99
50–59	93
60–69	85
70+	75

*For diagnostic purposes the NKDEP recommends laboratories report eGFR values ≥60 as "≥60 mL/min/1.73 m^2," not as an exact number.
*Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *Am J Kidney Dis*. 2003;41(1):1–12.

Adult:

A. Modification of Diet in Renal Disease (MDRD) equation (*Ann Intern Med*. 1999;130, 137–147): Although more cumbersome than Cockcroft-Gault, the MDRD equation is believed to be more accurate. The equation does not require weight; results are normalized to 1.73^2 body surface area (BSA), an accepted adult average BSA:

$$\text{GFR (mL/min/1.73 m}^2) = 175 \text{ for } (S_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

B. Cockcroft–Gault equation:

CrCl estimate

$$= \frac{(140 - \text{age}) \times \text{wt (kg)} \text{ (if female} \times 0.85)}{\text{SCr} \times 72}$$

Children:

Use the **Schwartz equation:**

$$\text{GFR (mL/min/1.73 m}^2) = k \text{ (height)/SCr}$$

Where:

- k = Constant (0.33, premature infant; 0.45, term infants to 1 yr; 0.55, children to 13 yr; 0.65, adolescent males; 0.55, adolescent females)
- Height in cm, and SCr in mg/dL

IV. 24-HR URINE STUDIES

- **Calcium, urine:** See also Section II Hypercalcuria (Absorptive, Renal and Resorptive) and Metabolic Stone Evaluation (24 hr Urine Studies)
  - Normally ordered as part of a urolithiasis metabolic evaluation:
    - Normal: Calcium-free diet <150 mg/24 h (3.7 mmol/d); average calcium diet (600–800 mg/24 h) 100–250 mg/24 h (2.5–6.2 mmol/d)
    - Increased: Hyperparathyroidism, hyperthyroidism, hypervitaminosis D, distal renal tubular acidosis (type I), sarcoidosis, immobilization, osteolytic lesions (bony metastasis, multiple myeloma), Paget disease, glucocorticoid excess
    - Decreased: Medications (thiazide diuretics, estrogens, oral contraceptives),

hypothyroidism, renal failure, steatorrhea, rickets, osteomalacia, vitamin D deficiency

- **Catecholamines, fractionated** (norepinephrine, epinephrine, and dopamine):
  - Used to evaluate pheochromocytoma and paraganglioma. Avoid drugs that can interfere with the test, leading to falsely high catecholamines: Tricyclic antidepressants, labet alol, levodopa, methyldopa, sotalol, benzodiazepines, amphetamines, decongestants, and most psychoactive agents. All these drugs should be discontinued 2 wk prior to testing:
    - Normal: Values are variable and depend on the assay method used. Norepinephrine 15–80 mg/24 h (89–473 nmol/24 h), epinephrine 0–20 mg/24 h (SI: 0–118 nmol/24 h), dopamine 65–400 mg/24 h (SI: 384–2,364 nmol/24 h)
    - Increased: Pheochromocytoma (levels are > twice the upper normal value), paraganglioma, epinephrine administration, presence of drugs (see above)
- **Cortisol, free:**
  - Used to evaluate adrenal cortical hyperfunction; screening test of choice for Cushing syndrome:
    - Normal: 10–55 μg/24 h (SI: 27–150 nmol)
    - Increased: Cushing syndrome (adrenal hyperfunction from a pituitary tumor secreting ACTH or ectopic secretion of ACTH by other tumors such as bronchial carcinoid or adrenal tumor secreting cortisol), stress during collection, pregnancy
- **Cystine:**
  - Used to detect cystinuria, homocystinuria:
  - Normal: <30–40 mg/d (0.13 mmol/d):
    - Increased: Homozygotic cystinuria: 400 mg/d (1.7 mmol/d); heterozygotes cystinuria and Fanconi syndrome: Up to 250 mg/d (1 mmol)
- **Electrophoresis, protein (24-hr urine protein, 24-hr urine globulins):**
  - Used to evaluate overall renal function; screen for myeloma, macroglobulinemia, lymphoma, amyloidosis; can differentiate types of proteinuria (see table below)

		Electrophoretic Zones				
Pattern Description (Type of Proteinuria)	Protein, Total (mg/d)	Albumin	α_1	α_2	β	γ
Normal	<150	±			±	±
Glomerular, mild	<1,500	++		+	+	
Glomerular, severe	>1,500	+++		++	++	
Glomerular, nonselective	>3,000	+++	++	++	++	++
Tubular	<1,500	Tr/+	Tr	++	++	Tr
Mixed, glomerular & tubular		+++	+	++	+	+
Albuminuria	>150	++				
Overflow, acute phase response		Tr/+	++	++	Tr	Tr
Overflow, monodonal spike					Sp/++	Sp/++

KEY: Tr = trace; Sp = spike; ± = may or may not be present; + = mildly elevated; ++ = moderately elevated; +++ = markedly elevated.

- **5-Hydroxyindoleacetic acid (5-HIAA):**
  - 5-HIAA is a serotonin metabolite and is useful in diagnosing carcinoid syndrome:
    - Normal: 2–8 mg (SI: 10.4–41.6 mmol)/24-hr urine collection
    - Increased: Carcinoid tumors (except rectal), certain foods (banana, pineapple, tomato, walnuts, avocado), phenothiazine derivatives
- **Heavy met als:**
  - Measures exposure to arsenic (total), arsenic (inorganic), cadmium, lead, and mercury,

usually following occupational or environmental exposure:
  - Normal: Arsenic (total): 0–50 μg/24 h (<50 μg/L); arsenic (inorganic): <20 μg/L; cadmium: <3.0 μg/24 h (<2 μg/g creatinine); lead: <80 μg/24 h (< 50 μg/L); mercury: <20 μg/L
  - Increased: Indicative of exposure
- **Metanephrines:**
  - These metabolic products of epinephrine and norepinephrine are a primary screening test for pheochromocytoma and paraganglioma (in conjunction with urinary catecholamines). Avoid drugs that can interfere with the test, leading to falsely high catecholamines: Tricyclics antidepressants, labet alol, levodopa, methyldopa (Aldomet), sotalol, benzodiazepines, amphetamines, decongestants, and most psychoactive agents. All these drugs should be discontinued 2 wk prior to testing:
    - Normal: <1.3 mg/24 h (7.1 mmol/L) for adults, but variable in children
    - Increased: Pheochromocytoma, paraganglioma, false positive with drugs (see above)
- **Protein** (see Section I Proteinuria):
  - Normal: <150 mg/24 h (<0.15 g/d)
  - Increased: Nephrotic syndrome is usually associated with >4 g/24 h.
- **17-Ketogenic steroids (17-KGS, corticosteroids):**
  - Overall adrenal function test, largely replaced by serum or urine cortisol levels:
    - Normal: Males: 5–24 mg/24 h (17–83 mmol/24 h); females: 4–15 mg/24 h (14–52 mmol/24 h)
    - Increased: Adrenal hyperplasia (Cushing syndrome), adrenogenital syndrome
    - Decreased: Panhypopituitarism, Addison disease, acute steroid withdrawal
- **17-Ketosteroids, total (17-KS):**
  - Measures dehydroepiandrosterone (DHEA), androstenedione (adrenal androgens); largely replaced by assay of individual elements in the blood (serum DHEA-S and serum androstenedione):
    - Normal: Adult males: 8–20 mg/24 h (28–69 mmol/L); adult females: 6–15 mg/dL (21–52 mmol/L). Note: Low values in prepubertal children
    - Increased: Adrenal cortex abnormalities (congenital adrenal hyperplasia, adrenal carcinoma, Cushing syndrome)
    - Decreased: Panhypopituitarism, Addison disease
- **Urea nitrogen, urine** (urine nitrogen, nitrogen balance, blood urea nitrogen (BUN):
  - Measures urine nitrogen concentration:
    - Normal: 12,000–20,000 mg/24 h
    - Increased: Nitrogen wasting with hyperalimentation, bladder tap with amniocentesis
    - Decreased: Poor nitrogen balance with hyperalimentation
- **Vanillylmandelic acid (VMA):**
  - VMA is the urinary product of both epinephrine and norepinephrine; the 24-hr urinary VMA excretion has poor diagnostic sensitivity and specificity compared to fractionated 24-hr urinary fractionated metanephrines. Can be affected by many foods. No longer recommended by most endocrinologists:
    - Normal: <7–9 mg/24 h (35–45 mmol/L)
    - Increased: Pheochromocytoma, paraganglioma, factitious (chocolate, coffee, tea,

methyldopa)

REFERENCES

Simerville JA. Urinalysis: A comprehensive review. *Am Fam Physician.* 2005;71(6):1153–1162.

Gomella LG. Urine studies. In: Gomella LG, Haist SA, eds. *Clinician's Pocket Reference*, 11th ed. New York, NY: McGraw-Hill, 2007.

SECTION V

Alternative and Complementary Urologic Therapies

Section Editors: Franklin Lowe, MD, MPH
Sven Wenske, MD

Introduction

National Center for Complementary and Alternative Medicine (NCCAM), a division of the National Institutes of Health (NIH), conducts and support research and provides information about complementary health. In a recent national survey, 38% of adults used some form of complementary and alternative medicine (1). “Complementary medicine” refers to use of Complementary and Alternative Medicine (CAM) together with conventional medicine, such as using acupuncture in addition to usual care to help lessen pain. Most use of CAM by Americans is complementary. “Alternative medicine” refers to use of CAM in place of conventional medicine. “Integrative medicine” combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness. It is also called integrated medicine.

CAM practices are often grouped into broad categories, such as natural products, mind and body medicine, and manipulative and body-based practices. Although these categories are not formally defined, they are useful for discussing CAM practices and some CAM practices may fit into more than 1 category. This chapter provides an overview of some of the CAM practices that are used or are related to the practice of urology.

Mind and Body Medicine

Mind and body practices focus on the interactions among the brain, mind, body, and behavior, with the intent to use the mind to affect physical functioning and promote health. Many CAM practices embody this concept in different ways. Meditation techniques, yoga, and acupuncture are some of these techniques.

Acupuncture, the application of solid needles inserted into defined spots in the skin, has been described thousands of years ago as part of ancient Chinese medicine. Although its main application has been to treat a variety of chronic conditions, such as back pain, obesity, addictions, and many others, more recently acupuncture has found its way into modern medicine and is nowadays part of daily clinical routine in many urologic practices. Especially urologic diseases that are difficult to treat, such as premature ejaculation, lower urinary tract symptoms (LUTS) and overactive bladder (OAB), chronic prostatitis/chronic pelvic pain syndrome (CPPS), or side effects (eg, hot flashes) of androgen-deprivation therapy (ADT) for advanced/metastatic prostate cancer, are the primary targets of acupuncture in urology (2).

Results from a clinical study in patients with LUTS or CPPS, 1 of the most difficult to treat urologic conditions, or patients with increased urinary frequency and urgency after radical prostatectomy, showed good results of acupuncture in decreasing symptoms and improving quality of life (3). Good success has also been reported in studies on patients that receive acupuncture for hot flashes, 1 of the most common side effects of ADT. A randomized placebo-controlled study showed recently the effects of acupuncture in the treatment of premature ejaculation in comparison to placebo and the standard treatment using paroxetine (4). Whereas paroxetine reduced the validated Premature Ejaculation Diagnostic Tool (PEDT) score from 17 to 10.5, acupuncture achieved a reduction from 16 to 11, which was significantly better than placebo. Usually, treatments are being applied twice per week for the 1st 6 wk. If patients respond to the treatment and if symptoms improve, the treatment frequency is reduced to once per week, and continues for a total of 12 wk. After that, a maintenance treatment schedule may be needed to prevent recurrent or increasing symptoms.

While the mechanisms of acupuncture are still not entirely understood, the main hypothesis

is that certain neurotransmitters (eg, serotonin, endorphins) are being released under needle stimulation, and that there exists an alternative connective tissue communication system unrelated to the peripheral and central nervous systems.

In addition to acupuncture, also pelvic floor muscle training (PFMT), relaxation, and yoga have all been shown to decrease muscle contractions and stress of the pelvic floor. One analysis from Stanford University studied the treatment of intra- and extrapelvic myofascial trigger point release therapy, and training in paradoxical relaxation including cognitive behavioral methods in patients with CPPS, with good results (5).

Overall, especially after exhausting standard treatments for common benign urologic disorders, acupuncture and other complementary and integrative therapies offer good alternative treatment approaches with limited potential for adverse events.

Manipulative and Body-Based Practices

Manipulative and body-based practices focus primarily on the structures and systems of the body, including the bones and joints, soft tissues, and circulatory and lymphatic systems. 2 commonly used therapies fall within this category: Spinal manipulation and massage therapy. Limited data is available but the literature suggests that 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) may benefit patients with urologic CPPS (6).

ACTIVE HEXOSE CORRELATED COMPOUND (AHCC)

AHCC is derived from the mycelia (branches) of shiitake (*Lentinula edodes*) of the basidiomycete mushroom family. It has been derived through hybridization of different shiitake subtypes. Characteristic for AHCC is its high content of **α**-glucans (a carbohydrate) and its low molecular weight, which renders it highly absorbable in the body. 1st described in an animal model in 1998, AHCC was shown to enhance immune response in an in vivo adenocarcinoma model in rats (12). Numerous subsequent human clinical studies have been performed on AHCC, showing that AHCC increases the activity of natural killer (NK) cells, T-cells, and dendritic cells that are all essential components of the human immune system. However, AHCC was also shown to act as an *immune regulator* through downregulation of an overactive immune system, thereby supporting the body's normal response to inflammatory processes during which the immune system may be upregulated. AHCC found urologic application in humans in a more recent study from 2009, where it was found to be beneficial in the treatment of castrate-resistant prostate cancer, reflected in a significant PSA response in a patient with metastatic castrate-resistant disease (13). As a complementary immunotherapy in patients with cancer, viral and nonviral hepatitis, HIV, and other immunocompromised patients, AHCC is being widely used, especially in Asia.

AFRICAN PLUM (*Pygeum africanum*)

The extract, tadenan, is derived from the bark of the African plum tree and is taken for the treatment of benign prostatic hypertrophy (BPH) and LUTS. Pygeum is usually found in most combination prostate health formulations. Its mode of action is thought to be via inhibition of fibroblast growth and anti-inflammatory effects. Some inconclusive data show a decrease in symptoms and an increase in flow rate. However, the T-IPSS study, a randomized double-

blind, placebo-controlled trial using tadenan was completed but never released or published (11). Only some minor gastrointestinal side effects have been noted with this product.

BAZOTON (*Radix urticae*)

This plant extract has been used in the treatment of benign prostatic hypertrophy (BPH). The active ingredients are thought to include its steroid–glycoside composition. It is an inhibitor of sex-steroid-binding globulin. There is a paucity of clinical data that show it decreases symptom scores, and it has little effect on flow rates. Side effects are minor and usually related to its smell and taste.

BROCCOLI SEED EXTRACT (*Sulforaphane*)

Multiple epidemiologic mouse models and cell-based studies indicate that the broccoli-derived isothiocyanate *Sulforaphane [(-)-1-isothiocyanato-(4R)-methylsulfinylbutane]* may affect the development of various types of cancers and especially prostate tumors. A recent analysis by Traka et al. (15) in PTEN-deficient mice showed that *sulforaphane* had positive effects to counteract changes downstream of PTEN loss. The PTEN is a tumor suppressor gene, and its deletion in an epithelial stem cell can be an early initiating event leading to prostatic intraepithelial neoplasia (PIN), and subsequently to cancer. The authors also found a significant overlap in changes in gene expression induced by *sulforaphane* in mouse prostate tissue with PTEN loss, with that induced in prostate tissue of men consuming a broccoli-rich diet.

CAPSAICIN (*capsicum*)

Capsaicin is the main pungent ingredient of hot peppers. It has been used as an intravesical therapy for overactive bladder (OAB). The mode of action is by selective activation of sensory nerve fibers and by a neurotoxic effect on afferent C fibers. Multiple studies have documented its efficacy in terms of symptom improvement and urodynamic changes (16). Adverse effects include suprapubic pain, hematuria, and incontinence, which are all self-limiting.

COMMON NATURAL PRODUCTS USED IN UROLOGY

This area of CAM includes use of a variety of herbal medicines (also known as botanicals), vitamins, minerals, and other “natural products.” Many are sold over the counter as dietary supplements. Some uses of dietary supplements – eg, taking a multivitamin to meet minimum daily nutritional requirements or taking calcium to promote bone health – are not thought of as CAM. The World Health Organization has estimated that 80% of the world's population uses some type of herbal medicine. Women are more likely than men to use complementary and alternative medicine (7).

These common agents are not US Food and Drug Administration (FDA) approved, but are available through health food stores and other commercial outlets. Phytotherapies and other supplements are under study, but few have undergone trials in the United States. Most have not demonstrated any significant efficacy, and many of these products are sold as part of combination therapies, and sold under various trade names. There have been growing

concerns about the potential toxicities of these products and their interactions with standard pharmaceuticals. According to the FDA, manufacturers of dietary supplements can make claims about how their products affect the structure or function of the body, but they may not claim to prevent, treat, cure, mitigate, or diagnose a disease without prior FDA approval. The FDA does monitor many of these compounds for undisclosed ingredients that can impact their efficacy. Limited data is available on the substances in urology. However, there is an increasing amount of peer-reviewed literature that provides some support for a few of these alternative therapies while others have not been able to clearly demonstrate efficacy (8). A challenge for any natural compound is standardization of the product (9). The large NIH-sponsored CAMUS trial studied increasing doses of saw palmetto on lower urinary tract function. Unfortunately when subject to rigorous study parameters, increasing doses of a saw palmetto fruit extract did not reduce LUTS more than placebo (10).

CRANBERRY JUICE AND SUPPLEMENTS (*Vaccinium macrocarpon*)

Cranberry is widely used to prevent UTIs; it was originally believed that this fruit acidified the urine (17). However, cranberry appears to work by inhibiting the adhesion of type I and P-fimbriated uropathogens (eg, uropathogenic *Escherichia coli*) to the uroepithelium, thus impairing colonization and subsequent infection. It contains a unique blend of organic acids – quinic, malic, and citric – as well as nondialyzable polymeric compounds that provide this antibacterial adherence effect.

Studies using cranberry juice, cranberry–lingonberry juice, and cranberry tablets compared with placebo for preventing UTIs, bacteriuria, or pyuria concluded that cranberry juice and cranberry products significantly reduced UTIs among women with recurrent infections (18,19). Recommended doses range from 90 to 480 mL of cranberry cocktail twice daily or 15–30 mL of unsweetened 100% cranberry juice daily. The frozen concentrate has almost 30 times the strength of the juice, and 30–45 mL BID has been used. Capsule doses range between 1 and 6 capsules of 300–400 mg concentrated extract BID. High pediatric doses of $>$300 mL daily have been associated with adverse effects such as hypersensitivity or gastrointestinal distress such as diarrhea.

The findings of several reviews support the potential use of cranberry products in the prophylaxis of recurrent UTIs in young and middle-aged women, but it should not be used as a substitute for antibiotics, as it is an ineffective treatment for established infections. Patients with a history of nephrolithiasis should avoid the use of cranberry products (possible increases in urinary calcium and oxalate concentration). Due to the heterogeneity of clinical study designs and the lack of consensus regarding the dosage regimen and formulation to use, cranberry products cannot be broadly recommended for the prophylaxis of recurrent UTIs at this time. Note that it may potentiate anticoagulant effects of warfarin.

FLAXSEED (*Linum usitatissimum*)

Flaxseed is a member of the genus *Linum* in the family *Linaceae,* and contains high levels of dietary fiber as well as lignans, an abundance of micronutrients and ω-3 fatty acids. The lignans in flaxseed may provide some health benefits against cancers that are sensitive to hormones, such as breast and prostate. Some reports have published the effect of flaxseed on

lowering PSA and androgens. A randomized trial analyzing prostatectomy specimens in men randomized to flaxseed supplementation 3 wk before surgery showed significant differences in tumor proliferation rate, index, and apoptotic rate between men that had been randomized to take flaxseed supplements vs. those that stayed on normal diet (20,21). An effect on biochemical outcome and prostate cancer mortality has not been shown.

GINKGO BILOBA

Primarily used for memory deficits, dementia, and neurologic dysfunction, ginkgo biloba is also promoted as a treatment for impotence and selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction, with a recommended dose range of 60–80 mg standardized dry extract orally BID or TID (22). Studies have shown small cognition benefits with dementia, but no other demonstrated benefit in healthy adults (23). Use cautiously with aspirin (ASA), salicylates, and warfarin.

GOSHA-JINKI-GAN (GJG)

Gosha-jinki-gan (GJG) is a traditional Chinese blended herbal medicine composed of 10 different herbs. In canine studies, bladder contraction mediated by pelvic nerve stimulation and induced by acetylcholine administration was significantly inhibited by administration of 100 mg/kg GJG; effects were similar to that seen with 0.1 mg atropine. Human studies have reported mild improvements in International Prostate Symptom Scores (IPSS) and OAB symptoms in some patients (7). Mild adverse events include nausea, diarrhea, and urinary frequency.

GREEN TEA

In addition to several potent antioxidants, such as epigallocatechin-3-gallate (EGCG), in green tea, mainly its polyphenolic compounds have been suggested to decrease prostate cancer development and decelerate prostate cancer progression in several in vitro and in vivo animal studies (24,25). High green tea consumption in Japan may at least partially explain the low prostate cancer prevalence in Japanese men, as green tea plays a major role in the Asian diet. Despite the fact that results in human studies have mostly been controversial, some well-designed studies have also demonstrated a significant reduction in incidence of prostate cancer incidence in men with high-grade PIN who drink green tea. However, the protective role of tea in prostate cancer is still controversial (26).

HEATHER (*Calluna vulgaris*)

The medicinal portion of common heather consists of the entire herb (leaves, flower, roots) ground and boiled to create a product that is taken for its diuretic properties in the treatment of kidney ailments and BPH/LUTS. Active compounds are thought to include flavonoids and sitosterols. The claimed efficacy has never been documented. No clinical trials are available.

HORNY GOAT WEED (*Epimedium*)

Epimedium is a Chinese herbal remedy promoted as a safe and natural alternative to

sildenafil citrate (27,28). However, extracts of epimedium are strongly estrogenic due to the presence of novel potent phytoestrogens of the prenyl-flavone family. It has been reported to cause tachyarrhythmias.

LYCOPENE

Lycopene is a major carotenoid component of tomato, red pepper, and other red fruits and vegetables. The pigment acts basically as an antioxidant, protecting cells against damage from free radicals. In several studies it was found to have potential anticancer activity in many types of cancer, as numerous studies reported on inverse associations between lycopene intake and prostate cancer prevalence and grade (29). Overall, the protective effect of lycopene is unclear, as controversial results have been published. When taken, lycopene is better absorbed by the body when it is consumed in cooked, instead of raw or fresh products (30).

MODIFIED CITRUS PECTIN (MCP)

Pectin, a carbohydrate consisting of thousands of polysaccharide molecules, is found abundantly in the peels of apples, citrus fruits, and plums, but is also found in most other plants. Regular pectin is not absorbable by the human body, but in modified citrus pectin (MCP) the pectin has been altered through breaking of its long polysaccharide chains. It has been shown to inhibit cancer growth and breast and prostate cancer metastases in animal models, and was found to suppress cancerous proliferation and induce apoptosis of prostate cancer cells in vitro (31). MCP showed also antimetastatic properties, and potential for increasing apoptotic responses of tumor cells to chemotherapy by inhibiting antiapoptotic functions of galectin-3, and has therefore been established in the literature for its potential use in the treatment of multiple human malignancies (prostate, colon, breast, liver, and melanoma).

ω-3 FATTY ACIDS (FISH OIL)

These naturally occurring compounds, ω-3 fatty acids, polyunsaturated essential fatty acids, cannot be produced by the human body, but are required for normal performance of numerous organs and cell functions. However, there is a wide range of conflicting results in the literature on health benefits, especially in the cancer prevention and treatment.

One of the most extensive reviews of the literature on this topic from MacLean et al. (32) from 2006 in the Journal of the American Medical Association concluded that there is no association between ω-3 fatty acids and the prevention or the prevalence of cancer. A more recent analysis concluded similarly, also taking into account difficulties in assessing patient's exact dietary habits, but ω-3 fatty acids were consequently deemed neither a risk factor nor a beneficial factor with regard to cancers (33). However, as ω-3 fatty acids improve appetite and help gain weight, they may be of benefit in patients with advanced cancer and cachexia, as this may contribute to improved quality of life.

PC-SPES

This product is no longer commercially available because of issues associated with quality control. It was found to be tainted with diethylstilbestrol, warfarin, and alprazolam. It was used for treatment of prostate cancer, particularly in hormone-refractory patients. It consisted of 8 Chinese herbs (*Chrysanthemum, Isatis,* licorice*, Ganoderma lucidum, Panax pseudoginseng, Rabdosia rubescens, Scutellaria* [skullcap]*,* and saw palmetto berry) (34). It had potent antiestrogenic effects. Its use was associated with deep venous thrombosis, breast tenderness, loss of libido, and decreased PSA and testosterone levels. Other companies have made similar combinations but have not achieved a widespread usage (35).

PANAX GINSENG (*Korean red ginseng*)

This product has been used for numerous indications in traditional Chinese medicine. It is frequently used for decreased libido and erectile dysfunction. It reportedly has androgenic effects and stimulation, although improvements in penile endothelial L-arginine–nitric oxide activity have been suggested (36,37). Clinical trials are not conclusive of its effectiveness.

PERMIXON (*Serenoa repens*)

This is the branded saw palmetto extract produced in France. It is the lipidosterolic extract of the dried fruit (berry) of the dwarf palm. It is the most widely studied of all phytotherapies for the treatment of BPH/LUTS. From in vitro studies, it has been postulated to have many mechanisms of action including antiprostaglandin, antiandrogenic, and antiestrogenic effects (38). It has almost no effect upon prostate size and no effect upon PSA levels (39). There are no known significant health risks or adverse effects.

POMEGRANATE (*Punica granatum*)

Pomegranate juice is known for its high vitamin C content, as well as vitamin B5 (pantothenic acid), potassium, and natural phenols, such as ellagitannins and flavonoids with extremely effective free radical-scavenging properties.

Increasing evidence shows that pomegranate juice has potential to inhibit growth and reduce the invasion of prostate cancer cells both in vitro and in vivo. A phase II clinical trial, in which patients with rising PSA after primary treatment with curative intent of prostate cancer were given 8 oz of pomegranate juice per day, showed that the mean PSA doubling time increased significantly in men under treatment with pomegranate juice from 15 to 54 mo ($p < 0.001$) (40). Several subsequent studies have shown that pomegranate juice affects many of the cellular processes involved in cell death and also affects signaling pathways that could inhibit cell migration and invasion (41).

PUMPKIN SEED (*Cucurbita pepo*)

Fresh and dried seeds are taken whole or ground for the treatment of BPH or OAB. Active compounds are thought to be phytosterols (42,43). There are no recent clinical trials and therefore no evidence establishing its efficacy. There are no known side effects.

RESVERATROL

Resveratrol is a potent antioxidant found in wine, especially in high concentration in Pinot noir, but also in grapes and berries. Research has demonstrated that it inhibits cancer growth through reduction of cell proliferation and metastasis, and induction of cell apoptosis. On a molecular level, it has been shown that mechanisms involved are inhibition of Akt and suppression of IGF-1 receptor expression (44). These antitumor effects of resveratrol were observed in in vitro and in vivo xenograft studies with the common prostate cancer cell lines PC3, DU145, and LNCaP.

RYE POLLEN (*Secale cereale*)

A pollen extract obtained by microbial digestion and extraction by water and organic solvents. Cernilton is the branded product. Active ingredients are thought to be β-sitosterols (45). It is used for the treatment of BPH and prostatitis and CPPS (46). In vitro inhibition of epithelial and stromal cell growth has been demonstrated (45). No long-term conclusive clinical studies exist. Side effects are reportedly minimal.

SAW PALMETTO BERRY (*Serenoa repens, Sabal serrulata*)

There are many different extraction processes and therefore many different brands of saw palmetto. The composition of these brands is variable. A recent NIH-sponsored double-blind, placebo-controlled study using the Indena brand showed no statistical difference between placebo and saw palmetto berry for treatment of BPH/LUTS. Permixon brand is the most widely studied product (see “Permixon” above). Minimal side effects are associated with saw palmetto. Saw palmetto berry extract (SPBE) compounds are also sold for “prostate health.” SPBE includes ingredients such as β-sitosterol and stigmasterol with no reliable clinical data to support their use. A recent large meta-analysis documented no significant clinical benefit of *Serenoa repens* on LUTS or prostate volume (10). Saw palmetto extract does not affect serum prostate-specific antigen more than placebo, even at relatively high dose (47). In addition it appears safe with the saw palmetto extract used in the CAMUS trial showed no evidence of toxicity at doses up to 3 times the usual clinical dose during an 18-mo period.

SELENIUM

A trace mineral that may prevent the development of prostate cancer. Epidemiologic studies suggest a chemopreventive effect (48). 1 study of patients with high-grade PIN suggested that selenium reduced the incidence of prostate cancer on subsequent biopsy. The National Cancer Institute–sponsored SELECT trial was a 10-yr prospective trial that began in 2001 of over 35,000 men studying the prostate cancer chemopreventive effects of selenium and vitamin E alone and in combination (49). The data monitoring safety board (DMSB) halted the trial in the fall of 2008. Their concerns were that the supplements did not appear to offer any benefit. In particular, there was a statistically nonsignificant trend to increasing prostate cancer with vitamin E alone and increased diabetes risk in men on selenium alone.

SOUTH AFRICAN STAR GRASS (*Hypoxis rooperi*)

This extract is taken for BPH/LUTS. The active compound is thought to be β-sitosterols,

which are thought to induce apoptosis by transforming growth factor (TGF)-β_1; this is unproven clinically (50). Initial studies showed dramatic improvements in symptom scores and flow rates; however, confirmatory studies are still needed (51). Adverse effects are believed to be minimal.

STINGING NETTLE (*Urtica dioica, Urticae radix*)

Bazoton is a branded form of this extract; (see Bazoton section above). The clinical evidence of the effectiveness of nettle root is based primarily on open studies, and the significance of this must be confirmed (14, 52). Minimal toxicity is associated with stinging nettle use.

VITAMIN D3 (*Cholecalciferol*)

As a fat-soluble vitamin, vitamin D3 plays a key role in overall health, as it mainly maintains calcium and phosphate homeostasis. However, it has also been shown to exhibit antineoplastic effects on various types of cancer, such as colon, breast, and prostate cancers (53).

The Institute of Medicine (IOM) has reviewed and updated the dietary reference intakes (DRIs) for vitamin D. It found that there is strong evidence to support the use of vitamin D with calcium for bone health but that it was lacking for other health conditions. Dosages for patient with various health issues differ. The recommended daily allowance (RDA), as set in 2011, is based on age, as follows: For those 1–70 yr of age, 600 IU daily; for those 71 yr and older, 800 IU daily; and for pregnant and lactating women, 600 IU daily. The IOM further recommended that serum 25(OH)D levels of 20 ng/mL (50 nmol/L) is adequate, and levels $>$50 ng/mL (125 nmol/L) could have potential adverse effects. However, dosages for urologic patients may differ based on underlying health disorders and concomitant medications (underlying osteopenia, ADT, therapy with RANK-ligand inhibitors [Denosumab] or bisphos-phonates in patients with metastatic prostate cancer, etc.).

VITAMIN E (γ-*TOCOPHEROL*)

Vitamin E, another fat-soluble essential vitamin, was initially thought to prevent prostate cancer risk. However, the National Cancer Institute–sponsored SELECT trial, studying prostate cancer chemopreventive effects of selenium and vitamin E, reported in 2009 controversial results with no benefits of vitamin E supplementation (see “Selenium”) (54). Moreover, the follow-up publication in 2011 even reported a significantly increased prostate cancer risk in healthy men with dietary supplementation with vitamin E (55). In addition, vitamin E supplementation above dosages of $>$400 IU per day were found to significantly increase risks of cardiovascular events.

YOHIMBINE (PAUSINYSTALIA YOHIMBE) YOCON, YOHIMEX

An extract of the bark of the yohimbe tree has been used for erectile dysfunction and decreased libido. The mechanism of action is as an α-adrenergic antagonist. Conflicting studies show both positive and no effect when compared to placebo (56). It appears to have greatest utility for men with psychogenic impotence. Despite the advent of phosphodiesterase

5 (PDE5) inhibitors, there is still widespread utilization of this over-the-counter product. Side effects include anxiety, tremors, dizziness, hypertension, and tachycardia. Do not use with antidepressants (eg, MAOIs or similar agents).

ZYFLAMEND

Zyflamend, a formulation containing 10 different herbs, is a dietary supplement marketed for the support of cardiovascular and joint function and healthy inflammation response. It is thought to have anti-inflammatory, antiangiogenic, and antiproliferative properties. Several in vitro studies have shown that Zyflamend decreases COX-1 and COX-2 enzymatic activity, induces apoptosis, and reduces androgen receptor expression in LNCaP cells (57). Moreover, it was found to inhibit arachidonic acid pathways, in human prostate cancer PC3 cells. Moreover, it also inhibits the proliferation of oral squamous carcinoma, pancreatic cancer, and melanoma cells in vitro. In an animal model, it inhibited the growth of both hormone-naïve and castrate-resistant prostate cancer, and reduced the expression of PSA. However, the latter could not be shown in a phase I clinical trial in men with PIN at Columbia University Medical Center, where Zyflamend was well tolerated, but did not lead to any significant changes in serum PSA levels (58).

REFERENCES

1. National Center for Complementary and Alternative Medicine [NCCAM]. http://nccam.nih.gov/. Accessed April 3, 2014.
2. Blanchet KD. Acupuncture: Gaining acceptance in urology: Proves effective for a number of chronic conditions. *BJU Int.* 2012;109(2):ii–iv. doi:10.1111/j.1464–410X.2011.10828.x.
3. Cohen JM, Fagin AP, Hariton E, et al. Therapeutic intervention for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): A systematic review and meta-analysis. *PLoS One.* 2012;7(8):e41941. doi:10.1371/journal.pone.0041941.
4. Sunay D, Sunay M, Aydoğmusç Y, et al. Acupuncture versus paroxetine for the treatment of premature ejaculation: A randomized, placebo-controlled clinical trial. *Eur Urol.* 2011;59(5):765–771.
5. Anderson RU, Wise D, Sawyer T, et al. 6-day intensive treatment protocol for refractory chronic prostatitis/chronic pelvic pain syndrome using myofascial release and paradoxical relaxation training. *J Urol.* 2011;185(4):1294–1299.
6. Fitzgerald MP, Anderson RU, Potts J, et al. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urologic chronic pelvic pain syndromes. *J Urol.* 2013;189(1 suppl):S75–S85.
7. Chughtai B, Kavaler E, Lee R, et al. Use of herbal supplements for overactive bladder. *Rev Urol.* 2013;15(3):93–96.
8. Lowe FC, Patel T. Complementary and alternative medicine in urology: What we need to know in 2008. *BJU Int.* 2008;102:422–424.
9. Lee J, Andriole G, Avins A, et al. Redesigning a large-scale clinical trial in response to negative external trial results: The CAMUS study of phytotherapy for benign prostatic hyperplasia. *Clin Trials.* 2009;6(6):628–636.
10. Avins AL, Lee JY, Meyers CM, et al. Safety and toxicity of saw palmetto in the CAMUS trial. *J Urol.* 2013;189(4):1415–1420.

11. Ishani A, MacDonald R, Nelson D, et al. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: A systematic review and quantitative meta-analysis. *Am J Med*. 2000;109:654–664.
12. Matsushita K, Kuramitsu Y, Ohiro Y, et al. Combination therapy of active hexose correlated compound plus UFT significantly reduces the metastasis of rat mammary adenocarcinoma. *Anticancer Drugs*. 1998;9(4):343–350.
13. Turner J, Chaudhary U. Dramatic prostate-specific antigen response with activated hemicellulose compound in metastatic castration-resistant prostate cancer. *Anticancer Drugs*. 2009;20(3):215–216.
14. Schneider T, Rubben H. Stinging nettle root extract (Bazoton-uno) in long-term treatment of benign prostatic syndrome (BPS). Results of a randomized, double-blind, placebo-controlled multicenter study after 12 months. *Urologe A*. 2004;43:302–306.
15. Traka MH, Spinks CA, Doleman JF, et al. The dietary isothiocyanate sulforaphane modulates gene expression and alternative gene splicing in a PTEN null preclinical murine model of prostate cancer. *Mol Cancer*. 2010;9:189.
16. Chancellor MB. Intravesical capsaicin and resinife-ratoxin therapy: Spicing up the ways to treat the overactive bladder. *J Urol*. 1999;162:3–11.
17. Guay DR. Cranberry and urinary tract infections. *Drugs*. 2009;69(7):775–807.
18. Santillo VM, Lowe FC. Cranberry juice for the prevention and treatment of urinary tract infections. *Drugs Today (Barc)*. 2007;43:47–54.
19. Wojnicz D, Sycz Z, Walkowski S, et al. Study on the influence of cranberry extract Żuravit S·O·S(®) on the properties of uropathogenic Escherichia coli strains, their ability to form biofilm and its antioxidant properties. *Phytomedicine*. 2012;19(6):506–514.
20. Dalais FS, Meliala A, Wattanapenpaiboon N, et al. Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. *Urology*. 2004;64(3):510–515.
21. Saarinen NM, Tuominen J, Pylkkänen L, et al. Assessment of information to substantiate a health claim on the prevention of prostate cancer by lignans. *Nutrients*. 2010;2(2):99–115.
22. Cohen AJ. Ginkgo biloba for antidepressant-induced sexual dysfunction. *J Sex Marital Ther*. 1998;24(2):139–143.
23. Yeh KY, Wu CH, Tai MY, et al. Ginkgo biloba extract enhances noncontact erection in rats: The role of dopamine in the paraventricular nucleus and the mesolimbic system. *Neuroscience*. 2011;189:199–206.
24. Yang CS, Li G, Yang Z, et al. Cancer prevention by tocopherols and tea polyphenols. *Cancer Lett*. 2013;S0304–S3835(13)00097–9. doi:10.1016/j.canlet.2013.01.051.
25. Bettuzzi S, Rizzi F, Belloni L. Clinical relevance of the inhibitory effect of green tea catechins (GtCs) on prostate cancer progression in combination with molecular profiling of catechin-resistant tumors: An integrated view. *Pol J Vet Sci*. 2007;10(1):57–60.
26. Lin YW, Hu ZH, Wang X, et al. Tea consumption and prostate cancer: An updated meta-analysis. *World J Surg Oncol*. 2014;12:38. doi:10.1186/1477–7819–12–38.
27. Yong EL, Wong SP, Shen P, et al. Standardization and evaluation of botanical mixtures: Lessons from a traditional Chinese herb, Epimedium, with estrogenic properties. *Novartis Found Symp*. 2007;282:173–188; Discussion 188–191, 212–218.
28. Ho CC, Tan HM. Rise of herbal and traditional medicine in erectile dysfunction

management. *Curr Urol Rep*. 2011;12(6):470–478.
29. Teodoro AJ, Oliveira FL, Martins NB, et al. Effect of lycopene on cell viability and cell cycle progression in human cancer cell lines. *Cancer Cell Int*. 2012;12(1):36.
30. Wei MY, Giovannucci EL. Lycopene, tomato products, and prostate cancer incidence: a review and reassessment in the PSA screening era. *J Oncol*. 2012;2012:271063.
31. Jiang J, Eliaz I, Sliva D. Synergistic and additive effects of modified citrus pectin with two polybotanical compounds, in the suppression of invasive behavior of human breast and prostate cancer cells. *Integr Cancer Ther*. 2013;12(2):145–152.
32. MacLean CH, Newberry SJ, Mojica WA, et al. Effects of omega-3 fatty acids on cancer risk: A systematic review. *JAMA*. 2006;295(4):403–415.
33. Gerber M. Omega-3 fatty acids and cancers: A systematic update review of epidemiological studies. *Br J Nutr*. 2012;107(suppl 2):S228–S239.
34. Marks LS, DiPaola RS, Nelson P, et al. PC-SPES: Herbal formulation for prostate cancer. *Urology*. 2002;60(3):369–375; Discussion 376–367.
35. Shabbir M, Love J, Montgomery B. Phase I trial of PC-Spes2 in advanced hormone refractory prostate cancer. *Oncol Rep*. 2008;19(3):831–835.
36. Tamler R, Mechanick JI. Dietary supplements and nutraceuticals in the management of andrologic disorders. *Endocrinol Metab Clin North Am*. 2007;36:533–552.
37. Kim SD, Kim YJ, Huh JS, et al. Improvement of erectile function by Korean red ginseng (Panax ginseng) in a male rat model of metabolic syndrome. *Asian J Androl*. 2013;15(3):395–399.
38. Boyle P, Robertson C, Lowe F, et al. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU Int*. 2004;93:751–756.
39. Tacklind J, MacDonald R, Rutks I, et al. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2012;12:CD001423. doi:10.1002/14651858.CD001423.pub3.
40. Pantuck AJ, Leppert JT, Zomorodian N, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res*. 2006;12(13):4018–4026.
41. Rettig MB, Heber D, An J, et al. Pomegranate extract inhibits androgen-independent prostate cancer growth through a nuclear factor-kappaB-dependent mechanism. *Mol Cancer Ther*. 2008;7:2662–2671.
42. Carbin BE, Larsson B, Lindahl O. Treatment of benign prostatic hyperplasia with phytosterols. *Br J Urol*. 1990;66:639–641.
43. Ejike CE, Ezeanyika LU. Inhibition of the experimental induction of benign prostatic hyperplasia: A possible role for fluted pumpkin (Telfairia occidentalis Hook f.) seeds. *Urol Int*. 2011;87(2):218–224.
44. Sheth S, Jajoo S, Kaur T, et al. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. *PLoS One*. 2012;7(12):e51655. doi:10.1371/journal.pone.0051655.
45. Habib FK, Ross M, Lewenstein A, et al. The identification of a prostate inhibitory substance in a pollen extract. *Prostate*. 1995;26:133–139.
46. McNicholas T, Kirby R. Benign prostatic hyperplasia and male lower urinary tract symptoms (LUTS). *Clin Evid (Online)*. 2011;2011. pii: 1801.

47. Andriole GL, McCullum-Hill C, Sandhu GS, et al. The effect of increasing doses of saw palmetto fruit extract on serum prostate specific antigen: Analysis of the CAMUS randomized trial. *J Urol*. 2013;189(2):486–492.
48. Joniau S, Goeman L, Roskams T, et al. Effect of nutritional challenge in patients with isolated high-grade prostatic intra-epithelial neoplasia. *Urology*. 2007;69:1102–1106.
49. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39–51.
50. Klippel KF, Hiltl DM, Schipp B. Multi-center, placebo-controlled, double-blind clinical trial of β-sitosterol (phytosterol) for the treatment of benign prostatic hyperplasia. *Br J Urol*. 1997;80:427–432.
51. Wilt TJ, MacDonald R, Ishani A. Beta-sitosterol for the treatment of benign prostatic hyperplasia: A systematic review. *BJU Int*. 1999;83:976–983.
52. Chrubasik JE, Roufogalis BD, Wagner H, et al. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: Urticae radix. *Phytomedicine*. 2007;14:568–579.
53. Leyssens C, Verlinden L, Verstuyf A. Antineoplastic effects of 1,25(OH)2D3 and its analogs in breast, prostate and colorectal cancer. *Endocr Relat Cancer*. 2013;20(2):R31–R47.
54. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011 ;306(14):1549–1556.
55. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142(1):37–46.
56. Reid K, Surridge DH, Morales A, et al. Double-blind trial of yohimbine in the treatment of psychogenic impotence. *Lancet*. 1987;2:421–423.
57. Bemis DL, Capodice JL, Anastasiadis AG, et al. Zyflamend, a unique herbal preparation with nonselective COX inhibitory activity, induces apoptosis of prostate cancer cells that lack COX-2 expression. *Nutr Cancer*. 2005;52(2):202–212.
58. Capodice JL, Gorroochurn P, Cammack AS, et al. Zyflamend in men with high-grade prostatic intraepithelial neoplasia: Results of a phase I clinical trial. *J Soc Integr Oncol*. 2009;7(2):43–51.

SECTION VI

Urologic Drug Reference

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This section is designed to be a quick reference of medications commonly used in urology or of those that have significant impact on the GU system. Although some general information about the drug may be presented, this is not intended to be a complete authoritative listing for each medication; the focus here is on the practice of urology. You should be familiar with all the indications, contraindications, adverse effects, and drug interactions of any medication that you prescribe. Such detailed information is beyond the scope of this book but can be found in the manufacturer's package insert, product website, in the *Physicians' Desk Reference* (PDR), or from the American Hospital Formulary Service.

Medications are listed by generic name, with some of the more common trade names noted. Common uses and urology-specific uses are listed in addition to the official labeled indications (FDA approved), because many available medications are used to treat various conditions based only on the medical literature, and these uses are not listed in the package insert. Asterisks are placed before and after the official US FDA approved indications. This additional use information is based on the editorial review of the literature and is representative of urology practice patterns primarily in the US. Where no pediatric dosage is provided, the implication is that the use of the agent is not well established in this age group. Controlled substances are indicated by the symbol [C]. Increasingly, drug interaction and medication side effects can be related to a drug's metabolism and the cytochrome P450 enzymes are essential for the metabolism of many medications. There are more than 50 CYP450 enzymes, but the CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes metabolize 90% of drugs and are predominantly expressed in the liver. The table at the end of the chapter (page 975) summarizes some of the common medications and their CYP450 interactions that are noted for many of the medications listed here.

MEDICATION KEY

Medications are in alphabetical order by generic name. Some of the more commonly recognized trade names in the US are listed for each (in parentheses after the generic name). If a drug is available without prescription, it is noted as OTC (over-the-counter).

GENERIC DRUG NAME (SELECTED COMMON BRAND NAMES) [CONTROLLED SUBSTANCE DESIGNATION] [OTC]

WARNING: Summarized versions of the Black Box precautions deemed necessary by the FDA. These are significant precautions and contraindications concerning the individual medication.**Uses:** This includes both FDA-labeled indications bracketed by ** and other "off-label" uses of the medication. Because many medications are used to treat various conditions based on the medical literature, and these uses are not listed in their package insert, we list common uses of the medication in addition to official labeled indications (FDA approved) based on input from our editorial board. **Action:** How the drug works. This information is helpful in comparing classes of drugs and understanding side effects and contraindications. *Spectrum:* Specifies activity against selected microbes for antimicrobials. **Dose:** ***Adults & Peds:*** Where no specific pediatric dose is given, the implication is that this drug is not commonly used or indicated for that age group. At the end of the dosing line, important dosing

modifications may be noted (ie, take with food, avoid antacids, etc.). **W/P (Warning/Precautions):** (Pregnancy/fet al risk categories, breast-feeding [as noted below]) Cautions concerning the use of the drug in specific settings. **CI:** Contraindications. **Disp (Dispense):** Common dosing forms. **SE (Side Effects):** Common or significant side effects. **Notes:** Other key useful information about the drug including additions made by our editorial board.

CONTROLLED SUBSTANCE CLASSIFICATION

Medications under the control of the US Drug Enforcement Agency (DEA) (Schedules I–V controlled substances) are indicated by the symbol (C). Most medications are uncontrolled and do not require a DEA prescriber number or a special prescription pad. The following is a general description for the schedules of DEA-controlled substances.

Schedule (C-I) I: All nonresearch use forbidden (eg, heroin, etc.).

Schedule (C-II) II: High addictive potential; medical use accepted. No telephone call-in prescriptions; no refills.

Schedule (C-III) III: Low to moderate risk of physical dependence, high risk of psychologic dependence; prescription usually must be rewritten after 6 mo or 5 refills (eg, acetaminophen plus codeine).

Schedule (C-IV) IV: Limited potential for dependence; prescription rules same as for schedule III (eg, benzodiazepines, propoxyphene).

Schedule (C-V) V: Very limited abuse potential; prescribing regulations often same as for uncontrolled medications; some states have additional restrictions.

FDA FETAL RISK CATEGORIES

Category A: Adequate studies in pregnant women have not demonstrated a risk to the fetus in the 1st trimester of pregnancy; there is no evidence of risk in the last 2 trimesters.

Category B: Animal studies have not demonstrated a risk to the fetus, but no adequate studies have been done in pregnant women.

OR

Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus during the 1st trimester of pregnancy, and there is no evidence of risk in the last 2 trimesters.

Category C: Animal studies have shown an adverse effect on the fetus, but no adequate studies have been done in humans. The benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

OR

No animal reproduction studies and no adequate studies in humans have been done.

Category D: There is evidence of human fet al risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

Category X: Studies in animals or humans or adverse reaction reports, or both, have demonstrated fet al abnormalities. The risk of use in pregnant women clearly outweighs any possible benefit.

Category ?: No data available (not a formal classification; included to provide complete dataset).

BREAST-FEEDING CLASSIFICATION

No formally recognized classification exists for drugs and breast-feeding. This shorthand is based on information from the *Clinician's Pocket Drug Reference, 2015.*

+ Compatible with breast-feeding
M Monitor patient or use with caution
± Excreted, or likely excreted, with unknown effects or at unknown concentrations
?/– Unknown excretion, but effects likely to be of concern
– Contraindicated in breast-feeding
? No data available

This chapter is based on data in and modified from Gomella LG, Haist S, Adams A, eds. *Clinicians' Pocket Drug Reference, 2015 Edition*. New York: McGraw Hill, 2015, DailyMed (http://www.dailymed.nlm.nih.gov), Drugs@FDA (http://www.accessdata.fda.gov) and manufacturers web sites. Reproduced with permission of the copyright holder where appropriate.

ABIRATERONE (ZYTIGA)

USES: *Castrate-resistant metastatic PCa*
ACTIONS: CYP17 inhibitor;↓ testosterone precursors.
DOSE: 1,000 mg PO qd w/ 5 mg prednisone BID; w/o food 2 hr ac and 1 hr pc; ↓ w/ hepatic impair.
W/P: [X, N/A] w/ severe CHF, monitor for adrenocortical insuff/excess, w/ CYP2D6 substrate/CYP3A4 inhib or inducers; do not use with severe liver insufficiency.
CI: Pregnancy.
DISP: Tabs 250 mg.
SE: Fatigue, joint swelling/discomfort, edema, hot flush, diarrhea, vomiting, cough, ↑ BP, dyspnea, UTI, contusion; common lab abnormalities: Anemia, ↑ alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, ↓ K^+, ↑ AST, ↓ PO_4, ↑ ALT.

NOTES: Follow BP, edema status, LFTs, K^+; CYP17 inhib may ↑mineralocorticoid SEs; prednisone ↓ACTH limiting SEs (hypokalemia and hypertension); if taken with food excess absorption of drug.

ACETAMINOPHEN [APAP, *N*-ACETYL-*p*-AMINOPHENOL] (ACEPHEN, OFIRMEV IV [Rx] , TYLENOL, OTHER GENERIC) [OTC]

WARNING: May cause acute liver failure; associated w/ doses > 4,000 mg/d & taking APAP in >1 product.
USES: *Mild–mod pain, HA, fever*
ACTIONS: Nonnarcotic analgesic; ↓ CNS synth of prostaglandins & hypothalamic heat-

regulating center.

DOSE:

Adults: 325–650 mg PO or PR q4–6h or 1,000 mg PO 3–4 ×/d; max. 4 g/d. *IV:* <50 kg: 15 mg/kg IV q6h or 12.5 mg/kg IV q4h; max. 75 mg/kg/d. ≥50 kg: 650 mg IV q4h or 1,000 mg IV q6h; max. 4 g/d.
Peds: ***<12 y.*** 10–15 mg/kg/dose PO or PR q4–6h; max. 5 doses/24 h. Administer q6h if CrCl 10–50 mL/min & q8h if CrCl <10 mL/min. *IV:* 15 mg/kg IV q6h or 12.5 mg/kg IV q4h; max. 75 mg/kg/d.
W/P: [C, +] w/ hepatic/renal impair in elderly & w/ EtOH use (>3 drinks/d); w/ >4 g/d; EtOH liver Dz, G6PD deficiency; w/ warfarin; serious skin rxns (SJS, TEN, AGEP).
CI: Hypersens.
DISP: Tabs melt away/dissolving 80, 160 mg; tabs: 325, 500, 650 mg; chew tabs 80, 160 mg; gel caps 500 mg; liq 160 mg/5 mL, 500 mg/15 mL; drops 80 mg/0.8 mL; *Acephen* supp 80, 120, 325, 650 mL; Inj 10 mg/mL.
SE: Hepatotoxic; OD hepatotoxic at 10 g; 15 g can be lethal; Rx w/ *N*-acetylcysteine.
NOTES: No anti-inflammatory or plt-inhibiting action; avoid EtOH; 2014 MedWatch Safety Alert: FDA recommends providers stop using combo products w/> 325 mg APAP/dosage unit. No data that >325 mg APAP/dose is beneficial and this ↑ liver injury risk. ↓ dose also ↓ risk of APAP overdose. Most manufacturers have complied w/ 2011 FDA request to limit APAP to 325 mg/dosage unit; some Rx combos w/ >325 mg of APAP/dosage unit remain available. FDA advisory has rec ↓ in max. dose to 3,000 mg/d.

ACETAMINOPHEN/CODEINE (TYLENOL NO. 2, 3, AND 4) [C-III, C-V]

USES: *Mild–mod pain (No. 2–3); mod–severe pain (No. 4)*
ACTIONS: Combined APAP & narcotic analgesic.

DOSE:

Adults: 1–2 tabs q4–6h PRN or 30–60 mg/codeine q4–6h based on codeine content (max. dose APAP = 4 g/d).
Peds: APAP 10–15 mg/kg/dose; codeine 0.5–1 mg/kg dose q4–6h (guide: 3–6 yr, 5 mL/dose; 7–12 yr, 10 mL/dose) max. 2.6 g/d if < 12 yr; ↓ in renal/hepatic impairment.
W/P: [C, ?] Alcoholic liver disease; G6PD deficiency.
CI: Hypersensitivity.
DISP: Tabs 300 mg APAP + codeine (No. 2 = 15 mg, No. 3 = 30 mg, No. 4 = 60 mg); susp (C-V) APAP 120 mg + codeine 12 mg/5 mL.
SE: Drowsiness, dizziness, N/V.
NOTES: See Acetaminophen note

ACETAZOLAMIDE (DIAMOX)

WARNING: Fatalities due to reactions to sulfonamides (e.g., Stevens–Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitizations w/ a sulfonamide is readministration. With serious reactions occur, d/c use. Caution w/ high-dose aspirin and acetazolamide, as anorexia,

tachypnea, lethargy, coma, and death have been reported.
USES: *Diuresis, drug and CHF edema, glaucoma, prevent high-altitude sickness, refractory epilepsy*, metabolic alkalosis, resp stimulant in COPD.
ACTIONS: Carbonic anhydrase inhibitor; ↓ renal excretion of hydrogen & ↑ renal excretion of Na^+, K^+, HCO_3^-, & H_2O.

DOSE:

Adults: *Diuretic:* 250–375 mg IV or PO q24h. *Metabolic alkalosis:* 500 mg IV. *Diuretic*: 5 mg/kg/24 h PO or IV. *Alkalinization of urine:* 5 mg/kg/dose PO BID–TID; ↓ dose w/ CrCl 10–50 mL/min; avoid if CrCl < 10 mL/min.
W/P: [C, +/−]
CI: ↓ sodium and/or potassium; severe kidney/liver disease, adrenal failure, hyperchloremic acidosis, cirrhosis (hepatic encephalopathy risk), long-term use w/ chronic angle-closure glaucoma.
DISP: Tabs 125, 250 mg; ER caps 500 mg; Inj 500 mg/vial, powder for recons.
SE: Malaise, met allic taste, drowsiness, photosensitivity, hyperglycemia.
NOTES: Follow Na^+ & K^+; watch for metabolic acidosis; check CBC & plts; SR forms not for epilepsy.

ACETOHYDROXAMIC ACID (LITHOSTAT)

USES: *Adjunct for chronic urea-splitting UTI*, struvite calculi.
ACTION: ↓ Bacterial urease, ↓ ammonia and alkalinity in the urine d/t urea-splitting organisms.

DOSE:
Adults: 250 mg PO 3–4×/d, total 10–15 mg/kg/d; max. 1.5 g/day.
Peds: 10 mg/kg/d PO.
W/P: [X, −]; w/ pre-existing psych disorders.
CI: Patient amenable to definitive surgery; infection with nonurea-splitting organisms, SCr >2.5 mg/dL, females who do not use contraception, pregnancy, component hypersensitivity.
DISP: Tablets 250 mg.
SE: Hemolytic anemia, bone marrow suppression, hepatotoxicity, flushing, rash, nervousness, tremor, anorexia, N/V.
NOTES: Take on empty stomach (follow CBC and LFTs).

ACETYLCYSTEINE (ACETADOTE, MUCOMYST)

USES: *Mucolytic, antidote to acetaminophen hepatotox/OD, adjuvant treat chronic bronchopulmonary diseases & cystic fibrosis* prevent contrast-induced renal dysfunction.
ACTIONS: Splits mucoprotein disulfide linkages; restores glutathione in acetaminophen OD to protect liver.
DOSE: *Antidote:* PO or NG: 140 mg/kg load, then 70 mg/kg q4h × 17 doses (dilute 1:3 in carbonated beverage or OJ), repeat if emesis w/in 1 hr of dosing. *Acetadote:* 150 mg/kg IV over 60 min, then 50 mg/kg over 4 hr, then 100 mg/kg over 16 hr. *Prevent renal dysfunction:* 600–1,200 mg PO BID × 2 day.

W/P: [B, ?].
DISP: Soln, inhaled and oral 10%, 20%; Acetadote IV soln 20%.
SE: Bronchospasm (inhaled), N/V, drowsiness, anaphylactoid reactions w/ IV.
NOTES: Activated charcoal adsorbs PO acetylcysteine for acetaminophen ingestion; start treatment for acetaminophen OD w/in 6–8 hr.

ACYCLOVIR (ZOVIRAX, GENERIC)

USES: **Herpes simplex* (HSV) (genital/mucocutaneous, encephalitis, keratitis), *Varicella zoster*, *Herpes zoster* (shingles) infections*.
ACTIONS: Interferes w/ viral DNA synth.

DOSE:

Adults: Dose on IBW if obese (>125% IBW) PO. *Initial genital HSV:* 200 mg PO q4h while awake (5 caps/d) × 10 days or 400 mg PO TID × 7–10 days. *Chronic HSV suppression:* 400 mg PO BID. *Intermittent HSV Treat:* As initial, except Treat × 5 days, or 800 mg PO BID, at prodrome. *Topical: Initial herpes genitalis:* Apply q3h (6×/d) for 7 days. *HSV encephalitis:* 10 mg/kg IV q8h × 10 days. *Herpes zoster:* 800 mg PO 5/d for 7–10 days. *IV:* 10 mg/kg/dose IV q8h 7 days.
Peds: *Genital HSV:* ***3 mo–12 y:*** 40–80 mg/kg/d divided 3–4 doses (max 1 g); ***≥12 yr:*** 200 mg 5 times day or 400 mg 3 times a day for 5–10 d; IV: 5 mg/kg/dose q8h for 5–7 d Shingles: ***<12 y:*** 30 mg/kg/d PO or 1,500 mg/m^2/day IV ÷ q8h for 7–10 d; ↓ w/ CrCl <50 mL/min.
W/P: [B, +].
CI: Component hypersens.
DISP: Caps 200 mg; tabs 400, 800 mg; susp 200 mg/5 mL; Inj 500 & 1,000 mg/vial; Inj soln, 50 mg/mL oint 5% and cream 5%.
SE: Dizziness, lethargy, malaise, confusion, rash, IV site inflammation; transient ↑ Cr/BUN.
NOTES: PO better than topical for herpes genitalis.

ALDESLEUKIN [IL-2] (PROLEUKIN)

WARNING: Restrict to pts w/ nl cardiac/pulmonary functions as defined by formal testing. Caution w/ Hx of cardiac/pulmonary disease. Administer in hospital setting w/ physician experienced w/ anticancer agents. Assoc w/ capillary leak syndrome (CLS) characterized by ↓ BP and organ perfusion w/ potential for cardiac/respiratory tox, GI bleed/infarction, renal insufficiency, edema, and mental status changes. ↑risk of sepsis and bacterial endocarditis. Treat bacterial infection before use. Pts w/ central lines are at ↑ risk for infection. Prophylaxis w/ oxacillin, nafcillin, ciprofloxacin, or vancomycin may reduce staphylococcal infection. Hold w/ mod–severe lethargy or somnolence; continued use may result in coma.
USES: *Met RCC & melanoma*.
ACTIONS: Acts via IL-2 receptor; many immunomodulatory effects.
DOSE: 600,000 IU/kg q8h × max. 14 doses days 1–5 and days 15–19 of 28-day cycle (FDA dose/schedule for RCC); other schedules (eg, “high dose” 720,000 IU/kg IV q8h up to 12 doses, repeat 10–15 days later).
W/P: [C, ?/−].
CI: Organ allografts; abnormal thallium stress test or PFT.

DISP: Powder for recons 22 × 10^6 IU, when reconstituted 18 MIU/mL = 1.1 mg/mL.
SE: Flu-like syndrome (malaise, fever, chills), N/V/diarrhea, ↑ bili; capillary leak syndrome; ↓ BP, tachycardia, pulm & periph edema, fluid retention, & Wt gain; renal & mild hematologic tox (↓Hgb, plt, WBC), eosinophilia; cardiac tox (ischemia, atrial arrhythmias); neurotox (CNS depression, somnolence, delirium, rare coma); pruritic rashes, urticaria, & erythroderma common.

ALENDRONATE (BINOSTO, FOSAMAX, FOSAMAX PLUS D, GENERIC)

USES: *Treat & prevent osteoporosis male & postmenopausal female, Treat steroid-induced osteoporosis, Paget disease*.
ACTIONS: ↓ Nl & abnormal bone resorption, ↓ osteoclast action.
DOSE: *Osteoporosis:* Treat: 10 mg/d PO or 70 mg qwk; Fosamax plus D 1 tab qwk. *Steroid-induced osteoporosis:* Treat: 5 mg/d PO, 10 mg/d postmenopausal not on estrogen. *Prevention:* 5 mg/d PO or 35 mg qwk. *Paget disease:* 40 mg/d PO × 6 mo.
W/P: [C, ?] Not OK if CrCl <35 mL/min, w/ NSAID use.
CI: Esophageal anomalies, inability to sit/stand upright for 30 min, ↓ Ca^{2+}.
DISP: Tabs 5, 10, 35, 40, 70 mg. *Fosamax plus D*: Alendronate 70 mg w/ cholecalciferol (vit D_3) 2,800 or 5,600 IU. *Binosto:* Effervescent 7 mg tablet.
SE: Abdominal pain, acid regurgitation, constipation, diarrhea/N, dyspepsia, musculoskelet al pain, jaw osteonecrosis (w/ dental procedures, chemo).
NOTES: Take 1st thing in a.m. w/ H_2O (8 oz) >30 min before 1st food/beverage of day; do not lie down for 30 min after. Use Ca^{2+} & vit D supl w/ regular tab; may ↑ atypical subtrochanteric femur fractures.

ALFUZOSIN (UROXATRAL, GENERIC)

USES: *Symptomatic BPH*.
ACTIONS: α-Blocker.
DOSE: 10 mg PO daily immediately after the same meal; do not crush/chew.
W/P: [B, ?/−] w/ any Hx ↓ BP; use w/ PDE5 inhibitors may ↓ BP; may ↑ QTc interval; d/c with angina; intraoperative floppy iris syndrome during cataract surgery; w/ CrCl <30 mL/min.
CI: w/ CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir); mod–severe hepatic impairment; protease inhibitors for HIV.
DISP: Tabs 10 mg ER.
SE: Postural ↓ BP, dizziness, headache, fatigue, rare priapism.
NOTES: Do not cut or crush.

ALLOPURINOL (ALOPRIM, ZYLOPRIM, GENERIC)

USES: *Gout, hyperuricemia of malignancy, uric acid urolithiasis, recurrent calcium oxalate calculi (w/ urinary uric acid >800 mg/d in males and 750 mg/d in females.*
ACTIONS: Xanthine oxidase inhibitor; ↓ uric acid production.
DOSE:

Adults: *PO:* Initial 100 mg/d; usual 300 mg/d; max. 800 mg/d; ÷ dose if >300 mg/d. *IV:* 200–400 mg/m²/d (max. 600 mg/24 h); (after meal w/ plenty of fluid).
Peds: Only for hyperuricemia of malignancy if <10 yr: 10 mg/kg/d PO (max. 800 mg) or 50–100 mg/m² q8h (max. 300 mg/m²/d); 200–400 mg/m²/d IV (max. 600 mg) ↓ in renal impairment.
W/P: [C, M] Life-threatening syndrome (diffuse desquamative skin rash, fever, hepatic dysfunction, eosinophilia, worsening renal function); 80% have pre-existing renal insufficiency.
DISP: Tabs 100, 300 mg; Inj 500 mg/30 mL (Aloprim).
SE: Rash, N/V, renal impairment, angioedema.
NOTES: Aggravates acute gout; begin after acute attack resolves; IV dose of 6 mg/mL final conc as single daily Inf or ÷ 6-, 8-, or 12-hr intervals

ALPROSTADIL, INTRACAVERNOSAL (CAVERJECT, CAVERJECT IMPULSE, EDEX)

USES: *Erectile dysfunction.*
ACTIONS: A form of prostaglandin E_1; relaxes smooth muscles, dilates cavernosal arteries, ↑ lacunar spaces w/ blood entrapment.
DOSE: 2.5–60 µg intracavernosal; titrate in office.
W/P: [X, −].
CI: ↑ risk of priapism (eg, sickle cell, hematologic malignancies); penile deformities/implants; men in whom sexual activity inadvisable.
DISP: *Caverject:* 5-, 10-, 20-, 40-µg powder for Inj vials ± diluent syringes 10-, 20-, 40-µg amp. *Caverject impulse:* Self-contained syringe (29G) 10 & 20 µg (volume 0.5 mL), *Edex:* 10-, 20-, 40-µg cartridges.
SE: Local pain w/ Inj, priapism risk.
NOTES: Counsel about priapism, penile fibrosis, & hematoma risks.

ALPROSTADIL, URETHRAL SUPPOSITORY (MUSE)

USES: *Erectile dysfunction.*
ACTIONS: A form of prostaglandin E_1; urethral absorption; vasodilator, relaxes smooth muscle of corpus cavernosa.
DOSE: 125–250 µg PRN to achieve erection (max. 2 systems/24 h) duration 30–60 min.
W/P: [X, −].
CI: ↑ Priapism risk (especially sickle cell, myeloma, leukemia), penile deformities/urethral stricture/implants; men in whom sex inadvisable; component hypersensitivity.
DISP: 125, 250, 500, 1,000 µg w/ transurethral applicator system (microsuppositories 1.4 mm diameter by 3 mm or 6 mm length).
SE: ↓ BP, dizziness, syncope, penile/testicular pain, urethral burning/bleeding, priapism.
NOTES: Titrate dose in office; store in refrigerator; do not expose to temps >86 F; @ room temp max. storage 14 days.

ALVIMOPAN (ENTEREG)

WARNING: For short-term hospital use only (max. 15 doses).
USES: *Accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.*
ACTIONS: Opioid (μ) receptor antagonist; selectively binds GI receptors, antagonizes effects of opioids on GI motility/secretion.
DOSE: 12 mg 30 min–5 hr preop PO, then 12 mg BID up to 7 days; max. 15 doses.
W/P: [B,?/−] Not rec in complete bowel obstruction surgery, hepatic/renal impairment.
CI: Therapeutic opioids >7 consecutive days prior.
DISP: Caps 12 mg.
SE: ↓ K^+, dyspepsia, urinary retention, anemia, back pain.
NOTES: Hospitals must be registered to use.

AMIFOSTINE (GENERIC)

USES: *Xerostomia prophylaxis during RT (head, neck, etc.) where parotid is in radiation field; ↓ renal tox w/ repeated cisplatin (label specifies ovarian ca).*
ACTIONS: Prodrug, dephosphorylated to active thiol metabolite, free radical scavenger binds cisplatin metabolites.
DOSE: Chemo prevent: 910 mg/m^2/d 15-min IV Inf 30 min prechemo; *Xerostomia Px*: 200 mg/m^2 over 2 min 1×/d 15 min prerad.
W/P: [C,?/−].
DISP: 500-mg vials powder, reconstitute in NS.
SE: Transient ↓ BP (>60%), N/V, flushing w/ hot or cold chills, dizziness, ↓ Ca^{2+}, somnolence, sneezing, serious skin infection.
NOTES: Does not ↓ effectiveness of cyclophosphamide + cisplatin chemotherapy.

AMIKACIN (AMIKIN)

WARNING: May cause nephrotoxicity, neuromuscular blockade, & respiratory paralysis.
USES: *Serious gram(−) bacterial infections* & mycobacteria.
ACTIONS: Aminoglycoside; ↓ protein synth. *Spectrum:* Good gram(−) bacterial coverage: *Pseudomonas* & *Mycobacterium* sp.

DOSE:
Adults & Peds: *Conventional:* 5–7.5 mg/kg/dose q8h; once daily; 15–20 mg/kg q24h; ↑ interval w/ renal impairment. *Neonates < 1,200 g, 0–4 wk:* 7.5 mg/kg/dose q18–24h. *Age <7 d, 1,200–2,000 g:* 7.5 mg/kg/dose q12h *>2,000 g:* 7.5–10 mg/kg/dose q12h. *Age >7 d, 1,200–2,000 g:* 7.5–10 mg/kg/dose q8–12h *>2,000 g:* 7.5–10 mg/kg/dose q8h.
W/P: [O, +/−] Avoid w/ diuretics.
DISP: Inj 50 & 250 mg/mL.
SE: Renal impairment, oto toxicity.
NOTES: May be effective in gram (−) resistance to gentamicin & tobramycin; follow Cr; Levels: *Peak:* 30 min after Inf. *Trough* <0.5 hr before next dose. *Therapeutic: Peak* 20–30 μg/mL. *Trough:* <8 μg/mL. *Toxic peak* >35 μg/mL; *half-life:* 2 hr.

AMILORIDE (MIDAMOR, GENERIC)

WARNING: ↑ K^+ esp renal disease DM, elderly
USES: *HTN, CHF, & thiazide or loop diuretic induced ↓ K^+*
ACTIONS: K^+-sparing diuretic; interferes w/ K^+/Na^+ exchange in distal tubule & collecting duct

DOSE:
Adults: 5–10 mg PO daily (max 20 mg/d)
Peds: 0.4–0.625 mg/kg/d; ↓ w/ renal impairment
W/P: [B, ?] avoid CrCl <10 mL/min
CI: ↑ K^+, acute or chronic renal disease, diabetic neuropathy, w/ other K^+-sparing diuretics
DISP: Tabs 5 mg
SE: ↑ K^+; headache, dizziness, dehydration, impotence
NOTES: Check K^+

AMINOCAPROIC ACID (AMICAR)

USES: *Excessive bleeding from systemic hyperfibrinolysis & urinary fibrinolysis.*
ACTIONS: ↓ Fibrinolysis; inhibits TPA, inhibits conversion of plasminogen to plasmin.

DOSE:

Adults: 4–5 g IV or PO (1st hr) then 1 g/h IV or 1.25 g/h PO × 8 hr or until bleeding controlled; 30 g/d max.
Peds: 100 mg/kg IV (1st hr) then 1 g/m^2/h; max. 18 g/m^2/d; ↓ w/ renal insufficiency.
W/P: [C, ?] Not for upper urinary tract bleeding (firm clot obstruction risk).
CI: DIC.
DISP: Tabs 500 mg, syrup 1.25 g/5 mL; Inj 250 mg/mL.
SE: ↓ BP, ↓ HR, dizziness, headache, fatigue, rash, GI disturbance, skelet al muscle weakness, ↓ plt function.
NOTES: Urinary fibrinolysis (a normal physiologic phenomenon), may contribute to excessive urinary tract fibrinolytic bleeding associated with surgical hematuria (eg, following prostatectomy and nephrectomy) or nonsurgical hematuria (polycystic or neoplastic diseases, radiation cystitis). Administer × 8 hr or until bleeding controlled; has also been administered by bladder irrigation; obvious clots should be cleared before stating and saline CBI can help effectiveness.

AMINOGLUTETHIMIDE (CYTADREN)

USES: *Cushing syndrome,* adrenocortical carcinoma, breast cancer & PCa.
ACTIONS: ↓ Adrenal steroidogenesis & conversion of androgens to estrogens; 1st gen aromatase inhibitor.
DOSE: Initial 250 mg PO 4 × d, titrate q1–2wk max. 2 g/d; w/ hydrocortisone 20–40 mg/d; ↓ w/ renal insufficiency.
W/P: [D, ?].
DISP: Tabs 250 mg.

SE: Adrenal insufficiency, hypothyroidism, masculinization, ↓ BP, N/V, rare hepatotox, rash, myalgia, fever, drowsiness, lethargy, anorexia.
NOTES: No longer available in the US.

AMITRIPTYLINE (ELAVIL)

WARNING: Antidepressants may ↑ suicide risk; consider risks/benefits of use. Monitor pts closely.
USES: *Depression (not bipolar depression)* peripheral neuropathy, chronic pain, tension HAs, migraine headache prophylaxis PTSD* enuresis, interstitial cystitis.
ACTIONS: Tricyclic antidepressants; ↓ reuptake of serotonin & norepinephrine by presynaptic neurons.

DOSE:

Adults: *Initial:* 25–150 mg PO hs; may ↑ to 300 mg hs.
Peds: Do not use if <12 yr unless for chronic pain, *Initial:* 0.1 mg/kg PO hs, ↑ over 2–3 wk to 0.5–2 mg/kg PO hs; taper to D/C.
W/P: CV disease, seizures [D, +/−] narrow-angle glaucoma, hepatic impairment.
CI: w/ MAOIs or w/in 14 days of use, during AMI recovery.
DISP: Tabs 10, 25, 50, 75, 100, 150 mg; Inj 10 mg/mL.
SE: Strong anticholinergic SEs; OD may be fatal; urine retention, sedation, ECG changes BM suppression, orthostatic ↓ BP, photosensitivity.
NOTES: Levels: *Therapeutic:* 100–250 ng/mL, *Toxic:* >500 ng/mL; levels may not correlate w/ effect.

AMLODIPINE (NORVASC)

USES: *HTN, stable or unstable angina,*
ACTIONS: Calcium channel blocker; relaxes coronary vascular smooth muscle.
DOSE: 2.5–10 mg/d PO; ↓ w/ hepatic impairment.
W/P: [C, ?].
DISP: Tabs 2.5, 5, 10 mg.
SE: Edema, headache, palpitations, flushing, dizziness.
NOTES: Take w/o regard to meals.

AMLODIPINE/OLMESARTAN (AZOR)

WARNING: Use of renin–angiotensin agents in PREGNANCY can cause injury and death to fetus, D/C immediately when PREGNANCY detected.
USES: *Hypertension.*
ACTIONS: Calcium channel blocker w/ angiotensin II receptor blocker.

DOSE:

Adults: Initial 5 mg/20 mg, max. 10 mg/40 mg q day.
W/P: [D, −] w/ K^+ supl or K^+-sparing diuretics, renal impairment, RAS, severe CAD, AS.
CI: PREGNANCY.

DISP: Tabs amlodipine/olmesartan 5 mg/20 mg, 10/20, 5/40, 10/40.
SE: Edema, vertigo, dizziness, ↓ BP.

AMLODIPINE/VALSARTAN (HA EXFORGE)

WARNING: Use of renin–angiotensin agents in PREGNANCY can cause fet al injury and death, D/C immediately when PREGNANCY detected.
USES: *HTN.*
ACTIONS: Calcium channel blocker w/ angiotensin II receptor blocker.

DOSE:

Adults: Initial 5 mg/160 mg, may ↑ after 1–2 wk, max. 10 mg/320 mg q day, start elderly at 1/2 initial dose.
W/P: [D /−] w/ K^+ supl or K^+-sparing diuretics, renal impairment, RAS, severe CAD.
CI: PREGNANCY.
DISP: Tabs amlodipine/valsartan 5/160, 10/160, 5/320, 10 mg/320 mg.
SE: Edema, vertigo, nasopharyngitis, URI, dizziness, ↓ BP.

AMLODIPINE/VALSARTAN/HCTZ (EXFORGE HCT)

WARNING: Use of renin–angiotensin agents in PREGNANCY can cause fet al injury and death, D/C immediately when PREGNANCY detected.
USES: *Hypertension (not initial Treat).*
ACTIONS: Calcium channel blocker, angiotensin II receptor blocker, & thiazide diuretic.
DOSE: 5–10/160–320/12.5–25 mg 1 tab 1 × day may ↑ dose after 2 wk; max. dose 10/320/25 mg.
W/P: [D, −] w/ severe hepatic or renal impairment.
CI: Anuria, sulfonamide allergy.
DISP: Tabs amlodipine/valsartan/ HCTZ: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25 mg.
SE: Edema, dizziness, headache, fatigue, ↑/↓ K^+ ↑ BUN, ↑ SCr, nasopharyngitis, dyspepsia, N, back pain, muscle spasm, ↓ BP.

AMMONIUM ALUMINUM SULFATE [ALUM] [OTC]

USES: *Hemorrhagic cystitis when saline bladder irrigation fails.*
ACTIONS: Astringent, forms precipitates over bleeding surface.

DOSE:
Adult/Peds: 1–4% soln w/ constant NS bladder irrigation 200–250 mL/h.
W/P: [+/−].
DISP: Powder for recons; (typical 50 g in 5 L sterile water).
SE: Encephalopathy possible; check aluminum levels, especially w/ renal insufficiency; spasms; can precipitate & occlude catheters.
NOTES: Safe w/o anesthesia & w/ vesicoureteral reflux; effect often takes several days.

AMOXICILLIN (AMOXIL, MOXATAG, GENERIC)

USES: *Ear, nose, & throat, lower resp, skin, urinary tract infections from susceptible gram(+) bacteria* endocarditis prophylaxis, *H. pylori* eradication w/ other agents (gastric ulcers).
ACTIONS: β-Lactam antibiotic; ↓ cell wall synth. *Spectrum:* gram(+) (*Streptococcus* sp, *Enterococcus* sp); some gram(−) (*H. influenzae, E. coli, N. gonorrhoeae, H. pylori,* & *P. mirabilis*).

DOSE:

Adults: 250–500 mg PO TID or 500–875 mg BID ER 775 mg 1 × d.
Peds: 25–100 mg/kg/24 h PO ÷ q8h, ↓ in renal impairment.
W/P: [B, +].
DISP: Caps 250, 500 mg; chew tabs 125, 200, 250, 400 mg; susp 50, 125, 200, 250 mg/mL & 400 mg/5 mL; tabs 500, 875 mg; tab ER 775 mg.
SE: Diarrhea; rash.
NOTES: Cross-hypersens w/ PCN; many *E. coli* strains resistant; chew tabs contain phenylalanine.

AMOXICILLIN/CLAVULANIC ACID (AUGMENTIN, AUGMENTIN ES-600, AUGMENTIN XR)

USES: *Ear, lower resp, sinus, urinary tract, skin infections caused by β-lactamase–producing *H. influenzae, S. aureus,* & *E. coli.**
ACTIONS: β-Lactam antibiotic w/ β-lactamase inhibitor. *Spectrum:* gram(+) same as amoxicillin alone, MSSA; gram(−) as w/ amoxicillin alone, β-lactamase–producing *H. influenzae, Klebsiella* sp, *M. catarrhalis.*

DOSE:

Adults: 250–500 mg PO q8h or 875 mg q12h; XR 2,000 mg PO q12h.
Peds: 20–40 mg/kg/d as amoxicillin PO ÷ q8h or 45–90 mg/kg/d ÷ q12h; ↓ in renal impairment; take w/ food.
W/P: [B, enters breast milk].
DISP: Supplied (as amoxicillin/clavulanic): Tabs 250/125, 500/125, 875/125 mg; chew tabs 125/31.25, 200/28.5, 250/62.5, 400/57 mg; susp 125/31.25, 250/62.5, 200/28.5, 400/57 mg/5 mL; susp ES 600/42.9 mg/5 mL; XR tab 1,000/62.5 mg.
SE: Abdominal discomfort, N/V/diarrhea, allergic reaction, vaginitis.
NOTES: Do not substitute two 250-mg tabs for one 500-mg tab (possible OD of clavulanic acid); max. clavulanic acid 125 mg/dose.

AMPHOTERICIN B (FUNGIZONE)

USES: *Severe, systemic fungal infections; oral & cutaneous candidiasis.*
ACTIONS: Binds ergosterol in the fungal membrane to alter permeability.

DOSE:
Adults & Peds: 0.25–1.5 mg/kg/24 h IV over 2–6 h (25–50 mg/d or q other day). Total

varies w/ indication ↑ PR, N/V.
W/P: [B, ?].
DISP: Powder (Inj) 50 mg/vial.
SE: ↓ K^+/Mg^{2+} from renal wasting; anaphylaxis, headache, fever, chills, nephrotoxic, ↓ BP, anemia, rigors.
NOTES: Check Cr/LFTs/K^+/Mg^{2+}; ↓ in renal impairment; pretreatment w/ acetaminophen & diphenhydramine ± hydrocortisone can ↓ SE.

AMPHOTERICIN B CHOLESTERYL (AMPHOTEC)

USES: *Aspergillosis if intolerant/refractory to conventional amphotericin B*, systemic candidiasis.
ACTIONS: Binds ergosterol in fungal membrane, alters permeability.

DOSE:
Adults & Peds: 3–4 mg/kg/d; 1 mg/kg/h Inf, 7.5 mg/kg/d max.; ↓ w/ renal insufficiency.
W/P: [B, ?].
DISP: Powder for Inj 50, 100 mg/vial.
SE: Anaphylaxis; fever, chills, headache, ↓ PLT, N/V, ↑ HR, ↓ K^+, ↓ Mg^{2+}, nephrotoxic, ↓ BP, infusion reactions, anemia.
NOTES: Do not use in-line filter; check LFTs/lytes.

AMPHOTERICIN B LIPID COMPLEX (ABELCET)

USES: *Refractory invasive fungal infection in pts intolerant to conventional amphotericin B.*
ACTIONS: Binds ergosterol in fungal membrane, alters permeability.

DOSE:
Adults & Peds: 2.5–5 mg/kg/d IV × 1 daily.
W/P: [B, ?].
DISP: Inj 5 mg/mL.
SE: Anaphylaxis; fever, chills, headache, ↓ K^+, ↑ SCr ↓ Mg^{2+}, nephrotoxic, ↓ BP, anemia.
NOTES: Filter w/ 5-μm needle; do not mix in electrolyte-containing solns; if Inf >2 hr, manually mix bag.

AMPHOTERICIN B LIPOSOMAL (AMBISOME)

USES: *Refractory invasive fungal infection w/ intolerance to conventional amphotericin B; cryptococcal meningitis in HIV; empiric for febrile neutropenia; visceral leishmaniasis.*
ACTIONS: Binds ergosterol in fungal membrane, alters membrane permeability.

DOSE:
Adults & Peds: 3–6 mg/kg/d, Inf 60–120 min; varies by indication; ↓ in renal insufficiency.
W/P: [B, ?].
DISP: Powder Inj 50 mg.
SE: Anaphylaxis, fever, chills, headache, ↓ K^+, ↓ Mg^{2+} peripheral edema, insomnia, rash, ↑ LFTs, nephrotoxic, ↓ BP, anemia.

NOTES: Do not use <. 1-μm filter.

AMPICILLIN (GENERIC)

USES: *Resp, GU, or GI tract infections, meningitis d/t gram(−) & (+) bacteria; SBE prophylaxis.*
ACTIONS: β-Lactam antibiotic; ↓ cell wall synth. *Spectrum:* gram(+) (*Streptococcus* sp, *Staphylococcus* sp, *Listeria*); gram(−) (*Klebsiella* sp, *E. coli, H. influenzae, P. mirabilis, Shigella* sp, *Salmonella* sp).

DOSE:

Adults: 1,000 mg–2 g IM or IV q4–6h or 250–500 mg PO q6h; varies by indication.
Peds Neonates: ***<7 days:*** 50–100 mg/kg/24 h IV ÷ q8h.***Term infants:*** –150 mg/kg/24 h ÷ q6–8h IV or PO. ***Children >1 mo:*** 200 mg/kg/24 h ÷ q6h IM or IV; 50–100 mg/kg/24 h ÷ q6h PO up to 250 mg/dose; ↓ w/ renal impairment; take on empty stomach.
W/P: [B, M] Cross-hypersensitivity w/ PCN.
DISP: Caps 250, 500 mg; susp, 125 mg/5 mL, 250 mg/5 mL; powder (Inj) 125, 250, 500 mg, 1, 2, 10 g/vial.
SE: Diarrhea, rash, allergic reaction.
NOTES: Many *E. coli* resistant.

AMPICILLIN-SULBACTAM (UNASYN, GENERIC)

USES: *Gynecologic, intra-abdominal, skin infections d/t β-lactamase–producing *S. aureus, Enterococcus, H. influenzae, P. mirabilis*, & *Bacteroides* sp.*
ACTIONS: β-Lactam antibiotic & β-lactamase inhibitor. *Spectrum:* gram(+) & (−) as for amp alone; also *Enterobacter, Acinetobacter, Bacteroides.*

DOSE:

Adults: 1.5–3 g IM or IV q6h.
Peds: 100–400 mg ampicillin/kg/d (150–300 mg Unasyn) q6h; ↓ w/ renal insufficiency.
W/P: [B, M].
DISP: Powder for Inj 1.5, 3 g/vial, 15 g bulk package.
SE: Allergic reactions, rash, diarrhea, Inj site pain.
NOTES: A 2:1 ratio ampicillin:sulbactam.

ANIDULAFUNGIN (ERAXIS)

USES: *Candidemia, esophageal candidiasis, other *Candida* infections (peritonitis, intra-abdominal abscess).*
ACTIONS: Echinocandin; ↓ cell wall synth. *Spectrum: C. albicans, C. glabrata, C. parapsilosis, C. tropicalis.*
DOSE: *Candidemia, others*: 200 mg IV × 1, then 100 mg IV daily [Tx ≥ 4 days after last (+) culture]; 1.1 mg/min max. Inf rate.
W/P: [B, ?/−].
CI: Echinocandin hypersens.

DISP: Powder 50, 100 mg/vial.
SE: Histamine-mediated Inf reactions (urticaria, flushing, ↓ BP, dyspnea, etc.), fever, N/V/diarrhea, ↓ K^+, headache, ↑ LFTs, hep, worsening hepatic failure.
NOTES: ↓ Inf rate to <1.1 mg/min w/ Inf reactions.

APIXABAN (ELIQUIS)

WARNING: ↑ Risk of spinal/epidural hematoma w/ paralysis & ↑ thrombotic events w/ D/C in afib pts; monitor closely.
USES: *Prevent CVA/TE in nonvalvular afib.*
ACTIONS: Factor Xa inhibitor.
DOSE: 5 mg BID; 2.5 mg w/2 of the following: >80 yr, Wt <60 kg, SCr ≥1.5; 2.5 mg w/ strong dual inhibitor of CYP3A4 and P-glycoprotein; if on 2.5 mg do **NOT** use w/ strong dual inhibitor of CYP3A4 and P-glycoprotein.
W/P: [B, −] Do not use w/ prosthetic valves.
CI: Pathologic bleeding & apixaban hypersens.
DISP: Tabs 2.5, 5 mg.
SE: Bleeding.
NOTES: If missed dose, do **NOT** double next dose; no antidote to reverse; anticoagulant effect can last 24 hr after dose.

APREPITANT (EMEND, ORAL)

USES: *Prevents N/V associated w/ emetogenic cancer chemotherapy (eg, cisplatin) (use in combo w/ other antiemetics)*, postop N/V.*
ACTIONS: Substance P/neurokinin 1 (NK_1) receptor antagonist.
DOSE: 125 mg PO day 1, 1 hr before chemotherapy, then 80 mg PO q a.m. days 2 & 3; postop N/V: 40 mg w/in 3 hr of induction.
W/P: [B, ?/−]; substrate & mod CYP3A4 inhibitor; CYP2C9 inducer; ↓ effect OCP and warfarin.
CI: Use w/ pimozide or cisapride.
DISP: Caps 40, 80, 125 mg.
SE: Fatigue, asthenia, hiccups.
NOTES: See also Fosaprepitant (Emend, Injection).

ASPIRIN (BAYER, ECOTRIN, ST. JOSEPH'S) [OTC]

USES: *CABG, PTCA, carotid endarterectomy, ischemic stroke, TIA, ACS/MI, arthritis, pain, headache, fever, inflammation*, Kawasaki disease.
ACTIONS: Prostaglandin inhibitor by COX-2 inhibitor.

DOSE:

Adults: *Pain, fever:* 325–650 mg q4–6h PO or PR (4 g/d max.). *Plt inhibitor:* 81–325 mg PO daily.
Peds: *Antipyretic:* 10–15 mg/kg/dose PO or PR q4–6h; for all uses 4 g/d max.; avoid w/ CrCl <10 mL/min, severe liver disease.

W/P: [C, M] linked to Reye syndrome; avoid w/ viral illness in peds <16 yr.
CI: Allergy to ASA, chickenpox/ flu Sxs, syndrome of nasal polyps, angioedema, & bronchospasm to NSAIDs, bleeding disorder.
DISP: Tabs 325, 500 mg; chew tabs 81 mg; EC tabs 81, 162, 325, 500 mg, effervescent tabs 500 mg; supp 300, 600 mg; caplets 81, 375, 500 mg.
SE: GI upset, erosion, & bleeding.
NOTES: D/C 1 wk preop; avoid/limit EtOH; Salicylate levels: *Therapeutic:* 100–250 μg/mL; *Toxic:* >300 μg/mL.

ATENOLOL (TENORMIN, GENERIC)

WARNING: Avoid abrupt withdrawal (esp. CAD pts), gradual taper to ↓, acute ↑ HR, HTN +/− ischemia.
USES: *HTN, angina, post-MI.*
ACTIONS: Selective β-adrenergic receptor blocker.
DOSE: *HTN & angina:* 25–100 mg/d PO; ↓ in renal impairment.
W/P: [D, M] DM, bronchospasm; abrupt D/C can exacerbate angina & ↑ MI risk.
CI: ↓ HR, cardiogenic shock, cardiac failure, 2nd-/3rd-degree AV block, sinus node dysfunction, pulm edema.
DISP: Tabs 25, 50, 100 mg.
SE: ↓ HR, ↓ BP, 2nd-/3rd-degree AV block, dizziness, fatigue.

ATENOLOL & CHLORTHALIDONE (TENORETIC)

USES: *HTN.*
ACTIONS: β-Adrenergic blockade w/ diuretic.
DOSE: 50–100 mg/d PO based on atenolol; ↓ dose w/ CrCl <35 mL/min.
W/P: [D, ?/−] DM, bronchospasm.
CI: See atenolol; anuria, sulfonamide, cross-sensitivity.
DISP: Atenolol 50 mg/chlorthalidone 25 mg, atenolol 100 mg/chlorthalidone 25 mg.
SE: ↓ HR, ↓ BP, 2nd-/3rd-degree AV block, dizziness, fatigue, ↓ K^+, photosensitivity.

ATROPINE, BENZOIC ACID, HYOSCYAMINE SULFATE, METHENAMINE, METHYLENE BLUE, PHENYL SALICYLATE (URISED)

USES: *Lower urinary tract discomfort.*
ACTIONS: Methenamine in acidic urine releases formaldehyde (antiseptic), methylene blue/benzoic acid (mild antiseptic), phenyl salicylate (mild analgesic), hyoscyamine and atropine (parasympatholytic; ↓ muscle spasm).

DOSE:

Adults: 2 tablets PO QID.
Peds: ***>6 yr:*** Individualize.
W/P: [C, ?/−]; avoid w/ sulfonamides.
CI: Narrow-angle glaucoma, pyloric/duodenal obstruction, bladder outlet obstruction, coronary artery spasm.

DISP: Tablet; atropine 0.03 mg/benzoic acid 45 mg/hyoscyamine 0.03 mg/methenamine 40.8 mg/methylene blue 5.4 mg/phenyl salicylate 18.1 mg.
SE: Rash, dry mouth, flushing, ↑ pulse, dizziness, blurred vision, urine/feces discoloration, voiding difficulty.
NOTES: Take w/ plenty of fluid; can cause crystalluria; see also hyoscyamine and methenamine listings.

AVANAFIL (STENDRA)

USES: *Erectile dysfunction.*
ACTIONS: ↓ Phosphodiesterase type 5 (PDE5) (responsible for cGMP breakdown); ↑ cGMP activity to relax smooth muscles to ↑ flow to corpus cavernosum; onset 30–45 min (delayed 1–1.25 hr with high fat meal).
DOSE: (Men only) 100 mg PO as early as 15 min before sex activity, no more than 1 ×/d; ↑/↓ dose 50–200 mg based on effect; do not use w/ strong CYP3A4 inhibitor; use 50 mg w/ mod CYP3A4 inhibitor; w/ or w/o food.
W/P: [C, ?] Priapism risk; hypotension w/ BP meds or substantial alcohol; seek immediate attention w/ hearing loss or acute vision loss (may be NAION; w/ CYP3A4 inhibitor (eg, ketoconazole, ritonavir, erythromycin) ↑ effects; do not use w/ severe renal/ hepatic impairment.
CI: w/ Nitrates or if sex not advised.
DISP: Tabs 50, 100, 200 mg.
SE: Headache, flushing, nasal congestion, nasopharyngitis back pain.
NOTES: More rapid onset than sildenafil (15–30 min).

AXITINIB (INLYTA)

USES: *Advanced RCC.*
ACTIONS: Tyrosine kinase inhibitor.

DOSE:

Adults: 5 mg PO q12h; if tolerated >2 wk, ↑ to 7 mg q12h, then 10 mg q12h; w/ or w/o food; swallow whole; ↓ dose by ½ w/ moderate hepatic impairment; avoid w/ or ↓ dose by ½ if used w/ strong CYP3A4/5 inhibitor.
W/P: [D, ?] w/ brain mets, recent GI bleed.
DISP: Tabs 1, 5 mg.
SE: N/V/diarrhea/C, HTN, fatigue, asthenia, ↓ appetite, ↓ Wt, ↑ LFTs, hand–foot syndrome, venous/arterial thrombosis; hemorrhage, ↓ thyroid, GI perf/ fistula, proteinuria, hypertensive crisis, impaired wound healing, reversible posterior leukoencephalopathy syndrome.
NOTES: Hold 24 hr prior to surgery.

AZATHIOPRINE (AZASAN, IMURAN)

WARNING: May ↑ neoplasia w/ chronic use; mutagenic and hematologic tox possible.
USES: *Adjunct to prevent renal transplant rejection, rheumatoid arthritis*, SLE, Crohn's disease, ulcerative colitis.

ACTIONS: Immunosuppressive; antagonizes purine metabolism.

DOSE:

Adults: *Crohn and ulcerative colitis:* Start 50 mg/d, ↑ 25 mg/d q1–2wk, target dose 2–3 mg/kg/d.
Adults & Peds: *Renal transplant:* 3–5 mg/kg/d IV/PO single daily dose, then 1–3 mg/kg/d maint; *rheumatoid arthritis:* 1 mg/kg/d once daily or ÷ BID × 6–8 wk, ↑ 0.5 mg/kg/d q4wk to 2.5 mg/kg/d; ↓ w/ renal insufficiency.
W/P: [D, ?/−].
CI: PREGNANCY.
DISP: Tabs 50, 75, 100 mg; powder for Inj 100 mg.
SE: GI intolerance, fever, chills, leukopenia, ↑ LFTs, bilirubin, ↑ risk infections, thrombocytopenia.
NOTES: Handle Inj w/ cytotoxic precautions; interaction w/ allopurinol; do not administer live vaccines on drug; check CBC and LFTs; dose per local transplant protocol, usually start 1–3 days pretransplant.

AZITHROMYCIN (ZITHROMAX)

USES: *Community-acquired pneumonia, pharyngitis, otitis media, skin infections, nongonococcal (chlamydial) urethritis, chancroid & PID; Treat & prevention of MAC in HIV.*
ACTIONS: Macrolide antibiotic; bacteriostatic; ↓ protein synth. *Spectrum: Chlamydia, H. ducreyi, H. influenzae, Legionella, M. catarrhalis, M. pneumoniae, M. hominis, N. gonorrhoeae, S. aureus, S. agalactiae, S. pneumoniae, S. pyogenes.*

DOSE:

Adults: *Resp tract infections:* PO: Caps 500 mg day 1, then 250 mg/d PO × 4 days. *Nongonococcal urethritis:* 1 g PO × 1 *Gonorrhea, uncomplicated:* 2 g PO × 1; *Prevent MAC:* 1,200 mg PO once/wk.
Peds: *Otitis media:* 10 mg/kg PO day 1, then 5 mg/kg/d days 2–5. *Pharyngitis* (≥2 yr): 12 mg/kg/d PO × 5 days; take susp on empty stomach; tabs OK w/ or w/o food; ↓ w/ CrCl < 0 mL/mg.
W/P: [B, +] May ↑ QTc w/ arrhythmias.
DISP: Tabs 250, 500, 600 mg; Z-Pack (5-day, 250 mg); Tri-Pack (500-mg tabs × 3); susp 2 g; single-dose packet (Zmax) ER susp (2 g); susp 100, 200 mg/5 mL; Inj powder 500 mg; 2.5 mL.
SE: GI upset, met allic taste.

AZTREONAM (AZACTAM)

USES: *Aerobic gram(−) UTIs, lower resp, intra-abdominal, skin, gynecologic infections & septicemia.*
ACTIONS: *Monobactam:* ↓ Cell wall synth. *Spectrum:* gram(−) (*Pseudomonas, E. coli, Klebsiella, H. influenzae, Serratia, Proteus, Enterobacter, Citrobacter*).

DOSE:

Adults: 1–2 g IV/IM q6–12h. *UTI:* 500 mg–1 g IV q8–12h. *Meningitis:* 2 g IV q6–8h.
Peds: 90–120 mg/kg/d ÷ q6–8h ↓ in renal impairment.
W/P: [B, +].
DISP: Inj (soln), 1 g, 2 g/50 mL Inj powder for recons 1 g, 2 g.
SE: N/V/diarrhea, rash, pain at Inj site.
NOTES: No gram(+) or anaerobic activity; OK in PCN-allergic pts.

BACITRACIN, TOPICAL (BACIGUENT); BACITRACIN & POLYMYXIN B, TOPICAL (POLYSPORIN); BACITRACIN, NEOMYCIN, & POLYMYXIN B, TOPICAL (NEOSPORIN); BACITRACIN, NEOMYCIN, POLYMYXIN B, & HYDROCORTISONE, TOPICAL (CORTISPORIN)

USES: Prevent/Treat of *minor skin infections.*
ACTIONS: Topical antibiotic w/ added components (anti-inflammatory & analgesic).
DOSE: Apply sparingly BID–QID.
W/P: [C, ?] Not for deep wounds, puncture, or animal bites.
DISP: Bacitracin 500 U/g oint; bacitracin 500 U/polymyxin B sulfate 10,000 U/g oint & powder; bacitracin 400 U/neomycin 3.5 mg/ polymyxin B 5,000 U/g oint; bacitracin 400 U/neomycin 3.5 mg/polymyxin B 5,000 U/hydrocortisone 10 mg/g oint; Bacitracin 500 U/neomycin 3.5 mg/polymyxin B 5,000 U/lidocaine 40 mg/g oint.
NOTES: Ophthal, systemic, & irrigation forms available, not generally used d/t potential tox.

BASILIXIMAB (SIMULECT)

WARNING: Use only under the supervision of a physician experienced in immunosuppression Treat in an appropriate facility.
USES: *Prevent acute transplant rejection.*
ACTIONS: IL-2 receptor antagonists.

DOSE:
Adults & Peds: ***> 35 kg:*** 20 mg IV 2 hr before transplant, then 20 mg IV 4 days posttransplant.
Peds: ***< 35 kg:*** 10 mg 2 hr prior to transplant; same dose IV 4 days posttransplant.
W/P: [B, ?/−].
CI: hypersensitivity to murine proteins.
DISP: Inj powder 10, 20 mg.
SE: Edema, ↓ BP, HTN, headache, dizziness, fever, pain, infection, GI effects, electrolyte disturbances.
NOTES: A murine/human MoAb.

BCG [BACILLUS CALMETTE-GUéRIN] (THERACYS, TICE BCG)

WARNING: Contains live, attenuated mycobacteria; transmission risk; handle as biohazard; nosocomial & disseminated infections reported in immunosuppressed.
USES: *Intravesical treatment and prophylaxis of bladder CIS and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following TUR; not recommended

for Ta low-grade papillary tumors, unless they are judged to be at high risk of recurrence.*
ACTIONS: Attenuated live BCG culture, immunomodulator.
DOSE: Bladder cancer (FDA label), 1 vial prepared & instilled in bladder for 2 hr. Repeat once/wk × 6 wk; then 1 maintenance Tx at 3, 6, 12, 18, & 24 mo after.
W/P: [C, ?] Asthma w/ TB immunization.
CI: Immunosuppression, pregnancy, steroid use, febrile illness, symptomatic UTI, gross hematuria, w/ traumatic catheterization.
DISP: Powder 81 mg (*TheraCys*), 50 mg (*Tice BCG*) (both reconstituted to 50 mL volume).
SE: Intravesical: Hematuria, urinary frequency, dysuria, bacterial UTI, rare BCG sepsis malaise, fever, chills, pain, N/V, anorexia, anemia.
NOTES: Do not administer less than 2 wk after resection; do not administer intravesical forms SQ or IM; optimal number of induction instillations and optimal frequency and duration of maintenance instillations remain unknown; SWOG regimen BCG weekly ×6 then 3 weekly doses at 3/6/12/18/24/30 mo; with intravesical use, dispose/void in toilet w/ chlorine bleach; reduced dose administration (1/3, 1/10, 1/100th) used to manage side effects but not widely practiced.

BELATACEPT (NULOJIX)

WARNING: May ↑ risk of posttransplant lymphoproliferative disorder (PTLD) mostly CNS; ↑ risk of infection; for use by physicians experienced in immunosuppressive therapy; ↑ risk of malignancies; not for liver transplant.
USES: *Prevent rejection in EBV positive kidney transplant recipients.*
ACTIONS: T-cell costimulation blocker.
DOSE: Day 1 (transplant day, preop) & day 5 10 mg/kg; end of wk 2, wk 4, wk 8, wk 12 after transplant 10 mg/kg; Maint: End of wk 16 after transplant 4 wk 5 mg/kg.
W/P: [C, −] w/ CYP3A4 inhibitor/inducers, other anticoagulants or plt inhibitor.
CI: EBV seronegative or unknown EBV status.
DISP: 250 mg Inj.
SE: Anemia, N/V/diarrhea, UTI, edema, constipation, ↑ BP, pyrexia, graft dysfunction, cough, headache, ↑/↓ K^+, ↓ WBC.
NOTES: REMS; use in combo w/ basiliximab, mycophenolate mofetil (MMF), & steroids; PML w/ excess belatacept dosing.

BELLADONNA & OPIUM SUPPOSITORIES (GENERIC) [C-II]

USES: *Mod–severe pain associated w/ bladder spasms.*
ACTIONS: Antispasmodic, analgesic.

DOSE:
Adult: 1 supp PR 1–2/d (up to 4 doses/d).
Peds: ***10–15 kg:*** 1/4–1/2 suppository PRN.
W/P: [C, ?].
CI: Glaucoma, resp depression, severe renal or hepatic disease, convulsive disorder, acute alcoholism.
DISP: 30 mg opium/16.2 mg belladonna extract; 60 mg opium/16.2 mg belladonna extract.

SE: Anticholinergic (eg, sedation, urinary retention, constipation).

BENAZEPRIL (LOTENSIN)

WARNING: When used in pregnancy during the 2nd and 3rd trimesters, ACE inhibitors can cause injury and even death to the developing fetus.
USES: *HTN.*
ACTIONS: ACE inhibitor.
DOSE: 10–80 mg/d PO.
W/P: [D, −].
CI: Angioedema.
DISP: Tabs 5, 10, 20, 40 mg.
SE: Symptomatic ↓ BP w/ diuretics; dizziness, headache, ↑ K^+, nonproductive cough, ↑ SCr.

BENZOCAINE (AMERICAINE, HURRICANE, LANACANE, VARIOUS [OTC])

USES: *Topical anesthetic, lubricant on ET tubes, catheters, etc.; pain relief in external otitis, cerumen removal, skin conditions, sunburn, insect bites, mouth and gum irritation, hemorrhoids.*
ACTIONS: Topical local anesthetic.

DOSE:
Adults & Peds: ***>1 yr.*** *Anesthetic lubricant:* Apply evenly to tube/instrument; other uses per manufacturer instructions.
W/P: [C, −] Do not use on broken skin; see provider if condition does not respond; avoid in infants and those w/ pulmonary diseases.
DISP: Many site-specific OTC forms: creams, gels, liquids, sprays, 2–20%.
SE: Itching, irritation, burning, edema, erythema, pruritus, rash, stinging, tenderness, urticaria; methemoglobinemia (infants or in COPD).
NOTES: Use minimum amount to obtain effect; methemoglobinemia S/Sxs: headache, lightheadedness, SOB, anxiety, fatigue, pale, gray or blue colored skin, and tachycardia.

BETHANECHOL (URECHOLINE, GENERIC)

USES: *Acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention.*
ACTIONS: Stimulates cholinergic smooth muscle in bladder & GI tract.

DOSE:

Adults: Initial 5–10 mg PO, then repeat qh until response or 50 mg, typical 10–50 mg TID–QID, 200 mg/d max. TID–QID; 2.5–5 mg SQ TID–QID & PRN.
Peds: (Not FDA approved) 0.3–0.6 mg/kg/24 h PO ÷ TID–QID; take on empty stomach.
W/P: [C, −].
CI: Bladder outlet obstruction, PUD, epilepsy, hyperthyroidism, ↓ HR, COPD, AV conduction defects, Parkinsonism, ↓ BP, vasomotor instability.
DISP: Tabs 5, 10, 25, 50 mg.

SE: Abdominal cramps, diarrhea, salivation, ↓ BP.
NOTES: For overdose: SQ atropine 0.6 mg (adult), children 0.01 mg/kg (max. 0.4 mg).

BEVACIZUMAB (AVASTIN)

WARNING: Associated w/ GI perforation, wound dehiscence, & fatal hemoptysis.
USES: *Met colorectal cancer w/5-FU, NSCLC w/ paclitaxel and carboplatin; glioblastoma; metastatic RCC w/ IFN-α.*
ACTIONS: Vascular endothelial GF inhibitor.

DOSE:

Adults: *RCC:* 10 mg/kg IV q2wk w/ IFN-α.
W/P: [C, −] Do not use w/in 28 days of surgery if time for separation of drug & anticipated surgical procedures is unknown; D/C w/ serious adverse effects.
CI: None.
DISP: 100 mg/4 mL, 400 mg/16 mL vials.
SE: Wound dehiscence, GI perforation, tracheoesophageal fistula, arterial thrombosis, hemoptysis, hemorrhage, HTN, proteinuria, CHF, Inf reactions, diarrhea, leukopenia.
NOTES: Monitor for ↑ BP & proteinuria.

BICALUTAMIDE (CASODEX, GENERIC)

USES: *Stage D_2 metastatic prostate cancer with GnRH agonists (eg, leuprolide, goserelin).*
ACTIONS: Nonsteroidal antiandrogen/androgen receptor inhibitor.
DOSE: 50 mg/d.
W/P: [X, ?].
CI: Women.
DISP: Caps 50 mg.
SE: Hot flashes, ↓ loss of libido, impotence, edema, pain, diarrhea/N/V, gynecomastia, ↑ LFTs.
NOTES: 150 mg daily is not FDA approved for use alone or with other treatments.

BISACODYL (DULCOLAX) [OTC]

USES: *Constipation; preop bowel prep.*
ACTIONS: Stimulates peristalsis.

DOSE:

Adults: 5–15 mg PO or 10 mg PR PRN.
Peds: ***<2 yr:*** 5 mg PR PRN. ***>2 yr:*** 5 mg PO or 10 mg PR PRN (do not chew tabs or give w/in 1 hr of antacids or milk).
W/P: [C, ?].
CI: Abdominal pain or obstruction; N/V.
DISP: EC tabs 5, 10 mg supp 10 mg, enema soln 10 mg/30 mL.
SE: Abdominal cramps, proctitis, & inflammation w/ supps.

BLEOMYCIN SULFATE (GENERIC)

WARNING: Idiopathic reaction (↓ BP, fever, chills, wheezing) in lymphoma pts; pulm fibrosis; should be administered by chemo- experienced physician.
USES: *Testis cancer; Hodgkin disease & NHLs; cutaneous lymphomas; & squamous cell cancer (head & neck, larynx, cervix, skin, penis); malignant pleural effusion sclerosing agent.*
ACTIONS: Induces DNA breakage (scission).
DOSE: (Per protocols) Typical dosing: squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma: 0.25–0.50 U/kg (10–20 U/m^2) IM/IV/SC weekly or twice weekly; ↓ w/ renal impairment.
W/P: [D, ?].
CI: W/ hypersensitivity, idiosyncratic reaction.
DISP: Powder (Inj) 15, 30 U.
SE: Hyperpigmentation & allergy (rash to anaphylaxis); fever in 50%; lung tox (idiosyncratic & dose related); pneumonitis w/ fibrosis; Raynaud phenomenon, N/V.
NOTES: Test dose 1 U, especially in lymphoma pts; lung tox w/ total dose >400 U or single dose >30 U; avoid high FiO_2 in general anesthesia to ↓ tox.

BOTULINUM TOXIN TYPE A [ONABOTULINUMTOXINA] (BOTOX, BOTOX COSMETIC)

WARNING: Effects may spread beyond Tx area leading to swallowing/breathing difficulties (may be fatal); Sxs may occur hours to weeks after injection.
USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults w/ inadequate response or intolerant of an anticholinergic medication; urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication. Glabellar lines (cosmetic) <65 yr, blepharospasm, cervical dystonia, axillary hyperhidrosis, strabismus, chronic migraine, upper limb spasticity. *
ACTIONS: Neurotoxin, ↓ ACH release from nerve endings; denervates sweat glands/muscles.

DOSE:

Adults: *Bladder:* 100 U of *Botox* (max. recommended dose). Dilution is 100 U/10 mL. Needle inserted ~2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced ~1 cm apart; avoid the trigone. ***Reinjection:*** When the clinical effect of the previous injection has diminished (median time in clinical studies was 169 days [~24 wk]), but no sooner than 12 wk from the prior bladder injection.
W/P: [C, ?] w/ neurologic disease; do not exceed rec doses; sedentary pt to resume activity slowly after Inj; aminoglycosides and nondepolarizing muscle blockers may ↑↑ effects; local or total anesthesia.
CI: Hypersensitivity to components, infection at Inj site.
DISP: Inj powder, single-use vial (dilute w/ NS); (*Botox cosmetic*) 50, 100 U; (*Botox*) 100, 200 U vials; store 2–8°C.
SE: Anaphylaxis, erythema multiforme, dysphagia, dyspnea, syncope, headache, narrow-angle glaucoma, Inj site pain.

NOTES: Prophylactic antibiotics, except aminoglycosides, should be administered 1–3 days pretreatment, on the treatment day, and 1–3 days posttreatment; do not exceed total dose of 360 U q12–16wk; Botulinum toxin products not interchangeable; other botulinum toxins are not FDA approved for bladder use: abobotulinumtoxinA (*Dysport*), incobotulinumtoxinA (*Xeomin*) [rimabotulinumtoxinB] (Myobloc).

BROMOCRIPTINE (PARLODEL)

USES: *Parkinson disease, hyperprolactinemia, acromegaly, pituitary tumors.*
ACTIONS: Agonist to striatal dopamine receptors; ↓ prolactin secretion.
DOSE: Initial, 1.25 mg PO BID; titrate to effect, w/ food.
W/P: [B, −].
CI: Uncontrolled HTN, pregnancy, severe CAD or CVS disease.
DISP: Tabs 2.5 mg; caps 5 mg.
SE: ↓ BP, Raynaud phenomenon, dizziness, N, GI upset, hallucinations.

BUMETANIDE (BUMEX)

WARNING: Potent diuretic, may result in profound fluid & electrolyte loss.
USES: *Edema from CHF, hepatic cirrhosis, & renal disease.*
ACTIONS: Loop diuretic; ↓ reabsorption of Na^+ & Cl^-, in ascending loop of Henle & the distal tubule.

DOSE:

Adults: 0.5–2 mg/d PO; 0.5–1 mg IV/IM q8–24h (max. 10 mg/d).
Peds: 0.015–0.1 mg/kg PO q6–24h (max. 10 mg/d).
W/P: [C, ?/−].
CI: Anuria, hepatic coma, severe electrolyte depletion.
DISP: Tabs 0.5, 1, 2 mg; Inj 0.25 mg/mL.
SE: ↓ K^+, ↓ Na^+, ↑ Cr, ↑ uric acid, dizziness, ototox.
NOTES: Monitor fluid & lytes.

BUPIVACAINE (MARCAINE, SENSORCAINE, GENERIC)

WARNING: Avoid 0.75% for OB anesthesia d/t reports of cardiac arrest and death.
USES: *Local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures.*
ACTIONS: Local anesthetic onset 7–30 min; duration 5–7 hr; max.

DOSE:

Adults: 0.25% for infiltration anesthesia; max. dose 3 mg/kg.
Peds: 0.5 ml/kg of 0.25% .
W/P: [C, −] Severe bleeding, ↓ BP, shock & arrhythmias, local infections at site, septicemia.
CI: Obstetrical paracervical block anesthesia.
DISP: Inj 0.25%, 0.5%, 0.75%; with epinephrine 0.25%, 0.5%.
SE: ↓ BP, ↓ HR, dizziness, anxiety.

BUPIVACAINE, LIPOSOME (EXPAREL)

WARNING: Avoid 0.75% for OB anesthesia d/t reports of cardiac arrest and death.
USES: *Single-dose infiltration into the surgical site for postsurgical analgesia.
ACTIONS: Long lasting amide local anesthetic.

DOSE:
Adults & Peds: 0.25% for infiltration anesthesia; max. dose 3 mg/kg (eg, hemorrhoidectomy dose: 266 mg volume: 20 mL.
W/P: [C, −] Monitor of cardiovascular/neurologic status/vital signs; caution with hepatic disease; do not use other bupivacaine forms within 96 hr.
CI: Obstetrical paracervical block anesthesia.
DISP: 20 mL single-use vial, 1.3% (13.3 mg/mL) stored in refrigerator.
SE: N, vomiting, constipation.
NOTES: Do not mix with lidocaine; administer lidocaine and liposomal bupivacaine 20 min apart.

BUPRENORPHINE (BUPRENEX) [C-III]

USES: *Mod–severe pain.*
ACTIONS: Opiate agonist–antagonist.
DOSE: 0.3–0.6 mg IM or slow IV push q6h PRN.
W/P: [C, −].
DISP: 0.3 mg/mL.
SE: Sedation, ↓ BP, resp depression.
NOTES: Withdrawal potential if opioid dependent.

BUTABARBITAL, HYOSCYAMINE HYDROBROMIDE, PHENAZOPYRIDINE (PYRIDIUM PLUS)

USES: *Relieve urinary tract pain w/ UTI, procedures, trauma.*
ACTIONS: Phenazopyridine (topical anesthetic), hyoscyamine (parasympatholytic, ↓ spasm), butabarbital (sedative).
DOSE: 1 PO QID, pc & hs; w/ antibiotic for UTI, 2 days max.
W/P: [C, ?].
DISP: Tab butabarbital/hyoscyamine/phenazopyridine, 15 mg/0.3 mg/150 mg.
SE: headache, rash, itching, GI distress, methemoglobinemia, hemolytic anemia, anaphylactoid-like reactions, dry mouth, dizziness, drowsiness, blurred vision.
NOTES: Colors urine orange, may tint skin, sclera; stains clothing/contacts; see also Phenazopyridine.

BUTORPHANOL (STADOL) [C-IV]

USES: *Anesthesia adjunct, pain & migraine headache.*
ACTIONS: Opiate agonist–antagonist w/ central analgesic actions.
DOSE: 0.5–4 mg IM or IV q3–4h PRN.; ↓ in renal impairment.
W/P: [C, +].

DISP: Inj 1, 2 mg/mL; nasal 1 mg/spray (10 mg/mL).
SE: Drowsiness, dizziness, nasal congestion.
NOTES: May induce withdrawal in opioid dependency.

CABAZITAXEL (JEVTANA)

WARNING: Neutropenic deaths reported; check CBCs, CI w/ ANC ≤1,500 cells/mm^3; severe hypersens (rash/erythema, ↓ BP, bronchospasm) may occur, D/C drug & Tx; CI w/ Hx of hypersens to cabazitaxel or others formulated w/ polysorbate 80.
USES: *Hormone refractory metastatic PCa after taxotere.*
ACTIONS: Microtubule inhibitor.
DOSE: 25 mg/m^2 IV Inf (over 1 hr) q3wk w/ prednisone 10 mg PO daily; premed w/ antihistamine, corticosteroid, H_2 antagonist; do not use w/ bili >ULN, AST/ALT ≥1.5 × ULN.
W/P: [D, ?/−] w/ CYP3A inhibitor/inducers.
CI: See “Warning"
DISP: 40 mg/mL Inj.
SE: ↓ WBC, ↓ Hgb, ↓ plt, sepsis, N/V/diarrhea, constipation, Abdominal/back/jt pain, dysgeusia, fatigue, hematuria, neuropathy, anorexia, cough, dyspnea, alopecia, pyrexia, hypersens reaction, renal failure.
NOTES: Monitor closely pts >65 yr.

CALCITONIN (FORTICAL, MIACALCIN)

USES: *Miacalcin*: *Paget disease, emergent Treat hypercalcemia, postmenopausal osteoporosis*; *Fortical:* *Postmenopausal osteoporosis.*
ACTIONS: Polypeptide hormone (salmon derived), inhibits osteoclasts.
DOSE: *Paget disease:* 100 U/d IM/SQ initial, 50 U/d or 50–100 units q1–3d maint. *Hypercalcemia:* 4 U/kg IM/SQ q12h; ↑ to 8 U/kg q12h, max. q6h. *Osteoporosis:* 100 U/q other day IM/SQ; intranasal 200 U = 1 nasal spray/d.
W/P: [C, ?].
DISP: *Fortical, Miacalcin* nasal spray 200 IU/activation; Inj, *Miacalcin* 200 U/mL (2 mL).
SE: Facial flushing, N, Inj site edema, nasal irritation, polyuria, may ↑ granular casts in urine.
NOTES: For nasal spray alternate nostrils daily; ensure adequate calcium and vit D intake; *Fortical* is rDNA derived from salmon.

CALCITRIOL (ROCALTROL, CALCIJEX)

USES: *Predialysis reduction of ↑ PTH levels to treat bone disease; ↑ Ca^{2+} on dialysis.*
ACTIONS: 1,25-Dihydroxycholecalciferol (vit D analog); ↑ Ca^{2+} and phosphorus absorption; ↑ bone mineralization.

DOSE:

Adults: *Renal failure:* 0.25 µg/d PO, ↑ 0.25 µg/d q4–8wk PRN; 0.5–4 µg 3×/wk IV, ↑ PRN. *Hypoparathyroidism:* 0.5–2 µg/d.
Peds: *Renal failure:* 15 ng/kg/d, ↑ PRN; maint 30–60 ng/kg/d. *Hypoparathyroidism:* ***<5 yr:***

0.25–0.75 µg/d. >***6 yr:*** 0.5–2 µg/d.
W/P: [C, ?] ↑ Mg^{2+} possible w/ antacids.
CI: ↑ Ca^{2+}; vit D tox.
DISP: Inj 1 µg/mL (in 1 mL); caps 0.25, 0.5 µg; soln 1 µg/mL.
SE: ↑ Ca^{2+} possible.
NOTES: Check to keep Ca^{2+} WNL; use nonaluminum phosphate binders and low phosphate diet to control serum phosphate discomfort.

CALCIUM ACETATE (PHOSLO)

USES: *ESRD-associated hyperphosphatemia.*
ACTIONS: Ca^{2+} supl w/o aluminum to ↓ PO_4 absorption.
DOSE: 2–4 tabs PO w/ meals; usual 2,001–2,668 mg PO w/ meals.
W/P: [C, +].
CI: ↑ Ca^{2+} renal calculi.
DISP: Gel-Cap 667 mg.
SE: Can ↑ Ca^{2+}, hypophosphatemia, constipation.
NOTES: Monitor Ca^{2+}.

CALCIUM CARBONATE (TUMS, ALKA-MINTS) [OTC]

USES: *Hyperacidity-associated w/ peptic ulcer disease, hiatal hernia, etc.*, calcium supplementation.
ACTIONS: Neutralizes gastric acid.
DOSE: 500 mg–2 g PO PRN, 7 g/d max.; ↓ w/ renal impairment.
W/P: [C, ?].
CI: ↑ cancer, ↓ phos, renal calculi, suspected digoxin tox.
DISP: Chew tabs 350, 420, 500, 550, 750, 850 mg; susp.
SE: ↑ Ca^{2+}, ↓ PO^{4-}, constipation.

CALCIUM GLUBIONATE (CALCIONATE) [OTC]

USES: *Treat & prevent calcium deficiency.*
ACTIONS: Calcium supplement.
DOSE:
Adults: 1,000–1,200 mg/d ÷ doses.
Peds: 200–1,300 mg/d.
W/P: [C, ?].
DISP: OTC syrup 1.8 g/5 mL = elemental Ca 115 mg/5 mL.
SE: ↑ Ca^{2+}, ↓ PO^{4-}, constipation.

CALCIUM SALTS (CHLORIDE, GLUCONATE, GLUCEPTATE)

USES: *Calcium replacement*, VF, calcium blocker tox (calcium channel blocker),* severe ↑

hypermagnesemic tetany, hyperphosphatemia in ESRD.*
ACTIONS: calcium supl/replacement.

DOSE:

Adults: *Replacement:* 1–2 g/d PO. *Tetany:* 1 g CaCl over 10–30 min; repeat in 6 hr PRN; *Hyperkalemia/hypermagnesemia/calcium channel blocker overdose:* 500–1,000 mg (5–10 mL of 10% soln) IV; repeat PRN; comparable dose of 10% calcium gluconate is 15–30 mL.
Peds: *Tetany:* 10 mg/kg CaCl over 5–10 min; repeat in 6–8 hr or use Inf (200 mg/kg/d max.). *Hyperkalemia/hypermagnesemia/calcium channel blocker overdose:* Calcium chloride or gluconate 20 mg/kg (0.2 mL/kg) slow IV/IO, repeat PRN; central venous route preferred.
Adults & Peds: ↓ calcium d/t citrated blood Inf: 0.45 mEq Ca/100 mL citrated blood Inf (↓ in renal impairment).
W/P: [C, ?].
CI: ↑ Ca^{2+}, suspected digoxin tox.
DISP: CaCl Inj 10% = 100 mg/mL = Ca 27.2 mg/mL = 10-mL amp; Ca gluconate Inj 10% = 100 mg/mL = Ca 9 mg/mL; tabs 500 mg = 45-mg Ca, 650 mg = 58.5-mg Ca, 975 mg = 87.75-mg Ca, 1 g = 90-mg Ca; Ca gluceptate Inj 220 mg/mL = 18-mg/mL Ca.
SE: ↓ HR, cardiac arrhythmias, ↑ Ca^{2+}, constipation.
NOTES: CaCl 270 mg (13.6 mEq) elemental Ca/g & calcium gluconate 90 mg (4.5 mEq) Ca/g. RDA for Ca intake: ***Peds <6 mo:*** 200 mg/d; ***6 mo–1 yr:*** 260 mg/d; ***1–3 yr:*** 700 mg/d; ***4–8 yr:*** 1,000 mg/d; ***10–18 yr:*** 1,300 mg/d.***Adults:***, 000 mg/d; ***>50 yr:*** 1,200 mg/d.

CAPTOPRIL (CAPOTEN, OTHERS)

USES: *HTN, CHF, MI*, LVD, diabetic nephropathy.
ACTIONS: ACE inhibitor.

DOSE:

Adults: *HTN:* Initial, 25 mg PO BID–TID; ↑ to maint q1–2wk by 25 mg increments/dose (max. 450 mg/d) to effect. *CHF:* Initial, 6.25–12.5 mg PO TID; titrate PRN *LVD:* 50 mg PO TID. *DN:* 25 mg PO TID.
Peds: *Infants:* 0.15–0.3 mg/kg/dose PO ÷ 1–4 doses; ***Children:*** Initial, 0.3–0.5 mg/kg/dose PO; ↑ to 6 mg/kg/d max. in 2–4 ÷ doses; 1 hr ac; ↓ dose renal impairment.
W/P: [D, −].
CI: Hx Angioedema.
DISP: Tabs 12.5, 25, 50, 100 mg.
SE: Rash, proteinuria, cough, ↑ K^{+}.

CARBOPLATIN (GENERIC)

WARNING: Administration only by physician experienced in cancer chemotherapy; ↓ PLT, anemia, ↑ infection; BM suppression possible; anaphylaxis and V may occur.
USES: *Ovarian*, lung, head & neck, testicular, urothelial, & brain cancer, NHL & allogeneic & ABMT in high doses.
ACTIONS: DNA cross-linker; forms DNA-platinum adducts.
DOSE: Per protocols based on target (Calvert formula: mg = AUC × [25 + calculated

GFR]); adjust based on plt count, CrCl, & BSA (Egorin formula); up to 1,500 mg/m^2 used in ABMT setting (per protocols).
W/P: [D, ?] severe hepatic tox.
CI: Severe BM suppression, excessive bleeding.
DISP: Inj 50-, 150-, 450-, 650-mg vial (10 mg/mL).
SE: Pain, ↓ Na^+/Mg^{2+}/Ca^{2+}/K^+, anaphylaxis, ↓ BM, N/V/diarrhea, nephrotoxic, hematuria, neurotox, ↑ LFTs.
NOTES: Physiologic dosing based on Calvert or Egorin formula allows ↑ doses w/ ↓ tox.

CASPOFUNGIN (CANCIDAS)

USES: *Invasive aspergillosis refractory/intolerant to standard Treat, candidemia & other candida Inf*, empiric Treat in febrile neutropenia w/ presumed fungal infection.
ACTIONS: Echinocandin; ↓ fungal cell wall synth; highest activity in regions of active cell growth.
DOSE: 70 mg IV load day 1, 50 mg/d IV; slow Inf over 1 hr; ↓ in hepatic impairment.
W/P: [C, ?/−] Do not use w/ cyclosporine.
CI: Allergy to any component.
DISP: Inj 50, 70 mg powder for recons.
SE: Fever, headache, N/V, thrombophlebitis at site, ↑ LFTs ↓ BP, edema, ↑ HR, rash, ↓ K, diarrhea, Inf reaction.
NOTES: Monitor during Inf; limited experience beyond 2 wk of Treat.

CEFACLOR (GENERIC)

USES: *Bacterial infections of the upper & lower resp tract, skin, bone, urinary tract.*
ACTIONS: 2nd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* More gram(−) activity than 1st-gen cephalosporins; effective against gram(+) (*Streptococcus* sp, *S. aureus*); good gram(−) against *H. influenzae, E. coli, Klebsiella, Proteus.*

DOSE:

Adults: 250–500 mg PO > q8h.
Peds: 20–40 mg/kg/d PO ÷ 8–12 hr; ↓ renal impairment.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Caps 250, 500 mg; tabs ER 500 mg; susp 125, 250, 375 mg/5 mL.
SE: N/diarrhea, rash, eosinophilia, ↑ LFTs, headache, rhinitis, vaginitis.

CEFADROXIL (GENERIC)

USES: *Infections skin, bone, upper & lower resp tract, urinary tract.*
ACTIONS: 1st-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Good gram(+) (group A β-hemolytic *Streptococcus, Staphylococcus*); gram(−) (*E. coli, Proteus, Klebsiella*).

DOSE:

Adults: 1–2 g/d PO, 2 ÷ doses.

Peds: 30 mg/kg/d ÷ BID; ↓ in renal impairment.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Caps 500 mg; tabs 1 g; susp, 250, 500 mg/5 mL.
SE: N/V/diarrhea, rash, eosinophilia, ↑ LFTs.

CEFAZOLIN (ANCEF, KEFZOL, GENERIC)

USES: *Infections of skin, bone, upper & lower resp tract, urinary tract.*
ACTIONS: 1st-gen cephalosporin; β-lactam ↓ cell wall synth. *Spectrum:* Good gram(+) bacilli & cocci (*Streptococcus, Staphylococcus* [except *Enterococcus*]); some gram(−) (*E. coli, Proteus, Klebsiella*).

DOSE:

Adults: 1–2 g IV q8h.
Peds: 25–100 mg/kg/d IV ÷ q6–8h; ↓ in renal impairment.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Inj.
SE: Diarrhea, rash, eosinophilia, ↑ LFTs, Inj site pain.
NOTES: Widely used for surgical prophylaxis.

CEFDINIR (GENERIC)

USES: *Infections of the resp tract, skin, and skin structure.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Many gram(+) & (−) organisms; more active than cefaclor & cephalexin against *Streptococcus, Staphylococcus*; some anaerobes.

DOSE:

Adults: 300 mg PO BID or 600 mg/d PO.
Peds: 7 mg/kg PO BID or 14 mg/kg/d PO; ↓ in renal impairment.
W/P: [B, M] w/ PCN-sensitive pts.
CI: Hypersensitivity to cephalosporins.
DISP: Caps 300 mg; susp 125, 250 mg/5 mL.
SE: Anaphylaxis, diarrhea, rare pseudomembranous colitis, headache.

CEFDITOREN (SPECTRACEF)

USES: *Acute exacerbations of chronic bronchitis, pharyngitis, tonsillitis; skin infections.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Good gram(+) (*Streptococcus* & *Staphylococcus*); gram(−) (*H. influenzae* & *M. catarrhalis*)

DOSE:
Adults & Peds: ***>12 yr:*** *Skin also pharyngitis, tonsillitis:* 200 mg PO BID × 10 days. *Chronic bronchitis:* 400 mg PO BID × 10 days; avoid antacids w/in 2 hr; take w/ meals; ↓ in renal impairment.

W/P: [B, ?] Renal/ hepatic impairment.
CI: Cephalosporin/PCN allergy, milk protein, or carnitine deficiency.
DISP: Tabs 200, 400 mg.
SE: headache, N/V/diarrhea, colitis, nephrotoxic, hepatic dysfunction, SJS, TEN, allergic reactions.
NOTES: Causes renal excretion of carnitine; tabs contain milk protein.

CEFEPIME (MAXIPIME, GENERIC)

USES: *Comp/uncomp UTI, pneumonia, empiric febrile neutropenia, skin/soft-tissue infections, comp intra-abdominal infections.*
ACTIONS: 4th-gen cephalosporin; ↓ cell wall synth. *Spectrum:* gram(+) *S. pneumoniae, S. aureus*, gram(−) *K. pneumoniae, E. coli, P. aeruginosa, & Enterobacter* sp.

DOSE:

Adults: 1–2 g IV q8–12h.
Peds: 50 mg/kg q8h for febrile neutropenia; 50 mg/kg BID for skin/soft-tissue infections; ↓ in renal impairment.
W/P: [B, +]; seizure risk w/ CrCl < 60 mL/ min; adjust dose w/ renal insufficiency.
CI: Cephalosporin/PCN allergy.
DISP: Inj 500 mg, 1, 2 g.
SE: Rash, pruritus, N/V/diarrhea, fever, headache, (+) Coombs test w/o hemolysis.
NOTES: Can give IM or IV; concern over ↑ death rates not confirmed by FDA.

CEFIXIME (SUPRAX)

USES: *Resp tract, skin, bone, & urinary tract infections.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum: S. pneumoniae, S. pyogenes, H. influenzae, & enterobacteria.*

DOSE:

Adults: 400 mg PO ÷ daily–BID.
Peds: 8 mg/kg/d PO ÷ daily–BID; ↓ w/ renal impairment.
W/P: [B, ?].
CI: Cephalosporin/PCN allergy.
DISP: Tabs 400 mg, 100, 200 mg chew tab, susp 100, 200 mg/5 mL.
SE: N/V/diarrhea, flatulence, & abdominal pain.
NOTES: Check renal & hepatic function; use susp for otitis media.

CEFOTAXIME (CLAFORAN, GENERIC)

USES: *Infections of lower resp tract, skin, bone & jt, urinary tract, meningitis, sepsis, PID, GC.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Most gram(−) (not *Pseudomonas*), some gram(+) cocci *S. pneumoniae, S. aureus* (penicillinase/nonpenicillinase producing), *H. influenzae* (including ampicillin resistant), not *Enterococcus*; many PCN-

resistant pneumococci.

DOSE:

Adults: *Uncomplicated infection:* 1 g IV/IM q12h; *Mod–severe infection:* 1–2 g IV/IM q 8–12 h; *Severe/septicemia:* 2 g IV/IM q4–8h; *GC urethritis, cervicitis, rectal in female:* 0.5 g IM × 1; rectal GC men 1 g IM × 1;
Peds: 50–200 mg/kg/d IV ÷ q6–8h; ↓ w/ renal/hepatic impairment.
W/P: [B, +] Arrhythmia w/ rapid Inj; w/ colitis.
CI: Cephalosporin/PCN allergy.
DISP: Powder for Inj 500 mg, 1, 2, 10 g, premixed Inf 20 mg/mL, 40 mg/mL.
SE: diarrhea, rash, pruritus, colitis, eosinophilia, ↑ transaminases.

CEFOTETAN (GENERIC)

USES: *infections of the upper & lower resp tract, skin, bone, urinary tract, abdominal, & gynecologic system.*
ACTIONS: 2nd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Less active against gram(+) anaerobes including *B. fragilis*; gram(−), including *E. coli, Klebsiella, & Proteus.*

DOSE:

Adults: 1–3 g IV q12h.
Peds: 20–40 mg/kg/dose IV ÷ q12h (6 g/d max.) ↓ w/ renal impairment.
W/P: [B, +] May ↑ bleeding risk; w/ Hx of PCN allergies, w/ other nephrotoxic drugs.
CI: Cephalosporin/PCN allergy.
DISP: Powder for Inj 1, 2, 10 g.
SE: Diarrhea, rash, eosinophilia, ↑ transaminases, hypoprothrombinemia, & bleeding (d/t MTT side chain).
NOTES: May interfere w/ warfarin.

CEFOXITIN (GENERIC)

USES: *Infections of the upper & lower resp tract, skin, bone, urinary tract, Abdominal, & gynecologic system.*
ACTIONS: 2nd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Good gram(−) against enteric bacilli (ie, *E. coli, Klebsiella,* & *Proteus*); anaerobic: *B. fragilis.*

DOSE:

Adults: 1–2 g IV q6–8h.
Peds: 80–160 mg/kg/d ÷ q4–6h (12 g/d max.); ↓ w/ renal impairment.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Powder for Inj 1, 2, 10 g.
SE: Diarrhea, rash, eosinophilia, ↑ transaminases.

CEFPODOXIME (GENERIC)

USES: *Treat resp, skin, & urinary tract infections.*

ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum: S. pneumoniae* or non–β-lactamase–producing *H. influenzae*; acute uncomplicated *N. gonorrhoeae*; some uncomplicated gram(−) (*E. coli, Klebsiella, Proteus*)

DOSE:

Adults: 100–400 mg PO q12h.
Peds: 10 mg/kg/d PO ÷ BID; ↓ in renal impairment, w/ food.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Tabs 100, 200 mg; susp 50, 100 mg/5 mL.
SE: Diarrhea, rash, headache, eosinophilia, ↑ transaminases.
NOTES: Drug interactions w/ agents that ↑ gastric pH.

CEFPROZIL (GENERIC)

USES: *Treat resp tract, skin, & urinary tract infections.*
ACTIONS: 2nd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Active against MSSA, *Streptococcus,* & gram(−) bacilli (*E. coli, Klebsiella, P. mirabilis, H. influenzae, Moraxella*).

DOSE:

Adults: 250–500 mg PO daily–BID.
Peds: 7.5–15 mg/kg/d PO ÷ BID; ↓ in renal impairment.
W/P: [B, M].
CI: Cephalosporin/PCN allergy.
DISP: Tabs 250, 500 mg; susp 125, 250 mg/5 mL.
SE: Diarrhea, dizziness, rash, eosinophilia, ↑ transaminases.
NOTES: Use higher doses for otitis & pneumonia.

CEFTAROLINE (TEFLARO)

USES: *Tx skin/skin structure infection (SSSI) & community-acquired pneumonia.*
ACTIONS: Unclassified ("5th gen") cephalosporin; ↓ cell wall synthesis. *Spectrum:* gram(+) *Staph aureus* (MSSA/MRSA), *Strep pyogenes, Strep agalactiae, Strep pneumoniae*; gram(−) *E. coli, K. pneumoniae, K. oxytoca, H. influenzae.*

DOSE:

Adults: 600 mg IV q12h; CrCl 30–50 mL/min: 400 mg IV q12h; CrCl 15–29 mL/min: 300 mg IV q12h; CrCl < 15 mL/min: 200 mg IV q12h; Inf over 1 hr.
W/P: [B, ?/−] monitor for *C. difficile*-associated diarrhea.
CI: Cephalosporin sensitivity.
DISP: Inj 600 mg.
SE: Hypersens reaction, diarrhea/N, rash, constipation, ↓ K^+, phlebitis, ↑ LFTs.

CEFTAZIDIME (FORTAZ, TAZICEF, GENERIC)

USES: *Treat resp tract, skin, bone, urinary tract infections, meningitis, & septicemia.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum: P. aeruginosa* sp, good gram(−)

activity.

DOSE:

Adults: 500–2 g IV/IM q8–12h.
Peds: 30–50 mg/kg/dose IV q8h 6g/d max.; ↓ renal impairment.
W/P: [B, +] PCN sensitivity.
CI: Cephalosporin/PCN allergy.
DISP: Powder for Inj 500 mg, 1, 2, 6 g.
SE: Diarrhea, rash, eosinophilia, ↑ transaminases.
NOTES: Use only for proven or strongly suspected infection to ↓ development of drug resistance.

CEFTIBUTEN (CEDAX)

USES: *Treat resp tract, skin, urinary tract infections, & otitis media.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum: H. influenzae & M. catarrhalis*; weak against *S. pneumonia.*

DOSE:

Adults: 400 mg/d PO.
Peds: 9 mg/kg/d PO; ↓ in renal impairment; take on empty stomach (susp).
W/P: [B, +/−].
CI: Cephalosporin/PCN allergy.
DISP: Caps 400 mg; susp 90 mg/5 mL.
SE: diarrhea, rash, eosinophilia, ↑ transaminases.

CEFTRIAXONE (ROCEPHIN, GENERIC)

WARNING: Avoid in hyperbilirubinemic neonates or coinfusion w/ calcium-containing products.
USES: *Resp tract (pneumonia), skin, bone, abdominal & urinary tract infections, meningitis, septicemia, GC, PID, perioperative.*
ACTIONS: 3rd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Mod gram(+); excellent β-lactamase producers.

DOSE:

Adults: 1–2 g IV/IM q12–24h.
Peds: 50–100 mg/kg/d IV/IM ÷ q12–24h; decrease dose with renal insufficiency.
W/P: [B, +]. Postrenal acute renal failure (PARF) in children may require stenting.
CI: Cephalosporin allergy; hyperbilirubinemic neonates.
DISP: Powder for Inj 250 mg, 500 mg, 1, 2, 10 g; premixed 20, 40 mg/mL.
SE: Diarrhea, rash, ↑ WBC, thrombocytosis, eosinophilia, ↑ LFTs.

CEFUROXIME (CEFTIN [PO] , ZINACEF [PARENTERAL] , GENERIC)

USES: *Upper & lower resp tract, skin, bone, urinary tract, abdominal, gynecologic infections.*

ACTIONS: 2nd-gen cephalosporin; ↓ cell wall synth. *Spectrum:* Staphylococci, group B streptococci, *H. influenzae, E. coli, Enterobacter, Salmonella, & Klebsiella.*

DOSE:

Adults: 750 mg–1.5 g IV q8h or 250–500 mg PO BID.
Peds: 75–150 mg/kg/d IV ÷ q8h or 20–30 mg/kg/d PO ÷ BID; ↓ w/ renal impairment; take PO w/ food.
W/P: [B, +].
CI: Cephalosporin/PCN allergy.
DISP: Tabs 250, 500 mg; susp 125, 250 mg/5 mL; powder for Inj 750 mg, 1.5, 7.5 g.
SE: Diarrhea, rash, eosinophilia, ↑ LFTs.
NOTES: Cefuroxime film-coated tabs & susp not bioequivalent; do not substitute on a mg/mg basis; IV crosses blood–brain barrier.

CELECOXIB (CELEBREX)

WARNING: ↑ Risk of serious CV thrombotic events, MI, & stroke; can be fatal; ↑ risk of serious GI adverse events including bleeding, ulceration, & perforation of the stomach or intestines; can be fatal.
USES: *Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, primary dysmenorrhea.*
ACTIONS: NSAID; ↓ COX-2 pathway.
DOSE: 100–200 mg/d or BID; ↓ w/ hepatic impairment; take w/ food/milk.
W/P: [C/D (3rd tri), ?] w/ renal impairment.
CI: Sulfonamide allergy, perioperative CABG.
DISP: Caps 50, 100, 200, 400 mg.
SE: See “Warning"; GI upset, HTN, edema, renal failure, headache.
NOTES: Watch for Sxs of GI bleed; no effect on plt/bleeding time; can affect drugs metabolized by P-450 pathway.

CEPHALEXIN (KEFLEX, GENERIC)

USES: *Skin, bone, upper/lower resp tract (streptococcal pharyngitis), otitis media, uncomp cystitis infections.*
ACTIONS: 1st-gen cephalosporin; ↓ cell wall synth. *Spectrum: Streptococcus* (including β-hemolytic)*, Staphylococcus, E. coli, Proteus, & Klebsiella.*

DOSE:
Adults & Peds: *>15 yr:* 250–1,000 mg PO QID; Treat cystitis 7–14 days (4 g/d max.).
Peds: *<15 yr:* 25–100 mg/kg/d PO ÷ BID–QID; ↓ in renal impairment; w/ or w/o food.
W/P: [B, +].
CI: Cephalosporin/ PCN allergy.
DISP: Caps 250, 500 mg; susp, 125, 250 mg; susp 125, 250 mg/5 mL.
SE: Diarrhea, rash, eosinophilia, gastritis, dyspepsia, ↑ LFTs, *C. difficile* colitis, vaginitis.

CHLOROTHIAZIDE (DIURIL)

USES: *HTN, edema.*
ACTIONS: Thiazide diuretic; decreases urine calcium.

DOSE:

Adults: 500 mg–1 g PO daily–BID; 500–1,000 mg/d IV (for edema only).
Peds: *>6 mo:* 10–20 mg/kg/24 h PO ÷ BID; 4 mg/kg ÷ daily bio IV; OK w/ food.
W/P: [C, +].
CI: Sensitivity to thiazides/sulfonamides, anuria.
DISP: Tabs 250, 500 mg; susp 250 mg/5 mL; Inj 500 mg/vial.
SE: ↓ K^+, Na^+, dizziness, hyperglycemia, hyperuricemia, hyperlipidemia, photosensitivity.
NOTES: Do not use IM/SQ; take early in the day to avoid nocturia; use sunblock; monitor lytes.

CHLORTHALIDONE (GENERIC)

USES: *HTN, edema.*
ACTIONS: Thiazide diuretic.

DOSE:

Adults: 25–100 mg PO daily.
Peds: (Not FDA approved) 0.3–2 mg/kg/dose PO 3×/wk or 1–2 mg/kg/d PO;↓ in renal impairment; OK w/ food, milk.
W/P: [B, +].
CI: Cross-sensitivity w/ thiazides or sulfonamides; anuria.
DISP: Tabs 25, 50, 100 mg.
SE: ↓ K^+, dizziness, photosensitivity, ↑ glucose, hyperuricemia, sexual dysfunction; 25–50 mg/d for idiopathic hypercalciuria.

CHOLECALCIFEROL [VITAMIN D_3] (DELTA D)

USES: Dietary supl to Treat vit D deficiency.
ACTIONS: ↑ intestinal Ca^{2+} absorption.
DOSE: 400–1,000 IU/d PO.
W/P: [A (D doses above the RDA), +].
CI: ↑ Ca^{2+}, hypervitaminosis, allergy.
DISP: Tabs 400, 1,000 IU.
SE: Vit D tox (renal failure, HTN, psychosis).
NOTES: 1 mg cholecalciferol = 40,000 IU vit D activity.

CIPROFLOXACIN (CIPRO, CIPRO XR)

WARNING: ↑ Risk Achilles tendon rupture and tendonitis, ↑ in pts >60 yr, on steroids or with organ transplant; avoid w/ myasthenia gravis, may ↑ muscle weakness.
USES: *Treat lower resp tract, sinuses, skin & skin structure, bone/joints, complex intra-abdominal infection (w/ metronidazole), typhoid, infectious diarrhea, uncomp GC, inhal anthrax, UTI including prostatitis; Peds only for multi resistant UTI not as first agent.*

ACTIONS: Quinolone antibiotic; ↓ DNA gyrase. *Spectrum:* Broad gram(+) & (–) aerobics; little *Streptococcus*; good *Pseudomonas, E. coli, B. fragilis, P. mirabilis, K. pneumoniae, C. jejuni,* or *Shigella.*

DOSE:

Adults: 250–750 mg PO q12h; XR 500–1,000 mg PO q24h; or 200–400 mg IV q12h; ↓ in renal impairment.
Peds: 6–10 mg/kg/day IV.
W/P: [C, ?/−] Children <18 yr due to cartilage concerns; avoid in myasthenia gravis.
CI: Component sensitivity; w/ tizanidine.
DISP: Tabs 100, 250, 500, 750 mg; tabs XR 500, 1,000 mg; susp 5 g/100 mL, 10 g/100 mL; Inj 200, 400 mg; premixed piggyback 200, 400 mg/100 mL.
SE: Restlessness, N/V/diarrhea, rash, ruptured tendons, ↑ LFTs, peripheral neuropathy risk.
NOTES: Avoid antacids; reduce/restrict caffeine intake; interactions w/ theophylline, caffeine, sucralfate, warfarin, antacids, most tendon problems in Achilles, rarely shoulder and hand.

CISPLATIN (PLATINOL, PLATINOL AQ, GENERIC)

WARNING: Anaphylactic-like reaction, ototox, cumulative renal tox; doses >100 mg/m^2 q3–4wk rarely used, do not confuse w/ carboplatin.
USES: *Testicular, bladder, ovarian*, SCLC, NSCLC, breast, head & neck, & penile cancers; osteosarcoma; peds brain tumors.
ACTIONS: DNA binding; denatures double helix; intrastrand cross-linking.
DOSE: 10–20 mg/m^2/d for 5 days q3wk; 50–120 mg/m^2 q3–4wk (per protocols); ↓ w/ renal impairment.
W/P: [D, −] Cumulative renal tox may be severe; ↓ BM, hearing impairment, pre-existing renal insufficiency.
CI: w/ renal impairment, hearing impairment, myelosuppression, platinum-containing compound allergy.
DISP: Inj 1 mg/mL.
SE: Allergic reactions, N/V, nephrotoxic (↑ w/ administration of other nephrotoxic drugs; minimize by NS Inf & mannitol diuresis), high-frequency hearing loss in 30%, peripheral "stocking glove"-type neuropathy, cardiotox (ST-, T-wave changes), ↓ Mg^{2+}, mild ↓ BM, hepatotox; renal impairment dose related & cumulative.
NOTES: Give taxanes before platinum derivatives; check Mg^{2+}, lytes before & w/in 48 hr after cisplatin.

CITRIC ACID, GLUCONOLACTONE, AND MAGNESIUM CARBONATE (RENACIDIN)

USES: *Chemolysis of calculi/incrustations in the urinary tract composed of apatite (calcium carbonate-phosphate) or struvite (magnesium ammonium phosphates) in nonsurgical candidates; adjunctive therapy to dissolve residual apatite/struvite fragments postop; partial dissolution of calculi to facilitate surgical removal.*

ACTIONS: Dissolution of calculi by exchange of Mg^{2+} from irrigating solution for insoluble Ca^{2+} in calcification. Mg^{2+} salts are soluble in the citrate irrigating solution, dissolving calculus.
DOSE: *Intermittent bladder irrigation:* 30–50 mL via Foley, clamped for 30 min, repeated TID for encrustations and 4–6×/d for bladder stones; irrigation via dual nephrostomy tube (inflow/outflow) or into ureteral catheter with nephrostomy drainage; essential to keep pressure <80 cm H_2O by manometer.
W/P: [C, ?] Caution w/ irrigating the renal pelvis of patients with impaired renal function. Observe for early signs/symptoms of hypermagnesemia (nausea, lethargy, confusion and hypotension). Severe hypermagnesemia may result in hyporeflexia, dyspnea, apnea, coma, cardiac arrest, and subsequent death. Monitor magnesium levels and deep tendon reflexes should be evaluated.
CI: Obstructed urinary tract, extravasation, UTI.
DISP: Solution.
SE: Hypermagnesemia, irritation, sepsis, other infections.
NOTES: Suby solution G was modified by addition of magnesium salts to create Renacidin.

CLARITHROMYCIN (BIAXIN, BIAXIN XL)

USES: *Upper/lower resp tract, skin/skin structure infections, *H. pylori* infections, & infections caused by nontuberculosis (atypical) *Mycobacterium*; prevention of MAC infections in HIV infection.*
ACTIONS: Macrolide antibiotic, ↓ protein synth. *Spectrum: H. influenzae, M. catarrhalis, S. pneumoniae, M. pneumoniae, & H. pylori.*

DOSE:

Adults: 250–500 mg PO BID or 1,000 mg (2 × 500 mg XL tab)/d. *Mycobacterium:* 500 mg PO BID.
Peds: ***>6 mo:*** 7.5 mg/kg/dose PO BID; ↓ w/ renal impairment.
W/P: [C, ?] Antibiotic-associated colitis; rare ↑ QT & ventricular arrhythmias; not rec w/ PDE5 inhibitor.
CI: Macrolide allergy; w/ Hx jaundice w/ Biaxin; w/cisapride, pimozide, astemizole, terfenadine, ergotamines; PDE5 inhibitors (sildenafil, others); w/ colchicine & renal impairment; w/ statins; w/ ↑ QT or ventricular arrhythmias.
DISP: Tabs 250, 500 mg; susp 125, 250 mg/5 mL; 500 mg XL tab.
SE: ↑ QT interval, causes met allic taste, N/diarrhea, abdominal pain, headache, rash.
NOTES: Multiple drug interactions, ↑ theophylline & carbamazepine levels; do not refrigerate susp.

CLINDAMYCIN (CLEOCIN, CLEOCIN-T, OTHERS)

WARNING: Pseudomembranous colitis may range from mild to life threatening.
USES: *aerobic & anaerobic infections; topical for severe acne & Vag infections.*
ACTIONS: Bacteriostatic; interferes w/ protein synth. *Spectrum:* Streptococci (eg, pneumococci), staphylococci, & gram(+) & (–) anaerobes; no activity against gram(−)

aerobes.

DOSE:

Adults: *PO:* 150–450 mg PO q6–8h. *IV:* 300–600 mg IV q6h or 900 mg IV q8h. *Vag cream*: 1 applicator hs × 7 days. *Vag supp:* Insert 1 qhs × 3 days. *Topical:* Apply 1% gel, lotion, or soln BID.
Peds: ***Neonates:*** (Avoid use; contains benzyl alcohol) 10–15 mg/kg/24 h ÷ q8–12h. ***Children >1 mo:*** 10–30 mg/kg/24 h ÷ q6–8h, to a max. of 1.8 g/d PO or 4.8 g/d IV. *Topical:* Apply 1%, gel, lotion, or soln BID; ↓ in severe hepatic impairment.
W/P: [B, +] Can cause fatal colitis.
CI: Hx pseudomembranous colitis.
DISP: Caps 75, 150, 300 mg; susp 75 mg/5 mL; Inj 300 mg/2 mL; Vag cream 2%, topical soln 1%, gel 1%, lotion 1%, Vag supp 100 mg.
SE: Diarrhea may be *C. difficile* pseudomembranous colitis, rash, ↑ LFTs.
NOTES: D/C drug w/ diarrhea, evaluate for *C. difficile.*

CLOMIPHENE (CLOMID, SEROPHENE, GENERIC)

USES: *Tx ovulatory dysfunction in women desiring pregnancy.*
ACTIONS: Nonsteroidal ovulatory stimulant; estrogen antagonist, increases FSH and LH through blocking feedback inhibition on the pituitary.
DOSE: 50 mg × 5 days; if no ovulation ↑ to 100 mg × 5 days @ 30 d later; ovulation usually 5–10 days postcourse, time coitus w/ expected ovulation time.
W/P: [X, ?/−] r/o pregnancy & ovarian enlargement.
CI: Hypersensitivity, uterine bleed, pregnancy, ovarian cysts (not due to polycystic ovary syndrome), liver disease, thyroid/adrenal dysfunction.
DISP: Tabs 50 mg.
SE: Ovarian enlargement, vasomotor flushes.
NOTES: Off-label use in males to increase testosterone or for low sperm counts; >10% of men with azoospermia and hypoandrogenism have return of sperm to ejaculate after T normalizes using clomiphene.

CLONIDINE, ORAL (CATAPRES)

USES: *HTN* opioid, EtOH, & tobacco withdrawal, ADHD.
ACTIONS: Centrally α-adrenergic stimulant.

DOSE:

Adults: 0.1 mg PO BID, adjust daily by 0.1–0.2-mg increments (max. 2.4 mg/d).
Peds: 5–10 μg/kg/d ÷ q8–12h (max. 0.9 mg/d); ↓ in renal impairment.
W/P: [C, +/−] Avoid w/ β-blocker, elderly, severe CV disease, renal impairment; use w/ agents that affect sinus node may cause severe ↓ HR.
CI: Component sensitivity.
DISP: Tabs 0.1, 0.2, 0.3 mg.
SE: drowsiness, orthostatic ↓ BP, xerostomia, constipation, ↓ HR, dizziness.
NOTES: More effective for HTN if combined w/ diuretics; withdraw slowly, rebound HTN w/

abrupt D/C of doses >0.2 mg BID; (Duraclon epidural inj) used for chronic cancer pain.

CLOPIDOGREL (PLAVIX, GENERIC)

USES: *Reduce atherosclerotic events, acute coronary syndrome.*
ACTIONS: ↓ Plt aggregation.
DOSE: 75 mg/d; *ACS:* 300–600 mg PO loading dose, then 75 mg/d PO; full effects take several days.
W/P: [B, ?] Active bleeding; risk of bleeding from trauma & other; TTP; liver disease; other CYP2C19 (eg, fluconazole); OK w/ ranitidine, famotidine.
CI: Coagulation disorders, active/ intracranial bleeding; CABG planned w/in 5–7 days.
DISP: Tabs 75, 300 mg.
SE: ↑ Bleeding time, GI intolerance, headache, dizziness, rash, thrombocytopenia, ↓ WBC.
NOTES: Plt aggregation to baseline ~5 days after D/C, plt transfusion to reverse acutely; clinical response highly variable.

CLOTRIMAZOLE (LOTRIMIN, MYCELEX, OTHERS) [OTC]

USES: *Candidiasis & tinea infections.*
ACTIONS: Antifungal; alters cell wall permeability. *Spectrum:* Oropharyngeal candidiasis, dermatophytoses, superficial mycoses, cutaneous candidiasis, & vulvovaginal candidiasis.
DOSE: *PO: Prophylaxis:* 1 troche dissolved in mouth TID. *Treat:* 1 troche dissolved in mouth 5×/d for 14 days. *Vag 1% cream:* 1 applicator-full hs for 7 days. *2% cream:* 1 applicator-full hs for 3 days. *Tabs:* 100 mg vaginally hs for 7 days or 200 mg (2 tabs) vaginally hs for 3 days or 500-mg tabs vaginally hs once. *Topical*: Apply BID 10–14 days.
W/P: [B (C if PO), ?] Not for systemic fungal infection; safety in children <3 yr not established.
CI: Component allergy.
DISP: 1% cream; soln; troche10 mg; vag cream 1%, 2%.
SE: *Topical:* Local irritation; *PO:* N/V, ↑ LFTs.
NOTES: PO prophylaxis for immunosuppressed pts.

CLOTRIMAZOLE/BETAMETHASONE (LOTRISONE)

USES: *Fungal skin infections.*
ACTIONS: Imidazole antifungal & anti-inflammatory. *Spectrum:* Tinea pedis, cruris, & corporis.

DOSE:
Children ≥ 17 yr, Adults: Apply & massage into area BID for 2–4 wk.
W/P: [C, ?] Varicella infection.
CI: Children <12 yr.
DISP: Cream 1/0.05% 15, 45 g; lotion 1/0.05% 30 mL.
SE: Local irritation, rash.
NOTES: Not for diaper dermatitis or under occlusive dressings.

CODEINE [C-II]

USES: *Mild–mod pain; symptomatic relief of cough.*
ACTIONS: Narcotic analgesic; ↓ cough reflex.

DOSE:

Adults: *Analgesic:* 15–60 mg PO or IM q4h PRN; 360 mg max./24 h. *Antitussive:* 10–20 mg PO q4h PRN; max. 120 mg/d.
Peds: *Analgesic:* 0.5–1 mg/kg/dose PO q4–6h PRN. *Antitussive:* 1–1.5 mg/kg/24 h PO ÷ q4h; max. 30 mg/24 h; ↓ in renal/hepatic impairment.
W/P: [C (D if prolonged use or high dose at term), +] CNS depression, Hx drug abuse, severe hepatic impairment.
CI: Component sensitivity.
DISP: Tabs 15, 30, 60 mg; soln 30 mg/5 mL; Inj 15, 30 mg/mL.
SE: Drowsiness, constipation, ↓ BP.
NOTES: Usually combined w/ acetaminophen for pain or w/ agents (eg, terpin hydrate) as an antitussive; 120 mg IM = 10 mg IM morphine.

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (XIAFLEX)

WARNING: Corporal rupture and other serious penile injuries reported. Restricted distribution though XIAFLEX REMS Program.
USES: *Adult men with Peyronie's disease w/ a palpable plaque and curvature of at least 30 degrees; adults w/ Dupuytren's contracture with a palpable cord.*
ACTION: Collagenase that hydrolyzes collagen.
DOSE: (Peyronie's) 0.58 mg (0.25 mL)/injection into plaque; treatment course is max. 4 cycles (1 cycle = 2 injection procedures and 1 penile modeling procedure; see below); interval of 6 wk between cycles.
W/P: [N/A, N/A] Provider and facility must be certified by REMS program; avoid injection into other structures.
CI: Peyronie's plaques involving the penile urethra.
DISP: 0.9 mg vial w/ 3 mL diluent.
SE: Corporal rupture, severe hematoma, mild allergic reactions (pruritus).
NOTES: For details of procedure see package insert; administer only by experienced provider; If the deformity is <15 degrees after any treatment cycle subsequent cycles should not be administered

- Prior to each treatment cycle, identify the area as follows:
  - Induce an erection (eg, intracavernosal injection of 10 or 20 μg alprostadil).
  - Locate the plaque at the point of max. concavity (or focal point) in the bend of the penis.
  - Mark the point with a surgical marker, the target area in the plaque for the injection.
- Injection procedure:
  - Use local/topical anesthetic.
  - Use 1 mL syringe w/ 27G ½-inch needle to inject 0.25 mL Xiaflex transversely throughout the plaque; apply pressure/dressing as needed afterward.
  - The 2nd injection of each treatment cycle is 1–3 days after the 1st injection and located 2–3 mm apart from the 1st injection site.

- Penile modeling 1–3 days after 2nd injection:
  - Use local anesthetic if desired.
  - Grasp plaque 1 cm proximal and distal; use target plaque as fulcrum point, using both hands to apply firm steady pressure to elongate/stretch the plaque. Goal is to create bending opposite the plaque.
  - Hold pressure for 30 s and release; after 30 s rest; repeat 3 times.
  - Patient should perform self-modeling with spontaneous erection and stretch flaccid penis 3×/d.

CONIVAPTAN HCL (VAPRISOL)

USES: Euvolemic & hypervolemic hyponatremia.
ACTIONS: Dual arginine vasopressin V_{1A}/V_2 receptor antagonist.
DOSE: 20 mg IV × 1 over 30 min, then 20 mg cont IV Inf over 24 hr; 20 mg/d cont IV Inf for 1–3 more days; may ↑ to 40 mg/d if Na^+ not responding; 4 day max. use; use large vein, change site q24h.
W/P: [C, ?/−] Rapid ↑ Na^+ (> 12 mEq/L/24 h) may cause osmotic demyelination syndrome; impaired renal/hepatic function; may ↑ digoxin levels; CYP3A4 inhibitor.
CI: Hypovolemic hyponatremia; w/ CYP3A4 inhibitor; anuria.
DISP: Inj 20 mg /100 mL.
SE: Inf site reactions, headache, N/V/diarrhea, constipation, ↓ K^+, orthostatic ↓ BP, thirst, dry mouth, pyrexia, pollakiuria, polyuria, infection.
NOTES: Monitor Na^+, vol and neurologic status; D/C w/ very rapid ↑ Na^+; mix only w/ 5% dextrose.

CORTISONE

See Steroids Systemic and Topical Pages 968, 969

CYANOCOBALAMIN [VITAMIN B_{12}] (NASCOBAL)

USES: *Pernicious anemia & other vit B_{12} deficiency states; ↑ requirements d/t pregnancy; thyrotoxicosis; liver or kidney disease* supplementation may be necessary with urinary diversion if distal terminal ileum resected.
ACTIONS: Dietary vit B_{12} supl.

DOSE:

Adults: 30 µg/d × 5–10 days intranasal: 500 µg once/wk for pts in remission, 100 µg IM or SQ daily for 5–10 days, then 100 µg IM 2×/wk for 1 mo, then 100 µg IM monthly.
Peds: Use 0.2 µg/kg × 2 day test dose; if OK 30–50 µg/d for 2 or more wk (total 1,000 µg) then maint: 100 µg/mo.
W/P: [A (C if dose exceeds RDA), +].
CI: Allergy to cobalt; hereditary optic nerve atrophy; Leber disease.
DISP: Tabs 50, 100, 250, 500, 1,000, 2,500, 5,000 µg; Inj 1,000 µg/mL; intranasal (Nascobal) gel 500 µg/0.1 mL.

SE: Itching, diarrhea, headache, anxiety.
NOTES: PO absorption erratic; OK for use w/ hyperalimentation.

CYCLOPHOSPHAMIDE (CYTOXAN, NEOSAR)

USES: *Hodgkin disease & NHLs; multiple myeloma; small cell lung, breast, & ovarian cancers; mycosis fungoides; neuroblastoma; retinoblastoma; acute leukemias; allogeneic & ABMT in high doses; severe rheumatologic disorders (SLE, JRA, Wegner granulomatosis) "minimal change" nephrotic syndrome in children.*
ACTIONS: Alkylating agent.

DOSE:

Adults: (Per protocol) 500–1,500 mg/m^2; single dose at 2- to 4-wk intervals; 1.8 g/m^2–160 mg/kg (or at 12 g/m^2 in 75-kg individual) in the BMT setting (per protocols).
Peds: *SLE:* 500 mg–1g/m^2 q mo. *JRA:* 10 mg/kg q2wk; ↓ w/ renal impairment.
W/P: [D, −] w/ BM suppression, hepatic insufficiency.
CI: Component sensitivity.
DISP: Tabs 25, 50 mg; Inj 200 mg, 500 mg, 1 g, 2 g.
SE: ↓ BM; hemorrhagic cystitis, SIADH, alopecia, anorexia; N/V; hepatotox; rare interstitial pneumonitis; irreversible testicular atrophy possible; cardiotox rare; 2nd malignancies (bladder, ALL), risk 3.5% at 8 yr, 10.7% at 12 yr.
NOTES: Hemorrhagic cystitis prophylaxis: cont bladder irrigation & MESNA uroprotection; encourage hydration, long-term bladder cancer screening.

CYCLOSPORINE (GENGRAF, NEORAL, SANDIMMUNE)

WARNING: ↑ Risk neoplasm, ↑ risk skin malignancies, ↑ risk HTN and nephrotoxic.
USES: *Organ rejection in kidney, liver, heart, rheumatoid arthritis; psoriasis.*
ACTIONS: Immunosuppressant; reversible inhibition of immunocompetent lymphocytes; a calcineurin.

DOSE:
Adults & Peds: *PO:* 15 mg/kg/12 h pretransplant; after 2 wk, taper by 5 mg/wk to 5–10 mg/kg/d. *IV:* If NPO, give 1/3 PO dose IV; ↓ in renal/hepatic impairment.
W/P: [C, −] Dose-related risk of nephrotoxic/hepatotox/serious fatal infections; calcium channel antagonists (eg, diltiazem, verapamil, and nicardipine) and certain antibiotics (eg, erythromycin, doxycycline, and ketoconazole) increase levels of cyclosporine and predispose to nephrotoxicity; some antibiotics (eg, nafcillin, trimethoprim–sulfamethoxazole, isoniazid, and rifampin) and certain anticonvulsants (eg, phenytoin, phenobarbital, and carbamazepine) decrease levels of cyclosporine and thereby predispose the patient to infection; drugs that enhance the nephrotoxicity w/o altering blood levels: Amphotericin B, acyclovir, and NSAIDs; live, attenuated vaccines may be less effective; may induce fatal malignancy; many drug interactions; ↑ risk of infections after D/C.
CI: Renal impairment; uncontrolled HTN; w/ lovastatin, simvastatin.
DISP: Caps 25, 100 mg; PO soln 100 mg/mL; Inj 50 mg/mL.
SE: May ↑ BUN & Cr and mimic transplant rejection; HTN; headache; hirsutism.

NOTES: Administer in glass container; *Neoral* & *Sandimmune* not interchangeable; monitor BP, Cr, CBC, LFTs, interaction w/ St. John's wort; Levels: *Trough:* Just before next dose: *Therapeutic:* Variable 150–300 ng/mL RIA; acute cyclosporine toxicity (level > 300 ng/mL) causes vasoconstriction and renal ischemia (reversed by reducing the dosage). Chronic toxicity results in fixed vascular lesions and irreversible renal ischemia.

CYSTEAMINE (CYSTAGON, PROCYSBI DELAYED RELEASE)

USES: *Nephropathic cystinosis in children and adults.*
ACTIONS: Converts cystine into cysteine.
DOSE: New patient: ¼–⅙ of the maintenance dose; peds up to 12 yr: Maint 1.3 g/m²/d; patients >12 yrs and >110 lb: 2.0 g/d, divided 4 times (Cystagon) or BID (Procysbi); at least 2 hr after and at least 30 min before eating.
W/P: [C, +/−] Stop if skin rash develops.
DISP: *Cystagon* Caps 50, 150 mg; *Procysbi* Caps DR 25, 75 mg.
SE: Nausea, vomiting, anorexia and abdominal pain, lethargy.
NOTES: Follow WBC cystine or plasma cysteamine levels.

DABIGATRAN (PRADAXA)

WARNING: Pradaxa D/C w/o adequate anticoagulation may ↑ stroke risk; epidural or spinal hematomas may occur.
USES: *↓ Risk stroke/systemic embolism w/ nonvalvular afib; treat DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days.*
ACTIONS: Thrombin inhibitor.
DOSE: *CrCl > 30 mL/min:* 150 mg PO BID; *CrCl 15–30 mL/min*: 75 mg PO BID; do not chew/break/open caps.
W/P: [C, ?/−] Avoid w/ P-glycoprotein inducers (ie, rifampin); bleed risk ↑ w/ age.
CI: Active bleeding, prosthetic valve, hypersensitivity to dabigatran.
DISP: Caps 75, 150 mg.
SE: Bleeding, gastritis, dyspepsia.
NOTES: See label to convert between anticoagulants; caps sensitive to humidity (30-day life after opening bottle); routine coags not needed; ↑ PTT/INR/TT; w/ nl TT, no drug activity; half-life 12–17 hr.

DACLIZUMAB (ZENAPAX)

WARNING: Administer under skilled supervision in properly equipped facility.
USES: *Prevent acute organ rejection.*
ACTIONS: IL-2 receptor antagonist.
DOSE: 1 mg/kg/dose IV; 1st dose pretransplant, then 1 mg/kg q14d × 4 doses.
W/P: [C, ?].
CI: Component sensitivity.
DISP: Inj 5 mg/mL.
SE: Hyperglycemia, edema, HTN, ↓ BP, constipation, headache, dizziness, anxiety, nephrotox, pulm edema, pain, anaphylaxis/hypersens.

NOTES: Administer w/in 4 hr of prep.

DACTINOMYCIN (COSMEGEN)

WARNING: Administer under skilled supervision in properly equipped facility; powder and soln toxic, corrosive, mutagenic, carcinogenic, and teratogenic; avoid exposure and use precautions.
USES: *Choriocarcinoma, Wilms' tumor, Kaposi and Ewing sarcomas, rhabdomyosarcoma, uterine and testicular cancer.*
ACTIONS: DNA-intercalating agent.

DOSE:

Adults: 15 μg/kg/d for 5 d q3–6 wk or 400–600 μg/m^2 for 5d q3–6 wk
Peds: Sarcoma (per protocols); ↓ in renal impairment
W/P: [D, ?]
CI: Concurrent/recent chickenpox or herpes zoster; infants < 6 mo
DISP: Inj 0.5 mg
SE: Myelo/immunosuppression, severe N/V/diarrhea, alopecia, acne, hyperpigmentation, radiation recall phenomenon, tissue damage w/ extrav, hepatotox.
NOTES: Classified as antibiotic but not used as antimicrobial.

DALBAVANCIN (DALVANCE)

USES: *Acute bacterial SSSI.*
ACTIONS: Glycopeptide antibacterial (blocks cell wall synth). *Spectrum:* Includes methicillin-susceptible/resistant strains and Streptococcus pyogenes, enterococcus.
DOSE: 2-dose regimen: 1,000 mg then 500 mg 1 wk later.
W/P: [C, ?/−] Anaphylaxis reported; avoid rapid inf; ↑ALT, *C. difficile*-associated diarrhea reported.
CI: Component hypersensitivity.
DISP: 500 mg powder to reconstitute.
SE: N, D, HA.
NOTES: Not approved in peds.

DALTEPARIN (FRAGMIN)

WARNING: ↑ Risk of spinal/epidural hematoma w/ LP.
USES: *Unstable angina, non–Q-wave MI, prevent & Treat DVT following surgery (hip, abdominal), pt w/ restricted mobility, extended therapy Treat for PE/DVT in cancer pt.*
ACTIONS: LMW heparin.
DOSE: *DVT prophylaxis:* 2,500–5,000 U SQ 1–2 hr preop, then daily for 5–10 days. *Systemic anticoagulation:* 200 U/kg/d SQ or 100 U/kg BID SQ. *Cancer:* 200 IU/kg (max. 18,000 IU) SQ q24h × 30 days, mo 2–6 150 IU/kg SQ q24h (max, 18,000 IU).
W/P: [B, ?] w/ renal/hepatic impairment, active hemorrhage, cerebrovascular disease, cerebral aneurysm, severe HTN.
CI: Heparin-induced thrombocytopenia; pork product allergy; w/ mifepristone.

DISP: Inj multiple ranging from 2,500 U (16 mg/0.2 mL) to 25,000 U/mL (3.8 mL) prefilled vials.
SE: Bleeding, pain at site, ↓ plt.
NOTES: Predictable effects eliminates lab monitoring; not for IM/IV use.

DANTROLENE (DANTRIUM, REVONTO)

WARNING: Hepatotox reported; D/C after 45 days if no benefit observed.
USES: *Treat spasticity d/t upper motor neuron disorders (eg, spinal cord injuries, stroke, CP, MS); malignant hyperthermia.*
ACTIONS: Skelet al muscle relaxant.

DOSE:

Adults: *Spasticity:* 25 mg PO daily; ↑ 25 mg to effect to 100 mg PO q8h (400 mg/d max.).
Peds: 0.5 mg/kg/dose/d; ↑ by 0.5 mg/kg dose TID to 2 mg/kg/ dose TID (max. 400 mg/d).
Adults & Peds: *Malignant hyperthermia: Treat:* Cont rapid IV, start 1 mg/kg until Sxs subside or 10 mg/kg is reached. *Postcrisis follow-up:* 4–8 mg/kg/d in 3–4 ÷ doses for 1–3 days to prevent recurrence.
W/P: [C, ?] Impaired cardiac/pulm/hepatic function.
CI: Active hepatic disease; where spasticity needed to maintain posture or balance.
DISP: Caps 25, 50, 100 mg; powder for Inj 20 mg/vial.
SE: Hepatotoxic, ↑ LFTs, drowsiness, dizziness, rash, muscle weakness, diarrhea/N/V, pleural effusion w/ pericarditis, blurred vision, hep, photosensitivity.
NOTES: Monitor LFTs; avoid sunlight/EtOH/CNS depressants.

DARBEPOETIN ALFA (ARANESP)

WARNING: Associated w/ ↑ CV, thromboembolic events and/or mortality; D/C if Hgb > 12 g/dL; may increase tumor progression and death in cancer pts.
USES: *Anemia associated w/ CRF*, anemia in nonmyeloid malignancy w/ concurrent chemotherapy.
ACTIONS: ↑ Erythropoiesis, recombinant erythropoietin variant.
DOSE: 0.45 µg/kg single IV or SQ qwk; titrate, do not exceed target Hgb of 12 g/dL; use lowest doses possible, see PI to convert from *Epogen.*
W/P: [C, ?] May ↑ risk of CV &/or neurologic SE in renal failure; HTN; w/ Hx seizures.
CI: Uncontrolled HTN, component allergy.
DISP: 25, 40, 60, 100, 200, 300 µg/mL, 150 µg/0.75 mL in polysorbate or albumin excipient.
SE: May ↑ cardiac risk, CP, hypo/hypertension, N/V/diarrhea, myalgia, arthralgia, dizziness, edema, fatigue, fever, ↑ risk infection.
NOTES: Longer half-life than *Epogen*; check weekly CBC until stable.

DARIFENACIN (ENABLEX)

USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. *
ACTIONS: Muscarinic receptor antagonist.

DOSE: 7.5 mg/d PO; 15 mg/d max. (7.5 mg/d w/ mod hepatic impairment or w/ CYP3A4 inhibitor); w/ drugs metabolized by CYP2D6; swallow whole.
W/P: [C, ?/−] w/ hepatic impairment.
CI: Urinary/gastric retention, uncontrolled narrow-angle glaucoma, paralytic ileus.
DISP: Tabs ER 7.5, 15 mg.
SE: Xerostomia/ eyes, constipation, dyspepsia, abdominal pain, retention, abnormal vision, dizziness, asthenia.

DEGARELIX (FIRMAGON)

USES: *Advanced PCa.*
ACTIONS: Reversible LHRH antagonist, ↓ LH and testosterone w/o flare seen w/ LHRH agonists (transient ↑ in testosterone).
DOSE: Initial 240 mg SQ abdomen in two 120 mg doses (40 mg/mL); maint 80 mg SQ (20 mg/mL) q28d.
W/P: [Not for women] ↑ QT interval; anaphylaxis, urticaria and angioedema reported.
CI: Women.
SUPPLIED: Inj vial 120 mg (3 mL) (initial); 80 mg (4 mL) (maint).
SE: Inj site reactions, hot flashes, ↑ Wt, ↑ serum GGT.
NOTES: Requires 2 Inj initially (volume); 44% testosterone castrate (<50 ng/dL) at day 1, 96% day 3.

DENOSUMAB (PROLIA, XGEVA)

USES: *Tx osteoporosis postmenopausal women; ↑ BMD in men on ADT (*Prolia*); prevent skelet al events w/ bone mets from solid tumors (*Xgeva*).*
ACTIONS: RANK ligand (RANKL) inhibitor (human IgG2 MoAb); inhibits osteoclasts.
DOSE: *Prolia:* 60 mg SQ q6mo; *Xgeva*: 120 mg SQ q4wk; in upper arm, thigh, abdominal.
W/P: [X (Xgeva), D (Prolia), ?/−].
CI: Hypocalcemia.
DISP: Inj *Prolia* 60 mg/mL; *Xgeva* 70 mg/mL.
SE: ↓ Ca^{2+}, hypophosphatemia, serious infections, dermatitis, rashes, eczema, jaw osteonecrosis, pancreatitis, pain (musculoskelet al, back), fatigue, asthenia, dyspnea, N, abdominal pain, flatulence, hypercholesterolemia, anemia, cystitis.
NOTES: Give w/ calcium 1.000 mg & vit D 400 IU/d.

DESMOPRESSIN (ddAVP, DDAVP NASAL SPRAY, STIMATE)

WARNING: (Parenteral form) Not for hemophilia B or w/ factor VIII antibody; not for hemophilia A w/ factor VIII levels <5%.
USES: **Oral:* Central diabetes insipidus; primary nocturnal enuresis, bleeding d/t uremia; *Nasal spray:* Central diabetes insipidus; *Stimate Nasal spray:* Hemophilia A, & type I von Willebrand disease; *Parenteral:* Central diabetes insipidus; hemophilia A, & type I von Willebrand disease.*
ACTIONS: Synthetic analog of vasopressin (human ADH) (1-deamino-8-D-arginine vasopressin, ddAVP; ddAVP is a neuropeptide that differs from endogenous vasopressin by a

2-amino acid substitute which gives the compound potent antidiuretic effect but no vasopressor activity); ↑ factor VIII.
DOSE: *DI: Intranasal:* **Adults:** 0.1–0.4 mL (10–40 μg/d in 1–3 ÷ doses). **Peds:** ***3 mo–12 yr:*** 0.05–0.3 mL/d (5 μg/d) in 1 or 2 doses. *Parenteral:*
Adults: 0.5–1 mL (2–4 μg/d in 2 ÷ doses); converting from nasal to parenteral, use 1/10 nasal dose. *PO:* .05 mg BID; ↑ to max. of 1.2 mg. *Hemophilia A & von Willebrand disease (type I):*
Adults & Peds: ***>10 kg:*** 0.3 μg/kg in 50 mL NS, Inf over –30 min. **Peds:** ***<10 kg:*** As above w/ dilution to 10 mL w/ NS. *Nocturnal enuresis:* ***>6 yr:*** 20 μg intranasally hs or 0.2–0.6 mg hs PO.
W/P: [B, M] Avoid overhydration.
CI: (Varies by manufacturer) Hemophilia B; CrCl <50 mL/min, severe classic von Willebrand disease; pts w/ factor VIII antibodies; hyponatremia.
DISP: Tabs 0.1, 0.2, 0.4 mg; Inj 4 μg/mL; nasal spray 0.1 mg/mL (10 μg/spray) 1.5 mg/mL (150 μg/spray)
SE: Facial flushing, headache, dizziness, vulval pain, nasal congestion, pain at Inj site, ↓ Na^+, H_2O intoxication.
NOTES: In very young & old pts, ↓ fluid intake to avoid H_2O intoxication & ↓ Na^+;↓ urine output, ↑ urine osm, ↓ plasma osm; GI tract absorption limited (5%), the oral form is 1/10–1/20th the potency of the nasal form. Use of ddAVP for nocturia treatment is off-label (non-FDA approved) in the US. ddAVP has potentially severe side effects and should not be used over the age of 65.

DEXAMETHASONE (DECADRON)

See Steroids, Systemic and Steroids, Topical Pages 968, 969

DEXPANTHENOL (ILOPAN-CHOLINE [ORAL] , ILOPAN)

USES: *Minimize paralytic ileus, Treat postop distention.*
ACTIONS: Cholinergic agent.

DOSE:

Adults: *Relief of gas:* 2–3 tabs PO TID. *Prevent postop ileus:* 250–500 mg IM stat, repeat in 2 hr, then q6h PRN. *Ileus:* 500 mg IM stat, repeat in 2 hr, then q6h, PRN.
W/P: [C, ?].
CI: Hemophilia, mechanical bowel obst.
DISP: Inj 250 mg/mL; cream 2% (Panthoderm cream [OTC]).
SE: GI cramps.

DIAZEPAM (VALIUM, DIASTAT, GENERIC) [C-IV]

USES: *Anxiety, EtOH withdrawal, muscle spasm, status epilepticus, panic disorders, amnesia, preop sedation.*
ACTIONS: Benzodiazepine.

DOSE:

Adults: *Anxiety, muscle spasm:* 2–10 mg PO BID–QID or IM/IV q3–4h PRN. *Preop:* 5–10 mg PO or IM 20–30 min or IV just prior to procedure.
Peds: *Sedation, muscle relaxation:* 0.04–0.3 mg/kg/dose q2–4h IM or IV to max. of 0.6 mg/kg in 8 hr, or 0.12–0.8 mg/kg/24 h PO ÷ TID–QID; ↓ w/ hepatic impairment.
W/P: [D, ?/−].
CI: Coma, CNS depression, resp depression, narrow-angle glaucoma, severe uncontrolled pain, pregnancy.
DISP: Tabs 2, 5, 10 mg; soln 5 mg/mL; Inj 5 mg/mL; rectal gel 2.5, 5, 10, 20 mg/mL.
SE: Sedation, amnesia, ↓ HR, ↓ BP, rash, ↓ resp rate.
NOTES: 5 mg/min IV max in adults or 1–2 mg/min in peds (resp arrest possible); IM absorption erratic; avoid abrupt D/C.

DIBUCAINE (NUPERCAINAL) [OTC]

USES: *Hemorrhoids & minor skin conditions.*
ACTIONS: Topical anesthetic.
DOSE: Insert PR w/ applicator BID & after each bowel movement; apply sparingly to skin.
W/P: [C, ?] Topical use only.
CI: Component sensitivity.
DISP: 1% oint w/ rectal applicator.
SE: Local irritation, rash.

DICLOFENAC, ORAL (CATAFLAM, VOLTAREN, VOLTAREN-XR, ZORVOLEX)

WARNING: May ↑ risk of CV events & GI bleeding; CI in postop CABG.
USES: *Arthritis (RA/OA) & pain, oral and topical, actinic keratosis.*
ACTIONS: NSAID.
DOSE: RA/OA: 150–200 mg/d ÷ 2–4 doses DR; 100 mg/d XR; *Zorvolex*: 18 or 35 mg PO TID; w/ food or milk.
W/P: [C (avoid after 30 wk), ?] CHF, HTN, renal/hepatic dysfunction, & Hx PUD, asthma; different forms not interchangeable.
CI: NSAID/aspirin ASA allergy; porphyria; following CABG.
DISP: Tabs 50 mg; tabs DR 25, 50, 75, 100 mg; XR tabs 100 mg; *Zorvolex*: 18, 35 mg caps.
SE: *Oral:* Abd cramps, heartburn, GI ulceration, rash, interstitial nephritis.
NOTES: Do not crush tabs; watch for GI bleed; check CBC, LFTs.

DICLOXACILLIN (GENERIC)

USES: *Treat of pneumonia, skin, & soft-tissue infections, & osteomyelitis caused by penicillinase-producing staphylococci.*
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum: S. aureus* & *Streptococcus.*

DOSE:

Adults: 150–500 mg QID (2 g/d max.)
Peds: ***< 40 kg:*** 12.5–100 mg/kg/d ÷ QID; take on empty stomach.
W/P: [B, ?].
CI: Component or PCN sensitivity.
DISP: Caps 125, 250, 500 mg.
SE: N/diarrhea, abdominal pain.
NOTES: Monitor PTT if pt on warfarin.

DILTIAZEM (CARDIZEM, CARDIZEM CD, CARDIZEM LA, CARDIZEM SR, CARTIA XT, DILACOR XR, DILTIA XT, TAZTIA XT, TIAZAC)

USES: *Angina, prevention of reinfarction, HTN, AF or A flutter, & PAT.*
ACTIONS: Calcium channel blocker.
DOSE: *HTN:* SR: 60–120 mg PO BID; ↑ to 360 mg/d max. *CD or XR:* 120–360 mg/d (max. 540 mg/d) or LA 180–360 mg/d.
W/P: [C, +] ↑ Effect w/ amiodarone, cimetidine, fentanyl, Li, cyclosporine, digoxin, β-blockers, theophylline.
CI: SSS, AV block, ↓ BP, AMI, pulm congestion.
DISP: *Cardizem CD:* Caps 120, 180, 240, 300, 360 mg; *Cardizem LA*: Tabs 120, 180, 240, 300, 360, 420 mg; *Cardizem SR:* Caps 60, 90, 120 mg; *Cardizem:* Tabs 30, 60, 90, 120 mg; *Cartia XT:* Caps 120, 180, 240, 300 mg; *Dilacor XR:* Caps 120, 180, 240 mg; *Diltia XT:* Caps 120, 180, 240 mg; *Tiazac:* Caps 120, 180, 240, 300, 360, 420 mg; Inj 5 mg/mL; *Taztia XT:* 120, 180, 240, 300, 360 mg.
SE: Gingival hyperplasia, ↓ HR, AV block, ECG abnormalities, peripheral edema, dizziness,

headache.
NOTES: *Cardizem CD, Dilacor XR, & Tiazac* ***not*** interchangeable.

DIMETHYL SULFOXIDE [DMSO] (RIMSO-50)

USES: *Interstitial cystitis.*
ACTIONS: Unknown.
DOSE: Intravesical, 50 mL, retain for 15 min; repeat q2wk until relief.
W/P: [C, ?].
CI: Component sensitivity.
DISP: 50% soln.
SE: Cystitis, eosinophilia, GI, & taste disturbance.

DIPHENHYDRAMINE (BENADRYL, GENERIC) [OTC]

USES: *Treat & prevent allergic reactions, motion sickness, potentiate narcotics, sedation, cough suppression, & Treat of extrapyramidal reactions.*
ACTIONS: Antihistamine, antiemetic.

DOSE:

Adults: 25–50 mg PO, IV, or IM TID–QID.
Peds: ***>2 yr:*** 5 mg/kg/24 h PO or IM ÷ q6h (max. 300 mg/d); ↑ dosing interval w/ mod–severe renal insufficiency.
W/P: [B, −] Elderly, narrow-angle glaucoma, BPH, w/ MAOI.
CI: Acute asthma.
DISP: Tabs & caps 25, 50 mg; chew tabs 12.5 mg; elixir 12.5 mg/ 5 mL; syrup 12.5 mg/5 mL; liq 12.5 mg/5 mL; Inj 50 mg/mL, cream, gel, liq 2%.
SE: Anticholinergic (eg, xerostomia, urinary retention, sedation).

DIPHENOXYLATE/ATROPINE (LOMOTIL, LONOX, GENERIC) [C-V]

USES: *Diarrhea.*
ACTIONS: Constipating meperidine congener, ↓ GI motility.

DOSE:

Adults: Initial, 5 mg PO TID–QID until controlled, then 2.5–5 mg PO BID; 20 mg/d max.
Peds: ***>2 yr:*** 0.3–0.4 mg/kg/24 h (of diphenoxylate) BID–QID, 10 mg/d max.
W/P: [C, ?/−] Elderly, w/ renal impairment.
CI: Obstructive jaundice, diarrhea d/t bacterial infection; children <2 yr.
DISP: Tabs 2.5 mg diphenoxylate/0.025 mg atropine; liq 2.5 mg diphenoxylate/0.025 mg atropine/5 mL.
SE: Drowsiness, dizziness, xerostomia, blurred vision, urinary retention, constipation.

DOCETAXEL (TAXOTERE)

WARNING: Do not administer if neutrophil count <1,500 cells/mm^3; severe reactions possible in hepatic dysfunction.

USES: *Breast, ovarian, non-small cell lung, gastric, head, neck, and prostate cancers.*
ACTIONS: Antimitotic agent; promotes microtubular aggregation; semisynthetic taxoid.
DOSE: *Prostate cancer:* 75 mg/m^2 over 1 hr IV q3wk w/ prednisone 5 mg PO BID; ↓ dose w/ ↑ bili levels.
W/P: [D, −].
CI: Sensitivity to meds w/ polysorbate 80, component sensitivity.
DISP: Inj 20 mg/0.5 mL, 80 mg/2 mL.
SE: ↓ BM, neuropathy, N/V, alopecia, fluid retention syndrome; cumulative doses of 300–400 mg/m^2 w/o steroid prep & post-Tx & 600–800 mg/m^2 w/ steroid prep; allergy possible (rare w/ steroid prep).
NOTES: Check bili/SGOT/SGPT prior to each cycle; frequent CBC during Treat.

DOCUSATE CALCIUM (SURFAK)/DOCUSATE POTASSIUM (DIALOSE)/ DOCUSATE SODIUM (DOSS, COLACE) [OTC]

USES: *Constipation; adjunct to painful anorectal conditions (hemorrhoids).*
ACTIONS: Stool softener.

DOSE:

Adults: 50–500 mg PO ÷ daily–QID.
Peds: ***Infants–3 yr:*** 10–40 mg/24 h ÷ daily–QID. ***3–6 yr:*** 20–60 mg/24 h ÷ daily–QID. ***6–12 yr:*** 40–150 mg/24 h ÷ daily–QID.
W/P: [C, ?].
CI: Use w/ mineral oil; intestinal obst, acute abdominal pain, N/V.
DISP: *Calcium:* Caps 50, 240 mg. *Potassium:* Caps 100, 240 mg. *Na:* Caps 50, 100 mg; syrup 50, 60 mg/15 mL; liq 150 mg/15 mL; soln 50 mg/ mL; enema 283 mg/mL.
SE: Rare abdominal cramping, diarrhea.
NOTES: Take w/ full glass of water; no laxative action; do not use >1 wk.

DORIPENEM (DORIBAX)

USES: *Complicated intra-abdominal infection and UTI including pyelo.*
ACTIONS: Carbapenem, ↓ cell wall synth, a β-lactam. *Spectrum:* Excellent gram(+) (except MRSA and *Enterococcus* sp), excellent gram(−) coverage including β-lactamase producers, good anaerobic.
DOSE: 500 mg IV q8h, ↓ w/ renal impairment.
W/P: [B, ?].
CI: Carbapenem β-lactams hypersens.
DISP: 250, 500 mg vial.
SE: Headache, N/diarrhea, rash, phlebitis.
NOTES: May ↓ valproic acid levels; overuse may ↑ bacterial resistance; monitor for *C. difficile*-associated diarrhea 0.5%.
SE: Irritation, bitter taste, superficial keratitis, ocular allergic reaction.

DOXAZOSIN (CARDURA, CARDURA XL, GENERIC)

USES: *HTN & symptomatic BPH.*
ACTIONS: α_1-Adrenergic blocker; relaxes bladder neck smooth muscle.

DOSE:
Adult: *HTN:* Initial 1 mg/d PO; may be ↑ to 16 mg/d PO. *BPH:* Initial 1 mg/d PO, may ↑ to 8 mg/d; XL 4–8 mg q a.m.
Peds: (not FDA) <6 yr 0.5 mg daily; >6 yr 1 mg daily.
W/P: [C, ?] w/ Liver impairment; use w/ PDE5 inhibitor (eg, sildenafil) can cause ↓ BP.
CI: Component sensitivity.
DISP: Tabs 1, 2, 4, 8 mg; XL 4, 8 mg.
SE: Dizziness, headache, drowsiness, fatigue, malaise, sexual dysfunction, doses >4 mg ↑ postural ↓ BP risk; intraoperative floppy iris syndrome.
NOTES: 1st dose hs; syncope may occur w/in 90 min of initial dose.

DOXORUBICIN (ADRIAMYCIN, GENERIC)

USES: *Acute leukemias; Hodgkin disease & NHLs; soft tissue, osteo & Ewing sarcoma; Wilms' tumor; neuroblastoma; bladder, breast, ovarian, gastric, thyroid, & lung cancers*; intravesical for bladder cancer.
ACTIONS: Intercalates DNA; ↓ DNA topoisomerase I & II.
DOSE: 60–75 mg/m^2 q3wk; ↓ w/ hepatic impairment; IV use only ↓ cardiotox w/ weekly (20 mg/m^2/wk) or cont Inf (60–90 mg/m^2 over 96 hr); (per protocols).
W/P: [D, ?].
CI: Severe CHF, cardiomyopathy, pre-existing ↓ BM, previous Treat w/ total cumulative doses of doxorubicin, idarubicin, daunorubicin.
DISP: Inj 10, 20, 50, 150, 200 mg.
SE: ↓ BM, venous streaking & phlebitis, N/V/diarrhea, mucositis, radiation recall phenomenon, cardiomyopathy rare (dose related).
NOTES: Limit of 550 mg/m^2 cumulative dose (400 mg/m^2 w/ prior mediastinal irradiation); dexrazoxane may limit cardiac tox; tissue damage w/ extrav; red/orange urine; tissue vesicant w/ extrav, treat w/ dexrazoxane; liposomal formulations available; intravesical regimens include 30–50 mg in 25–50 mL saline, retain for 2 hr.

DOXYCYCLINE (ADOXA, ORACEA, VIBRAMYCIN, VIBRA-TABS)

USES: *Broad-spectrum antibiotic* acne vulgaris, uncomplicated GC, chlamydia, PID, Lyme disease, skin infections, anthrax, malaria prophylaxis.
ACTIONS: Tetracycline; bacteriostatic; ↓ protein synth. *Spectrum:* Limited gram(+) and (−), *Rickettsia* sp, *Chlamydia, M. pneumoniae, B. anthracis*

DOSE:

Adults: 100 mg PO q12h on 1st day, then 100 mg PO daily–BID or 100 mg IV q12h; acne q day, chlamydia × 7 days, Lyme × 21 days, PID × 14 days.
Peds: ***>8 yr:*** 5 mg/kg/24 h PO, 200 mg/d max ÷ daily–BID.
W/P: [D, −] hepatic impairment.
CI: Children <8 yr, severe hepatic dysfunction.

DISP: Tabs 20, 50, 75, 100, 150 mg; caps 50, 75, 100, 150 mg; *Oracea* 40 mg caps (30 mg timed release, 10 mg DR); syrup 50 mg/5 mL; susp 25 mg/5 mL; Inj 100/vial.
SE: Diarrhea, GI disturbance, photosensitivity.
NOTES: ↓ Effect w/ antacids; tetracycline of choice w/in renal impairment.

d-PENICILLAMINE (CUPRIMINE, DEPEN)

WARNING: Physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special dosage considerations, and therapeutic benefits. Penicillamine should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to report promptly any symptoms suggesting toxicity.
USES: *Refractory rheumatoid arthritis, Wilson disease, cystinuria.*
ACTIONS: Chelating agent.

DOSE:
Adult: *Cystinuria:* Titrate to keep cystine excretion 100–200 mg/d (<100 mg/d with history of urolithiasis), 1–4 g/d PO in divided doses q6h, typical dose 2 g/d.
Peds: Titrate to keep cystine excretion 100–200 mg/d (<100 mg/d with history of urolithiasis), 30 mg/kg/d in 4 divided doses.
W/P: [D, −]; w/ other meds that act as hematopoietic depressants.
CI: Hypersensitivity to components, renal insufficiency, previous aplastic anemia due to drug, pregnancy.
DISP: Caps 250 mg.
SE: Allergic reactions in up to 33%; agranulocytosis, aplastic anemia, diarrhea, anorexia, abdominal pain, dermatologic manifestations, nephrotic syndrome.
NOTES: Do not d/c therapy in cystinuria; interruptions of a few days can cause hypersensitivity with resumption of therapy; monitor CBC, UA (proteinuria, hematuria), urinary cysteine levels; use THIOLA if intolerant of d-penicillamine.

DULOXETINE (CYMBALTA)

WARNING: Antidepressants may ↑ risk of suicidality; consider risks/benefits of use. Closely monitor for clinical worsening, suicidality, or behavior changes; not for peds.
USES: *Depression, diabetic peripheral neuropathic pain, generalized anxiety disorder (GAD), fibromyalgia, chronic osteoarthritis & back pain.*
ACTIONS: Selective serotonin & norepinephrine reuptake inhibitor (SSNRI).
DOSE: *Depression:* 40–60 mg/d PO ÷ BID. *DM neuropathy:* 60 mg/d PO; *GAD:* 60 mg/d, max. 120 mg/d; *Fibromyalgia, Osteoarthritis/back pain:* 30–60 mg/d, 60 mg/d max.
W/P: [C, ?/−]; use in 3rd tri; avoid if CrCl <30 mL/min, narrow-angle glaucoma, w/ fluvoxamine, inhibitor of CYP2D6 TCAs, phenothiazines, type class 1C anti-arrhythmics.
CI: ↑ risk serotonin syndrome w/ MAOIs [linezolid or IV meth blue] MAOI use w/in 14 days, w/ thioridazine, narrow-angle glaucoma, hepatic insufficiency.
DISP: Caps delayed release 20, 30, 60 mg.
SE: N, dry mouth, somnolence, fatigue, constipation, ↓ appetite, hyperhidrosis.
NOTES: Swallow whole; monitor BP; avoid abrupt D/C; approved for stress incontinence in

some countries (not US).

DUTASTERIDE (AVODART)

USES: *Symptomatic BPH to improve symptoms, ↓ risk of retention and BPH surgery alone or in combo w/ tamsulosin.*
ACTIONS: 5α-reductase inhibitor; ↓ intracellular dihydrotestosterone (DHT).
DOSE: *Monotherapy:* 0.5 mg PO/d. *Combination:* 0.5 mg PO q day w/ tamsulosin 0.4 mg q day.
W/P: [X, −] Hepatic impairment; pregnant women should not handle pills; R/O cancer before starting.
CI: Women, peds.
DISP: Caps 0.5 mg.
SE: ↑ Testosterone, ↑ TSH, impotence, ↓ libido, gynecomastia, ejaculatory disturbance, may ↑ risk of high-grade prostate cancer.
NOTES: No blood donation until 6 mo after D/C; ↓ PSA, check new baseline PSA at 6 mo (corrected PSA × 2); any PSA rise on dutasteride suspicious for cancer; now available in fixed dose combination w/ tamsulosin (see *Jalyn*); not approved to prevent prostate cancer.

DUTASTERIDE/TAMSULOSIN (JALYN)

USES: *Symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.*
ACTIONS: 5α-Reductase inhibitor (↓ intracellular DHT) w/ α-blocker.
DOSE: 1 capsule daily after same meal.
W/P: [X, −] w/ CYP3A4 and CYP2D6 inhibitor may ↑ SEs; pregnant women should not handle pills; R/O cancer before starting; intraoperative floppy iris syndrome (tamsulosin related) discuss w/ ophthalmologist before cataract surgery; rare priapism; w/ warfarin; may ↑ risk of high-grade prostate cancer.
CI: Women, peds, component sens.
DISP: Caps 0.5 mg dutasteride w/ 0.4 mg tamsulosin.
SE: Impotence, decreased libido, ejaculation disorders, and breast disorders.
NOTES: No blood donation until 6 mo after D/C; ↓ PSA, check new baseline PSA at 6 mo (corrected PSA × 2); any PSA rise on dutasteride suspicious for cancer (see dutasteride and tamsulosin individual listings).

ECONAZOLE (ECOZA, SPECTAZOLE, GENERIC)

USES: *Tinea, cutaneous *Candida,* & tinea versicolor Infxns.*
ACTIONS: Topical antifungal.
DOSE: Apply to areas BID *Candida;* (daily for tinea versicolor) for 2–4 wk.
W/P: [C, ?].
CI: Component sensitivity.
DISP: Topical cream 1%; *Ecoza* foam 1%.
SE: Local irritation, pruritus, erythema.
NOTES: Early Sx/clinical improvement; complete course to avoid recurrence.

ENALAPRIL (ENALAPRILAT, EPANED KIT, VASOTEC)

WARNING: ACE inhib used during PRG can cause fet al injury & death.
USES: *HTN, CHF, LVD*, DN.
ACTIONS: ACE inhib.

DOSE:

Adults: 2.5–40 mg/d PO; 1.25 mg IV q6h.
Peds: 0.05–0.08 mg/kg/d PO q12–24h; ↓ w/ renal impairment.
W/P: [C (1st tri; D 2nd & 3rd tri), +] D/C immediately w/ PRG, w/ NSAIDs, K^+ suppl.
CI: Bilateral RAS, angioedema.
DISP: Tabs 2.5, 5, 10, 20 mg; *Enalaprilat* IV 1.25 mg/mL; *Epaned Kit* powder for oral (1 mg/mL).
SE: ↓ BP w/ initial dose (esp w/ diuretics), ↑ K^+, ↑ Cr, cough, angioedema.
NOTES: Monitor Cr; D/C diuretic for 2–3 days prior to start.

ENOXAPARIN (LOVENOX)

WARNING: Recent or anticipated epidural/spinal anesthesia, ↑ risk of spinal/epidural hematoma w/ subsequent paralysis.
USES: *Prevention & Treat of DVT; Treat PE; unstable angina & non–Q-wave MI.*
ACTIONS: LMW heparin; inhibit thrombin by complexing w/ antithrombin III.

DOSE:

Adults: *Prevention:* 30 mg SQ BID or 40 mg SQ q24h. *DVT/PE Treat:* 1 mg/kg SQ q12h or 1.5 mg/kg SQ q24h.*;* CrCl < 30 mL/min ↓ to 1 mg/kg SQ q day.
Peds: *Prevention:* 0.5 mg/kg SQ q12h. *DVT/PE Treat:* 1 mg/kg SQ q12h; ↓ dose w/ CrCl < 30 mL/min.
W/P: [B, ?] Not for prophylaxis in prosthetic heart valves.
CI: Active bleeding, heparin-induced thrombocytopenia Ab, heparin, pork sens.
DISP: Inj 10 mg/0.1 mL (30-, 40-, 60-, 80-, 100-, 120-, 150-mg syringes); 300-mg/mL multi-dose vial.
SE: Bleeding, hemorrhage, bruising, thrombocytopenia, fever, pain/hematoma at site, ↑ AST/ALT.
NOTES: No effect on bleeding time, plt function, PT, or aPTT; monitor plt for heparin-induced thrombocytopenia, clinical bleeding; may monitor antifactor Xa; not for IM.

ENZALUTAMIDE (XTANDI)

USES: *Metastatic castration-resistant prostate cancer w/ or w/o previous docetaxel.*
ACTIONS: Androgen receptor inhibitor.
DOSE: (men only): 160 mg daily, do not chew/open caps.
W/P: [X, −] w/ seizure risk; avoid w/ strong CYP2C8 inhibitor, strong/mod CYP3A4 or CYP2C8 induc, avoid CPY3A4, CYP2C9, CYP2C19 substrates w/ narrow therapeutic index.
CI: Pregnancy
DISP: Caps 40 mg.

SE: Headache, dizziness, insomnia, fatigue, anxiety, MS pain, muscle weakness, paresthesia, back pain, spinal cord compression, cauda equina syndrome, arthralgias, edema, URI, lower resp infection, hematuria, ↑ BP.
NOTES: If on warfarin check INR

EPHEDRINE (GENERIC)

USES: *Acute bronchospasm, bronchial asthma, nasal congestion*, ↓ BP, narcolepsy, enuresis, & myasthenia gravis.
ACTIONS: Sympathomimetic; stimulates α/β receptors; bronchodilator.

DOSE:
Adults: *Congestion:* 12.5–25 mg PO q4h PRN w/ expectorant; ↓ *BP:* 25–50 mg IV q5–10min, 150 mg/d max.
Peds: 0.2–0.3 mg/kg/dose IV q4–6h PRN.
W/P: [C, ?/−].
CI: Arrhythmias; narrow-angle glaucoma.
DISP: Caps 25 mg; Inj 50 mg/mL; nasal spray 0.25%.
SE: CNS stimulation (nervousness, anxiety, trembling), tachycardia, arrhythmia, HTN, xerostomia, dysuria.
NOTES: Protect from light; monitor BP, HR, urinary output; can cause false (+) amphetamine EMIT; take last dose 4–6 hr before hs; abuse potential, OTC sales mostly banned/restricted retrograde ejaculation 50 mg QID × 2 wk.

EPOETIN ALFA [ERYTHROPOIETIN, EPO] (EPOGEN, PROCRIT)

WARNING: ↑ Mortality, serious CV/thromboembolic events, and tumor progression. Renal failure pts experienced ↑ greater risks (death/CV events) on erythropoiesis-stimulating agents (ESAs) to target Hgb levels 11 g/dL. Maintain Hgb 10–12 g/dL. In cancer pt, ESAs ↓ survival/time to progression in some cancer when dosed Hgb ≥ 2 g/dL. Use lowest dose needed. Use only for myelosuppressive chemotherapy. D/C following chemotherapy. Preop ESA ↑ DVT. Consider DVT prophylaxis.
USES: *CRF-associated anemia, zidovudine treat in HIV-infected pts, cancer chemotherapy; ↓ transfusions associated w/ surgery.*
ACTIONS: Induces erythropoiesis.

DOSE:
Adults & Peds: 50–150 U/kg IV/SQ 3×/wk; adjust dose q4–6wk PRN. *Surgery:* 300 U/kg/d × 10 days before to 4 days after; ↓ dose if Hct ~36% or Hgb, ↑ > ≅ 12 g/dL or Hgb ↑ >1 g/dL in 2-wk period; hold dose if Hgb >12 g/dL.
W/P: [C, ?/−].
CI: Uncontrolled HTN.
DISP: Inj 2,000, 3,000, 4,000, 10,000, 20,000, 40,000 U/mL.
SE: HTN, headache, fatigue, fever, tachycardia, N/V.
NOTES: Refrigerate; monitor baseline & posttreatment Hct/Hgb, BP, ferritin.

ERTAPENEM (INVANZ)

USES: *Complicated intra-abdominal, acute pelvic, & skin infections, pyelonephritis, community-acquired pneumonia.*
ACTIONS: α-carbapenem; β-lactam antibiotic, ↓ cell wall synth. *Spectrum*: Good gram(+/–) & anaerobic coverage, not *Pseudomonas,* PCN-resistant pneumococci, MRSA, *Enterococcus,* β-lactamase (+) *H. influenzae, Mycoplasma, Chlamydia.*

DOSE:

Adults: 1 g IM/IV daily; 500 mg/d in CrCl <30 mL/min.
Peds: ***3 mo–12 yr:*** 15 mg/kg BID IM/IV, max. 1 g/d.
W/P: [B, ?/−] seizure Hx, CNS disorders, β-lactam & multiple allergies, probenecid ↓ renal clearance.
CI: Component hypersens or amide anesthetics.
DISP: Inj 1 g/vial.
SE: Headache, N/V/diarrhea, Inj site reactions, thrombocytosis, ↑ LFTs.
NOTES: Can give IM × 7 days, IV × 14 days; 137 mg Na^+ (6 mEq)/g ertapenem; do not mix with dextrose infusion.

ERYTHROMYCIN (E-MYCIN, EES, ERY-TAB, ERYPED, ILOTYCIN, GENERIC)

USES: *Bacterial infections; bowel prep, acne vulgaris *; ↑ GI motility (*prokinetic*).
ACTIONS: Bacteriostatic; interferes w/ protein synth. *Spectrum:* Group A streptococci (*S. pyogenes*), *S. pneumoniae, N. gonorrhoeae* (if PCN-allergic), *Legionella, M. pneumonia.*

DOSE:

Adults: *Base* 250–500 mg PO q6–12h or *ethylsuccinate* 400–800 mg q6–12h; 500 mg–1 g IV q6h. *Prokinetic:* 250 mg PO TID 30 min ac.
Peds: 30–50 mg/kg/d PO ÷ q6–8h or 20–40 mg/kg/d IV ÷ q6h, max. 2 g/d.
W/P: [B, +] Pseudomembranous colitis risk, ↑ tox of carbamazepine, cyclosporine, digoxin, methylprednisolone, theophylline, felodipine, warfarin, simvastatin/lovastatin; ↓ sildenafil dose w/ use.
CI: Hepatic impairment, pre-existing liver disease (estolate), use w/ pimozide ergotamine dihydroergotamine.
DISP: *Lactobionate (Ilotycin): Powder for Inj* 500 mg, 1 g. *Base:* Tabs 250, 333, 500 mg; caps 250 mg. *Stearate (Erythrocin):* Tabs 250, 500 mg. *Ethylsuccinate (EES, EryPed):* Chew tabs 200 mg; tabs 400 mg; susp 200, 400 mg/5 mL.
SE: Headache, abdominal pain, N/V/diarrhea; ↑ QT, torsades de pointes, ventricular arrhythmias/tachycardias (rarely); cholestatic jaundice (estolate).
NOTES: 400 mg ethylsuccinate = 250 mg base/estolate; w/ food minimizes GI upset; lactobionate contains benzyl alcohol (caution in neonates).

ESTERIFIED ESTROGENS (MENEST)

WARNING: ↑ Risk endometrial cancer. Do not use in the prevention of CV disease or

dementia; ↑ risk of MI, stroke, breast cancer, PE, DVT, in postmenopausal.
USES: *Vasomotor Sxs or vulvar/Vag atrophy w/ menopause; female hypogonadism, palliation of advanced prostate cancer.*
ACTIONS: Estrogen supl.
DOSE: *Menopausal vasomotor Sx:* 0.3–1.25 mg/d, cyclically 3 wk on, 1 wk off; add progestin 10–14 days w/ 28-day cycle w/ uterus intact; *Vulvovaginal atrophy:* Same regimen except use 0.3–1.25 mg; *Hypogonadism:* 2.5–7.5 mg/d PO × 20 days, off × 10 days; add progestin 10–14 days w/ 28-day cycle w/ uterus intact.
W/P: [X, −].
CI: Undiagnosed genital bleeding, breast cancer, estrogen-dependent tumors, thromboembolic disorders, thrombophlebitis, recent MI, pregnancy, severe hepatic disease.
DISP: Tabs 0.3, 0.625, 1.25, 2.5 mg.
SE: N, headache, bloating, breast enlargement/tenderness, edema, venous thromboembolism, hypertriglyceridemia, gallbladder disease.
NOTES: Use lowest dose for shortest time (see WHI data [www.whi.org]).

ESTRADIOL, GEL (DIVIGEL)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Vasomotor Sx in menopause.*
ACTIONS: Estrogen.
DOSE: 0.25 g q day on right or left upper thigh (alternate).
W/P: [X, +/−] May ↑ thyroid binding globulin (TBD) w/ thyroid disease.
CI: Alcohol, caution around flames until dry, not for Vag use.

ESTRADIOL, METERED GEL (ELESTRIN, ESTROGEL)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Postmenopausal vasomotor Sxs.*
ACTIONS: Estrogen.
DOSE: Apply 0.87–1.7 g to upper arm skin q day; add progestin × 10–14 days/28-day cycle w/ intact uterus; use lowest effective estrogen dose.
W/P: [X, ?].
CI: AUB, breast cancer, estrogen-dependent tumors, hereditary angioedema, thromboembolic disorders, recent MI, PREGNANCY, severe hepatic disease.
DISP: Gel 0.06%; metered dose/activation.
SE: Thromboembolic events, MI, stroke, ↑ BP, breast/ovarian/endometrial cancer, site reactions, Vag spotting, breast changes, abdominal bloating, cramps, headache, fluid retention.
NOTES: Wait >25 min before sunscreen; avoid concomitant use for >7 days; BP, breast exams.

ESTRADIOL, ORAL (DELESTROGEN, ESTRACE, FEMTRACE, GENERIC)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Atrophic vaginitis, menopausal vasomotor Sxs, prevent osteoporosis, ↑ low estrogen levels, palliation breast and PCa.*
ACTIONS: Estrogen.
DOSE: *PO:* 1–2 mg/d, adjust PRN to control Sxs. *Vag cream:* 2–4 g/d × 2 wk, then 1 g 1–3×/wk. *Vasomotor Sx/Vag atrophy:* 10–20 mg IM q4wk, D/C or taper at 3- to 6-mo intervals. *Hypoestrogenism:* 10–20 mg IM q4wk. *PCa:* 30 mg IM q12wk.
W/P: [X, −].
CI: Genital bleeding of unknown cause, breast cancer, porphyria, estrogen-dependent tumors, thromboembolic disorders, thrombophlebitis; recent MI; hepatic impairment.
DISP: Tabs 0.5, 1, 2 mg; depot Inj (*Delestrogen*) 10, 20, 40 mg/mL.
SE: N, headache, bloating, breast enlargement/tenderness, edema, ↑ triglycerides, venous thromboembolism, gallbladder disease.
NOTES: When estrogen used in postmenopausal w/ uterus, use w/ progestin.

ESTRADIOL, SPRAY (EVAMIST)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr)
USES: *Vasomotor Sx in menopause.*
ACTIONS: Estrogen supl.
DOSE: 1 spray on inner surface of forearm.
W/P: [X, +/−] May ↑ PT/PTT/plt aggregation w/ thyroid disease.
CI: Undiagnosed genital bleeding, breast cancer, estrogen-dependent tumors, thromboembolic disorders, thrombophlebitis, recent MI, PREGNANCY, severe hepatic disease.
DISP: 1.53 mg/ spray (56-spray container).
SE: N, headache, bloating, breast enlargement/tenderness, edema, venous thromboembolism, ↑ BP, hypertriglyceridemia, gallbladder disease.
NOTES: Contains alcohol, caution around flames until dry; not for Vag use.

ESTRADIOL, TRANSDERMAL (ALORA, CLIMARA, ESTRADERM, VIVELLE DOT)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr)
USES: *Severe menopausal vasomotor Sxs; female hypogonadism.*
ACTIONS: Estrogen supl.
DOSE: Start 0.0375–0.05 mg/d patch 1–2×/wk based on product (*Climara* 1×/wk; *Alora* 2×wk) adjust PRN to control Sxs; w/ intact uterus cycle 3 wk on 1 wk off or use cyclic progestin 10–14 days.

W/P: [X, −] See estradiol.
CI: Pregnancy, AUB, porphyria, breast cancer, estrogen-dependent tumors, Hx thrombophlebitis, thrombosis.
DISP: Transdermal patches (mg/24 h) 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1.
SE: N, bloating, breast enlargement/tenderness, edema, headache, hypertriglyceridemia, gallbladder disease.
NOTES: Do not apply to breasts, place on trunk, rotate sites; see estradiol, oral notes.

ESTRADIOL, VAGINAL (ESTRING, FEMRING, VAGIFEM)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 y). ↑ Dementia risk in postmenopausal (≥ 65 y).
USES: *Postmenopausal Vag atrophy *(Estring)** *vasomotor Sxs and vulvar/vag atrophy associated w/ menopause *(Femring)** *atrophic vaginitis (*Vagifem)**
ACTIONS: Estrogen supl.
DOSE: *Estring:* Insert ring into upper 3rd of Vag vault; remove and replace after 90 d; reassess 3–6 mo; *Femring:* Use lowest effective dose, insert vaginally, replace q3mo; *Vagifem:* 1 tab vaginally q day × 2 wk, then maint 1 tab 2×/ wk, D/C or taper at 3–6 mo.
W/P: [X, −] May ↑ PT/PTT/plt aggregation w/ thyroid disease, toxic shock reported.
CI: Undiagnosed genital bleeding, breast cancer, estrogen- dependent tumors, thromboembolic disorders, thrombophlebitis, recent MI, pregnancy, severe hepatic disease.
DISP: *Estring ring:* 0.0075 mg/24 h; *Femring ring:* 0.05 and 0.1 mg/d *Vagifem tab (Vag):* 10 µg.
SE: Headache, leukorrhea, back pain, candidiasis, vaginitis, Vag discomfort/hemorrhage, arthralgia, insomnia, abdominal pain; see estradiol, oral notes.

ESTRADIOL/LEVONORGESTREL, TRANSDERMAL (CLIMARA PRO)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Menopausal vasomotor Sx; prevent postmenopausal osteoporosis.*
ACTIONS: Estrogen & progesterone.
DOSE: 1 patch 1×/wk.
W/P: [X, −] w/ ↓ thyroid.
CI: AUB, estrogen-sensitive tumors, Hx thromboembolism, liver impairment, pregnancy, hysterectomy.
DISP: Estradiol 0.045 mg/levonorgestrel 0.015 mg/day patch.
SE: Site reaction, Vag bleed/spotting, breast changes, abdominal bloating/ cramps, headache, retention fluid, edema, ↑ BP.
NOTES: Apply in lower abdomen; for osteoporosis give Ca^{2+}/vit D supl; follow breast exams.

ESTRADIOL/NORETHINDRONE (ACTIVELLA, FEMHRT, GENERIC)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in

postmenopausal (≥65 yr).
USES: *Menopause vasomotor Sxs; vulvar and vaginal atrophy; prevent osteoporosis.*
ACTIONS: Estrogen/progestin; plant derived.
DOSE: 1 tab/d start w/ lowest dose combo.
W/P: [X, −] w/ ↓ Ca^{2+}/thyroid.
CI: Pregnancy; Hx breast cancer; estrogen-dependent tumor; abnormal genital bleeding; Hx DVT, PE, or related disorders; recent (w/in past year) arterial thromboembolic disease (CVA, MI).
DISP: *Femhrt:* Tabs 2.5/0.5, 5 μg/1 mg; *Activella:* Tabs 1/0.5, 0.5 mg/0.1 mg.
SE: Thrombosis, dizziness, headache, libido changes, insomnia, emotional instability, breast pain.
NOTES: Use in women w/ intact uterus; caution in heavy smokers; combo also used as oral contraceptive.

ESTRAMUSTINE PHOSPHATE (EMCYT)

USES: *Palliative treatment of metastatic and/or progressive carcinoma of the prostate.*
ACTIONS: Estradiol w/ nitrogen mustard; exact mechanism unknown.
DOSE: 14 mg/kg/d in 3–4 ÷ doses; on empty stomach, no dairy products.
W/P: [NA, not used in females].
CI: Active thrombophlebitis or thromboembolic disorders.
DISP: Caps 140 mg.
SE: N/V, exacerbation of pre-existing CHF, edema, hepatic disturbances, thrombophlebitis, MI, PE, gynecomastia in 20–100%.
NOTES: Low-dose breast irradiation before may ↓ gynecomastia.

ESTROGEN, CONJUGATED (PREMARIN)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Mod–severe menopausal vasomotor Sxs; atrophic vaginitis; hypoestrogenism; palliation of advanced breast and prostate cancer; prevention osteoporosis.*
ACTIONS: Estrogen replacement.
DOSE: 0.3–1.25 mg/d PO; intravaginal cream 0.5–2 g × 21 days, then off × 7 days or 0.5 mg twice weekly.
W/P: [X, −].
CI: Severe hepatic impairment, genital bleeding of unknown cause, breast cancer, estrogen-dependent tumors, thromboembolic disorders, thrombosis, thrombophlebitis, recent MI.
DISP: Tabs 0.3, 0.45, 0.625, 0.9, 1.25 mg; Vag cream 0.625 mg/g.
SE: ↑ Risk of endometrial cancer, gallbladder disease, thromboembolism, headache, & possibly breast cancer.
NOTES: Generic products not equivalent.

ESTROGEN, CONJUGATED/MEDROXYPROGESTERONE (PREMPRO,

PREMPHASE)
WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Mod–severe menopausal vasomotor Sxs; atrophic vaginitis; prevent postmenopausal osteoporosis.*
ACTIONS: Hormonal replacement.
DOSE: *Prempro* 1 tab PO daily; *Premphase* 1 tab PO daily.
W/P: [X, −].
CI: Severe hepatic impairment, genital bleeding of unknown cause, breast cancer, estrogen-dependent tumors, thromboembolic disorders, thrombosis, thrombophlebitis.
DISP: (As estrogen/medroxyprogesterone) *Prempro:* Tabs 0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5 mg; *Premphase:* Tabs 0.625/0 (days 1–14) & 0.625/5 mg (days 15–28).
SE: Gallbladder disease, thromboembolism, headache, breast tenderness.
NOTES: See WHI (www.whi.org); use lowest dose/shortest time possible.

ESTROGEN, CONJUGATED SYNTHETIC (CENESTIN, ENJUVIA)

WARNING: ↑ Risk endometrial cancer. Do not use to prevent CV disease or dementia; ↑ risk MI, stroke, breast cancer, PE, and DVT in postmenopausal (50–79 yr). ↑ Dementia risk in postmenopausal (≥65 yr).
USES: *Vasomotor menopausal Sxs, vulvovaginal atrophy.*
ACTIONS: Multiple estrogen replacement.
DOSE: For all w/ intact uterus progestin × 10–14 days/28-day cycle; *Vasomotor:* 0.3–1.25 mg (*Enjuvia*) 0.625–1.25 mg (*Cenestin*) PO daily; *Vag atrophy:* 0.3 mg/d.
W/P: [X, −].
CI: See Estrogen, conjugated.
DISP: Tabs, *Cenestin*, 0.3, 0.45, 0.625, 0.9, 1.25 mg; *Enjuvia* ER 0.3, 0.45, 0.625, 0.9, 1.25 mg.
SE: ↑ Risk endometrial/breast cancer, gallbladder disease, thromboembolism.

ETHAMBUTOL (MYAMBUTOL, GENERIC)

USES: *Pulmonary TB* and other mycobacterial infections, mycobacterium avium complex (MAC).
ACTION: ↓ RNA synthesis.

DOSE:
Adults & Peds: ***>12 yr:*** 15–25 mg/kg/d PO single dose; ↓ in renal impairment, take w/ food, avoid antacids.
W/P: [C, +].
CI: Unconscious patients, optic neuritis.
DISP: Tablets 100, 400 mg.
SE: Headache, hyperuricemia, acute gout, abdominal pain, ↑ LFTs, optic neuritis (decreased visual acuity), GI upset.

ETIDRONATE DISODIUM (DIDRONEL, GENERIC)

USES: *Paget disease, heterotopic ossification.*
ACTIONS: ↓ Nl & abnormal bone resorption.
DOSE: *Paget disease:* 5–10 mg/kg/d PO ÷ doses (for 3–6 mo). ↑ Ca^{2+}*:* 20 mg/kg/d IV × 30–90 days.
W/P: [B PO (C parenteral),?] Bisphosphonates may cause severe musculoskelet al pain.
CI: Esophageal abnormalities.
DISP: Tabs 200, 400 mg.
SE: GI intolerance (↓ by ÷ daily doses); hyperphosphatemia, hypomagnesemia, bone pain, abnormal taste, fever, convulsions, nephrotoxic.
NOTES: Take PO on empty stomach 2 hr before or 2 hr pc; not approved for osteoporosis.

ETOPOSIDE [VP-16] (ETOPOPHOS, GENERIC)

WARNING: Should be administered under the supervision of a qualified physician experienced in the use of chemotherapy. Severe myelosuppression with resulting infection or bleeding may occur.
USES: *Small cell lung cancer* testicular cancer, Hodgkin disease, & NHLs, peds ALL, & BMT in high doses.*
ACTIONS: Topoisomerase II inhibitor.
DOSE: 50 mg/m^2/d IV for 3–5 days; 50 mg/m^2/d PO for 21 days (PO availability = 50% of IV); 2–6 g/m^2 or 25–70 mg/kg in BMT (per protocols); ↓ in renal/hepatic impairment.
W/P: [D, −].
CI: IT administration.
DISP: Caps 50 mg; Inj 20 mg/mL.
SE: N/V (emesis in 10–30%), ↓ BM, alopecia, ↓ BP w/ rapid IV, anorexia, anemia, leukopenia, ↑ risk secondary leukemias.

EVEROLIMUS (AFINITOR, AFINITOR DISPERZ)

USES: **Afinitor:* Hormone receptor positive, HER2-negative breast cancer w/ exemestane after failure of letrozole or anastrozole; unresectable progressive neuroendocrine tumors of pancreatic origin (PNET); advanced renal cell carcinoma (RCC) after failure of sunitinib or sorafenib; adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. *Afinitor and Afinitor Disperz:* Pediatric and adult with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be resected.*
ACTIONS: mTOR inhibitor.
DOSE: 10 mg PO daily, ↓ to 5 mg w/ SE or hepatic impairment; avoid w/ high-fat meal.
W/P: [D, ?] Avoid w/ live vaccines; w/ CYP3A4 inhibitor.
CI: Compound/rapamycin-derivative hypersens.
DISP: Tabs 2.5, 5, 7.5, 10 mg; Disperz for suspen 2, 3, 5 mg.
SE: Noninfectious pneumonitis, ↑ infection risk, oral ulcers, asthenia, cough, fatigue, diarrhea, ↑ glucose/SCr/lipids; ↓ hemoglobin/WBC/plt.
NOTES: Follow CBC, LFT, glucose, lipids; see also everolimus (*Zortress*).

EVEROLIMUS (ZORTRESS)

USES: *Prevent renal and liver transplant rejection; combo w/ basiliximab w/ ↓ dose of steroids and cyclosporine.*
ACTIONS: mTOR inhibitor (mammalian rapamycin target).
DOSE: 0.75 mg PO BID, adjust to trough levels 3–8 ng/ mL.
W/P: [D, ?].
CI: Compound/rapamycin-derivative hypersens.
DISP: Tabs 0.25, 0.5, 0.75 mg.
SE: Peripheral edema, constipation, ↑ BP, N, ↓ Hct, UTI, ↑ lipids.
NOTES: Follow CBC, LFT, glucose, lipids; *Trough level* 3–8 ng/mL w/ cyclosporine see also everolimus (*Afinitor*).

FAMCICLOVIR (FAMVIR, GENERIC)

USES: *Acute herpes zoster (shingles) & genital herpes.*
ACTIONS: ↓ Viral DNA synth.
DOSE: *Zoster:* 500 mg PO q8h × 7 days. *Simplex:* 125–250 mg PO BID; ↓ w/ renal impairment.
W/P: [B, −].
CI: Component sensitivity.
DISP: Tabs 125, 250, 500 mg.
SE: Fatigue, dizziness, headache, pruritus, N/diarrhea.
NOTES: Best w/in 72 hr of initial lesion.

FEBUXOSTAT (ULORIC)

USES: *Hyperuricemia and gout.*
ACTIONS: Xanthine oxidase inhibitor (enzyme that converts hypoxanthine to xanthine to uric acid).
DOSE: 40 mg PO 1 × day, ↑ 80 mg if uric acid not <6 mg/dL after 2 wk.
W/P: [C, ?/−].
CI: Use w/ azathioprine, mercaptopurine, theophylline.
SUPPLIED: Tabs 40, 80 mg.
SE: ↑ LFTs, rash, myalgia.
NOTES: OK to continue w/ gouty flare or use w/ NSAIDs.

FENTANYL, INJECTION (SUBLIMAZE, GENERIC) [C-II]

USES: *Short-acting analgesic in anesthesia* & patient controlled analgesia.
ACTIONS: Narcotic analgesic.

DOSE:

Adults: 1–2 µg/kg *or* 25–100 µg/dose IV/IM titrated; *Anesthesia:* 5–15 µg/kg; *Pain:* 200 µg over 15 min, titrate to effect.
Peds: 1–2 µg/kg IV/IM q1–4h titrate; ↓ in renal impairment, elderly.
W/P: [B,+] To be used only by those experienced with medication; hypotension possible w/

tranquilizer use.
CI: Opioid intolerance.
DISP: Inj 0.05 mg/mL.
SE: Sedation, ↓ BP, ↓ HR, constipation, N, resp depression, miosis.
NOTES: 50 µg = 0.05 mg = 1 mL; 0.1 mg fentanyl = 10 mg morphine IM.

FENTANYL, TRANSDERMAL (DURAGESIC, GENERIC) [C-II]

WARNING: Potential for abuse and fatal OD; resp depression possible; accidental exposure can be fatal; initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal OD; avoid heat to application site, can cause OD.
USES: *Persistent mod–severe chronic pain in pts already tolerant to opioids.*
ACTIONS: Narcotic.
DOSE: Apply patch to upper torso q72h; dose based on narcotic requirements in previous 24 hr; start 25 µg/h patch q72h; ↓ in renal impairment.
W/P: [B, +] w/ CYP3A4 inhibitor or D/C CYP3A4 inducer may ↑ fentanyl effect, w/ Hx substance abuse.
CI: Not opioid tolerant, short-term pain management, postop outpatient pain in outpatient surgery, mild pain, PRN use, ↑ ICP, resp depression, severe renal/hepatic impairment, peds <2 yr.
DISP: Patches 12.5, 25, 50, 75, 100 µg/h.
SE: Resp depression (can be fatal), sedation, ↓ BP, ↓ HR, constipation, N, miosis.
NOTES: 0.1 mg fentanyl = 10 mg morphine IM; do not cut patch; peak level in PREGNANCY 24–72 hr.

FENTANYL, TRANSMUCOSAL (ABSTRAL, ACTIQ, FENTORA, LAZANDA, ONSOLIS, GENERIC) [C-II]

WARNING: Potential for abuse and fatal OD; use only in pts w/ chronic pain who are opioid tolerant; CI in acute/postop pain; do not substitute for other fentanyl products; fentanyl can be fatal to children, keep away; use w/ strong CYP3A4 inhibitor may ↑ fentanyl levels. *Abstral, Onsolis* restricted distribution.
USES: *Breakthrough cancer pain w/ tolerance to opioids.*
ACTIONS: Narcotic analgesic, transmucosal absorption.
DOSE: Titrate to effect.

- *Abstral:* Start 100 µg SL, 2 doses max. per pain breakthrough episode; wait 2 hr for next breakthrough dose; limit to <4 breakthrough doses w/ successful baseline dosing.
- *Actiq*: Start 200 µg PO × 1, may repeat × 1 after 30 min.
- *Fentora*: Start 100 µg buccal tab × 1, may repeat in 30 min, 4 tabs/dose max.
- *Lazanda:* Through TIRF REMS Access Program; initial 1 × 100 µg spray; if no relief, titrate for breakthrough pain as follows: 2 × 100 µg spray (1 in each nostril); 1 × 400 µg; 2 × 400 µg (1 in each nostril); wait 2 hr before another dose; max. 4 doses/24 h.
- *Onsolis*: Start 200 µg film, ↑ 200 µg increments to max. four 200-µg films or single 1,200-µg film.

W/P: [B, +] resp/CNS depression possible; CNS depressants/CYP3A4 inhibitor may ↑ effect;

may impair tasks (driving, machinery); w/ severe renal/hepatic impairment.
CI: Opioid intolerant pt, acute/postop pain.
DISP:
- *Abstral:* SL tabs 100, 200, 300, 400, 600, 800 µg
- *Actiq:* Lozenges on stick 200, 400, 600, 800, 1,200, 1,600 µg
- *Fentora:* Buccal tabs 100, 200, 400, 600, 800 µg
- *Lazanda:* Nasal spray metered dose audible and visual counter, 8 doses/bottle, 100/400 µg/spray
- *Onsolis:* Buccal soluble film 200, 400, 600, 800, 1,200 µg

SE: Sedation, ↓ BP, ↓ HR, constipation, N/V, ↓ resp, dyspnea, headache, miosis, anxiety, confusion, depression, rash dizziness.
NOTES: 0.1 mg fentanyl = 10 mg IM morphine.

FERRIC CARBOXYMALTOSE (INJECTAFER)

USES: *Iron-deficiency anemia.*
ACTIONS: Fe Supl.

DOSE:

Adults: ≥50 kg: 2 doses 750 mg IV separated by 7 days; <50 kg: 2 doses of 15 mg/kg IV separated by 7 days.
W/P: [C, M] Hypersens rxn (monitor during & 30 min after inf).
CI: Component hypersens.
DISP: Inj 750 mg iron/15 mL single-use vial.
SE: N, HTN, flushing, hypophosphatemia, dizziness, HTN.

FERROUS GLUCONATE (FERGON [OTC] , OTHERS)

WARNING: Accidental OD of iron-containing products is a leading cause of fatal poisoning in children <6 yr. Keep out of reach of children.
USES: *Iron-deficiency anemia* & Fe supl.
ACTIONS: Dietary supl.

DOSE:

Adults: 100–200 mg of elemental Fe/d ÷ doses.
Peds: 4–6 mg/kg/d ÷ doses; on empty stomach (OK w/ meals if GI upset occurs); avoid antacids.
W/P: [A,?].
CI: Hemochromatosis, hemolytic anemia.
DISP: Tabs Fergon 240 (27 mg Fe), 246 (28 mg Fe), 300 (34 mg Fe), 324 mg (38 mg Fe).
SE: GI upset, constipation, dark stools, discoloration of urine, may stain teeth.
NOTES: 12% elemental Fe; false (+) stool guaiac; keep away from children; severe tox in OD.

FERROUS GLUCONATE COMPLEX (FERRLECIT)

USES: *Iron-deficiency anemia or supl to erythropoietin Treat therapy.*
ACTIONS: Fe supl.
DOSE: *Test dose:* 2 mL (25 mg Fe) IV over 1 hr, if OK, 125 mg (10 mL) IV over 1 hr. *Usual cumulative dose:* 1 g Fe over 8 sessions (until favorable Hct).
W/P: [B, ?].
CI: Non–Fe-deficiency anemia; CHF; Fe overload.
DISP: Inj 12.5 mg/mL Fe.
SE: ↓ BP, serious allergic reactions, GI disturbance, Inj site reaction.
NOTES: Dose expressed as mg Fe; may infuse during dialysis.

FERROUS SULFATE (OTC)

USES: *Fe-deficiency anemia & Fe supl.*
ACTIONS: Dietary supl.

DOSE:

Adults: 100–200 mg elemental Fe/d in ÷ doses.
Peds: 1–6 mg/kg/d ÷ daily–TID; on empty stomach (OK w/ meals if GI upset occurs); avoid antacids.
W/P: [A, ?] ↑ Absorption w/ vit C; ↓ absorption w/ tetracycline, fluoroquinolones, antacids, H_2 blockers, proton pump inhibitor.
CI: Hemochromatosis, hemolytic anemia.
DISP: Tabs 187 (60 mg Fe), 200 (65 mg Fe), 324 (65 mg Fe), 325 mg (65 mg Fe); SR caplets & tabs 160 (50 mg Fe), 200 mg (65 mg Fe); gtt 75 mg/0.6 mL (15 mg Fe/0.6 mL); elixir 220 mg/5 mL (44 mg Fe/5 mL); syrup 90 mg/5 mL (18 mg Fe/5 mL).
SE: GI upset, constipation, dark stools, discolored urine.

FERUMOXYTOL (FERAHEME)

USES: *Iron-deficiency anemia in chronic kidney disease.*
ACTIONS: Fe replacement.

DOSE:

Adults: 510 mg IV × 1, then 510 mg IV × 1 3–8 days later; give 1 mL/s.
W/P: [C, ?/−] Monitor for hypersens & ↓ BP for 30 min after dose, may alter MRI studies.
CI: Iron overload; hypersens to ferumoxytol.
DISP: IV soln 30 mg/mL (510 mg elemental Fe/17 mL).
SE: N/diarrhea, constipation, dizziness, hypotension, peripheral edema, hypersens reaction.
NOTES: Check hematologic response 1 mo after 2nd dose.

FESOTERODINE (TOVIAZ)

USES: * Overactive bladder w/ urge urinary incontinence, urgency, frequency.*
ACTIONS: Competitive muscarinic receptor antagonist, ↓ bladder muscle contractions.
DOSE: 4 mg PO qd, ↑ to 8 mg PO daily PRN.
W/P: [C, /?] Avoid >4 mg w/ severe renal insufficiency or w/ CYP3A4 inhibitor (eg,

ketoconazole, clarithromycin); w/ bladder outlet obstruction, ↓ GI motility/constipation, narrow-angle glaucoma, myasthenia gravis.
CI: Urinary/gastric retention, or uncontrolled narrow-angle glaucoma, hypersens to class.
DISP: Tabs 4, 8 mg.
SE: Dry mouth, constipation, ↓ sweating can cause heat prostration.

FIDAXOMICIN (DIFICID)

USES: **Clostridium difficile*-associated diarrhea.*
ACTIONS: Macrolide antibiotic.
DOSE: 200 mg PO BID × 10 days.
W/P: [B, +/−] Not for systemic infection or <18 yr; to ↓ resistance, use only when diagnosis suspected/ proven.
DISP: Tabs 200 mg.
SE: N/V, abdominal pain, GI bleed, anemia, neutropenia.

FINASTERIDE (PROSCAR [GENERIC] , PROPECIA)

USES: *BPH & androgenetic alopecia.*
ACTIONS: ↓ 5-α-reductase.
DOSE: *BPH:* 5 mg/d PO. *Alopecia:* 1 mg/d PO; food ↓ absorption.
W/P: [X, −] Hepatic impairment.
CI: Pregnant women should avoid handling pills, teratogen to male fetus.
DISP: Tabs 1 mg (*Propecia*), 5 mg (*Proscar*).
SE: ↓ Libido, vol ejaculate, erectile dysfunction, gynecomastia; may slightly ↑ risk of high-grade prostate cancer.
NOTES: Both ↓ PSA by ~50%; reestablish PSA baseline 6 mo (double PSA for "true" reading); 3–6 mo for effect on urinary Sxs; continue to maintain new hair, not for use in women.

FLAVOXATE (GENERIC)

USES: *Relief of Sx of dysuria, urgency, nocturia, suprapubic pain, urinary frequency, incontinence.*
ACTIONS: Antispasmodic.
DOSE: 100–200 mg PO TID–QID.
W/P: [B, ?].
CI: GI obst, GI hemorrhage, ileus, achalasia, BPH.
DISP: Tabs 100 mg.
SE: Drowsiness, blurred vision, xerostomia.
NOTE: Urispas brand discontinued.

FLUCONAZOLE (DIFLUCAN, GENERIC)

USES: *Candidiasis (esophageal, oropharyngeal, urinary tract, Vag, prophylaxis); cryptococcal meningitis, prophylaxis w/ BMT.*
ACTIONS: Antifungal; ↓ cytochrome P-450 sterol demethylation. *Spectrum:* All *Candida* sp

except *C. krusei.*

DOSE:
Adults: 100–400 mg/d PO or IV. *Vaginitis:* 150 mg PO daily.
Peds: 3–6 mg/kg/d PO or IV; 12 mg/kg/d/systemic infection; ↓ in renal impairment.
W/P: [C, Vag candidiasis (D high or prolonged dose), −] Do not use w/ clopidogrel (↓ effect).
CI: Hypersensitivity, terfenadine with high dose fluconazole; w/ drugs that ↑ QT interval and are metabolized via CYP3A4 (cisapride, astemizole, erythromycin, pimozide, quinidine).
DISP: Tabs 50, 100, 150, 200 mg; susp 10, 40 mg/mL; Inj 2 mg/mL.
SE: Headache, rash, GI upset, ↓ K^+, ↑ LFTs.
NOTES: PO (preferred) = IV levels; cong anomalies w/ high dose 1st tri.

FLUDROCORTISONE ACETATE (GENERIC)

USES: *Adrenocortical insufficiency, Addison disease, salt-wasting adrenogenital syndrome.*
ACTIONS: Mineralocorticoid.

DOSE:

Adults: 0.1–0.2 mg/d PO.
Peds: 0.05–0.1 mg/d PO.
W/P: [C, ?].
CI: Systemic fungal infections; known hypersensitivity.
DISP: Tabs 0.1 mg.
SE: HTN, edema, CHF, headache, dizziness, convulsions, acne, rash, bruising, hyperglycemia, hypothalamic—pituitary–adrenal suppression, cataracts.
NOTES: For adrenal insufficiency, use w/ glucocorticoid; dose adjustments based on plasma renin activity.

FLUOROURACIL, INJECTION [5-FU] (GENERIC)

WARNING: Administration by experienced chemotherapy physician only; pts should be hospitalized for 1st course d/t risk for severe reaction.
USES: *Palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas*, head, neck, bladder cancers.
ACTIONS: Inhibits thymidylate synthetase (↓ DNA synth, S-phase specific).
DOSE: 370–1,000 mg/m^2/d × 1–5 days IV push to 24-hr cont Inf; protracted venous Inf of 200–300 mg/m^2/d (per protocol); 800 mg/d max.
W/P: [D, ?] ↑ Tox w/ allopurinol; do not give live vaccine before 5-FU.
CI: Poor nutritional status, depressed BM function, thrombocytopenia, major surgery w/in past mo, G6PD enzyme deficiency, pregnancy, serious infection, bili >5 mg/dL.
DISP: Inj 50 mg/mL.
SE: Stomatitis, esophagopharyngitis, N/V/diarrhea, anorexia, ↓ BM, rash/dry skin/photosensitivity, tingling in hands/feet w/ pain (palmar-plantar erythrodysesthesia), phlebitis/discoloration at Inj sites.
NOTES: ↑ Thiamine intake; contraception OK.

FLUOROURACIL, TOPICAL [5-FU] (CARAC, EFUDEX, FLUOROPLEX, GENERIC)

USES: *Basal cell carcinoma (when standard therapy impractical); actinic/solar keratosis* carcinoma in situ (CIS) of the penis,
ACTIONS: Inhibits thymidylate synthetase (↓ DNA synth, S-phase specific),
DOSE: 5% cream BID × 2–6 wk,
W/P: [D, ?] Irritant chemotherapy,
CI: Component sensitivity,
DISP: Cream 0.5, 1, 5%; soln 1%, 2%, 5%.
SE: Rash, dry skin, photosensitivity.
NOTES: Healing may not be evident for 1–2 mo; wash hands thoroughly; avoid occlusive dressings; do not overuse; typical penile regimen described: apply 12 hr every 48 hr for 28 days.

FLUOXETINE (GABOXETINE, PROZAC, PROZAC WEEKLY, SARAFEM, GENERIC)

WARNING: Closely monitor for worsening depression or emergence of suicidality, particularly in ped pt.
USES: *Depression, OCD, panic disorder, bulimia (*Prozac*)* premature ejaculation* PMDD (*Sarafem*).*
ACTIONS: SSRI.
DOSE: 20 mg/d PO (max. 80 mg/d ÷ dose); weekly 90 mg/wk after 1–2 wk of standard dose. *Bulimia:* 60 mg q a.m. *Panic disorder:* 20 mg/d. *OCD:* 20–80 mg/d. *PMDD:* 20 mg/d or 20 mg intermittently, start 14 days prior to menses, repeat w/ each cycle; ↓ in hepatic failure.
W/P: [C, ?/−] Serotonin syndrome w/ MAOI, SSRI, serotonin agonists, linezolid; QT prolongation w/ phenothiazines; do not use w/ clopidogrel (↓ effect).
CI: w/ MAOI/thioridazine (wait 5 wk after D/C before MAOI).
DISP: *Prozac:* Caps 10, 20, 40 mg; scored tabs 10, 20 mg; *Prozac Weekly:* SR weekly caps 90 mg; soln 20 mg/5 mL. *Sarafem:* Caps 10, 15, 20 mg.
SE: N, nervousness, Wt loss, headache, insomnia.

FLUOXYMESTERONE (GENERIC) [C-III]

USES: *Hypogonadism (primary, hypogonadotropic), delayed puberty in males; postmenopausal metastatic breast cancer.*
ACTIONS: Synthetic androgen; ↓ secretion of LH & FSH (feedback inhibition).
DOSE: *Breast cancer:* 10–40 mg/d ÷ × 1–3 mo. *Hypogonadism:* 5–20 mg/d.
W/P: [X, ?/−] ↑ Effect w/ anticoagulants, cyclosporine, insulin, lithium, narcotics.
CI: Men with carcinomas of the breast or with known/suspected prostate cancer; women who are/may become pregnant.
DISP: Tabs 10 mg.
SE: Priapism, edema, virilization, amenorrhea & menstrual irregularities, hirsutism, alopecia, acne, N, cholestasis; suppression of factors II, V, VII, & X, & polycythemia; ↑ libido, headache, anxiety,

NOTES: Radiographic exam of hand/wrist q6mo in prepubertal children; ↓ total T_4 levels.

FLUTAMIDE (GENERIC)

WARNING: Liver failure & death reported. Measure LFTs before, monthly, & periodically after; D/C immediately if ALT 2 × ULN or jaundice develops.
USES: Advanced *PCa* (w/ LHRH agonists); w/ radiation & LHRH agonists for localized CaP.
ACTIONS: Nonsteroidal antiandrogen.
DOSE: 250 mg PO TID (750 mg total).
W/P: [D, ?].
CI: Severe hepatic impairment.
DISP: Caps 125 mg.
SE: Hot flashes, loss of libido, impotence, N/V/diarrhea, gynecomastia, hepatic failure, aniline-like toxicity (methemoglobinemia, hemolytic anemia, cholestatic jaundice).
NOTES: Check LFTs, avoid EtOH.

FONDAPARINUX (ARIXTRA)

WARNING: When epidural/spinal anesthesia or spinal puncture is used, pts anticoagulated or scheduled to be anticoagulated w/ LMW heparins, heparinoids, or fondaparinux are at risk for epidural or spinal hematoma, which can result in long-term or permanent paralysis.
USES: *DVT prophylaxis* w/ hip fracture, hip or knee replacement, abdominal surgery; w/ DVT or PE in combo w/ warfarin.
ACTIONS: Synth inhibitor of activated factor X; a pentasaccharide.
DOSE: *Prophylaxis* 2.5 mg SQ daily, up to 5–9 days; start >6 hr postop; Tx: 7.5 mg SQ daily (<50 kg: 5 mg SQ daily; >100 kg: 10 mg SQ daily); ↓ w/ renal impairment.
W/P: [B, ?] ↑ Bleeding risk w/ anticoagulants, anti-plts, drotrecogin alfa, NSAIDs.
CI: Wt <50 kg, CrCl <30 mL/min, active bleeding, SBE ↓ plt w/ anti-plt Ab.
DISP: Prefilled syringes w/ 27G needle: 2.5/0.5, 5/0.4, 7.5 /0.6, 10/0.8 mg/mL.
SE: Thrombocytopenia, anemia, fever, N.
NOTES: D/C if plts <100,000 cells/μL; only give SQ; may monitor antifactor Xa levels.

FORMALIN (40% FORMALDEHYDE)

(Note: This medication is not FDA approved for this use. Medication usually prepared by hospital pharmacy.)
USES: Intractable hemorrhagic cystitis refractory to conservative management.
ACTIONS: Fixation of bladder wall mucosa through protein cross-linking.
DOSE: Fill bladder to capacity with 1–2% formalin initially under gravity (<15 cm water) for up to 10–15 min; must be under general or spinal anesthesia with patient in reverse Trendelenburg (minimize reflux); if needed can repeat with higher concentration (4–10%).
W/P: [C, ?].
DISP: Formalin solution 1–10%.
SE: Bladder fibrosis, skin irritation with contact, reflux resulting in acidosis, ureteral fibrosis and obstruction or papillary necrosis; extravasation causes peritonitis and/or fistulas.
NOTES: Cystogram required to rule out reflux and bladder perforation; coat perineum

petroleum jelly and vaginal vault packed with petroleum gauze to protect shin from formalin contact.

FOSFOMYCIN (MONUROL, GENERIC)

USES: *Uncomplicated UTI in women.*
ACTIONS: ↓ Cell wall synth. *Spectrum:* gram(+) *Enterococcus,* staphylococci, pneumococci; gram(−) (*E. coli, Salmonella, Shigella, H. influenzae, Neisseria,* indole(−) *Proteus, Providencia); B. fragilis* & anaerobic gram(−) cocci are resistant.
DOSE: 3 g PO in 90–120 mL of H_2O single dose; ↓ in renal impairment.
W/P: [B, ?] Not for pyelo;↓ absorption w/ antacids/Ca salts.
CI: Component sensitivity.
DISP: Granule packets 3 g.
SE: Headache, GI upset.
NOTES: May take 2–3 days for Sxs to improve.

FOSINOPRIL (GENERIC)

USES: *HTN, CHF*, diabetic nephropathy.
ACTIONS: ACE inhibitor.
DOSE: 10 mg/d PO initial; max. 40 mg/d PO; ↓ in elderly; ↓ in renal impairment.
W/P: [D, +] ↑ K^+ w/ K^+ supls, ARBs, K^+-sparing diuretics; ↑ renal after effects w/ NSAIDs, diuretics, hypovolemia.
CI: Hereditary/idiopathic angioedema or angioedema w/ ACE inhibitor, bilateral RAS.
DISP: Tabs 10, 20, 40 mg.
SE: Cough, dizziness, angioedema, ↑ K^+.

FUROSEMIDE (LASIX [ORAL] , GENERIC)

USES: *CHF, HTN, edema*, ascites.
ACTIONS: Loop diuretic; ↓ Na & Cl reabsorption in ascending loop of Henle & distal tubule.
DOSE:
Adults: 20–80 mg PO or IV BID.
Peds: 1 mg/kg/dose IV q6–12h; 2 mg/kg/ dose PO q12–24h (max. 6 mg/kg/dose); ↑ doses w/ renal impairment.
W/P: [C, +] ↓ K^+, ↑ risk digoxin tox & ototox w/ aminoglycosides, cisplatin (especially in renal dysfunction).
CI: Sulfonylurea allergy; anuria; hepatic coma; electrolyte depletion.
DISP: Tabs 20, 40, 80 mg; soln 10 mg/mL, 40 mg/5 mL; Inj 10 mg/mL.
SE: ↓ BP, hyperglycemia, ↓ K^+.
NOTES: Check lytes, renal function; high doses IV may cause ototox.

GABAPENTIN (NEURONTIN, GENERIC)

USES: *Postherpetic neuralgia (PHN); adjunct in partial seizures*; chronic pain synds.

ACTIONS: Anticonvulsant; GABA analog.

DOSE:
Adults & Peds: > ***12 yr:*** *Anticonvulsant:* 300 mg PO TID, ↑ max. 3,600 mg/d. *PHN:* 300 mg day 1, 300 mg BID day 2, 300 mg TID day 3, titrate (1,800–3,600 mg/d);
Peds: ***3–12 yr:*** 0–15 mg/kg/d ÷ TID, ↑ over 3 days, ***3–4 yr:*** 40 mg/kg/d given TID. ≥***5 yr:*** 25–35 mg/kg/d ÷ TID, 50 mg/kg/d max. ↓ w/ renal impairment.
W/P: [C, ?] Use in peds 3–12 yr w/ epilepsy may ↑ CNS-related adverse events.
CI: Component sensitivity.
DISP: Caps 100, 300, 400 mg; soln 250 mg/5 mL; scored tab 600, 800 mg.
SE: Somnolence, dizziness, ataxia, fatigue.
NOTES: Not necessary to monitor levels; taper ↑ or ↓ over 1 wk.

GANCICLOVIR (CYTOVENE, VITRASERT, GENERIC)

Toxicity includes granulocytopenia, anemia and thrombocytopenia. In animal studies ganciclovir was carcinogenic, teratogenic and caused aspermatogenesis. Ganciclovir for injection indicated only in the treatment of CMV retinitis in immunocompromised patients and to prevent CMV at risk transplant patients.
USES: *Treat & prevent CMV retinitis, prevent CMV disease* in transplant recipients.
ACTIONS: ↓ Viral DNA synth.

DOSE:
Adults & Peds: *IV:* 5 mg/kg IV q12h for 14–21 days, then maint 5 mg/kg/d IV × 7 d/ wk or 6 mg/kg/d IV × 5 d/wk.
Adults: *PO:* Following induction, 1,000 mg PO TID. *Prevention:* 1,000 mg PO TID; w/ food; ↓ in renal impairment.
W/P: [C, −] ↑ Effect w/ immunosuppressives, imipenem/cilastatin, zidovudine, didanosine, other nephrotoxic Treat.
CI: ANC <500 cells/mm^3, plt <25,000 cells/mm^3, intravitreal implant.
DISP: Caps 250, 500 mg; Inj 500 mg, ocular implant 4.5 mg.
SE: Granulocytopenia & thrombocytopenia, fever, rash, GI upset.
NOTES: Not a cure for CMV; handle Inj w/ cytotoxic cautions; no systemic benefit w/ implant.

GEMCITABINE (GEMZAR, GENERIC)

USES: *Pancreatic cancer (single agent), breast cancer w/ paclitaxel, NSCLC w/ cisplatin, ovarian cancer w/ carboplatin*, gastric cancer, urothelial carcinoma (systemic and intravesical).
ACTIONS: Antimetabolite; nucleoside metabolic inhibitor; ↓ ribonucleotide reductase; produces false nucleotide base-inhibiting DNA synth.
DOSE: 1,000–1,250 mg/ m^2 over 30 min–1 hr IV Inf/wk × 3–4 wk or 6–8 wk; modify dose based on hematologic function (per protocol).
W/P: [D, ?/−] Hemolytic uremic syndrome (HUS), pulmonary toxicity, embryofet al toxicity, ↑ radiation therapy toxicity, capillary leak syndrome, posterior reversible encephalopathy syndrome (PRES).

CI: Pregnancy.
DISP: Inj 200 mg, 1 g.
SE: ↓ BM, N/V/diarrhea, drug fever, skin rash.
NOTES: Reconstituted soln 38 mg/mL; monitor hepatic/renal function; intravesical regimen described: 40 mg/mL (2,000 mg in 50 mL saline) weekly.

GENTAMICIN, INJECTABLE (GENERIC)

USES: *Septicemia, serious bacterial infection of CNS, urinary tract, resp tract, GI tract, including peritonitis, skin, bone, soft tissue, including burns; severe infection *P. aeruginosa* w/ carbenicillin; group D streptococci endocarditis w/ PCN-type drug; serious staphylococcal infections, but not the antibiotic of 1st choice; mixed infection w/ staphylococci and gram(−).*
ACTIONS: Aminoglycoside, bactericidal; ↓ protein synth. *Spectrum:* gram(−) (not *Neisseria, Legionella, Acinetobacter*); weaker gram(+) but synergy w/ PCNs.

DOSE:

Adults: *Standard:* 1–2 mg/kg IV q8–12h or daily dosing 4–7 mg/kg q24h IV. *Gram(+) Synergy:* 1 mg/kg q8h.
Peds: ***Infants <7 days <1,200 g:*** 2.5 mg/kg/dose q18–24h. ***Infants >1,200 g:*** 2.5 mg/kg/dose q12–18h. ***Infants >7 days:*** 2.5 mg/kg/dose IV q8–12h. ***Children:*** 2.5 mg/kg/d IV q8h; ↓ w/ renal insufficiency; if obese, dose based on IBW.
W/P: [C, +/−] Avoid other nephrotoxics.
CI: Aminoglycoside sensitivity.
DISP: Premixed Inf 40, 60, 70, 80, 90, 100, 120 mg; ADD-Vantage Inj vials 10 mg/mL; Inj 40 mg/mL; IT preservative-free 2 mg/mL.
SE: Nephro/oto/neurotox.
NOTES: Follow CrCl, SCr, & serum conc for dose adjustments; use IBW to dose (use adjusted if obese >30% IBW); OK to use intraperitoneal for peritoneal dialysis-related infections. *Levels: Peak:* 30 min after Inf; *Trough:* <0.5 hr before next dose; *Therapeutic: Peak:* 5–8 μg/mL, *Trough:* <2 μg/mL, if >2 μg/mL associated w/ renal tox.

GOSERELIN (ZOLADEX)

USES: *Used with flutamide for the management of locally confined carcinoma of the prostate and palliative treatment of advanced carcinoma of the prostate, *endometriosis, breast cancer.
ACTIONS: LHRH agonist, transient ↑ then ↓ in LH, w/ ↓ testosterone.
DOSE: 3.6 mg SQ (implant) q28d or.10.8 mg SQ q3mo; usually upper abdominal wall.
W/P: [X, −].
CI: Pregnancy, breast-feeding, 10.8-mg implant not for women.
DISP: SQ implant 3.6 (1 mo), 10.8 mg (3 mo).
SE: Hot flashes, ↓ libido, gynecomastia, & transient exacerbation of cancer-related bone pain (“flare reaction” 7–10 days after 1st dose).
NOTES: Inject SQ into fat in abdominal wall; do not aspirate; females must use contraception.

HEPARIN (GENERIC)

USES: *Treat & prevention of DVT & PE*, unstable angina, AF w/ emboli, & acute arterial occlusion.
ACTIONS: Acts w/ antithrombin III to inactivate thrombin & ↓ thromboplastin formation.

DOSE:

Adults: *Prophylaxis:* 3,000–5,000 U SQ q8–12h. *DVT/PE Treat:* Load 50–80 U/kg IV (max. 10,000 U), then 10–20 U/kg IV qh (adjust based on PTT).
Peds/Infants: Load 50 U/kg IV bolus, then 20 U/kg/h IV by cont Inf. ***Children:*** Load 50 U/kg IV, then 15–25 U/kg cont Inf or 100 U/kg/dose q4h IV intermittent bolus (adjust based on PTT).
W/P: [C, +] ↑ Risk of hemorrhage w/ anticoagulants, ASA, anti-plt, cephalosporins w/ MTT side chain.
CI: Uncontrolled bleeding, severe thrombocytopenia, suspected ICH.
DISP: Unfractionated Inj 10, 100, 1,000, 2,000, 2,500, 5,000, 7,500, 10,000, 20,000, 40,000 U/mL.
SE: Bruising, bleeding, thrombocytopenia.
NOTES: Follow PTT, thrombin time, or activated clotting time; little PT effect; therapeutic PTT 1.5–2 control for most conditions; monitor for heparin-induced thrombocytopenia w/ plt counts; new "USP" formulation heparin is ~10% less effective than older formulations.

HEXAMINOLEVULINATE (CYSVIEW)

USES: *An optical imaging agent used in the cystoscopic detection of nonmuscle invasive papillary cancer of the bladder in patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Used with the Karl Storz D-Light C photodynamic diagnostic (PDD) system to perform cystoscopy with blue (360–450 nm) and white light.
ACTIONS: An ester of the heme precursor, aminolevulinic acid; concentrates in abnormal cells and fluoresces red under blue light.
DOSE: 50 mL instilled intravesically; cysto 30 min after evacuation of Cysview, but no less than 1 or more than 3 hr after instillation.
W/P: [C, −] Not a replacement for random bladder biopsies; not for repetitive use; false positive fluorescence: inflammation, cystoscopic trauma, scar tissue or previous bladder biopsy.
CI: Porphyria, gross hematuria, BCG or intravesical chemo w/in 90 days; hypersensitivity product.
DISP: Kit w/ 100 mg Cysview and 50 mL diluent.
SE: Bladder spasm, dysuria, hematuria, bladder pain, procedural pain, urinary retention, headache, anaphylaxis.
NOTES: Perform a complete cysto under white light and then under blue light. Document information about location and appearance of suspicious lesions and areas seen under both white and blue lights. Abnormalities of the bladder mucosa during blue light cystoscopy are characterized by the detection of red, homogenous and intense fluorescence. Necrotic cells generally do not fluoresce. (Product is Hexvix in Europe)

HISTRELIN ACETATE (SUPPRELIN LA, VANTAS)

USES: *Advanced PCa [*Vantas*], central precocious puberty [*Supprelin LA*].*
ACTIONS: GNRH agonist; paradoxically ↑ release of GnRH w/ ↓ LH from anterior pituitary; in men ↓ testosterone.
DOSE: *Vantas*: 50 mg SQ implant q12mo inner aspect of the upper arm; *Supprelin LA:* 1 implant q12mo.
W/P: [X, −] Transient "flare reaction" at 7–14 days after 1st dose [LH/testosterone surge before suppression]); w/ impending cord compression or urinary tract obstruction; ↑ risk DM, CV disease, MI.
CI: GNRH sensitivity, pregnancy.
DISP: 50 mg 12-mo SQ implant.
SE: Hot flashes, fatigue, implant site reaction, testis atrophy, gynecomastia.
NOTES: Nonsteroidal antiandrogen (eg, bicalutamide) may block flare in men w/ PCa.

HUMAN PAPILLOMAVIRUS RECOMBINANT VACCINE (CERVARIX [TYPES 16, 18] , GARDASIL [TYPES 6, 11, 16, 18])

USES: *Prevent cervical cancer, precancerous genital lesions (*Cervarix and Gardasil*), genital warts, anal cancer and oral cancer (*Gardasil*) d/t to HPV types 16, 18 (*Cervarix*) and types 6, 11, 16, 18 (*Gardasil*) in females 9–26 yr*; prevent genital warts, anal cancer, and anal intraepithelial neoplasia in males 9–26 yr (*Gardasil*).*
ACTIONS: Recombinant vaccine, passive immunity.
DOSE: 0.5 mL IM, then 1 and 6 mo (*Cervarix*), or 2 and 6 mo (*Gardasil*) (upper thigh or deltoid).
W/P: [B, ?/−].
DISP: Single-dose vial & prefilled syringe: 0.5 mL.
SE: Erythema, pain at Inj site, fever, syncope, venous thromboembolism.
NOTES: 1st cancer prevention vaccine, 90% effective in preventing CIN 2 or more severe disease in HPV naive populations; report adverse events to Vaccine Adverse Events Reporting System (VAERS: 1-800-822-7967); continue cervical cancer screening. Hx of genital warts, abn Pap smear, or + HPV DNA test is not contraindication to vaccination.

HYDROCHLOROTHIAZIDE (MICROZIDE, GENERIC)

USES: *Edema, HTN,* prevent stones in hypercalciuria.
ACTIONS: Thiazide diuretic; ↓ distal tubule Na^+ reabsorption; Thiazides urine calcium ↓ possibly by an increase in calcium absorption in the proximal tubule, induced by volume contraction.

DOSE:

Adults: 25–100 mg/d PO single or ÷ doses; 200 mg/d max.
Peds: ***<6 mo:*** 2–3 mg/kg/d in 2 ÷ doses. ***>6 mo:*** 2 mg/kg/d in 2 ÷ doses.
W/P: [D, +] Idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma; latent DM may become manifest.
CI: Anuria, sulfonamide allergy, renal insufficiency.

DISP: Tabs 25, 50, mg; caps 12.5 mg; PO soln 50 mg/5 mL.
SE: ↓ K^+, hyperglycemia, hyperuricemia, ↓ Na^+; sun sensitivity.
NOTES: Follow K^+, may need supplementation.

HYDROCHLOROTHIAZIDE/AMILORIDE (MODURETIC, GENERIC)

USES: *HTN.*
ACTIONS: Combined thiazide & K^+-sparing diuretic.
DOSE: 1–2 tabs/d PO.
W/P: [D, ?].
CI: Renal failure, sulfonamide allergy.
DISP: Tabs (amiloride/HCTZ) 5 mg/50 mg.
SE: ↓ BP, photosensitivity, ↑ K^+/ ↓ K^+, hyperglycemia, ↓ Na^+, hyperlipidemia, hyperuricemia.

HYDROCHLOROTHIAZIDE/SPIRONOLACTONE (ALDACTAZIDE, GENERIC)

USES: *Edema, HTN.*
ACTIONS: Thiazide & K^+-sparing diuretic.
DOSE: 25–200 mg each component/d, ÷ doses.
W/P: [D, +].
CI: Sulfonamide allergy.
DISP: Tabs (HCTZ/spironolactone) 25/25, 50/50 mg.
SE: Photosensitivity, ↓ BP, ↑ or ↓ K^+, ↓ Na^+, hyperglycemia, hyperlipidemia, hyperuricemia.

HYDROCHLOROTHIAZIDE/TRIAMTERENE (DYAZIDE, MAXZIDE, GENERIC)

USES: *Edema & HTN.*
ACTIONS: Combo thiazide & K^+-sparing diuretic.
DOSE: *Dyazide:* 1–2 caps PO daily–BID. *Maxzide:* 1 tab/d PO.
W/P: [D, +/−].
CI: Sulfonamide allergy.
DISP: (Triamterene/HCTZ) 37.5/25, 75/50 mg.
SE: Photosensitivity, ↓ BP, ↑ or ↓ K^+, ↓ Na^+, hyperglycemia, hyperlipidemia, hyperuricemia.
NOTES: HCTZ component in Maxzide more bioavailable than in Dyazide.

HYDROCODONE (ZOHYDRO ER)

WARNING: Addiction, abuse, misuse, overdose and death risk. Fatal respiratory depression; overdose especially in children can be fatal. With pregnancy neonatal opioid withdrawal syndrome possible. Do not consume alcohol.
USES: *Pain severe enough to require daily, around-the-clock, long-term opioid.*
ACTIONS: Opioid analgesic.

DOSE: *1st Opioid Analgesic:* 10 mg cap Q 12 hr. *Not Opiod tolerant:* 10 mg cap Q 12 hr (Opioid tolerant: Receiving, for >1 wk, at least 60 mg oral morphine/d, 25 μg transdermal fentanyl/h, 30 mg oral oxycodone/d, 8 mg oral hydromorphone/d, 25 mg oral oxymorphone/d, or an equianalgesic dose of another opioid) increase in increments of 10 mg every 12 hr every 3–7 days to effect; Conversion from other oral opioids see package insert.
W/P: [D, +/−] see "Warning"; w/ other CNS depressants, monitor elderly, debilitated for resp depression; CYP3A4 inhibitors may ↑ effect.
CI: Significant respiratory depression; severe bronchial asthma or hypercarbia; paralytic ileus; hypersensitivity to ingredients.
DISP: ER caps 10/15/20/30/40/50 mg.
SE: Constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, others.
NOTES: Swallow capsules whole; do not crush/chew; not a PRN use drug.

HYDROCODONE/ACETAMINOPHEN (HYCET, LORCET, GENERIC) [C-III]

WARNING: Acetaminophen has been associated with acute liver failure (liver transplant and death possible). Most cases associated with doses >4,000 mg/d and often involve more than 1 acetaminophen-containing product.
USES: *Mod–severe pain.*
ACTIONS: Narcotic analgesic w/ nonnarcotic analgesic.

DOSE:

Adults: 1–2 caps or tabs PO q4–6h PRN; soln 15 mL q4–6h.
Peds: Soln (*Hycet*) 0.27 mL/kg q4–6h.
W/P: [C, M].
CI: CNS depression, severe resp depression.
DISP: Many formulations; specify hydrocodone/acetaminophen dose; caps 5/500 mg; tabs 2.5/500, 5/300, 5/325, 5/500, 7.5/300, 7.5/325, 7.5/500, 7.5/650, 7.5/750,10/300, 10/325, 10/500, 10/650, 10/660, 10/750 mg; soln Hycet (fruit punch) 7.5 mg hydrocodone/325 mg acetaminophen/15 mL.
SE: GI upset, sedation, fatigue.
NOTES: Do not exceed >4 g acetaminophen/d; see Acetaminophen note.

HYDROCODONE/IBUPROFEN (REPREXAIN, VICOPROFEN, GENERIC) [C-III]

USES: *Mod–severe pain (<10 days).*
ACTIONS: Narcotic w/ NSAID.
DOSE: 1–2 tabs q4–6h PRN.
W/P: [C, M] Renal insufficiency; ↓ effect w/ ACE inhibitor & diuretics; ↑ effect w/ CNS depressants, EtOH, MAOI, ASA, tricyclic antidepressants, anticoagulants.
CI: Component sensitivity.
DISP: Tabs 2.5/5/7.5/10 mg hydrocodone/200 mg ibuprofen.
SE: Sedation, fatigue, GI upset.
NOTES: Not for arthritis.

HYDROCORTISONE, RECTAL (ANUSOL-HC SUPPOSITORY, CORTIFOAM RECTAL, PROCTOCORT, OTHERS, GENERIC)

USES: *Painful anorectal conditions*, radiation proctitis, ulcerative colitis.
ACTIONS: Anti-inflammatory steroid.

DOSE:

Adults: Ulcerative colitis: 10–100 mg PR daily–BID for 2–3 wk.
W/P: [B, ?/−].
CI: Component sensitivity.
DISP: *Hydrocortisone acetate:* Rectal aerosol 90 mg/applicator; supp 25 mg. *Hydrocortisone base:* Rectal 0.5%, 1%, 2.5%; rectal susp 100 mg/60 mL.
SE: Minimal systemic effect.

HYDROCORTISONE, SYSTEMIC (CORTEF, SOLU-CORTEF, GENERIC)

See also Steroids Systemic and Topical.
USE: Adrenal insufficiency.
ACTION: Glucocorticoid.
DOSE: 2 mg/kg IV/IO bolus; max. dose 100 mg.
W/P: [B, −].
CI: Viral, fungal, or tubercular skin lesions; serious infections (except septic shock or TB meningitis).
SE: *Systemic:* ↑ Appetite, insomnia, hyperglycemia, bruising.
NOTES: May cause hypothalamic–pituitary–adrenal axis suppression.

HYDROMORPHONE (DILAUDID, DILAUDID HP, GENERIC) [C–II]

WARNING: A potent Schedule II opioid agonist; highest potential for abuse and risk of resp depression. HP formula is highly concentrated; do not confuse w/ standard formulations, OD and death could result. Alcohol, other opioids, CNS depressants ↑ resp depressant effects.
USES: *Mod–severe pain.*
ACTIONS: Narcotic analgesic.
DOSE: 1–4 mg PO, IM, IV, or PR q4–6h PRN; 3 mg PR q6–8h PRN; ↓ w/ hepatic failure.
W/P: [B (D if prolonged use or high doses near term), ?] ↑ Resp depression and CNS effects, CNS depressants, phenothiazines, tricyclic antidepressants.
CI: CNS lesion w/ ↑ ICP, COPD, cor pulmonale, emphysema, kyphoscoliosis, status asthmaticus; HP-Inj form in OB analgesia.
DISP: Tabs 2, 4, 8 mg scored; liq 5 mg/5 mL or 1 mg/mL; Inj 1, 2, 4 mg, *Dilaudid HP* is 10 mg/mL; supp 3 mg.
SE: Sedation, dizziness, GI upset.
NOTES: Morphine 10 mg IM = hydromorphone 1.5 mg IM.

HYDROXYZINE (ATARAX, VISTARIL, GENERIC)

USES: *Anxiety, sedation, itching.*
ACTIONS: Antihistamine, antianxiety.

DOSE:
Adults: *Anxiety/sedation:* 50–100 mg PO or IM QID or PRN (max. 600 mg/d). *Itching:* 25–50 mg PO or IM TID–QID.
Peds: 0.5–1.0 mg/kg/24 h PO or IM q6h; ↓ w/ hepatic impairment.
W/P: [C, +/−] ↑ Effects w/ CNS depressants, anticholinergics, EtOH.
CI: Component sensitivity.
DISP: Tabs 10, 25, 50 mg; caps 25, 50 mg; syrup 10 mg/5 mL; susp 25 mg/5 mL; Inj 25, 50 mg/mL.
SE: Drowsiness, anticholinergic effects.
NOTES: Used to potentiate narcotic effects; not for IV/SQ (thrombosis & digital gangrene possible).

HYOSCYAMINE (ANASPAZ, CYSTOSPAZ, LEVSIN, OTHERS, GENERIC)

USES: *Spasm w/ GI & bladder disorders.*
ACTIONS: Anticholinergic.

DOSE:

Adults: 0.125–0.25 mg (1–2 tabs) SL/PO TID–QID, ac & hs; 1 SR caps q12h.
W/P: [C, +] ↑ Effects w/ amantadine, antihistamines, antimuscarinics, haloperidol, phenothiazines, tricyclic antidepressants, MAOI.
CI: Bladder outlet obstruction, GI obst, narrow-angle glaucoma, myasthenia gravis, paralytic ileus, ulcerative colitis, MI.
DISP: (*Cystospaz-M, Levsinex*) time-release caps 0.375 mg; elixir (EtOH); soln 0.125 mg/5 mL; Inj 0.5 mg/mL; tab 0.125 mg; tab (*Cystospaz*) 0.15 mg; XR tab (*Levbid*) 0.375 mg; SL (*Levsin SL*) 0.125 mg.
SE: Dry skin, xerostomia, constipation, anticholinergic SE, heat prostration w/ hot weather.
NOTES: Administer tabs ac.

HYOSCYAMINE, ATROPINE, SCOPOLAMINE, & PHENOBARBITAL (DONNATAL, OTHERS, GENERIC)

USES: *Irritable bowel, spastic colitis, peptic ulcer*, spastic bladder.
ACTIONS: Anticholinergic, antispasmodic.
DOSE: 0.125–0.25 mg (1–2 tabs) TID–QID, 1 caps q12h (SR), 5–10 mL elixir TID–QID or q8h.
W/P: [D, M].
CI: Glaucoma, obstructive uropathy, GI obstruction, unstable patient with hemorrhage, severe ulcerative colitis.
DISP: Many combos/manufacturers. Caps *(Donnatal, others):* Hyoscyamine 0.1037 mg/atropine 0.0194 mg/scopolamine .0065 mg/phenobarbital 16.2 mg. Tabs *(Donnatal, others):* Hyoscyamine 0.1037 mg/atropine .0194 mg/scopolamine 0.0065 mg/phenobarbital 16.2 mg. *LA (Donnatal):* Hyoscyamine 0.311 mg/ atropine 0.0582 mg/scopolamine 0.0195 mg/phenobarbital .6 mg. Elixirs *(Donnatal, others):* Hyoscyamine 0.1037 mg/atropine .0194 mg/scopolamine 0.0065 mg/phenobarbital 16.2 mg/5 mL.
SE: Sedation, xerostomia, constipation.
NOTE: FDA has classified the indications as “possibly” effective.

IBANDRONATE (BONIVA, GENERIC)

USES: *Treat osteoporosis in postmenopausal women.*
ACTIONS: Bisphosphonate, ↓ osteoclast-mediated bone resorption.
DOSE: 2.5 mg PO daily or 150 mg 1 × mo on same day (do not lie down for 60 min after); 3 mg IV over 15–30 s q3mo; w/ low risk for fracture, consider D/C after 3–5 yr.
W/P: [C, ?/−] Do not use w/ CrCl <30 mL/min; w/ inability to stand/sit upright for 60 min (PO); anaphylaxis reported; tissue damage with inappropropriate IV administration.
CI: Hypocalcemia, component hypersensitivity.
DISP: Tabs 2.5, 150 mg, Inj IV 3 mg/3 mL.
SE: Osteonecrosis of the jaw (ONJ) (avoid extensive dental procedures) N/diarrhea, headache, dizziness, asthenia, HTN, infection, dysphagia, esophagitis, esophageal/gastric ulcer, musculoskelet al pain.
NOTES: Take 1st thing in a.m. w/ water (6–8 oz) >60 min before 1st food/beverage & any meds w/ multivalent cations; give adequate Ca^{2+} & vit D supls; possible association between bisphosphonates & severe muscle/bone/joint pain; may ↑ atypical subtrochanteric femur fractures.

IBUPROFEN, ORAL (ADVIL, MOTRIN, MOTRIN IB, RUFEN, OTHERS, GENERIC) [OTC]

WARNING: May ↑ risk of CV events & GI bleeding.
USES: *Arthritis, pain, fever.*
ACTIONS: NSAID.

DOSE:

Adults: 200–800 mg PO BID–QID (max. 2.4 g/d).
Peds: 30–40 mg/kg/d in 3–4 ÷ doses (max. 40 mg/kg/d); w/ food.
W/P: [C (D ≥30 wk gestation), +] May interfere w/ ASAs anti-plt effect if given <8 hr before ASA.
CI: 3rd-tri PREGNANCY, severe hepatic impairment, allergy, use w/ other NSAIDs, upper GI bleeding, ulcers.
DISP: Tabs 100, 200, 400, 600, 800 mg; chew tabs 50, 100 mg; caps 200 mg; susp 50 mg/1.25 mL, 100 mg/2.5 mL, 100 mg/5 mL, 40 mg/mL (Motrin IB & Advil OTC 200 mg are the OTC forms).
SE: Dizziness, peptic ulcer, plt inhibition, worsening of renal insufficiency.

IBUPROFEN, PARENTERAL (CALDOLOR)

WARNING: May ↑ risk of CV events & GI bleeding.
USES: *Mild–mod pain, as adjunct to opioids, ↓ fever.*
ACTIONS: NSAID.
DOSE: *Pain:* 400–800 mg IV over 30 min q6h PRN; *Fever:* 400 mg IV over 30 min, the 400 mg q4–6h or 100–200 mg q4–6h PRN.
W/P: [C <30 wk, D after 30 wk, ?/−] May ↓ ACE effects; avoid w/ ASA, and <17 yr.
CI: Hypersensitivity NSAIDs; asthma, urticaria, or allergic reactions w/ NSAIDs, periop CABG.

DISP: Vials 400 mg/4 mL, 800 mg/8 mL.
SE: N/V, headache, flatulence, hemorrhage, dizziness.
NOTES: Keep well hydrated; use lowest dose/shortest duration possible.

IFOSFAMIDE (IFEX, GENERIC)

WARNING: Administer only under supervision by an MD experienced in chemotherapy; hemorrhagic cystitis, myelosupp; confusion, coma possible.
USES: *Testis cancer, 3rd line with other agents.*
ACTIONS: Alkylating agent.
DOSE: (Per protocol) 1.2 g/m^2/d for 5-day bolus or cont Inf; 2.4 g/m^2/d for 3 days; w/ mesna uroprotection; ↓ in renal/hepatic impairment.
W/P: [D, M] ↑ Effect w/ phenobarbital, carbamazepine, phenytoin; St. John's wort may ↓ levels.
CI: ↓ BM function, PREGNANCY.
DISP: Inj 1, 3 g.
SE: Hemorrhagic cystitis, nephrotoxic, N/V, mild–mod leukopenia, lethargy & confusion, alopecia, ↑ LFT.
NOTES: Administer w/ mesna to prevent hemorrhagic cystitis; WBC nadir 10–14 days; recovery 21–28 days.

IMIPENEM/CILASTATIN (PRIMAXIN, GENERIC)

USES: *Serious infections: Lower respiratory, UTI, intra-abdominal, gyn, sepsis, bone and joint, skin and skin structure, endocarditis, polymicrobial infections* d/t susceptible bacteria.
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* gram(+) (*S. aureus,* group A & B streptococci), gram(−) (not *Legionella*), anaerobes.

DOSE:

Adults: 250–1,000 mg (imipenem) IV q6–8h, 500–750 mg IM.
Peds: 60–100 mg/kg/24 h IV ÷ q6h; ↓ if CrCl is <70 mL/min.
W/P: [C, +/−] Probenecid ↑ tox.
CI: Peds pts w/ CNS infection (↑ seizure risk) & <30 kg w/ renal impairment.
DISP: Inj (imipenem/cilastatin) 250/250, 500/500 mg.
SE: Seizures if drug accumulates, GI upset, thrombocytopenia.

IMIPRAMINE (TOFRANIL, GENERIC)

WARNING: Close observation for suicidal thinking or unusual changes in behavior.
USES: *Depression, enuresis in children >6 yo.*
ACTIONS: Tricyclic antidepressant; ↑ CNS synaptic serotonin or norepinephrine.

DOSE:

Adults: *Hospitalized:* Initial 100 mg/24 h PO in ÷ doses; ↑ over several wk 300 mg/d max. *Outpatient:* Maint 50–150 mg PO hs, 300 mg/24 h max.
Peds: *Antidepressant:* 1.5–5 mg/kg/24 h ÷ daily–QID. *Enuresis:* ***>6 yr:*** 10–25 mg PO qhs; ↑

by 10–25 mg at 1–2-wk intervals (max. 50 mg for 6–12 yr, 75 mg for >12 yr); Treat for 2–3 mo, then taper.
W/P: [D, ?/−].
CI: Use w/ MAOIs, narrow-angle glaucoma, recovery from AMI, pregnancy, CHF, angina, CV disease, arrhythmias.
DISP: Tabs 10, 25, 50 mg; caps 75, 100, 125, 150 mg.
SE: CV Sxs, dizziness, xerostomia, discolored urine.
NOTES: Less sedation than amitriptyline; retrograde ejaculation 25 mg TID × 2 wk.

IMIQUIMOD CREAM (ALDARA, ZYCLARA, GENERIC)

USES: *Anogenital warts, HPV, condylomata acuminata (*Aldara, Zyclara*); actinic keratosis (*Zyclara*); basal cell carcinoma (*Aldara*)* penile CIS.
ACTIONS: Inducer of interferon-α, enhances cell-mediated cytolytic activity.

DOSE:
Adults/Peds: ***>12 yr:*** *Warts:* 1 × day up to 8 wk (*Zyclara*); apply 3×/wk, leave on 6–10 h & wash off w/ soap & water, continue 16 wk max. (*Aldara*); *Actinic keratosis*: apply daily two 2 × wk cycle separate by 2 wk; *Basal cell:* Apply 5 d/wk × 6 wk, dose based on lesion size (see label).
W/P: [B, ?] Topical only, not intravaginal or intra-anal.
CI: Component sensitivity.
DISP: 2.5% packet, 3.75% packet or pump (*Zyclara*); single-dose packets 5% (250-mg cream *Aldara*).
SE: Local skin reactions, flu-like syndrome.
NOTES: Not a cure; may weaken condoms/Vag diaphragms, wash hands before & after use; efficacy was not demonstrated for molluscum contagiosum in children 2–12 yr; typical penile regimen described: apply 12 hr every 48 hr for 28 days.

INDIGO CARMINE, INJECTION [INDIGOTINDISULFONATE] (GENERIC)

USES: *Localization of ureteral orifices during cystoscopy,* identification of urinary tract injury intraoperatively.
ACTIONS: Excreted and appears in urine as blue color usually within 10 min of injection.
DOSE: 5 mL IV (preferred) or IM.
W/P: [C, ?].
CI: Allergy to compound.
DISP: 5 mg vials for injection; do not dilute or inject with other solutions.
SE: Mild pressor, rare idiosyncratic reaction.
NOTES: May transiently alter pulse oximeter; originally used as a renal function test. Label is not officially approved by the FDA.

INDOMETHACIN (INDOCIN, TIVORBEX, GENERIC)

WARNING: May ↑ risk of CV events & GI bleeding; not for post-CABG pain
USES: *Arthritis (gouty, osteo, rheumatoid); ankylosing spondylitis; close ductus arteriosus; ** *Tivorbex*: acute pain*

ACTIONS: ↓ Prostaglandins.

DOSE:

Adults: 25–50 mg PO BID–TID, max. 200 mg/d. ***Infants:*** 0.2–0.25 mg/kg/dose IV; may repeat in 12–24 hr max 3 doses; w/ food.
W/P: [C, +].
CI: ASA/NSAID sensitivity, peptic ulcer/active GI bleed, precipitation of asthma/urticaria/rhinitis by NSAIDs/ASA, premature neonates w/ NEC, ↓ renal Fxn, active bleeding, thrombocytopenia, 3rd tri PRG.
DISP: Inj 1 mg/vial; caps 25, 50 mg; susp 25 mg/5 mL; *Tivorbex*: 20, 40 mg caps.
SE: GI bleeding or upset, dizziness, edema.
NOTES: Monitor renal Fxn.

INTERFERON ALFA-2B (INTRON-A)

WARNING: Can cause or aggravate fatal or life-threatening neuropsychiatric autoimmune, ischemic, and infectious disorders. Monitor closely (systemic).
USES: *Hairy cell leukemia, Kaposi sarcoma, melanoma, CML, chronic hep B & C, follicular NHL, condylomata acuminate,* RCC, superficial bladder cancer.
ACTIONS: Antiproliferative; modulates host immune response; ↓ viral replication in infected cells.
DOSE: Per protocols.
Adults: Per protocols. *Condyloma*: 1 MU/lesion (max. 5 lesions) 3×/wk (on alternate days) for 3 wk. *Bladder CIS:* High dose (50–100 MU) intravesically weekly; different regimens described; typically 6 wk. *Bladder carcinoma, superficial BCG refractory*: Used in combination with intravesical BCG (either standard or reduced dose BCG) with 50–100 MU interferon-α 2b for 6 wk; maintenance regimens described.
CI: Benzyl alcohol sensitivity, decompensated liver disease, autoimmune hep immunosuppressed, pregnancy, CrCl <50 mL/ min in combo w/ ribavirin.
DISP: Inj forms: powder 10/18/50 MIU; soln 6/10 MIU/mL (see also polyethylene glycol [PEG]-interferon).
SE: Flu-like Sxs, fatigue, anorexia, neurotox at high doses; up to 40% neutralizing Ab w/ Treat; not FDA approved for intravesical use; with systemic therapy follow baseline CXR and ECG; CBC w/ diff/platelets (baseline and routinely), LFTs, creatinine, electrolytes, triglycerides, thyroid function.

IRBESARTAN (AVAPRO)

WARNING: D/C immediately if pregnancy detected.
USES: *HTN, diabetic nephropathy*, CHF.
ACTIONS: Angiotensin II receptor antagonist.
DOSE: 150 mg/d PO, may ↑ to 300 mg/d.
W/P: [C (1st tri; D 2nd/3rd tri), ?/−].
CI: Component sensitivity; w/ aliskiren in diabetics
DISP: Tabs 75, 150, 300 mg
SE: Fatigue, ↓ BP, ↑ K

ISONIAZID (INH)

WARNING: Severe & sometimes fatal hep may occur usually w/in 1st 3 mo of Tx, although may develop after mo of Tx.
USES: *Treat & prophylaxis of TB.*
ACTIONS: Bactericidal; interferes w/ mycolic acid synth, disrupts cell wall.

DOSE:

Adults: *Active TB:* 5 mg/kg/24 h PO or IM (usually 300 mg/d) or *DOT:* 15 mg/kg (max. 900 mg) 3×/wk. *Prophylaxis:* 300 mg/d PO for 6–12 mo or 900 mg 2×/wk.
Peds: *Active TB:* 10–15 mg/kg/d daily PO or IM 300 mg/d max. *Prophylaxis:* 10 mg/kg/24 h PO; ↓ in hepatic/renal dysfunction.
W/P: [C, +] Liver disease, dialysis; avoid EtOH.
CI: Acute liver disease, Hx INH hep.
DISP: Tabs 100, 300 mg; syrup 50 mg/5 mL; Inj 100 mg/ mL.
SE: Hep, peripheral neuropathy, GI upset, anorexia, dizziness, skin reaction.
NOTES: Use w/ 2–3 other drugs for active TB, based on INH resistance patterns when TB acquired & sensitivity results; prophylaxis usually w/ INH alone. IM rarely used. ↓ Peripheral neuropathy w/ pyridoxine 50–100 mg/d. See CDC guidelines (http://www.cdc.gov/tb/) for current TB recommendations.

ITRACONAZOLE (ONMEL, SPORANOX, GENERIC)

WARNING: CI w/ cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol. Serious CV events (eg, ↑ QT, torsades de pointes, VT, cardiac arrest, and/or sudden death) reported w/ these meds and other CYP3A4 inhibitor. Do not use for onychomycosis w/ ventricular dysfunction. Negative inotropic effects have been observed following IV administration D/C/reassess use if S/Sxs of HF occur during Tx.
USES: *Fungal infections (aspergillosis, blastomycosis, histoplasmosis, candidiasis, onychomycosis).*
ACTIONS: Azole antifungal, ↓ ergosterol synth.
DOSE: Dose based on indication. 200 mg PO daily–TID (caps w/ meals or cola/grapefruit juice); PO soln on empty stomach; avoid antacids.
W/P: [C, −] Numerous interactions.
CI: See “Warning"; pregnancy or considering pregnancy; ventricular dysfunction CHF.
DISP: Caps 100 mg; soln 10 mg/mL.
SE: N/V, rash, hepatotoxic, ↓ K^+, CHF, ↑ BP, neuropathy.
NOTES: Soln & caps not interchangeable; useful in pts who cannot take amphotericin B; follow LFTs.

KETOCONAZOLE, ORAL (NIZORAL, GENERIC)

WARNING: (Oral use) Risk of fatal hepatotox. Concomitant dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, ranolazine are CI d/t serious CV adverse events.
USES: *Systemic fungal infections (*Candida,* blastomycosis, histoplasmosis, etc.); refractory

topical dermatophyte infection*; PCa when rapid ↓ testosterone needed or hormone refractory; Cushing's disease medical therapy when surgery not possible.
ACTIONS: Azole, ↓ fungal cell wall synth; high dose blocks P450, to ↓ testosterone production.
DOSE: *PO:* 200 mg PO daily; ↑ to 400 mg PO daily for serious infection. *PCa:* 400 mg PO TID w/ hydrocortisone 20–40 mg divided BID; best on empty stomach.
W/P: [C, −/−] w/ Any agent that ↑ gastric pH (↓ absorption); may enhance anticoagulants; w/ EtOH (disulfiram-like reaction); numerous interactions including statins, niacin; do not use w/ clopidogrel (↓ effect).
CI: CNS fungal infections, w/ dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, ranolazine. Ketoconazole can cause elevated plasma concentrations of these drugs and may prolong QT intervals.
DISP: Tabs 200 mg.
SE: N, rashes, hair loss, headache, ↑ Wt gain, dizziness, disorientation, fatigue, impotence, hepatox, adrenal suppression, acquired cutaneous adherence ("sticky skin syndrome").
NOTES: Monitor LFTs; can rapidly ↓ testosterone levels at high dose.

KETOROLAC, INJECTION (GENERIC)

WARNING: For short-term (≤5 days) Treat of mod–severe acute pain; CI w/ PUD, GI bleed, post CABG, anticipated major surgery, severe renal insufficiency, bleeding diathesis, L&D, nursing, and w/ ASA/NSAIDs. NSAIDs may cause ↑ risk of CV/thrombotic events (MI, stroke). PO CI in peds <16 yr, dose adjustments for <50 kg.
USES: *Pain.*
ACTIONS: NSAID; ↓ prostaglandins.

DOSE:

Adults: 15–30 mg IV/IM q6h; 10 mg PO QID only as continuation of IM/IV; max. IV/IM 120 mg/d, max. PO 40 mg/d; ↓ if >65 yr, elderly, w/ renal impairment, <50 kg.
Peds: ***2–16 yr:*** 1 mg/kg IM × 1 dose; 30 mg max.; IV: 0.5 mg/kg, 15 mg max.; do not use for >5 days.
W/P: [C (D 3rd tri), −] w/ ACE inhibitor, diuretics, BP meds, warfarin.
CI: See "Warning"; as prophylactic analgesic before any major surgery.
DISP: Tabs 10 mg; Inj 15 mg/mL, 30 mg/mL.
SE: Bleeding, peptic ulcer disease, ↑ Cr & LFTs, ↑ BP, edema, dizziness, allergy.
NOTES: Volume depletion increases renal toxicity.

KETOROLAC, NASAL (SPRIX)

WARNING: For short-term (5 days) use; CI w/ PUD, GI bleed, suspected bleeding risk, postop CABG, advanced renal disease or risk of renal failure w/ vol depletion; risk CV thrombotic events (MI, stroke). Not indicated for use in children.
USES: *Short-term (<5 days) Treat pain requiring opioid level analgesia.*
ACTIONS: NSAID; ↓ prostaglandins.
DOSE: ***<65 yr:*** 31.5 mg (one 15.75-mg spray each nostril) q6–8h; max. 126 mg/d. ***≥65 yr, w/ renal impairment or <50 kg:*** 15.75 mg (one 15.75-mg spray in only 1 nostril) q6–8h;

max. 63 mg/d.
W/P: [C (D 3rd tri), −] Do not use w/ other NSAIDs; can cause severe skin reactions; do not use w/ critical bleeding risk; w/ CHF.
CI: See “Warning"; prophylactic to major surgery/L&D, w/ Hx allergy to other NSAIDs recent or Hx of GI bleed or perforation.
DISP: Nasal spray 15.75-mg ketorolac/100-μL spray (8 sprays/bottle).
SE: Nasal discomfort/rhinitis, ↑ lacrimation, throat irritation, oliguria, rash, ↓ HR, ↓ urine output, ↑ ALT/AST, ↑ BP.
NOTES: Discard open bottle after 24 hr.

KUNECATECHINS [SINECATECHINS] (VEREGEN)

USES: *External genital/perianal warts.*
ACTIONS: Unknown; green tea extract.
DOSE: Apply 0.5-cm ribbon to each wart 3×/d until all warts clear; not >16 wk.
W/P: [C, ?].
DISP: Oint 15%.
SE: Erythema, pruritus, burning, pain, erosion/ulceration, edema, induration, rash, phimosis.
NOTES: Wash hands before/after use; not necessary to wipe off prior to next use; avoid on open wounds, may weaken condoms & Vag diaphragms, use in combo is not recommended.

LACTOBACILLUS (LACTINEX GRANULES) [OTC]

USES: *Control of diarrhea*, especially after antibiotic Treat.
ACTIONS: Replaces normal intestinal flora, lactase production; *Lactobacillus acidophilus* and *Lactobacillus helveticus*.

DOSE:
Adults & Peds: ***>3 yr:*** 1 packet, 1–2 caps, or 4 tabs QD–QID
W/P: [A, +] Some products may contain whey.
CI: Milk/lactose allergy.
DISP: Tabs, caps; granules in packets (all OTC).
SE: Flatulence.
NOTES: May take granules on food.

LANTHANUM CARBONATE (FOSRENOL)

USES: *Hyperphosphatemia in end-stage renal disease.*
ACTIONS: Phosphate binder.
DOSE: 750–1,500 mg PO daily in ÷ doses, w/ or immediately after meal; titrate q2–3wk based on PO_4 levels.

W/P: [C, ?/−] No data in GI disease; not for peds.
CI: Bowel obstruction, fecal impaction, ileus.
DISP: Chew tabs 500, 750, 1,000 mg.
SE: N/V, graft occlusion, headache, ↓ BP.
NOTES: Chew tabs before swallowing; separate from meds that interact w/ antacids by 2 hr.

LEUPROLIDE (ELIGARD, LUPRON, LUPRON DEPOT, LUPRON DEPOT-PED, GENERIC)

USES: *Advanced PCa (all except Depot-Ped), endometriosis (*Lupron*), uterine fibroids (*Lupron*), & precocious puberty (*Lupron-Ped*).*
ACTIONS: LHRH agonist; paradoxically ↓ release of GnRH w/ ↓ LH from anterior pituitary; in men ↓ testosterone, in women ↓ estrogen.

DOSE:

Adults: *PCa: Lupron DEPOT*: 7.5 mg IM q28d or 22.5 mg IM q3mo or 30 mg IM q4mo or 45 mg IM q6mo. *Eligard:* 7.5 mg SQ q28d or 22.5 mg SQ q3mo or 30 mg SQ q4mo or 45 mg SQ 6 mo. *Endometriosis (Lupron DEPOT):* 3.75 mg IM qmo × 6 or 11.25 IM q3mo × 2. *Fibroids:* 3.75 mg IM qmo × 3 or 11.25 mg IM × 1.
Peds: *CPP (Lupron DEPOT- Ped):* 50 μg/kg/d SQ Inj; ↑ by 10 μg/kg/d until total downregulation achieved. *Lupron DEPOT:* ***<25 kg:*** 7.5 mg IM q4wk; ***>25–37.5 kg:*** 11.25 mg IM q4wk; ***>37.5 kg:*** 15 mg IM q4wk, ↑ by 3.75 mg q4wk until response.
W/P: [X, −] w/ Impending cord compression in PCa, ↑ QT w/ meds or pre-existing CV disease; postmarketing reports of seizures.
CI: AUB, implant in women/peds; pregnancy.
DISP: Inj 5 mg/mL; *Lupron DEPOT:* 3.75 mg (1 mo for fibroids, endometriosis); *Lupron DEPOT* for PCa: 7.5 mg (1 mo), 11.25 (3 mo), 22.5 (3 mo), 30 mg (4 mo), 45 mg (6 mo); *Eligard depot* for PCA: 7.5 (1 mo); 22.5 (3 mo), 30 (4 mo), 45 mg (6 mo); *Lupron DEPOT-Ped:* 7.5, 11.25, 15, 30 mg.
SE: Hot flashes, gynecomastia, N/V, alopecia, anorexia, dizziness, headache, insomnia, paresthesias, depression exacerbation, peripheral edema, & bone pain (transient "flare reaction" at 7–14 days after the 1st dose [LH/testosterone surge before suppression]); ↓ BMD w/ >6 mo use, bone loss possible, abnormal menses, hyperglycemia.
NOTES: Nonsteroidal antiandrogen (eg, bicalutamide) may block flare in men w/ PCa; Viadur 12 mo form unavailable to new patients.

LEVOFLOXACIN (LEVAQUIN, GENERIC)

WARNING: ↑ Risk Achilles tendon rupture and tendonitis, ↑ in pts >60 yr, on steroids or with organ transplant; avoid w/ myasthenia gravis, may ↑ muscle weakness.
USES: *SSSI, UTI, chronic bacterial prostatitis, acute pyelo, acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, including multidrug-resistant *S. pneumoniae*, nosocomial pneumonia; Treat inhalational anthrax in adults & peds ≥6 mo.*
ACTIONS: Quinolone, ↓ DNA gyrase. *Spectrum:* Excellent gram(+) except MRSA & *E. faecium;* excellent gram(−) except *Stenotrophomonas maltophilia & Acinetobacter* sp; poor anaerobic.

DOSE:

Adults: ***≥18 yr:*** IV/PO: *Bronchitis:* 500 mg qd × 7 days. *Community-acquired pneumonia:* 500 mg qd × 7–14 days or 750 mg qd × days. *Sinusitis:* 500 mg qd × 10–14 days or 750 mg qd × days. *Prostatitis:* 500 mg qd × 28 days. *Uncomp SSSI:* 500 mg qd × 7–10 days. *Comp SSSI/nosocomial pneumonia:* 750 mg qd × 7–14 days. *Anthrax:* 500 mg qd × 60 days; *Uncomp*

UTI: 250 mg qd × 3 days. *Comp UTI/acute pyelo*: 250 mg qd × 10 days or 750 mg qd × 5 days. CrCl 10–19 mL/min: 500 mg then 250 mg q other day or 750 mg, then 500 mg q48h. *Hemodialysis:* 750 mg, then 500 mg q48h.
Peds: ≥***6 mo:*** *Anthrax >50 kg:* 500 mg q24h × 60 days, <50 kg: 8 mg/kg (250 mg/dose max.) q12h for 60 days ↓ w/ renal impairment avoid antacids w/ PO; oral soln 1 hr before, 2 hr after meals; *Community-acquired pneumonia:* ≥6 mo–≤4 yr: 8 mg/kg/dose q12h (max. 750 mg/d), 5–16 yr: 8 mg/kg/dose once daily (750 mg/d).
W/P: [C, −] w/ Cation-containing products (eg, antacids), w/ drugs that ↑ QT interval.
CI: Quinolone sensitivity.
DISP: Tabs 250, 500, 750 mg; premixed IV 250, 500, 750 mg, Inj 25 mg/mL; Leva-Pak 750 mg × 5 days.
SE: N/D, dizziness, rash, GI upset, photosensitivity, CNS stimulant w/ IV use, *C. difficile* enterocolitis; rare fatal hepatox, peripheral neuropathy risk.
NOTES: Use w/ steroids ↑ tendon risk; only for anthrax in peds.

LIDOCAINE; LIDOCAINE W/ EPINEPHRINE (ANESTACON TOPICAL, XYLOCAINE, XYLOCAINE VISCOUS, XYLOCAINE MPF, OTHERS)

USES: *Local anesthetic, epidural/caudal anesthesia, regional nerve blocks, topical on mucous membranes (mouth/pharynx/urethra).*
ACTIONS: Anesthetic; stabilizes neuronal membranes; inhibits ionic fluxes required for initiation and conduction.

DOSE:

Adults: *Local Inj anesthetic:* 4.5 mg/kg max. total dose or 300 mg; w/ epi 7 mg/kg or total 500 mg max. dose. *Oral:* 15 mL viscous swish and spit or *pharyngeal* gargle and swallow, do not use <3-hr intervals or >8 × in 24 hr. *Urethra:* Jelly 5–30 mL (200–300 mg) in men, 3–5 mL female urethra; 600 mg/24 h max.
Peds: *Topical:* Apply max. 3 mg/kg/ dose. *Local Inj anesthetic:* Max. 4.5 mg/kg.
W/P: [B, +] Epi-containing soln may interact w/ tricyclic antidepressants or MAOI and cause severe ↑ BP.
CI: Do not use lidocaine w/ epi on penis, digits, ears, or nose (vasoconstriction & necrosis).
DISP: *Inj local:* 0.5%, 1%, 1.5%, 2%, 4%, 10%, 20%; Inj w/ epi 0.5%/1:200,000, 1%/1:100,000, 2%/1:100,000; (MPF) 1%/1:200,000, 1.5%/1:200,000, 2%/1:200,000; cream 2%, 3%, 4%; lotion 30%, jelly 2%, gel 2%, 2.5%, 4%, 5%; oint 5%; liq 2.5%; soln 2, 4%; viscous 2% topical spray 9.6%.
SE: Dizziness, paresthesias, & seizures associated w/ tox.

LIDOCAINE/PRILOCAINE (EMLA, ORAQ IX)

USES: *Topical anesthetic for intact skin or genital mucous membranes*; adjunct to phlebotomy or dermal procedures.
ACTIONS: Amide local anesthetics.

DOSE:

Adults: *EMLA cream,* thick layer 2–2.5 g to intact skin over 20–25 cm^2 of skin surface, cover

w/ occlusive dressing (eg, Tegaderm) for at least 1 hr. *Anesthetic disc:* 1 g/10 cm^2 for at least 1 hr.
Peds: *Max. dose:* ***<3 mo or <5 kg:*** 1 g/10 cm^2 for 1 hr. ***3–12 mo & >5 kg:*** 2 g/20 cm^2 for 4 hr. ***1–6 yr & >10 kg:*** 10 g/100 cm^2 for 4 hr. ***7–12 yr & >20 kg:*** 20 g/200 cm^2 for 4 hr.
W/P: [B, +].
CI: Methemoglobinemia use on mucous membranes, broken skin, eyes; allergy to amide-type anesthetics.
DISP: Cream 2.5% lidocaine/2.5% prilocaine; anesthetic disc (1 g); periodontal gel 2.5/2.5%.
SE: Burning, stinging, methemoglobinemia.
NOTES: Longer contact time ↑ effect.

LIDOCAINE/TETRACAINE, PATCH (SYNERA) CREAM (PLIAGLIS)

USES: *Topical anesthesia for venipuncture and dermatologic procedures (*Synera*); dermatologic procedures (*Pliaglis*).*
ACTIONS: Combo amide and ester local anesthetic.

DOSE:
Adults & Peds: *Synera:* Apply patch 20–30 min before procedure.
Adults: *Pliaglis:* Apply cream 20–60 min before procedure, volume based on site surface (see label).
W/P: [B, ?/−] Use on intact skin only; avoid eyes; not for mucous membranes; do not use w/ Hx methemoglobinemia anaphylaxis reported; caution w/ Class I antiarrhythmic drugs; remove before MRI.
CI: Component sensitivity (PABA or local anesthetics).
DISP: *Synera* 70 mg lidocaine/70 mg tetracaine in 50 cm^2 patch; *Pliaglis* 70 mg lidocaine/70 mg tetracaine/g (7%/7%) cream 30, 60, 100 g tube.
SE: Erythema, blanching, and edema.

LINDANE (GENERIC)

WARNING: Only for pts intolerant/failed 1st-line Treat w/ safer agents. Seizures and deaths reported w/ repeated/prolonged use. Caution d/t increased risk of neurotox in infants, children, elderly, w/ other skin conditions, and if <50 kg. Instruct pts on proper use and inform that itching occurs after successful killing of scabies or lice.
USES: *Head lice, pubic "crab" lice, body lice, scabies.*
ACTIONS: Ectoparasiticide & ovicide.

DOSE:
Adults & Peds. *Cream or lotion:* Thin layer to dry skin after bathing, leave for 8–12 hr, rinse; also use on laundry. *Shampoo:* Apply 30 mL to dry hair, develop a lather w/ warm water for 4 min, comb out nits.
W/P: [C, −].
CI: Premature infants, uncontrolled seizure disorders, Norwegian scabies, open wounds.
DISP: Lotion 1%; shampoo 1%.
SE: Arrhythmias, seizures, local irritation, GI upset, ataxia, alopecia, N/V, aplastic anemia.

NOTES: Caution w/ overuse (may be absorbed); caution w/ hepatic in pts may repeat Treat in 7 days; try OTC 1st w/ pyrethrins (*Pronto*, *Rid*, others).

LINEZOLID (ZYVOX)

USES: *Infections caused by gram(+) bacteria (including VRE), pneumonia, skin infections.*
ACTIONS: Unique, binds ribosomal bacterial RNA; bactericidal for streptococci, bacteriostatic for enterococci & staphylococci. *Spectrum:* Excellent gram(+) including VRE & MRSA.

DOSE:

Adults: 600 mg IV or PO q12h.
Peds: Ä ≤*11 y:* 10 mg/kg IV or PO q8h (q12h in preterm neonates).
W/P: [C, ?/−].
CI: Concurrent MAOI use or w/in 2 wk, uncontrolled HTN, thyrotoxicosis, vasopressive agents, carcinoid tumor, SSRIs, tricyclics, w/ MAOI (may cause serotonin syndrome when used w/ these psych meds), avoid foods w/ tyramine & cough/cold products w/ pseudoephedrine; w/ ↓ BM.
DISP: Inj 200, 600 mg; tabs 600 mg; susp 100 mg/5 mL.
SE: Lactic acidosis, peripheral/optic neuropathy, HTN, N/diarrhea, headache, insomnia, GI upset, ↓ BM, tongue discoloration prolonged use C. diff infection.
NOTES: Check weekly CBC; not for gram(−) infection, ↑ deaths in catheter-related infections; MAOI activity.

LISINOPRIL (PRINIVIL, ZESTRIL, GENERIC)

WARNING: ACE inhibitor can cause fet al injury/death in 2nd/3rd tri; D/C w/ *pregnancy*.
USES: *HTN, CHF, prevent diabetic nephropathy & acute MI*
ACTIONS: ACE inhibitor.
DOSE: 5–40 mg/24 h PO daily–BID, CHF target 40 mg/d. *AMI:* 5 mg w/in 24 hr of MI, then 5 mg after 24 hr, 10 mg after 48 hr, then 10 mg/d; ↓ in renal insufficiency; use low dose, ↑ slowly in elderly.
W/P: [C (1st tri) D (2nd, 3rd tri), −] w/ Aortic stenosis/ cardiomyopathy.
CI: Pregnancy, ACE inhibitor sensitivity, idiopathic or hereditary angioedema.
DISP: Tabs 2.5, 5, 10, 20, 30, 40 mg.
SE: Dizziness, headache, cough, ↓ BP, angioedema, ↑ K^+, ↑ Cr, rare ↓ BM.
NOTES: To prevent DN, start when urinary microalbuminuria begins; check BUN, Cr, K^+, WBC.

LISINOPRIL/HYDROCHLOROTHIAZIDE (PRINZIDE, ZESTORETIC, GENERIC)

WARNING: ACE inhibitor can cause fet al injury/death in 2nd/3rd tri; D/C w/ pregnancy.
USES: *HTN.*
ACTIONS: ACE inhibitor w/ diuretic (HCTZ).
DOSE: Initial 10 mg lisinopril/12.5 mg HCTZ, titrate upward to effect; >80 mg/d lisinopril or >50 mg/day HCTZ are not recommended; ↓ in renal insufficiency; use low dose, ↑ slowly

in elderly.
W/P: [C 1st tri, D after, −] w/ Aortic stenosis/cardiomyopathy, bilateral RAS.
CI: Pregnancy, ACE inhibitor, idiopathic or hereditary angioedema, sensitivity (angioedema).
DISP: Tabs (mg lisinopril/mg HCTZ) 10/12.5, 20/12.5; *Zestoretic* also available as 20/25.
SE: Anaphylactoid reaction (rare), dizziness, headache, cough, fatigue, ↓ BP, angioedema, ↑ / ↓ K^+, ↑ Cr, rare ↓ BM/cholestatic jaundice.
NOTES: Use only when monotherapy fails; check BUN, Cr, K^+, WBC.

LOSARTAN (COZAAR, HYZAAR, GENERIC)

WARNING: Can cause fet al injury and death if used in 2nd & 3rd tri. D/C Treat if pregnancy detected.
USES: *HTN, DN, HTN w/ LVH.*
ACTIONS: Angiotensin II receptor antagonist.

DOSE:

Adults: 25–50 mg PO daily–BID, max. 100 mg; ↓ in elderly/hepatic impairment.
Peds: ***≥6 yr:*** *HTN:* Initial 0.7 mg/kg qd, ↑ to 50 mg/d PRN; 1.4 mg/kg/d or 100 mg/d max.
W/P: [C (1st tri, D 2nd, & 3rd tri), ?/−] w/ NSAIDs; w/ K^+-sparing diuretics, supl may cause ↑ K^+; w/ RAS, hepatic impairment.
CI: Pregnancy, component sensitivity.
DISP: Tabs 25, 50, 100 mg.
SE: ↓ BP in pts on diuretics; ↑ K^+; GI upset, facial/angioedema, dizziness, cough, weakness, ↓ renal function.
NOTES: w/ DM risk check glucose.

LULICONAZOLE (LUZU)

USES: *Tinea pedis, tinea cruris, tinea corporis.*
ACTIONS: Azole antifungal, inhibits ergosterol synthesis.
DOSE: Tinea pedis apply 1 ×/d for 2 wk; tinea corporis, tinea cruris apply 1 ×/d for 1 wk.
W/P: [C, ?/-].
CI: None.
DISP: Cream, 1%; 30/60 g.
SE: Site reaction, rare.

LYMPHOCYTE IMMUNE GLOBULIN [ANTITHYMOCYTE GLOBULIN, ATG] (ATGAM)

WARNING: Should only be used by physician experienced in immunosuppressive therapy or management of solid organ and/or BMT pts. Adequate lab and supportive resources must be readily available.
USES: *Allograft rejection in renal transplant pts; aplastic anemia if not candidates for BMT*, GVHD after BMT.
ACTIONS: ↓ Circulating antigen-reactive T lymphocytes; a human, & equine product.

DOSE:

Adults: *Prevent rejection:* 15 mg/kg/d IV × 14 days, then q other day × 7 days for total 21 doses in 28 days; initial w/in 24 hr before/after transplant. *Treat rejection:* Same but use 10–15 mg/kg/d; max. 21 doses in 28 days, qd 1st 14 days. *Aplastic anemia:* 10–20 mg/kg/d × 8–14 days, then q other day × 7 doses for total 21 doses in 28 days.
Peds: *Prevent renal allograft rejection:* 5–25 mg/kg/d IV; *aplastic anemia* 10–20 mg/kg/day IV 8–14 days then q other day for 7 more doses.
W/P: [C, ?/−] D/C if severe unremitting thrombocytopenia, leukopenia.
CI: Hx previous reaction or reaction to other equine γ-globulin prep, ↓ plt and WBC.
DISP: Inj 50 mg/mL.
SE: D/C w/ severe ↓ plt and WBC; rash, fever, chills, ↓ BP, headache, CP, edema, N/V/diarrhea, lightheadedness.
NOTES: Test dose: 0.1 mL 1:1,000 dilution in NS, a systemic reaction precludes use; give via central line; pretreat w/ antipyretic, antihistamine, and steroids; monitor WBC, plt; plt counts usually return to nl w/o D/C Treat 4 hr Inf.

MAGNESIUM HYDROXIDE (MILK OF MAGNESIA) [OTC]

USES: *Constipation*, hyperacidity, Mg^{2+} replacement.
ACTIONS: NS laxative.

DOSE:

Adults: *Antacid:* 5–15 mL (400 mg/5 mL) or 2–4 tabs (311 mg) PO PRN up to QID. *Laxative:* 30–60 mL (400 mg/5 mL) or 15–30 mL (800 mg/5 mL) or 8 tabs (311 mg) PO qhs or ÷ doses.
Peds: *Antacid and* <12 yr not OK. *Laxative:* <2 yr not OK. ***2–5 yr:*** 5–15 mL (400 mg/5 mL) PO qhs or ÷ doses. ***6–11 yr:*** 15–30 mL (400 mg/5 mL) or 7.5–15 mL (800 mg/5 mL) PO qhs or ÷ doses. ***3–5 yr:*** 2 (311 mg) tabs PO qhs or ÷ doses. ***6–11 yr:*** 4 (311 mg) tabs PO qhs or ÷ doses.
W/P: [B, +] w/ Neuromuscular disease or renal impairment.
CI: Component hypersens.
DISP: Chew tabs 311, 400 mg; liq 400, 800 mg/5 mL (OTC).
SE: Diarrhea, abdominal cramps.
NOTES: For occasional use in constipation, different forms may contain Al^{2+}.

MAGNESIUM OXIDE (MAG-OX 400, OTHERS) [OTC]

USES: *Replace low Mg^{2+} levels.*
ACTIONS: Mg^{2+} supl.
DOSE: 400–800 mg/d or ÷ w/ food in full glass of H_2O; ↓ w/ renal impairment.
W/P: [B, +] w/ Neuromuscular disease & renal impairment, w/ bisphosphonates, calcitriol, CCBs, neuromuscular blockers, tetracyclines, quinolones.
CI: Component hypersens.
DISP: Caps 140, 250, 500, 600 mg; tabs 400 mg (OTC).
SE: Diarrhea, N.

MAGNESIUM SULFATE (GENERIC)

USES: *Replace low Mg^{2+}; preeclampsia, eclampsia, & premature labor, cardiac arrest, AMI arrhythmias, cerebral edema, barium poisoning, seizures, pediatric acute nephritis*; refractory ↓ K^+ & ↓ Ca^{2+}.
ACTIONS: Mg^{2+} supl, bowel evacuation, ↓ acetylcholine in nerve terminals, ↓ rate of sinoatrial node firing.

DOSE:

Adults: 1 g q6h IM × 4 doses & PRN 1–2 g q3–6h IV then PRN to correct deficiency.
Peds & Neonates: 25–50 mg/kg/dose IV, repeat PRN; max. 2 g single dose.
W/P: [A/C (manufacturer specific), +] w/ Neuromuscular disease; interactions see Magnesium Oxide and aminoglycosides.
CI: Heart block, myocardial damage.
DISP: Premix Inj: 10, 20, 40, 80 mg/mL; Inj 125, 500 mg/mL; oral/topical powder 227, 454, 1,810, 2,720 g.
SE: CNS depression, diarrhea, flushing, heart block, ↓ BP, vasodilation.
NOTES: Different formulation may contain Al^{2+}, monitor Mg^{2+} levels.

MANNITOL, INTRAVENOUS (GENERIC)

USES: *Cerebral edema, ↑ IOP, renal impairment, poisonings.*
ACTIONS: Osmotic diuretic.
DOSE: *Test dose:* 0.2 g/kg/dose IV over 3–5 min; if no diuresis w/in 2 hr, D/C. *Oliguria:* 50–100 g IV over 90 min ↑ *IOP:* 0.25–2 g/kg IV over 30 min. *Cerebral edema:* 0.25–1.5 g/kg/dose IV q6–8h PRN, maintain serum osmolarity < 300–320 mOsm/kg.
W/P: [C, ?/M] w/ CHF or vol overload, w/ nephrotoxic drugs & lithium.
CI: Anuria, dehydration, heart failure, PE intracranial bleeding.
DISP: Inj 5%, 10%, 15%, 20%, 25%.
SE: May exacerbate CHF, N/V/diarrhea, ↓ / ↑ BP, ↑ HR.
NOTES: Monitor for vol depletion.

MEGESTROL ACETATE (MEGACE, MEGACE-ES)

USES: *Anorexia, cachexia, or an unexplained significant weight loss in patients with AIDS; palliative treatment of advanced carcinoma of the breast or endometrium.*
ACTIONS: Hormone; anti-leuteinizing; progesterone analog.
DOSE: *Appetite: Megace-ES* 625 mg/day (5 mL or 1 teaspoon/d). *Breast cancer*: 160 mg/d (40 mg QID); *Endometrial cancer*: 40–320 mg/d divided doses.
W/P: [D (tablet)/X (suspension), −] Thromboembolism; handle w/ care.
CI: Pregnancy.
DISP: Tabs 20, 40 mg; susp 40 mg/ mL, *Megace-ES* 125 mg/mL.
SE: DVT, edema, menstrual bleeding, photosensitivity, N/V/diarrhea, headache, mastodynia, ↑ Ca, ↑ glucose, insomnia, rash, ↓ BM, ↑ BP, CP, palpitations.
NOTES: Do not D/C abruptly; Megace-ES not equivalent to others mg/mg.

MELPHALAN [L-PAM] (ALKERAN, GENERIC)

WARNING: Administer under the supervision of a qualified physician experienced in the use of chemotherapy; severe BM depression, leukemogenic, & mutagenic hypersens (including anaphylaxis in ~2%).
USES: *Palliative treatment multiple myeloma and ovariant cancer*, breast & testicular cancer, melanoma; allogenic & ABMT (high dose), neuroblastoma, rhabdomyosarcoma.
ACTIONS: Alkylating agent, nitrogen mustard.

DOSE:

Adults: *Multiple myeloma:* 16 mg/ m^2 IV q2wk × 4 doses then at 4-wk intervals after tox resolves; w/ renal impairment ↓ IV dose 50% or 6 mg PO qd × 2–3 wk, then D/C up to 4 wk, follow counts then 2 mg qd. *Ovarian cancer:* 0.2 mg/kg qd × 5 days, repeat q4–5wk based on counts, ↓ in renal insufficiency.
W/P: [D, ?/−] w/ Cisplatin, digitalis, live vaccines extravasation, need central line.
CI: Allergy or resistance.
DISP: Tabs 2 mg; Inj 50 mg.
SE: N/V, secondary malignancy, AF, ↓ LVEF, ↓ BM, secondary leukemia, alopecia, dermatitis, stomatitis, pulm fibrosis; rare allergic reactions, thrombocytopenia.
NOTES: Take PO on empty stomach, false(+) direct Coombs test.

MEPERIDINE (DEMEROL, GENERIC) [C–II]

USES: *Mod–severe pain*, postoperative shivering, rigors from amphotericin B.
ACTIONS: Narcotic analgesic.

DOSE:

Adults: 50–150 mg PO or IV/IM/SQ q3–4h PRN.
Peds: 1–1.5 mg/kg/ dose PO or IM/SQ q3–4h PRN, up to 100 mg/dose; hepatic impairment, avoid in renal impairment, avoid use in elderly.
W/P: [C, −] risk for dependency, ↓ seizure threshold, adrenal insufficiency, head injury, ↑ ICP, hepatic impairment, not OK in sickle cell disease.
CI: w/ MAOIs.
DISP: Tabs 50, 100 mg; syrup/soln 50 mg/5 mL; Inj 25, 50, 75, 100 mg/mL.
SE: Resp/CNS depression, seizures, sedation, constipation, ↓ BP, rash N/V, biliary and urethral spasms, dyspnea.
NOTES: Analgesic effects potentiated w/ hydroxyzine; 75 mg IM = 10 mg morphine IM; not best in elderly; do not use oral for acute pain; not OK for repetitive use in ICU setting, naloxone does not reverse neurotox, used as analgesic, is not recommended, limit Tx to <48 hr.

MEROPENEM (MERREM, GENERIC)

USES: *Intra-abdominal infections, bacterial meningitis, skin infection.*
ACTIONS: Carbapenem; ↓ cell wall synth. *Spectrum:* Excellent gram(+) (except MRSA, methicillin-resistant *S. epidermidis* [MRSE] & *E. faecium*); excellent gram(−) including

extended-spectrum β-lactamase producers; good anaerobic.

DOSE:

Adults: *Abdominal infection:* 1–2 g IV q8h. *Skin infection:* 500 mg IV q8h.
Peds: ***>3 mo, <50 kg:*** *Abdominal infection:* 20 mg/kg IV q8h. *Skin infection:* 10 mg/kg IV q8h; ***Peds >50 kg.*** Use adult dose; max. 2 g IV q8h; ↓ in renal insufficiency (see package insert).
W/P: [B, ?/M] w/ Probenecid, valproic acid.
CI: β-Lactam anaphylaxis.
DISP: Inj 1 g, 500 mg.
SE: Less seizure potential than imipenem; *C. difficile* enterocolitis, diarrhea, ↓ plt.
NOTES: Overuse ↑ bacterial resistance.

MESNA (MESNEX [ORAL] , GENERIC [IV])

USES: *Prevent hemorrhagic cystitis d/t ifosfamide* or cyclophosphamide.
ACTIONS: Antidote, reacts w/ acrolein and other metabolites to form stable compounds (sodium 2-mercaptoethane sulfonate).
DOSE: Per protocol; dose as % of ifosfamide or cyclophosphamide dose. *IV bolus:* 20% (eg, 10–12 mg/kg) IV at 0, 4, & 8 hr; *IV Inf:* 20% prechemotherapy, 40% w/ chemotherapy for 12–24 hr; *Oral:* 100% ifosfamide dose given as 20% IV at hour 0 then 40% PO at hours 4 & 8; if PO dose vomited repeat or give dose IV; mix PO w/ juice.
W/P: [B; ?/−].
CI: Thiol sensitivity.
DISP: Inj 100 mg/mL; (*Mesnex*) tabs 400 mg.
SE: ↓ BP, ↓ plt, ↑ HR, ↑ RR allergic reactions, rash, headache, GI upset, taste perversion; false positive urinary ketones.
NOTES: Hydration helps ↓ hemorrhagic cystitis; higher dose for BMT; IV contains benzyl alcohol.

METHENAMINE HIPPURATE (HIPREX)

USES: *Suppress recurrent UTI long term; use only after infection cleared by antibiotics.*
ACTIONS: Converted to formaldehyde & ammonia in acidic urine; nonspecific bactericidal action.

DOSE:

Adults: 1 g PO BID.
Peds: ***6–12 yr:*** 0.5–1 g PO BID PO ÷ BID; w/ food, ascorbic acid w/ hydration.
W/P: [C, +] Large doses (8 g/d for 3–4 wk) have caused bladder irritation, painful/frequent micturition, albuminuria, and gross hematuria.
CI: Renal insufficiency, severe hepatic disease, severe dehydration w/ sulfonamides (may precipitate in urine).
DISP: Tabs 1 g.
SE: Rash, GI upset, dysuria, ↑ LFTs, super infection w/ prolonged use, *C. difficile*-associated diarrhea.

NOTES: Not indicated in peds <6 yr. Not for pts w/ indwelling catheters as dwell time in bladder required for action.

METHENAMINE COMBINATION PRODUCTS (HYOPHEN, URIBEL, UROGESIC BLUE, OTHERS)

(Note: This labeling has not been approved by the FDA)
USES: *Relief of local symptoms, such as inflammation, hypermotility, and pain, which accompany lower UTIs and symptoms caused by diagnostic procedures.*
ACTIONS: Based on individual components: *Methenamine* in acid urine releases formaldehyde (antiseptic); *phenyl salicylate* is a mild analgesic; *methylene blue/benzoic acid* are mild antiseptics; hyoscyamine is parasympatholytic (belladonna alkaloid) ↓ bladder spasm; *sodium phosphate monobasic* is an acidifier to maintain an acid pH for the degradation of methenamine.

DOSE:
Adults & Peds: ***>12 yr:*** 1 tab PO QID w/ liberal fluid intake.
W/P: [C, ?/−] Avoid w/ sulfonamides, narrow-angle glaucoma, pyloric/duodenal obst, bladder outlet obstruction, coronary artery spasm.
CI: Component hypersens.
DISP: Tabs and capsules (see representative products below).
- **HYOPHEN** (methenamine, benzoic acid, phenyl salicylate, methylene blue, hyoscyamine sulfate) tablet
- **PROSED** (methenamine, phenyl salicylate, methylene blue, benzoic acid, hyoscyamine) tablet
- **URIBEL** (methenamine, sodium phosphate monobasic monohydrate, phenyl salicylate, methylene blue, hyoscyamine sulfate) capsule
- **URIMAR-T, URIN D/S, UROGESIC BLUE, UTIRA-C** (methenamine, sodium phosphate monobasic, phenyl salicylate, methylene blue, hyoscyamine sulfate) tablet
- **USTELL** (methenamine, sodium phosphate monobasic, phenyl salicylate, methylene blue, and hyoscyamine sulfate) capsule.

SE: Rash, dry mouth, flushing, ↑ pulse, dizziness, blurred vision, urine/feces discoloration (blue/light green), voiding difficulty/retention.
NOTES: Take w/ plenty of fluid, can cause crystalluria; not rec in peds ≤6 yr; Not for pts w/ indwelling catheters as dwell time in bladder required for action; see also hyoscyamine and phenazopyridine listings.

METHOTREXATE (RHEUMATREX DOSE PACK, TREXALL, GENERIC)

WARNING: Administration only by experienced physician; do not use in women of child-bearing age unless absolutely necessary (teratogenic); impaired elimination w/ impaired renal function, ascites, pleural effusion; severe ↓ BM w/ NSAIDs; hepatotox, occasionally fatal; can induce life-threatening pneumonitis; diarrhea and ulcerative stomatitis require D/C; lymphoma risk; may cause tumor lysis syndrome; can cause severe skin reaction, opportunistic infections; w/ RT can ↑ tissue necrosis risk. Preservatives make this agent unsuitable for intrathecal IT or higher-dose use.

USES: *ALL, AML, leukemic meningitis, trophoblastic tumors (choriocarcinoma, hydatidiform mole), breast, lung, head, & neck, cancers, Burkitt's lymphoma, mycosis fungoides, osteosarcoma, Hodgkin disease & NHL, psoriasis; rheumatoid arthritis, JRA, SLE*, chronic disease.
ACTIONS: ↓ Dihydrofolate reductase-mediated prod of tetrahydrofolate, causes ↓ DNA synth.

DOSE:

Adults: *Cancer:* Per protocol. *Rheumatoid arthritis:* 7.5 mg/wk PO 1/wk or 2.5 mg q12h PO for 3 doses/wk. *Psoriasis:* 2.5–5 mg PO q12h × 3 d/wk or 10–25 mg PO/IM qwk. *Chronic:* 15–25 mg IM/SQ qwk, then 15 mg/wk.
Peds: JIA: 10 mg/m^2 PO/IM qwk, then 5–14 mg/m^2 × 1 or as 3 divided doses 12 hr apart; ↓ elderly, w/ renal/hepatic impairment.
W/P: [X, −] w/ Other nephro/hepatotoxic meds, multiple interactions, w/ seizure, profound ↓ BM other than cancer related.
CI: Severe renal/hepatic impairment, pregnancy/lactation.
DISP: Dose pack 2.5 mg in 8, 12, 16, 20, or 24 doses; tabs 2.5, 5, 7.5, 10, 15 mg; Inj 25 mg/mL; Inj powder 20 mg, 1 g.
SE: ↓ BM, N/V/diarrhea, anorexia, mucositis, hepatotox (transient & reversible; may progress to atrophy, necrosis, fibrosis, cirrhosis), rashes, dizziness, malaise, blurred vision, alopecia, photosensitivity, renal failure, pneumonitis; rare pulm fibrosis; chemical arachnoiditis & headache w/ IT delivery.
NOTES: Monitor CBC, LFTs, Cr, MTX levels & CXR; "high dose" >500 mg/m^2 requires leucovorin rescue to ↓ tox; w/ IT, use preservative-/alcohol-free soln; systemic levels: *Therapeutic:* >0.01 μmole; *Toxic:* >10 micromole over 24 hr.

METHYLENE BLUE (UROLENE BLUE, VARIOUS)

USES: *Methemoglobinemia, vasoplegic syndrome, ifosfamide-induced encephalopathy, cyanide poisoning, dye in therapeutics/diagnosis.*
ACTIONS: Low IV dose converts methemoglobin to hemoglobin; excreted, appears in urine as green/green-blue color; MAOI activity.
DOSE: 1–2 mg/kg or 25–50 mg/m^2 IV over 5–10 min, repeat q1h; direct instillation into fistulous tract.
W/P: [X, −] w/ Severe renal impairment w/ psych meds such as SSRI, SNRI, TCA (may cause serotonin syndrome), w/ G6PD deficiency.
CI: Intra spinal Inj, severe renal insufficiency.
DISP: 1, 10 mL Inj.
SE: *IV use:* N, abdominal, CP, sweating, fecal/urine discoloration, hemolytic anemia.
NOTES: Component of some oral medications; stains tissue blue, limits repeat use in surgical visualization.

METHYLPREDNISOLONE (DEPO-MEDROL, MEDROL, MEDROL DOSEPAK, SOLU-MEDROL, GENERIC) [SEE STEROIDS]

USES: *Steroid responsive conditions (endocrine, rheumatic, collagen, dermatologic, allergic,

ophthalmic, respiratory, hematologic, neoplastic, edematous, GI, CNS, others).*
ACTIONS: Glucocorticoid.

DOSE:
See Steroids Peds: *Status asthmaticus, anaphylactic shock:* 2 mg/kg IV/IO/IM (max. 60 mg). *Maint:* 0.5 mg/kg IV q6h or 1 mg/kg q12h to 120 mg/d.
W/P: [C, ?/M] May mask Infx, cataract w/ prolonged use; avoid vaccines.
CI: Fungal Infx, component allergy.
DISP: Oral (*Medrol*) 4, 8, 16, 32 mg, (*Medrol Dosepak*) 21 4-mg tabs taken over 6 days; Inj acetate (*Depo-Medrol*) 20, 40, 80 mg/mL; Inj succinate (*Solu-Medrol*) 40, 125, 500 mg, 1, 2 g.
SE: Fluid and electrolyte disturbances, muscle weakness/loss, ulcers, impairment wound healing, others (see label).
NOTES: Taper dose to avoid adrenal insufficiency.

METOCLOPRAMIDE (METOZOLV, REGLAN, GENERIC)

WARNING: Chronic use may cause tardive dyskinesia; D/C if Sxs develop; avoid prolonged use (> 2 wk).
USES: *Diabetic gastroparesis, symptomatic GERD; chemo & postop N/V, facilitate small bowel intubation & upper GI radiologic exam*, *GERD, diabetic gastroparesis *(Metozolv)* stimulate gut in prolonged postop ileus.*
ACTIONS: ↑ Upper GI motility; blocks dopamine in chemoreceptor trigger zone, sensitized tissues to ACH.

DOSE:

Adults: *Gastroparesis (Reglan):* 10 mg PO 30 min ac & hs for 2–8 wk PRN, or same dose IM/IV for 10 days, then PO. *Reflux:* 10–15 mg PO 30 min ac & hs. *Chemo antiemetic:* 1–2 mg/kg/dose IV 30 min before chemo, then q2h × 2 doses, then q3h × 3 doses. *Postop:* 10–20 mg IV/IM q4–6h PRN.
Adults & Peds: ***>14 yr:*** *Intestinal intubation:* 10 mg IV × 1 over 1–2 min.
Peds: *Reflux:* 0.1–0.2 mg/kg/dose PO 30 min ac & hs. *Chemo antiemetic:* 1–2 mg/kg/dose IV as adults. *Postop:* 0.25 mg/kg IV q6–8h PRN.
Peds: *Intestinal intubation:****6–14 yr:*** 2.5–5 mg IV × 1 over 1–2 min; ***<6 yr:*** Use 0.1 mg/kg IV × 1.
W/P: [B, M] Drugs w/ extrapyramidal ADRs, MAOIs, tricyclic antidepressants, sympathomimetics.
CI: w/ EPS meds, GI bleeding, pheochromocytoma, seizure disorders, GI obst.
DISP: Tabs 5, 10 mg; syrup 5 mg/5 mL; ODT *(Metozolv)* 5, 10 mg; Inj 5 mg/mL.
SE: Dystonic reactions common w/ high doses (Treat w/ IV diphenhydramine), fluid retention, restlessness, diarrhea, drowsiness.
NOTES: ↓ w/ Renal impairment/elderly; check baseline Cr.

METRONIDAZOLE (FLAGYL, FLAGYL ER, METROCREAM, METROGEL, METROLOTION)

WARNING: Carcinogenic in rats.
USES: *Bone/joint, endocarditis, intra-abdominal, meningitis, & skin infections; amebiasis & amebic liver abscess; trichomoniasis in pt and partner; bacterial vaginosis; PID; giardiasis; antibiotic-associated pseudomembranous colitis (*C. difficile*), eradicate *H. pylori* w/ combo Treat, rosacea, prophylactic in postop colorectal surgery.*
ACTIONS: Interferes w/ DNA synth. *Spectrum:* Excellent anaerobic, *C. difficile.*

DOSE:

Adults: *Anaerobic* infections: 500 mg IV q6–8h. *Trichomonas:* 250 mg PO TID for 7 days or 2 g PO × 1 (Treat partner). *C. difficile:* 500 mg PO or IV q8h for 7–10 days (PO preferred; IV only if pt NPO), if no response, change to PO vancomycin. *Vaginosis:* 1 applicator intravag qd or BID × 5 days, or 500 mg PO BID × 7 days or 750 mg PO qd × 7 days. *Acne rosacea/skin:* Apply BID.
Peds: *Anaerobic infections*: PO: 15–35 mg/kg/d ÷ q8h *IV*: 30 mg/kg IV/d ÷ q6H, 4 g/d max. ÷ dose; *Trichomonas:* 15–30 mg/kg/d PO ÷ q8h × 7 days. *C. difficile:* 30 mg/kg/d PO ÷ q6h × 10 days, max. 2 g/d; ↓ w/ severe hepatic/renal impairment.
W/P: [B, −] Avoid EtOH, w/ warfarin, CYP3A4 substrates, ↑ Li levels.
CI: 1st tri pregnancy.
DISP: Tabs 250, 500 mg; ER tabs 750 mg; caps 375 mg; IV 500 mg/100 mL; lotion 0.75%; gel 0.75, 1%; intravag gel 0.75% (5 g/applicator 37.5 mg in 70-g tube), cream 0.75, 1%.
SE: Disulfiram-like reaction; dizziness, headache, GI upset, anorexia, urine discoloration, flushing, met allic taste.
NOTES: For trichomoniasis, Treat pt's partner; no aerobic bacteria activity; use in combo w/ serious mixed infections; wait 24 hr after 1st dose to breast-feed or 48 hr if extended Treat, take ER on empty stomach.

MICAFUNGIN (MYCAMINE)

USES: *Candidemia, acute dissem and esophageal candidiasis, *Candida* peritonitis & abscesses; prophylaxis *Candida* infection w/ HSCT.*
ACTIONS: Echinocandin; ↓ fungal cell wall synth.
DOSE: *Candidemia, acute disseminated candidiasis, Candida peritonitis & abscesses:* 100 mg IV daily; *Esophageal candidiasis:* 150 mg IV daily; *Prophylaxis of Candida infection:* 50 mg IV daily over 1 hr.
W/P: [C, ?/−] w/ Sirolimus, nifedipine, itraconazole dosage adj may be necessary.
CI: Component or other echinocandin allergy.
DISP: Inj 50, 100 mg vials.
SE: N/V/diarrhea, headache, pyrexia, abdominal pain, ↓ K^+, ↓ plt, histamine Sxs (rash, pruritus, facial swelling, vasodilatation), anaphylaxis, anaphylactoid reaction, hemolysis, hemolytic anemia, ↑ LFTs, hepatotox, renal impairment.

MICONAZOLE (MONISTAT 1 COMBO, MONISTAT 3, MONISTAT 7 [OTC]) (MONISTAT-DERM)

USES: *Candidal infections, dermatomycoses (tinea pedis/ tinea cruris/tinea corporis/tinea versicolor/candidiasis).*
ACTIONS: Azole antifungal, alters fungal membrane permeability.
DOSE: *Intravag:* 100 mg supp or 2% cream intravag qhs × 7 days or 200 mg supp or 4% cream intravag qhs × 3 days. *Derm:* Apply BID, a.m./p.m. *Tinea versicolor:* Apply qd. Treat tinea pedis and tinea corporis for 1 mo and other infections for 2 wk.
Peds: ≥ ***12 yr:*** 100 mg supp or 2% cream intravag qhs × 7 days or 200 mg supp or 4% cream intravag qhs × 3 days. Not for OTC use in children <2 yr.
W/P: [C, ?] Azole sensitivity.
DISP: *Monistat-Derm:* (Prescription) Cream 2%; *Monistat 1 combo:* 2% cream w/ 1,200 mg supp, *Monistat 3:* Vag cream 4%, supp 200 mg; *Monistat 7:* cream 2%, supp 100 mg; lotion 2%; powder 2%; effervescent tab 2%, oint 2%, spray 2%; Vag supp 100, 200, 1,200 mg; Vag cream 2%, 4%; [OTC].
SE: Vag burning; on skin contact dermatitis, irritation, burning.
NOTES: May interfere w/ condom and diaphragm, do not use w/ tampons.

MICONAZOLE/ZINC OXIDE/PETROLATUM (VUSION)

USES: *Candidal diaper rash.*
ACTIONS: Combo antifungal.

DOSE:

Peds: ≥ ***4 wk:*** Apply at each diaper change × 7 days.
W/P: [C, ?].
CI: None.
DISP: Miconazole/zinc oxide/petrolatum oint 0.25/15/81.35%, 50-, 90-g tube.
SE: None.
NOTES: Keep diaper dry, not for prevention.

MINERAL OIL [OTC]

USES: *Constipation, bowel irrigation, fecal impaction.*
ACTIONS: Lubricant laxative.

DOSE:

Adults: *Constipation:* 15–45 mL PO/d PRN. *Fecal impaction or after barium:* 118 mL rectally × 1.
Peds: > ***6 yr:*** *Constipation:* 5–25 mL PO qd. ***2–12 yr:*** *Fecal impaction:* 59 mL rectally × 1.
W/P: [?, ?] w/ N/V, difficulty swallowing, bedridden pts; may ↓ absorption of vits A, D, E, K, warfarin.
CI: Colostomy/ileostomy, appendicitis, diverticulitis, ulcerative colitis.
DISP: All [OTC] liq, PO microemulsion 2.5 mL/5 mL, rectal enema 118 mL.
SE: Lipid pneumonia (aspiration of PO mineral oil), N/V, temporary anal incontinence.

NOTES: Take PO upright, do not use PO in peds <6 yr; no longer recommended as lubricant for surgical instruments (not water soluble).

MINERAL OIL/PRAMOXINE HCL/ZINC OXIDE (TUCKS OINTMENT [OTC])

USES: *Temporary relief of anorectal disorders (itching, etc.).*
ACTIONS: Topical anesthetic.

DOSE:
Adults & Peds: ≥***12 yr:*** Cleanse, rinse, & dry, apply externally or into anal canal w/ tip 5×/d × 7 days max.
W/P: [?, ?] Do not place into rectum.
CI: None.
DISP: Oint 1% 30-g tube.
SE: Local irritation.
NOTES: D/C w/ or if rectal bleeding occurs or if condition worsens or does not improve w/in 7 days.

MINOCYCLINE (DYNACIN, MINOCIN, SOLODYN, GENERIC)

USES: *Mod–severe nonnodular acne (*Solodyn*), anthrax, rickettsiae, skin infection, URI, UTI, nongonococcal urethritis, amebic dysentery, asymptomatic meningococcal carrier, *Mycobacterium marinum.**
ACTIONS: Tetracycline, bacteriostatic, ↓ protein synth.

DOSE:
Adults & Peds: >***12 yr:*** *Usual:* 200 mg, then 100 mg q12h or 100–200 mg IV or PO, then 50 mg QID. *Gonococcal urethritis, men:* 100 mg q12h × 5 days. *Syphilis:* Usual dose × 10–15 days. *Meningococcal carrier:* 100 mg q12h × 5 days. *M. marinum:* 100 mg q12h × 6–8 wk. *Uncomp urethral, endocervical, or rectal infection:* 100 mg q12h × 7 days minimum.
Adults & Peds: >***12 yr:*** *Acne:* (*Solodyn*) 1 mg/kg PO qd × 12 wk. > ***yr:*** 4 mg/kg initially then 2 mg/kg q12h w/ food to ↓ irritation, hydrate well, ↓ dose or extend interval w/ renal impairment.
W/P: [D, −] Associated w/ pseudomembranous colitis, w/ renal impairment, may ↓ OCP, or w/ warfarin may ↑ INR.
CI: Allergy, children <8 yr.
DISP: Tabs 50, 75, 100 mg; tabs ER (*Solodyn*) 45, 65, 90, 115, 135 mg, caps (*Minocin*) 50, 100 mg, susp 50 mg/mL.
SE: diarrhea, headache, fever, rash, joint pain, fatigue, dizziness, photosensitivity, hyperpigmentation, SLE syndrome, pseudotumor cerebri.
NOTES: Do not cut/crush/chew; keep away from children, tooth discoloration in <8 yr or w/ use last half of pregnancy.

MIRABEGRON (MYRBETRIQ)

USES: *Overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and

urinary frequency. *
ACTIONS: β-3 adrenergic agonist; relaxes smooth muscle.
DOSE: Start 25 mg PO daily; ↑ to 50 mg daily after 8 wk PRN; 25 mg max. daily w/ severe renal or mod hepatic impairment; swallow whole, do not cut/chew.
W/P: [C, −] w/ Severe uncontrolled HTN; urinary retention w/ bladder outlet obstruction & antimuscarinic drugs; w/ drugs metabolized by CYP2D6 (eg, thioridazine, flecainide, propafenone); do not use w/ ESRD or severe hepatic impairment; monitor serum digoxin when starting both together.
CI: None.
DISP: Tabs ER 25, 50 mg.
SE: ↑ BP, headache, UTI, nasopharyngitis, N/diarrhea, constipation, abdominal pain, dizziness, tachycardia, URI, arthralgia, fatigue.

MITOMYCIN (GENERIC)

WARNING: Administer only by physician experienced in chemotherapy; myelosuppressive; can induce HUS w/ irreversible renal failure.
USES: *Stomach, pancreas*, breast, colon cancer; squamous cell carcinoma of the anus; NSCLC, head & neck, cervical; bladder cancer (intravesically).
ACTIONS: Alkylating agent; generates oxygen-free radicals w/ DNA strand breaks.
DOSE: (Per protocol) 20 mg/m^2 q6–8wk IV or 10 mg/m^2 combo w/ other myelosuppressive drugs q6–8wk. *Bladder cancer:* 20–40 mg in 40 mL NS via a urethral catheter once/wk; immediately postop if no evidence of extravasation × 1 to reduce recurrences following TURBT; ↓ in renal/hepatic impairment.
W/P: [D, −] w/ Cr >1.7 mg/dL/ ↑ cardiac tox w/ vinca alkaloids/doxorubicin.
CI: ↓ Plt, coagulation disorders, ↑ bleeding tendency, pregnancy.
DISP: Inj 5, 20, 40 mg.
SE: ↓ BM (persists for 3–8 wk, may be cumulative; minimize w/ lifetime dose <50–60 mg/m^2), N/V, anorexia, stomatitis, renal tox, microangiopathic hemolytic anemia w/ renal failure (HUS), veno-occlusive liver disease, interstitial pneumonia, alopecia, extrav reactions, contact dermatitis; CHF w/ doses >30 mg/m^2.

MITOTANE (LYSODREN)

WARNING: Administer only by physician experienced in chemotherapy; discontinue temporarily immediately following shock or severe trauma since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances.
USES: *Inoperable adrenocortical carcinoma (functioning/nonfunctioning).
ACTIONS: Adrenal cytotoxic agent, suppresses cortisol production by inhibiting 11β-hydroxylase (ortho-para-DDD).
DOSE: 2–6 g/d in divided dose TID–QID; increase as tolerated to max. tolerated dose (generally 2–18 g/d); decrease dose with side effects; administer with glucocorticoid and if needed mineralocorticoid replacement.
W/P: [C/?]; increases warfarin metabolism.
CI: Hypersensitivity to compound.

DISP: Tablets 500 mg.
SE: Adrenal insufficiency, GI distress, depression, lethargy, somnolence, dizziness, vertigo, orthostasis.
NOTES: Neuropsychiatric testing with use >2 yr; higher doses of glucocorticoid required due to metabolism; treat until there is no clinical benefit.

MITOXANTRONE (GENERIC)

WARNING: Administer only by physician experienced in chemotherapy; except for acute leukemia, do not use w/ ANC count of <1,500 cells/mm^3; severe neutropenia can result in infection, follow CBC; cardiotoxic (CHF), secondary AML reported.
USES: *Combination for myelogenous, promyelocytic, monocytic, and erythroid acute leukemias, progressive relapsing MS; pain related to advanced hormone refractory prostate cancer. *
ACTIONS: Anthracenedione; DNA-intercalating agent; ↓ DNA synth by interacting w/ topoisomerase II.
DOSE: Per protocol; Cap 12–14 mg/m^2 short IV infusion every 21 days with steroids (such as prednisone 10 qd or 5 mg PO BID); ↓ dose w/ hepatic impairment, leukopenia, thrombocytopenia.
W/P: [D, −] Reports of secondary AML, w/ MS ↑ CV risk, do not treat MS pt w/ low LVEF.
CI: Pregnancy, sig ↓ in LVEF.
DISP: Inj 2 mg/mL.
SE: ↓ BM, N/V, stomatitis, alopecia (infrequent), cardiotox, urine discoloration, secretions & scleras may be blue-green.
NOTES: Maintain hydration; baseline CV evaluation w/ ECG & LVEF; cardiac monitoring prior to each dose; not for intrathecal use.

MORPHINE (AVINZA XR, ASTRAMORPH/PF, DURAMORPH, INFUMORPH, MS CONTIN, KADIAN SR, ORAMORPH SR, ROXANOL) [C-II]

WARNING: Do not crush/chew SR/CR forms; swallow whole or sprinkle on applesauce. 100 and 200 mg for opioid-tolerant pt only for mod–severe pain when pain control needed for an extended period and not PRN. Be aware of misuse, abuse, diversion. No alcoholic beverages while on therapy.
USES: *Treat severe pain*, AMI, acute pulmonary edema.
ACTIONS: Narcotic analgesic; SR/CR forms for chronic use.

DOSE:

Adults: *Short-term use PO:* 5–30 mg q4h PRN; *IV/IM:* 2.5–15 mg q2–6h; *Supp:* 10–30 mg q4h. SR formulations 15–60 mg q8–12h (do not chew/crush); use w/ caution; can be reversed w/ 0.4–2 mg IV naloxone.
Peds: ***>6 mo:*** 0.1–0.2 mg/kg/dose IM/IV q2–4h PRN; 0.15–0.2 mg/kg PO q3–4h PRN.
W/P: [C, +/−] Severe resp depression possible; w/ head injury; chewing delayed release forms can cause severe rapid release of morphine.
CI: (Many product specific) Severe asthma, resp depression, GI obst/ileus; *Oral soln:* CHF d/t

lung disease, head injury, arrhythmias, brain tumor, acute alcoholism, DTs, seizure disorders; *MS Contin and Kadian* CI include hypercarbia.
DISP: IR tabs 15, 30 mg; soln 10, 20, 100 mg/5 mL; supp 5, 10, 20, 30 mg; Inj 2, 4, 5, 8, 10, 15, 25, 50 mg/mL; *MS Contin CR* tabs 15, 30, 60, 100, 200 mg; *Oramorph SR* tabs 15, 30, 60, 100 mg; *Kadian SR caps* 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200 mg; *Avinza XR* caps 30, 60, 90, 120 mg; *Duramorph/Astramorph PF:* Inj 0.5, 1 mg/mL; *Infumorph* 10, 25 mg/mL.
SE: Narcotic SE (resp depression, sedation, constipation, N/V, pruritus, diaphoresis, urinary retention, biliary colic), granulomas w/ IT.
NOTES: May require scheduled dosing to relieve severe chronic pain.

MOXIFLOXACIN (AVELOX)

WARNING: ↑ Risk Achilles tendon rupture and tendonitis, ↑ in pts >60 yr, on steroids or with organ transplant; avoid w/ myasthenia gravis, may ↑ muscle weakness.
USES: *Acute sinusitis & bronchitis, skin/soft-tissue/intra-abdominal infections, conjunctivitis, community-acquired pneumonia* TB, anthrax, endocarditis.
ACTIONS: 4th-gen quinolone; ↓ DNA gyrase. *Spectrum:* Excellent gram(+) except MRSA & *E. faecium;* good gram(−) except *P. aeruginosa, Stenotrophomonas maltophilia, & Acinetobacter* sp; good anaerobic.
DOSE: 400 mg/d PO/IV daily; avoid cation products, antacids TID.
W/P: [C, −] Quinolone sensitivity; interactions w/ Mg^{2+}, Ca^{2+}, Al^{2+}, Fe^{2+}-containing products, & class IA & III antiarrhythmic agents.
CI: Quinolone/component sensitivity.
DISP: Tabs 400 mg, ABC Pak 5 tabs, Inj.
SE: Dizziness, N, QT prolongation, seizures, photosensitivity, peripheral neuropathy risk.

MUPIROCIN (BACTROBAN, BACTROBAN NASAL)

USES: *Impetigo (oint); skin lesion infect w/ *S. aureus* or *S. pyogenes*; eradicate MRSA in nasal carriers.*
ACTIONS: ↓ Bacterial protein synth.
DOSE: *Topical:* Apply small amount 3×/d × 5–14 days. *Nasal:* Apply 1/2 single-use tube BID in nostrils × 5 days.
W/P: [B, ?/M].
CI: Do not use w/ other nasal products.
DISP: Oint 2%; cream 2%; nasal oint 2% 1-g single-use tubes.
SE: Local irritation, rash.
NOTES: Pt to contact healthcare provider if no improvement in 3–5 days.

MYCOPHENOLATE MOFETIL (CELLCEPT, GENERIC)

WARNING: ↑ Risk of infections, lymphoma, other cancers, progressive multifocal leukoencephalopathy (PML); risk of pregnancy loss and malformation; female of child-bearing potential must use contraception.
USES: *Prevent organ rejection after transplant.*
ACTIONS: Cytostatic to lymphocytes.

DOSE:

Adults: 1 g PO BID, doses differ based on transplant.
Peds: *BSA 1.2–1.5 m²:* 750 mg PO BID. *BSA >1.5 m²:* 1 g PO BID; used w/ steroids & cyclosporine or tacrolimus; ↓ in renal insufficiency or neutropenia. *IV:* Infuse over >2 hr. *PO:* Take on empty stomach, do not open caps.
W/P: [D, −].
CI: Component allergy; IV use in polysorbate 80 allergy.
DISP: Caps 250, 500 mg; susp 200 mg/mL, Inj 500 mg.
SE: N/V/diarrhea, pain, fever, headache, infection, HTN, anemia, leukopenia, edema.
NOTES: *Cellcept & Myfortic* are not interchangeable.

NAFCILLIN (GENERIC)

USES: *Infections d/t susceptible strains of *Staphylococcus & Streptococcus.**
ACTIONS: Bactericidal; antistaphylococcal PCN; ↓ cell wall synth. *Spectrum:* Good gram(+) except MRSA & enterococcus, no gram(−), poor anaerobe.

DOSE:

Adults: 1–2 g IV q4–6h.
Peds: 50–200 mg/kg/d ÷ q4–6h.
W/P: [B, ?].
CI: PCN allergy, allergy to corn-related products.
DISP: Inj powder l, 2 g.
SE: Interstitial nephritis, N/diarrhea, fever, rash, allergic reaction.
NOTES: In setting of both hepatic & renal impairment, modification of dose may be necessary.

NALOXONE (GENERIC, EVZIO)

USES: *Opioid addiction (diagnosis) & OD.*
ACTIONS: Competitive opioid antagonist.

DOSE:

Adults: 0.4–2 mg IV, IM, or SQ q2–3 min; via endotracheal tube, dilute in 1–2 mL NS; may be given intranasal; total dose 10 mg max.; *Evzio:* 0.4 mg IM or sub-Q.
Peds: 0.01–0.1 mg/kg/dose IV, IM, or SQ; repeat IV q3min × 3 doses PRN; *Reverse narcotic effects:* 0.1 mg/kg q2min PRN; max. dose 2 mg; smaller doses (1–5 μg/kg may be used); cont Inf 2–160 μg/kg/h.
W/P: [C, ?], *Evzio* [B, ?/-], may precipitate withdrawal in addicts.
CI: Component hypersensitivity.
DISP: Inj 0.4, 1 mg/mL; *Evzio* 0.4 mg/0.4mL prefilled auto-injector, w/ electronic voice instructions.
SE: ↓ BP, ↑ BP, fever, tachycardia, VT, VF, irritability, agitation, coma, GI upset, pulm edema, tremor, piloerection, sweating.
NOTES: If no response after 10 mg, suspect nonnarcotic cause; w/ *Evzio* use in the field, seek

emergent care immediately; duration of action less than most opioids, may need repeat dosing; for by-stander use, administer in anterolateral thigh.

NAPROXEN (ALEVE [OTC] , ANAPROX, ANAPROX DS, EC-NAPROSYN, NAPRELAN, NAPROSYN, GENERIC)

WARNING: May ↑ risk of CV events & GI bleeding.
USES: *Arthritis & pain.*
ACTIONS: NSAID; ↓ prostaglandins.

DOSE:
Adults & Peds: ***>12 yr:*** 200–500 mg BID–TID to 1,500 mg/d max. ***>2 yr:*** *JRA* 5 mg/kg/dose BID; ↓ in hepatic impairment.
W/P: [C, (D 3rd tri), −].
CI: NSAID or ASA triad sensitivity, peptic ulcer, post-CABG pain, 3rd-tri pregnancy.
DISP: *Tabs:* 250, 375, 500 mg; *DR:* 375, 500, 750 mg; *CR:* 375, 550 mg; susp 25 mg/5 mL (*Aleve*) 200 mg multiple OTC forms.
SE: Dizziness, pruritus, GI upset, peptic ulcer, edema.
NOTES: Take w/ food to ↓ GI upset; 220 mg naproxen sodium = 200 mg naproxen base.

NEOMYCIN (NEO-FRADIN, GENERIC)

WARNING: Systemic absorption of oral route may cause neuro/oto/nephrotoxic; resp paralysis possible w/ any route of administration.
USES: *Hepatic coma, bowel prep.*
ACTIONS: Aminoglycoside, poorly absorbed PO; ↓ GI bacterial flora

DOSE:

Adults: 3–12 g/24 h PO in 3–4 ÷ doses; 12 g/d max.
Peds: 50–100 mg/kg/24 h PO in 3–4 ÷ doses.
W/P: [C, ?/−] Renal failure, neuromuscular disorders, hearing impairment.
CI: Intestinal obst.
DISP: Tabs 500 mg; *Neo-Fradin* PO soln 125 mg/5 mL.
SE: Hearing loss w/ long-term use; rash, N/V.
NOTES: Do not use parenterally (↑ tox); also topical forms.

NEOMYCIN-POLYMYXIN BLADDER IRRIGANT [NEOSPORIN GU IRRIGANT]

USES: *Short-term use (up to 10 days) as a continuous irrigant in the urinary bladder of abacteriuric patients to help prevent bacteriuria and gram-negative rod septicemia associated with the use of indwelling catheters.*
ACTIONS: Bactericidal; not for *Serratia* sp or streptococci.
DOSE: 1 mL irrigant in 1 L of 0.9% NaCl; cont bladder irrigation w/ 1 L of soln/24 h 10 days max.
W/P: [D].
CI: Component allergy; aminoglycoside allergy.

DISP: Soln neomycin sulfate 40 mg & polymyxin B 200,000 U/mL; amp 1, 20 mL.
SE: Rash, neomycin oto/nephrotoxic (rare).
NOTES: Potential for bacterial/fungal super-infection; not for Inj; use only 3-way catheter for irrigation.

NIFEDIPINE (ADALAT CC, AFEDITAB CR, PROCARDIA, PROCARDIA XL, GENERIC)

USES: *HTN*; tocolytic.
ACTIONS: Calcium channel blocker.

DOSE:

Adults: SR tabs 30–90 mg/d.
Peds: 0.25–0.5 mg/kg/24 h ÷ 3–4×/d.
W/P: [C, +] Heart block, aortic stenosis, cirrhosis.
CI: Component hypersensitivity.
DISP: Caps 10, 20 mg; SR/XL tabs 30, 60, 90 mg.
SE: Headache common on initial Treat; reflex tachycardia may occur w/ regular-release dosage forms; peripheral edema, ↓ BP, flushing, dizziness.
NOTES: Adalat CC & Procardia XL not interchangeable; used for medical expulsive therapy for ureterolithiasis; considered to be inferior to α-1 blockers such as tamsulosin.

NILUTAMIDE (NILANDRON)

WARNING: Interstitial pneumonitis possible; most cases in 1st 3 mo; check CXR before and during Treat.
USES: *Combo w/ surgical castration for metastatic PCa.*
ACTIONS: Nonsteroidal antiandrogen.
DOSE: 300 mg/d PO × 30 days, then 150 mg/d.
W/P: [Not used in females].
CI: Severe hepatic impairment, resp insufficiency.
DISP: Tabs 150 mg.
SE: Interstitial pneumonitis, hot flashes, ↓ libido, impotence, N/V/diarrhea, gynecomastia, hepatic dysfunction.
NOTES: May cause reaction when taken w/ EtOH, follow LFTs/CXR.

NITROFURANTOIN (FURADANTIN, MACROBID, MACRODANTIN, GENERIC)

USES: *Prophylaxis & Treat UTI.*
ACTIONS: Interferes w/ metabolism & cell wall synthesis. *Spectrum:* Some gram(+) & (−) bacteria; *Pseudomonas, Serratia,* & most *Proteus* resistant.

DOSE:

Adults: *Prophylaxis:* 50–100 mg/d PO. *Treat:* 50–100 mg PO QID × 7 days; *Macrobid* 100 mg PO BID × 7 days.

Peds: *Prophylaxis:* 1–2 mg/kg/d ÷ in 1–2 doses, max. 100 mg/d. *Treat:* 5–7 mg/kg/24 h in 4 ÷ doses (w/ food/milk/antacid).
W/P: [B, +/not OK if child < 1 mo] Avoid w/ CrCl <60 mL/min.
CI: Anuria, oliguria, or significant impairment of renal function (CrCl <60 mL/min), infants <1 mo, pregnancy at term; history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin.
DISP: Caps 25, 50, 100 mg; (*Furadantin*) susp 25 mg/5 mL.
SE: GI effects, dyspnea, various acute/chronic pulm reactions, peripheral neuropathy, hemolytic anemia w/ G6PD deficiency, rare aplastic anemia.
NOTES: Macrocrystals (eg, *Macrodantin*) <nausea than other forms; not for comp UTI; may turn urine brown; ineffective for pyelonephritis or cystitis.

NORFLOXACIN (NOROXIN)

WARNING: ↑ Risk Achilles tendon rupture and tendonitis, ↑ in pts >60 yr, on steroids or with organ transplant; avoid w/ myasthenia gravis, may ↑ muscle weakness.
USES: *Comp & uncomp UTI, prostatitis due to *E. Coli,* gonorrhea*, infectious diarrhea, conjunctivitis.
ACTIONS: Quinolone, ↓ DNA gyrase, bactericidal. *Spectrum:* Broad gram(+) and (–) *E. faecalis, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, S. epidermidis, S. saprophyticus.*
DOSE: *Uncomp UTI (E. coli, K. pneumoniae, P. mirabilis):* 400 mg PO BID × 3 days; other uncomp UTI Treat × 7–10 days. *Comp UTI:* 400 mg PO q12h for 10–21 days. *Gonorrhea:* 800 mg × 1 dose. *Prostatitis:* 400 mg PO BID × 28 days. *Gastroenteritis, traveler's diarrhea:* 400 mg PO BID × 1–3 days; take 1 hr ac or 2 hr pc.
Adults & Peds: ***>1 yr:*** Ophthal: 1 gtt each eye QID for 7 days; CrCl < 0 mL/min use 400 mg qd.
W/P: [C, −] Quinolone sensitivity, w/ some antiarrhythmics ↑ QT.
CI: Hx allergy or tendon problems due to quinolones.
DISP: Tabs 400 mg; ophthal 3 mg/mL.
SE: Photosensitivity, headache, dizziness, asthenia, GI upset, pseudomembranous colitis; ocular burning w/ ophthal, peripheral neuropathy risk w/ PO only.
NOTES: Interactions w/ antacids, theophylline, caffeine; good conc in the kidney & urine, poor blood levels; not for urosepsis; CDC suggests do not use for GC.

NYSTATIN (GENERIC)

USES: *Mucocutaneous *Candida* infections (oral, skin, vaginal).*
ACTIONS: Alters membrane permeability. *Spectrum:* Susceptible *Candida* sp.

DOSE:
Adults & Peds: *PO:* 400,000–600,000 U PO "swish & swallow" QID. *Vag:* 1 tab Vag hs × 2 wk. *Topical:* Apply BID–TID to area.
Peds Infants: 200,000 U PO q6h.
W/P: [B (C PO), +].
DISP: PO susp 100,000 U/ mL; PO tabs 500,000 U; troches 200,000 U; Vag tabs 100,000 U; topical cream/oint 100,000 U/g, powder 100,000 U/g.

SE: GI upset, SJS.
NOTES: Not absorbed through mucus membranes/intact skin, poorly absorbed through GI; not for systemic infections; see also triamcinolone/nystatin.

OFLOXACIN (FLOXIN)

WARNING: ↑ Risk Achilles tendon rupture and tendonitis, ↑ in pts >60 yr, on steroids or with organ transplant; avoid w/ myasthenia gravis, may ↑ muscle weakness.
USES: *Lower resp tract, skin, & skin structure, & UTI, prostatitis, uncomp gonorrhea, & *Chlamydia* infections.*
ACTIONS: Bactericidal; ↓ DNA gyrase. *Broad-spectrum gram(+) & (–): S. pneumoniae, S. aureus, S. pyogenes, H. influenzae, P. mirabilis, N. gonorrhoeae, C. trachomatis, E. coli.*

DOSE:

Adults: 200–400 mg PO BID or IV q12h. ↓ in renal impairment, take on empty stomach.
W/P: [C, −] ↓ Absorption w/ antacids, sucralfate, Al^{2+}, Ca^{2+}, Mg^{2+}, Fe^{2+}, Zn^{+} -containing drugs, Hx seizures.
CI: Quinolone allergy.
DISP: Tabs 200, 300, 400 mg; Inj 20, 40 mg/mL; ophthal & otic 0.3%.
SE: N/V/diarrhea, photosensitivity, insomnia, headache, local irritation, ↑ QTc interval, peripheral neuropathy risk.
NOTES: *Floxin* brand D/C.

ONDANSETRON (ZOFRAN, ZOFRAN ODT, GENERIC)

USES: *Prevent chemotherapy-associated & postop N/V.*
ACTIONS: Serotonin receptor (5-HT_3) antagonist.

DOSE:
Adults & Peds: *Chemotherapy:* 0.15 mg/kg/dose IV prior to chemotherapy, then 4 & 8 hr after 1st dose or 4–8 mg PO TID; 1st dose 30 min prior to chemotherapy & give on schedule, not PRN.
Adults: *Postoperation:* 4 mg IV immediately preanesthesia or postoperation.
Peds: *Postoperation:* ***<40 kg:*** 0.1 mg/kg. ***>40 kg:*** 4 mg IV; ↓ w/ hepatic impairment.
W/P: [B, +/−] Arrhythmia risk, may ↑ QT interval.
DISP: Tabs 4, 8, 24 mg, soln 4 mg/5 mL, Inj 2 mg/mL; *Zofran* ODT tabs 4, 8 mg.
SE: Diarrhea, headache, constipation, dizziness.
NOTES: ODT contains phenylalanine. No single IV dose > 6 mg.

ONDANSETRON, ORAL SOLUBLE FILM (ZUPLENZ)

USES: *Prevent chemotherapy/RT-associated & postop N/V.*
ACTIONS: Serotonin receptor (5-HT_3) antagonist.

DOSE:

Adults: *Highly emetogenic chemo:* 24 mg (8 mg film × 3) 30 min prechemo; *RT N& V:* 8 mg

film TID.
Adults & Peds: *>12 yr. Mod emetogenic chemo:* 8 mg film 30 min prechemo, then 8 mg in 8 hr; 8 mg film BID × 1–2 days after chemo.
Adults: *Postop: 16 mg (8 mg film × 2) 1 hr preop;* ↓ w/ hepatic impairment.
W/P: [B, +/−].
CI: w/ Apomorphine.
DISP: Oral soluble film 4, 8 mg.
SE: Headache, malaise/ fatigue, constipation, diarrhea.
NOTES: Use w/ dry hands, do not chew/swallow; place on tongue, dissolves in 4–20 s; peppermint flavored.

OSPEMIFENE (OSPHENA)

WARNING: ↑ Risk endometrial Ca; ↑ risk of CVA, DVT/PE.
USES: *Treatment of moderate–severe dyspareunia.*
ACTIONS: Estrogen agonist/antagonist.

DOSE:

Adults: 1 tab daily.
W/P: [X, −] Do not use w/ estrogens and estrogen agonists/antagonists, fluconazole & rifampin ↓ effect, ketoconazole ↑ effect, ↑ side effects w/ drugs that inhibit CYP3A4 and CYP2C9; highly protein bound, may be displaced by other highly bound drugs.
CI: Undiagnosed abnormal genital bleeding; known/suspected estrogen-sensitive cancer; pregnancy.
DISP: Tab 60 mg.
SE: DVT/PE, hemorrhagic or thrombotic stroke, arterial thromboembolic dz, hot flashes; vaginal discharge; hyperhidrosis; muscle cramps; metabolized by CYP3A4, CYP2C9, and CYP2C19.
NOTES: Do not use w/ severe liver disease.

OXACILLIN (GENERIC)

USES: *infections d/t susceptible *S. aureus, Streptococcus & other organisms.**
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* Excellent gram(+), poor gram(−).

DOSE:

Adults: 250–500 mg (2 g severe) IM/ IV q4–6h.
Peds: 150–200 mg/kg/d IV ÷ q4–6h.
W/P: [B, M].
CI: PCN sensitivity.
DISP: Powder for Inj 500 mg, 1, 2, 10 g.
SE: GI upset, interstitial nephritis, blood dyscrasias, may ↓ OCP effectiveness.

OXYBUTYNIN (DITROPAN, DITROPAN XL, GENERIC)

USES: Relief of symptoms of bladder instability associated with voiding in patients with

uninhibited neurogenic or reflex neurogenic bladder (ie, urgency, frequency, urinary leakage, urge incontinence, dysuria). *Ditropan XL*: Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency; pediatric patients >6 yr with symptoms of detrusor overactivity associated w/ a neurologic condition (eg, spina bifida).
ACTIONS: Anticholinergic, relaxes bladder smooth muscle, ↑ bladder capacity.

DOSE:

Adults: 5 mg BID–TID, 5 mg 4×/d max. XL 5–10 mg/d, 30 mg/d max.
Peds: ***>5 yr:*** 5 mg PO BID–TID; 15 mg/d max.
Peds: ***1–5 yr:*** 0.2 mg/kg/dose 2–4×/d (syrup 5 mg/5 mL); 15 mg/d max.; ↓ in elderly; periodic drug holidays OK.
W/P: [B, ?].
CI: Narrow-angle glaucoma, myasthenia gravis, GI/GU obst, ulcerative colitis, megacolon.
DISP: Tabs 5 mg; XL tabs 5, 10, 15 mg; syrup 5 mg/5 mL.
SE: Anticholinergic (drowsiness, xerostomia, constipation, tachycardia), ↑ QT interval, memory impairment; ER form empty shell expelled in stool.
NOTES: See topical forms of oxybutynin.

OXYBUTYNIN, TOPICAL (GELNIQUE)

USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.*
ACTIONS: Anticholinergic, relaxes bladder smooth muscle, ↑ bladder capacity.
DOSE: 1 g sachet qd to dry skin (abdominal/shoulders/thighs/upper arms).
W/P: [B, ?/−].
CI: Gastric or urinary retention; narrow-angle glaucoma.
DISP: Gel 10%, 1-g sachets (100 mg oxybutynin).
SE: Anticholinergic (lethargy, xerostomia, constipation, blurred vision, ↑ HR); rash, pruritus, redness, pain at site; UTI.
NOTES: Cover w/ clothing, skin-to-skin transfer can occur; gel is flammable; after applying wait 1 hr before showering.

OXYBUTYNIN TRANSDERMAL SYSTEM (OXYTROL, OXYTROL FOR WOMEN [OTC])

USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.*
ACTIONS: Anticholinergic, muscarinic antagonist; relaxes bladder smooth muscle, ↑ bladder capacity.
DOSE: One 3.9 mg/d system apply 2×/wk (q3–4d) to abdomen, hip, or buttock.
W/P: [B, ?/−].
CI: GI/GU obst, untreated narrow-angle glaucoma.
DISP: 3.9 mg/d transdermal patch (Rx and OTC).
SE: Anticholinergic, itching/ redness at site.
NOTES: Do not apply to same site w/in 7 days.

OXYCODONE/ACETAMINOPHEN ER (XARTEMIS XR) [CII]

WARNING: Addiction risk, risk of resp depression. Accidental consumption, esp. peds, can be fatal. Use during PRG can cause neonatal opioid withdrawal. Contains acetaminophen, associated with liver failure, transplant and death.
USES: *Acute pain that requires opioids where alternatives are inadequate.*
ACTIONS: Opioid agonist and acetaminophen.
DOSE: 2 tabs q12h, w/o regard to food; do not crush/chew.
W/P: [C, -] Do not use before delivery; not equivalent to other combo products; caution: w/ other CNS depressants, MAOI, neuromusc blockers, elderly, debilitated, w/ hepatic impair; may ↑ ICP (check pupils); assoc w/ skin reactions; may ↓ BP; acetaminophen hepato tox >4,000 mg, avoid w/ other acetaminophen products; impairs mental/physical abilities; drugs that ↓ CYP3A4 may ↓ oxycodone clearance.
CI: Component hypersens; resp dep, severe asthma/hypercarbia, ileus.
DISP: Tabs oxycodone/acetaminophen: 7.5/325 mg.
SE: ↓ resp, ↓ BP, sedation, coma.

OXYCODONE (OXYCONTIN, ROXICODONE, GENERIC) [C-II]

WARNING: High abuse potential similar to morphine; controlled release only for extended chronic pain, not for PRN use; 60-, 80-, 160-mg tab only for opioid-tolerant pts; or single dose >40 mg or total daily dose of >80 mg can cause fatal respiratory depression if intolerant; do not crush, break, or chew.
USES: *Mod– severe pain, usually in combo w/ nonnarcotic analgesics.*
ACTIONS: Narcotic analgesic.

DOSE:

Adults: 5 mg PO q6h PRN (immediate release). *Mod–severe chronic pain:* 10–160 mg PO q12h (ER); can give ER q8h if effect does not last 12 hr.
Peds: ***6–12 yr:*** 1.25 mg PO q6h PRN. >***12 yr:*** 2.5 mg q6h PRN; ↓ w/ severe liver/renal disease, elderly; w/ food.
W/P: [B (D if prolonged use/near term), M].
CI: Allergy, resp depression, acute asthma, ileus w/ microsomal morphine.
DISP: CR Roxicodone tabs 15, 30 mg; ER (OxyContin) 10, 15, 20, 30, 40, 60, 80, 160 mg; liq 5 mg/5 mL; soln conc 20 mg/mL.
SE: ↓ BP, sedation, resp depression, dizziness, GI upset, constipation, risk of abuse.
NOTES: *OxyContin* for chronic cancer pain; do not crush/chew/cut ER product; sought after as drug of abuse; reformulated *OxyContin* is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication.

OXYCODONE/ACETAMINOPHEN (PERCOCET, TYLOX) [C-II]

WARNING: Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 mg/d, and often involve more than 1 acetaminophen-containing product.

USES: *Mod– severe pain.*
ACTIONS: Narcotic analgesic.

DOSE:

Adults: 1–2 tabs/caps PO q4–6h PRN (acetaminophen max. dose 4 g/d).
Peds: Oxycodone 0.05–0.15 mg/kg/dose q4–6h PRN, 5 mg/dose max.
W/P: [C (D prolonged use or near term), M].
CI: Allergy, paralytic ileus, resp depression.
DISP: Percocet tabs, mg oxycodone/mg acetaminophen: 2.5/325, 5/325, 7.5/325, 10/325, 7.5/500, 10/650; Tylox caps 5 mg oxycodone, 500 mg acetaminophen; soln 5 mg oxycodone & 325 mg acetaminophen/5 mL.
SE: ↓ BP, sedation, dizziness, GI upset, constipation.
NOTES: See Acetaminophen note.

OXYCODONE/ASPIRIN (PERCODAN) [C-II]

USES: *Mod–severe pain.*
ACTIONS: Narcotic analgesic w/ NSAID.

DOSE:

Adults: 1–2 tabs/caps PO q4–6h PRN.
Peds: Oxycodone 0.05–0.15 mg/kg/dose q4–6h PRN, up to 5 mg/dose; ↓ in severe hepatic failure.
W/P: [D, −] w/ Peptic ulcer, CNS depression, elderly, Hx seizures.
CI: Component allergy, children (<16 yr) w/ viral infection (Reyes syndrome), resp depression, ileus, hemophilia.
DISP: *Generics:* 4.83 mg oxycodone hydrochloride, 0.38 mg oxycodone terephthalate, 325 mg aspirin; *Percodan* 4.83 mg oxycodone hydrochloride, 325 mg ASA.
SE: Sedation, dizziness, GI upset/ulcer, constipation, allergy.
NOTES: Monitor for possible drug abuse; max. 4 g aspirin/d.

OXYCODONE/IBUPROFEN (COMBUNOX) [C-II]

WARNING: May ↑ risk of serious CV events; CI in perioperative CABG pain; ↑ risk of GI events such as bleeding.
USES: *Short-term (not >7 days) management of acute mod–severe pain.*
ACTIONS: Narcotic w/ NSAID.
DOSE: 1 tab q6h PRN 4 tab max./24 h; 7 days max.
W/P: [C, −] w/ Impaired renal/hepatic function; COPD, CNS depression, avoid in pregnancy.
CI: Paralytic ileus, 3rd-tri pregnancy, allergy to ASA or NSAIDs, where opioids are CI.
DISP: Tabs 5 mg oxycodone/400 mg ibuprofen.
SE: N/V, somnolence, dizziness, sweating, flatulence, ↑ LFTs.
NOTES: Check renal function; abuse potential w/ oxycodone.

PACLITAXEL (ABRAXANE, TAXOL, GENERIC)

WARNING: Administration only by physician experienced in chemotherapy; fatal anaphylaxis and hypersens possible; severe myelosuppression possible.
USES: *Ovarian & breast cancer, Kaposi sarcoma, non-small cell lung cancer.*
ACTIONS: Mitotic spindle poison; promotes microtubule assembly & stabilization against depolymerization.
DOSE: Per protocols; use glass or polyolefin containers (eg, nitroglycerin tubing set); PVC sets leach plasticizer; ↓ in hepatic failure.
W/P: [D, −].
CI: Neutropenia ANC <1,500 cells/mm^3, <1,000 cells/mm^3 in w/ AIDS-related Karposi's syndrome; solid tumors, component allergy.
DISP: Inj 6 mg/mL, vial 5, 16.7, 25, 50 mL; (*Abraxane*) 100 mg/vial.
SE: ↓ BM, peripheral neuropathy, transient ileus, myalgia, ↓ HR, ↓ BP, mucositis, N/V/diarrhea, fever, rash, headache, phlebitis; hematologic tox schedule dependent; leukopenia dose limiting by 24-hr Inf; neurotox limited w/ short (1–3 hr) Inf; allergic reactions (dyspnea, ↓ BP, urticaria, rash).
NOTES: Maintain hydration; allergic reaction usually w/in 10 min of Inf; minimize w/ corticosteroid, antihistamine pretreatment.

PALONOSETRON (ALOXI)

USES: *Prevent acute & delayed N/V w/ emetogenic chemotherapy; prevent postoperative N/V up to 24 hr.*
ACTIONS: 5-HT3-receptor antagonist.

DOSE:

Adults: *Chemotherapy:* 0.25 mg IV 30 min prechemo; 0.5 mg PO 1 hr prechemo w/o regard to food. *Postoperative N/V:* 0.075 mg immediately before induction.
Peds: 1 mo–17yr 20 μg/kg (max. 1.5 mg) × 1 IV over 15 min, 30 min prechemo.
W/P: [B, ?] May ↑ QTc interval.
CI: Component allergy.
DISP: 0.05 mg/mL (1.5 & 5 mL vials); 0.5 mg caps.
SE: HA, constipation, dizziness, abdominal pain, anxiety.

PAMIDRONATE (GENERIC)

USES: *Hypercalcemia of malignancy, Paget disease, palliate symptomatic osteolytic mets of multiple myeloma and breast cancer.*
ACTIONS: Bisphosphonate; ↓ nl & abnormal bone resorption.
DOSE: *Hypercalcemia:* 60–90 mg IV over 2–24 hr or 90 mg IV over 24 hr if severe; may repeat in 7 days. *Paget disease:* 30 mg/d IV slow Inf over 4 hr × 3 days. *Osteolytic bone mets in myeloma*: 90 mg IV over 4 hr qmo. *Osteolytic bone mets breast cancer:* 90 mg IV over 2 hr q3–4wk; 90 mg/max. single dose.
W/P: [D, ?/−] Avoid invasive dental procedures w/ use.
CI: Bisphosphonate sensitivity.
DISP: Inj 30, 60, 90 mg.
SE: Fever, malaise, convulsions, Inj site reaction, uveitis, fluid overload, HTN, abdominal

pain, N/V, constipation, UTI, bone pain, ↓ K^+, ↓ Ca^{2+}, ↓ Mg^{2+}, hypophosphatemia; jaw osteonecrosis (mostly cancer pts; avoid dental work), renal tox.
NOTES: Perform dental exam pretherapy; follow Cr, hold dose if Cr ↑ by 0.5 mg/dL w/ nl baseline or by 1 mg/dL w/ abnormal baseline; restart when Cr returns w/in 10% of baseline; may ↑ atypical subtrochanteric femur fractures.

PAPAVERINE; PAPAVERINE/PHENTOLAMINE ("BIMIX"); PAPAVERINE/PHENTOLAMINE/PROSTAGLANDIN E_1 ("TRIMIX")

(Note: These medications are not FDA approved for this use. These medications are prepared by compounding pharmacies.)
USES: Erectile dysdunction.
ACTIONS: *Prostaglandin E_1*: Vasodilator, relaxes smooth muscle of corpus cavernosa; *papaverine:* smooth muscle relaxation w/ vasodilatation; *phentolamine* blocks α-adrenergic receptors, results in vasodilation.
DOSE: Based on formulation, typical starting volumes of 0.1–0.5 mL and titrated in the office; self-administered using insulin syringe with a 26–30G 1/2-inch needle through the lateral shaft of the mod penis into one corporeal body; erection should occur in a few minutes.
W/P: [n/a, n/a].
CI: No official information, probably similar to intracorporeal alprostadil: ↑ Priapism risk (especially sickle cell, myeloma, leukemia), penile deformities/urethral stricture/implants; men in whom sex inadvisable; component hypersensitivity.
DISP: Based on compounding pharmacy; reported concentrations: Papaverine 5–30 mg/mL; BiMix (papaverine 5.88–30 mg and phentolamine 1–4 mg); TriMix (papaverine 5–30 mg/mL, phentolamine 0.1–5 mg/mL, prostaglandin E_1 5–40 μg/mL).
SE: Penile pain, penile nodule formation, transient increases in LFTs, and hematoma priapism.
NOTES: Titrate dose in office.

PASIREOTIDE (SIGNIFOR)

USES: *Cushing disease where pituitary surgery not an option*
ACTIONS: Somatostatin analogue inhibitor ACTH secretion.

DOSE:

Adults: 0.6–0.9 mg SQ 2×/d; titrate on response/tolerability; hepatic impairment (Child-Pugh B): 0.3–0.6 mg SQ twice daily, (Child-Pugh C): avoid.
W/P: [C, −] w/ Risk for ↓ HR or ↑ QT; w/ drugs that ↓ HR, ↑ QT, cyclosporine, bromocriptine.
CI: None.
DISP: Inj single-dose 0.3, 0.6, 0.9 mg/mL.
SE: N/V/diarrhea, hyperglycemia, headache, abdominal pain, cholelithiasis, fatigue, DM, hypocortisolism, ↓ HR, QT prolongation, ↑ glucose, ↑ LFTs, ↓ pituitary hormones, Inj site reaction, edema, alopecia, asthenia, myalgia, arthralgia.
NOTES: Prior to and periodically (see label), check TSH/T_4 , HbA1c, LFTs, ECG, gallbladder

US.

PAZOPANIB (VOTRIENT)

WARNING: Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing.
USES: *Advanced RCC; metastatic soft-tissue sarcoma after chemotherapy.*
ACTIONS: Tyrosine kinase inhibitor.
DOSE: 800 mg PO once daily, ↓ to 200 mg daily if moderate hepatic impairment, not rec in severe hepatic disease (bili >3 × ULN).
W/P: [D, −] Avoid w/ CYP3A4 inducers/inhibitor and QTc prolonging drugs, all SSRI; follow thyroid function tests; risk of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and HUS; simvastatin increases the risk of ALT elevations.
CI: Severe hepatic disease.
DISP: 200-mg tablet.
SE: ↑ BP, N/V/diarrhea, GI perf, anorexia, hair depigmentation, ↓ WBC, ↓ plt, ↑ bleeding, ↑ AST/ALT/bili, ↓ Na, CP, ↑ QTc; reversible posterior leukoencephalopathy syndrome; proteinuria (hold w/ >3 g protein/24 h).
NOTES: Hold for surgical procedures. Take 1 hr ac or 2 hr pc.

PEGFILGRASTIM (NEULASTA)

USES: *↓ Frequency of infection in pts w/ nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs that cause febrile neutropenia.*
ACTIONS: Granulocyte and macrophage-stimulating factor.

DOSE:

Adults: 6 mg SQ × 1/chemotherapy cycle.
W/P: [C, M] w/ Sickle cell.
CI: Allergy to *E. coli*-derived proteins or filgrastim.
DISP: *Syringes:* 6 mg/0.6 mL.
SE: Splenic rupture, headache, fever, weakness, fatigue, dizziness, insomnia, edema, N/V/diarrhea, stomatitis, anorexia, constipation, taste perversion, dyspepsia, abdominal pain, granulocytopenia, neutropenic fever, ↑ LFTs & uric acid, arthralgia, myalgia, bone pain, ARDS, alopecia, worsen sickle cell disease.
NOTES: Never give between 14 days before & 24 hr after dose of cytotoxic chemotherapy.

PENCICLOVIR (DENAVIR)

USES: *Herpes simplex (herpes labialis/cold sores).*
ACTIONS: Competitive inhibitor of DNA polymerase.
DOSE: Apply at 1st sign of lesions, then q2h while awake × 4 days.
W/P: [B, ?/−].
CI: Allergy, previous reaction to famciclovir.
DISP: Cream 1%.

SE: Erythema, headache.
NOTES: Do not apply to mucous membranes.

PENICILLIN G, AQUEOUS (POTASSIUM OR SODIUM) (PFIZERPEN, PENTIDS)

USES: *Bacteremia, endocarditis, pericarditis, resp tract infections, meningitis, neurosyphilis, SSSI.*
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* Most gram(+) (not staphylococci), streptococci, *N. meningitidis,* syphilis, clostridia, & anaerobes (not *Bacteroides*).

DOSE:

Adults: Based on indication range 0.6–24 MU/d in ÷ doses q4h.
Peds: *Newborns < wk:* 25,000–50,000 U/ kg/dose IV q12h. *Infants 1 wk–<1 mo:* 25,000–50,000 U/kg/dose IV q8h. *Children:* 100,000–400,000 U/kg/24h IV ÷ q4h; ↓ in renal impairment.
W/P: [B, M].
CI: Allergy.
DISP: Powder for Inj.
SE: Allergic reactions; interstitial nephritis, diarrhea, seizures.
NOTES: Contains 1.7 mEq of K^+/MU.

PENICILLIN V (PEN-VEE K, VEETIDS, OTHERS)

USES: Susceptible streptococcal infections, otitis media, URIs, skin/soft-tissue infections (PCN-sensitive staphylococci).
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* Most gram(+), including streptococci.

DOSE:

Adults: 250–500 mg PO q6h, q8h, q12h.
Peds: 25–50 mg/kg/24 h PO in 3–4 ÷ dose above the age of 12 yr, dose can be standardized vs. Wt based; ↓ in renal impairment; take on empty stomach.
W/P: [B, M].
CI: Allergy.
DISP: Tabs 125, 250, 500 mg; susp 125, 250 mg/5 mL.
SE: GI upset, interstitial nephritis, anaphylaxis, convulsions.
NOTES: A well-tolerated oral PCN; 250 mg = 400,000 U of PCN G.

PENICILLIN G BENZATHINE (BICILLIN)

USES: *Single-dose regimen for streptococcal pharyngitis, rheumatic fever, glomerulonephritis prophylaxis, & syphilis.*
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* See Penicillin G.

DOSE:

Adults: 1.2–2.4 MU deep IM Inj q2–4wk.

Peds: 50,000 U/kg/dose, 2.4 MU/dose max.; deep IM Inj q2–4 wk.
W/P: [B, M].
CI: Allergy.
DISP: Inj 300,000, 600,000 U/mL; Bicillin L-A benzathine salt only; Bicillin C-R combo of benzathine & procaine (300,000 U procaine w/ 300,000 U benzathine/mL or 900,000 U benzathine w/ 300,000 U procaine/2 mL).
SE: Inj site pain, acute interstitial nephritis, anaphylaxis.
NOTES: IM use only; sustained action, w/ levels up to 4 wk; drug of choice for noncongenital syphilis.

PENICILLIN G PROCAINE (WYCILLIN, OTHERS)

USES: *Infections of resp tract, skin/soft tissue, scarlet fever, syphilis.*
ACTIONS: Bactericidal; ↓ cell wall synth. *Spectrum:* PCN G-sensitive organisms that respond to low, persistent serum levels.

DOSE:

Adults: 0.6–4.8 MU/d in ÷ doses q12–24h; give probenecid at least 30 min prior to PCN to prolong action.
Peds: 25,000–50,000 U/kg/d IM ÷ daily–BID.
W/P: [B, M].
CI: Allergy.
DISP: Inj 300,000, 500,000, 600,000 U/mL.
SE: Pain at Inj site, interstitial nephritis, anaphylaxis.
NOTES: LA parenteral PCN; levels up to 15 hr.

PENTAZOCINE (TALWIN, TALWIN COMPOUND, TALWIN NX) [C-IV]

WARNING: Oral use only; severe and potentially lethal reactions from misuse by Inj.
USES: *Mod–severe pain.*
ACTIONS: Partial narcotic agonist–antagonist; combination with other pain relief agents (see Disp).

DOSE:

Adults: 30 mg IM or IV; 50–100 mg PO q3–4h PRN.
Peds: ***5–8 yr:*** 15 mg IM q4h PRN. ***9–14 yr:*** 30 mg IM q4h PRN; ↓ in renal/hepatic impairment.
W/P: [C (1st tri, D w/ prolonged use/high dose near term), +/−].
CI: Allergy, ↑ ICP (unless ventilated).
DISP: *Talwin Compound* tab 12.5 mg + 325 mg aspirin; *Talwin NX* 50 mg + 0.5 mg naloxone; *Talwin* Inj 30 mg/mL.
SE: Considerable dysphoria; drowsiness, GI upset, xerostomia, seizures.
NOTES: 30–60 mg IM = 10 mg of morphine IM; Talwin NX has naloxone to curb abuse by nonoral route.

PENTOSAN POLYSULFATE SODIUM (ELMIRON)

USES: *Relieve pain/discomfort w/ interstitial cystitis.*
ACTIONS: Bladder wall buffer.
DOSE: 100 mg PO TID; on empty stomach w/ H_2O 1 hr ac or 2 hr pc.
W/P: [B, ?/−].
CI: Hypersensitivity to pentosan or related compounds (LMWH, heparin).
DISP: Caps 100 mg.
SE: Alopecia, N/diarrhea, headache, ↑ LFTs, anticoagulant effects, ↓ plts, rectal bleed.
NOTES: Reassess after 3 mo; related to LMWH, heparin; role for hemorrhagic cystitis suggested.

PERMETHRIN (ELIMITE, NIX, GENERIC [OTC])

USES: *Treat lice/scabies.*
ACTIONS: Pediculicide.

DOSE:
Adults & Peds: ***>2 yr:*** *Lice:* Saturate hair & scalp; allow 10 min before rinsing. *Scabies:* Apply cream head to toe; leave for 8–14 hr, wash w/ H_2O.
W/P: [B, ?/−].
CI: Allergy >2 mo.
DISP: Topical lotion 1%; cream 5%.
SE: Local irritation.
NOTES: Sprays available (*Rid, A200, Nix*) to disinfect clothing, bedding, combs, & brushes; lotion not OK in peds <2 mo; may repeat after 7 days.

PHENAZOPYRIDINE (PYRIDIUM, GENERIC) (AZO, MANY OTHER OTC FORMS)

USES: *Relief of pain, burning, urgency, frequency, and other discomforts d/t irritation of the lower urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters. *
ACTIONS: Anesthetic on urinary tract mucosa.

DOSE:

Adults: 100–200 mg PO TID; 2 days max. w/ antibiotics for UTI; ↓ w/ renal insufficiency.
W/P: [B, ?] Hepatic disease; methemoglobinemia w/ acute overdose.
CI: Renal failure, component hypersensitivity.
DISP: Tabs (*Pyridium, Rx*) 100, 200 mg; OTC Tabs 45, 95, 97.2, 97.5, 99.5 mg.
SE: GI disturbances, red-orange urine color (can stain clothing, contacts), yellow tinge to skin/sclera, rash, headache, dizziness, acute renal failure, methemoglobinemia, tinting of sclera/skin.
NOTES: Take w/ food, hydrate well. For peds phenazopyridine can be compounded with glycerin to form a suspension yielding a 10 mg/mL solution, the dose is 4 mg/kg/dose TID.

PHENYLEPHRINE, ORAL (SUDAFED, OTHERS [OTC])

WARNING: Not for use in peds <2 yr.
USES: *Nasal congestion.*
ACTIONS: α-Adrenergic agonist.

DOSE:

Adults: 10–20 mg PO q4h PRN, max. 60 mg/d.
Peds: 4–5 y: 2.5 mg q4h max. 6 doses/d; >6–12: 5 mg q4h, max. 30 mg/d ≥12: adult dosing.
W/P: [C, +/−] HTN, acute pancreatitis, hep, coronary disease, narrow-angle glaucoma, hyperthyroidism.
CI: MAOI w/in 14 days, narrow-angle glaucoma, severe ↑ BP or CAD, urinary retention.
DISP: Liq 7.5 mg/5 mL; drops: 1.25/0.8 mL, 2.5 mg/5 mL; tabs 5, 10 mg; chew tabs 10 mg; tabs once daily 10 mg; strips: 1.25, 2.5, 10 mg; many combo OTC products.
SE: Arrhythmias, HTN, headache, agitation, anxiety, tremor, palpitations; can be chemically processed into methamphetamine; products now sold behind pharmacy counter w/o prescription.
NOTES: 60 mg 4 times daily for 6 wk for retrograde ejaculation.

PIPERACILLIN/TAZOBACTAM (ZOSYN, GENERIC)

USES: *Infections of skin, bone, resp & urinary tract, abdominal, sepsis.*
ACTIONS: 4th-gen PCN plus β-lactamase inhibitor; bactericidal; ↓ cell wall synth. *Spectrum:* Good gram(+), excellent gram(−); anaerobes & β-lactamase producers.

DOSE:

Adults: 3.375–4.5 g IV q6h; ↓ in renal insufficiency.
W/P: [B, M].
CI: PCN or β-lactam sensitivity.
DISP: Frozen and powder for Inj: 2.25, 3.375, 4.5 g.
SE: Diarrhea, headache, insomnia, GI upset, serum sickness-like reaction, pseudomembranous colitis.
NOTES: Often used in combo w/ aminoglycoside.

PODOFILOX [PODOPHYLLIN] (PODOCON-25, CONDYLOX, CONDYLOX GEL 0.5%)

USES: *Topical Treat of benign growths (genital & perianal warts [condylomata acuminata]*, papillomas, fibromas).
ACTIONS: Direct antimitotic effect; exact mechanism unknown.
DOSE: *Condylox gel & Condylox:* Apply BID for 3 consecutive d/wk then hold for 4 days, may repeat 4 × 0.5 mL/d max.; *Podocon-25:* Use sparingly on the lesion, leave on for only 30–40 min for 1st application, then 1–4 hr on subsequent applications, thoroughly wash off; limit <5 mL or <10 cm^2/Treat.
W/P: [X, ?] Immunosuppression.
CI: DM, bleeding lesions.
DISP: *Podocon-25* (w/ benzoin) 15-mL bottles; *Condylox gel* 0.5% 35-g clear gel; *Condylox soln*

0.5% 35-g clear.
SE: Local reactions, sig absorption; anemias, tachycardia, paresthesias, GI upset, renal/hepatic damage.
NOTES: *Podocon-25* applied by the clinician; do not dispense directly to pt.

POLYETHYLENE GLYCOL [PEG] 3350 (MIRALAX [OTC])

USES: *Occasional constipation*, constipation/dysfunctional elimination syndrome in peds.
ACTIONS: Osmotic laxative.

DOSE:
Adult: 17-g powder (1 heaping tsp) in 8 oz (1 cup) of H_2O & drink; max. 14 d.
Peds: ***>6 mo:*** (Not FDA) 0.5–1.5 g/kg daily, max. dose 17 g/d.
W/P: [C, ?] Rule out bowel obst before use.
CI: GI obst, allergy to PEG.
DISP: Powder for reconstitution; bottle cap holds 17 g.
SE: Upset stomach, bloating, cramping, gas, severe diarrhea, hives.
NOTES: Can add to H_2O, juice, soda, coffee, or tea.

POTASSIUM CITRATE (UROCIT-K, GENERIC)

USES: *Alkalinize urine, prevention of urinary stones (uric acid, calcium stones if hypocitraturic).*
ACTIONS: Urinary alkalinizer.
DOSE: 30–60 mEq/d based on severity of hypocitraturia. Max. 100 mEq/d.
W/P: [A, +].
CI: Severe renal impairment, dehydration, ↑ K^+, peptic ulcer; w/ K^+-sparing diuretics, salt substitutes.
DISP: Tabs 5, 10, 15 mEq/d.
SE: GI upset, ↓ Ca^{2+}, ↑ K^+ (more likely with renal insufficiency); metabolic alkalosis.
NOTE: Maintain high fluid intake; gastrointestinal upset is the primary SE; treatment should be avoided when the urine pH is >6.5.

POTASSIUM SUPPLEMENTS (KAON, KAOCHLOR, K-LOR, SLOW-K, MICRO-K, KLORVESS, GENERIC)

USES: *Prevention or Treat of ↓ K^+* (eg, diuretic use).
ACTIONS: K^+ supl.

DOSE:

Adults: 20–100 mEq/d PO ÷ 1–4×/d; IV 10–20 mEq/h, max. 40 mEq/h & 150 mEq/d (monitor K^+ levels frequently and in presence of continuous ECG monitoring w/ high-dose IV).
Peds: Calculate K^+ deficit; 1–3 mEq/kg/d PO ÷ 1–4×/d; IV max. dose 0.5–1 mEq/kg/× 1–2 hr.
W/P: [A, +] Renal insufficiency, use w/ NSAIDs & ACE inhibitor.

CI: ↑ K^+.
DISP: PO forms see table at top of page, Inj.
SE: GI irritation; ↓ HR, ↑ K^+, heart block.
NOTES: Mix powder & liq w/ beverage (unsalted tomato juice, etc.); swallow SR tabs must be swallowed whole; follow monitor K^+; Cl^- salt OK w/ alkalosis; w/ acidosis use acetate, bicarbonate, citrate, or gluconate salt; do not administer IV K^+ undiluted.

Commonly Used Potassium Supplements

Brand Name	Salt	Form	mEq Potassium/ Dosing Unit
Glu-K	Gluconate	Tablet	2 mEq/tablet
Kaon elixir	Gluconate	Liquid	20 mEq/15 mL
Kaon-Cl 10	KCl	Tablet, SR	10 mEq/tablet
Kaon-Cl 20%	KCl	Liquid	40 mEq/15 mL
K-Dur 20	KCl	Tablet, SR	20 mEq/tablet
KayCiel	KCl	Liquid	20 mEq/15 mL
K-Lor	KCl	Powder	20 mEq/packet
K-lyte/Cl	KC /bicarbonate	Effervescent tablet	25 mEq/tablet
Klorvess	KCl/bicarbonate	Effervescent tablet	20 mEq/tablet
Klotrix	KCl	Tablet, SR	10 mEq/tablet
K-Lyte	Bicarbonate/citrate	Effervescent tablet	25 mEq/tablet
Klor-Con/EF	Bicarbonate/citrate	Effervescent tablet	25 mEq/tablet
K-Tab	KCl	Tablet, SR	10 mEq/tablet
Micro-K	KCl	Capsule, SR	8 mEq/capsule
Potassium Chloride 10%	KCl	Liquid	20 mEq/15 mL
Potassium Chloride 20%	KCl	Liquid	40 mEq/15 mL
Slow-K	KCl	Tablet, SR	8 mEq/tablet
Tri-K	Acetate/ bicarbonate and citrate	Liquid	45 mEq/15 mL
Twin-K	Citrate/gluconate	Liquid	20 mEq/5 mL

Based on data in and modified from Gomella LG, Haist S, Adams A, eds. *Clinicians' Pocket Drug Reference, 2015 Edition*. New York, NY: McGraw-Hill.

PRAMOXINE (ANUSOL OINTMENT, PROCTOFOAM-NS, OTHERS)

USES: *Relief of pain & itching from hemorrhoids, anorectal surgery*; topical for burns & dermatosis.
ACTIONS: Topical anesthetic.
DOSE: Apply freely to anal area 3–5 ×/d.
W/P: [C, ?].
DISP: [OTC] All 1%; foam (*ProctoFoam-NS*), cream, oint, lotion, gel, pads, spray.
SE: Contact dermatitis, mucosal thinning w/ chronic use.

PRAMOXINE/HYDROCORTISONE (PROCTOFOAM-HC)

USES: *Relief of pain & itching from hemorrhoids.*
ACTIONS: Topical anesthetic, anti-inflammatory.
DOSE: Apply freely to anal area TID–QID.
W/P: [C, ?/−].
DISP: *Cream:* Pramoxine 1% acetate 1/2.5/2.35%, *foam:* Pramoxine 1% hydrocortisone 1%; *lotion:* Pramoxine 1% hydrocortisone 1/2.5%; ointment pramoxine 1% & hydrocortisone 1/2.5%.
SE: Contact dermatitis, mucosal thinning w/ chronic use

PRAZOSIN (MINIPRESS, GENERIC)

USES: *HTN *
ACTIONS: Peripherally acting α-adrenergic blocker.

DOSE:

Adults: 1 mg PO TID; can ↑ to 20 mg/d max. PRN.
Peds: 0.05–0.1 mg/kg/d in 3 ÷ doses; max. 0.5 mg/kg/d.
W/P: [C, ?] Use w/ phosphodiesterase-5 (PDE5) inhibitor (eg, sildenafil) can cause ↓ BP.
CI: Component allergy, concurrent use of PDE5 inhibitor.
DISP: Caps 1, 2, 5 mg; tabs ER 2.5, 5 mg.
SE: Dizziness, edema, palpitations, fatigue, GI upset.
NOTES: Can cause orthostatic ↓ BP, take the 1st dose hs; tolerance develops to this effect; tachyphylaxis may result.

PREDNISOLONE (FLO-PRED, OMNIPRED, PEDIAPRED, GENERIC)

See Steroids pages 968, 969

PREDNISONE (GENERIC)

See Steroids pages 968, 969

PREGABALIN (LYRICA, GENERIC)

USES: *DM peripheral neuropathy pain; postherpetic neuralgia; fibromyalgia; adjunct w/ adult partial onset seizures
ACTIONS: Nerve transmission modulator, antinociceptive, antiseizure effect; mechanism uncertain; related to gabapentin.
DOSE: *Neuropathic pain:* 50 mg PO TID, ↑ to 300 mg/d w/in 1 wk based on response, 300 mg/d max. *Postherpetic neuralgia:* 75–150 mg BID or 50–100 mg TID; start 75 mg BID or 50 mg TID; ↑ to 300 mg/d w/in 1 wk PRN; if pain persists after 2–4 wk, ↑ to 600 mg/d. *Partial onset seizure:* Start 150 mg/d (75 mg BID or 50 mg TID) may ↑ to max. 600 mg/d; ↓ w/ CrCl <60; w/ or w/o food.
W/P: [C, −] w/ Sig renal impairment (see PI), w/ elderly & severe CHF avoid abrupt D/C.
CI: Hypersensitivity.
DISP: Caps 25, 50, 75, 100, 150, 200, 225, 300 mg; soln 20 mg/mL.
SE: Dizziness, drowsiness, xerostomia, edema, blurred vision, Wt gain, difficulty concentrating; suicidal ideation.
NOTES: w/ D/C, taper over at least 1 wk.

PROBENECID (PROBALAN, GENERIC)

USES: *Prevent gout & hyperuricemia; extends levels of PCNs & cephalosporins.*
ACTIONS: Uricosuric, renal tubular blocker of weak organic anions.

DOSE:

Adults: *Gout:* 250 mg BID × 1 wk, then 500 mg PO BID; can ↑ by 500 mg/mo up to 2–3 g/d.

Antibiotic effect: 1–2 g PO 30 min before dose.
Peds: ***>2 yr:*** 25 mg/kg, then 40 mg/kg/d PO QID.
W/P: [B, ?].
CI: Uric acid kidney stones, initiations during acute gout attack, coadministration of salicylates, age <2 yr, MDD, renal impairment.
DISP: Tabs 500 mg.
SE: Headache, GI upset, rash, pruritus, dizziness, blood dyscrasias.

PROPANTHELINE (PRO-BANTHINE, GENERIC)

USES: *Adjunctive therapy in the treatment of peptic ulcer *, symptomatic Treat small intestine hypermotility, spastic colon, ureteral spasm, bladder spasm, pylorospasm.
ACTIONS: Antimuscarinic.

DOSE:

Adults: 15 mg PO ac & 30 mg PO hs; ↓ in elderly.
Peds: 2–3 mg/kg/24 h PO ÷ 3–4×/d.
W/P: [C, ?].
CI: Glaucoma, severe ulcerative colitis, toxic megacolon, GI atony in elderly, myasthenia gravis, GI/GU obst.
DISP: 15 mg.
SE: Anticholinergic (eg, xerostomia, blurred vision).

PROPRANOLOL (INDERAL LA, INNOPRAN XL, GENERIC)

USES: *HTN, angina, MI, hyperthyroidism, essential tremor, hypertrophic subaortic stenosis, pheochromocytoma; prevents migraines & atrial arrhythmias*, thyrotoxicosis.
ACTIONS: β-Adrenergic receptor blocker, β_1, β_2; only β-blocker to block conversion of T_4 to T_3.

DOSE:

Adults: *Angina:* 80–320 mg/d PO ÷ 2–4×/d or 80–320 mg/d SR. *Arrhythmia*: 10–30 mg/dose PO q6–8h or 1 mg IV slowly, repeat q5min, 5 mg max. *HTN:* 40 mg PO BID or 60–80 mg/d SR, weekly to max. 640 mg/d. *Hypertrophic subaortic stenosis:* 20–40 mg PO 3–4×/d. *MI:* 180–240 mg PO ÷ 3–4×/d. *Migraine prophylaxis:* 80 mg/d ÷ 3–4×/d, ↑ weekly 160–240 mg/d ÷ 3–4 ×/d max.; wean if no response in 6 wk. *Pheochromocytoma:* 30–60 mg/d ÷ 3–4×/d. *Thyrotoxicosis:* 1–3 mg IV × 1; 10–40 mg PO q6h. *Tremor:* 40 mg PO BID, ↑ PRN 320 mg/d max. ***ECC 2010***. *SVT:* 0.5–1 mg IV given over 1 min; repeat PRN up to 0.1 mg/kg.
Peds: *Arrhythmia:* 0.5–1.0 mg/kg/d ÷ 3–4×/d, ↑ PRN q3–7d to 8 mg/kg max.; 0.01–0.1 mg/kg IV over 10 min, 1 mg max. infants, 3 mg max. children. *HTN:* 0.5–1.0 mg/kg ÷ 3–4×/day, PRN q3–7d to 8 mg/kg/d max.; ↓ in renal impairment.
W/P: [C (1st tri, D if 2nd or 3rd tri), +].
CI: Uncompensated CHF, cardiogenic shock, HR, heart block, PE, severe resp disease.
DISP: Tabs 10, 20, 40, 80 mg; SR caps 60, 80, 120, 160 mg; oral soln 4, 8, mg/ mL; Inj 1 mg/mL.

SE: ↓ HR, ↓ BP, fatigue, GI upset, erectile dysfunction.

PROTAMINE (GENERIC)

WARNING: Severe ↓ BP, CV collapse, noncardiogenic pulm edema, pulm vasoconstriction, and pulm HTN can occur; risk factors: high dose/ overdose, repeat doses, prior protamine use, current or use of prior protamine-containing product (eg, NPH or protamine zinc insulin, some β-blockers), fish allergy, prior vasectomy, severe LV dysfunction, abnormal pulm testing; weigh risk/benefit in pts w/ 1 or more risk factors; resuscitation equipment must be available.
USES: *Reverse heparin effect.*
ACTIONS: Neutralize heparin by forming a stable complex.
DOSE: Based on degree of heparin reversal; give IV slowly; 1 mg reverses ~100 U of heparin given in the preceding 30 min; 50 mg max.
W/P: [C, ?].
CI: Allergy.
DISP: Inj 10 mg/mL.
SE: Follow coagulation markers; anticoagulant effect if given w/o heparin; ↓ BP, ↓ HR, dyspnea, hemorrhage.
NOTES: Check aPTT ~15 min after use to assess response.

PROTHROMBIN COMPLEX CONCENTRATE, HUMAN (KCENTRA)

WARNING: Risk vit K antag reversal w/ a thromboembolic event, must be weighed against the risk of NOT reversing vitamin K antag; this risk is higher in those who have had a prior thromboembolic event. Fatal and non-fatal arterial and venous thromboembolic events have occurred. Monitor. May not be effective in pts w/ thromboembolic events in the prior 3 mo.
USES: *Urgent reversal of acquired coagulation factor deficiencies caused by vit K antagonists; only for acute major bleeding.*
ACTIONS: Reverse vit K antag coagulopathy; replaces Factor II, VII, IX, X & Protein C & S.
DOSE: Based on INR and wgt: INR 2–4, 25 U/kg, 2,500 U max.; INR 4–6, 35 U/kg, 3,500 U max.; INR >6, 50 U/kg, 5,000 U max.; 100 mg/kg max.; give w/ vit K.
W/P: [C, ?] Hypersensitivity reaction; arterial/venous thrombosis; risk of viral Infxn including variant CJD.
CI: Anaphylaxis/reactions to: heparin, albumin or coag factors (Protein C & S, antithrombin III); known HIT DIC.
DISP: Single vial, to reconstitute, see package; separate IV for inf.
SE: Thromboembolic events (stroke, DVT/PE); DIC; ↓ BP, HA, N/V, HA, arthralgias.
NOTES: INR should be <1.3 w/in 30 min; risk of transmitting variant CJD, viral Dz (human blood product), and other Infxn (Hep A, B & C, HIV, etc.).

PSEUDOEPHEDRINE (MANY OTC MONO AND COMBINATION BRANDS)

USES: *Decongestant*, retrograde ejaculation.
ACTIONS: Stimulates α-adrenergic receptors w/ vasoconstriction.

DOSE:

Adults: *IR:* 60 mg PO q4–6h PRN; *ER:* 120 mg PO q12h, 240 mg/d max.; *Retrograde ejaculation*: Up to 60 mg, PO QID for 2–14 days.
Peds: ***2–5 yr:*** 15 mg q4–6h, 60 mg/24 h max. ***6–12 yr:*** 30 mg q4–6h, 120 mg/24 h max.; ↓ w/ renal insufficiency.
W/P: [C, +] Not rec for use in peds <6 yr.
CI: Poorly controlled HTN or CAD, w/ MAOIs w/in 14 days, urinary retention.
DISP: Immediate release tabs 30, 60 mg; ER caplets 60, 120 mg; ER tabs 120, 240 mg; liq 15, 30 mg/5 mL; syrup 15, 30 mg/5mL; multiple combo OTC products.
SE: HTN, insomnia, tachycardia, arrhythmias, nervousness, tremor.
NOTES: Found in many OTC cough/cold preparations; OTC restricted distribution by state (illicit ingredient in methamphetamine production).

PYRAZINAMIDE (GENERIC)

USES: *Active TB in combo w/ other agents.*
ACTIONS: Bacteriostatic; unknown mechanism.

DOSE:

Adults: Dose varies based on Tx option chosen daily 1 × 2 wk–3 × wk; dosing based on lean body Wt; ↓ dose in renal/hepatic impairment.
Peds: 20–40 mg/kg/d PO ÷ daily–BID; ↓ W/ renal/hepatic impairment.
W/P: [C, +/−].
CI: Severe hepatic damage, acute gout.
DISP: Tabs 500 mg.
SE: Hepatotox, malaise, GI upset, arthralgia, myalgia, gout, photosensitivity.
NOTES: Use in combo w/ other anti-TB drugs; consult http://www.cdc.gov/tb/ for latest TB recommendations; dosage regimen differs for “directly observed” Treat.

PYRIDOXINE [VITAMIN B_6] (GENERIC)

USES: *Treat & prevention of vit B_6 deficiency* supplement when on INH, idiopathic hyperoxaluria.
ACTIONS: Vit B_6 supl.

DOSE:

Adults: *Deficiency:* 10–20 mg/d PO. *Drug-induced neuritis:* 100–200 mg/d; 25–100 mg/d prophylaxis.
Peds: 5–25 mg/d × 3 wk.
W/P: [A (C if doses exceed RDA), +].
CI: Component allergy tabs 25, 50, 100, 250, 500 mg, tab SR 500 mg; liquid 200 mg, 15 mg; Inj: 100 mg/mL; caps: 50, 250.

QUINAPRIL (ACCUPRIL, GENERIC)

WARNING: ACE inhibitor used during pregnancy can cause fet al injury & death.
USES: *HTN, CHF, DN, post-MI.*

ACTIONS: ACE inhibitor.
DOSE: 10–80 mg PO daily; ↓ in renal impairment.
W/P: [D, +] w/ RAS, vol depletion.
CI: ACE inhibitor sensitivity, angioedema, pregnancy.
DISP: Tabs 5, 10, 20, 40 mg.
SE: Dizziness, headache, ↓ BP, impaired renal function, angioedema, taste perversion, cough.

QUINUPRISTIN/DALFOPRISTIN (SYNERCID)

USES: *Vancomycin-resistant infections d/t *E. faecium* & other gram(+).*
ACTIONS: ↓ Ribosomal protein synth. *Spectrum:* Vancomycin-resistant *E. faecium,* methicillin-susceptible *S. aureus, S. pyogenes;* not against *E. faecalis.*

DOSE:
Adults & Peds: 7.5 mg/kg IV q12h (central line preferred); incompatible w/ NS or heparin; flush IV w/ dextrose; ↓ w/ hepatic failure.
W/P: [B, M] Multiple drug interactions w/ drugs metabolized by CYP3A4 (eg, cyclosporine).

RADIUM-223 DICHLORIDE (XOFIGO)

USES: *Castration-resistant prostate cancer, symptomatic bone metastases w/o visceral metastatic disease.*
ACTIONS: α-emitting radioactivity, forms complexes in bone in area of ↑ bone turnover.

DOSE:

Adults: *Men only:* 50 kBq/kg, Q 4 wk × 6 doses.
W/P: [X, -] not indicated in women.
CI: Preg.
DISP: Single vial, 1,000 kBq/mL or 6,000 kBq/vial.
SE: Anemia, ↓ lymphocytes, ↓ WBC, ↓ plts, ↓ neutrophils; N/V/D, edema.
NOTES: Slow IV infusion over 1 min; follow radiation safety and pharmaceutical quality control requirements; men should use condoms during Tx & to 6 mo post-Tx and female partners should use 1 method because of potential effects of radiation on sperm; less bone marrow toxicity than β-emitters such as strontium.

RALOXIFENE (EVISTA)

WARNING: Increased risk of venous thromboembolism and death from stroke.
USES: *Prevent osteoporosis, breast cancer prevention.*
ACTIONS: Partial antagonist of estrogen, behaves like estrogen.
DOSE: 60 mg/d.
W/P: [X, −].
CI: Thromboembolism, pregnancy.
DISP: Tabs 60 mg.
SE: CP, insomnia, rash, hot flashes, GI upset, hepatic dysfunction, leg cramps.

RAMIPRIL (ALTACE, GENERIC)

WARNING: ACE inhibitor used during pregnancy can cause fet al injury & death.
USES: *HTN, CHF, DN, post-MI.*
ACTIONS: ACE inhibitor.
DOSE: 1.25–20 mg/d PO ÷ daily–BID; ↓ in renal failure.
W/P: [C-1st tri/D-2nd & 3rd, +].
CI: ACE inhibitor-induced angioedema.
DISP: Caps 1.25, 2.5, 5, 10 mg.
SE: Cough, headache, dizziness, ↓ BP, renal impairment, angioedema.
NOTES: OK in combo w/ diuretics.

RASBURICASE (ELITEK)

WARNING: Anaphylaxis possible; do not use in G6PD deficiency and hemolysis; can cause methemoglobinemia; can interfere w/ uric acid assays; collect blood samples and store on ice.
USES: *Reduce ↑ uric acid d/t tumor lysis.*
ACTIONS: Catalyzes uric acid.

DOSE:
Adult & Peds: 0.20 mg/kg IV over 30 min, daily × 5; do not bolus, redosing-based uric acid levels.
W/P: [C, ?/−] Falsely ↓ uric acid values.
CI: Anaphylaxis, screen for G6PD deficiency to avoid hemolysis, methemoglobinemia.
DISP: 1.5, 7.5 mg powder Inj.
SE: Fever, neutropenia, GI upset, headache, rash.
NOTES: Place blood test tube for uric acid level on ice to stop enzymatic reaction; removed by dialysis; doses as low as 0.05 mg/kg have been used effectively in clinical trials.

RIFAMPIN (RIFADIN, RIMACTANE, GENERIC)

USES: *TB & Treat & prophylaxis of *N. meningitidis, H. influenzae,* or *S. aureus* carriers*; adjunct w/ severe *S. aureus.*
ACTIONS: ↓ DNA-dependent RNA polymerase.

DOSE:

Adults: *N. meningitidis* & *H. influenzae carrier:* 600 mg/d PO for 4 d. *TB:* 600 mg PO or IV daily or 2×/wk w/ combo regimen.
Peds: 10–20 mg/kg/dose PO or IV daily–BID; ↓ in hepatic failure.
W/P: [C, +] w/ Fosamprenavir, multiple drug interactions.
CI: Allergy, active *N. meningitidis* infection, w/ saquinavir/ritonavir.
DISP: Caps 150, 300 mg; Inj 600 mg.
SE: Red-orange–colored bodily fluids, ↑ LFTs, flushing, headache.
NOTES: Never use as single agent w/ active TB.

RISEDRONATE (ACTONEL, ACTONEL W/ CALCIUM, GENERIC)

USES: *Paget disease; Treat/prevention glucocorticoid-induced/postmenopausal osteoporosis, ↑ bone mass in osteoporotic men; w/ calcium only FDA approved for female osteoporosis.*

ACTIONS: Bisphosphonate; ↓ osteoclast-mediated bone resorption.
DOSE: *Paget disease:* 30 mg/d PO for 2 mo. *Osteoporosis Treat/prevention:* 5 mg daily or 35 mg qwk or 150 mg qmo; 30 min before 1st food/drink of the day; stay upright for at least 30 min after dose.
W/P: [C, ?/−] Ca^{2+} supls & antacids ↓ absorption; jaw osteonecrosis, avoid dental work.
CI: Component allergy, ↓ Ca^{2+}, esophageal abnormalities, unable to stand/sit for 30 min, CrCl < 30 mL/min.
DISP: Tabs 5, 30, 35, 150 mg; Risedronate 35 mg (4 tabs)/calcium carbonate 1,250 mg (24 tabs).
SE: Back pain, headache, abdominal pain, dyspepsia, arthralgia; flu-like Sxs, hypersensitivity (rash, etc.), esophagitis, bone pain, eye inflammation.
NOTES: Monitor LFTs, Ca^{2+}, PO^{3+}, K^{+}; may ↑ atypical subtrochanteric femur fractures.

RISEDRONATE, DELAYED RELEASE (ATELVIA)

USES: *Postmenopausal osteoporosis.*
ACTIONS: See Risedronate.
DOSE: One 35 mg tab 1 × wk; in a.m. following breakfast w/ 4-oz water; do not lie down for 30 min.
W/P: [C, ?/−] Ca^{2+} & Fe^{2+} supls/ antacids ↓ absorption; do not use w/ Actonel or CrCl < 30 mL/min; jaw osteonecrosis reported, avoid dental work; may ↑ subtrochanteric femur fractures; severe bone/ jt pain.
CI: Component allergy, ↓ Ca^{2+}, esophageal abnormalities, unable to stand/sit for 30 min.
DISP: DR Tabs 35 mg.
SE: Diarrhea, influenza, arthralgia, back/abdominal pain; rare hypersens, eye inflam.
NOTES: Correct ↓ Ca^{2+} before use; check Ca^{2+}.

RIVAROXABAN (XARELTO)

WARNING: May ↑ risk of spinal/epidural hematoma w/ paralysis & increase risk of stroke w/ premature D/C, monitor closely.
USES: *Prevention of DVT in knee/hip replacement surgery & prevention of stroke and systemic embolism in pts w/ nonvalvular Afib.*
ACTIONS: Factor Xa inhibitor.
DOSE: 10 mg PO qd × 35 d (hip) or 12 d (knee), stroke 20 mg daily; w or w/o food.
W/P: [C, −] w/ CYP3A4 inhibitor/inducers, other anticoagulants or plt inhibitor; avoid w/ CrCl < 30 mL/min or mod/severe hepatic impairment.
CI: Active bleeding; component hypersens.
DISP: Tabs 10 mg.
SE: Bleeding.
NOTES: See PI for information about timing of stopping or starting dosage in relation to other anticoagulants.

SARGRAMOSTIM [GM-CSF] (LEUKINE)

USES: *Myeloid recovery following BMT or chemotherapy.*
ACTIONS: Recombinant GF, activates mature granulocytes & macrophages.

DOSE:
Adults & Peds: 250 μg/m²/d IV cont until ANC >1,500 cells/m² for 3 consecutive days.
W/P: [C, ?/−] Li, corticosteroids.
CI: >10% blasts, allergy to yeast, concurrent chemotherapy/RT.
DISP: Inj 250, 500 μg.
SE: Bone pain, fever, ↑ BP, tachycardia, flushing, GI upset, myalgia.
NOTES: Rotate Inj sites; use acetaminophen PRN for pain.

SEVELAMER CARBONATE (RENVELA)

USES: *Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.*
ACTIONS: Intestinal phosphate binder.
DOSE: Start 0.8 or 1.6 g PO TID w/ meals; titrate 0.8 g/meal for target PO_4 3.5–5.5 mg/dL; switch g/g among sevelamer forms, titrate PRN.
W/P: [C, ?] w/ Swallow disorders, bowel problems, may ↓ absorption of vits D, E, K, ↓ ciprofloxacin & other medicine levels.
CI: Bowel obst.
DISP: Tab 800 mg, powder 0.8/2.4 g.
SE: N/V/diarrhea, dyspepsia, abdominal pain, flatulence, constipation.
NOTES: Separate other meds 1 hr before or 3 hr after.

SEVELAMER HYDROCHLORIDE (RENAGEL)

USES: *Control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis. *
ACTIONS: Binds intestinal PO_4.
DOSE: *Initial:* PO_4 >5.5 and <7.5 mg/dL: 800 mg PO TID; ≥7.5 mg/dL: 1,200–1,600 mg PO TID. *Switching from sevelamer carbonate:* per-g basis; titrate ↑/↓ 1 tab/meal 2-wk intervals PRN; take w/ food 2–4 caps PO TID w/ meals; adjust based on PO_4; max. 4 g/dose.
W/P: [C, ?] May ↓ absorption of vits D, E, K, ↓ ciprofloxacin & other medicine levels.
CI: ↓ PO_4, bowel obst.
DISP: Tab 400, 800 mg.
SE: N/V/diarrhea, dyspepsia, ↑ Ca^{2+}.
NOTES: Do not open/chew caps; separate other meds 1 hr before or 3 hr after; 800 mg sevelamer = 667 mg Ca acetate.

SILDENAFIL (VIAGRA, REVATIO)

USES: *Viagra:* *erectile dysfunction*; *Revatio:* *Pulm artery HTN (adult only).*
ACTIONS: ↓ Phosphodiesterase type 5 (PDE5) (responsible for cGMP breakdown); ↑ cGMP activity to relax smooth muscles & ↑ flow to corpus cavernosum and pulm vasculature;

possibly antiproliferative on pulm artery smooth muscle; onset 15–60 min, duration 4 hr.
DOSE: *Erectile dysfunction:* 25–100 mg PO 1 hr before sexual activity, max. 1/d; ↓ if >65 yr.
W/P: [B, ?] w/ CYP3A4 inhibitor, retinitis pigmentosa; hepatic/severe renal impairment; w/ sig hypo/hypertension.
CI: w/ Nitrates or if sex not advised; w/ protease inhibitor.
DISP: Tabs *Viagra:* 25, 50, 100 mg, tabs. *Revatio:* Tabs 20 mg; Inj 5–10 mg/vial.
SE: Headache; flushing; dizziness; blue haze visual change (reacts with PDE6 in retina), hearing loss, priapism.
NOTES: Cardiac events in the absence of nitrates debatable; postpone dose for 4 hr after taking α-adrenergic antagonist; transient global amnesia reports; report of ↑melanoma risk; avoid fatty food w/ dose; not for peds use.

SILODOSIN (RAPAFLO)

USES: *BPH*
ACTIONS: α-blockers of prostatic α_{1a}.
DOSE: 8 mg/d; 4 mg/d w/ CrCl 30–50 mL/min; take w/ food.
W/P: [B, ?] Not for use in females; do not use w/ other α-blockers or glycoprotein inhibitor (ie, cyclosporine); R/O PCa before use; intraoperative floppy iris syndrome possible w/ cataract surgery.
CI: Severe hepatic/renal impairment (CrCl <30 mL/min), w/ CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, itraconazole, ritonavir).
DISP: Caps 4, 8 mg.
SE: Retrograde ejaculation, dizziness, diarrhea, syncope, somnolence, orthostatic ↓ BP, nasopharyngitis, nasal congestion, intraoperative floppy iris syndrome during contract surgery.
NOTES: Not for use as antihypertensive; no effect on QT interval.

SILVER NITRATE (GENERIC)

USES: *Removal of granulation tissue & warts; prophylaxis in burns*, control hemorrhagic cystitis.
ACTIONS: Caustic antiseptic & astringent.
DOSE:
Adults & Peds: Apply to moist surface 2–3 × wk for 2–3 wk or until effect; 0.5–1% solution instilled in bladder for up to 20 min (R/O reflux before, requires anesthesia.
W/P: [C, ?].
CI: Do not use on broken skin.
DISP: Topical impregnated applicator sticks, soln 0.5, 10, 25, 50%; topical ointment 10%.
SE: May stain tissue black, usually resolves; local irritation, methemoglobinemia.
NOTES: D/C if redness or irritation develops; no longer used in US for newborn prevention of gonococcus conjunctivitis

SILVER SULFADIAZINE (SILVADENE, GENERIC)

USES: *Prevention & Treat of infection in 2nd- & 3rd-degree burns.*
ACTIONS: Bactericidal.

DOSE:
Adults & Peds: Aseptically cover the area w/ 1/16-in coating BID.
W/P: [B unless near term, ?/−].
CI: Infants <2 mo, pregnancy near term.
DISP: Cream 1%.
SE: Itching, rash, skin discoloration, blood dyscrasias, hep, allergy.
NOTES: Systemic absorption w/ extensive application.

SIPULEUCEL-T (PROVENGE)

USES: *Asymptomatic/minimally symptomatic metastatic castrate-resistant PCa.*
ACTIONS: Autologous (pt specific) cellular immunotherapy.
DOSE: 3 doses over 1 mo @ 1-wk intervals; premed w/ acetaminophen & diphenhydramine.
W/P: [N/A, N/A] Confirm identity/expir date before Inf; acute transfusion reaction possible; not tested for transmissible disease.
CI: None.
DISP: 50 MU autologous CD54+ cells activated w/ PAP GM-CSF in 250 mL LR.
SE: Chills, fatigue, fever, back pain, N, joint ache, headache.
NOTES: Pt must undergo leukapheresis, w/ shipping and autologous cell processing at manufacturing facility before each Inf. Confirm/maintain testosterone <50 ng/mL.

SIROLIMUS [RAPAMYCIN] (RAPAMUNE)

WARNING: Use only by physicians experienced in immunosuppression; immunosuppression associated w/ lymphoma,↑ infection risk; do not use in lung transplant (fatal bronchial anastomotic dehiscence); do not use in liver transplant: ↑ risk hepatic artery thrombosis, graft failure, and mortality (w/ evidence of infection).
USES: *Prevent organ rejection in new renal Tx pts.*
ACTIONS: ↓ T-lymphocyte activation and proliferation.

DOSE:

Adults: ***>40 kg:*** 6 mg PO on day 1, then 2 mg/d PO.
Peds: ***<40 kg & ≥13 y:*** 3 mg/m^2 load, then 1 mg/ m^2/d (in H_2O/orange juice; no grapefruit juice w/ sirolimus); take 4 hr after cyclosporine; ↓ in hepatic impairment.
W/P: [C, ?/−] Impaired wound healing & angioedema; grapefruit juice, ketoconazole.
CI: Component allergy.
DISP: Soln 1 mg/mL, tab 0.5, 1, 2 mg.
SE: HTN, edema, CP, fever, headache, insomnia, acne, rash, ↑ cholesterol, GI upset, ↑/↓ K^+, infections, blood dyscrasias, arthralgia, tachycardia, renal impairment, graft loss & death in liver transplant (hepatic artery thrombosis), ascites.
NOTES: Levels: *Trough:* 4–20 ng/mL; varies w/ assay method and indication.

SODIUM BICARBONATE [$NAHCO_3$] (GENERIC)

USES: *Alkalinization of urine, RTA, metabolic acidosis, ↑ K^+, tricyclic antidepressants OD*, alkalize bladder urine to retrieve sperm in retrograde ejaculation.
ACTIONS: Alkalinizing agent.

DOSE:

Adults: ***ECC 2010:*** Cardiac arrest w/ good ventilation, hyperkalemia, OD of TCAs, ASA, cocaine, diphenhydramine: 1 mEq/kg IV bolus; repeat 1/2 dose q10min PRN. *Metabolic acidosis:* 2–5 mEq/kg IV over 8 hr & PRN based on acid–base status. ↑ K^+: 50 mEq IV over 5 min. *Alkalinize urine:* 4 g (48 mEq) PO, then 12–24 mEq q4h; adjust based on urine pH; 2 amp (100 mEq)/1 L D_5W at 100–250 mL/h IV, monitor urine pH & serum bicarbonate. *Chronic renal failure:* 1–3 mEq/kg/d. *Distal RTA:* 0.5–2 mEq/kg/d in 4–5 ÷ doses.
Peds: *Severe metabolic acidosis, hyperkalemia:* 1 mEq/kg IV slow bolus; 4.2% conc in infants <1 mo. *Chronic renal failure:* See Adult dosage. *Distal RTA:* 2–3 mEq/kg/d PO. *Proximal RTA:* 5–10 mEq/kg/d; titrate based on serum bicarbonate. *Urine alkalinization:* 84–840 mg/kg/d (1–10 mEq/kg/d) in ÷ doses; adjust based on urine pH.
W/P: [C, ?].
CI: Alkalosis, ↑ Na^+, severe pulm edema, ↓ Ca^{2+}.
DISP: Powder, tabs; 325 mg = 3.8 mEq; 650 mg = 7.6 mEq; Inj 1 mEq/1 mL, 4.2% (5 mEq/10 mL), 7.5% (8.92 mEq/ mL), 8.4% (10 mEq/10 mL) vial or amp.
SE: Belching, edema, flatulence, ↑ Na^+, metabolic alkalosis.
NOTES: 1 g neutralizes 12 mEq of acid; 50 mEq bicarbonate = 50 mEq Na; can make 3 amps in 1 L D_5W = D_5NS w/ 150 mEq bicarbonate.

SODIUM CITRATE/CITRIC ACID (ORACIT)

USES: *Chronic metabolic acidosis, alkalinize urine; dissolve uric acid & cysteine stones.*
ACTIONS: Urinary alkalinizer.

DOSE:

Adults: 10–30 mL in 1–3- oz H_2O pc & hs.

Peds: 5–15 mL in 1–3-oz H_2O pc & hs; best after meals.

W/P: [?, ?].
CI: Severe renal impairment, oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramp, anuria, severe myocardial damage, and hyperkalemia.
DISP: 15- or 30-mL unit dose: 16 (473 mL) or 4 fl oz.
SE: Tetany, metabolic alkalosis, ↑ K^+, GI upset; avoid use of multiple 50-mL amps; can cause ↑ Na^+/hyperosmolality.
NOTES: 1 mL = 1 mEq Na & 1 mEq bicarbonate.

SODIUM PHOSPHATE (OSMOPREP, VISICOL)

WARNING: Acute phosphate nephropathy reported w/ permanent renal impairment risk; w/

↑ age, hypovolemia, bowel obstr or colitis, baseline kidney disease, w/ meds that affect renal perf/function (diuretics, ACE inhibitor, ARB, NSAIDs).
USES: *Bowel prep prior to colonoscopy in adults*, short-term constipation.
ACTIONS: Hyperosmotic laxative.
DOSE: 3 tabs PO w/ at least 8-oz clear liq q15min for 6 doses; then 2 additional tabs in 15 min, 3–5 hr prior to colonoscopy;3 tabs q15 min for 6 doses, then 2 additional tabs in 15 min.
W/P: [C, ?] Renal impairment, electrolyte disturbances.
CI: Megacolon, bowel obst.
DISP: Tabs 0.398, 1.102 g (32/bottle).
SE: ↑ QT, ↑ PO_4, ↓ calcium, diarrhea, flatulence, cramps, abdominal bloating/pain.
NOTES: Acute phosphate nephropathy is associated w/ calcium-phosphate crystal deposits in the renal tubules and may result in permanent renal dysfunction. Risk factors for acute phosphate nephropathy: Age >55 yr, hypovolemia, pre-existing renal impairment, bowel obstruction, or active colitis; w/ meds that may affect renal perfusion/function (eg, diuretics, ACE inhibitors, ARBs, and possibly NSAIDs).

SODIUM POLYSTYRENE SULFONATE (KAYEXALATE, KIONEX, GENERIC)

USES: *Treat of ↑ K^+*
ACTIONS: Na^+/K^+ ion-exchange resin.
DOSE:
Adults: 15–60 g PO or 30–50 g PR q6h based on serum K^+.
Peds: 1 g/kg/dose PO or PR q6h based on serum K^+.
W/P: [C, ?].
CI: Obstructive bowel disease; ↑ Na^+; neonates w/ ↓ gut motility.
DISP: Powder; susp 15 g/60 mL sorbitol.
SE: ↑ Na^+, ↓ K^+, GI upset, fecal impaction.
NOTES: Enema acts more quickly than PO; PO most effective, onset action >2 hr.

SOLIFENACIN (VESICARE)

USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. *
ACTIONS: Muscarinic antagonist, ↓ detrusor contractions.
DOSE: 5 mg PO daily, 10 mg/d max.; ↓ w/ renal/hepatic impairment.
W/P: [C,?/−] Bladder outlet obstruction or GI obst, ulcerative colitis, myasthenia gravis, renal/hepatic impairment, QT prolongation risk.
CI: Uncontrolled narrow-angle glaucoma, urinary/gastric retention.
DISP: Tabs 5, 10 mg.
SE: Constipation, xerostomia, dyspepsia, blurred vision, drowsiness.
NOTES: CYP3A4 substrate; azole antifungals ↑ levels; recent concern over cognitive effects.

SORAFENIB (NEXAVAR)

USES: *Advanced RCC, differentiated thyroid carcinoma, unresectable hepatocellular carcinoma, advanced thyroid carcinoma refractory to radioactive iodine.
ACTIONS: Tyrosine kinase inhibitor.

DOSE:

Adults: 400 mg PO BID on empty stomach.
W/P: [D, −] w/ Irinotecan, doxorubicin, warfarin; avoid conception (male and female); avoid inducers.
CI: Hypersensitivity; combo with carboplatin and paclitaxel in squamous cell lung cancer.
DISP: Tabs 200 mg.
SE: Hand–foot syndrome; treatment emergent hypertension; bleeding, ↑ INR, cardiac infarction/ischemia; ↑ pancreatic enzymes, hypophosphatemia, lymphopenia, anemia, fatigue, alopecia, pruritus, diarrhea, GI upset, headache, neuropathy.
NOTES: Monitor BP 1st 6 wk; may require ↓ dose (daily or q other day); impaired metabolism w/ Asian descent; may effect wound healing, D/C before major surgery.

SPIRONOLACTONE (ALDACTONE, GENERIC)

WARNING: Tumorigenic in animal studies; avoid unnecessary use.
USES: *Hyperaldosteronism, HTN, class III/IV CHF, ascites from cirrhosis.*
ACTIONS: Aldosterone antagonist; K^+-sparing diuretic.

DOSE:

Adults: *CHF* (NYHA class III–IV) 12.5–25 mg/d (w/ ACE and loop diuretic); *HTN* 25–50 mg/d; *Ascites:* 100–400 mg q a.m w/ 40–160 mg of furosemide, start w/ 100 mg/40 mg, wait at least 3 days before ↑ dose.
Peds: 1–3.3 mg/kg/24 h PO ÷ BID q12–24h, take w/ food.
W/P: [C, + (D/C w/ breast-feeding)].
CI: ↑ K^+, acute renal failure, anuria.
DISP: Tabs 25, 50, 100 mg.
SE: ↑ K^+ & gynecomastia, arrhythmia, sexual dysfunction, confusion, dizziness, diarrhea/N/V, abnormal menstruation.

STARCH, TOPICAL, RECTAL (TUCKS SUPPOSITORIES [OTC])

USES: *Temporary relief of anorectal disorders (itching, etc.)*.
ACTIONS: Topical protectant.

DOSE:
Adults & Peds: ***≥12 y:*** Cleanse, rinse, and dry, insert 1 supl rectally 6×/d × 7 d max.
W/P: [?, ?]
CI: None
DISP: Supp
SE: D/C w/ or if rectal bleeding occurs or if condition worsens or does not improve w/in 7 days.

STEROIDS, SYSTEMIC (SEE TABLE AT BOTTOM OF PAGE)

The following relates only to the commonly used systemic glucocorticoids.

USES: *Endocrine disorders (adrenal insufficiency), rheumatoid disorders, collagen–vascular diseases, derm diseases, allergic states, cerebral edema*, nephritis, nephrotic syndrome, immunosuppression for transplantation, ↑ Ca^{2+}, malignancies (breast, lymphomas), preop (pt who has been on steroids in past year, known hypoadrenalism, preop for adrenalectomy); Inj into joints/tissue.

ACTIONS: Glucocorticoid.

DOSE: Varies w/ use & institutional protocols.

- *Adrenal Insufficiency, acute:* ***Adults:*** *Hydrocortisone:* 100 mg IV; then 300 mg/d ÷ q8h for 48 hr then convert to 50 mg PO q8h × 6 doses, taper to 30–50 mg/d ÷ BID. ***Peds:*** *Hydrocortisone:* 1–2 mg/kg IV, then 150–250 mg/d ÷ q6h–q8h.
- *Adrenal Insufficiency, chronic (physiologic replacement):* May need mineralocorticoid supl such as Florinef. ***Adults:*** *Hydrocortisone:* 20 mg PO q a.m., 10 mg PO q p.m.; *cortisone:* 25–35 mg PO daily. *Dexamethasone:* 0.03–0.15 mg/kg/d or 0.6–0.75 mg/ m^2/d ÷ q6–12h PO, IM, IV. ***Peds:*** *Hydrocortisone:* 8–10 mg/m^2/d ÷ q8h; some may require up to 12 mg/m^2/d. *Hydrocortisone succinate:* 0.25–0.35 mg/kg/d IM.
- *Asthma, acute:* ***Adults:*** *Methylprednisolone* 40–80 mg/d in 1–2 ÷ dose PO/IV or *dexamethasone* 12 mg IV q6h. ***Peds:*** *Prednisolone* 1–2 mg/kg/d or *prednisone* 1–2 mg/kg/d ÷ daily–BID for up to 5 days; *methylprednisolone* 12 mg/kg/d IV ÷ BID; *dexamethasone* 0.1–0.3 mg/kg/d ÷ q6h.
- *Congenital adrenal hyperplasia:* ***Peds:*** Initial *hydrocortisone* 10–20 mg/m^2/d in 3 ÷ doses.
- *Extubation/airway edema:* ***Adults:*** *Dexamethasone:* 0.5–2 mg/kg/d IM/IV ÷ q6h (start 24 hr prior to extubation; continue × 4 more doses). ***Peds:*** *Dexamethasone:* 0.5–2 mg/kg/d ÷ q6h (start 24 hr before & cont for 4–6 doses after extubation).
- *Immunosuppressive/anti-inflammatory:* ***Adults & Older Peds:*** *Hydrocortisone:* 15–240 mg PO, IM, IV q12h. *Methylprednisolone:* 2–60 mg/d PO in 1–4 ÷ doses, taper to lowest effective dose. *Methylprednisolone Na succinate:* 10–80 mg/d IM or 10–40 mg/d IV. ***Adults:*** *Prednisone or prednisolone:* 5–60 mg/d PO ÷ daily–QID. ***Infants & Younger Children:*** *Hydrocortisone:* 2.5–10 mg/kg/d PO ÷ q6–8h; 1–5 mg/kg/d IM/IV ÷ BID–daily.
- *Nephrotic syndrome:* ***Peds:*** *Prednisolone or prednisone:* 2 mg/kg/d PO TID–QID until urine is protein-free for 5 days, use up to 28 days; for persistent proteinuria, 4 mg/kg/ dose PO q other day max., 120 mg/d for an additional 28 days; maint 2 mg/kg/dose q other day for 28 days; taper over 4–6 wk (max. 80 mg/d).
- *Septic shock (controversial):* ***Adults:*** *Hydrocortisone:* 50 mg IV q6h; max. 300 mg/d; some suggest 200 mg/d cont Inf. ***Peds:*** *Hydrocortisone:* 1–2 mg/kg/d intermittent or continuous Inf; may titrate up to 50 mg/kg/d.
- *Status asthmaticus:* ***Adults & Peds:*** *Hydrocortisone:* 1–2 mg/kg/dose IV q6h for 24 hr; then ↓ by 0.5–1 mg/kg q6h.
- *Rheumatic disease:* ***Adults:*** *Intra-articular: Hydrocortisone acetate:* 25–37.5 mg large jt, 10–25 mg small jt. *Methylprednisolone acetate:* 20–80 mg large jt, 4–10 mg small jt. *Intrabursal: Hydrocortisone acetate:* 25–37.5 mg. *Intraganglial: Hydrocortisone acetate:* 25–37.5 mg. *Tendon sheath: Hydrocortisone acetate:* 5–12.5 mg.

Commonly Used Systemic Steroids

	Relative Equivalent		Relative Mineralocorticoid	
Drug	Dose (mg)	Activity	Duration (hr)	Route
Betamethasone	0.75	0	36–72	PO, IM
Cortisone (Cortone)	25	2	8–12	PO, IM
Dexamethasone (Decadron)	0.75	0	36–72	PO, IV
Hydrocortisone (Solu-Cortef, Hydrocortone)	20	2	8–12	PO, IM, IV
Methylprednisolone acetate (Depo-Medrol)	4	0	36–72	PO, IM, IV
Methylprednisolone succinate (Solu-Medrol)	4	0	8–12	PO, IM, IV
Prednisone (Deltasone)	5	1	12–36	PO
Prednisolone (Delta-Cortef)	5	1	12–36	PO, IM, IV

Based on data in and modified from Gomella LG, Haist S, Adams A, eds. *Clinicians' Pocket Drug Reference, 2015 Edition*. New York, NY: McGraw–Hill.

- *Perioperative steroid coverage: Hydrocortisone:* 100 mg IV night before surgery, 1 hr preop, intraoperative, & 4, 8, & 12 hr postop; postop day No. 1 100 mg IV q6h; postop day No. 2 100 mg IV q8h; postop day No. 3 100 mg IV q12h; postop day No. 4 50 mg IV q12h; postop day No. 5 25 mg IV q12h; resume prior PO dosing if chronic use or D/C if only perioperative coverage required.
- *Cerebral edema: Dexamethasone:* 10 mg IV; then 4 mg IV q4–6h.

W/P: [C/D, ?].
CI: Active varicella infection, serious infection except TB, fungal infections.
DISP:
SE: ↑ Appetite, hyperglycemia, ↓ K^+, osteoporosis, nervousness, insomnia, "steroid psychosis," adrenal suppression.
NOTES: Hydrocortisone succinate for systemic, acetate for intra-articular; never abruptly D/C steroids, taper dose; also used for bacterial and TB meningitis.

STEROIDS, TOPICAL (SEE TABLE NEXT PAGE)

USES: *Steroid-responsive dermatoses (seborrheic/atopic dermatitis, neurodermatitis, anogenital pruritus, psoriasis).*
ACTIONS: Glucocorticoid; ↓ capillary permeability, stabilizes lysosomes to control inflammation; controls protein synthesis; ↓ migration of leukocytes, fibroblasts.
DOSE: Use lowest potency produce for shortest period for effect (see Table next page).
W/P: [C, +] Do not use occlusive dressings; high potency topical products not for rosacea, perioral dermatitis; not for use on face, groin, axillae; none for use in a diapered area.
CI: Component hypersens.
DISP: See Table on next page.

Commonly Used Topical Steroids

Agent	Common Trade Names Dosage/Strength	Potency	Apply
Alclometasone dipropionate	**Aclovate**, cream, oint 0.05%	Low	BID/TID
Amcinonide	Cream, lotion, oint 0.1%	High	BID/TID
Betamethasone			
Betamethasone valerate	Cream, lotion, oint 0.1%	Low	q day/BID
Betamethasone valerate	**Luxiq** foam 0.12%	Intermediate	q day/BID
Betamethasone dipropionate	Cream, lotion, oint 0.05%; aerosol 0.1%	High	q day/BID
Betamethasone dipropionate, augmented	**Diprolene** oint, lotion, gel 0.05% **Diprolene AF** cream 0.05%	Ultrahigh	q day/BID
Clobetasol propionate	**Temovate, Clobex, Cormax** cream, gel, oint, lotion, foam, aerosol, shampoo, sol, 0.05%	Ultrahigh	BID (2 wk max.)
Clocortolone pivalate	**Cloderm** cream 0.1%	Intermediate	q day–QID
Desonide	**DesOwen**, cream, oint, lotion 0.05%	Low	BID–QID
Desoximetasone			
Desoximetasone 0.05%	**Topicort** cream, gel 0.05%	Intermediate	q day–QID
Desoximetasone 0.25%	**Topicort** cream, gel 0.025%	High	q day–BID
Dexamethasone base	Aerosol 0.01% Cream 0.1%	Low	BID–QID
Diflorasone diacetate	**ApexiCon** cream, oint 0.05%	Ultrahigh	BID/QID
Fluocinolone			
Fluocinolone acetonide 0.01%	**Synalar** cream, soln 0.01% **Capex** shampoo 0.01%	Low	BID/TID
Fluocinolone acetonide 0.025%	**Synalar** oint, cream 0.025%	Intermediate	BID/TID
Fluocinonide 0.1%	**Vanos** cream 0.1%	High	qd/BID
Flurandrenolide	**Cordran** cream, oint 0.25% tape 4 mcg/cm^2	Intermediate	qd
Fluticasone propionate	**Cutivate** cream, lotion 0.05%, oint 0.005%	Intermediate	BID
Halobetasol	**Ultravate** cream, oint 0.05%	Very high	BID
Halcinonide	**Halog** cream oint 0.1%	High	qd/TID
Hydrocortisone			
Hydrocortisone	**Cortizone, Caldecort, Hycort, Hytone,** others aerosol 1%, cream 0.5, 1, 2.5%, gel 0.5%, oint 0.5, 1, 2.5%, lotion 0.5, 1, 2.5%, paste 0.5%, soln 1%	Low	TID/QID
Hydrocortisone acetate	Cream, oint 0.5, 1%	Low	TID/qid
Hydrocortisone butyrate	**Locoid** oint, cream, lotion soln 0.1%	Intermediate	BID/TID
Hydrocortisone valerate	Cream, oint 0.2%	Intermediate	BID/TID
Mometasone furoate	Elocon cream, oint, lotion, sol 0.1%	Intermediate	qd
Prednicarbate	Dermatop cream, oint 0.1%	Intermediate	BID
Triamcinolone			
Triamcinolone acetonide 0.025%	Cream, oint, lotion 0.025%	Low	TID/QID
Triamcinolone acetonide 0.1%	Cream, oint, lotion 0.1% **Kenalog Aerosol** 0.147 mg/g	Intermediate	TID/QID
Triamcinolone acetonide 0.5%	Cream, oint 0.5%	High	TID/QID

Based on data in and modified from Gomella LG, Haist S, Adams A, eds. *Clinicians' Pocket Drug Reference, 2015 Edition*. New York, NY: McGraw-Hill.

SE: Skin atrophy w/ chronic use; chronic administration or application over large area may cause adrenal suppression or hyperglycemia.

STREPTOMYCIN (GENERIC)

WARNING: Neuro/oto/renal toxicity possible; neuromuscular blockage w/ respiratory paralysis possible.
USES: *TB combo therapy, nontuberculous infections (eg, Pasteurella pestis [plague], Francisella tularensis [tularemia], others, see package insert).
ACTIONS: Aminoglycoside; ↓ protein synthesis.

DOSE:

Adults: *TB:* 15 mg/kg/d (up to 1 g), directly observed therapy (DOT) 2× wk 20–30 mg/kg/dose (max. 1.5 g), DOT 3 × wk 25–30 mg/kg/dose (max. 1 g).

Peds: 15 mg/kg/d; DOT 2 × wk 20–40 mg/kg/dose (max. 1 g); DOT 3 × wk 25–30 mg/kg/dose (max. 1 g);↓ w/ renal insufficiency, either IM or IV over 30–60 min.
W/P: [D, +]. CI: Pregnancy.
DISP: Injectable 400 mg/mL (1-g vial).
SE: ↑ Incidence of vestibular and auditory toxicity, ↑ neurotoxicity risk in patients w/ impaired renal function.
NOTES: Monitor levels: *Peak:* 20–30 μg/mL, *Trough:* <5 μg/mL; *Toxic peak:* >50, *Trough:* >10; IV over 30–60 min.

STRONTIUM-89 CHLORIDE (METASTRON)

USES: Bone pain in patients with osseous metastasis.
ACTIONS: Ca^{2+} analogue taken up by bone in areas of active osteogenesis with selective radiation of metastasis.
DOSE: 148 MBq (4 mCi) IV slowly, or 15–22 MBq/kg.
W/P: [D, −].
CI: Pregnancy.
DISP: Injectable.
SE: Platelets nadir about 12–16 wk after treatment.
NOTES: Administered by radiation oncology; caution with platelet counts <60,000 or WBC of <2,400.

SUCROFERRIC OXYHYDROXIDE (VELPHORO)

USES: *↓ phos in ESRD/CKD.*
ACTIONS: Binds phosphate.

DOSE:

Adults: Chew 500 mg TID w/ meals; may ↑ dose weekly to target phos <5.5 mg/dL; max. dose studied 3,000 mg/d.
W/P: [B, +] check Fe^{+2} w/ peritonitis during peritoneal dialysis, hepatic or GI disorders, post-GI surgery or Dz resulting in Fe^{+2} accumulation.
CI: None.
DISP: Tab 500 mg.
SE: D, discolored feces.
NOTES: DO NOT prescribe with levothyroxine or vit D; take alendronate or doxycycline 1 hr before.

SUNITINIB (SUTENT)

WARNING: Hepatotox that may be severe and/or result in fatal liver failure.
USES: *Advanced GI stromal tumor (GIST) refractory/intolerant of imatinib; advanced RCC; well-differentiated pancreatic neuroendocrine tumors unresectable, locally advanced, metastatic.*
ACTIONS: Tyrosine kinase inhibitor; VEGF inhibitor.

DOSE:

Adults: 50 mg PO daily × 4 wk, followed by 2 wk holiday = 1 cycle; ↓ to 37.5 mg w/ CYP3A4 inhibitor, to ↑ 87.5 mg or 62.5 mg/d w/ CYP3A4 inducers.
CI: None.
W/P: [D, −] Multiple interactions require dose modification (eg, St. John's wort); TEN and SJS reported.
DISP: Caps 12.5, 25, 50 mg.
SE: ↓ WBC & plt, bleeding, ↑ BP, ↓ ejection fraction, ↑ QT interval, pancreatitis, DVT, seizures, adrenal insufficiency, N/V/diarrhea, skin discoloration, oral ulcers, taste perversion, hypothyroidism.
NOTES: Monitor left ventricular ejection fraction, ECG, CBC/plts, chemistries (K^+/Mg^{2+}/phosphate), TFT & LFTs periodically; ↓ dose in 12.5-mg increments if not tolerated.

TACROLIMUS, EXTENDED RELEASE (ASTAGRAF XL)

WARNING: Only physicians experienced in immunosuppression should prescribe. ↑ Risk of malignancy; use in liver transplant not rec due to ↑mortality in female patients.
USES: *Px kidney transplant rejection w/ MMF and steroids, w/ or w/o basiliximab induction.*
ACTIONS: Calcineurin inhib/immunosuppressant.
DOSE: w/ basiliximab induct: 0.15 mg/kg/d (target level day 1–60: 5–17 ng/mL; Mo 3–12: 4–12 ng/mL w/o induct: Preop 0.1 mg/kg/d; postop 0.2 mg/kg/d (target level: Day 1–60: 6–20 ng/mL; Mo 3–12: 6–14 ng/mL; take daily q a.m; empty stomach; do not take w/ alcohol or grapefruit juice; take whole.
W/P: [C, −] not interchangeable w/ immediate release; follow glucose, Cr, K^+, can ↑ BP, can ↑ QT interval; do not use w/ sirolimus, CYP3A inhib/inducers; avoid live vaccines, monitor for red cell aplasia w/ Cyclosporine; avoid topical if <2 yr; Neuro & nephrotox, ↑ risk opportunistic Infxns; avoid grapefruit juice.
CI: Component allergy, castor oil allergy w/ IV form.
Disp: ER Caps 0.5, 1, 5 mg.
SE: N, D, constipation, edema, tremor, anemia.
NOTES: Monitor levels; African Americans may need ↑ dose; see tacrolimus immediate release.

TACROLIMUS, IMMEDIATE RELEASE (PROGRAF, GENERIC)

WARNING: ↑ Risk of infection and lymphoma. Only physicians experienced in immunosuppression should prescribe.
USES: *Prevent organ rejection (kidney/liver/heart).*
ACTIONS: Calcineurin inhibitor/immunosuppressant.

DOSE:

Adults: IV: 0.03–0.05 mg/kg/d in kidney and liver, 0.01 mg/kg/d in heart IV Inf.
Peds: IV: 0.03–0.05 mg/kg/d as cont Inf. *PO:* 0.15–0.2 mg/kg/d PO ÷ q12h.
Adults & Peds: *Eczema:* Take on empty stomach; ↓ w/ hepatic/renal impairment.
W/P: [C, −] w/ Cyclosporine; avoid topical if <2 yr; Neuro & nephrotoxic, ↑ risk

opportunistic infections; avoid grapefruit juice.
CI: Component allergy, castor oil allergy w/ IV form.
DISP: Caps 0.5, 1, 5 mg; Inj 5 mg/mL.
SE: HTN, edema, headache, insomnia, fever, pruritus, ↑/↓ K^+, hyperglycemia, GI upset, anemia, leukocytosis, tremors, paresthesias, pleural effusion, seizures, lymphoma, PRES, BK nephropathy, PML.
NOTES: Monitor levels; *Trough:* 5–12 ng/mL based on indication and time since transplant.

TADALAFIL (CIALIS)

USES: *Erectile dysfunction, BPH, alone or together.*
ACTIONS: PDE5 inhibitor, ↑ cyclic guanosine monophosphate (cGMP) & NO levels; relaxes smooth muscles, dilates cavernosal arteries; 15–120 min, duration 24–36 hr.

DOSE:

Adults: *PRN:* 10 mg PO before sexual activity (5–20 mg max. based on response) 1 dose/24 h. *Daily dosing:* 2.5 mg qd, may ↑ to 5 mg qd, *BPH*; 5 mg PO qd; w/o regard to meals; BPH therapy initiated with tadalafil and finasteride, tadalafil dose is 5 mg/d for up to 26 wk; ↓ w/ renal/hepatic insufficiency; 5 mg not more than once in every 72 hr w/ CrCl <30 mL/min/ESRD on dialysis.
W/P: [B, −] w/ α-Blockers (except tamsulosin); use w/ CYP3A4 inhibitor 2.5 mg/daily dose or 5 mg PRN dose; CrCl <0 mL/min, hemodialysis/severe hepatic impairment, do not use daily dosing.
CI: Nitrates.
DISP: Tabs 2.5, 5, 10, 20 mg.
SE: Headache, flushing, dyspepsia, back/limb pain, myalgia, nasal congestion, urticaria, SJS, dermatitis, visual field defect, nonarteritic anterior ischemic optic neuropathy (NIAON), sudden ↓/loss of hearing, tinnitus.
NOTES: Longest acting of class (36 hr); daily dosing may ↑ drug interactions; excessive EtOH may ↑ orthostasis; transient global amnesia reports; not recommended in combo with α-blocker for BPH.

TAMSULOSIN (FLOMAX, GENERIC)

USES: *BPH,* medical expulsive therapy for ureteral stones.
ACTIONS: Antagonist of prostatic α_1-receptors.

DOSE: 0.4 mg/d, may ↑ to 0.8 mg PO daily.
W/P: [B, ?] Floppy iris syndrome w/ cataract surgery.
DISP: Caps 0.4 mg.
SE: Headache, dizziness, syncope, somnolence, ↓ libido, GI upset, retrograde ejaculation, rhinitis, rash, angioedema, intraoperative floppy iris syndrome.
NOTES: Not for use as antihypertensive; do not open/crush/chew; approved for use w/ dutasteride for BPH; also available a combination (Jalyn); for patients with a ureteral stone <10 mm and well-controlled symptoms, a period of observation along with medical expulsive therapy should be considered with α_1-blockers, the preferred agent.

TEMSIROLIMUS (TORISEL)

USES: *Advanced RCC.*
ACTIONS: Multikinase inhibitor, ↓mTOR (mammalian target of rapamycin), ↓ hypoxic-induced factors, ↓ VEGF.
DOSE: 25 mg IV 30–60 min 1×/wk. Hold w/ ANC <1,000 cells/μL, plt <75,000 cells/μL, or NCI grade 3 tox. Resume when tox grade 2 or less, restart w/ dose ↓ 5 mg/wk not <15 mg/wk. w/ CYP3A4 inhibitor: ↓ 12.5 mg/wk. w/ CYP3A4 inducers ↑ 50 mg/wk.
W/P: [D, −] Avoid live vaccines, ↓ wound healing, avoid periop.
CI: Bili >1.5 × ULN.
DISP: Inj 25 mg/mL w/ 250 mL diluent.
SE: Rash, asthenia, mucositis, N, bowel perforation, angioedema, impaired wound healing; interstitial lung disease anorexia, edema, ↑ lipids, ↑ glucose, ↑ triglycerides, ↑ LFTs, ↑ Cr, ↓ WBC, ↓ HCT, ↓ plt, ↓ PO^4.
NOTES: Premedicate w/ antihistamine; check lipids, CBC, plt, Cr, glucose; w/ sunitinib dose-limiting tox likely; females use w/ contraception.

TERAZOSIN (HYTRIN, GENERIC)

USES: *BPH, HTN.*
ACTIONS: α_1-Blocker (blood vessel & bladder neck/prostate).
DOSE: Initial, 1 mg PO hs; ↑ 20 mg/d max.; may ↓ w/ diuretic or other BP medicine.
W/P: [C, ?] w/ β-Blocker, calcium channel blocker, ACE inhibitor; use w/ phosphodiesterase-5 (PDE5) inhibitor (eg, sildenafil) can cause ↓ BP, intra-op floppy iris syndrome w/ cataract surgery.
CI: Component sensitivity.
DISP: Tabs 1, 2, 5, 10 mg; caps 1, 2, 5, 10 mg angina.
SE: Angina, ↓ BP, & syncope following 1st dose or w/ PDE5 inhibitor; dizziness, weakness, nasal congestion, peripheral edema, palpitations, GI upset.
NOTES: Caution w/ 1st dose syncope; if for HTN, combine w/ thiazide diuretic.

TERBINAFINE (LAMISIL, LAMISIL AT, GENERIC [OTC])

USES: *Onychomycosis, athlete's foot, jock itch, ringworm*, cutaneous candidiasis, pityriasis versicolor.
ACTIONS: ↓ Squalene epoxidase resulting in fungal death.
DOSE: *PO:* 250 mg/d PO for 6–12 wk. *Topical:* Apply to area tinea pedis BID, tinea cruris & corporis daily–BID, tinea versicolor soln BID; ↓ PO in renal/hepatic impairment.
W/P: [B, −] PO ↑ effects of drug metabolism by CYP2D6, w/ liver/renal impairment.
CI: CrCl <50 mL/min, WBC <1,000/mm^3, severe liver disease.
DISP: Tabs 250 mg; oral granules 125 mg/pkt, 187.5 mg/ pkt *Lamisil AT* [OTC] cream, gel, soln 1%.
SE: Headache, DIV/N dizziness, rash, pruritus, alopecia, GI upset, taste perversion, neutropenia, retinal damage, SJS, ↑ LFTs.
NOTES: Effect may take months d/t need for new nail growth; topical not for nails; do not use occlusive dressings; PO follow CBC/LFTs.

TERCONAZOLE (TERAZOL 3, TERAZOL 7, GENERIC)

USES: *Vag fungal infections.*
ACTIONS: Topical triazole antifungal.
DOSE: 1 applicator-full or 1 supp intravag hs × 3–7 days.
W/P: [C, ?].
CI: Component allergy.
DISP: Vag cream (Terszol 7) 0.4, (Terszol 3), 0.8%, (Terszol 3) Vag supp 80 mg.
SE: Vulvar/Vag burning.
NOTES: Insert high into vagina.

TERIPARATIDE (FORTEO)

WARNING: ↑ Osteosarcoma risk in animals, therefore only use in patients for whom the potential benefits outweigh risks.
USES: *Severe/refractory osteoporosis.*
ACTIONS: PTH (recombinant).
DOSE: 20 µg SQ daily in thigh or abdomen.
W/P: [C, ?/−].
CI: w/ Paget disease, prior radiation, bone metastases, hypercalcemia, caution in urolithiasis.
DISP: 3-mL prefilled device (discard after 28 days).
SE: Orthostatic ↓ BP on administration, N/diarrhea, hypercalcemia; leg cramps.
NOTES: 2 yr max. use; osteosarcoma in animals.

TESTOSTERONE, IMPLANT (TESTOPEL) [C-III]

USES: *Male hypogonadism (congenital/acquired).*
ACTIONS: Testosterone replacement.
DOSE: 150–450 mg (2–6 pellets) SQ implant q3–6mo (implant two 75-mg pellets for each 25 mg testosterone required weekly; eg, for 75 mg/wk, implant 450 mg or 6 pellets.
W/P: [X, −] May cause polycythemia, worsening of BPH Sx, prostate cancer, edema may worsen CHF; may ↓ blood glucose and insulin requirements; venous thrombosis risk.
CI: PCa, male breast CA, PRG women.
DISP: 75 mg/implant (3.2 mm × 9 mm).
SE: Pain/inflammation at site, gynecomastia, excessive erections, oligospermia, hirsutism, male pattern baldness, acne, retention of sodium and electrolytes, suppression of clotting factors, polycythemia, N, jaundice, ↑ LFT/cholesterol, polycythemia, rare hepatocellular neoplasms and peliosis hepatitis, ↑/↓ libido, sleep apnea, ↑ PSA.
NOTES: Check levels and adjust PRN (300–1,000 ng/dL testosterone range); follow periodic LFT and CBC; typical site upper outer posterior gluteal region using sterile technique, local anesthesia, 4 mm stab wound and provided 16G insertion trocar.

TESTOSTERONE, NASAL GEL (NATESTO) [C-III]

WARNING: Virilization reported in children exposed to topical testosterone products. Children to avoid contact w/ unwashed or unclothed application sites.
USES: *Adult male hypogonadism (congenital/ acquired).*

ACTIONS: Testosterone replacement.
DOSE: 2 pumps each nostril (11 mg testosterone) in each nostril TID (total 33 mg/day); blow nose before use; avoid blowing for 1 hr after.
W/P: [X, −] Avoid with nasal pathology; monitor BPH Sx and for DVT; may cause azoospermia, edema, sleep apnea; not rec if <18 yr; venous thrombosis risk.
CI: Prostate cancer, male breast cancer, women.
DISP: metered-dose pump; 1 pump = 5.5 mg of testosterone.
SE: ↑ PSA, headache, rhinorrhea, epistaxis, nasal discomfort, nasopharyngitis, bronchitis, URI, sinusitis, nasal scab. 1 pump = 5.5 mg of testosterone.
NOTES: Previously known as *CompleoTRT*; may minimize exposure of testosterone to women or children; check testosterone, PSA, Hgb, LFTs, and lipids periodically.

TESTOSTERONE, TOPICAL (ANDROGEL 1%, ANDROGEL 1.62% ANDRODERM, AXIRON, FORTESTA, STRIANT, TESTIM, VOGELXO) [C-III]

WARNING: Virilization reported in children exposed to topical testosterone products. Children to avoid contact w/ unwashed or unclothed application sites.
USES: *Male hypogonadism (congenital/acquired).*
ACTIONS: Testosterone replacement; ↑ lean body mass, libido.
DOSE: All daily applications: *AndroGel 1%:* 50 mg (4 pumps); *AndroGel 1.62%:* 40.5 mg (2 pumps); apply to clean skin on upper body only. *Androderm:* Two 2.5-mg or one 5-mg patch daily. *Axiron:* 60 mg (1 pump = 30 mg each axilla) q a.m. *Fortesta:* 40 mg (4 pumps) on clean, dry thighs; adjust form 1–7 pumps based on blood test 2 hr after (days 14 and 35). *Striant:* 30-mg buccal tabs BID. *Testim:* One 5-g gel tube. *Vogelxo:* 50 mg (1 tube or packet or 4 pump actuations) daily at same time.
W/P: [X, −] May cause polycythemia, worsening of BPH Sx.
CI: PCa, male breast CA, women, venous thrombosis risk.
DISP: *AndroGel 1%: 12.5 mg/pump; AndroGel 1.62%: 20.25 mg/pump; Androderm:* 2.5-, 5-mg patches; *Axiron:* Metered-dose pump 30 mg/pump; *Fortesta:* Metered-dose gel pump 10 mg/pump*; Striant:* 30-mg buccal tab; *Vogelxo*:50 mg tube or packet, 12.5 mg/pump.
SE: Site reactions, acne, edema, Wt gain, gynecomastia, HTN, ↑ sleep apnea, prostate enlargement, ↑ PSA.
NOTES: PO agents (*methyltestosterone & oxandrolone*) associated w/ hepatic tumors; transdermal/mucosal/implant forms preferred; wash hands immediately after topical applications *AndroGel* forms not equivalent; check T levels and adjust PRN (300–1,000 ng/dL testosterone range).

TESTOSTERONE UNDECANOATE, INJECTABLE (AVEED)

WARNING: Pulmonary oil microembolism (POME) reactions (urge to cough, dyspnea, throat tightening, chest pain, dizziness, syncope) and episodes of anaphylaxis, including life-threatening reactions, have been reported after the administration; observe patients for 30 min after dosing.
USES: *Male hypogonadism (congenital/acquired).*
ACTIONS: Testosterone replacement; ↑ lean body mass, libido.

DOSE: 3 mL (750 mg) IM (gluteal) initially, at 4 wk, every 10 wk thereafter; observe for 30 min for POME or anaphylaxis.
W/P: [X, −] May worsen BPH Sx, azoospermia possible, edema with pre-existing cardiac/renal/hepatic Dz, sleep apnea with other risk factors, monitor PSA, hgb/Hct, lipids periodically; may reduce insulin requirements, monitor INR if on warfarin; w/ steroids may ↑ fluid retention; venous thrombosis risk.
CI: PCa, male breast cancer, women, component sensitivity.
DISP: 3-mL (750 mg) in castor oil and benzyl benzoate.
SE: Acne, injection site pain, ↑ PSA and estradiol, hypogonadism, fatigue, irritability, ↑ hemoglobin, insomnia, mood swings.
NOTES: Available only through a restricted program (Aveed REMS); other IM forms not commonly used; testosterone enanthate (*Delatestryl; Generic)* & testosterone cypionate (*Depo-Testosterone*) dosed q14–28d w/ variable serum levels.

TETRACYCLINE (GENERIC)

USES: *Broad-spectrum antibiotic.*
ACTIONS: Bacteriostatic; ↓ protein synth. *Spectrum:* gram(+): *Staphylococcus, Streptococcus.* gram(−): *H. pylori.* Atypicals: *Chlamydia, Rickettsia,* & *Mycoplasma.*

DOSE:

Adults: 250–500 mg PO BID–QID.
Peds: >***8 yr:*** 25–50 mg/kg/24 h PO q6–12h; ↓ w/ renal/hepatic impairment, w/o food preferred.
W/P: [D, −].
CI: PREGNANCY, children <8 yr.
DISP: Caps 100, 250, 500 mg; tabs 250, 500 mg; PO susp 250 mg/5 mL.
SE: Photosensitivity, GI upset, renal failure, pseudotumor cerebri, hepatic impairment.
NOTES: Can stain tooth enamel & depress bone formation in children; do not administer w/ antacids or milk products.

TICAGRELOR (BRILINTA)

WARNING: ↑ Bleeding risk; can be fatal; daily aspirin >100 mg may ↓ effectiveness; do not start w/ active bleeding, Hx intracranial bleed, planned CABG; if hypotensive and recent procedure, suspect bleeding; manage any bleed w/o D/C of ticagrelor.
USES: *↓ CV death and heart attack in ACS.*
ACTIONS: Oral antiplatelet; reversibly binding ADP receptor antagonist inhibitor.
DOSE: Initial 180 mg PO w/ ASA 325 mg, then 90 mg BID w/ ASA 75–100 mg/d.
W/P: [C, −] w/ Mod hepatic impairment; w/ strong CYP3A inhibitor or CYP3A inducers.
CI: Hx intracranial bleed, active pathologic bleeding, severe hepatic impairment.
DISP: Tabs 90 mg.
SE: Bleeding, SOB.
NOTES: REMS; D/C 5 days preop.

TICARCILLIN/POTASSIUM CLAVULANATE (TIMENTIN)

USES: *Infections of the skin, bone, resp & urinary tract, abdominal, sepsis.*
ACTIONS: Carboxy-PCN; bactericidal; ↓ cell wall synth; clavulanic acid blocks β-lactamase.
Spectrum: Good gram(+), not MRSA; good gram(−) & anaerobes.

DOSE:

Adults: 3.1 g IV q4–6h max. 24 g ticarcillin component/d.
Peds: ***Ä 60 kg:*** (if ≥60 kg, adult dose). 200–300 mg/kg/d IV ÷ q4–6h; ↓ in renal failure.
W/P: [B, +/−] PCN sensitivity.
DISP: Inj ticarcillin/clavulanate acid 3.1/0.1-g vial.
SE: Hemolytic anemia, false(+) proteinuria.
NOTES: Often used in combo w/ aminoglycosides; penetrates CNS w/ meningeal irritation.

TINIDAZOLE (TINDAMAX)

WARNING: Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent.
USES: *Trichomoniasis, giardiasis and amebiasis: in patients aged 3 and older; bacterial vaginosis: in nonpregnant adult.*
ACTIONS: Nitroimidazole antimicrobial.

DOSE:

Adults: *Trichomoniasis, Giardiasis:* 2 g PO w/ food × 1. For trichomoniasis treat sexual partners; *Bacterial vaginosis*: Nonpregnant, adult women: 2 g daily for 2 days w/ food, or 1 g once daily for 5 days w/ food.
Peds: ***>3 yr:*** *Giardiasis*: 50 mg/kg (up to 2 g) × 1 w/ food; Amebiasis 50 mg/kg/d (up to 2 g per day) × 3 days w/ food; Amebic liver abscess same up to 5 days.
W/P: [C, OK 3 days after D/C] Seizures/nephropathy reported; vaginal candidiasis.
CI: Component allergy; 1st tri pregnancy, breast-feeding.
DISP: Tabs 250, 500 mg.
SE: Met allic/bitter taste, nausea, anorexia dyspepsia, weakness/fatigue, headache, dizziness.

TIOCONAZOLE (GENERIC [OTC])

USES: *Vaginal fungal infections.*
ACTIONS: Topical antifungal.
DOSE: 1 applicator-full intravag hs (single dose).
W/P: [C, ?].
CI: Component allergy.
DISP: Vag oint 6.5%.
SE: Local burning, itching, soreness, polyuria.
NOTES: Insert high into vagina; may damage condom or diaphragm.

TIOPRONIN (THIOLA)

USES: *Prevent cystine urolithiasis in patients with severe homozygous cystinuria with

urinary cystine >500 mg/d, who are resistant to conservative measures (high fluid intake, alkali and diet modification), or have adverse reactions to D-penicillamine.*
ACTIONS: Combines with cystine to increase solubility (α-mercaptopropionylglycine).

DOSE:
Adults & Peds: ***>9 yr:*** Encourage conservative hydration therapy with 3 L fluid/d (>2 L urine output) before initiating therapy. 800 mg/d initially (peds 15/mg/kg/d) divided TID, 1 hr ac or 2 hr pc; titrate based on urinary cysteine levels; typical adult dose 1,000 mg/d.
W/P: [D, −].
CI: Pregnancy, prior history of agranulocytosis or thrombocytopenia on Thiola.
DISP: Tablets 100 mg.
SE: Fever, rash, arthralgia, lymphadenopathy, hypogeusia, wrinkling and friable skin.
NOTES: Maintain urine pH 6.5–7.0 (potassium alkali supplements over sodium alkali due to reduced hypercalciuria risks); check urinary cysteine after 1 mo and then every 3 mo to adjust dose. Better tolerated than D-penicillamine.

TOBRAMYCIN (NEBCIN)

USES: *Serious gram(−) infections.*
ACTIONS: Aminoglycoside; ↓ protein synth. *Spectrum:* gram(−) bacteria (including *Pseudomonas*).

DOSE:

Adults: Conventional dosing: 1–2.5 mg/kg/dose IV q8–12h. *Once-daily dosing:* 5–7 mg/kg/dose q24h.
Peds: 2.5 mg/kg/dose IV q8h; ↓ w/ renal insufficiency.
W/P: [D, −].
CI: PREGNANCY; aminoglycoside sensitivity.
DISP: Inj 10, 40 mg/mL.
SE: Nephro/ototox.
NOTES: Follow CrCl & levels. Levels: *Peak:* 30 min after Inf; *Trough:* <0.5 hr before next dose; *Therapeutic Conventional: Peak:* 5–10 μg/mL, *Trough:* <2 μg/mL.

TOLTERODINE (DETROL, DETROL LA, GENERIC)

USES: *Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.*
ACTIONS: Anticholinergic; muscarinic receptor antagonist.
DOSE: *Detrol:* 1–2 mg PO BID; *Detrol LA:* 2–4 mg/d.
W/P: [C, −] w/ CYP2D6 & 3A3/4 inhibitor; w/ QT prolongation.
CI: Urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma.
DISP: Tabs 1, 2 mg; *Detrol LA* tabs 2, 4 mg.
SE: Xerostomia, blurred vision, headache, constipation.
NOTES: LA form may see “intact” ghost pill in stool.

TRAMADOL (RYBIX ODT, RYZOLT ER, ULTRAM, ULTRAM ER, GENERIC)

(C-IV)
USES: *Mod–severe pain.*
ACTIONS: Centrally acting synthetic opioid analgesic.

DOSE:

Adults: 50–100 mg PO q4–6h PRN, start 25 mg PO q a.m., ↑ q3d to 25 mg PO QID; ↑ 50 mg q3d, 400 mg/d max. (300 mg if >75 yr); ER 100–300 mg PO daily; Rybix ODT individualize ↑ 50 mg/d q3d to 200 mg/d or 50 mg QID; after titration 50–100 mg q4–6 PRN, 400 mg/d max.
Peds: (ER form not rec) 1–2 mg/kg q4–6h (max. dose 100 mg); ↓ w/ renal insufficiency.
W/P: [C, −] Suicide risk in addiction prone, w/ tranquilizers or antidepressants; ↑ seizures risk w/ MAOI; serotonin syndrome.
CI: Opioid dependency; w/ MAOIs; sensitivity to opioids, acute alcohol intoxication, hypnotics, centrally acting analgesics, or w/ psychotropic drugs.
DISP: Tabs 50 mg; ER 100, 200, 300 mg; Rybix ODT 50 mg.
SE: Dizziness, headache, somnolence, GI upset, resp depression, anaphylaxis.
NOTES: ↓ Seizure threshold; tolerance/dependence may develop; abuse potential d/t μ-opioid agonist activity; Avoid EtOH; do not cut, chew ODT tabs.

TRAMADOL/ACETAMINOPHEN (ULTRACET) (C-IV)

USES: *Short-term Treat acute pain (<5 days).*
ACTIONS: Centrally acting opioid analgesic w/ acetaminophen.
DOSE: 2 tabs PO q4–6h PRN; 8 tabs/d max. *Elderly/renal impairment:* Lowest possible dose; 2 tabs q12h max. if CrCl <30 mL/min.
W/P: [C, −] Seizures, hepatic/renal impairment, suicide risk in addiction prone, w/ tranquilizers or antidepressants.
CI: Acute intoxication, w/ ethanol, hypnotics, central-acting analgesics or psychotropic drugs, hepatic dysfunction.
DISP: Tab 37.5 mg tramadol/325 mg acetaminophen.
SE: SSRIs, TCAs, opioids, MAOIs ↑ risk of seizures; dizziness, somnolence, tremor, headache, N/V/diarrhea, constipation, xerostomia, liver tox, rash, pruritus, ↑ sweating, physical dependence.
NOTES: Avoid EtOH; abuse potential μ-opioid agonist activity (tramadol); see acetaminophen note.

TRIAMCINOLONE/NYSTATIN (GENERIC)

USES: *Cutaneous candidiasis.*
ACTIONS: Antifungal & anti-inflammatory.
DOSE: Apply lightly to area BID; max. 25 mg/d.
W/P: [C, ?].
CI: Varicella; systemic fungal infections.
DISP: Cream & oint: Triamcinolone 1 mg/g and 100,000 U nystatin/g.
SE: Local irritation, hypertrichosis, pigmentation changes.
NOTES: For short-term use (<7 days). See also nystatin.

TRIAMTERENE (DYRENIUM)

WARNING: Hyperkalemia can occur.
USES: *Edema associated w/ CHF, cirrhosis.*
ACTIONS: K^+-sparing diuretic.

DOSE:

Adults: 100–300 mg/24 h PO ÷ daily–BID.
Peds: *HTN:* 2–4 mg/kg/d in 1–2 ÷ doses; ↓ w/ renal/hepatic impairment.
W/P: [C (Expert opinion), ?].
CI: ↑ K^+, renal impairment; caution w/ other K^+-sparing diuretics.
DISP: Caps 50, 100 mg.
SE: ↓ K^+, ↓ BP, bradycardia, cough, headache.
NOTES: Do not use in hypercalciuria due to triamterene stone risk.

TRIETHYLENETHIOPHOS-PHORAMIDE (THIOTEPA)

USES: *Breast, ovarian cancers, lymphomas (infrequently used) preparative regimens for allogeneic & ABMT w/ high doses, intravesical for bladder cancer, intracavitary effusion control.*
ACTIONS: Polyfunctional alkylating agent.
DOSE: Per protocol typical 0.3–0.4 mg/kg IV q1–4 wk. *Effusions:* Intracavitary 0.6–0.8 mg/kg; 60 mg into the bladder & retained 2 hr q1–4wk; 900–125 mg/m^2 in ABMT regimens (highest dose w/o ABMT is 180 mg/m^2); ↓ in renal failure.
W/P: [D, −] w/ BM suppression, renal and hepatic impairment.
CI: Component allergy.
DISP: Inj 15 mg/vial.
SE: ↓ BM, N/V, dizziness, headache, allergy, paresthesias, alopecia.
NOTES: Intravesical use in bladder cancer infrequent today; due to critical US shortage in 2013 TEPADINA, a European product, was allowed to be distributed in the US.

TRIMETHOPRIM (PRIMSOL, GENERIC)

USES: *UTI d/t susceptible gram(+) & gram(−) organisms; Treat PCP w/ dapsone* suppression of UTI.
ACTIONS: ↓ Dihydrofolate reductase. *Spectrum:* Many gram(+) & (–) except *Bacteroides, Branhamella, Brucella, Chlamydia, Clostridium, Mycobacterium, Mycoplasma, Nocardia, Neisseria, Pseudomonas,* & *Treponema.*

DOSE:

Adults: 100 mg PO BID or 200 mg PO daily; PCP 15 mg/kg ÷ in 3 days w/ dapsone.
Peds: ≥***2 mo:*** 4–6 mg/kg/d in 2 ÷ doses; otitis media (≥6 mo): 10 mg/kg/d in 2 ÷ doses × 10 days; For prophylaxis: 2 mg/kg/day.
W/P: [C, +]. ↓ w/ renal failure.
CI: Megaloblastic anemia d/t folate deficiency.
DISP: Tabs 100 mg; (*Primsol*) PO soln 50 mg/5 mL.

SE: Rash, pruritus, megaloblastic anemia, hepatic impairment, blood dyscrasias.
NOTES: Take w/ plenty of H_2O.

TRIMETHOPRIM (TMP)/SULFAMETHOXAZOLE (SMX) [CO-TRIMOXAZOLE, TMP-SMX] (BACTRIM, BACTRIM DS, SEPTRA DS, GENERIC)

USES: *UTI Treat & prophylaxis, otitis media, sinusitis, bronchitis, prevent PCP pneumonia (w/ CD4 count <200 cells/mm^3).*
ACTIONS: SMX ↓ synth of dihydrofolic acid, TMP ↓ dihydrofolate reductase to impair protein synth. *Spectrum:* Includes *Shigella,* PCP, & *Nocardia* infections, *Mycoplasma, Enterobacter* sp, *Staphylococcus, Streptococcus,* & more.
DOSE: All doses based on TMP.
Adults: 1 DS tab PO BID or 8–20 mg/kg/24 h IV in 1–2 ÷ doses. *PCP:* 15–20 mg/kg/d IV or PO (TMP) in 4 ÷ doses. *Nocardia:* 10–15 mg/kg/d IV or PO (TMP) in 4 ÷ doses. PCP prophylaxis: 1 reg tab daily or DS tab 3 × wk. *UTI prophylaxis:* 1 PO BID.
Peds: 8–10 mg/kg/24 h PO ÷ in 2 doses or 3–4 doses IV; do not use in <2 mo.
W/P: [C (D if near term), -]. ↓ in renal failure; maintain hydration.
CI: Sulfonamide sensitivity, porphyria, megaloblastic anemia w/ folate deficiency, PRF, breast-feeding Inf <2 mo, sig hepatic impairment.
DISP: Regular tabs 80 mg TMP/400 mg SMX; DS tabs 160 mg TMP/800 mg SMX; PO susp 40 mg TMP/200 mg SMX/5 mL; Inj 80 mg TMP/400 mg SMX/5 mL.
SE: Allergic skin reactions, photosensitivity, GI upset, SJS, blood dyscrasias, hep.
NOTES: Synergistic combo, interacts w/ warfarin.

TRIPTORELIN (TRELSTAR 3.75, TRELSTAR 11.25, TRELSTAR 22.5)

USES: *Advanced prostate cancer.*
ACTIONS: LHRH analog; ↓ GNRH w/ cont dosing; transient ↑ in LH, FSH, testosterone, & estradiol 7–10 days after 1st dose; w/ chronic use (usually 2–4 wk), sustained ↓ LH & FSH w/ ↓ testicular & ovarian steroidogenesis similar to surgical castration.
DOSE: 3.75 mg IM q4wk; or 11.25 mg IM q12wk or 22.5 mg q24wk.
W/P: [X, N/A].
CI: Pregnancy, component hypersensitivity.
DISP: Inj Depot 3.75 mg; 11.25 mg; 22.5 mg.
SE: Dizziness, emotional lability, fatigue, headache, insomnia, HTN, diarrhea, vomiting, erectile dysfunction, retention, UTI, pruritus, anemia, Inj site pain, musculoskelet al pain, osteoporosis, allergic reactions.
NOTES: Check periodic testosterone levels & PSA.

TROSPIUM (SANCTURA, SANCTURA XR, GENERIC)

USES: *OAB w/ Sx of urge incontinence, urgency, frequency.*
ACTIONS: Muscarinic antagonist, ↓ bladder smooth muscle tone.
DOSE: 20 mg tab PO BID; 60 mg ER caps PO daily a.m., 1 hr ac or on empty stomach. ↓ w/ CrCl <30 mL/min and elderly.
W/P: [C, +/−] w/ EtOH use, in hot environments, ulcerative colitis, myasthenia gravis,

renal/hepatic impairment.
CI: Urinary/gastric retention, narrow-angle glaucoma.
DISP: Tab 20 mg; caps ER 60 mg.
SE: Dry mouth, constipation, headache, rash.

VALACYCLOVIR (VALTREX, GENERIC)

USES: *Herpes zoster; genital herpes; herpes labialis.*
ACTIONS: Prodrug of acyclovir; ↓ viral DNA replication. *Spectrum:* Herpes simplex I & II.
DOSE: *Zoster:* 1 g PO TID × 7 days. *Genital herpes (initial episode):* 1 g BID × 7–10 days, *(recurrent)* 500 mg PO BID × 3 days. *Herpes prophylaxis:* 500–1,000 mg/d. *Herpes labialis:* 2 g PO q12h × 1 day ↓ w/ renal failure.
W/P: [B, +] ↑ CNS effects in elderly.
DISP: Caplets 500, 1,000 mg; tab 500, 1,000 mg.
SE: Headache, GI upset, ↑ LFTs, dizziness, pruritus, photophobia.

VALRUBICIN (VALSTAR)

USES: *Intravesical therapy of BCG-refractory bladder CIS in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.*
ACTIONS: An anthracycline; alkylating agent.
DOSE: 800 mg intravesically 1 × wk for 6 wk (4 vials diluted in 55 mL NS, total volume of 75 mL).
W/P: [C, -] do not administer with perforated bladder.
CI: Hypersensitivity to anthracyclines or polyoxyl castor oil, UTI, bladder capacity <75 mL.
DISP: 5 mL single-use vials (200 mg/5mL).
SE: Frequency, dysuria, urgency, spasm, hematuria, pain, incontinence.
NOTES: monitor closely for disease recurrence or progression; if there is not a complete response of CIS to treatment after 3 mo or if CIS recurs, cystectomy must be reconsidered. Procedures for proper handling and disposal of anticancer drugs should be used. Spills should be cleaned up with undiluted chlorine bleach.

VANCOMYCIN (VANCOCIN, GENERIC)

USES: *Serious MRSA infections; enterococcal infections; PO Treat of *S. aureus* and *C. difficile* pseudomembranous colitis.*
ACTIONS: ↓ Cell wall synth. *Spectrum:* gram(+) bacteria & some anaerobes (includes MRSA, *Staphylococcus*, *Enterococcus*, *Streptococcus* sp, *C. difficile*).

DOSE:

Adults: 15–20 mg/kg IV q8–48h based on CrCl, 15–20 mg/kg/dose; *C. difficile:* 125–500 mg PO q6h × 7 days.
Peds: 40–60 mg/kg/d IV in ÷ doses q6–12 h; *C. difficile:* 40 mg/kg/d PO in ÷ 3–4 doses × 7–10 days.
W/P: [B oral + C Inj, -].
CI: Component allergy; avoid in Hx hearing loss.

DISP: Caps 125, 250 mg; powder for Inj.
SE: Oto/nephrotoxic, GI upset (PO).
NOTES: Not absorbed PO, effect in gut only; give IV slowly (over 1–3 hr) to prevent "red-man syndrome" (flushing of head/neck/upper torso); IV product used PO for colitis. *Levels: Trough:* <0.5 hr before next dose; *Therapeutic: Trough:* 10–20 μg/mL; *Trough:* 15–20 μg/mL. *Half-life:* 6–8 hr; peak monitoring is not rec (toxic >80 μg/mL).

VARDENAFIL (LEVITRA, STAXYN, GENERIC)

USES: *Erectile dysfunction.*
ACTIONS: PDE5 inhibitor, increases cGMP and NO levels; relaxes smooth muscles, dilates cavernosal arteries; onset 15–60 min, duration 2–8 hr.
DOSE: *Levitra* 10 mg PO 60 min before sexual activity; titrate; max. × 1 = 20 mg; 2.5 mg w/ CYP3A4 inhibitor; *Staxyn* 1 (10 mg ODT) 60 min before sex, max. 1×/d.
W/P: [B, −] w/ CV, hepatic, or renal disease or if sex activity not advisable; potentiate the hypotensive effects of nitrates, α-blockers, and antihypertensives.
CI: w/ Nitrates.
DISP: *Levitra* Tabs 2.5, 5, 10, 20 mg tabs; *Stayxn* 10 mg ODT (contains phenylalanine).
SE: ↑ QT interval ↓ BP, headache, dyspepsia, priapism, flushing, rhinitis, sinusitis, flu syndrome, sudden ↓/loss of hearing, tinnitus, NIAON.
NOTES: Do not use w/ type 1A or type 3 antiarrhythmics or w/ long QT syndrome; concomitant α-blockers may cause ↓ BP; transient global amnesia reports; place Staxyn on tongue to disintegrate w/o liquids; ODT not interchangeable to oral pill; gets higher levels.

VERAPAMIL (CALAN, COVERA HS, ISOPTIN, VERELAN, GENERIC)

USES: *Angina, HTN, PSVT, AF, atrial flutter*, migraine prophylaxis, hypertrophic cardiomyopathy, bipolar disease, Peyronie disease.
ACTIONS: Calcium channel blocker.

DOSE:

Adults: *Arrhythmias:* 2nd line for PSVT w/ narrow QRS complex & adequate BP 2.5–10 mg IV over 1–2 min; repeat 5–10 mg in 15–30 min PRN (30 mg max.). *Angina:* 80–120 mg PO TID, ↑ 480 mg/24 h max. *HTN:* 80–180 mg PO TID or SR tabs 120–240 mg PO daily to 240 mg BID.
Peds: ***<1 yr:*** 0.1–0.2 mg/kg IV over 2 min (may repeat in 30 min). ***1–16 yr:*** 0.1–0.3 mg/kg IV over 2 min (may repeat in 30 min); 5 mg max. *PO:* 3–4 mg/kg/d PO ÷ in 3 doses, max. 8 mg/kg/d up to 480 mg/d. ***>5 yr:*** 80 mg q6–8h; ↓ in renal/hepatic impairment.
W/P: [C, +] Amiodarone/β-blockers/flecainide can cause ↓ HR; statins, midazolam, tacrolimus, theophylline levels may be ↑; use w/ clonidine may cause severe ↓ HR w/ elderly pts.
CI: EF <30%, severe LV dysfunction, BP <90 mm Hg, SSS, 2nd-, 3rd-AV block AF/atrial flutter w/ bypass tract.
DISP: *Calan SR:* Caps 120, 180, 240 mg; *Verelan SR:* Caps 120, 180, 240, 360 mg; *Verelan PM*: Caps (ER) 100, 200, 300 mg; *Calan:* Tabs 80, 120 mg; *Isoptin SR* 24-hr 120, 180, 240 mg; Inj 2.5 mg/mL.
SE: Gingival hyperplasia, constipation, ↓ BP, bronchospasm, HR or conduction disturbances;

edema; ↓ BP and bradyarrhythmias taken w/ telithromycin.
NOTES: topical use reported in Peyronie disease.

VINBLASTINE (GENERIC)

WARNING: Chemotherapeutic agent; handle w/ caution; only individuals experienced in use of vinblastine should administer.
USES: *Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, Wilms' tumor, acute leukemia.*
ACTIONS: ↓ Microtubule assembly.
DOSE: 0.1–0.5 mg/kg/wk (4–20 mg/m^2) (based on specific protocol); ↓ in hepatic failure.
W/P: [D, ?].
CI: Granulocytopenia, bacterial infection.
DISP: Inj 1 mg/mL in 10-mg vial.
SE: ↓ BM (especially leukopenia), N/V, constipation, neurotox, alopecia, rash, myalgia, tumor pain.
NOTES: Use can be fatal.

VINCRISTINE (MARQIBO, GENERIC)

WARNING: Chemotherapeutic agent; handle w/ caution; fatal if administered IT; IV only; administration by individuals experienced in use of vincristine only; severe w/ extrav.
USES: *ALL, breast & small-cell lung cancer, sarcoma (eg, Ewing tumor, rhabdomyosarcoma), Wilms tumor, Hodgkin disease & NHLs, neuroblastoma, multiple myeloma.*
ACTIONS: Promotes disassembly of mitotic spindle, causing metaphase arrest, vinca alkaloid.
DOSE: 0.4–1.4 mg/m^2 (single doses 2 mg/max.); ↓ in hepatic failure.
W/P: [D, −].
CI: Charcot–Marie–Tooth syndrome
DISP: Inj 1 mg/mL.
SE: Neurotox commonly dose limiting, jaw pain (trigeminal neuralgia), fever, fatigue, anorexia, constipation & paralytic ileus, bladder atony; no sig ↓ BM w/ standard doses; tissue necrosis w/ extrav; myelosuppression.

WARFARIN (COUMADIN, JANTOVEN, GENERIC)

WARNING: Can cause major/fatal bleeding. Monitor INR. Drugs, dietary changes, other factors affect INR. Instruct pts about bleeding risk.
USES: *Prophylaxis & Treat of PE & DVT, AF w/ embolization*, other postop indications.
ACTIONS: ↓ Vit K-dependent clotting factors in this order: VII-IX-X-II.

DOSE:

Adults: Titrate, INR 2.0–3.0 for most; mechanical valves INR is 2.5–3.5. *American College of Chest Physicians guidelines:* 5 mg initial, may use 7.5–10 mg; ↓ if pt elderly or w/ other bleeding risk factors; maint 2–10 mg/d PO, follow daily INR initial to adjust dosage.
Peds: 0.05–0.34 mg/kg/24 h PO or IV; follow PT/INR to adjust dosage; monitor vit K intake; ↓ w/ hepatic impairment/elderly.

W/P: [X, +].
CI: Bleeding, peptic ulcer, pregnancy.
DISP: Tabs 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg; Inj.
SE: Bleeding d/t over anticoagulation or injury & therapeutic INR; bleeding, alopecia, skin necrosis, purple toe syndrome.
NOTES: Monitor vit K intake (↓ effect); INR preferred test; to rapidly correct overanticoagulation: vit K, fresh-frozen plasma, or both. Caution pt on taking w/ other meds that can ↑ risk of bleed. *Common warfarin interactions: Potentiated by:* Acetaminophen, EtOH (w/ liver disease), amiodarone, cimetidine, ciprofloxacin, cotrimoxazole, erythromycin, fluconazole, flu vaccine, isoniazid, itraconazole, metronidazole, omeprazole, phenytoin, propranolol, quinidine, tetracycline. *Inhibited by:* Barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, dicloxacillin, nafcillin, rifampin, sucralfate, high–vit K foods. Consider genotyping for VKORC1 & CYP2C9.

WITCH HAZEL (TUCKS PADS, OTHERS [OTC])

USES: After bowel movement, cleansing to decrease local irritation or relieve hemorrhoids; after anorectal surgery, episiotomy, Vag hygiene.
ACTIONS: Astringent; shrinks blood vessels locally.
DOSE: Apply PRN.
W/P: [?, ?] External use only.
CI: None.
SUPPLIED: Presoaked pads.
SE: Mild itching or burning.

ZOLEDRONIC ACID (RECLAST, ZOMETA, GENERIC)

USES: *Hypercalcemia of malignancy (HCM), ↓ skelet al-related events in community-acquired pneumonia, multiple myeloma, & metastatic bone lesions (*Zometa*)*; *prevent/Treat of postmenopausal osteoporosis, Paget disease, ↑ bone mass in men w/ osteoporosis, steroid-induced osteoporosis (*Reclast*).*
ACTIONS: Bisphosphonate; ↓ osteoclastic bone resorption.
DOSE: *Zometa HCM:* 4 mg IV over ≥15 min; may retreat in 7 days w/ adequate renal function. *Zometa bone lesions/myeloma:* 4 mg IV over >15 min, repeat q3–4wk PRN; extend w/ ↑ Cr. *Reclast Treat osteoporosis:* 5 mg IV annually. *Reclast:* Prevent postmenopausal osteoporosis 5 mg IV q2y. *Paget:* 5 mg IV × 1.
W/P: [D, ?/−] w/ Diuretics, aminoglycosides; ASA-sensitive asthmatics; avoid invasive dental procedures.
CI: Bisphosphonate allergy; hypocalcemia, angioedema, CrCl <35.
DISP: Vial 4 mg, 5 mg.
SE: Fever, flu-like syndrome, GI upset, insomnia, anemia; electrolyte abnormalities, bone, joint and muscle pain, AF, ONJ, atyp femur Fx.
NOTES: Requires vigorous prehydration; do not exceed rec doses/Inf duration to ↓ renal dysfunction; follow Cr; effect prolonged w/ Cr ↑; avoid oral surgery; dental exam recommended prior to Treat; ↓ dose w/ renal dysfunction; give Ca^{2+} and vit D supls; may ↑

atypical subtrochanteric femur fractures.

Cytochrome P-450 enzymes and common medication interactions

CYP1A2
Substrates: Acetaminophen, caffeine, cyclobenzaprine, clozapine, imipramine, mexiletine, naproxen, propranolol, theophylline
Inhibitors: Amiodarone, cimetidine, most fluoroquinolone antibiotics, fluvoxamine, verapamil
Inducers: Carbamazepine, charcoal-broiled foods, cruciferous vegetables, omeprazole, modafinil, tobacco smoking

CYP2C9
Substrates: Most NSAIDs (including COX-2), glipizide, irbesartan, losartan, phenytoin, tamoxifen, warfarin
Inhibitors: Amiodarone, fluconazole, isoniazid (INH), ketoconazole, metronidazole
Inducers: Aprepitant, barbiturates, rifampin

CYP2C19
Substrates: Amitriptyline, clopidogrel, cyclophosphamide, diazepam, lansoprazole, omeprazole, pantoprazole, phenytoin, rabeprazole
Inhibitors: Fluoxetine, fluvoxamine, isoniazid, ketoconazole, lansoprazole, omeprazole, ticlopidine
Inducers: Barbiturates, carbamazepine, prednisone, rifampin

CYP2D6
Substrates:
Antidepressants: Most tricyclic antidepressants, clomipramine, fluoxetine, paroxetine, venlafaxine
Antipsychotics: Aripiprazole, clozapine, haloperidol, risperidone, thioridazine
β-blockers: Carvedilol, metoprolol, propranolol, timolol
Opioids: Codeine, hydrocodone, oxycodone, tramadol
Others: Amphetamine, dextromethorphan, duloxetine, encainide, flecainide, mexiletine, ondansetron, propafenone, selegiline, tamoxifen
Inhibitors: Amiodarone, bupropion, cimetidine, clomipramine, doxepin, duloxetine, fluoxetine, haloperidol, methadone, paroxetine, quinidine, ritonavir
Inducers: Dexamethasone, rifampin

CYP3A
Substrates:
Anticholinergics: Darifenacin, oxybutynin, solifenacin, tolterodine
Benzodiazepines: Alprazolam, diazepam, midazolam, triazolam
Calcium channel blockers: Amlodipine, diltiazem, felodipine, nifedipine, nimodipine, nisoldipine, verapamil
Chemotherapy: Cyclophosphamide, erlotinib, ifosfamide, paclitaxel, tamoxifen, vinblastine, vincristine
HIV protease inhibitors: Atazanavir, indinavir, nelfinavir, ritonavir, saquinavir
HMG-CoA reductase inhibitors: Atorvastatin, lovastatin, simvastatin
Immunosuppressive agents: Cyclosporine, tacrolimus
Macrolide-type antibiotics: Clarithromycin, erythromycin, telithromycin, troleandomycin
Opioids: Alfentanil, cocaine, fentanyl, methadone, sufentanil
Steroids: Budesonide, cortisol, 17-β-estradiol, estrogens, progesterone, testosterone, prednisone
Others: Acetaminophen, amiodarone, carbamazepine, delavirdine, efavirenz, nevirapine, quinidine, repaglinide, sildenafil, tadalafil, trazodone, vardenafil
Inhibitors: Amiodarone, amprenavir, aprepitant, atazanavir, ciprofloxacin, cisapride, clarithromycin, diltiazem, erythromycin, fluconazole, fluvoxamine, grapefruit juice (in high ingestion), indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, norfloxacin, ritonavir, saquinavir, telithromycin, troleandomycin, verapamil, voriconazole
Inducers: Carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, phenytoin, phenobarbital, rifabutin, rifapentine, rifampin, St. John's wort

Lynch T, Price A The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am Fam Physician*. 2007;76(3):391–396.
Gomella LG, Haist S, Adams A, eds. *Clinicians' Pocket Drug Reference, 2015 Edition*. New York, NY: McGraw-Hill.
Katzung B, ed. *Basic and Clinical Pharmacology*. 12th ed. New York, NY: McGraw-Hill; 2012.

SECTION VII

Reference Tables

Aging Male Survey (AMS)

(See also Section II: Aging Male Survey)

AMS Questionnaire

Which of the following symptoms apply to you at this time? Please mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none."

Symptoms	Score =	None 1	Mild 2	Moderate 3	Severe 4	Extremely severe 5
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)		☐	☐	☐	☐	☐
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)		☐	☐	☐	☐	☐
3. **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)		☐	☐	☐	☐	☐
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)		☐	☐	☐	☐	☐
5. **Increased need for sleep, often feeling tired**		☐	☐	☐	☐	☐
6. **Irritability** (feeling aggressive, easily upset about little things, moody)		☐	☐	☐	☐	☐
7. **Nervousness** (inner tension, restlessness, feeling fidgety)		☐	☐	☐	☐	☐
8. **Anxiety** (feeling panicky)		☐	☐	☐	☐	☐
9. **Physical exhaustion/lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)		☐	☐	☐	☐	☐
10. **Decrease in muscular strength** (feeling of weakness)		☐	☐	☐	☐	☐
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)		☐	☐	☐	☐	☐
12. **Feeling that you have passed your peak**		☐	☐	☐	☐	☐
13. **Feeling burnt out, having hit rock-bottom**		☐	☐	☐	☐	☐
14. **Decrease in beard growth**		☐	☐	☐	☐	☐
15. **Decrease in ability/frequency to perform sexually**		☐	☐	☐	☐	☐
16. **Decrease in the number of morning erections**		☐	☐	☐	☐	☐
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)		☐	☐	☐	☐	☐

Have you got any other major symptoms? Yes ☐ No ☐

If Yes, please describe: _____

Thank you very much for your cooperation

Reproduced with permission from Moore C, Huebler D, Zimmermann T, et al. The Aging Males Symptom Scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol.* 2004;46:80–87.

Antibiotic Prophylaxis: AUA Guidelines

Patients undergoing urologic surgery should be considered for appropriate antibiotic prophylaxis. The American Urologic Association (AUA) has made the following recommendations to help with decisions regarding use of antimicrobial prophylaxis in urologic surgery based on upper or lower urinary tract surgery. The selection of agent and determination of appropriate dosing should always consider the patient's specific circumstances (allergy, etc.).
Key points in the AUA guidelines:

- The duration of surgical prophylaxis should extend throughout the period in which bacterial invasion is facilitated and/or is likely to establish an infection.
- Begin infusion of the 1st dose within 60 minutes of the incision (except 120 min for IV fluoroquinolones and vancomycin).
- Do not extend prophylaxis beyond 24 hr after a procedure except with prosthetic materials, if a urinary catheter is present prior to or is placed at the time of the procedure in patients with risk factors, or in the presence of documented bacteriuria.
- For surgical prophylaxis, all agents should be administered IV (except for oral medications for fluoroquinolones, trimethoprim–sulfamethoxazole, bowel preparation agents, and some agents given at catheter removal); in addition, intramuscular administration for antimicrobials for transrectal prostate biopsy is acceptable.
- With an existing infection, a therapeutic course of antimicrobials should be given in an attempt to sterilize the field or suppress the bacterial count. Prophylaxis can be omitted if urine culture shows no growth.
- Standard dosing regimens are noted. Dose adjustments based on body weight. Additional intraoperative doses are required intraoperatively if the procedure extends beyond 2 half-lives of the initial dose.
- Oral agents used for bowel preparation include erythromycin base: 1–2 g PO (variable), Metronidazole: 1–2 g PO (variable), Neomycin (for bowel preparation): 1–2 g PO (variable).
- Antimicrobial prophylaxis for genitourinary procedures solely to prevent infectious endocarditis is no longer recommended by the American Heart Association as the risk of adverse events exceeds the benefit.
- For patients with orthopedic considerations see Section II: "Joint Replacement, Urologic Considerations".

This version was updated on January 1, 2014 and this information and the tables below are based on data from "Urologic Surgery Antimicrobial Prophylaxis" https://www.auanet.org/education/guidelines/antimicrobial-prophylaxis.cfm (Accessed August 29, 2014). Please refer to this site for additional details.

PROPHYLAXIS FOR LOWER URINARY TRACT INSTRUMENTATION

Procedure (Organisms)[1]	Prophylaxis Indicated	Antimicrobial(s) of Choice[2]	Alternative Antimicrobial(s)[2]
Removal of external urinary catheter,[3,4] (GU tract)	Patients with risk factors[5,7]		*Aminoglycoside ± ampicillin:* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose Ampicillin: 1–2 g IV (q6h) OR *1st gen. cephalosporin:* Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h) OR *2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *Amoxicillin/clavulanate:* 875 mg PO (q12h)
Cystography, urodynamic study or simple Cystourethroscopy (GU tract)	Patients with risk factors[5,7]	*Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h) OR *TMP-SMX (Trimethoprim–sulfamethoxazole):* 1 double-strength tablet PO (q12h)	
Cystourethroscopy with manipulation[6] (GU tract)	All patients		
Prostate brachytherapy or cryotherapy (skin)	Uncertain	*1st gen. cephalosporin:* Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h)	*Clindamycin:* 600 mg IV (q8h)
Transrectal prostate biopsy (intestine)	All patients	*Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h) OR *1st gen. cephalosporin:* Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h) OR *2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *3rd gen. cephalosporin:* (oral agents not listed) Ceftizoxime: 1 g IV (q8h) Ceftazidime: 1 g IV (q12h) Ceftriaxone: 1–2 IV single dose Cefotaxime: 1 g IV (q8h)	*TMP-SMX (Trimethoprim–sulfamethoxazole):* 1 double-strength tablet PO (q12h) OR *Aminoglycoside* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose OR *Aztreonam:* 1–2 g IV (q8h)

Key: gen. = generation; GU = genitourinary.

1. Organisms common to the GU tract: *E. coli, Proteus sp., Klebsiella sp., Enterococcus;* Intestine: *E. coli, Klebsiella sp., Enterobacter, Serratia sp., Proteus sp., Enterococcus,* and Anaerobes; Skin: *S. aureus, coagulase negative Staph. sp.,* Group A *Strep. sp.* Skin organisms: *S. aureus, coagulase negative Staph. sp.,* Group A *Strep. sp.* Intestinal organisms: *E. coli, Klebsiella sp., Enterobacter, Serratia sp, Serratia sp., Proteus sp., Enterococcus,* and anaerobes.
2. Order of agents is not indicative of preference.
3. If urine culture shows no growth prior to procedure, antimicrobial prophylaxis is not necessary.
4. Or full course of culture-directed antimicrobials for documented infection (treatment not prophylaxis).
5. Risk factors: Advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, distant coexistent infection, prolonged hospitalization.
6. Includes transurethral resection of bladder tumor and prostate, and any biopsy, resection, fulguration, foreign body removal, urethral dilation or urethrotomy, or ureteral instrumentation including catheterization or stent placement/removal.
7. If culture negative pre op, prophylaxis not necessary.

PROPHYLAXIS FOR UPPER URINARY TRACT INSTRUMENTATION

Procedure (Organisms)[1]	Prophylaxis Indicated	Antimicrobial(s) of Choice[2]	Alternative Antimicrobial(s)[2]
Shock-wave lithotripsy (GU tract)	If risk factors[3]	*Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h) OR *TMP-SMX (Trimethoprim–sulfamethoxazole):* 1 double-strength tablet PO (q12h)	*Aminoglycoside ± ampicillin* 1st/2nd gen. cephalosporin Amoxicillin/clavulanate
Ureteroscopy (GU tract)	All patients		
Percutaneous renal surgery (GU tract and skin)	All patients	*1st gen. cephalosporin:* Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h) OR *2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *Aminoglycoside* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose WITH *Metronidazole:* 1 g IV (q12h) OR *Clindamycin:* 600 mg IV (q8h)	*Ampicillin/sulbactam:* 1.5–3 g IV (q6h) OR *Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h)
Vaginal surgery (GU tract, skin, and Group B *Strep.*)	All patients	*1st gen. cephalosporin:* Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h) OR *2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *Aminoglycoside:* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose WITH *Metronidazole:* 1 g IV (q12h) OR *Clindamycin:* 600 mg IV (q8h)	*Ampicillin/sulbactam:* 1.5–3 g IV (q6h) OR *Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h)
Involving entry into the urinary tract (GU tract and skin)	All patients		

Key: gen. = generation; GU = genitourinary.

1. Organisms common to the GU tract: *E. coli, Proteus sp., Klebsiella sp., Enterococcus;* Intestine: *E. coli, Klebsiella sp., Enterobacter, Serratia sp., Proteus sp., Enterococcus,* and Anaerobes; Skin: *S. aureus, coagulase negative Staph. sp.,* Group A *Strep. sp.* Skin organisms: *S. aureus, coagulase negative Staph. sp.,* Group A *Strep. sp.* Intestinal organisms: *E. coli, Klebsiella sp., Enterobacter, Serratia sp, Serratia sp., Proteus sp., Enterococcus.*
2. Order of agents is not indicative of preference.
3. Risk factors: Advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, distant coexistent infection, prolonged hospitalization.
4. For surgery involving colon, bowel preparation with oral neomycin plus either erythromycin base or metronidazole can be added to or substituted for systemic agents.

PROPHYLAXIS FOR UPPER URINARY TRACT INSTRUMENTATION (Continued)

Without entering urinary tract (skin)	Patients with risk factors[3]	*1st gen. cephalosporin (single dose):* Cephalexin: 500 mg PO Cephradine: 500 mg PO Cefadroxil: 500 mg PO Cefazolin: 1 g IV	*Clindamycin*: 600 mg IV single dose
Involving intestine[4] (GU tract, skin, and intestine)	All patients	*2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *3rd gen. cephalosporin:* (oral agents not listed) Ceftizoxime: 1 g IV (q8h) Ceftazidime: 1 g IV (q12h) Ceftriaxone: 1–2 IV single dose Cefotaxime: 1 g IV (q8h) OR *Aminoglycoside:* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose WITH *Metronidazole:* 1 g IV (q12h) OR *Clindamycin*: 600 mg IV (q8h)	*Ampicillin/sulbactam:* 1.5–3 g IV (q6h) OR *Ticarcillin/clavulanate:* 3.1 g IV (q6h) OR *Piperacillin/tazobactam:* 3.375 g IV (q6h) OR *Fluoroquinolones:* Levofloxacin: 500 mg PO single dose Ciprofloxacin: 500 mg PO (q12h) Ofloxacin: 400 mg PO (q12h)
Involving implanted prosthesis (GU tract and skin)	All patients	*Aminoglycoside:* Gentamicin: 5 mg/kg IV single dose Tobramycin: 5 mg/kg IV single dose Amikacin: 15 mg/kg IV single dose WITH *1st gen. cephalosporin*: Cephalexin: 500 mg PO (q6h) Cephradine: 500 mg PO (q6h) Cefadroxil: 500 mg PO (q12h) Cefazolin: 1 g IV (q8h) OR *2nd gen. cephalosporin:* Cefaclor: 500 mg PO (q8h) Cefprozil: 500 mg PO (q12h) Cefuroxime: 500 mg PO (q12h) Cefoxitin: 1–2 g IV (q8h) OR *Vancomycin*: 1 g IV (q12h)	*Ampicillin/sulbactam:* 1.5–3 g IV (q6h) OR *Ticarcillin/clavulanate:* 3.1 g IV (q6h) OR *Piperacillin/tazobactam:* 3.375 g IV (q6h)

Key: gen. = generation; GU = genitourinary.

1. Organisms common to the GU tract: *E. coli, Proteus sp., Klebsiella sp., Enterococcus;* Intestine: *E. coli, Klebsiella sp., Enterobacter, Serratia sp., Proteus sp., Enterococcus,* and Anaerobes; Skin: *S. aureus, coagulase negative Staph. sp.*, Group A *Strep. sp.* Intestinal organisms: *E. coli, Klebsiella sp., Enterobacter, Serratia sp, Serratia sp., Proteus sp., Enterococcus.*
2. Order of agents is not indicative of preference.
3. Risk factors: Advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized endogenous/exogenous material, distant coexistent infection, prolonged hospitalization.
4. For surgery involving colon, bowel preparation with oral neomycin plus either erythromycin base or metronidazole can be added to or substituted for systemic agents.

Anticoagulation and Antiplatelet Therapy in Urologic Practice

The following is based on Anticoagulation and Antiplatelet Therapy in Urologic Practice: ICUD and AUA Review Paper. The American Urologic Association (AUA) and the International Consultation on Urological Disease (ICUD) collaborated on this review. http://www.auanet.org/common/pdf/education/clinical-guidance/Anticoagulation-Antiplatelet-Therapy.pdf (Accessed July 12, 2014)

Patients often have multiple comorbidities and require urologic surgical intervention. Conditions can include coronary arterial disease requiring percutaneous coronary artery intervention with angioplasty, bare metal coronary stents, drug eluting coronary stent, cardiac dysrhythmias (such as atrial fibrillation, others), valvular heart disease, deep venous thrombosis, and inferior vena cava filters. This table provides guidelines on the management of anticoagulation and antiplatelet (AP) therapy in urologic practice. These are only general guidelines with the most effective approach for an individual patient best determined by the patient's clinical conditions and in collaboration with a multidisciplinary medical team that may include internists, cardiologists, or neurologists where appropriate.

- Anticoagulant (AC)
  - Heparins
  - Warfarin
  - Novel oral anticoagulants (NOACs) include thrombin inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban, and apixaban
- Oral Anti Platelet (AP)
  - AP medications: aspirin, clopidogrel, ticagrelor, ticlopine, dipyridamole

1. **Deep venous thrombosis and pulmonary embolism** are discussed in Section I: "Deep Venous Thrombosis and Pulmonary Embolus, Urologic Considerations" and Section II: "Deep Venous Thrombosis, Prophylaxis, AUA Guidelines."

2. **For patients on clopidogrel or aspirin for secondary stroke prevention:** continue aspirin through the perioperative period.

3. **Coronary artery stents:** Dual AP therapy should not be stopped before urologic surgery within 12 mo of drug eluding stent or within 3 mo of a bare metal stent. For urologic procedures outside of these limits discontinuation of the clopidogrel, prasugrel, or ticagrelor, and continuation of aspirin, is recommended if procedural bleeding risks are acceptable.

4. **Mechanical heart valves:** AC bridge therapy is recommended.

5. **Cardiac risk factors on low-dose aspirin monotherapy**: continue in perioperative period without increased risk of major bleeding.

6. **Low-dose aspirin without specific indication:** may be scheduled electively, discontinuing the aspirin until directed by the team.

7. **Patients on** NOACs **(apixaban, dabigatran, rivaroxaban), with nonvalvular atrial fibrillation should be risk stratified:**

- Minor bleeding risk: these agents do not have to be modified, similar to the management with warfarin or low-molecular-weight heparin.
- Urgent procedure: delay for 24–36 hr and obtain consultation.
- Emergency procedure: if bleeding risk increased, expert consultation and avoid spinal/epidural anesthesia.
- With operative loss of nephrons determine renal function post-op and adjust these agents.

8. **Atrial fibrillation in high-risk procedure**: stop warfarin 5 days before surgery; restart 12–24 hr post-op if bleeding risk acceptable.

9. **Higher risk of thromboembolic events (eg, mechanical valves) on warfarin**: bridging anticoagulation with unfractionated heparin or low-molecular-weight heparin. The NOACs apixaban, dabigatran, or rivaroxaban, would be stopped 2–5 days before elective surgery based on the bleeding risk of the procedure. Rivaroxaban may increase stroke risk if stopped; bridging with some other AC such as heparin is recommended.

10. **Prosthetic heart valves:** follow standard guidelines (ie, the American College of Cardiology, American Heart Association, etc.).

- **Low risk of thrombosis:** bileaflet mechanical AVR and no risk factors (eg, atrial fib, previous thromboembolism, left ventricular dysfunction, hypercoagulable conditions, older generation thrombogenic valves, mechanical tricuspid valves or more than one mechanical valve). Stop warfarin 48–72 hr pre-op and restarted within 24 hr post-op. Heparin is usually unnecessary. Check INR immediately pre-op to ensure that the INR is >1.5.
- **High risk of thrombosis:** (any mechanical mitral valve replacement or a mechanical aortic valve with any risk factor [see above for risk factors]) begin bridging when the INR <2 (usually 48 hr pre-op); dose adjust aPTT 2–3 times the control. Unfractionated heparin is stopped 4–6 hours pre-op and restarted post-op based on bleeding stability. Restart warfarin as soon as possible postoperatively; unfractionated heparin is continued until the INR is therapeutic for at least 48 hr.

11. **Bridging regimens:** As recommended by the American College of Chest Physicians:

- A high-dose (therapeutic-dose) heparin bridging (eg, LMW heparin: enoxaparin 1 mg/kg BID or 1.5 mg/kg daily, dalteparin 100 IU/kg BID or 200 IU/kg daily, tinzaparin 175 IU/kg daily, or IV unfractionated heparin to keep aPTT 1.5–2 times control).
- A low-dose (prophylactic-dose) heparin regimen (eg, enoxaparin 30 mg BID or 40 mg daily, dalteparin 5,000 IU daily, unfractionated heparin 5,000–7,500 IU BID).
- An intermediate-dose regimen (eg, enoxaparin 40 mg BID).

12. **ESWL:** oral ACs and APs agents should be stopped and or reversed. Coordinate with multidisciplinary team.

13. **Ureteroscopy:** can be performed with continuing oral ACs and APs agents.

14. **Percutaneous nephrostolithotomy (PCNL):** oral ACs and APs agents discontinued prior to PCNL and patients bridged where deemed necessary.

15. **Laser prostatectomy:** In appropriately selected patients can be safely accomplished with a therapeutic INR who has a significant risk of thrombosis without stopping oral ACs and APs agents.

16. **Standard electrosurgical TURP:** The use of oral ACs and APs agents in patients undergoing TURP is associated with an increased risk of bleeding. Anticoagulation should be carefully assessed and managed; alternative treatment of the bladder outlet may be preferable.

17. **Prostate biopsy:** safe on low-dose aspirin. With oral ACs small studies suggest this can be performed without significant major bleeding risk. Stopping APs agents before biopsy, when medical evaluation demonstrates a low risk of thromboembolic complications, is associated with a lower rate of minor complications.

18. **Perioperative continuation of aspirin:** this may be associated with a minor risk of increased bleeding, but the transfusion rate is not increased and the consequences of bleeding are minor. The exception is with transurethral resection of the prostate.

AUA Symptom Index/International Prostate Symptom Score (I-PSS)

(See also Section II: AUA (American Urologic Association) Symptom Index for BPH and International Prostate Symptom Score (IPSS))

American Urological Association (AUA) Symptom Index for BPH

	Not at all 0	Less than 1 time in 5 1	Less than half the time 2	About half the time 3	More than half the time 4	Almost always 5
1. INCOMPLETE EMPTYING Over the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
2. FREQUENCY During the last month or so, how often have you had to urinate again <2 hours after you finished urinating?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
3. INTERMITTENCY During the last month or so, how often have you stopped and started again several times when you urinated?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
4. URGENCY During the last month or so, how often have you found it difficult to postpone urination?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
5. WEAK STREAM During the last month or so, how often have you had a weak urinary stream?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
6. STRAINING During the last month or so, how often have you had to push or strain to begin urination?	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5
7. SLEEPING During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	○ 0	○ 1	○ 2 (times at night)	○ 3	○ 4	○ 5

SCORE: (0-35) ☐

The **International Prostate Symptom Score (IPSS)** uses the same 7 questions as the AUA Symptom Index, but adds a "Disease Specific Quality of Life Question" (sometimes referred to as the "bother score") and scored on a scale from 0 to 6 points ("delighted" to "terrible").

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

Delighted	Pleased	Mostly satisfied	Mixed	Mostly disappointed	Unhappy	Terrible
0 ○	1 ○	2 ○	3 ○	4 ○	5 ○	6 ○

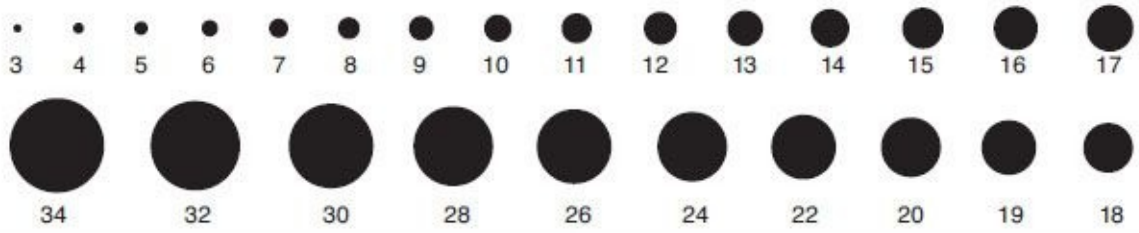
Based on American Urological Association. Guideline on the Management of Benign Prostatic Hyperplasia (BPH), Linthicum, MD: American Urological Association Education and Research, Inc. 2003, with permission.

CATHETER GUIDE

(See also Section II: "French Catheter Scale".)

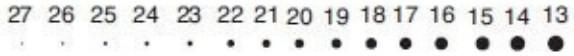
French Catheter Scale

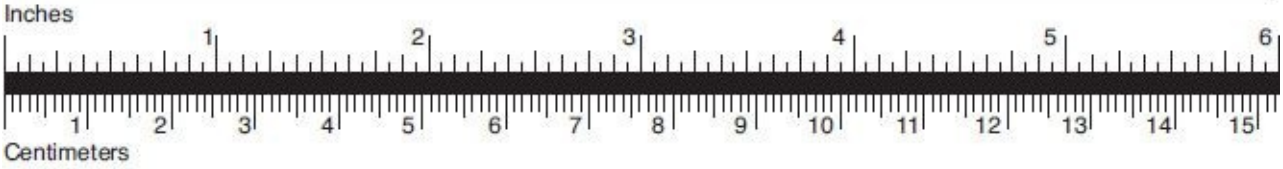
In French Units (1 French = 1/3 mm diameter)



3 French = 1.0 mm = .039 inches
18 French = 6 mm = .236 inches

Needle Gauge





(With permission from Cook Urological, Inc., "French Catheter Scale")

Contrast Agents, Genitourinary

Contrast agents used in urology include intravascular (CT, excretory urography, vascular studies, etc.), gastrointestinal (oral contrast), body cavity (fistulogram and tube studies), uroradiological (cystogram, urethrogram, retrograde pyelography, etc.), and MRI contrast agents (gadolinium-based paramagnetic compounds). Commonly used intravascular and uroradiological agents are shown in the tables below. See also Section I: "Contrast Allergy and Reactions" and Section II: "Contrast Induced Nephropathy (CIN)" and "Nephrogenic Systemic Fibrosis/Fibrosing Dermatopathy (NSF/NFD)."

Key points:

- Intravascular contrast agents are classified as ionic or nonionic and high, low, or iso-osmolar relative to serum (290 mOsm/kg H_2O). High-osmolar contrast media (HOCM) are the oldest intravascular agents and ionize in solution (osmolality typically >1,000). Low-osmolar contrast media (LOCM) and iso-osmolar contrast media (IOCM) are nonionic compounds (no ionization in solution). The toxicity of contrast agents generally decreases as osmolality approaches that of serum. Typical osmolality (in mOsm/kg H_2O) is as follows: HOCM > 1,000, LOCM ~ 400–800, and IOCM 290.
- Uroradiologic contrast agents are not injected into the circulation so that issues relating to potential toxicity are almost nonexistent.
- MRI contrast agents: Nephrogenic systemic fibrosis (NSF) is associated with the administration of intravenous gadolinium. The primary risk factor is renal insufficiency (dialysis patient or with a GFR < 30).

Intravascular Contrast Agents

Agents sorted by osmolarity from highest to lowest and represent commonly used agents in the United States.

Product	Chemical Structure	Anion	Cation	Osmolality (mOsm/kg H_2O)
MD-76™ (Covidien)	Ionic	Diatrizoate	Meglumine Sodium	1,551
Conray™ Covidien)	Ionic	Iothalamate	Meglumine	1,400
Conray™ 43 (Covidien)	Ionic	Iothalamate	Meglumine	1,000
Omnipaque™–350 (GE Healthcare)	Iohexol 755 mg	Nonionic	Nonionic	844
Isovue®–370 (Bracco)	Iopamidol 75.5%	Nonionic	Nonionic	796
Optiray™ 350 (Covidien)	Ioversol 74%	Nonionic	Nonionic	792
Ultravist® 370 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	774
Oxilan® 350 (Guerbet)	Ioxilan 72.7%	Nonionic	Nonionic	721
Optiray™ 320 (Covidien)	Ioversol 68%	Nonionic	Nonionic	702
Omnipaque™–300 (GE Healthcare)	Iohexol 647 mg	Nonionic	Nonionic	672
Cholografin® (Bracco)	Ionic	Iodipamide	Meglumine	664
Optiray™ 300 (Covidien)	Ioversol 64%	Nonionic	Nonionic	651
Isovue®–300 (Bracco)	Iopamidol 61.2%	Nonionic	Nonionic	616
Oxilan® 300 (Guerbet)	Ioxilan 62.3%	Nonionic	Nonionic	610
Ultravist® 300 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	607
Conray™ 30 (Covidien)	Ionic	Iothalamate	Meglumine	600
Hexabrix™ (Covidien)	Ionic	Ioxaglate	Meglumine Sodium	=600
Isovue®–250 (Bracco)	Iopamidol 51%	Nonionic	Nonionic	524
Omnipaque™ 240 (GE Healthcare)	Iohexol 518 mg	Nonionic	Nonionic	520
Optiray™ 240 (Covidien)	Ioversol 51%	Nonionic	Nonionic	502
Ultravist® 240 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	483
Isovue®–200 (Bracco)	Iopamidol 40.8%	Nonionic	Nonionic	413
Ultravist® 150 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	328
Omnipaque™ 140 (GE Healthcare)	Iohexol 302 mg	Nonionic	Nonionic	322
Visipaque™ 270 (GE Healthcare)	Iodixanol 550 mg	Nonionic	Nonionic	290
Visipaque™–320 (GE Healthcare)	Iodixanol 652 mg	Nonionic	Nonionic	290

Uroradiologic Contrast Agents

Product	Chemical Structure	Anion	Cation	Osmolality (mOsm/kg H_2O)
Cystografin® (Bracco)	Ionic	Diatrizoate	Meglumine	556
Cystografin® Dilute (Bracco)	Ionic	Diatrizoate	Meglumine	349
Cysto-Conray™ II (Covidien)	Ionic	Iothalamate	Meglumine	~400
Conray™ 43 (Covidien)	Ionic	Iothalamate	Meglumine	1000
Omnipaque™ 240 (GE Healthcare)	Nonionic Iohexol	Nonionic	Nonionic	520
Omnipaque™ 300 (GE Healthcare)	Nonionic Iohexol	Nonionic	Nonionic	672
Omnipaque™ 350 (GE Healthcare)	Iohexol	Nonionic	Nonionic	844
Visipaque™ 270 (GE Healthcare)	Iodixanol	Nonionic	Nonionic	290
Visipaque™ 320 (GE Healthcare)	Iodixanol	Nonionic	Nonionic	290

Tables based on data from ACR Manual on Contrast Media Version 9. ACR Committee on Drugs and Contrast Media 2013 http://www.acr.org/quality-safety/resources/~/media/ (Accessed August 31, 2014).

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Patient Questionnaire

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. Your answers will help your doctor to choose the most effective treatment suited to your condition. In answering the questions, the following definitions apply:

- **sexual activity** includes intercourse, caressing, foreplay, and masturbation
- **sexual intercourse** is defined as sexual penetration of your partner
- **sexual stimulation** includes situation such as foreplay, erotic pictures etc.
- **ejaculation** is the ejection of semen from the penis (or the feeling of this)
- **orgasm** is the fulfilment or climax following sexual stimulation or intercourse

	Over the past 4 weeks:	*Please check **one** box only*
☐ Q1	**How often were you able to get an erection during sexual activity?**	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	**When you had erections with sexual stimulation, how often were your erections hard enough for penetration?**	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	**When you attempted intercourse, how often were you able to penetrate (enter) your partner?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	**During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	**During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?**	0 Did not attempt intercourse 1 Extremely difficult 2 Very difficult 3 Difficult 4 Slightly difficult 5 Not difficult
☐ Q6	**How many times have you attempted sexual intercourse?**	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	**When you attempted sexual intercourse, how often was it satisfactory for you?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q8	**How much have you enjoyed sexual intercourse?**	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	**When you had sexual stimulation or intercourse, how often did you ejaculate?**	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always

(Continued on next page)

☐ Q10	**When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?**	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	**How often have you felt sexual desire?**	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	**How would you rate your level of sexual desire?**	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	**How satisfied have you been with your overall sex life?**	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied and dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	**How satisfied have you been with your sexual relationship with your partner?**	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	**How do you rate your confidence that you could get and keep an erection?**	1 Very low 2 Low 3 Moderate 4 High 5 Very high

Total Score _____

Interpretation of IEEF

IIEF Domains	Maximum Score
A. Erectile Function (Questions 1, 2, 3, 4, 5, 15)	30
B. Orgasmic Function (Questions 9, 10)	10
C. Sexual Desire (Questions 11, 12)	10
D. Intercourse Satisfaction (Questions 6, 7, 8)	15
E. Overall Satisfaction (Questions 13, 14)	10

A score of 0–5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire, and intercourse satisfaction.

Analysis of the questionnaire should, therefore, be viewed as an adjunct to, rather than a substitute for, a detailed sexual history and examination. The following guidelines are typical based on the IIEF scores and are based on the recommendations of the British Association of Urologic Surgeons:

1. Low IIEF scores (<14 out of 30) in Domain A (Erectile Function) may be considered for a trial course of therapy with Sildenafil unless contraindicated. Specialist referral is indicated if this is unsuccessful.
2. Patients demonstrating primary orgasmic or ejaculatory dysfunction (Domain B) should be referred for specialist investigation.
3. Patients with reduced sexual desire (Domain C) require testing of blood levels of androgen and prolactin.
4. Psychosexual counselling should be considered if low scores are recorded in Domains D and E but there is only a moderately lowered score (14 to 25) in Domain A.

Based on data from Rosen R, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49:822–830 and the British Association of Urologic Surgeons http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Patient%20information/iief.pdf.

Male Sexual Health Questionnaire (MSHQ) Short Form

MSHQ is a 25 question self-administered questionnaire for assessing key domains of sexual function and satisfaction in aging men with urogenital health concerns. (Rosen RC, Catania J, Pollack L. Male Sexual Health Questionnaire (MSHQ): Scale development and psychometric validation. *Urology.* 2004;64(4):777–782.)

A modified form, known as the MSHQ Short Form is commonly used for assessing ejaculatory dysfunction (also called the MSHQ-EjD). See also Section II: Male Sexual Health Questionnaire (MSHQ) and the MSHQ short form

In the past month:						
Ejaculatory Function						
1. How often have you been able to ejaculate or "cum" when having sexual activity?	All the time (5)	Most of the time (4)	About half the time (3)	Less than half the time (2)	None of the time/could not ejaculate (1)	
2. How would you rate the strength or force of your ejaculation?	As strong as it always was (5)	A little less strong than it used to be (4)	Somewhat less strong than it used to be (3)	Much less strong than it used to be (2)	Very much less strong than it used to be (1)	Could not ejaculate (0)
3. How would you rate the amount or volume of semen or fluid when you ejaculate?	As much as it always was (5)	A little less than it used to be (4)	Somewhat less than it used to be (3)	Much less than it used to be (2)	Very much less than it used to be (1)	Could not ejaculate (0)
Bother/Satisfaction						
4. If you have had any ejaculation difficulties or have been unable to ejaculate, have you been bothered by this?	No problem with ejaculation (0)	Not at all bothered (1)	A little bothered (2)	Moderately bothered (3)	Very bothered (4)	Extremely bothered (5)

Rosen RC, Catania JA, Althof SE, et al. Development and validation of four-item version of male sexual health questionnaire to assess ejaculatory dysfunction. *Urology*. 2007;69(5):805–809, with permission.

National Institutes of Health (NIH) Chronic Prostatitis Symptom Index (CPSI)

(See also Section II: National Institutes of Health (NIH) Chronic Prostatitis Symptom Index. Form is to be filled out by patient.)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

		Yes	No
a.	Area between rectum and testicles (perineum)	❑1	❑0
b.	Testicles	❑1	❑0
c.	Tip of the penis (not related to urination)	❑1	❑0
d.	Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

		Yes	No
a.	Pain or burning during urination?	❑1	❑0
b.	Pain discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑0 Never
❑1 Rarely
❑2 Sometimes
❑3 Often
❑4 Usually
❑5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑ ❑
0 1 2 3 4 5 6 7 8 9 10
NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑0 Not at all
❑1 Less than 1 time in 5
❑2 Less than half the time
❑3 About half the time
❑4 More than half the time
❑5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

8. How much did you think about your symptoms, over the last weeks?

❑0 None
❑1 Only a little
❑2 Some
❑3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑0 Delighted
❑1 Pleased
❑2 Mostly satisfied
❑3 Mixed (about equally satisfied and dissatisfied)
❑4 Mostly dissatisfied
❑5 Unhappy
❑6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: Development and validation of a new outcome measure. *J Urol*. 1999;162(2):369–375, with permission.

Prostate Cancer Screening Guidelines

Screening for prostate cancer is highly controversial. This table summarizes some of the major US and international medical groups recommendations in this area.

Organization (Year)	Recommendation
American Cancer Society (ACS) (2010)	1. No routine screening; after informed discussion of risk and benefits for those who wish to be screened 2. No screening with <10-yr life expectancy 3. Screen with PSA, w/ or w/o DRE, at age 50 with >10 yr life expectancy; if PSA >2.5 ng/mL, screen yearly, otherwise screen every 2 yr 4. Beginning screening discussions at age 40–45 if at high risk of developing prostate cancer (eg, black men, or with a first-degree relative with prostate cancer diagnosed before age 65). 5. Biopsy referral threshold is 4 ng/mL. With PSA 2.5–4 ng/mL, encourage individualized decision making and assessment (http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp), which can include age, race, family history, DRE, previous biopsy results, and use of 5 α-reductase inhibitors.
American College of Physicians (2013)	1. Inform men age 50–69 about limited benefits and harms; screen only if patient wants it 2. Do not screen <age 50 if average risk, over 69, or <10–15-yr life expectancy
American Urological Association (2013)	1. No screening under 40; not recommended if average risk 40–54; individualize if high risk[c] 2. Shared decision making for men age 55–69 3. No screening over age 75 or any man <10–15-yr life expectancy some men over age 70 in excellent health might benefit from screening. 4. Reduce the harms of screening, a screening interval of 2 yr or more may be preferred. 5. Lack of evidence for using any tests (eg, PSA derivatives, PSA kinetics, PSA molecular markers, urinary markers, imaging, or risk calculators) other than PSA for triggering a biopsy referral. No specific threshold for biopsy referral.
Australian Cancer Council (2011)	1. Does not support population-based screening 2. Recommends a patient-centered approach that individualizes the decision
Canadian Task Force on Preventive Health Care (2006; 2014 Update pending)	1. Recommends against screening for prostate cancer with PSA or TRUS 2. Insufficient evidence to recommend for or against screening with DRE
European Society for Medical Oncology (ESMO) (2013)	1. Recommends against population-based screening; favors individualized shared decision making 2. There is inconsistent evidence screening men <50 and 70–75 yr of age; evidence that the harms of screening outweigh the benefits for men over age 75.
National Comprehensive Cancer Network (NCCN) (2014)	1. Informed discussion with all 2. Baseline DRE and PSA age 45; if PSA <1 repeat age 50; if PSA >1, repeat every 1–2 yr 3. Age 50–70 with normal DRE and PSA <3, repeat every 1–2 yr 4. Use caution screening if > age 70 and only if very healthy; few > age 75 benefit from screening
United Kingdom National Screening Committee (2010)	1. Does not recommend screening for prostate cancer
United States Preventive Services Task Force (USPSTF) (2012)	1. No role in any man unless symptoms (grade D) 2. Men requesting screening be supported in making an informed decision.

All PSA values are ng/mL

[a]African American or have a 1st-degree relative diagnosed with PCa at <65 yr of age.

[b]Several 1st-degree relatives diagnosed with PCa at <65 yr of age.

[c]Positive family history or African American race.

Modified from Gomella LG, et al. *CJU*. 2011;18(5):5875; ACP 2013 guidelines (www.acponline.org); NCCN 2014 Prostate Cancer Early Detection Guidelines Version 1.2014 (www.nccn.org); Hoffman RM. Screening for Prostate Cancer uptodate.com (Accessed August 31, 2014).

SEXUAL HEALTH INVENTORY FOR MEN
IIEF-5

Patient's Study ID Number_____

Date of evaluation_____

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction is one type of very common sexual complaint. There are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your physician identify if you may be experiencing erectile dysfunction and to potentially discuss treatment options.

Each question has several responses from which you are asked to choose the one that best describes your own situation. Please be sure that you select at least one but only one response by circling the number that best fits your answer.

Over the past six months:

How do you rate your confidence that you could get and keep an erection?		Very low 1	Low 2	Moderate 3	High 4	Very high 5
When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity 0	Almost never/never 1	A few times (musch less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
During sexual intercourse, how often were you able to maintain your erection after you had penertrated (entered) your partner?	Did not attempt intercourse 0	Almost never/never 1	A few times (musch less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse 0	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse 0	Almost never/never 1	A few times (musch less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5

Score_____

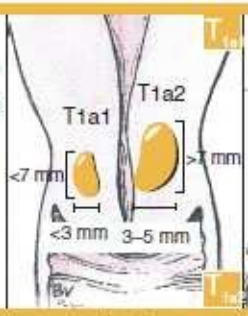
If your score is 21 or less, you show signs of erectile dysfunction, and your doctor can suggest treatment options that can improve your condition.

Sexual Health Inventory for Men. An abridged 5-item version of the 15-item International Index of Erectile Function (IIEF-5) was developed to diagnose the presence and severity of erectile dysfunction (ED). Reprinted with permission from Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res*. 1999;11:319–326.

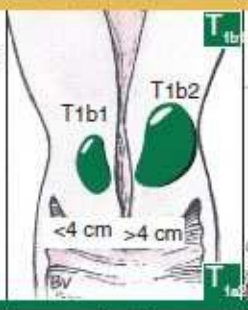
TNM Classification: Cervix Cancer

DEFINITION OF TNM

T1
Cervical carcinoma confined to uterus
(T1a) Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5 mm measured from the base of the epithelium and a horizontal spread of ≤7 mm. Vascular space involvement, venous or lymphatic, does not affect classification.
(T1a1) Measured stromal invasion ≤3 mm in depth and ≤7 mm in horizontal spread
(T1a2) Measured stromal invasion >3 mm and not >5 mm with a horizontal spread ≤7 mm

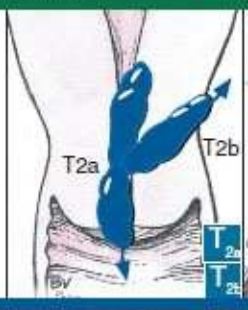


T1b
Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
(T1b1) Clinically visible lesion ≤4 cm in greatest dimension
(T1b2) Clinically visible lesion >4 cm in greatest dimension



N0
No regional lymph node metastasis

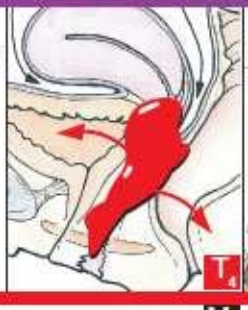
T2
Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
(T2a) Tumor without parametrial invasion
(T2a1) Clinically visible lesion ≤4 cm in greatest dimension
(T2a2) Clinically visible lesion >4 cm in greatest dimension
(T2b) Tumor with parametrial invasion

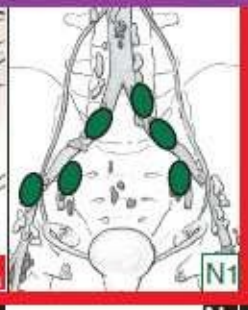


T3
Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
(T3a) Tumor involves lower third of vagina, no extension to pelvic wall
(T3b) Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney

N1
Regional lymph node metastasis

T4
Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)





M0
No distant metastasis

M1
Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

M_1 N_m

STAGE GROUPINGS

Stage IA
T1 N0 M0
T1a N0 M0
T1a1 N0 M0
T1a2 N0 M0

Stage IB
T1b N0 M0
T1b1 N0 M0
T1b2 N0 M0

Stage II
T2 N0 M0
T2a N0 M0
T2b N0 M0

Stage III
T3 N0 M0
T3a N0 M0

Stage IIIB
T1 N1 M0
T2 N1 M0
T3a N1 M0
T3b Any N M0

Stage IVA
T4 Any N M0

Stage IVB
Any T Any N M1

0 IA1/A2 IB1/B2 IIA IIB IIIA IIIB IVA IVB

From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 525.

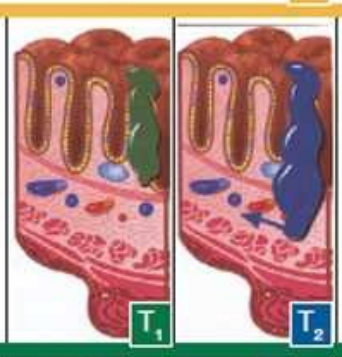
TNM Classification: Colon Cancer

DEFINITION OF TNM

T1
Tumor invades submucosa

T2
Tumor invades muscularis propria

N0
No regional lymph node metastasis



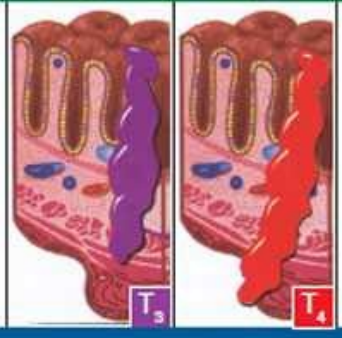
STAGE GROUPINGS

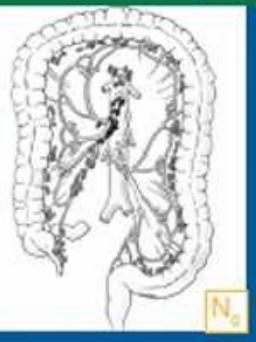
Stage I
T1 N0 M0
T2 N0 M0

T3
Tumor invades through the muscularis propria into pericolorectal tissues

T4
Tumor directly invades other organs or structures, and/or perforates visceral peritoneum

N0
No regional lymph node metastasis





Stage IIA
T3 N0 M0

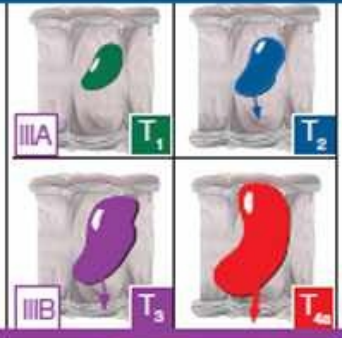
Stage IIB
T4a N0 M0

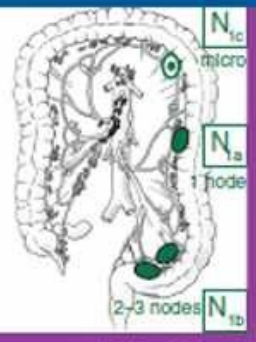
Stage IIC
*T4b N0 M0

*not shown

T4a
Tumor penetrates to the surface of the visceral peritoneum**

N1a
Metastasis in 1 regional lymph node
N1b
Metastasis in 2–3 regional lymph nodes
N1c
Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis





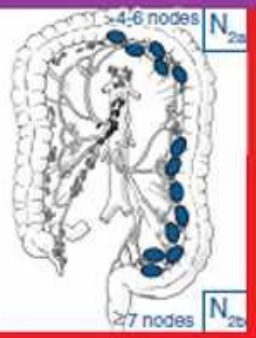
Stage IIIA
T1–T2 N1–N1c M0
T1 N2a M0

Stage IIIB
T3–T4a N1 N1c M0
*T2 T3 N2a M0
*T1 T2 N2b M0

*not shown

T4b
Tumor directly invades or is adherent to other organs or structures **,***

N2
Metastasis in 4 or more regional lymph nodes
N2a
Metastasis in 4–6 regional lymph nodes
N2b
Metastasis in 7 or more regional lymph nodes



Stage IIIC
T4a N2a
T3–T4a N2b
T4b N1–N2

M1
Distant metastasis
M1a
Metastasis confined to 1 organ or site (eg, liver, lung, ovary, nonregional node)
M1b
Metastases in more than 1 organ/site or the peritoneum

Stage IVA
Any T Any N M1a

Stage IVB
Any T Any N M1b

**Note: Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (eg, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).
***Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1–4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

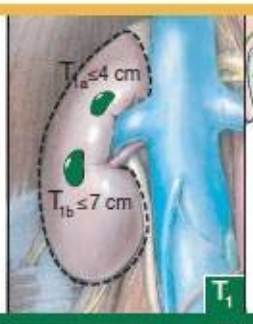
From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 327.

TNM Classification: Kidney Cancer

DEFINITION OF TNM

T1
Tumor ≤7 cm in greatest dimension, limited to the kidney
(T1a) Tumor ≤4 cm in greatest dimension, limited to the kidney
(T1b) Tumor >4 cm but not >7 cm in greatest dimension, limited to the kidney

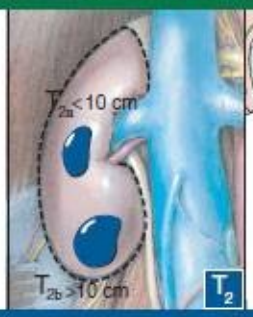
N0
No regional lymph node metastasis



I

T2
Tumor >7 cm in greatest dimension, limited to the kidney
(T2a) Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
(T2b) Tumor >10 cm, limited to the kidney

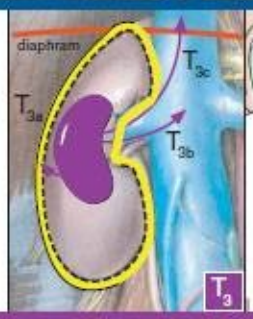
N0
No regional lymph node metastasis

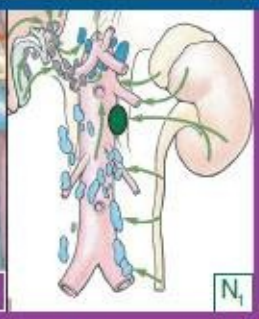


II

T3
Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
(T3a) Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
(T3b) Tumor grossly extends into the vena cava below the diaphragm
(T3c) Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

N1
Metastasis in a single regional lymph node

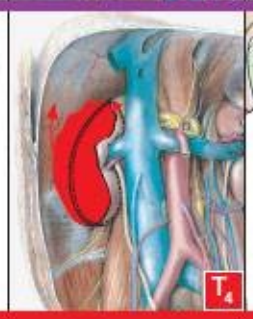


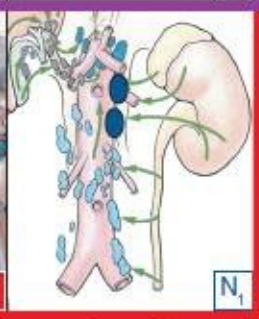


III

T4
Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

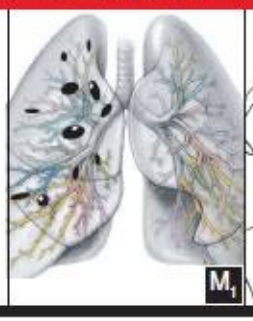
M0
No distant metastasis

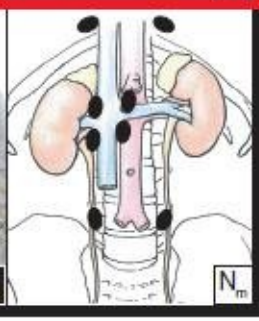




IV

M1
Distant metastasis





IV

STAGE GROUPINGS

Stage I
T1 N0 M0

Stage II
T2 N0 M0

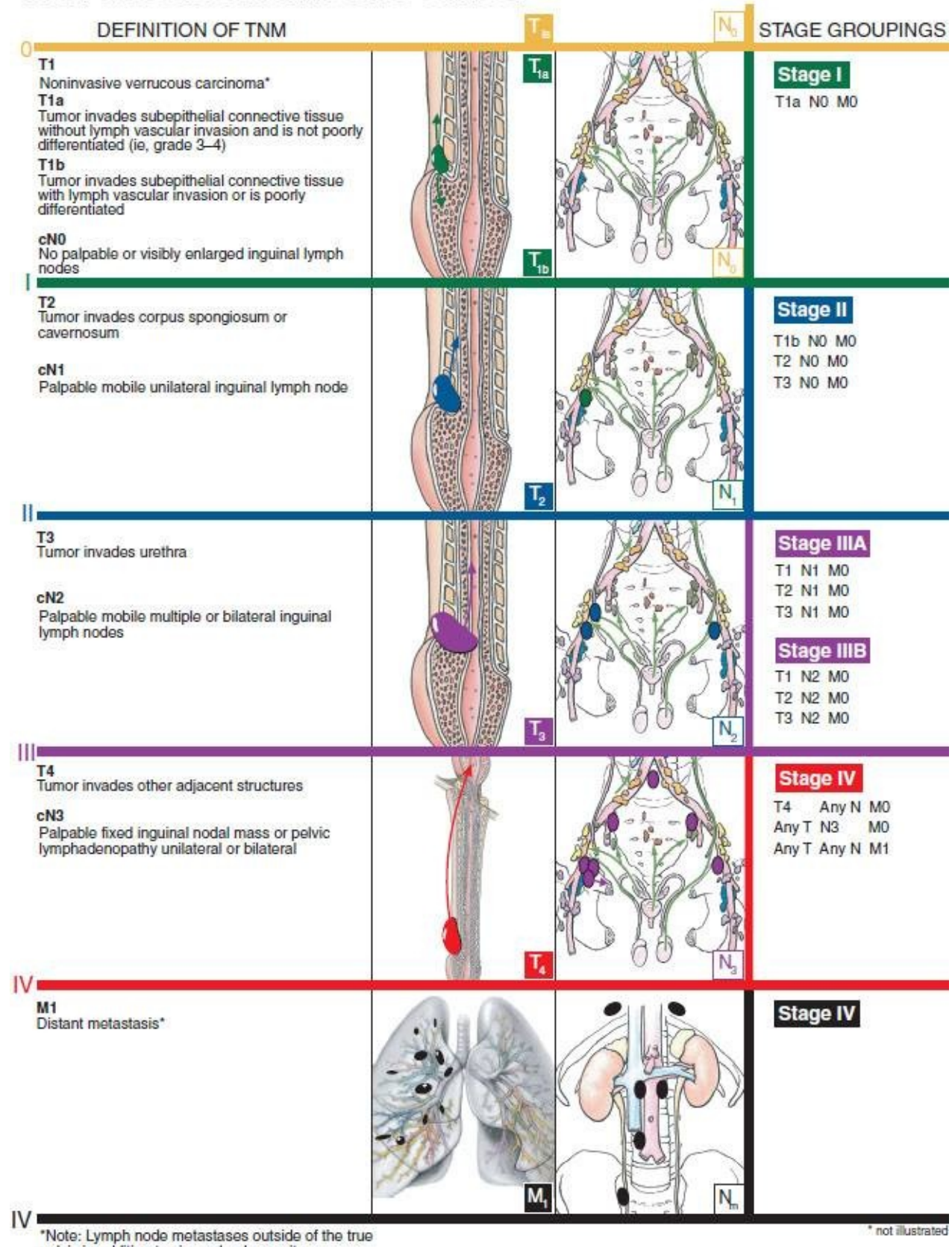
Stage III
T1 or T2 N1 M0*
T3 N0 or N1 M0*

Stage IV
T4 Any N M0*
Any T Any N M1

* not illustrated

From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 393.

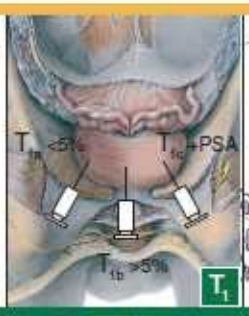
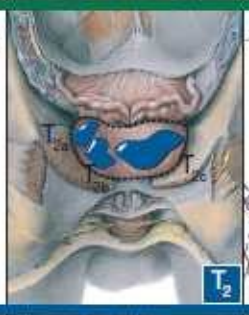
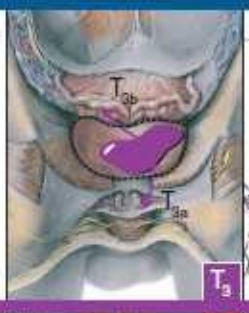
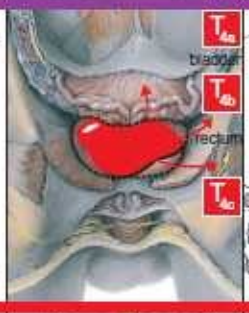
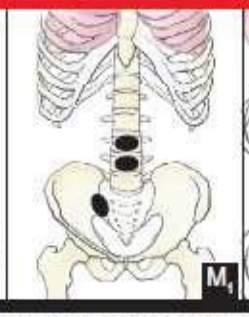
TNM Classification: Penis Cancer



From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 437.

TNM Classification: Prostate Cancer

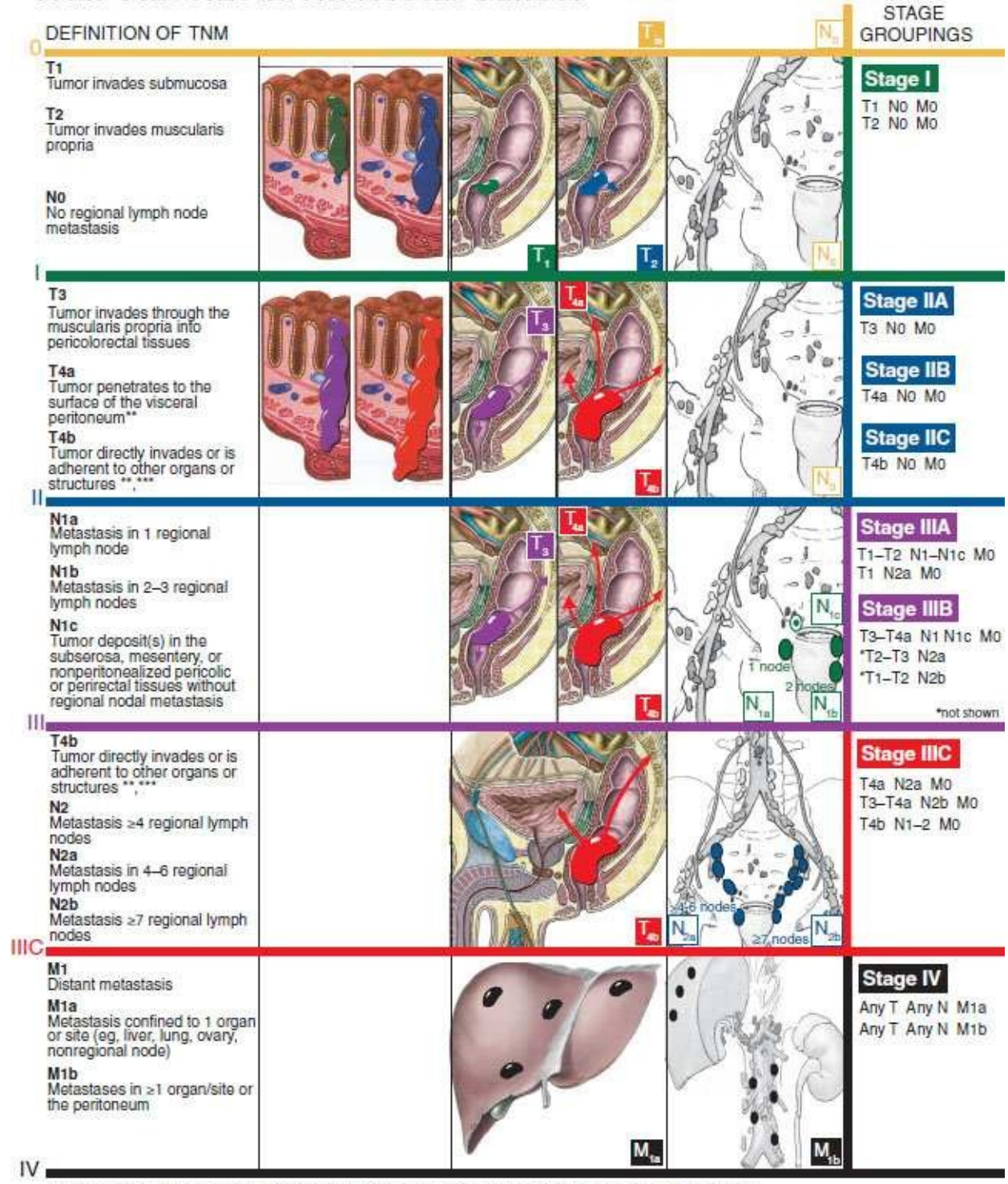
Note: Prostate cancer can be staged clinically (eg: cT1b) or pathologically (eg: pT2b). Pathologic and clinical staging are similar except that there is no pathological T1 stage.

DEFINITION OF TNM	PSA		GLEASON	STAGE GROUPINGS
T1 Clinically inapparent tumor neither palpable nor visible by imaging (T1a) Tumor incidental histologic finding in 5% or less of tissue resected (T1b) Tumor incidental histologic finding in more than 5% of tissue resected (T1c) Tumor identified by needle biopsy (eg, because of elevated PSA) **N0** No regional lymph node metastasis **G1** - Well differentiated (Gleason 2–4)	<10			**Stage I** T1a–c N0 M0 G1 T2a N0 M0 G1 T1–2a N0 M0 GX
T2 Tumor confined within prostate* (T2a) Tumor involves one-half of one lobe or less (T2b) Tumor involves more than one-half of one lobe but not both lobes (T2c) Tumor involves both lobes **G2** Moderately differentiated (moderate anaplasia Gleason 5–6) **G3–4** Poorly differentiated/undifferentiated (marked anaplasia Gleason 7–10)	<20			**Stage IIA** T1a N0 M0 G2, 3–4 T1b N0 M0 Any G T1c N0 M0 Any G T2a N0 M0 Any G T2b N0 M0 Any G **Stage IIB** T2c N0 M0 Any G T1-2 N0 M0 Any G
T3 Tumor extends through the prostate capsule** (T3a) Extracapsular extension (unilateral or bilateral) (T3b) Tumor invades seminal vesicle(s) **N0** No regional lymph node metastasis	>20			**Stage III** T3 N0 M0 Any G
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall **N0** No regional lymph node metastasis **N1** Metastasis in regional lymph node(s) **M0** No distant metastasis	any			**Stage IV** T4 N0 M0 Any G Any T N1 M0 Any G Any T Any N M1 Any G
M1 Distant metastasis (M1a) Nonregional lymph node(s) (M1b) Bone(s) (M1c) Other site(s) with or without bone disease *Note: when more than 1 site of metastasis is present, the most advanced category is used. pM1c is most advanced.	any			**Stage IV**

*Note: Tumor found in 1 or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 425.

TNM Classification: Rectal Cancer

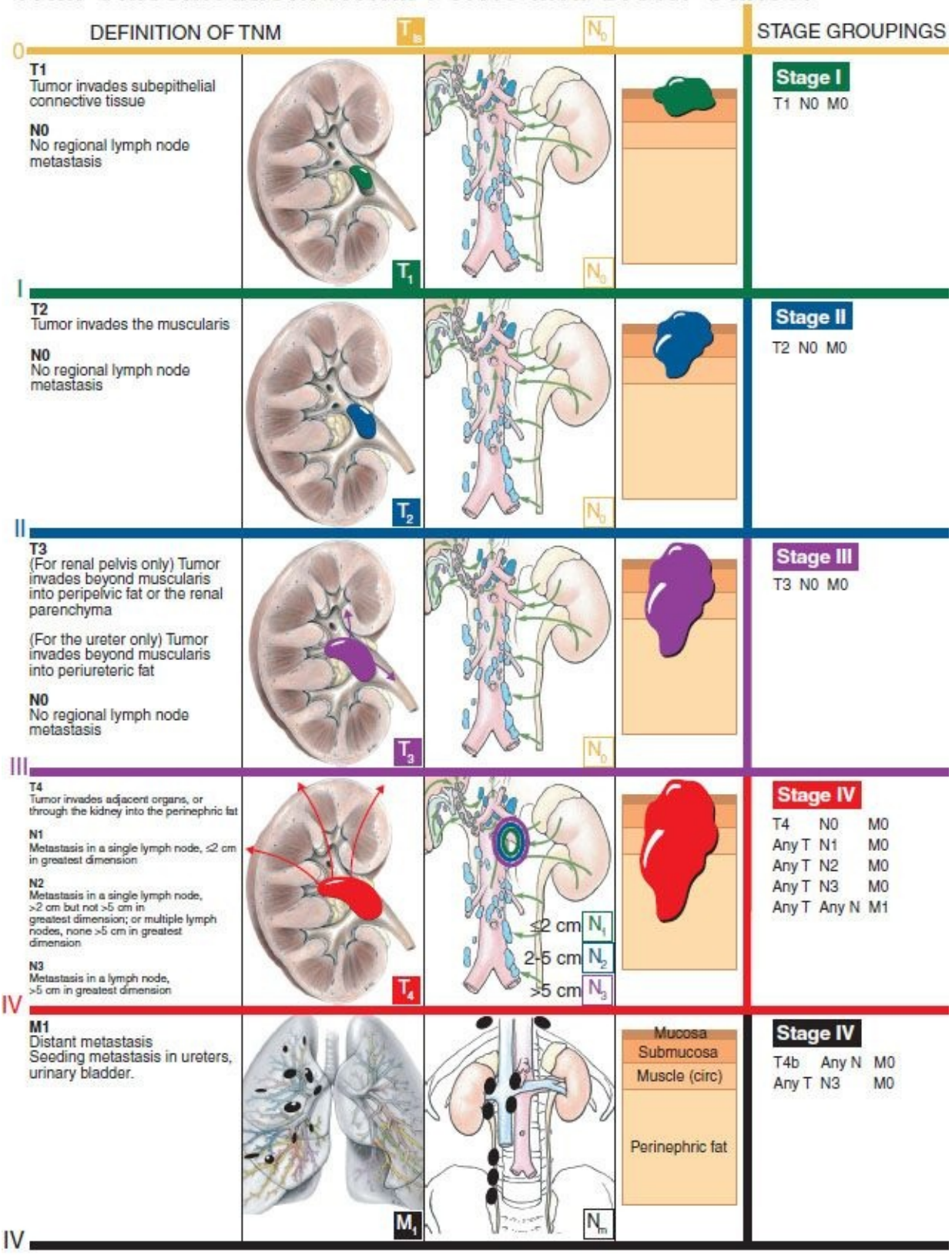


**Note: Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (ie, respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

***Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1–4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.

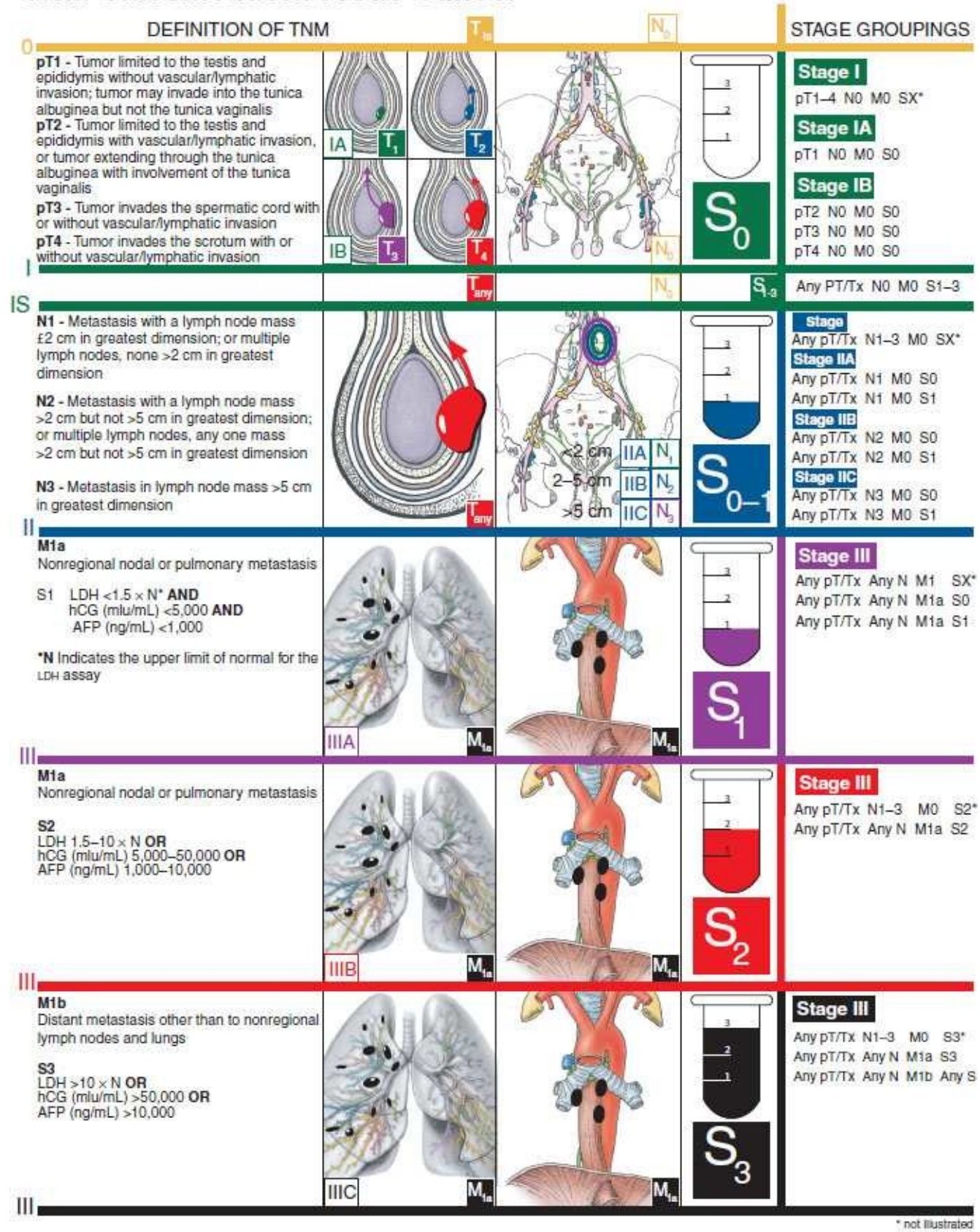
From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 355.

TNM Classification: Renal Pelvis and Ureter Cancer



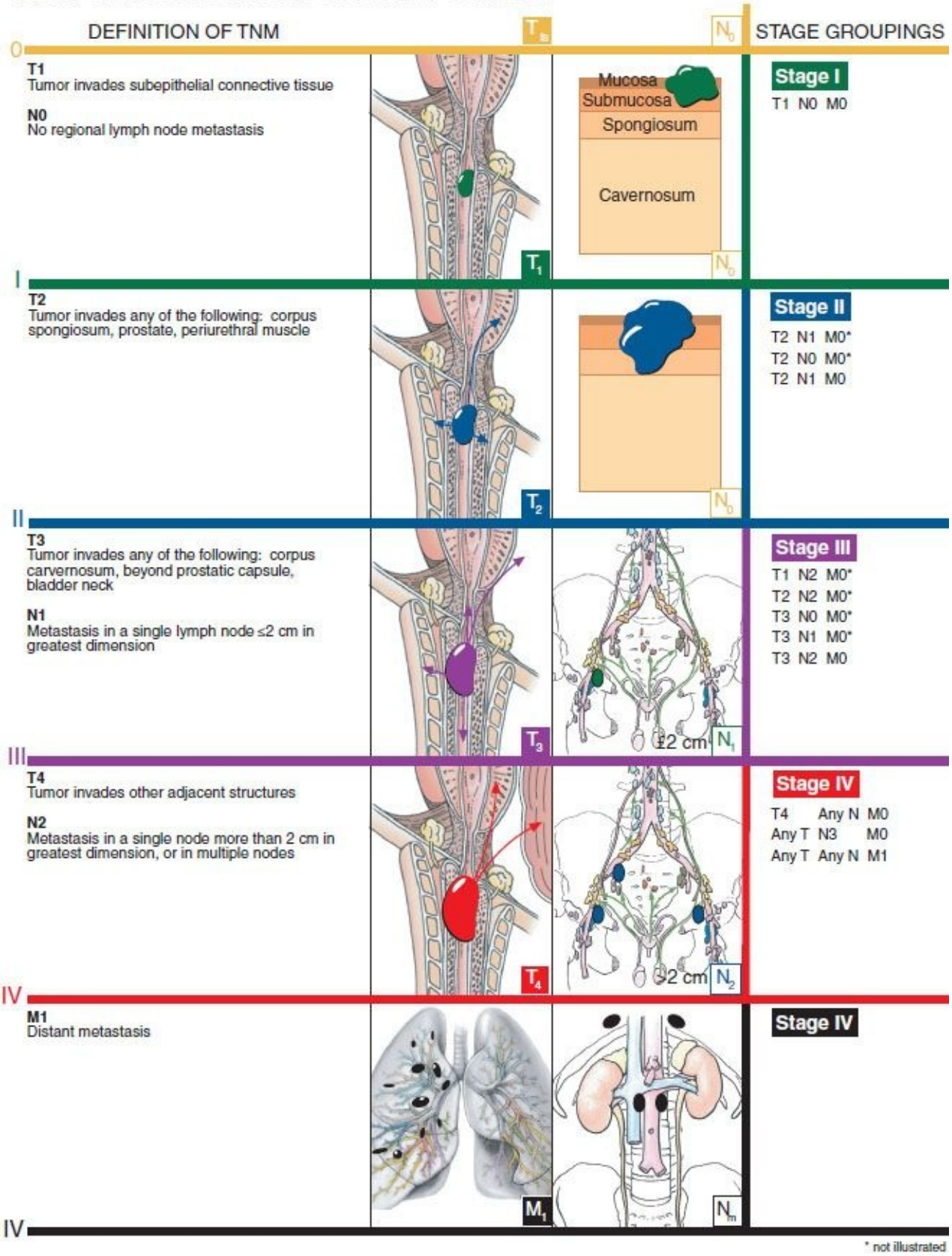
From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 405.

TNM Classification: Testis Cancer



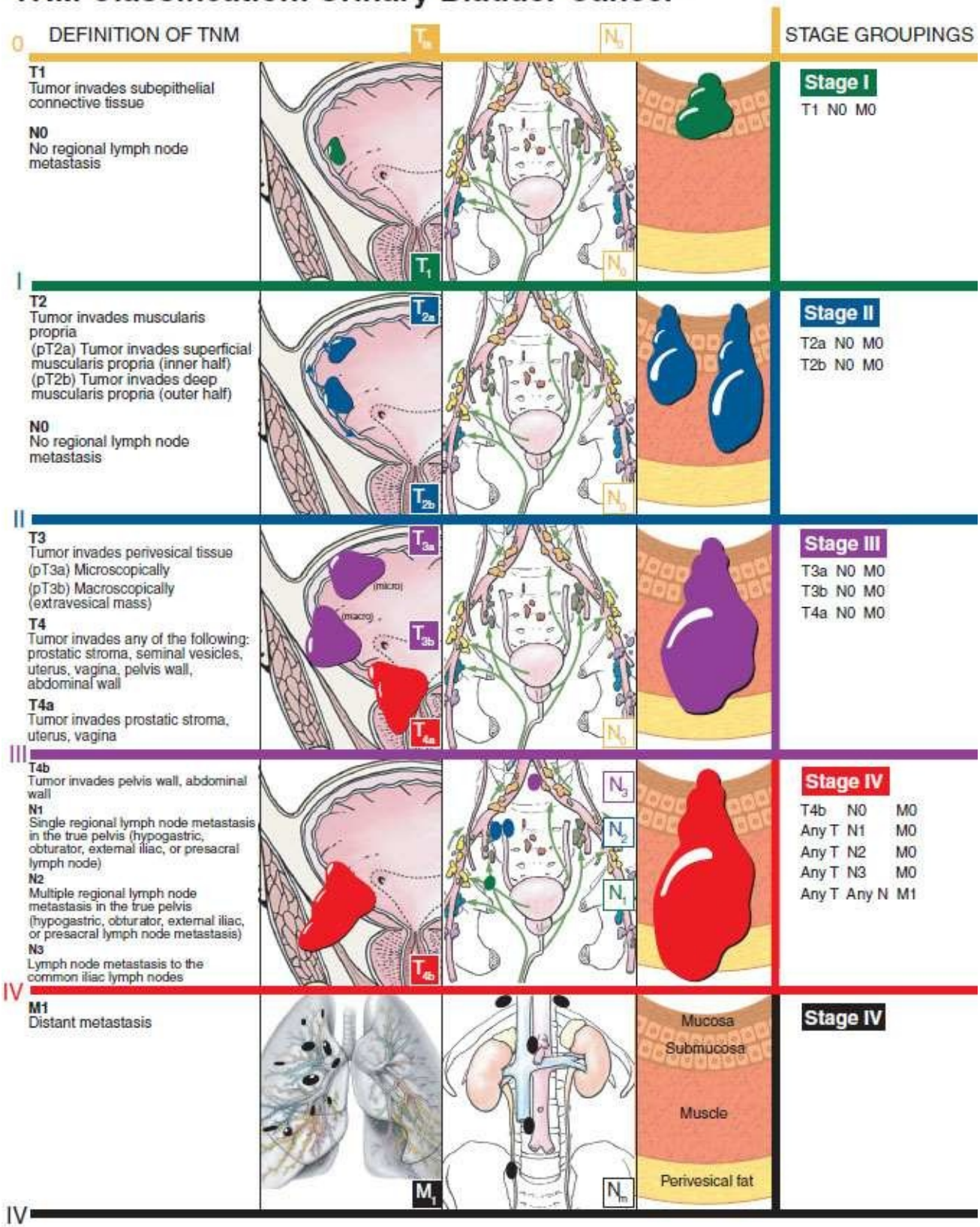
From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 457.

TNM Classification: Urethral Cancer



From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 447.

TNM Classification: Urinary Bladder Cancer



From Rubin P, Hansen JT, eds. *TNM Staging Atlas with Oncoanatomy*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012, 415.

URORADIOLOGY SIGNS (See also Section II: "Uroradiology Signs")

Sign (Typical Modality)	Description	Diagnosis
Arterial cut-off sign (CT or MR w/contrast)	Abrupt termination of contrast material within the renal artery	Renal artery obstruction from thrombosis, embolus or dissection from trauma
Ball-on-Tee, Lobster Claw, signet ring (XR, retrograde urography)	Patterns of renal papillary excavation; signet ring occurs when the necrotic papillary tip remains in the pelvis and then it is filled with contrast material (acts as the "stone" for the ring)	Papillary necrosis (nonsteroidal anti-inflammatory drugs [NSAIDs], sickle cell anemia, analgesic nephropathy, Infection-TB, and diabetes mellitus)
Balloon on a string (XR)	High exit point of ureter from a dilated renal pelvis (can be seen with hydronephrotic rim sign, crescent sign, or on its own)	Ureteropelvic junction obstruction
Bear's paw (CT)	Dilated multiloculated appearing renal calyces with contracted renal pelvis (in setting of obstructing stone)	Diffuse xanthogranulomatous pyelonephritis
Bullet on a Bodkin (XR, CT)	Encasement of the ureter; dilated ureter (the bullet) on top of the smaller encased ureter (the bodkin)	Metastatic disease, extension from an adjacent tumor, lymphoma, or retroperitoneal fibrosis
Cobra head sign (XR)	Dilatation of the distal ureter that is surrounded by a thin lucent line	Orthotopic ureteroceles
Cobweb (CT)	Exaggerated appearance of perirenal septa	Multiple disease processes but commonly seen in acute ureteral obstruction from stones
Coiled catheter sign (XR)	Related to goblet sign: Dilated ureteral segment provides a space for catheter to coil within	Urothelial carcinoma
Comet sign (CT)	Focal density with adjacent, tapering, noncalcified "tail"	Phlebolith
Concentric ring sign—aka Target sign (MR, best T1 weighted)	Rings of hyper and hypointensity within a hematoma (inner bright ring signifies hemoglobin degradation)	Renal hematoma present for greater than 3 wk
Corkscrew ureter (XR)	Healing stages of tuberculosis involving the ureter	Late ureteral tuberculosis
Crescent sign (CT w/contrast)	Concentrated contrast material in collecting tubules, parallel to a dilated calyx	Prolonged, incomplete obstruction of collecting system. (Typically indicates that renal function is still recoverable upon relief of the obstruction)
Dromedary hump (any modality)	A pseudomass appearing in the left kidney, that is drained by a normal collecting system element	Normal variant of kidney is molded by the adjacent spleen creating a protrusion that can be mistakenly identified as a mass
Drooping lily sign (XR)	Dilated upper moiety ureter in a duplicated system that places downward and/or lateral pressure on the functional lower moiety	Completely duplicated system with an obstructed upper moiety

Angio, angiography; CT, computed tomography; MR, magnetic resonance imaging; XR, plain x-ray; IVP or retrograde pyelogram.

Sign (Typical Modality)	Description	Diagnosis
Faceless kidney (any modality)	Normal renal parenchyma, lacking central renal sinus structures (duplicated system) OR any edema that eliminates the typical appearance of the kidney	Renal duplication (slice in between duplicated systems); edema obliterating normal kidney appearance can signify any inflammatory condition or infiltrative condition such as lymphoma or renal cell carcinoma
Fragmented staghorn (XR)	Disrupted densities following the outline of the renal pelvis; usually associated with renal enlargement	Pyonephrosis or Xanthogranulomatous pyelonephritis
Goblet sign (Retrograde XR)	Ureteral dilatation below an intraluminal filling defect; usually a chronic process	Urothelial cell carcinoma; less likely metastatic disease or endometriosis
Growing calculus sign (XR)	Apparent enlargement of medullary calcifications contained in ectatic tubules pre- and postcontrast administration	Medullary nephrocalcinosis caused by medullary sponge kidney
Horseshoe	Kidneys joined by a lower pole isthmus that crosses anterior to the aorta, just inferior to the Inferior mesenteric artery	Most common congenital fusion abnormality of the kidney (Horseshoe kidney)
Hydronephrotic rim sign (CT or MR w/contrast)	Variable enhancement of residual but atrophic renal parenchyma surrounding dilated renal pelvis and calyces (inner margin of rim is concave toward hilum, can also have enhancement of cortical columns)	Chronic hydronephrosis
Keyhole sign (US)	Thick bladder wall and dilated posterior urethra	Posterior urethral valves
Kidney sweat (US, CT, MR)	Extracapsular hypoechoic rim of fluid around kidney (perirenal edema)	Renal failure
Loop-to-loop colon	Transverse colon extends lateral to abdominal wall, descending colon then courses medially to fill renal fossa creating a loop of colon	Renal agenesis
Lying down (pancake) adrenal gland	Typical shape of adrenal gland is dependent on kidney; when kidney absent, the adrenal gland (when present) can assume a flattened appearance	Renal agenesis
Maiden waist deformity (XR)	Medial deviation of bilateral ureters; ureters are drawn toward each other in the lumbosacral region	Retroperitoneal fibrosis
Mulberry (XR)	Density in the urinary system with less developed spikes (mamillated appearance)	Calcium oxalate dihydrate stone
Pear sign (XR, CT)	Symmetric compression of the bladder	Pelvic fluid (hematoma, lymphocele, urinoma, abscess), pelvic lipomatosis, vascular dilatation from aneurysms or collateral vessels, lymph node enlargement or psoas hypertrophy
Phantom calyx sign (XR)	No identifiable collecting system element where one should be seen	Inflammation (tuberculosis, acute pyelonephritis), neoplasm, stricture from trauma and/or stone passage, ischemia, congenital anomaly, renal contusion or technical error of underfilling

Angio, angiography; CT, computed tomography; MR, magnetic resonance imaging; XR, plain x-ray; IVP or retrograde pyelogram.

Sign (Typical Modality)	Description	Diagnosis
Pie-in-the-sky sign (XR)	High position of contrast opacified bladder in pelvis	Pelvic hematoma from pelvic trauma; high suspicion of urethral injury
Pipestem ureter	Ureter is straight and rigid	Ureteral tuberculosis
Putty kidney	Calcifications outlining the entire, or close to the entire kidney	Genitourinary tuberculosis (end-stage finding in kidney)
Reverse rim sign (CT or MR w/contrast)	Hypoattenuating renal cortex with medullary enhancement	Disruption of cortical blood flow with development of cortical necrosis. Can be caused by shock, intravascular hemolysis, toxins, and rejection in transplanted kidney
Rim sign of vascular compromise (CT or MR w/contrast)	Rim of subcapsular enhancement	Renal artery obstruction from thrombosis, embolus or dissection from trauma (most commonly). Renal vein thrombosis and acute tubular necrosis (less commonly)
Sawtooth ureter	Dilatation and ragged irregularity of the ureter	Early ureteral tuberculosis
Soft-tissue rim sign (CT)	Focal density with surrounding edema of ureteral wall	Ureteral stone; usually impacted; may be absent with stones >4 mm or when at UVJ. Can help distinguish stone from phlebolith as it is uncommon for phlebolith to have soft tissue rim
Spaghetti sign (XR, CT)	Linear filling defect within the bladder	Gross hematuria; this sign implies blood has come from above the bladder (ureter acts as a mold for the blood clot)
Spoked wheel pattern (US, CT, MR)	Peripheral "rim" vessel branching into centripetal "spoke" vessels within a mass; can have a central area of decreased perfusion (central scar)	Renal cell carcinoma; oncocytoma
Spotted nephrogram (CT or MR w/contrast, renal angio)	Patchy irregular enhancement of the renal parenchyma	Small vessel occlusion, caused by scleroderma, hypertensive nephrosclerosis, or periarteritis nodosa
Staghorn (XR)	Branching radiopaque densities following the outline of the renal pelvis	Renal calculus that fills the entire renal collecting system, forming a cast of the renal pelvis
Stipple sign (XR)	Contrast material trapped between the papillary projections of urothelial cell carcinoma	Urothelial cell carcinoma, best seen in large papillary bladder tumors
String of pearls (Angio)	Arteries with thickened ridges, alternating with wall thinning and aneurysm formation	Fibromuscular dysplasia
Thimble bladder	Thick wall of calcification in the bladder that reduces its capacity	Tuberculosis of the bladder
Threads and streaks sign (Angio, CT, MR)	Linear string/thread-like vessels supplying the intravascular tumor in the affected vasculature	Vascularized tumor thrombus extending into the renal vein or IVC
Toy jacks (XR)	Spiked density in the urinary system	Calcium oxalate dihydrate stone
Tramline or railroad track calcifications	Thin rims of dystrophic calcifications on both sides of renal cortex	Renal cortical necrosis (most commonly). Glomerulonephritis, hyperoxaluria, Alport syndrome (less common)

Angio, angiography; CT, computed tomography; MR, magnetic resonance imaging; XR, plain x-ray; IVP or retrograde pyelogram.

Based on select data from Dyer RB, Chen MY, Zagoria RJ. Classic signs in uroradiology. *Radiographics.* 2004;24:S247–S280.

Voiding Diary

(See also Section II: "Voiding Diary (Frequency Volume Chart (FVC])." This form is meant to be completed by the patient.)

This voiding diary records your amount of fluid intake, amount you void and if there is any leakage of urine. It should be completed for an entire 24-hr period. For the most useful results, it should be done over 2 or 3 separate 24-hr periods. You must measure and complete this form every time you void or experience urinary leakage. Please bring these voiding diary records to your next Urology office visit. Copy additional pages if needed.

How to complete this form:

1. Begin the record with your first morning void after you wake up for the day.
2. Measure all fluid intake and the amount voided in mL or ounces. Ladies can measure the amount of urine by placing a plastic bowl or collection container that we can provide to you on the toilet seat. Men can void into a suitable collection jar or other container.
3. If you experience sudden leakage of urine, note the activity you were doing at the time of leakage (laughing, coughing, sneezing, lifting, etc.).
4. If you experience urinary leakage, use the following scale to estimate the amount of urine that you leaked:

    1 = Dampness
    2 = Wet underwear or pad
    3 = Soaked through or emptied bladder

5. Indicate by **Yes/No** if when you leaked you had an urge to void. FVC

Your Name: ______________________________ **Date:** ____________________________

Your Physician's Name: ____

Time (AM or PM)	**Fluid Intake** (Type and amount in ounces or mL)	**Amount Voided** (In ounces or mL)	**Leak Volume** (See above for estimate)	**Did you have an urge with leakage?** (Yes/No)	**Physical activity at time of leakage**

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