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PREFACE

This all-new second edition of *Manual of Family Practice* is intended to provide fast, reliable answers to everyday clinical questions concerning the most common problems in primary care, presented from the family physician perspective. The book's content continues to emphasize ambulatory care, plus pertinent hospital and home-based health problems. The authors stress new clinical methods and other information that the practicing physician might not already know. Topics include frequently encountered diagnostic challenges such as jaundice and chest pain, management of common disorders such as fibromyalgia and heart failure, and selected procedures such as obstetric ultrasound and no-scalpel vasectomy. Throughout the book, there is attention to evidence-based health care, as well as to disease prevention and health maintenance. The reader will find specific management strategies used by experienced family physicians; cross-references to related topics in other chapters; and selected institutions, books, and web sites where the reader might seek further information.

New chapter topics in the second edition include “Valvular Heart Disease,” “Sexual Assault,” and “Cerebral Concussion.” There is also a new section on Therapeutic Choices, which has new chapters on “Pain Management” and “Herbal Medicine.” To assure a family practice viewpoint, the primary authors of all chapters are family physicians.

The book's chapter topics are selected with attention to the Program Requirements for Residency Training in Family Practice of the Accreditation Council on Graduate Medical Education (ACGME), as well as practice patterns of United States family physicians (American Academy of Family Physicians. *Facts about Family Practice*. Kansas City, Missouri; http://www.aafp.org/). In addition to serving as a handy practice reference, the book should prove useful when preparing for family practice certification and recertification examinations.

I am grateful to the 206 contributing authors and to the following persons who participated in development of and preparation of the manuscript: Coelleda O'Neil and Lily Cha of the Oregon Health Sciences University Department of Family Medicine, as well as Executive Editor Richard Winters, Senior Developmental Editor Michelle LaPlante, and Production Editor Robert Pancotti at Lippincott Williams & Wilkins.

I hope that you, the clinician, find this a useful, quick-reference guide to the current practice of family medicine and that this will be *the* book you consult when you need quick, current information during a busy practice day.

NORMAL LABORATORY VALUES/ADULT PATIENTS

NORMAL LABORATORY VALUES / ADULT PATIENTS

CLINICAL CHEMISTRY TESTS

Alanine aminotransferase (ALT, SGPT)	0 - 35 U/L
Albumin	3.6 - 5.2 gm/dL
Alkaline phosphatase	35 - 120 U/L
Amylase, serum	44 - 128 units/L
Aspartate aminotransferase (AST, SGOT)	0 - 35 U/L
Bicarbonate	18 - 23 mEq/L
Bilirubin, total	0.2 - 1.2 mg/dL
Calcium	8.5 - 10.5 mg/dL
Carbon dioxide (CO_2), total	23 - 30 mEq/L
Chloride	98 - 109 mEq/L
Creatinine	0.7 - 1.2 mg/dL
Creatine kinase (CK, CPK)	30 - 130 units/L
Gamma glutamyltransferase (GGT)	5 - 40 U/L
Glucose, fasting	65 - 110 mg/dL
Hemoglobin A1C	5.0 - 7.0 % of total Hb
Iron binding capacity, total (TIBC)	270 - 390 µg/dL
Iron, serum	50 - 170 µg/dL
Lactate, serum (venous)	5.0 - 20.0 mg/dL
Lactate dehydrogenase (LDH)	20 - 200 units/L
Lipase	10 - 140 units/L
Magnesium	1.5 - 2.5 mg/dL
Potassium	3.5 - 5.1 mEq/L
Prostate-specific antigen	0 - 4 ng/mL
Protein, total	6.1 - 7.9 gm/dL
Sodium	136 - 147 mEq/L
Troponin I	<2.5 ng/mL
Troponin T	<0.2 ng/mL
Urea nitrogen	6.0 - 23.0 mg/dL
Uric acid	2.6 - 7.2 mg/dL

LIPID PANEL

Cholesterol, total	160 - 240 mg/dL
Triglycerides	55 - 200 mg/dL
HDL cholesterol	> 40 mg/dL
LDL cholesterol	< 130 mg/dL

THYROID FUNCTION TESTS

Triiodothyronine (T_3) resin uptake (T_3 RU)	25% - 45%
Triiodothyronine (T_3)	70 - 200 ng/dL
Thyroxine (T_4), total	4.0 - 12.0 µg/dL
Thyroxine (T_4), free	0.8 - 2.4 ng/dL
Thyroid stimulating hormone (TSH)	2 - 11 µU/mL

NORMAL LABORATORY VALUES / ADULT PATIENTS

HEMATOLOGY and COAGULATION TESTS

White cell count	3.4 - 10.0 K/cu mm
Red cell (RBC) count	3.80 - 5.20 M/cu mm
Hemoglobin	12.2 - 15.0 gm/dL
Hematocrit	37.0 - 52.0 %
Mean corpuscular volume (MCV)	85.0 - 95.0 fL
Mean corpuscular hemoglobin (MCH)	29.0 - 32.0 pg/cell
MCH concentration (MCHC)	32.6 - 36.0 gm/dL
Red cell distribution width (RDW)	11.5 - 15.0 %
Platelet count	150.0 - 420.0 K/cu mm
Reticulocyte count	0.5 - 1.5 % of RBCs
Neutrophils	38 - 70 %
Lymphocytes	16 - 49 %
Atypical lymphocytes	0 - 8 %
Monocytes	2 - 9 %
Eosinophils	0 - 5 %
Basophils	0 - 2 %
Sedimentation rate	
Adult male	≤ 20 mm/h
Adult female	≤ 30 mm/h
Fibrinogen	200 - 400 mg/dL
Partial thromboplastin time (PTT)	60 - 85 seconds
Activated PTT	25 - 35 seconds
Prothrombin time (PT)	11 - 14 seconds

NOTE: The reference intervals shown are for adults and may vary according to technique or laboratory, or as new methods are introduced. Always consult the reference range for your own laboratory.

Figure. Normal Laboratory Values

Contents

I. DISEASE PREVENTION AND HEALTH SCREENING

1.1
HEALTH MAINTENANCE FOR INFANTS AND CHILDREN

Bruce W. Goldberg

Health maintenance visits provide the physician an excellent opportunity to practice preventive medicine and establish an ongoing relationship with the child and his or her family. At each visit, the child should be evaluated for early disease processes and developmental and behavioral problems. In addition, the appropriate screening tests, immunizations, anticipatory guidance, and counseling must be provided.

I. History and physical examination

A. History.

The initial history should be complete and include information regarding family history, social history, living environment, birth history, allergies, medications, and complete medical history, including injuries, dietary history, growth and development, behavioral problems, and a review of systems. Subsequent historical information should be guided by anticipated problems and circumstances for the age.

B. Physical examination.

The physical examination should be complete, with particular attention to those aspects appropriate for the child's age.

C. Developmental assessment.

A child's developmental level should be assessed at each visit. The Denver Developmental Screening Test is a widely used assessment tool. Table 1.1-1 includes a listing of some developmental highlights that can be used for a more rapid and informal developmental screening.

Age	Developmental milestones
2 wk	Lifts head prone Follows to midline Responds to noise
2 mo	Smiles responsively Follows past midline Lifts head 45 degrees
4 mo	Grasps rattle Rolls over one way Laughs Squeals
6 mo	Sits briefly without support Reaches for objects Smiles spontaneously
9 mo	Transfers object from one hand to another Stands holding on Plays peek-a-boo Feeds self a cracker
1 yr	Stands momentarily Walks holding on to furniture Says mama, dada (now specific) Thumb-finger grasp
15 mo	Stands alone Walks alone Drinks from a cup Says three words other than mama, dada
18 mo	Mimics household chores (sweeping) Makes tower of two or three cubes Indicates wants
2 yr	Points to body parts Scribbles Handles a spoon well Says two-word sentences Kicks a ball

[a] Seventy-five percent to 90% of children should have attained these by the age indicated.

Table 1.1-1. Developmental milestone[a]

II. Screening.

See Table 1.1-2 for a summary of the screening recommendations outlined below.

Test/Examination	Screening recommendation
Blood pressure	Age 3 and every 1–2 yr thereafter
Hearing	Subjective assessment at all visits, pure-tone audiometry at 4 yr
Vision	Red reflex and corneal light reflex during first week of life and at 6 mo; visual activity and cover–uncover at 3 yr and 5–6 yr
Anemia	Age 9 mo and consider repeat at 3–4 yr
Tuberculosis	No routine screening; annually in high-risk populations
Lead	Blood testing at 1 yr and again at 2 yr of age; screen with questionnaire at 6 mo to 6 yr
Cholesterol	No routine screening; screen high-risk children after age 2 yr
Urinalysis	Consider screening urinalysis in preschool children

Table 1.1-2. Recommended childhood prevention screening

A. Growth.

Measuring growth and following its progression over time can help identify significant childhood conditions. Height, weight, and head circumference should be measured at birth, at 2–4 weeks, and at 2, 4, 6, 9, 12, 15, 18, and 24 months of age. Height and weight should be measured at ages 3, 4, 5, 6, and every 2 years thereafter.

B. Newborn screening.

Every state has its own regulations and, as such, clinicians should be familiar with their own state's guidelines and screen accordingly. At a minimum, all infants should be screened for congenital hypothyroidism and phenylketonuria (PKU) within the first week of life. Infants screened for PKU earlier than 24 hours after birth should be screened again before the second week of life. Screening for hemoglobinopathies, such as sickle cell disease and thalassemia, should be done for those in high-risk groups.

C. Blood pressure.

Blood pressure should be measured beginning at 3 years of age and every 1–2 years thereafter during routine office visits. Hypertension in children is defined as persistent blood pressure elevation at or above the 95th percentile according to gender and age (1).

D. Hearing.

Most speech and language development occurs between birth and age 3 years. Early detection of hearing impairment is therefore important. A subjective assessment of hearing, including checking for a response to noise produced outside an infant's field of vision, noting an absence of babbling at 6 months of age, assessing speech development, and inquiring about parental concerns, should be performed repeatedly, especially during the first year of life. There is no clear consensus among authorities regarding the routine use of pure-tone audiometry for screening in normal-risk children, but it is reasonable to consider such screening (using earphones) once, at age 4 years. Hand-held audiometers are of unproved effectiveness in screening children.

E. Vision.

All children should be screened for a red reflex and a symmetrical corneal light reflex during the first week of life and again at 6 months of age.

At age 3 years, all children should have visual acuity testing with a wall chart and be tested for strabismus using the cover-uncover test. Visual acuity testing should be repeated at 5–6 years of age.

F. Anemia.

All children should be screened for anemia using either hemoglobin or hematocrit testing at approximately 9 months of age. The cut points for a diagnosis of anemia at this age are a hemoglobin below 11 g/dL or a hematocrit below 33.0% (2). Cut points should be adjusted upward for children who live at high altitudes. Clinicians may also consider repeat screening at age 3–4 years. Cut points for this age are a hemoglobin of 11.2 g/dL or a hematocrit of 34.0%.

G. Urinalysis.

There is no consensus on either the necessity or timing of screening urinalysis to detect hematuria, proteinuria, glucosuria, or occult infection. However, it may be clinically prudent to perform a screening urinalysis in preschool children. Midstream clean-catch specimens are best, and the use of a plastic bag applied to the perineum should be avoided.

H. Tuberculosis.

Annual tuberculosis (TB) testing is recommended for children in high-risk populations, such as those born abroad in high-prevalence countries; medically underserved, low-income populations; and individuals with medical conditions known to substantially increase the risk of TB. The Mantoux test (0.1 mL of purified protein derivative containing 5 tuberculin units injected intradermally) should be used. The test should be read in 48–72 hours by measuring the diameter of induration. A reaction is generally considered positive if either of the following is true:

- The diameter of induration is 5 mm or greater and there is known or suspected HIV infection, close contact with an individual who has infectious TB, or a chest radiograph likely to represent old, healed TB.
- The diameter of induration is 10 mm or greater in children younger than 4 years and those at high risk for TB.
- The diameter of induration is 15 mm or greater in low-risk children.

In general, bacille Calmette-Guérin-vaccinated individuals with positive Mantoux test results should be considered to have true infection (see Chapter 10.4).

I. Lead.

All children should be screened at age 12 months and, if the initial test result is less than 10 µg/dL and if resources allow, again at age 24 months. In addition, all children aged 6 months to 6 years should be assessed for risk of lead exposure using a structured questionnaire (see questions below). Any child for whom an answer to any of the questions is yes should be considered high risk and should have whole-blood lead level testing. Those with blood levels less than 10 µg/dL should be retested once a year until age 6 years.

Following are recommended questions for assessing lead exposure risk:

1. Does your child live in or regularly visit a house that was built before 1960 and has peeling or chipping paint?
2. Does your child live in or regularly visit a house built before 1960 with recent, ongoing, or planned renovation or remodeling?
3. Does your child have a brother or sister, housemate, or playmate being followed or treated for lead poisoning (blood lead levels greater than 15 µg/dL)?
4. Does your child live with an adult whose job or hobby involves exposure to lead? (Examples include stained glass work, furniture refinishing, and ceramics.)
5. Does your child live near an active lead smelter, battery recycling plant, or other industry likely to release lead?

J. Cholesterol.

Universal screening of children is not recommended. Children older than 2 years who have a parent with a total cholesterol level of 240 mg/ dL or greater should be screened with a random total cholesterol. A blood cholesterol less than 170 mg/dL is considered acceptable. Such children and their families should be provided with information on risk factor reduction, and cholesterol should be measured again within 5 years. A blood cholesterol greater than or equal to 200 mg/dL is considered high. Such children should have a lipoprotein analysis. Those children with a cholesterol between 170 and 199 mg/dL should be retested and the result averaged with the previous measurement. If the average is greater than 170 mg/dL, a lipoprotein analysis should be performed. If it is less than 170 mg/dL, the child should be tested again within 5 years (also see Chapter 17.4).

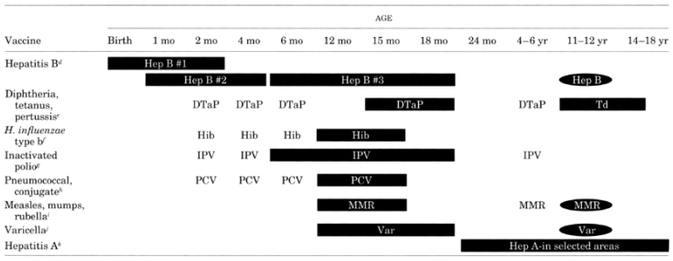
Children older than 2 years with a family history of premature cardiovascular disease in a parent or grandparent should be screened with a lipoprotein analysis. A lipoprotein analysis should be performed after children have ingested nothing but water for 12 hours. A low-density lipoprotein (LDL) cholesterol below 110 mg/dL is generally considered acceptable. Clinicians should refer to the National Cholesterol Education Program guidelines for full recommendations regarding follow-up of lipoprotein analysis in children (3).

K. Depression and suicide.

Routine screening for depression and suicide is not recommended, but clinicians should be attentive for symptoms of depression in children. Risk factors for depression in children include a history of verbal, physical, or sexual abuse; a history of parental depression; frequent separation from or loss of a loved one; and chronic illness (also see Chapter 5.2).

III Immunization.

The Advisory Committee on Immunization Practices (ACIP), the Committee on Infectious Diseases of the American Academy of Pediatrics, and representatives from the American Academy of Family Physicians have worked together to develop the recommended childhood immunization schedule shown in Table 1.1-3 .



DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; Hep A, hepatitis A; Hep B, hepatitis B; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine; MMR, measles, mumps, and rubella; PCV, pneumococcal vaccine; Td, tetanus and diphtheria toxoids; Var, varicella.

[a] Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

[b] Vaccines are listed under routinely recommended ages. Bars indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. Ovals indicate vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.

[c] This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines as of 11/1/00 for children through 18 yr of age. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

[d] *Infants born to HBsAg-negative mothers* should receive the first dose of hepatitis B (Hep B) vaccine by age 2 mo. The second dose should be at least 1 mo after the first dose. The third dose should be administered at least 4 mo after the first dose and at least 2 mo after the second dose, but not before 6 mo of age for infants. *Infants born to HBsAg-positive mothers* should receive hepatitis B vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 h of birth at separate sites. The second dose is recommended at 1–2 mo of age and the third dose at 6 mo of age. *Infants born to mothers whose HBsAg status is unknown* should receive hepatitis B vaccine within 12 h of birth. Maternal blood should be drawn at the time of delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than 1 wk of age). *All children and adolescents* who have not been immunized against hepatitis B should begin the series during any visit. Special efforts should be made to immunize children who were born in or whose parents were born in areas of the world with moderate or high endemicity of hepatitis B virus infection.

[e] The fourth dose of DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) may be administered as early as 12 mo of age, provided 6 mo have elapsed since the third dose and the child is unlikely to return at age 15–18 mo. Td (tetanus and diphtheria toxoids) is recommended at 11–12 yr of age if at least 5 yr have elapsed since the last dose of DTP, DTaP, or DT. Subsequent routine Td boosters are recommended every 10 yr.

[f] Three *H. influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB or Comvax [Merck]) is administered at 2 and 4 mo of age, a dose at 6 mo is not required. Because clinical studies in infants have demonstrated that using some combination products may induce a lower immune response to the Hib vaccine component, DTaP/Hib combination products should not be used for primary immunization in infants at 2, 4, or 6 mo of age, unless FDA-approved for these ages.

[g] An all-IPV schedule is recommended for routine childhood polio vaccination in the United States. All children should receive four doses of IPV at 2 mo, 4 mo, 6–18 mo, and 4–6 yr of age. Oral polio vaccine (OPV) should be used only in selected circumstances. (See *MMWR* 2000;49[RR-5]:1–22.)

[h] The heptavalent conjugate pneumococcal vaccine (PCV) is recommended for all children 2–23 mo of age. It also is recommended for certain children 24–59 mo of age. (See *MMWR* 2000;49[RR-9]:1–35.)

[i] The second dose of measles, mumps, and rubella (MMR) vaccine is recommended routinely at 4–5 yrs of age but may be administered during any visit, provided at least 4 wk have elapsed since receipt of the first dose and that both doses are administered beginning at or after 12 mo of age. Those who have not previously received the second dose should complete the schedule by the 11–12-yr-old visit.

[j] Varicella (Var) vaccine is recommended at any visit on or after the first birthday for susceptible children, i.e., those who lack a reliable history of chickenpox (as judged by a health care provider) and who have not been immunized. Susceptible children 13 yr of age or older should receive two doses, given at least 4 wk apart.

[k] Hepatitis A (Hep A) is shaded to indicate its recommended use in selected states and/or regions, and for certain high-risk groups; consult your local public health authority. (See *MMWR* 1999;48[RR-12]:1–37.)

[l] For additional information about the vaccines listed above, please visit the National Immunization Program Home page at http:/www.cdc.gov/nip/ or call the National Immunization Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Table 1.1-3. Recommended U.S. childhood immunization schedule, January-December 2001 *[a, b, c, l]*

A. Diphtheria, tetanus, and pertussis.

All children should be immunized against diphtheria, tetanus, and pertussis (DTP) at 2, 4, and 6 months of age. The fourth vaccine should be given at age 15–18 months but can be given anytime between 12 and 18 months, provided at least 6 months has passed since the third vaccination. The diphtheria, tetanus, and acellular pertussis (DTaP) vaccine is now recommended for the entire series. This vaccine contains an acellular pertussis preparation that has many fewer side effects than whole-cell pertussis preparations. If a child younger than 7 years has a contraindication to pertussis vaccine, DT should be used. The recommended dosage of DTaP and DT is 0.5 mL, given intramuscularly.

1. Contraindications to vaccination include encephalopathy within 7 days of administration of a previous DTP or DTaP; fever exceeding 40.5°C (104.9°F), collapse, or shock-like state within 48 hours of previous DTP or DTaP; seizures within 3 days of previous DTP or DTaP; and persistent, inconsolable crying lasting 3 hours or more within 48 hours of previous DTP or DTaP.
2. Adverse reactions. Redness, swelling, or pain at injection site, fever greater than 38°C (100.4°F), and mild drowsiness, anorexia, and vomiting are common.

B. Haemophilus influenzae type b.

All children should receive a primary series of *H. influenzae* type b (Hib) vaccine beginning at age 2 months. There are currently three types of conjugate vaccine licensed for infant use. Ideally, the same type of vaccine should be given throughout the entire primary series, although current recommendations do allow for some interchangeability (4). Hib vaccine is given intramuscularly.

1. **Contraindications.** Previous anaphylactic reaction to the vaccine is the only specific contraindication to use of the Hib vaccine.
2. **Adverse reactions.** Mild fever and pain, redness, or swelling at the injection site are possible side effects.

C. Hepatitis B.

All children should receive a complete series of hepatitis B immunizations during the first 18 months of life. Infants born to hepatitis B surface antigen-positive mothers should begin receiving these immunizations at birth. All older children and adolescents at high risk for hepatitis B infections should receive a complete series of immunizations.

1. **Contraindications.** History of an anaphylactic reaction to common baker's yeast and known serious adverse reaction to the vaccine are the only contraindications.
2. **Adverse reactions.** Pain at the injection site (3%–29%) and fever greater than 38°C (100.4°F) may occur in 1%–6% of children.

D. Measles, mumps, and rubella.

All children should receive a series of two measles-mumps-rubella (MMR) vaccinations. The first is given at age 12–15 months. The second vaccine should be administered at age 4–6 years. Those who have not received the second dose should complete the schedule no later than age 11–12 years. It is administered subcutaneously at a dose of 0.5 mL. MMR may be given simultaneously with other childhood immunizations but at a separate site.

1. **Contraindications.** Children with anaphylactic reactions to eggs and neomycin and those with immunodeficiency should not receive MMR vaccine. Pregnancy and receipt of immune globulin within the preceding 3–11 months are also contraindications.
2. **Adverse reactions.** Fever greater than 39.4°C (103°F) may develop 5–12 days after immunization and last up to 5 days. One percent of children may develop mild joint pain and stiffness and even arthritis 1–2 weeks after receiving the vaccine. A transient rash may occur in 5% of vaccinees, and some children may experience swollen cervical and posterior auricular lymph nodes 1–2 weeks after immunization.

E. Poliovirus.

To eliminate the risk for vaccine associated paralytic poliomyelitis, use of an all inactivated poliovirus vaccine (IPV) schedule is now recommended. All children should receive four doses of IPV at age 2 months, 4 months, 6–18 months, and 4–6 years.

1. **Contraindications.** IPV should not be administered to persons who have experienced a severe allergic (anaphylactic) reaction after a previous dose of IPV or to streptomycin, polymyxin B, or neomycin.

F. Varicella.

All children who have no history of varicella infection should be given the varicella zoster vaccine (VZV) at 12–18 months of age. Older children who have not been vaccinated and who lack a reliable history of chickenpox should be vaccinated by 13 years of age. VZV is administered as a single 0.5-mL subcutaneous dose.

1. **Contraindications.** VZV is a live attenuated preparation. Those who should not receive the vaccine include immunocompromised children, those receiving high-dose corticosteroids, individuals with a history of an anaphylactic reaction to neomycin or gelatin, pregnant women, and those with moderate or severe intercurrent illness. VZV should not be administered within 5 months of having received immune globulin or other blood products. VZV may be given to individuals who live in households with immunocompromised individuals. Vaccinees who develop a rash should avoid contact with immunocompromised individuals for the duration of the rash.
2. **Adverse reactions.** Approximately 25% of children experience tenderness and erythema at the injection site. A generalized maculopapular or vesicular rash 1 month after immunization may occur in 5%–8% of those receiving the vaccine. Transmission of the vaccine virus from healthy individuals who have been vaccinated to others is possible but has not been documented.

G. Hepatitis A.

Because of hepatitis A outbreaks, hepatitis A vaccine is recommended for use in selected high-risk locales and states. Local health officials or the U.S. Centers for Disease Control and Prevention (CDC) guidelines should be consulted to determine high-risk areas (5).

H. Pneumococcal disease.

7-Valent pneumococcal conjugate vaccine (Prevnar) is recommended for all children aged 2–23 months and for children aged 24–59 months who are at increased risk for pneumococcal disease (e.g., those with sickle cell disease, HIV infection, and other immunocompromised or chronic medical conditions). The vaccine is administered intramuscularly as a 0.5 mL dose. It can also be administered at the same time as other routine childhood vaccinations in a separate syringe at a separate injection site. The vaccine should be given at age 2 months, 4 months, and 6 months, followed by a fourth dose at age 12–15 months. Children aged 24–59 months with underlying medical conditions should receive 2 doses administered 2 months apart, followed by 1 dose of 23-valent pneumococcal conjugate vaccine administered at least 2 months after the second dose. 7-Valent pneumococcal conjugate vaccine should be considered in children aged 24–59 months with priority given to (a) children aged 24–35 months, (b) children who are of Alaska Native, American Indian, and African-American descent, and (c) children who attend group day care centers.

1. Contraindications. 7-Valent pneumococcal conjugate vaccine is contraindicated in persons known to have hypersensitivity to any component of the vaccine.
2. Adverse reactions. Fever greater than 100.4° F (38° C) and local induration, tenderness, and erythema at the injection site are common. Fever is the most common reaction and occurs in 15%–25% of recipients. The rate of fevers greater than 102.2° F (39° C) appears to increase after dose 2.

I. Combination vaccines.

New combination vaccines have been tested and may be licensed sometime during 2001. Combination vaccines represent one solution to the problem of increased numbers of injections during clinic visits. Package insert instructions and CDC recommendations (http://www.cdc.gov/) regarding appropriate use should be followed (4).

IV. Anticipatory guidance and counseling

A. Anticipatory guidance.

Providing anticipatory guidance and health education surrounding issues likely to be encountered at specific ages is a cornerstone of the pediatric health maintenance visit. Clinicians should be familiar with common parental questions and be prepared to provide counseling and advice about child development, child behavior, discipline, nutrition, and safety.

B. Dental and oral health.

Dental and oral health counseling should be provided routinely, with referral for a dental visit occurring at 2–3 years of age. Parents should be instructed to wipe their infant's gums and teeth after each feeding with a moist washcloth. Once multiple teeth have appeared, parents should brush their infant's teeth daily using a pea-sized amount of toothpaste. To prevent tooth decay, infants should not be permitted to nurse throughout the night or fall asleep with a bottle containing anything other than water. Infants should be encouraged to begin using a cup instead of a bottle at age 1 year.

Fluoride supplementation should be administered according to the following guidelines:

- Infants who are exclusively breast-fed and those who live in an area without adequately fluoridated water should receive fluoride supplementation beginning at age 2 weeks and continuing until approximately age 16 years.
- Children who live in an area where the local water supply contains less than 0.3 part per million (ppm) of fluoride should receive 0.25 mg fluoride daily until age 3 years, 0.5 mg fluoride daily from 3 years to 6 years, and 1.00 mg daily from 6 years to 16 years.
- Children who live in an area where the local water supply contains 0.3–0.6 ppm of fluoride require no supplementation until age 3. From age 3 to 6 years, they should receive 0.25 mg fluoride daily, and from age 6 to 16 years, they should receive 0.50 mg daily.
- No fluoride supplementation is required for children living in areas with more than 0.6 ppm of fluoride in the local water supply.

C. Safety.

Age-specific safety counseling should be provided routinely. Among the safety issues to be addressed are the following:

- Sudden infant death syndrome: A sleeping infant should be positioned on his or her back and should not sleep prone.
- Always use an appropriate car safety seat for infants and small children.
- Older children should use seat belts.
- Use stair and window gates to prevent falls.
- Keep objects that can cause suffocation and choking away from small children.
- Avoid scald burns by reducing the water temperature of hot water heaters to below 120°F.
- Keep medicines and other dangerous substances locked up and in child-resistant containers.
- Always ensure that children wear safety helmets when riding bicycles.
- Smoke alarms should be installed and maintained in the home.
- Encourage parents not to keep a firearm in the home. If a gun is kept in the home, it should be stored unloaded and locked away, separately from ammunition.

References

1. Rosner B, Prineas RJ, Loggie JMH, et al. Blood pressure nomograms for children and adolescents by height, sex, and age, in the United States. *J Pediatrics* 1993;123: 871–886.

2. CDC criteria for anemia in children and childbearing aged women. *MMWR* 1989; 8:400.

3. *Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.* Bethesda, MD: National Institutes of Health. USDHHS Publication No. NIH 91-2732, 1991.

4. Combination vaccines for childhood immunization. *MMWR* 1999;48:1–15.

5. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 1999;48:1–37.

1.2
HEALTH MAINTENANCE FOR ADOLESCENTS

Norman J. Montalto

I. Background.

The delivery of health care to adolescents (11–21 years old) is a challenge that can be met through an organized, coordinated approach that includes health risk assessments, health guidance, prevention, and acute and chronic health care service delivery. Many preventive interventions provide teens with positive benefits immediately and may continue as the teens mature into adults. Four causes of death result in 72% of deaths among 10- to 24-year-olds: motor vehicle accidents (31%), homicide (18%), suicide (12%), and unintentional injuries, such as those associated with falls, fires, and drownings (11%). Among adults (≥25 years old), two thirds of mortality is attributable to just two causes: cardiovascular disease (42%) and cancer (24%). Therefore, the U.S. Centers for Disease Control and Prevention (CDC) suggests that six behaviors that are initiated in adolescence are interrelated and impact on the causes of both teen and adult morbidity and mortality. These behaviors include (a) acts that result in unintentional and intentional injuries; (b) use of alcohol and other drug or substance use; (c) sexual behaviors; (d) tobacco use; (e) unhealthy dietary patterns; and physical inactivity (1). By focusing on these six behavioral (lifestyle) areas,

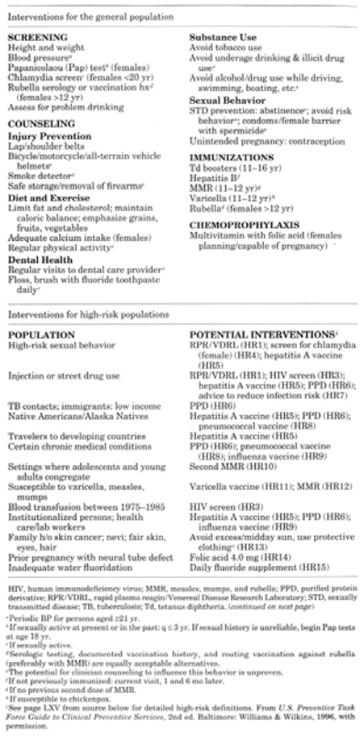
health care providers who deliver care to teens can encourage healthy behaviors that may reduce premature death and disability into adulthood.

This chapter reviews the suggested preventive health care guidelines for 11- to 20-year-olds, primarily based on the Guidelines for Adolescent Preventive Services (GAPS) (2) and Bright Futures: Guidelines for Health Supervision of Infants, Children, an Adolescents (3) (see Table 1.2-1). The GAPS recommendations provide 24 specific recommendations to clinicians divided into delivery of health services (3), screening history and physical assessments (13), health guidance (7), and immunizations for 11- to 21-year-old patients (1). Bright Futures is unique because it provides very detailed suggestions for encouraging dialogue among parent and teen and physician and teen. Specific questions for interviewing parents, assessing social and emotional development, family functioning, school performance, and community interaction, provide a broad basis for evaluation.

1. U.S. Department of Health and Human Services. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services*, 2nd ed. Baltimore: Williams & Wilkins, 1996:17. (See Table 1.2-2.) See *http://text.nlm.nih.gov/*. Accessed August 16, 2000.
2. American Academy of Family Physicians. *Age Charts for Periodic Health Examinations*. Kansas City: American Academy of Family Physicians, 1994. See *http://www.aafp.org/exam/*. Accessed August 1, 2000.
3. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. Recommendations for pediatric preventive health care. *Pediatrics* 1995;967:373–374. *http://www.aap.org/policy/RE9939.html*. Accessed August 16, 2000.
4. The American Medical Association (AMA). *Guidelines for Adolescent Health Services (GAPS)*. Chicago, 1992. Available at: *http://www.ama-asn.org/adolhlth/recommend/monogrf1.htm*. Accessed June 6, 2000.
5. National Center for Education in Maternal and Child Health. *Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents*. Arlington, VA, 1994. See *http://www.brightfutures.org*. Accessed June 8, 2000.

Table 1.2-1. Organizations offering recommendations for office-based interventions for the care of teens

Used together, these guidelines equip the clinician with the structure to organize and deliver preventive care to teens. Table 1.2-1 provides additional references for adolescent preventive services. The U.S. Preventive Services Task Force (USPSTF) may provide the most evidence-based suggestions (Table 1.2-2). Lack of outcomes-based research may partly explain why each organization's recommendations differ slightly (4). These guidelines are available online (Table 1.2-1). Obtaining a hard copy of these recommendations is strongly encouraged.



Interventions for the general population

SCREENING
Height and weight
Blood pressure[a]
Papanicolaou (Pap) test[b] (females)
Chlamydia screen[c] (females <20 yr)
Rubella serology or vaccination hx[d] (females >12 yr)
Assess for problem drinking

COUNSELING
Injury Prevention
Lap/shoulder belts
Bicycle/motorcycle/all-terrain vehicle helmets[e]
Smoke detector[e]
Safe storage/removal of firearms[e]
Diet and Exercise
Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables
Adequate calcium intake (females)
Regular physical activity[e]
Dental Health
Regular visits to dental care provider[e]
Floss, brush with fluoride toothpaste daily[e]

Substance Use
Avoid tobacco use
Avoid underage drinking & illicit drug use[e]
Avoid alcohol/drug use while driving, swimming, boating, etc.[e]
Sexual Behavior
STD prevention: abstinence[e]; avoid risk behavior[e]; condoms/female barrier with spermicide[e]
Unintended pregnancy: contraception

IMMUNIZATIONS
Td boosters (11–16 yr)
Hepatitis B[f]
MMR (11–12 yr)[g]
Varicella (11–12 yr)[h]
Rubella[d] (females >12 yr)

CHEMOPROPHYLAXIS
Multivitamin with folic acid (females planning/capable of pregnancy)

Interventions for high-risk populations

POPULATION	POTENTIAL INTERVENTIONS[i]
High-risk sexual behavior	RPR/VDRL (HR1); screen for chlamydia (female) (HR4); hepatitis A vaccine (HR5)
Injection or street drug use	RPR/VDRL (HR1); HIV screen (HR3); hepatitis A vaccine (HR5); PPD (HR6); advice to reduce infection risk (HR7)
TB contacts; immigrants: low income	PPD (HR6)
Native Americans/Alaska Natives	Hepatitis A vaccine (HR5); PPD (HR6); pneumococcal vaccine (HR8)
Travelers to developing countries	Hepatitis A vaccine (HR5)
Certain chronic medical conditions	PPD (HR6); pneumococcal vaccine (HR8); influenza vaccine (HR9)
Settings where adolescents and young adults congregate	Second MMR (HR10)
Susceptible to varicella, measles, mumps	Varicella vaccine (HR11); MMR (HR12)
Blood transfusion between 1975–1985	HIV screen (HR3)
Institutionalized persons; health care/lab workers	Hepatitis A vaccine (HR5); PPD (HR6); influenza vaccine (HR9)
Family h/o skin cancer; nevi; fair skin, eyes, hair	Avoid excess/midday sun, use protective clothing[e] (HR13)
Prior pregnancy with neural tube defect	Folic acid 4.0 mg (HR14)
Inadequate water fluoridation	Daily fluoride supplement (HR15)

HIV, human immunodeficiency virus; MMR, measles, mumps, and rubella; PPD, purified protein derivative; RPR/VDRL, rapid plasma reagin/Venereal Disease Research Laboratory; STD, sexually transmitted disease; TB, tuberculosis; Td, tetanus diphtheria. (*continued on next page*)

[a] Periodic BP for persons aged ≥21 yr.
[b] If sexually active at present or in the past: q ≤ 3 yr. If sexual history is unreliable, begin Pap tests at age 18 yr.
[c] If sexually active.
[d] Serologic testing, documented vaccination history, and routing vaccination against rubella (preferably with MMR) are equally acceptable alternatives.
[e] The potential for clinician counseling to influence this behavior is unproven.
[f] If not previously immunized: current visit, 1 and 6 mo later.
[g] If no previous second dose of MMR.
[h] If susceptible to chickenpox.
[i] See page LXV from source below for detailed high-risk definitions. From *U.S. Preventive Task Force Guide to Clinical Preventive Services*, 2nd ed. Baltimore: Williams & Wilkins, 1996, with permission.

Table 1.2-2. Interventions considered and recommended for the periodic health examination: ages 11–24 yr

II. Recommendations for health maintenance for adolescents

Recommendation 1. All adolescents aged 11–21 years should have an annual preventive services visit. GAPS recommends a yearly screening examination that at the minimum would include blood pressure, body mass index (or height and weight), and a complete physical examination once during each of the following ages: 11–14; 15–17; and 18–21. Other guidelines recommend a skin examination, teaching breast and testicular self-examining, and evaluation for dental hygiene. Evaluation for scoliosis should be

performed. For girls who are sexually active, a Pap smear should be obtained (see Table 1.2-2). For boys who are sexually active, a genital exam should be performed and tests for sexually transmitted diseases (STDs) carried out. The clinician should look for the development of breast buds by age 14 and testicular enlargement in boys by age 15. If these indexes of maturation are not present, further assessment may be required. GAPS, the American Academy of Pediatrics (AAP) and Bright Futures suggest an annual preventive service visit. The American Academy of Family Physicians (AAFP) and the USPSTF suggest that this type of visit be made every 1–3 years. A complete physical exam is recommended in the 11–14, 15–17, and 18–21 age ranges. **Recommendation 2.** Preventive services should be age and developmentally appropriate, and should incorporate sensitivity to individual and sociocultural differences. Careful attention to these variables, in addition to sex, race/ethnicity, and educational level, helps determine both risk and interventional strategies.

Recommendation 3. Physicians should establish office policies regarding confidential care for adolescents and how parents will be involved in that care. These policies should be made clear to adolescents and their parents. Adolescents are more likely to communicate with and seek health care from physicians who are perceived as honest and respectful and who assure confidentiality. Office policies regarding confidentiality should be established and made clear to adolescents and their parent(s)/caregiver. Teens must feel comfortable in disclosing concerns and asking questions without fear of judgment. Assure teens that you will not disclose sensitive information unless it may cause them or someone else harm. Written office policies regarding the confidential management of adolescent health concerns and the manner in which parents will be involved should be provided to both adolescent and guardian/parent(s) to ensure understanding of and agreement with management of teen health concerns. Encourage teens to discuss important issues with their parent(s)/caregiver/guardian if feasible.

Recommendation 4. Parents or other adult caregivers should receive health guidance at least once during their child's early adolescence, once during middle adolescence, and, preferably, once during late adolescence. Adolescent caregivers should be counseled regarding age-appropriate changes in attitude and behavior. Inform them of the need to educate and support teens about the six behaviors discussed previously. In addition, they should be given the opportunity to ask questions about their concerns.

Recommendation 5. All adolescents should receive health guidance annually to promote a better understanding of their physical growth, psychosocial and psychosexual development, and the importance of becoming actively involved in discussions regarding health care. Many teens have questions about their psychosocial and sexual development. Appropriate reassurance of a broad range of normal developmental responses may be comforting. Be open to questions and encourage dialogue.

Recommendation 6. All adolescents should receive health guidance annually to promote the reduction of injuries. One way to screen for the risks of unintentional and intentional injuries is by inquiring about what sports, hobbies, or recreational activities the teen participates in. Suggest that a helmet be worn when biking, rollerblading, skateboarding, skiing, snowboarding, or when BMX bikes, motorcycles, or all-terrain vehicles are used. Use of seat belts, at all times, should be stressed. Gun safety should be discussed for patients who have firearms in the home. Swimming and diving precautions should be mentioned. Discuss safe use of headsets to reduce hearing loss and sport-dependent use of other safety equipment, such as wrist protection or knee/elbow pads for skateboarding, snowboarding, rollerblading, and so forth. Suggest the use of reflective clothing at night.

Ask how safe the teen feels at home, at school, and in the neighborhood. Ask about weapons that the teen may be carrying and if he or she has been involved in fighting.

Recommendation 7. All adolescents should receive health guidance annually about dietary habits, including the benefits of a healthy diet as well as ways to achieve a healthy diet and safe weight management. Assess frequency of fast-food and/or high-fat snack food ingestion. Many fast-food habits and preferences will continue to cause intake of excess calories and fat that increase the risk of obesity, diabetes, and heart disease later in life. Lack of adequate

physical activity will complicate this. Provide information about healthy eating behaviors.

Recommendation 8. All adolescents should receive annual health guidance about the benefits of physical activity and should be encouraged to engage in safe physical activities on a regular basis. Frequency of aerobic activity should be evaluated and leisure time activity encouraged. Athletes who are overtraining, attempting to achieve a weight that seems unrealistic, or training when injured should be counseled (wrestlers, gymnasts, runners). Strength, cardiovascular endurance, and flexibility are important components of fitness.

Recommendation 9. All adolescents should receive health guidance annually regarding responsible sexual behaviors, including abstinence. Information on latex condoms to prevent STDs, including human immunodeficiency virus (HIV) infection, and appropriate methods of birth control should be made available, as should instructions on ways to use them effectively. Counsel that abstinence reduces the incidence of STDs, HIV, and pregnancy. For adolescents who are sexually active, suggest the use of birth control and condoms. Explore the teens' beliefs about what sexual activity means and encourage them to consider how pregnancy may impact their lives. More than half of female teenagers in the United States aged 15–19 years are sexually active, and teenage girls are becoming sexually active at an earlier age. Sexual activity increases with age.

Adolescent pregnancy rates in the United States are higher than in most other industrialized nations. Emergency contraception should be considered in selected cases (see Chapter 14.1).

Recommendation 10. All adolescents should receive health guidance annually to promote avoidance of tobacco, alcohol and other abusable substances, and anabolic steroids. Marijuana is the most common illicit drug used by children. Steroids are most commonly used by male adolescents who participate in contact sports and lift weights. Two school-based curricula are recommended by the CDC as effective in reducing tobacco use. They are project Towards No Tobacco Use (TNT) and Life Skills Training. They are available online at http://www2.edc.org/NTP/PTW/ptwtnt.html and http://www.lifeskillstraining.com/.

Recommendation 11. All adolescents should be screened annually for hypertension according to the protocol developed by the National Heart, Lung, and Blood Institute Second Task Force on Blood Pressure Control in Children. If systolic or diastolic blood pressure based on gender or age are ≥90th percentile, repeat blood pressures three times in the next 4 weeks. A value above 95% requires a complete evaluation and possible treatment.

Recommendation 12. Selected adolescents should be screened to determine their risks of developing hyperlipidemia and adult coronary heart disease, following the protocol developed by the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. This information can be reviewed at http://www.aap.org/policy/re9805.html.

Recommendation 13. All adolescents should be screened annually for eating disorders and obesity by determining weight and stature and asking about body image and dieting patterns. Explore concerns about body image, weight

control, and current eating and diet. Evaluate fat content, fast-food intake, snack foods, and fruit and vegetable intake. Body mass index (BMI) should be calculated using the formula: BMI = weight ÷ height^2 × 703 (ounces and fractions must be entered as decimal values). The latest tables for 2- to 20-year-olds can be accessed at www.cdc.gov/growthcharts. At-risk and overweight patients should be considered for weight management programs (see Recommendation 7, Recommendation 8, Recommendation 9 and Recommendation 10). If a patient is underweight, determine if an underlying eating disorder is present.

Recommendation 14. All adolescents should be asked annually about their use of tobacco products, including cigarettes (bidis*, kreteks†) and smokeless tobacco. Eighty percent of smokers become addicted to tobacco before the age of 18. Consequently, interventions should be aimed at stopping the progression of tobacco use (curiosity, experimentation, routine use, addiction). Prevention of tobacco use should be a high priority due to the association with heart disease, lung disease, cancer, and stroke. Adolescents at high risk for tobacco use include those with poor academic performance, a history of drug and alcohol use, low self-esteem, and friends and/or family members who use tobacco.

Recommendation 15. All adolescents should be asked annually about their use of alcohol and other abusable substances, and about their use of over-the-counter or prescription drugs for nonmedical purposes, including anabolic steroids. Marijuana is the most commonly used illicit drug. Ask about inhalant use. All adolescents should be asked about their use of over-the-counter herbal preparations for weight loss, weight gain, strength, or endurance. Alcohol or other substance abuse is associated with accidents, suicides, and homicides among youth. As adolescents mature, the likelihood that they will experiment with substances increases. High-risk youth may have been physically or mentally abused, have a dysfunctional family, or have a comorbid psychiatric illness. Parental drug use or permissive attitudes toward substance abuse also contribute to adolescent use of substances.

Recommendation 16. All adolescents should be asked annually about involvement in sexual behaviors that may result in unintended pregnancy and STDs, including HIV. Sexual behavior requires testing for STDs and pregnancy prevention counseling (see Recommendation 17 and Recommendation 18). Use of health departments for testing may protect the patient from getting a bill for services that may need to be kept confidential. For those who are not sexually active, suggest that delaying sexual activity until the age of 19 reduces morbidity from STDs, especially human papillomavirus (HPV).

Recommendation 17. Sexually active adolescents should be screened for STDs, including HIV. In comparison with other age groups, adolescents have the highest STD rate (primarily gonorrhea and chlamydia) and an increasing morbidity and mortality caused by HIV, cervical cancer secondary to genital warts (HPV infection), and infertility caused by pelvic inflammatory disease.

Recommendation 18. Adolescents at risk for HIV infection should be offered confidential HIV screening with enzyme-linked immunosorbent assay (ELISA) and a confirmatory test (see Recommendation 16).

Recommendation 19. Female adolescents who are sexually active or any woman 18 or older should be screened annually for cervical cancer by use of a Pap test. Sexually active adolescents should receive counseling to reduce STD and pregnancy risk, evaluation for STDs, and a Pap smear.

Recommendation 20. All adolescents should be asked annually about behaviors or emotions that indicate recurrent or severe depression or risk of suicide. The suicide rate for adolescents increases as they mature, and there may be some genetic predisposition to both depression and suicide. Points to consider when evaluating this may include multiple somatic complaints, new or increased substance abuse, reduced academic performance, friends who have committed suicide, and previous suicide attempts. Girls seem to have

greater frequency of suicide attempts, but boys seem to be more successful. Increased risk-taking behaviors, a focus on death, apathy, and exaggerated responses to life events may also indicate potential suicide risks. Be alert for anxiety disorders, depression, or attention-deficit/hyperactivity disorder (AD/ HD), which may be associated with tobacco, alcohol, or other drug use.

Recommendation 21. All adolescents should be asked annually about a history of emotional, physical, or sexual abuse. Assess remote or recent history of abuse that may be associated with substance use and psychiatric disorders. Clinicians should assess the safety of the teen in his or her environment and may need to notify protective service authorities.

Recommendation 22. All adolescents should be asked annually about learning or school problems. A dramatic or subtle change in school performance or attitude may indicate a need to assess for depression, drug use, learning disabilities, hearing or visual impairments, or AD/HD. Evaluate long-term ambition (school/work/sports) and the teen's plan to accomplish the goals. Explore behaviors that may be inconsistent with the stated goals.

Recommendation 23. Adolescents should receive a tuberculin skin test if they have been exposed to active tuberculosis, have lived in a homeless shelter, have been incarcerated, have lived in or spent time in an area with a high prevalence of tuberculosis, or currently work in a health care setting.

Recommendation 24. All adolescents should receive prophylactic immunizations according to the guidelines established by the federally convened Advisory Committee on Immunization Practices (ACIP). These recommendations change intermittently and can be accessed at the following website: www.cdc.gov/nip/. Clinicians should administer the recommended immunizations as scheduled. In addition, flu shots and pneumonia shots should be considered for high-risk teens (chronic cardiovascular, pulmonary, metabolic, immunocompromised conditions) or those employed in nursing home or health care settings, and those in contact with elderly or severely debilitated patients.

III. Summary.

Many national groups recommend similar services, indicating some degree of consensus on which preventive interventions should be provided to adolescents (5). Delivery of these services during annual, routine, or acute health care visits may be most effective and cost efficient, and helps encourage and reinforce clinician-teen communication, which creates opportunities for health screening, guidance, and early intervention. GAPS provides screening questionnaires that can be completed by both caregiver and teen while waiting to identify areas of concern for the clinician rapidly. Table 1.2-3 provides a mnemonic that may be helpful in recalling these recommendations for adolescents during a clinical encounter. Implementing adolescent preventive services in a clinical practice requires an organized, systematic approach for their delivery. The physician's goal is to identify and change high-risk behaviors and encourage healthy behaviors in addition to providing traditional care. Healthy habits adopted in adolescence may also reduce the primary causes of adult morbidity and mortality.

H	=	Home, habits, hobbies
E	=	Education, employment, exercise
A	=	Accidents, ambition, activities, abuse
D	=	Drugs (tobacco, alcohol, others), diet, depression
S	=	Sex, suicide

Adapted from Goldenring JM, Lohen E. Getting into adolescent heads. *Contemp Pediatr* 1988: 75–90, with permission.

Table 1.2-3. HEADS: a mnemonic useful in the evaluation of adolescent patients

References

1. U.S. Centers for Disease Control and Prevention. Youth risk behavior surveillance: United States, 1999. *MMWR* 2000;49(No. SS-5).

2. Elster A, Kuznets NJ. *American Medical Association Guidelines for Adolescent Preventive Services (GAPS): recommendations and rationale*. Baltimore: Williams & Wilkins, 1994.

3. Green M, Palfrey JS. *Bright futures: guidelines for health supervision of infants, children, and adolescents,* 2nd ed. Arlington, VA: National Center for Education in Maternal and Child Health, 2000.

4. Elster AB. Comparison of recommendations for adolescent clinical preventive services developed by national organizations. *Arch Pediatr Adolesc Med* 1998;152: 193–198.

5. Tenore JL, Lipsky MS. Preventive services for the adolescent (13–20 years). *Clin Fam Pract* 2000;2:289–311.

* Bidis are flavored (cherry, chocolate, etc.) tobacco wrapped in tendu or temburni leaf. Bidis produce higher levels of carbon monoxide, nicotine, and tar than cigarettes.

† Kreteks are clove-flavored cigarettes.

1.3
HEALTH MAINTENANCE FOR THE ADULT PATIENT

Evan W. Kligman

Frank A. Hale

Health maintenance is an integral component of the care and treatment of adult patients and one of the most important aspects of responsible health care by family physicians. Counseling and patient education activities, directed at asymptomatic healthy individuals, are as highly valued as the diagnosis and treatment of illnesses (1). The leading causes of death and disability among adults are largely related to personal health and lifestyle behaviors and may, therefore, be preventable through routine health maintenance interventions in the form of counseling, screening, immunization, and chemoprophylaxis. These interventions are best delivered as an integral component of the provider-patient contact longitudinally—whatever the chief complaint—rather than as periodic, annual, or comprehensive physical examinations.

The family physician's adult patients (defined here as persons aged 19–64) are assumed to be motivated to protect and improve their health status and capable of being responsible for the maintenance of their health. Adults are motivated by economic issues related to work and family care responsibilities as well as the need for independence and security for their future as retirees. In addition, there are important differences between young (ages 19–39) and middle (ages 40–64) adulthood with respect to risk factors and appropriate preventive interventions. As many provider-patient encounters occur only during times of illness or injury, the family physician must be prepared to be “opportunistic” and address health maintenance as a clinical issue whenever “teachable moments” arise, keeping in mind that, ultimately, patients must feel empowered to be responsible for their own health status.

Family physicians and other primary care providers should follow guidelines and customize interventions based on the patient's personal profile (e.g., age, gender, family history, and other indicators of high-risk status). They should also use efficient office systems to monitor and track the effectiveness of preventive interventions and to ensure compliance with recommendations. This chapter focuses on what to do and how to do it.

I Scientific basis for health maintenance

A. Minimum preventive interventions.

The recommendations in this chapter are based on the findings of two expert panels: the U.S. Preventive Services Task Force (1) and the Commission on Public Health and Scientific Affairs of the American Academy of Family Physicians (2). Recommendations listed in Table 1.3-1 cover minimal preventive interventions with widespread acceptability.

Intervention	Yrs of age: 19	25	30	35	40	45	50	55	60	64
SCREENING										
Blood pressure	Every 2 yr									
Height and weight	Periodically									
Cholesterol	Every 5 yr									
Mammography					Every 1–2 yr (women)					
Pap smear	Every 1–3 yr (women)									
Prostate-specific antigen							Yearly (men)			
Sigmoidoscopy							Every 3–5 yr			
Stool occult blood							Yearly			
Urinalysis										Periodically
Dental	Yearly									
Vision/glaucoma					Every 2–4 yr					
Breast	Every 1–4 yr						Yearly (women)			
Exams for cancer [thyroid, mouth, skin, lymph nodes, rectum (40+), prostate (men 50+)]	Every 3 yr						Yearly			
IMMUNIZATIONS										
Tetanus-diphtheria	Every 10 yr									
Pneumococcal										Once
Influenza	Annual if indicated									
COUNSELING										
Smoking, alcohol and drugs, sexual behavior, HIV exposure, nutrition, physical activity, violence and guns, family planning, injuries, occupational health	Periodically									
CHEMOPROPHYLAXIS										
Folate (women 12–45)										
Aspirin (men 40+)	Periodically									
Estrogen (women 45+)										

Table 1.3-1. Preventive interventions for patients ages 19–64

B. Actual causes of death ranked by risk factor

(3)

- Tobacco
- Diet and activity patterns
- Alcohol
- Microbial agents
- Toxic agents
- Firearms
- Sexual behavior
- Motor vehicles
- Illicit use of drugs

C. Ten leading causes of death in adults

(4). See Table 1.3-2 for leading causes of death.

Young adults (aged 19–39)	Middle adulthood (aged 40–64)
Motor vehicle crashes	Heart disease
Homicide	Lung cancer
Suicide	Cerebrovascular disease
Injuries (non–motor vehicle)	Breast cancer
Heart disease	Colorectal cancer
HIV infection (men)	Obstructive lung disease
	HIV infection (men)

Ten leading causes of death (all ages)	
1. Heart disease	31.0%
2. Malignant neoplasms	23.2%
3. Cerebrovascular diseases	6.8%
4. COPD	4.8%
5. Accidents	4.2%
6. Pneumonia and influenza	3.9%
7. Diabetes mellitus	2.8%
8. Suicide	1.3%
9. Renal disease	1.1%
10. Cirrhosis	1.1%

Table 1.3-2. Leading causes of death in adults

II. Counseling and patient education to promote healthy lifestyles

A. Definition.

Adult health maintenance programs should promote lifestyle change by explaining the links between risk factors and health status. Risk factor assessment and counseling with adult patients should help them acquire information, motivation, and skills to adopt and maintain healthy behaviors.

B. Recommended counseling topics

1. **Diet.** Nutritional assessment of intake of fat (saturated fats, polyunsaturated fatty acids [PUFAs], monounsaturated fatty acids [MUFAs]), cholesterol, complex carbohydrates, fiber, sodium, iron, and calcium (women) should be initiated. The Food Guide Pyramid and the Dietary Guidelines for Americans should be discussed: Eat a variety of foods; maintain a healthy weight; choose a diet low in saturated fat and cholesterol; choose a diet with plenty of vegetables, fruits, and grain products; use complex carbohydrates in moderation and limit intake of simple carbohydrates; use salt and sodium in moderation; and, if alcoholic beverages are used, use them in moderation (5). Calcium is especially important for women beginning in their teens decade to reduce the risk of osteoporosis and bone fracture. Average daily intake should be 1,000–1,500 mg. The adverse effect of carbonated drinks with phosphorus on calcium and bone growth should also be discussed. Vitamin (especially antioxidants) and mineral supplementation should also be discussed with patients. Scientific evidence

to date suggests that improving diet is more effective than supplementation alone (6).

2. **Exercise.** Patients should be given at least a brief exercise prescription, including selection of an exercise program to provide a source of regular physical activity. Such a program should be tailored to their health status and lifestyle, such as dynamic movement of large muscle groups for at least 20 minutes, 3 or more days per week, at an intensity of at least 60% of the maximum heart rate (220 beats per minute - age in years). Exercise at lower intensity and frequency levels can improve strength, flexibility, and cardiovascular fitness. Weight-bearing exercise is especially important for perimenopausal and postmenopausal women to avoid or decrease bone loss and osteoporosis (1).
3. **Substance use.** Include advice on cessation of tobacco use, limiting of alcohol consumption, health effects of other drugs, and not driving or doing other dangerous activities while under the influence of intoxicants (see Chapter 5.7). Smoking is the leading cause of preventable death in the United States. Studies have shown that multiple intervention strategies (one-to-one counseling, self-help materials, referral to community programs, prescription of nicotine substitutes) are most effective (7). The basics of smoking cessation counseling should include providing a smoke-free office and hospital, designating an office smoking cessation coordinator, asking patients at every opportunity whether they smoke and assessing their readiness to stop if they do, using chart stickers if the patient smokes as a way of cueing office staff for ongoing interventions, providing multiple interventions to assist the smoker to stop, and following up to support patients who are motivated to stop.
4. **Sexual practices.** Counseling efforts should focus on prevention of sexually transmitted diseases, including human immunodeficiency virus (HIV), and “safe-sex” recommendations: partner selection, condom use, and precautions regarding anal intercourse (see also Chapter 19.4). Clinicians should take a complete sexual and drug history (8). Sexually active adults should be advised that the most effective strategy to prevent infection is to abstain or maintain a mutually monogamous sexual relationship with an uninfected partner. Women of childbearing age need to be advised of the dangers of HIV and other sexually transmitted infections during pregnancy. Prevention of unintended pregnancy should also be discussed with individuals of childbearing age. Contraceptive options should be discussed with sexually active adults including information on efficacy limitations and proper use of available contraception techniques (see Chapter 14.1). Empathy and confidentiality are important aspects of this counseling.
5. **Injury prevention.** Minimum counseling efforts in this area should include use of safety belts and helmets, prevention of violent behavior, safe use and storage of firearms, use of smoke and carbon monoxide detectors, not smoking near bedding or upholstery, and performing back conditioning exercises to prevent back pain and injuries. Intentional injuries include suicide and violence. Patients should be questioned regarding their risk of suicide and violence, with directed interventions when indicators are present. Injury to women as a result of domestic violence is one of the nation's most widespread and least reported health problems.

   Unintentional injuries include motor vehicle-related injuries and environmental and household injuries. Advise patients never to drive while under the influence. To avoid other types of injuries, patients should be advised against alcohol, tobacco, or psychoactive drug use when participating in potentially dangerous activities; advised to check their smoke detectors regularly; and counseled to child-proof their homes and to prevent falls among elderly household members by securing loose throw rugs and electrical cords in pathways.

6. **Dental health.** Good personal oral hygiene, daily brushing and flossing, use of fluoride, and avoidance of sugary foods can control plaque and

gingivitis. Individuals with current or history of use of tobacco or heavy use of alcohol are at risk for oral-pharyngeal cancers and should be advised to get a thorough checkup every 3 years up to age 40 and annually thereafter. Individuals engaged in sports potentially leading to dental trauma should be encouraged to use mouth guards.

7. **Preconception counseling.** Counseling and risk assessment, in addition to emphasizing general health promotion (abstinence from alcohol, drugs, and tobacco products and lowering risk of sexually transmitted disease) can reduce risk of congenital malformations and low birth weight, markedly improving outcomes by reducing infant morbidity and mortality. Health maintenance evaluations of a couple considering conception can include determining their emotional readiness to have children, the availability of sufficient financial resources, the risk of occupational toxin exposure for either person, and the need for genetic counseling and possible genetic diagnostic interventions. Counseling to reduce exposure to infections (rubella, cytomegalovirus, hepatitis B, toxoplasmosis, herpes simplex virus, chlamydia, human papillomavirus, and other sexually transmitted diseases) is very important. Exposure history should also be elicited to determine reproductive risk (e.g., diethylstilbestrol [DES]), other teratogens) (9).

C.

Recommended counseling strategies include the following:

1. Develop a therapeutic alliance.
2. Counsel all patients.
3. Ensure that patients understand the relationship between behavior and health.
4. Jointly assess barriers to change.
5. Gain patient commitment to change.
6. Involve patients in selecting risk factors to change.
7. Be creative, flexible, and practical, and use a combination of strategies.
8. Design a behavior modification plan.
9. Monitor progress through follow-up contact.
10. Involve office staff (team approach).

III. Screening

A. Definition.

Screening of asymptomatic adults is an important component in adult health maintenance and can often be accomplished at any patient visit. Scientific evidence strongly supports the screening of all adults for cardiovascular risk factors (tobacco use, hypertension, hyperlipidemia, sedentary lifestyle, family history), women older than 40 for breast cancer, and all adult women for cervical and ovarian cancer. Screening for colorectal cancer is recommended for adults older than 40 years.

B. Criteria for screening.

Frame (10) developed criteria to consider when selecting a disease and test to use for screening:

1. The condition must have a significant effect on the quality and quantity of life.
2. Acceptable methods of treatment must be available.
3. The condition must have an asymptomatic period during which detection and treatment significantly reduce morbidity and mortality.
4. Treatment in the asymptomatic phase must yield a therapeutic result superior to that obtained by delaying treatment until symptoms appear.
5. Tests that are acceptable to patients must be available at a reasonable cost to detect the condition in the asymptomatic period.
6. The incidence of the condition must be sufficient to justify the cost of screening. Test sensitivity, specificity, and positive predictive value are important factors in the selection and evaluation of screening tests. Poor sensitivity or specificity can lead to a high rate of false-positive and false-negative results, both of which carry potentially serious consequences for patients.

C. Selected screening interventions

1. **Cancer screening** (1,11)
   a. **Breast cancer.** There is universal consensus to offer mammography every 1–2 years for women aged 40 to 50, and annually thereafter.

The American Cancer Society (ACS) recommends obtaining a baseline mammogram at age 35. There is no consensus at what age to stop screening. The U.S. Preventive Services Task Force (USPSTF) recommends routine screening until age 69, with continuing mammograms on an individual basis. Factors such as life expectancy, comorbidities, and general health are reasonable considerations for this and other screening tests. The ACS and the American College of Obstetricians and Gynecologists recommend that clinical breast examinations be started prior to age 40. These examinations should be performed annually after age 40. There is insufficient evidence to recommend for or against teaching breast self-examination (see Chapter 13.8).

b. **Colorectal cancer.** This is another important cause of cancer-related death in the United States (see Chapter 11.11). Colonoscopic screening should be directed to adults at higher than average risk. It is important to elicit family history to determine risk status. This should include history of colon cancer or adenomas and sporadic polyps in first-degree relatives, all now considered to be important predictors (12). Persons with a positive family history should receive a colonoscopy by age 50. However, a recent study suggests that colonoscopic screening can detect advanced neoplasms in asymptomatic adults that were not detected with sigmoidoscopy (13). To date, few insurers will cover colonoscopies for the asymptomatic individual without a family history, and fecal occult blood tests (FOBTs) remains the most cost-effective screening tool in people older than age 50. If the test result is positive, follow-up examination with colonoscopy or flexible sigmoidoscopy plus air contrast barium enema (ACBE) should be undertaken. People older than 50 years may also benefit from screening with flexible sigmoidoscopy every 3–5 years. With a history of colon polys, people should receive a colonoscopic screening every 5–10 years. The percentage of lesions detected by each method and the relative cost of the tests are estimated to be as shown in Table 1.3-3 .

Method	Lesions detected (%)	Relative cost ($)
Fecal occult-blood testing	20–50	5
Flexible sigmoidoscopy	40	100–200
Air contrast barium enema	66–92	200
Colonoscopy	95	300–500

Table 1.3-3. Percentage of colorectal cancer lesions detected by method and relative costs of tests

c. **Prostate cancer.** Prostate-specific antigen (PSA) for prostate cancer is not recommended by the USPSTF but is recommended by the ACS and most other expert panels. The benefits of PSA screening remain controversial, whereas the risks resulting from screening are quantifiable and substantial. Digital rectal examination is not recommended as a screen for prostate cancer. If PSA tests are obtained, age-specific reference ranges should be used to eliminate unnecessary biopsies in patients older than 60 years with elevations due to the normal aging process (14) (see Chapter 12.5).

d. **Cervical cancer screening.** Regular Pap testing is recommended for all women who are or have been sexually active and who have a cervix. Screening should begin with onset of sexual activity and be repeated at least every 3 years (see Chapter 13.4).

e. **Melanoma and other skin cancers.** Patients with a history of skin cancer should have a complete skin exam annually. All adults

with significant sun exposure and/or a prior history of sunburn(s) should also receive a complete skin exam periodically.

2. **Screening for coronary artery disease and hypercholesterolemia.** Blood pressure readings should be obtained at every office visit and at least once every 2 years. Total cholesterol should be measured periodically in men aged 35–65 and women aged 45–65; there is insufficient evidence to recommend for or against routine screening of younger men and women. Also, the appropriate frequency of and interval between screenings has not been established. However, after age 40, given the prevalence of cardiovascular disease, screening should occur at least every 5 years. Given the importance of lipid subfractions in therapeutic decisions, a fasting lipid profile should be obtained. All patients should be counseled about intake of dietary saturated fat and other measures to reduce coronary heart disease (CAD) (see Chapter 17.4). The most important risk factors for CAD to screen for remain smoking, diabetes, and hypertension as well as hypercholesterolemia. See Table 1.3-4 for the relative risk of various markers for coronary artery disease (15).

Marker	Relative risk
Depression (men)	1.71
Depression (women)	1.73
Homocysteine	2.0
LDL-cholesterol	2.4
Apolipoprotein B	3.4
Total cholesterol/HDL ratio	3.4
High sensitivity C-reactive protein	4.4
Hostility	2.56

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 1.3-4. Relative risk for coronary artery disease from various markers

3. It is important to have blood samples analyzed by an accredited laboratory. Abnormal results should be followed up by a second test, especially after 1–3 months of nonpharmacologic intervention (e.g., diet and exercise).
4. **Screening for osteoporosis.** Osteoporosis affects more than 25 million Americans, including 50% of women older than 45 years, and osteoporosis risk factors should be screened for in all women (see Chapter 17.6). Perimenopausal women at increased risk are Caucasian or Asian, have a history of bilateral oophorectomy before menopause, have a slender build, smoke or have smoked tobacco, have low calcium consumption patterns, a sedentary lifestyle, and a positive family history of the condition. There is insufficient evidence to recommend for or against routine bone density screening in asymptomatic men. After age 60, men also are at risk of osteoporosis, with at least 20% of the 10 million Americans with osteoporosis being men. Only 3% of women older than 50 with an osteoporotic fracture ever received bone density evaluation. Screening by bone density measurement should be considered for high-risk individuals and all individuals older than 64 when the decision to use pharmacologic agents is to be based on bone mineral density measurements.

D. Follow-up of screened patients is an important adult health maintenance strategy.

The single most important factor predicting whether cancer screening is obtained in the office setting may be the incorporation of a routine health maintenance visit in the practice regime (16). Screening results must be evaluated and incorporated into the patient record. This information is necessary to identify individuals for needed follow-up testing. Accuracy in testing and reporting of results is an important consideration. Laboratories

used to analyze screening tests must adhere to national standards. Potential screening costs and morbidity may become issues for patients in the event of follow-up testing and treatment.

IV. Immunizations

A. Definition.

Vaccination against infectious diseases is an important and cost-effective component of adult health maintenance. Many adults have not received the vaccines and toxoids that are indicated to protect them against potentially life-threatening diseases.

B. Recommended immunizations

- Tetanus-diphtheria (TD) booster every 10 years
- Hepatitis A vaccine for health care and lab workers, for injection or street drug users and their partners, for institutionalized persons and their caregivers, as well as for persons traveling abroad to endemic areas or wherever periodic outbreaks occur.
- Hepatitis B vaccine if high-risk status (health care workers, intravenous drug users, homosexual persons, dialysis recipients, blood product recipients).
- Pneumococcal vaccine if with medical condition or conditions that increase the risk of pneumococcal infection (chronic organ disease, HIV infection, sickle cell disease, asplenia, or older than age 55 and in an institution).
- Influenza vaccine annually if immune suppressed, a resident of a chronic care facility, or a health care provider; new evidence suggests that all adults should receive this vaccine to reduce days lost from work.
- Measles-mumps-rubella vaccine if born after 1956 and lacking evidence of immunity to measles.
- Varicella vaccine—consider for healthy persons without a history of chickenpox or prior immunization (consider serologic titer option).
- Occupational and environmental exposure-specific immunizations (17).

C.

Office procedures to improve compliance with immunization recommendations are recommended and consistent with general office-based strategies to incorporate preventive services.

1. Have office staff routinely assess patient's immunization status, making sure that appropriately complete checklists are being used.
2. Generate reminders automatically.
3. Send reminder postcards.
4. Standing orders on outpatient and inpatient charts allow nurses to administer routine immunizations (e.g., annual influenza vaccine).
5. Provide patients with materials on vaccine-preventable diseases.
6. Provide chart audit feedback to clinicians on their patients' panel immunization rates.

V. Chemoprophylaxis

A. Definition.

This important component of adult health maintenance, often underprescribed, involves the use of medications or supplements prospectively to prevent potential future diseases. Indications (benefits), risks of use and nonuse, dosage, precautions, and possible side effects of chemoprophylactic agents are basic issues for the family physician in helping patients decide whether or not to adopt a specific intervention as a health maintenance strategy.

B. Recommended chemoprophylactic agents

1. **Aspirin therapy.** Recent longitudinal trials indicate a benefit for women as well as men from daily or every-other-day use of aspirin after age 40 to prevent vascular disease, especially if the patient is at high risk or has a family history of coronary artery disease and no risk of stroke or bleeding.

   Other recent studies have suggested that regular aspirin at doses recommended for prevention of cardiovascular disease may also decrease the risk of and mortality from colorectal cancer for both men and women. There remains disagreement surrounding appropriate dosing and frequency of use.

2. **Hormone replacement therapy (HRT)** (see also Chapter 13.6). There is general agreement for the use of estrogen alone (in women with no uterus) or an estrogen-progesterone combination (in women with intact uterus) for prevention and treatment of osteoporosis, especially for patients with early menopause or at a high risk of osteoporosis. Recent data suggest that the cardioprotective benefit of HRT during the first year is in question, with only possible benefit after 4–5 years of use. HRT should be avoided among women with above-average risk of breast cancer and with a history of deep venous thrombosis.
3. **Skin protection from ultraviolet light.** Chronic overexposure to sunlight is responsible for 95% of all basal cell carcinomas. Individuals should be prescribed a sunscreen with a protection factor of at least 15 and encouraged to use it.
4. **Postexposure prophylaxis.** The USPSTF recommends prophylactic agents for people with exposure to *Haemophilus influenzae* type b disease and meningococcal infection (oral rifampin), hepatitis A (immune globulin), tuberculosis (isoniazid), hepatitis B (hepatitis B immune globulin and hepatitis B vaccine), and rabies (immune globulin) (see Chap. 6.3, Chap 10.4, and Chap 11.5).

VI. Effective physician and office-based strategies.

The following strategies have been shown to enhance the quality and quantity of health maintenance interventions (18).

A. Involve the office staff.

A team approach to the delivery of preventive services is highly effective. Nursing and other office or clinic staff are often able to communicate with patients very effectively. Examples of specific staff functions include reviewing records to prompt clinicians and patients regarding preventive care, updating patient care flow sheets or computerized records, issuing reminders to patients and clinicians, following up on test results, and helping patients gain access to community resources. All immunizations and many screening activities can be successfully provided by nurses or allied health professionals. The team approach resolves the major barrier physicians face in implementing preventive care and recommendations: lack of time (19).

B. Incorporate routine documentation tools into your practice.

The “Put Prevention into Practice” (PPIP) education and action kit of the U.S. Public Health Service targets the patient, the provider, and the office staff and system with easy-to-use materials and tools to foster a health maintenance approach. These include reminder postcards for patients to alert them of the need for specific prevention interventions, patient flow sheets for preventive care that may be added to the patient's chart (e.g., smoker, due for TD or mammogram), charts and posters that inform patients that health maintenance is a practice priority, and prevention prescription pads to allow the clinician to write brief risk-reduction behavioral prescriptions for patients. The *Clinician's Handbook of Clinical Preventive Services* is a user-friendly manual providing the basic steps of performing more than 60 preventive services. The kit also includes a Personal Health Guide as a portable health maintenance record for adults. (The PPIP kit can be obtained from the American Academy of Family Physicians Order Dept., 800-944-0000.)

C. Facilitate patient compliance.

Make available patient education materials and information regarding community resources to help patients. Patient-held mini-records, such as the PPIP Personal Health Guide (see above), promote increased responsibility among patients for their own health maintenance activities and are available in Spanish and English. Patient education materials should also be appropriately directed in terms of the patient's literacy level and other pertinent factors (older than 60 years, requiring large print, etc.).

D. Establish health maintenance guidelines (standards and objectives) for the practice and evaluate achievement through audits and continuous quality improvement approaches.

Practice systems to foster adult health maintenance activities can be most effectively evaluated

through periodic reviews of charts and specifying other indicators of quality. To obtain or maintain National Commission on Quality Assurance (NCQA) accreditation, health care organizations are now required to conduct such audits, which usually include such indicators as immunization history, various cancer screening tests, and other health screening indicators such as hypertension, hypercholesterolemia, and domestic violence.

E. Develop mini-counseling topics.

Ten preventive topics, 3–10 minutes in duration and updated as necessary, can maximize the impact of “teachable moments.” The list may include exercise, smoking cessation, stress reduction, injury prevention, discipline and parenting skills, and family health promotion.

F. Reminder or prompting systems.

Generate compliance reminders, either manually or by computer, as a systemized approach to tracking patients in need of routine preventive care (20).

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1.4

HEALTH MAINTENANCE FOR OLDER ADULTS

James P. Richardson

The proportion of the population that is elderly continues to grow. Due to the large influx of “baby boomers” into this group beginning in 2010, this demographic group will increase in size dramatically, guaranteeing that geriatric medicine will be a large part of every family physician's practice. Today's 65-year-old has an average of 13–17 years of life left. Thus health promotion is not an activity that patients “outgrow.”

As noted in previous chapters, many health promotion activities recommended in the past have not been supported by evidence of their effectiveness. Physicians are often confused by the plethora of recommendations from government agencies, professional groups, and experts. A good source for the practitioner is the second edition of *Guide to Clinical Preventive Services* of the United States Preventive Services Task Force (USPSTF) (1). This report concisely reviews the evidence for 70 health promotion activities, ranking recommendations by the strength of the evidence. Besides making their own recommendations, this resource also includes the recommendations of organizations such as the American Cancer Society and evaluates whether these recommendations are supported by evidence from reliable studies. The task force now evaluates prevention topics on a continuing basis, and the literature should be monitored for future recommendations and revisions. A useful internet site that contains the task force recommendations is http://www.guidelines.gov/.

The following recommendations are largely consistent with the USPSTF guidelines but are the author's own. These recommendations apply only to asymptomatic people without risk factors.

I. Incorporating health maintenance into practice

A.

Elderly patients are less likely than younger ones to request health promotion activities and are less tolerant of long appointments. A useful approach, therefore, is to attempt to include some elements of health maintenance activities with every visit. For example, a visit for hypertension follow-up in the fall is a good time to inquire about influenza, pneumococcal, and tetanus- diphtheria (Td) immunizations.

B.

Many studies show that physicians believe they recommend health maintenance to their patients more often than can actually be demonstrated. Reminder systems and aids have been found effective in increasing health promotion use. The most effective are those that remove the physician from the decision loop (2). In other words, physicians can provide health promotion activities by involving their nurses and other staff, or by using questionnaires to initiate discussions of health promotion. Office protocols also are effective (e.g., immunizations, making a return appointment for cervical cancer screening). For a more detailed discussion of implementation strategies, see Chapter 1.3 .

C.

As with all health care in the elderly, health promotion activities should take into account quality-of-life issues and patient preferences.

II. Primary prevention

A. Definition.

Interventions that are primary types of prevention seek to prevent a given disease from ever beginning. A good example is immunizations to prevent infectious diseases.

B. Infectious diseases.

Prevention of infectious diseases is often neglected by patients and providers (2). Together, influenza and pneumonia are the fifth leading cause of death in the elderly.

1. **Influenza.** Influenza vaccine should be administered in October or November in the United States to all elderly who consent and are not allergic to eggs. The vaccine is effective in reducing the incidence of influenza and pneumonia, as well as hospitalizations for these diseases.

2. **Pneumococcal vaccine.** This vaccine should be given at least once to all elderly, as well as to younger patients with chronic diseases, such as pulmonary disease, chronic liver disease, and diabetes mellitus. High-risk individuals, defined as those older than 75 years or with severe chronic disease, should receive another booster after 5 years.
3. **Tetanus-diphtheria (Td).** In the United States, tetanus is now a disease of the elderly. Immunity to tetanus and diphtheria can be maintained by giving Td boosters every 10 years to patients who have had the primary series of three immunizations over 6 months. However, careful inquiry should be undertaken of all elderly receiving Td boosters because many seniors, especially women, have never received primary immunization, and these individuals will not be protected with one booster (3). Administration of tetanus immune globulin is necessary to elderly with tetanus-prone (i.e., "dirty") wounds who have never completed a primary series.
4. **Tuberculosis.** Routine purified protein derivative (PPD) testing is not necessary for community-dwelling elderly who are not HIV-positive but should be administered on admission to nursing homes. Two-stage testing (repeating the PPD 1–2 weeks after the first in those with an initial negative result) is necessary because of the booster phenomenon.
5. **Prevention of sexually transmitted disease.** As with younger age groups, sexually active elderly should be counseled to avoid high-risk sexual behavior and to use condoms with new partners.
6. **Routine dental care** remains important in the elderly.

C. Injury prevention.

Injuries are a frequent cause of death in the elderly.

1. Elderly patients should be counseled regarding the dangers of falls and the benefits of exercise. Avoidable causes of falls include environmental hazards, such as poor lighting or throw rugs, visual deficits, and debilitation. Physicians should counsel older adults to gradually increase their exercise capacity by walking, gardening, or doing household chores. In addition to reduced fall risk, benefits demonstrated in population studies include lower incidence of cardiovascular disease, improved mood, and lower incidence of osteoporosis.
2. Everyone should be counseled to wear safety belts (and bicycle or motorcycle helmets if applicable), to maintain working smoke detectors, to store firearms safely, and to keep hot water temperatures below 120°F.
3. Although screening of all older drivers is not advocated, all providers should know the local laws governing driving restrictions should they become aware that a patient is no longer a safe driver. Many hospitals now offer testing by occupational therapists that might help with this determination.

D. Osteoporosis.

Hormone replacement therapy (HRT) (estrogen and progestin for women with a uterus, estrogen alone for those without) should be considered for women at risk of osteoporosis (see Chapter 13.6 and Chapter 17.6). Calcium supplementation (daily total of at least 1,000–1,500 mg of elemental calcium) should be recommended whether or not HRT is given. While the task force did not recommend routine screening, the National Osteoporosis Foundation recommends bone mineral density testing on all white women 65 years or older (4).

E. Smoking cessation.

Benefits accrue to those who stop smoking at any age. Patients' smoking history should be obtained, and smokers should be encouraged to quit. Counseling patients to stop smoking is an effective intervention.

F. Alcohol.

As alcoholism develops in some older people late in life, screening with the CAGE (Cut down, Annoyed, Guilty, and Eye opener) questions (see Chapter 5.3) is recommended.

G. Dyslipoproteinemia (hypercholesterolemia).

Whereas secondary prevention of cardiovascular diseases with lipid-lowering drug therapy is well established, primary prevention is controversial. The National Cholesterol Education Program advocates screening elderly persons with a good life expectancy by measuring high-density lipoprotein and total cholesterol (5). Most

authorities recommend against treating elderly patients without known ischemic heart disease with lipid-lowering drugs because only one trial has been done that included men and women older than 65 years and large numbers of patients must be treated to prevent one adverse outcome (6). The decision must be individualized, based on the senior's quality of life, life expectancy, other risk factors, cost, and patient preference.

III. Secondary prevention:Cancer screening

A. Definition.

Interventions that seek to detect disease before individuals become symptomatic are secondary preventive measures. Examples include blood pressure measurement to detect hypertension and prevent cardiovascular diseases and cervical smears to detect cervical cancer.

B. Breast cancer.

Half of all breast cancers in women occur in those aged 65 years and older. Breast self-examination has never been shown to be an effective tool in reducing mortality but is recommended by the American Cancer Society. A yearly clinical breast examination is also recommended. Mammography screening is more controversial because studies of mammography have included few women older than 75 years, and there is no evidence that mammography is effective after this age. Mammography combined with clinical breast examination has been proven to reduce mortality from breast cancer in women aged 50 through 69 years. The USPSTF guidelines recommend cessation of breast cancer screening at age 70. Nevertheless, because the aging breast has an increased proportion of fat, which makes it easier to examine radiologically (and therefore mammography has a higher positive predictive value in the elderly), clinical breast examination and mammography performed every 2 years can be recommended to women older than 70 with a good life expectancy who would have surgery should a suspicious lesion be found (7).

C. Cervical cancer.

A significant proportion of elderly women have never had cervical (Pap) smears. Women with cervixes who are or have been sexually active should have smears at least every 3 years. Smears may be obtained at the physician's discretion in women 65 or older who have had consistently normal smears (see Chapter 13.4).

D. Colorectal cancer.

Rectal examination is not a useful screen in the asymptomatic patient. Fecal occult blood testing done yearly has been shown to reduce mortality from colon cancer by 33% (8,9), although the utility of this test may be less in the elderly due to a higher false-positive rate (and therefore lower positive predictive value) in the elderly. Rigid sigmoidoscopy has also been demonstrated to be effective in reducing mortality from cancer in the distal colon, but the optimal frequency of this screening is not clear (10). There is insufficient evidence to recommend one test over the other.

E. Prostate cancer.

A digital rectal examination for prostate cancer has a very low yield. The prostate-specific antigen (PSA) test is elevated in the elderly not only in those with prostate cancer but in men with benign prostatic hypertrophy as well. Although PSA testing identifies significant numbers of men with prostate cancer confined to the gland, it does not appear that mortality is reduced in those in whom early prostate cancer is found. Men older than 65–70 most likely will die of a comorbid condition other than prostate cancer (11). Therefore, with the possible exception of patients who request testing and have been informed of its drawbacks, PSA screening is not recommended for elderly men.

F. Skin.

A yearly examination of all skin for patients with significant sunlight exposure or with a history of skin cancer is recommended.

IV. Secondary prevention:Other diseases

A. Glaucoma.

Routine screening by primary care physicians is not recommended. High-risk populations (blacks older than 40, whites older than 65, and those with a positive family history, diabetes, or severe myopia) may be referred to eye specialists for screening. The optimal interval for screening is not known.

B. Hypertension.

Blood pressure should be measured at least yearly.

C. Hypothyroidism.

Routine screening is not recommended, but clinicians should have a low threshold for ordering a serum thyroid-stimulating hormone level (TSH) because of its subtle presentation.

V. Geriatric assessment.

Although not as strongly supported by evidence as the above recommendations, most experts recommend some or all of the following activities for the elderly (12).

A. Special senses.

Visual and hearing loss contribute to functional decline and cognitive impairment. Vision may be tested with Snellen's chart, and hearing loss may be screened by history.

B. Polypharmacy.

Simplifying drug regimens improves compliance, reduces the incidence of adverse drug reactions, and saves money. Common offending drugs are those whose indications were never clear or the indications for which have disappeared (e.g., digoxin, H_2 antagonists).

C. Cognitive impairment and depression.

Both of these are common in the elderly. The Folstein Mini-Mental State Examination (13) is specific but not very sensitive for dementia. Many depression-screening instruments (e.g., Geriatric Depression Scale) are available (12).

D. Advance directives.

Although all elderly should be encouraged to record their desires in formal advance directive instruments, simply recording the patient's desires in the medical record is often very helpful to other providers and family members should the patient become unable to make his or her own decisions (see Chapter 22.5).

VI. Chemoprophylaxis

A. Aspirin.

Although the value of aspirin is well established for secondary prevention of stroke and myocardial infarction, its role in primary prevention is less clear (for further discussion, see Chapter 1.3).

B. Multivitamins.

The role of vitamin supplementation in the prevention of cardiovascular disease is still evolving, but diet supplementation with one multivitamin a day is safe and benefits those older adults with poor diets.

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1.5
HEALTH CARE FOR THE INTERNATIONAL TRAVELER

Nancy C. Elder

Emporiatics, or travel medicine, is a rapidly expanding health field. Contrary to many travelers' popular beliefs, exotic tropical diseases are not the primary causes of morbidity and mortality (1). Excess mortality abroad is mainly due to accidents, and morbidity is primarily from traveler's diarrhea. Family physicians can help travelers prevent mortality and morbidity with education and appropriate use of medications and immunizations.

I. Approach to a pretravel visit

A. History.

Information should be obtained about previous travel, including any problems encountered during the travel. The current itinerary should be explored, including a listing of destinations, length of stay, and type of accommodations at each site. Personal history, including age, chronic diseases, disabilities and lifestyle, occupations and avocations, should be reviewed to assess for individual risks.

B. Examination.

Young, healthy patients may need no special examination, whereas chronically ill patients may need special attention to maximize their current health before departure.

C. Patient education.

Based on analysis of the itinerary and the individual patient, a personalized education plan is developed for each patient. Prevention is the key to a healthy trip, and education is the most important part of a pretravel visit.

D. Medications.

Prescriptions should be written and recommendations given for over-the-counter medications as determined by the travel itinerary.

E. Immunizations.

In addition to immunizations against specific travel diseases, attention should be paid to the status of routine immunizations.

II. Common medical problems of travelers

A. Traveler's diarrhea

1. **Epidemiology and etiology.** Traveler's diarrhea affects 30%–50% of visitors to developing countries. Bacterial pathogens cause 80% of traveler's diarrhea, and although the specific pathogens vary geographically, enterotoxigenic *Escherichia coli* predominates. Other important agents include *Shigella* species, *Campylobacter jejuni*, *Aeromonas* species, *Plesiomonas shigelloides*, *Salmonella*, and noncholera *Vibrio* (2). The role of viruses and parasites is less clear. The most common sources of traveler's diarrhea are contaminated food and, to a lesser degree, contaminated water.
2. **Clinical signs and symptoms.** Traveler's diarrhea usually manifests with at least three unformed stools in a 24-hour period together with nausea, vomiting, abdominal pain or cramps, fecal urgency, or the passage of bloody or mucoid stools. The typical illness lasts for 3–5 days. Abdominal cramps are common, but fever, vomiting, and bloody stool (dysentery) each occurs in only 10%–20% of cases. The diarrhea lasts longer than 1 week in only 10% of patients (2).
3. **Prevention.** Primary prevention of all food and water-borne illnesses is in the proper preparation and ingestion of food and water. The adage "Cook it, boil it, peel it, or forget it" succinctly guides the traveler. Other sources for safe drinking water besides boiling (2–3 minutes is sufficient, even at high altitudes) include filter pumps, iodine (3–4 mg/L, with 15–30 minutes contact time), chlorine (1 mg/L, 15–30 minutes contact time), and commercially bottled water. Freezing does not kill most pathogens, so ice cubes must be considered to be possibly contaminated. In addition, only safe drinking water should be used for brushing teeth and washing any foods.

   Although the daily use of antibiotics and bismuth subsalicylate are effective in the prevention of traveler's diarrhea, they are not generally recommended because of their potential side effects (2). In rare instances, physicians may want to recommend prophylactic medications to their patients on a short-term basis. Prophylactic drugs that have been found effective include bismuth subsalicylate, 2 tablets qid; norfloxacin, 400 mg; ciprofloxacin, 500 mg; ofloxacin, 300 mg; doxycycline, 100 mg; or trimethoprim-sulfamethoxazole (TMP-SMX), one double-strength tablet daily. Resistance is common against these last two drugs, but they are appreciably less expensive than the quinolones.

4. **Treatment.** For most healthy adults, dehydration is unlikely, and replacement with clean drinking water, bottled water, glucose, mineral water, or other fluids is adequate. Saltine crackers may be eaten as well. Children, the elderly, and those with certain chronic illnesses may need to watch electrolyte balance more closely. Prepared solutions for infants and children, such as Pedialyte or Rice-Lyte, may be available, or packets of oral rehydration solution (ORS) can be prepared with clean water. ORS is widely available overseas.

   Antidiarrheal agents can shorten the duration and severity of the diarrhea. Both bismuth subsalicylate and loperamide have been shown to reduce diarrhea by 50% and 85%, respectively (2). The dosage for bismuth subsalicylate is 30 mL, or 2 tablets, every 30 minutes for five doses, which may be repeated on day 2. Dosage for loperamide is 4 mg initially and then 2 mg after each diarrheal stool, not to exceed 16 mg/d. Neither drug should be taken for more than 48 hours.

   Antibiotics are more effective in curing the infection, but their onset of action is slower than that of the antidiarrheal agents. Antibiotics tend to decrease the duration of diarrhea by 30–60 hours (2). TMP-SMX is standard therapy for noncoastal areas of Mexico, but in other geographic regions, the quinolones are more consistently effective. The antibiotics (TMP-SMX double strength; norfloxacin, 400 mg; ciprofloxacin, 500 mg; or ofloxacin, 300 mg) are given bid for 3 days.

   Dysentery symptoms (bloody stools and fever) should be treated with antibiotics alone, whereas uncomplicated diarrhea may be treated with antidiarrheals alone or with a combination of antidiarrheals and antibiotics. Antidiarrheal and antibiotic treatment is not recommended for children younger than 2 years or for pregnant women. For older children, appropriate doses for age may be given. Medical care should be sought if the diarrhea continues past 3 days or if dehydration becomes evident.

B. Malaria

1. **Epidemiology and etiology.** Malaria is passed from infected *Anopheles* mosquitoes. Although four species of *Plasmodium* can infect humans and cause illness (*P. malariae, P. vivax, P. falciparum,* and *P. ovale*), only *P. falciparum* is potentially life threatening. Areas of risk for malaria include parts of Central and South America, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania (3).
2. **Clinical signs and symptoms.** Malaria initially presents with flu-like symptoms, including fever, chills, muscle aches, headache, and sometimes vomiting, diarrhea, and coughing. Patients with severe *P. falciparum* malaria may develop liver and kidney failure, seizures, and coma. Infections with *P. vivax* and *P. ovale* are usually less serious, but the parasites may remain dormant in the liver, causing a reappearance of symptoms months or years later.
3. **Prevention.** Malaria prophylaxis begins first with the prevention of mosquito bites and second with the use of prophylactic medications. Patients should be advised to remain in well-screened or indoor areas from dusk to dawn. They should use mosquito nets and wear clothing that covers most of the body. Insect repellent containing diethyltoluamide (deet), especially high concentrations (>35%), are effective in preventing bites.

However, deet is contraindicated for young children. Clothing and bed nets can be sprayed with permethrin to help repel insects from clothing.

Resistance to antimalarial drugs is constantly changing. Sources for up-to-date treatment recommendations can be found in Section IV of this chapter. Drugs used for malaria prophylaxis include chloroquine (Aralen), which can be given to adults, children (5 mg/kg), and pregnant women. Rare, minor side effects include upset stomach, headache, dizziness, blurred vision, and itching. The dose for adults is one 500-mg tablet per week. Mefloquine (Lariam) is for use in chloroquine-resistant areas. It is not for use by pregnant women or children weighing less than 30 pounds. Minor side effects include gastric irritation and dizziness, but severe side effects have been reported, especially in those with seizure disorders, a psychiatric history, or cardiac conduct abnormalities (4). The dose for adults is one 250-mg tablet per week. Doxycycline (Vibramycin) is for use in chloroquine- and mefloquine-resistant areas. It is not for pregnant women or children younger than 8 years. Side effects include a photosensitivity reaction. The adult dose is one 100-mg tablet per day. Atovaquone plus proguanil (Malarone) was approved by the U.S. Food and Drug Administration (FDA) in 2000 for prevention in areas of chloroquine and mefloquine resistance and for those who cannot tolerate mefloquine. The medication must be taken daily, but it is begun only 1 day before arrival in the malarial zone and continued for 1 week after leaving. The dose in adults is one tablet of 250 mg atovaquone/100 mg proguanil per day. The dosing for children is one 62.5/25-mg pediatric tablet for 11–20 kg, two tablets for 21–30 kg, and three tablets for 31–40 kg. No data are available on the safety or efficacy in children weighing less than 11 kg. Side effects are mild and include abdominal pain, nausea and vomiting, headache, and a mild itch in children. All other drugs for malaria prophylaxis should be started 1 week before departure, and continued while visiting malarial areas and for 4 weeks after return home.

4. **Treatment.** Travelers spending extended time in chloroquine-resistant areas far from health care facilities should bring with them pyrimethamine-sulfadoxine (Fansidar) to take in case they develop the symptoms of malaria. These individuals should also seek medical care as soon as possible. The dosage is three tablets taken at one time. It is contraindicated in sulfa-allergic patients. Malarone is a second option for self-treatment. The dose is four adult tablets once a day for three days. In several countries, over-the-counter self-diagnosis urine kits are available for purchase. Their accuracy in untrained users is uncertain, and they are not yet recommended for general use by travelers.

C. Accidents and sexually transmitted diseases

1. **Epidemiology.** Death rates due to injury are increased by a factor of 2–3 in young adult travelers, and most of these deaths are traffic or swimming related. Casual sexual contacts may play a major role in the transmission of sexually transmitted diseases (STDs) (1). Many casual sexual contacts by young adult travelers are related to the use of alcohol and do not involve the use of condoms.
2. **Prevention.** The patient should be counseled to avoid motorcycles and open trucks; to avoid small, nonscheduled aircraft; to use seat belts and require them as a condition of vehicle rental; to select swimming areas with care; and to avoid alcohol while driving and swimming. Such measures can decrease a patient's chance of suffering serious injury. In addition, the risk of STDs should be explained to patients, and abstinence and the use of condoms encouraged.

D. Traveling with chronic health problems

1. **Epidemiology.** For American travelers, the most common cause of death abroad is the same as for those staying in the United States: cardiovascular disease. More disabled, elderly, and chronically ill people are traveling than ever before (1). Advance planning can help increase a patient's chance of having a healthy trip.

2. **Prevention of complications.** Patients needing medications that may be life sustaining (e.g., asthma inhalers, antianginal medications) should be advised to bring twice as much medication as they will need for the trip in two separate containers carried in two separate locations (one of which should be carry-on baggage). Travelers should carry a list of all their medications with generic names and doses detailed. It is safer to carry medicines in their original containers when crossing through international borders. In addition, patients should carry with them copies of their diagnoses and any pertinent medical records (e.g., electrocardiograms). Pregnant travelers with high-risk pregnancies should avoid international travel, and all pregnant women should avoid travel to areas with resistant malaria.

E. Altitude illness

1. **Epidemiology and etiology.** Altitude illness presents with three main clinical entities: acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). AMS usually begins within 4–12 hours after ascent to at least 8,000 ft (2,438 m). At 10,000 ft (3,048 m), a majority of people have at least some symptoms. HAPE begins 24–96 hours after arriving at altitude and affects more than 10% of individuals above 14,500 ft (4,420 m). HACE is quite rare, but it is the most serious form of altitude illness. It usually begins above 12,000 ft (3,656 m) and occurs 48–72 hours after arrival at altitude.
2. **Clinical signs and symptoms.** Commonly AMS presents with mild symptoms such as headache, mild nausea, dizziness, weakness, and insomnia. More severe AMS symptoms include severe headache, irritability, and shortness of breath with exercise and irregular breathing at night, including periodic apnea. HAPE presents with the classic symptoms of pulmonary edema, including shortness of breath, cough, wheezing, increased heart and respiratory rate, and, ultimately, irregular periodic breathing, confusion, and coma. HACE presents with severe headache unrelieved with analgesics, lack of coordination, confusion and bizarre behavior, and, ultimately, unconsciousness.
3. **Prevention.** Altitude illness can sometimes be prevented, or at least modified, by paying attention to the height of the ascent, the speed of the ascent, and how long one stays at the altitude. “Staging” is the process of remaining at an intermediate altitude for a few days before attempting the ultimate altitude. The initial stage should be between 6,600 and 9,800 ft (2,012 and 2,988 m). Then, depending on symptoms, ascent can continue at the rate of 1,000 ft (305 m) per day for 10,000–14,000 ft (3,048 to 4,267 m) and 1,000 ft per 2 days over 14,000 ft. If symptoms of AMS occur, further ascent should be delayed until symptoms resolve. If symptoms worsen, or if symptoms of HAPE or HACE occur, then descent should begin immediately. Adequate hydration can also help decrease symptoms, as can good physical conditioning (but even athletes in excellent condition can experience altitude illness). The climber's advice to “climb high and sleep low” is an excellent practice for those going over 12,000 ft (3,656 m).

   Medication can also help prevent altitude illness. Acetazolamide can be useful in those with a history of altitude illness or who must plan a rapid ascent. Dosage is 250 mg orally twice daily, starting the day before ascent and continuing for 2–3 days at altitude. Acetazolamide is contraindicated in those with sulfa allergies. Dexamethasone may also reduce the severity and incidence of altitude illness. The dose is 2–4 mg every 6 hours, begun the day of the ascent, continued for 3 days at the higher altitude, and then tapered over 5 days.

4. **Treatment.** The only definitive treatment for altitude illness is to “get off the hill.” A descent of as little as 1,000 ft (305 m) can improve symptoms dramatically. Oxygen at 1–2 L/min can also help to improve symptoms. With mild AMS symptoms, the ascent should be stopped, acetazolamide 250 mg given twice daily, and rest, fluids, and mild analgesics used for

headache. If symptoms resolve, slow ascent may resume. Severe AMS symptoms or HAPE or HACE symptoms necessitate immediate descent. If extenuating circumstances prevent immediate descent, oxygen and bed rest should be used. A portable hyperbaric oxygen chamber can help ameliorate the symptoms of severe HACE and HAPE at very high altitudes and should be considered part of the necessary equipment for extremely-high-altitude attempts.

5. **Illness at lower altitudes.** While the classic triad of AMS, HAPE and HACE rarely occurs below 8,000 ft (2,438 m), travelers with respiratory and cardiac problems might experience problems at altitudes as low as 5,000 ft. Travelers with these problems should consult their physician before advancing to a significant altitude.

III. Immunizations

A. Current guidelines.

Recommendations for vaccinations change frequently as outbreaks, endemics, and new vaccines develop. Up-to-date sources are discussed in Section IV .

B. Common immunizations

1. **Tetanus and diphtheria.** These diseases remain serious problems, and all travelers should be current (within 10 years) on these vaccines.
2. **Yellow fever.** Several countries in yellow fever-endemic areas (predominantly equatorial countries in Africa and South America) require documentation of immunization against yellow fever. The vaccine is live, is available for individuals older than 9 months, and requires a booster every 10 years. Reactions to yellow fever vaccine are generally mild. The vaccine should be avoided in those with egg hypersensitivity or immunosuppression. The vaccine is available only through registered yellow fever vaccine centers. A list of these centers can be obtained from your state health department.
3. **Hepatitis A.** Two inactivated hepatitis A vaccines have been licensed in the United States: Havrix and Vaqta. The vaccine is administered with a booster in 6–12 months, but the initial vaccine achieves 77%–100% seroconversion by 14 days (5). The vaccine is available for children older than 2 years old and adults. If travel is planned in less than 14 days, immune serum globulin may be given simultaneously with the hepatitis A vaccine.
4. **Hepatitis B.** Vaccination against hepatitis B is unfeasible for many travelers because 6 months is needed for the primary series. However, because some protection is provided by one or two doses, consideration should be given to initiating the series for individuals at high risk, even when it cannot be completed before travel.
5. **Polio.** Because polio is endemic in many parts of the world, travelers should make sure they have received their primary series (3) of polio vaccine. Adults should then receive one additional booster of polio vaccine before travel to endemic areas. This additional polio vaccine is only needed once in adulthood.
6. **Typhoid.** Oral and parenteral vaccines against typhoid are available and effective (70%–90%) and offer protection for 2–5 years. Ty21a, the oral preparation, is a live attenuated strain that is given as one capsule every other day for four doses. Ty21a should not be taken concurrently with mefloquine, as mefloquine can inhibit the growth of Ty21a. Typhim Vi, a purified polysaccharide vaccine, is for adults and children aged 2 years and older and is given in one dose. An inactivated typhoid vaccine for adults and children 6 months and older is given in two doses a month apart.

C. Less commonly used immunizations.

Cholera vaccines currently available are generally less than 50% effective and give minimal protection after 6 months; they are not recommended for travelers.

Japanese encephalitis occurs in the summer and autumn in areas of India and Asia. The risk to short-term travelers and those who only visit urban

areas is low. The vaccine, given on days 0, 7, and 30, should be reserved for those with extended visits to rural areas during the rainy season.

Rabies, transmitted by bites of infected animals, is endemic in some countries. Travelers at risk include those spending extended periods of time in rural and wilderness areas. Pre-exposure vaccine with 3 doses (days 0, 7, and 21 or 28) of rabies vaccine is recommended for high-risk travelers only. The vaccination does not eliminate the need for additional therapy after a rabies exposure.

Chloroquine and mefloquine should not be taken until after completion of the three doses of rabies vaccine.

Meningococcal meningitis occurs frequently in sub-Saharan Africa during the dry season, and travelers to this area should receive a single dose of vaccine, which covers serogroups A/C/Y/W-135.

IV. Sources for current travel recommendations

A. U.S. Centers for Disease Control and Prevention.

The CDC offers a variety of sources of up-to-date information for both travelers and physicians. The yearly book, *Health Information for International Travel,* is available from the U.S. Government Printing Office in Washington, DC. This “yellow book” provides a country-by-country listing of malaria prophylaxis recommendations, as well as information on immunizations and other disease prevention strategies prepared by the CDC. It can also be downloaded from the CDC web site (http://www.cdc.gov/travel/travel.html). The web site also contains information about specific diseases, regions and countries, immunizations and medications. All of the information on the web site can also be ordered through the fax information service at 888-232-3299. There is also a traveler's hotline at 888-FYI-TRIP that contains prerecorded messages.

B. Other web based resources.

Shorelands Travel Health Online (www.tripprep.com/index/html) also provides general information to the public about individual countries, as well as information about road safety and civil disturbances.

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II. COMMON PRESENTING PROBLEMS

2.1
WEIGHT LOSS

David B. Graham

Involuntary weight loss is a challenging problem, often surrounded by fears on the part of both patient and physician of an occult malignancy. Though malignancy is a leading cause of weight loss, extensive and costly workups for occult cancers are rarely beneficial (1,2,3,4 and 5). The evaluation of weight loss is accomplished through simple and concise history, physical examination, and laboratory testing. Weight loss is a common complaint in primary care offices (1,3,5); however, there are very few clinical studies that investigate this diagnostic dilemma. Up to 50% of patients do not have true weight loss (1), and no cause is ever found in up to 25% of patients with documented weight loss and thorough evaluation (3,5). Depression, dementia, and social factors account for 33% of cases (1,2).

I. Diagnostic approach.

The key to the diagnosis of involuntary weight loss is a careful and complete history and physical examination. The approach begins broadly and then quickly focuses on specifics derived from the initial evaluation.

A. Quantify loss.

A loss of 5% of the baseline body weight (not ideal body weight) over 6 months is significant (1,2 and 3,5). Serial measurements are the best method of verifying weight loss, but key markers include numerical estimates, family report, and changes in clothing or belt size. Changes in growth parameters for infants and children are red flags to initiate a diagnostic evaluation.

B. Categories of weight loss.

The causes of weight loss can be divided into four major categories: decreased intake; increased nutrient loss; increased metabolic demand; and impaired absorption (Table 2.1-1).

Decreased intake
Malignancy, congestive heart failure, medications, dementia, depression, grief, electrolyte disturbances, poor dentition or taste, gastric or esophageal disease, electrolyte disorders, alcoholism, financial hardship, social isolation, HIV and AIDS
Increased nutrient loss
Profuse vomiting or diarrhea, diabetes mellitus
Increased metabolic demand
Fever, malignancy, tuberculosis, hyperthyroidism chronic infection, drug abuse (cocaine, stimulants)
Impaired absorption
Cholestasis, infection (parasitic, other), medications, pancreatic insufficiency, diabetic or HIV enteropathy, inflammatory bowel disease, celiac sprue, surgery

HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

Table 2.1-1. Major causes of weight loss

C. Special considerations.

A tailored approach in the elderly includes greater emphasis on social and environmental factors. (An excellent review can be found in Ref. 6 .) The approach in HIV and AIDS is more comprehensive, and special attention is given to disease specific infections, nutritional changes and neoplasia. (A useful review is given in Ref. 7 .)

II. History.

A. Initial data.

One should begin with general questioning and a complete review of systems. Is the loss intentional? Inquiry about dieting, diuretics, and eating disorders is important. These would be classified as voluntary weight loss. It is valuable to quantify the patient's average daily or weekly intake of food and calories. The frequency of meals, appetite changes, and difficulty with food preparation can be additional clues. Thorough tobacco, alcohol, and drug histories are very important and frequently lead to other considerations. Concise past medical, surgical, psychiatric, and family histories are always pertinent. These can identify chronic conditions that further narrow the differential diagnosis. Social factors, including stress, isolation, and the cost and effort required to prepare and consume food, can have major impact on weight.

B. Specific historical data.

The patient's symptoms and complaints should direct the clinician to greater detail. Remember to focus on the four main categories and major causes (Table 2.1-1).

III. Physical examination.

Physical findings are present in 66% of cases of involuntary weight loss (1,2,5). First, one must quantify loss by serial weight measurements. Measurement of vital signs, including temperature, blood pressure, oxygen saturation, respiratory and heart rates, is always important. A focused examination based on clues from the history is appropriate. Specific attention should be directed to areas of concern. Cachexia with a long smoking history or an abdominal mass is worrisome for cancer. However, peripheral edema, pulmonary rales, and an S_4 heart sound are suspicious for congestive heart failure.

IV. Testing.

A. Basic laboratories.

Debate continues regarding the most useful and cost-effective laboratory testing for involuntary weight loss. A simple and structured approach is best (1,2,3,4 and 5). The first line of testing should include complete blood count, thyrotropin (thyroid-stimulating hormone; TSH) assay, urinalysis, and fecal occult blood testing. A comprehensive chemistry panel including albumin, transaminases, blood urea nitrogen, creatinine, and electrolytes (calcium, magnesium, phosphorus, sodium, and potassium) is essential. A chest radiograph is often useful but is not required (1).

B. Comprehensive analysis.

Further testing should be done only as directed by the initial findings. Careful observation and follow-up are superior management strategies to undirected diagnostic testing (1,2,3,4 and 5). When indicated, upper gastrointestinal radiographs, endoscopy, and colonoscopy are the most useful second-line tests (3). National Cancer Institute or U.S. Preventive Services Task Force age-specific screening guidelines should be evaluated and up-to-date for the patient. These can be accessed on the Internet through the National Library of Medicine (http://www.nlm.nih.gov/). Computed tomography and other expensive investigations are seldom beneficial in the absence of a specific indication (3,4).

V. Differential diagnosis.

The integration of history, examination, and laboratory data will usually reveal the cause for involuntary weight loss. Cancer, including gastrointestinal malignancies, accounts for 16%-36 % of cases, whereas lung cancer represents 5%–10%. Other gastrointestinal diseases account for another 14%–23% (1,3). If the initial steps in the evaluation are not conclusive, the best approach is careful observation. Follow-up examinations and testing should be done monthly for 6 months. If a physical cause exists, it will almost always be found within this period of time (1). If an organic cause is present, this simple approach will expose it more than 75% of the time (1,2 and 3).

If an organic cause is not identified within the first 6 months, it is unlikely that one will be found (1,2 and 3). However, these undifferentiated patients typically do well, and assuming they do not have continued and progressive weight loss, they have an excellent overall prognosis (1). Malignancy is a significant cause of weight loss; however, a truly occult malignancy is rare, and an exhaustive search for one is neither cost effective nor supported by the literature (1,2,3,4 and 5).

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2.2
FATIGUE

John W. Saultz

Fatigue consistently ranks among the ten most commonly described symptoms in primary care practice. Women complain of fatigue to the physician 1.5–3.9 times more often than men. Fatigued patients see their physicians more often than nonfatigued patients and have more diagnoses on their medical records (1).

I. Clinical evaluation and diagnosis.

A. Acute fatigue.

Acute fatigue most commonly presents as an incidental symptom after stressful life experiences, because of sleep deprivation, or as a symptom of common illnesses, pregnancy, or medication side effects. The evaluation of acute fatigue is best considered in the context of the patient's other symptoms. The history should focus on areas of psychosocial and family stress, the patient's sleep and nutritional habits, a review of the patient's medications, and careful documentation of associated symptoms. The etiologic factors of acute fatigue are usually evident to both the patient and the physician with a basic history and physical examination.

B. Chronic fatigue.

Patients with unexplained fatigue lasting for at least 6 months have chronic fatigue. They have often seen other physicians previously and may be frustrated by the lack of a specific diagnosis to explain their symptoms. As many as 50% of patients with chronic fatigue continue to be fatigued a year after their initial presentation to the physician (1). In most cases, the physician is unable to identify a specific cause of the chronic fatigue, and a flexible and systemic management plan will be necessary.

1. **History.** History at the time of the initial visit should include information regarding development of the fatigue and associated symptoms, family history, occupational history, and medication history. Special attention should be given to the patient's sleep habits, symptoms of depression, history of blood loss, thyroid disorders, exercise habits, cardiovascular fitness, sexual history, and risk factors for human immunodeficiency virus infection. Patients should be encouraged to share past experiences with medical evaluations of the fatigue and any frustrations they may have with previous care. All previous medical records should be reviewed. A history of alcohol or drug abuse should be elicited, and a family genogram or other method of family assessment should be considered.
2. **Physical examination.** A complete physical examination should be performed. This will improve the doctor-patient relationship and establish that the physician takes the complaint of chronic fatigue seriously. Nevertheless, it is unlikely that the physical examination will be helpful in establishing a definitive diagnosis.
3. **Laboratory evaluations.** Laboratory evaluations are only helpful to the management of such patients in a small percentage of cases. No tests should be ordered until previous medical records are reviewed

when the patient has undergone prior evaluations for fatigue. The basic laboratory evaluation includes a complete blood count, renal function tests, liver enzymes, urinalysis, and a sedimentation rate. Thyroid function studies should be considered. Additional tests should be ordered only if indicated by the history or physical examination. Tests of immune function, Epstein-Barr virus titers, and lymphocyte subpopulation analysis are of no established benefit in evaluating these patients (2). Neither is it helpful to do rheumatologic or serologic evaluation of these patients in the absence of associated symptoms suggesting these disorders (3).

4. **Differential diagnosis.** The differential diagnosis can best be remembered in broad categories, such as infectious diseases (including viral syndromes, mononucleosis, hepatitis, endocarditis), toxin and drug effects (such as medication side effects and alcohol or drug abuse), endocrine and metabolic problems (including electrolyte disorders, hypothyroidism, diabetes, and malnutrition), neoplastic conditions (such as leukemia, lymphoma, and occult malignancy), vascular disorders (such as congestive heart failure, valvular heart disease, and cardiomyopathies), pulmonary conditions (including chronic obstructive pulmonary disease or restrictive lung diseases), miscellaneous conditions (such as anemia, pregnancy, connective tissue disease), and psychosocial problems (such as depression, anxiety, adjustment reactions, situational life stress, sexual dysfunction, family violence, occupational stress, and professional burnout).

C. Chronic fatigue syndrome (CFS).

In 1988, the U.S. Centers for Disease Control and Prevention (CDC) first approved diagnostic criteria for chronic fatigue syndrome. Fewer than 5% of patients with chronic fatigue in a family practice met these diagnostic criteria for chronic fatigue syndrome. Thus, although patients have often read about this disorder, the majority of patients with chronic fatigue do not qualify for this diagnosis. Chronic fatigue syndrome is now considered to be a subset of chronic fatigue in which patients have four or more of the following symptoms recurrently during a period of 6 consecutive months: sore throat, tender lymphadenopathy, muscle pain, arthralgias without arthritis, headaches of recent onset, unrefreshing sleep, and postexertional malaise lasting for more than 24 hours. The CDC's web site is a good source of information about which conditions are sufficient explanations for chronic fatigue to exclude a diagnosis of chronic fatigue syndrome (4).

II. Management of fatigue.

Successful treatment of patients with chronic fatigue requires empathy and trust in the doctor-patient relationship. The following principles of management are suggested:

A.

Be as interested and concerned about the effects of the patient's fatigue as you are about its cause. In many cases, no diagnosis is forthcoming after the initial evaluation. It is therefore necessary to focus also on the effect the symptoms are having on the patient's life and occupation and the lives of family members. This willingness to address both cause and effect broadens the doctor-patient relationship and allows for constructive approaches to the patient's problem while the diagnostic workup is under way.

B.

Explain to patients that the most common causes of fatigue in family practice are depression and psychosocial problems. Often it takes several office visits for the patient to become sufficiently comfortable to provide additional history about problems such as family violence, sexual abuse, depression, and substance abuse. Discussing these issues early and repeatedly in the course of the evaluation rather than after physical disorders have been ruled out is beneficial.

C.

Elicit the patient's and the family's thoughts about the most likely explanations for the fatigue. A symptom diary can be completed by the patient and used by both physician and patient to identify patterns in the symptoms.

D.

Consider convening the patient's family to explore health beliefs and to provide education.

E.

Consider providing articles about chronic fatigue syndrome and professional burnout to patients.

F.

Use consultants to support and reinforce the care plan. Communicate clearly with consultants about the purpose of the referrals. Although consultants rarely provide new insight into the cause of the patient's fatigue, they can be helpful as part of a team approach to help the patient understand and cope more effectively.

G.

A targeted exercise program is more effective in helping patients with chronic fatigue than is prolonged rest.

III. Prognosis.

Whereas patients who are acutely fatigued are most commonly exhibiting a self-limiting condition that will resolve on its own, chronic fatigue is much more likely to be refractory to medical management. In one study, 57% of patients with chronic fatigue in a family practice setting continued to be fatigued a year after their initial evaluation (1). Particularly in patients who have longstanding histories of chronic fatigue, a palliative rather than curative approach to management is appropriate. Using this approach, most patients are eventually able to return to work or school and to live productive lives.

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2.3
DIZZINESS

Philip D. Sloane

Dizziness requires a flexible diagnostic and therapeutic approach. There are nearly a hundred diseases that can present as dizziness, so the physician must efficiently sort through the possibilities. The majority of dizziness problems are not life threatening, and many resolve without treatment. Therefore, the best approach is as follows:

- If the patient has new-onset dizziness, conduct a careful history to narrow your differential diagnosis. Based on your history, conduct a focused physical examination and (possibly) limited laboratory testing. Look for a single diagnosis. If life-threatening conditions are ruled out, be willing to use a therapeutic trial or observation over time to clarify the diagnosis.
- If the patient has chronic, persistent dizziness that impairs function, a comprehensive evaluation is indicated. Usually multiple diseases and/or conditions are contributing to the problem, and your strategy should be to identify and treat those that can be alleviated. Improvement in function rather than cure is often the goal in chronic dizziness.
- Use laboratory tests sparingly. Although a variety of specialized tests are available (e.g., 24-hour cardiac monitoring, brain imaging, electronystagmography), they rarely make the diagnosis.
- Begin with a broad differential diagnosis. Table 2.3-1 provides a guide to some of the diagnoses to consider.

Condition	Key findings
Potentially life-threatening conditions	
Acute infection (e.g., pneumonia)	Light-headedness, fever, acute onset, localized findings, leukocytosis
Electrolyte/biochemical abnormality (e.g. hyponatremia, hypoglycemia)	Continuous light-headedness with fatigue; risk factors
Gastrointestinal bleeding	Light-headedness, abdominal pain, blood in stool, anemia
Stroke/transient ischemic attack	Vertigo (25% have vertigo alone), cranial nerve or peripheral neurologic symptoms, risk factors for vascular disease
Toxin exposure (e.g., carbon monoxide)	Nonspecific dizziness, history of exposure
Common, treatable conditions	
Anxiety/panic disorder/depression	Continuous dizziness, mood disorder, associated symptoms (e.g., headache) (see Chaps. 5.1 and 5.2)
Cervical osteoarthritis	Vertigo or light-headedness associated with neck stiffness/pain and arthritis
Drug reaction	Any dizziness + new drug exposure
Sinusitis/otitis media	Light-headedness or vertigo; history and examination supporting diagnosis (see Chaps. 8.2 and 8.5)
Migraine	Episodic vertigo (may precede or not be accompanied by headache); light-headedness (see Chap. 6.1)
Vasovagal dizziness	Light-headedness precipitated by anxiety, pain, micturition, defecation, or other vagal stimulus
Self-limited conditions	
Acute neurolabyrinthitis	Acute vertigo with horizontal nystagmus, vomiting, improving over days or weeks
Benign paroxysmal positional vertigo	Vertigo episodes lasting less than 1 min, beginning abruptly and diminishing in frequency and intensity over days or weeks
Recurrent vestibulopathy	Vertigo episodes lasting 1–2 d, recurring 1–2 times/yr
Rare conditions to rule out	
Acoustic neuroma	Gradual onset unilateral hearing loss, occasionally with mild dizziness
Eighth-nerve vascular compression	Disabling positional vertigo increasing over months; positive brain stem evoked potentials
Perilymphatic fistula	History of severe blow to the ear followed by vertigo on sneezing or coughing

Table 2.3-1. Selected diagnoses to consider in the dizzy patient

I. Taking a history

A. Dizziness is a subjective sensation of movement or disorientation in space.

It can be a “head” sensation, a “body” sensation, or both. Common terms used include spinning, light-headedness, giddiness, vertigo, imbalance, and a falling sensation.

B. Subtypes of dizziness.

Try to define the problem as one of these symptom categories:

1. **Vertigo**—a sensation of movement, often of rotation, sometimes of tilting. It is generally associated with disorders of the vestibular system, although some psychological diagnoses (e.g., panic disorder) are accompanied by vertigo. Common diagnoses include benign positional vertigo, acute labyrinthitis, serous otitis media, vertebrobasilar distribution transient ischemic attack or stroke, Meniere's disease, atypical migraine, cervical vertigo, and recurrent vestibulopathy.
2. **Presyncopal light-headedness**—a sensation that one is about to faint, caused by inadequate circulation to the cerebral cortex. Cardiovascular causes, postural hypotension, certain medications, viral illnesses, hypovolemia, and vasovagal attacks are common causes (see Chapter 3.4).
3. **Imbalance (disequilibrium)**—a sensation of unsteadiness. Imbalance is always worse when the patient is standing or walking. It often is a secondary symptom to another type of dizziness; as an isolated symptom it indicates neurologic disease, such as a cerebellar (e.g., cerebellar degeneration due to alcoholism), axonal (e.g., multiple sclerosis), or peripheral (e.g., peripheral neuropathies from vitamin B deficiency or diabetes mellitus) disorder.
4. **Other**—dizziness that is vague and difficult to describe. It is commonly associated with a psychological condition, such as anxiety and depression. Ocular dizziness (due to a change in eye refraction, as with new glasses) is a subtype.

   The majority of dizziness complaints in young and middle-aged adults fit into one of these categories. Most older adults complain of multiple sensations, so this categorization is less useful in the elderly.

C. Episodic versus continuous dizziness.

Clarifying the temporal pattern of the dizziness often helps establish the diagnosis.

1. Continuous dizziness tends to be due to chronic conditions or psychological disorders, or both.
2. Episodic dizziness often has a pattern that is unique to certain diagnoses:
   a. Benign paroxysmal positional vertigo—vertigo episodes lasting <1 minute.
   b. Vasovagal episodes or cardiac arrhythmia—presyncopal light-headedness lasting <1 minute.
   c. Transient ischemic attacks or migraine—vertigo episodes lasting 10 minutes to 2 hours.
   d. Meniere's disease—vertigo episodes lasting 2 hours to 2 days, accompanied by tinnitus, and often preceded by ear stuffiness, with gradual development of permanent low-frequency hearing loss.
   e. Recurrent vestibulopathy—infrequent vertigo attacks, usually lasting a day.

D. Associated symptoms

can sometimes help establish the diagnosis.

1. History of rhinitis, sneezing, stuffiness, or headache can indicate sinusitis or serous otitis media.
2. Dizziness brought on by arm movement can indicate subclavian steal syndrome.
3. Numbness or tingling around the mouth or in the hands can indicate anxiety or hyperventilation.
4. Loss of consciousness can indicate arrhythmia, vasovagal episode, or seizure.
5. Neck pain on movement may indicate cervical osteoarthritis.
6. Unilateral hearing loss or tinnitus can indicate Meniere's disease, acoustic neuroma, or middle ear disease.

II. Physical examination and laboratory testing

A.

Physical examination should be focused, depending on the history. When the history is unclear, concentrate on vital signs and cardiovascular, otologic, and neurologic examinations.

1. If benign paroxysmal positional vertigo is suspected, perform the Hallpike (also called Barany) maneuver. In this test, the patient is rapidly moved from a sitting to a head-hanging (30 degrees to left or right) position. A positive result involves vertigo, rotatory nystagmus, latency of onset (3–10 seconds), and fatigability with recurrent testing.
2. Forced hyperventilation usually precipitates psychological dizziness.

B.

Laboratory testing should be judicious.

1. Head imaging. Magnetic resonance imaging is preferable to computed tomography because most causes to be ruled out involve small areas in the posterior fossa.
2. Causes of dizziness that can be detected on biochemical testing include hypoglycemia, hypothyroidism, anemia, uremia, and vitamin B_{12} deficiency.
3. Electronystagmography helps to identify whether a vestibular problem is present. It is useful in a few elderly patients.
4. Doppler ultrasound examination of the vertebrobasilar system is useful in cervical vertigo to rule out subclavian steal and may help differentiate between vascular and arthritic causes of cervical vertigo.
5. Holter monitoring. Use only if history suggests arrhythmia (see Chapter 68 and Chapter 69).

III. Management principles

A.

Make a diagnosis, if possible.

B.

Use medications sparingly.

1. Drugs cause or worsen dizziness more often than they ameliorate it.
2. Meclizine (Bonine) is useful during acute labyrinthitis, Meniere's disease, or recurrent vestibulopathy; otherwise it generally is not useful.
3. Diazepam (Valium) suppresses central responses to vestibular stimuli; it is useful in some chronic dizziness problems.
4. Antidepressants often ameliorate panic and anxiety disorders.
5. If migraine is suspected, appropriate medication can help.

C.

Physical therapy is useful for most older persons with chronic dizziness because physical deconditioning is generally present and worsens the symptoms. Specific physical therapy modalities exist to help benign positional vertigo, bilateral or severe unilateral vestibular loss, cervical vertigo due to arthritis, and cerebellar ataxias.

2.4
COUGH

Jonathan E. Rodnick

James K. Gude

Cough is the chief complaint for 3.6% of office visits to U.S. physicians (about 25 million annually). At any time, 18% of Americans have a cough. A cough is considered chronic if it persists for longer than 3 weeks. In the nonsmoker with a chronic cough who is not taking angiotensin-converting enzyme (ACE) inhibitors and who has a normal chest radiograph, one of three diagnoses is likely: postnasal drip syndrome (PNDS), asthma, or gastroesophageal reflux disease (GERD). Many patients have more than one cause (1,2,3 and 4).

I. Cough due to postnasal drip.

A. Presentation.

Singly or in combination with other conditions, PNDS is the most common cause of all chronic cough. This syndrome is due to a variety of upper airway conditions including the common cold, allergic rhinitis, vasomotor rhinitis, postinfectious rhinitis, rhinitis due to environmental or medication irritants, and acute and/or chronic (bacterial) sinusitis. These various entities overlap and may best be called rhinosinusitis. In the history one should search for clues such as the seasonal nature of symptoms, respiratory allergies, previous respiratory infections, and use of nasal drugs. There is usually, but not always, a sensation of needing to clear the throat or something dripping into the throat. Nasal congestion or hoarseness is often present. On physical examination one can usually find drainage or a cobblestone appearance of the posterior pharynx. The nasal mucosa may be injected or boggy. There may be sinus tenderness or a purulent nasal discharge suggestive of sinusitis (see Chapter 8.5). The clinical presentation is relatively sensitive but not specific. A minority of patients have no significant signs of PNDS.

B. Diagnosis.

There are no definitive diagnostic criteria for PNDS. A favorable response to therapy is the best way to make the diagnosis. Allergy testing can be helpful in some patients, but positive skin tests do not prove that allergy is the cause. Direct nasolaryngoscopy may also be useful. A four-view sinus radiograph or, preferably, a sinus coronal CT scan will show the presence of chronic sinusitis, provided it is obtained at least 6 weeks after an acute episode to avoid false positives (3).

C. Management.

Empirical therapy for PNDS should be tried before beginning an extensive diagnostic workup. For vasomotor or postinfectious rhinitis, the older generation of antihistamine/decongestants has been shown to be effective (4). To reduce side effects, initiate therapy at bedtime. The newer generation antihistamines, either alone or in combination with pseudoephedrine, have not been shown to reduce cough associated with the common cold. The use of ipratropium or azelastine nasal sprays (2 sprays in each nostril bid) may also be effective. For PNDS due to allergic rhinitis, all oral antihistamines, nasal cromolyn, and nasal steroids are effective. Nasal steroids are the drug of choice and their administration may be necessary for at least 3 months. Saline nasal washes are also effective. A good delivery system is a pump-driven irrigation device (e.g., Water-pic). For chronic sinusitis, a minimum of 3 weeks of an older-generation antihistamine/decongestant and/or nasal decongestants has been shown to be effective in descriptive studies. Antibiotics used to treat chronic sinusitis include amoxicillin (Amoxil) 500 mg tid, trimethoprim-sulfamethoxazole (Septra DS) bid, or erythromycin (Erythromycin Filmtab) 250 mg qid (all for 3 weeks); or azithromycin (Zithromax), two 250-mg tablets on day 1, followed by one tablet daily on days 2–5, with the regimen repeated after 1 week off. (See Chapter 8.5 .) Nasal washes may also be helpful.

D. Prevention.

In a cigarette smoker, cessation of smoking should be strongly urged. If environmental irritants are suspected, avoidance of exposure or improved ventilation is key.

II. Cough variant asthma. (See also Chapter 10.1 .)

A. Presentation.

This entity is easily overlooked because breathlessness or wheezing may be minimal. A viral respiratory illness or a bacterial or atypical bronchitis may initiate this cough variant asthma. This postinfectious type of cough variant asthma is a common clinical occurrence. Seasonal or specific allergies can also precipitate this syndrome. The cough is usually nonproductive and occurs throughout the day and night.

B. Diagnosis.

Office spirometry with flow-volume loop recordings often reveal an abnormal FEV_1 or $FEF_{25\%-75\%}$ value; the FEV_1 reflects larger airway obstruction, whereas the $FEF_{25\%-75\%}$ value indicates smaller airways obstruction. However, if these values are normal and the diagnosis is suspected, a methylcholine challenge test will unmask the asthma underlying an otherwise unexplained cough. Refer to a pulmonary specialist for this testing.

C. Treatment.

A pulse of oral prednisone, starting at 60 mg/d and tapered over 10 days, usually stops the coughing. If successful, long-term cough suppression can be achieved by the use of inhaled corticosteroids. Fluticasone (Flovent 220) 1–8 puffs per day by metered-dose inhaling is one example. Starting at 2 puffs twice daily with a spacer and titrating upward or downward at 1-month intervals is a reasonable approach. The goal is to keep the

cough in remission with the smallest possible dose of inhaled steroid. Combining inhaled corticosteroids with long-acting β_2 agents, such as salmeterol (Serevent) inhaler 1 or 2 puffs by spacer twice daily, leukotriene blockers such as montelukast (Singulair) 10 mg once daily at bedtime, or cromolyn (Intal) or necrodomil (Tilade) sodium 2 to 4 puffs with spacer twice daily, often makes possible a reduction in steroid dosage or a more effective treatment. If the diagnosis is established and a good response achieved, inhaled steroids are usually continued for a year.

D. Prevention.

An annual flu vaccination is recommended. The pneumococcal vaccine should be given each decade to those at high risk or than 65 years.

III. Cough due to GERD

A. Presentation.

Many patients with cough have typical gastrointestinal (GI) symptoms, such as sour taste, heartburn, and regurgitation. However, some have no GI complaints, and the reflux is only discovered upon workup (5). If there is enough reflux to cause micro- or macroaspiration, patients likely will have more pronounced GI symptoms. In addition, laryngeal symptoms, such as sore throat and hoarseness, can be present. With larger amounts of reflux, pulmonary symptoms, such as purulent sputum, wheezing, and dyspnea, are present. GI symptoms of dysphagia and choking while eating suggest esophageal motility disorders.

B. Diagnosis.

In patients with typical GI symptoms or those in whom a GI cause is suspected, 24-hour ambulatory esophageal pH monitoring is the best test (5). In addition to quantifying the amount of reflux, it also helps to show if there is a temporal relationship between the reflux and cough. Empirical therapy with an antireflux regimen may be a reasonable approach to diagnosis in some settings. However, if treatment fails, a more thorough investigation of GERD is recommended because medical treatment may not have been adequate.

C. Management.

Management of cough due to GERD is aimed at decreasing the frequency and severity of reflux. Conservative measures, such as a vigorous effort at weight reduction, elevation of the head of the bed, stopping smoking, not eating or snacking before lying down, and avoidance of foods and beverages with a low pH or that can relax the esophageal sphincter, should be tried in all patients. The H_2 antagonists, such as cimetidine (Tagamet) 800 mg qd or ranitidine (Zantac) 150 mg bid, are the mainstays of drug therapy (4). As some patients' symptoms may not improve for 2–3 months, long-term treatment may be necessary. Interestingly, both cough symptoms and reflux continue to be suppressed for more than 6 weeks after H_2 blockers are stopped. Proton pump inhibitors, such as omeprazole (Prilosec) 20 mg qd to 40 mg bid, are also used and may be tried if there is no response to or poor toleration of H_2 blockers. It is difficult to predict which patients will respond to therapy. Antireflux surgery, now frequently done by laparoscopy, is reserved for patients with continued symptoms who fail medical therapy, including proton pump inhibitors.

D. Prevention.

Dietary measures, as noted above, include weight loss, cessation of smoking, and maintaining a prudent diet.

IV. Cough due to other causes

The fourth most common cause of cough is chronic bronchitis, usually due to smoking. Other causes of cough include (not in order of frequency) ACE inhibitor drugs, auditory canal stimulation, bronchiectasis, bronchogenic or mediastinal tumor, congestive heart failure, environmental and occupational irritants, lung abscess, neck and upper airway masses, pertussis, psychogenic causes, pulmonary embolism, pulmonary fibrosis, sarcoidosis, tuberculosis, and any abdominal process that irritates the diaphragm.

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2.5
CHEST PAIN

Michael S. Klinkman

Chest pain is a clinical syndrome that may be caused by almost any condition affecting the thorax, abdomen, or internal organs. It is critically important to distinguish the two major presentations of chest pain: emergent and nonemergent (also referred to as acute and nonacute), as their clinical epidemiologic factors are very different.

Emergent (acute) chest pain is usually defined as the type of pain that cannot be ignored and that prompts most individuals to seek immediate medical attention, usually in the emergency room. Most of the medical literature on the subject of chest pain describes this type of pain, for which the probability of acute cardiac ischemia or unstable coronary artery disease is quite high (1). Nonemergent (nonacute) chest pain is less compelling, and patients usually seek medical care during routine office hours. It is a common complaint in the primary care setting, representing 1%–2% of office visits (2). Although few studies have described these patients, it is clear that the probability of acute cardiac ischemia or unstable coronary artery disease in this setting is significantly lower than is seen in the emergency setting: the most frequently recorded diagnoses are musculoskeletal chest pain and gastrointestinal (GI) tract conditions (3,4 and 5). A significant proportion of cases remain undiagnosed or labeled atypical or noncardiac chest pain (6,7).

This chapter presents a suggested approach to the diagnosis of nonemergent chest pain as seen in routine office practice, followed by common clinical presentations of the most frequently seen conditions, and laboratory and ancillary studies helpful in establishing a diagnosis. Specific management recommendations can be found in the chapters describing each condition in more detail.

I. General approach to the evaluation of chest pain

A. Perform severity and acuity assessment.

If the patient has emergently sought care at the office for acute onset of severe pain or pain associated with diaphoresis or difficulty breathing, evaluate as for emergent chest pain. Diagnostic evaluation should focus on the exclusion of severe cardiac disease as outlined in Chapter 9.2 . Otherwise, proceed to the steps outlined below.

B. Use probabilities to focus attention on the most likely diagnostic possibilities.

Begin with the prevalence data supplied in Section II as a crude estimate of the prior probability of possible diagnoses, then adjust these probabilities up or down, based on experience and the five key clinical features shown in Table 2.5-1 : predisposing factors, onset, duration and character of pain, and factors providing relief of pain. Do not begin by attempting to rule out specific conditions. Premature use of examination findings, laboratory studies, and ancillary testing to exclude specific diagnoses leads to excessive use of medical resources. More important, the use of some ancillary tests (e.g., graded exercise tests) on populations with a low probability of the disease in question results in a high rate of false-positive errors in test interpretation.

	Diagnostic category		
Clinical feature	Cardiac	Gastrointestinal	Musculoskeletal
Predisposing factors ("risk factors")	Male sex Smoking Hypertension Hyperlipidemia Family history of myocardial infarction	Smoking Alcohol use	Physically active New activity Overuse Repeated activity
Onset	At consistent level of exertion	After meals, on empty stomach	With or after activity
Duration	Minutes	Minutes to hours	Hours to days
Character	Pressure or "tightness"	Pressure or "gnawing" pain	Sharp, localized, movement-related
Relieved by	Rest; sublingual nitrates	Food; antacids	Rest; analgesics, NSAIDs

NSAIDS, nonsteroidal anti-inflammatory drugs.

Table 2.5-1. Clinical features associated with specific diagnostic categories of nonemergent chest pain

C. Perform directed physical examination and laboratory assessment.

A complete physical examination is often not necessary when history alone

strongly suggests a specific cause. For example, in patients with costochondritis, reproducibility of pain on palpation can confirm the diagnosis without need for further examination or laboratory studies.

D. Use follow-up visits to reassess chest pain when diagnosis is uncertain.

Time can be both a diagnostic and therapeutic agent in the primary care setting. Clinical clues to the diagnosis may only appear over time, and pain may resolve spontaneously. Specific diagnosis and intervention are not always necessary at the initial visit.

E. Consider empiric therapy.

When a specific diagnosis is likely but not yet proved, consider a trial of empirical therapy based on the tentative diagnosis. If therapy is successful, confirmation of the diagnosis through laboratory studies or ancillary testing may no longer be necessary.

II. Common clinical conditions causing nonemergent chest pain, including their prevalence, characteristic clinical features, and helpful tests

(note prevalence estimates from Ref. 4)

A. Musculoskeletal conditions (36%)

1. **Muscular chest pain, chest wall muscle pain, pectoralis strain (20%).** This condition is most commonly seen in active young men and women. Suggestive history includes sharp pain of recent onset, associated with minor trauma or repeated use of arms or shoulders, and pain with movement, radiating to shoulder, back, or arm, without associated systemic symptoms. Characteristic physical examination findings include tenderness on musculoskeletal palpation or exacerbated by movement. In this clinical setting, laboratory studies are not necessary.
2. **Costochondritis (Tietze's syndrome) (13%).** This condition is most often seen in young women, particularly black women. Suggestive history includes pain with the use of the chest wall muscles and sometimes chest ache at rest or pain with deep inspiration, without history of trauma. If tried, over-the-counter anti-inflammatory agents have often provided relief. The characteristic physical examination finding is tenderness to palpation over the costochondral margins, often worse over

the left third or fourth margin. Laboratory studies are not helpful in establishing the diagnosis.

3. Another musculoskeletal condition causing chest pain is **rib frac-ture (2%).**

B. GI conditions (19%)

1. **Gastroesophageal reflux disease, reflux esophagitis, dyspepsia, gastritis (13%).** This condition affects persons at any age and of either sex (see also Chapter 11.2). Clinical history may vary considerably, but suggestive findings include late postprandial discomfort (half an hour or more after food intake), pain on an empty stomach, night or morning cough or both, associated abdominal or epigastric discomfort, sharp retrosternal pain or pressure, dysphagia or odynophagia, hoarse voice, water brash, and presence of significant external stressors. Patients may report relief with antacid or food intake. There are few characteristic physical examination findings; epigastric tenderness is a common but nonspecific finding. Laboratory studies helpful in establishing the diagnosis include upper GI radiography (UGI), esophagogastroduodenoscopy (EGD), esophageal manometry and pH measurement, and Bernstein's test (see Chapter 11.2).
2. **Esophageal spasm (4%).** This condition may be more common in patients with gastroesophageal reflux disease. Clinical history is quite variable but may include the following: sudden onset of nonexertional squeezing substernal chest pain or pressure, sharp substernal pain that can at times be localized by the patient with one finger, often relieved by antacids or eructation, positional (worst when recumbent) but not affected by movement. The pain can last from moments to hours and can be associated with dysphagia. There are no characteristic physical examination findings. Laboratory studies are often necessary to establish the diagnosis: barium swallow (nutcracker esophagus) and esophageal manometry (markedly elevated muscle tone) are especially useful, and UGI, EGD, or esophageal pH measurement may confirm associated gastroesophageal reflux.

   Differential diagnosis for these patients must include angina pectoris. The similarity of symptoms makes it extremely difficult to distinguish esophageal spasm from angina without confirmatory laboratory testing.

3. **Other GI conditions causing chest pain:** Peptic ulcer disease (1%), cholelithiasis and cholecystitis (1%), esophageal muscular and motility disorders (<1%).

C. Cardiac conditions (16%)

1. **"Typical" cardiac ischemia: angina pectoris (10%), unstable (crescendo) angina (1.5%).** This condition is most commonly seen in middle-aged to elderly men and postmenopausal women (see also Chapter 9.2). Suggestive history includes diffuse substernal chest tightness or discomfort with consistent level of physical exertion, sometimes with emotional exertion, often associated with radiation to jaw, left arm, or back and sometimes accompanied by dyspnea, nausea, diaphoresis, or sudden fatigue. Pain is not affected by respiration and not relieved by antacids or position changes; however, it is usually relieved by rest or sublingual nitrates. Women with cardiac ischemia may more frequently present with atypical symptoms such as back pain or indigestion (8). Between episodes there are no characteristic physical examination findings. During episodes, patients may have hypertension or hypotension, palpably displaced point of maximal cardiac impulse, systolic murmur of mitral insufficiency, transient third or fourth heart sound (S_3 or S_4), or other signs suggestive of congestive heart failure. Helpful laboratory studies include electrocardiography (ST-segment depression during episode), graded exercise testing (GXT), stress thallium scan, stress echocardiography, and cardiac catheterization.

Blood tests to rule out myocardial infarction (e.g., creatine phosphokinase isoenzymes, cardiac troponins, or myoglobin) should only be performed in an emergency department or inpatient setting. If clinical suspicion of myocardial infarction is sufficiently high to warrant these tests, the patient should be immediately transported to an emergency department or dedicated chest pain center (where available), or admitted to the hospital for cardiac monitoring and consideration of thrombolytic therapy.

The clinician must differentiate between stable and unstable angina. If patient has no previous diagnosis of angina (all new-onset angina is by definition unstable until symptom pattern is established) or if there is an increase in frequency, intensity, or other change from established pattern of anginal episodes, the diagnosis is unstable angina, and aggressive management is indicated.

2. **"Atypical" angina pectoris (vasospastic angina, variant angina) (<1%).** This condition primarily affects young to middle-aged women (see also Chapter 9.2). Suggestive history includes diffuse substernal chest tightness or discomfort occurring at rest, sometimes radiating to the jaw, left arm, or back, occasionally accompanied by dyspnea, nausea, diaphoresis, or sudden fatigue. The pain is not associated with inspiration or expiration and is not relieved by antacids or position changes. Between episodes, there are usually no specific physical examination findings. During an episode, patients may have the examination findings listed in Section II.C.1 . Helpful laboratory studies include electrocardiography (ST elevation during episode), GXT, stress thallium, stress echocardiography, and cardiac catheterization with ergonovine challenge testing.
3. **Mitral valve prolapse syndrome (1.5%).** This condition is almost exclusively seen in young to middle-aged women. Patients often report substernal chest pain of variable duration, sharp or dull, often accompanied by palpitations, which may worsen with exertion or in the presence of significant external stressors. The characteristic physical examination finding is a mid-systolic click followed by systolic murmur on cardiac auscultation (click-murmur). Two-dimensional echocardiography confirms this diagnosis. If echocardiography is normal, the clinician should consider alternative diagnoses, such as anxiety-related chest pain, panic disorder, or variant angina.
4. **Other cardiac conditions causing chest pain.** Cardiac dysrhythmias (1%) and acute and subacute pericarditis (<1%)

D. Psychosocial conditions (9%)

1. **Anxiety- or stress-related chest pain (8%).** This condition is usually seen in healthy young men and women. Characteristic symptoms include chest tightness associated with dyspnea, difficulty in taking a deep breath, or hyperventilation, often associated with other stress-related symptoms (headache, GI symptoms) or the presence of significant external stressors; usual duration may be hours to days. On physical examination, patients often exhibit distress out of proportion to objective findings. Laboratory studies are usually not helpful, but a brief mental health screening instrument, such as the PRIME-MD (9), may assist in establishing a diagnosis of anxiety, depression, or somatization disorder. Differential diagnosis should include esophageal reflux or motility disorder, panic disorder, anxiety disorder, depression, and somatization disorder (see Chapter 5.1).
2. **Panic attacks or panic disorder (<1%).** These conditions are most commonly seen in young women, who usually present with sudden episodes of chest tightness accompanied by some of the following autonomic symptoms: dyspnea, "smothering" sensation, dizziness, palpitations, trembling, sweating, nausea, paresthesias, hot flashes, depersonalization, and fear of dying or of "going crazy" (see also Chapter 5.1).

Between episodes, physical examination is nonspecific, sometimes characterized by anxiety. During episodes, patients may have a rapid respiratory rate, tachycardia, and increased tremulousness. Laboratory studies are usually not helpful, but a brief mental health screening instrument or review of the diagnostic criteria for panic disorder with the patient may assist in establishing the diagnosis. Differential diagnosis should include mitral valve prolapse and generalized anxiety disorder.

E. Pulmonary conditions (5%).

1. **Bronchitis (2%).** This condition is more likely to occur in smokers. Suggestive history includes dull chest ache often accompanied by a productive cough, with occasional sharp pain upon coughing (see Chapter 10.2). Physical examination may reveal upper airway congestion, rhonchi clearing with cough, or diffuse wheezing on pulmonary auscultation. Laboratory studies are not necessary unless chest radiography is performed to rule out pneumonia.
2. **Pleurisy, pleurodynia (1%–2%).** This condition often accompanies viral or bacterial respiratory infections or inflammatory conditions. Suggestive history includes acute onset of sharp pain associated with breathing or movement sometimes accompanied by other symptoms of inflammation (e.g., joint stiffness or pain or rash). Physical examination may reveal a pleural friction rub. Laboratory studies, such as serum rheumatoid factor, antinuclear antibody screen, and erythrocyte sedimentation rate, may be useful to exclude underlying rheumatologic or connective tissue disease. Chest radiography may be helpful in excluding pneumonia.
3. **Pneumonia (1%).** This condition affects all ages and both sexes. Suggestive history includes sharp or "raw" pain exacerbated by inspiration and cough, often accompanied by systemic symptoms of severe cough, fever, and dyspnea (see Chapter 10.2). Characteristic physical examination findings include toxic appearance, rapid respiratory rate, fever, and consolidation or localized wheezing on pulmonary auscultation. Useful laboratory studies include chest radiograph and sputum culture.
4. **Other pulmonary conditions causing chest pain.** Pulmonary embolism (<1%), pneumothorax (<1%).

F. Other conditions (13%)

Nonspecific or atypical chest pain (13%). This ill-defined diagnostic label refers to the absence of an identifiable cause for chest pain, but most descriptions of this entity refer to relatively young patients with vaguely defined pain occurring without a specific pattern. Pain is often described as "squeezing" and not well localized. Patients are usually alarmed by these symptoms, attribute them to cardiac disease, and present for reassurance. This diagnosis is often reached only after an extensive and negative evaluation for cardiac disease has been completed.

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2.6
ABDOMINAL PAIN

Peter B. Kozisek

Abdominal pain is a common presenting problem in family practice. Despite the advances in diagnostic imaging and laboratory testing, clinical judgment on the part of the physician remains the cornerstone of diagnosis and treatment in the vast majority of cases. When the cause of abdominal pain constitutes a medical emergency, prompt diagnosis and treatment is mandatory. In nonemergent cases, the physician is called on to be efficient and cost effective in the use of laboratory and diagnostic imaging studies and to render an accurate diagnosis in a timely fashion. In either case, the evaluation and treatment of abdominal pain represents one of the most challenging and intellectually rewarding clinical problems for the family physician (1,2,3 and 4).

I. Diagnostic approach

A. History.

A detailed history is of paramount importance in elucidating the cause of abdominal pain. Patients should be asked about the severity and quality of their pain as well as its location and the presence or absence of radiation. The setting and the time of origin of the pain should also be ascertained, as should any remissions or exacerbations. Factors that produce or worsen the pain and those that ease the pain require delineation. Associated symptoms such as nausea, vomiting, diarrhea, hematemesis, hematochezia or melena, and light-headedness should also be explored in detail.

B. Physical examination.

A thorough and systematic physical examination, including inspection, auscultation, percussion, and palpation, is critical to an accurate and timely diagnosis of the cause of abdominal pain. Pelvic and rectal examinations are almost always indicated in the evaluation of abdominal pain and can yield valuable information. Rebound tenderness is an important finding indicating peritoneal irritation. Its presence should raise the index of suspicion for a potentially serious disorder, such as appendicitis, perforated diverticulum, ruptured ectopic pregnancy, perforated gastric or duodenal ulcer, ruptured abdominal aortic aneurysm, or bacterial peritonitis.

C. Diagnostic studies.

1. **Laboratory tests**
   a. **Urinalysis**
      1. **Hematuria.** >5 RBC/high-powered field (hpf) is suggestive of nephrolithiasis.
      2. **Pyuria.** >5 WBC/hpf is suggestive of pyelonephritis.
   b. **Complete blood count (CBC).** The white blood cell (WBC) count is frequently elevated in appendicitis, diverticulitis, cholelithiasis, mesenteric lymphadenitis, inflammatory bowel disease, pyelonephritis, pancreatitis, pelvic inflammatory disease (PID), gastroenteritis, and perforated viscus.
   c. **Human chorionic gonadotropin (hCG).** A positive pregnancy test should alert the examiner to the possibility of an ectopic pregnancy.
   d. **Amylase.** A significant elevation suggests pancreatitis. Serum amylase is sometimes elevated in inflammatory processes of the bowel mucosa, such as gastroenteritis.

e. **Liver function tests (LFTs).** Elevations commonly occur in cholelithiasis, hepatitis, and pancreatitis.

2. **Diagnostic imaging**
   a. **Abdominal radiographs** Air-fluid levels suggest obstruction or adynamic ileus. A sentinel loop of dilated bowel may sometimes be present adjacent to an inflamed structure in the abdomen, such as the appendix, gallbladder, or pancreas. Free air beneath the diaphragm in upright films is suggestive of perforated viscus.
   b. **Abdominal ultrasonography** is frequently helpful in the diagnosis of cholelithiasis, nephrolithiasis, pancreatitis, abdominal aortic aneurysm, ectopic pregnancy, PID, and ovarian cysts.
   c. **Computed tomography (CT).** CT scanning is helpful in the diagnosis of pancreatitis, abdominal aortic aneurysm, intra-abdominal abscess, and carcinoma.

II. The acute abdomen

This refers to an acute and potentially life threatening abdominal illness that requires immediate intervention. Differentiation of the acute abdomen from other, less serious causes of abdominal pain is the first challenge at the initial visit for abdominal pain. Signs and symptoms indicative of an acute abdomen include rebound tenderness, fever, an elevated WBC count with a left shift, severe or progressively worsening abdominal pain, abdominal distention, hypotension, shock, hematemesis, and rectal bleeding. The following illnesses may commonly present with an acute abdomen:

A. Acute appendicitis.

Acute appendicitis is frequently accompanied by anorexia, nausea, vomiting, and pain, which is initially periumbilical and later localizes in the right lower quadrant over McBurney's point. Patients often have low-grade fevers, and the CBC shows a leukocytosis with a left shift in typical cases. Immediate surgical referral is indicated when appendicitis is suspected.

B. Perforated viscus.

Perforation of the gallbladder or pancreas, peptic ulcer, or infected diverticulum may cause peritonitis, accompanied by the signs and symptoms of an acute abdomen. The chemical irritation of the peritoneum from bile, gastric secretions, and the contents of the pancreas typically cause abrupt and severe pain at the time of rupture. However, perforation of a diverticulum usually results in a more progressive evolution of peritonitis.

History, physical examination, laboratory studies, and appropriate imaging studies all contribute to the diagnosis of a perforated viscus. Immediate surgical referral is indicated if a ruptured viscus is suspected.

C. Intestinal obstruction.

Mechanical obstruction of the large or small bowel from tumor, volvulus, strangulated hernia, inflammatory bowel disease, impaction, adhesions, or a mass extrinsic to the bowel represents an acute abdominal emergency. Currently, about 20% of all admissions for acute abdominal pain are thought to be secondary to intestinal obstruction. Intestinal obstruction is initially manifested by nausea, vomiting, abdominal pain, and the absence of flatus. As the obstruction continues, abdominal distention becomes more prominent.

Auscultation of the abdomen may reveal “tinkles” or “high-pitched rushes” as the peristaltic action of the bowel encounters the obstruction. Abdominal radiographs in the supine and upright positions, along with a posteroanterior film of the chest, are the most important diagnostic tools in the diagnosis of obstruction. The presence of air-fluid levels on abdominal films indicates obstruction, although such findings can also be present with an adynamic ileus. Immediate surgical referral is indicated when intestinal obstruction is diagnosed.

D. Mesenteric vascular occlusion.

Thrombotic or embolic occlusion of the mesenteric arteries or veins may result in intestinal infarction and gangrene of the affected bowel segment. Anorexia and steady, severe, slowly progressive abdominal pain followed by bloody diarrhea are the hallmarks of intestinal infarction. CT, arteriography, or direct visualization of the affected bowel segment may be necessary to make the diagnosis. Prompt surgical intervention is necessary to preserve both bowel function and life.

E. Ruptured abdominal aortic aneurysm.

The rupture of an abdominal aortic aneurysm constitutes an acute medical emergency and necessitates immediate surgical intervention. The onset of rupture is manifested by shock and vascular collapse accompanied by abdominal or flank pain. The diagnosis is usually made clinically on the basis of the presentation and the finding on examination of a pulsating abdominal mass. However, a ruptured aneurysm may not always pulsate, and in some cases ultrasonography, arteriography, or CT may be necessary to make the diagnosis. If surgery is performed within 1–2 hours of rupture, survival is more likely. Delay in diagnosis and surgical intervention is associated with high mortality secondary to vascular collapse and renal failure.

F. Ectopic pregnancy.

(see Chapter 14.5). Ectopic pregnancy should be included in the differential diagnosis of abdominal pain in women of reproductive age. History, physical examination, quantitative ß-hCG analysis, and ultrasonography aid in the diagnosis. A history of prior tubal sterilization should not deter the physician from considering ectopic pregnancy in the differential diagnosis.

III. Subacute and chronic abdominal pain

Abdominal pain that is subacute or chronic may indicate a range of problems, from a potentially serious evolving illness to a self-limited illness requiring no further evaluation or treatment. Examples of such problems include the following:

A. Mesenteric lymphadenitis.

Mesenteric lymph nodes occasionally become inflamed and painful, presumably in response to viral infection. Symptoms may mimic those of acute appendicitis, and the diagnosis is sometimes made at the time of surgery. This illness is otherwise self-limited and requires no special treatment or intervention.

B. Gastritis or duodenitis.

(see Chapter 11.1). Inflammation of the mucosal lining of the stomach and duodenum typically produces a dull, burning pain in the epigastrium or right upper quadrant. Symptomatic treatment is indicated as long as care is taken not to miss a bleeding or perforating ulcer.

C. Irritable bowel syndrome.

(see Chapter 11.8). Irritable bowel syndrome is a self-limited illness that presents as a symptom complex of lower quadrant abdominal pain typically relieved by defecation, a mucous-like component of the stools, and periods of diarrhea alternating with constipation.

Symptomatic treatment, with patient education, stress management, bulk laxatives, and antispasmodic medications, is the foundation of treatment.

D. Diverticulitis.

(see Chapter 11.7). Inflammation and infection of a colonic diverticulum may produce a symptom complex of abdominal pain, fever, and anorexia. Typically occurring in older adults, diverticulitis is a potentially serious condition that can lead to intra-abdominal sepsis if rupture occurs.

Antibiotics are the treatment of choice with surgical consultation recommended in the more serious cases.

E. Cholelithiasis.

(see Chapter 11.4). Right upper quadrant pain, particularly after a fatty meal, is a common presentation for cholelithiasis. Diagnosis is confirmed with ultrasonographic scanning of the gallbladder.

F. Inflammatory bowel disease.

(see Chapter 11.9). Crohn's disease and ulcerative colitis often present with abdominal pain and diarrhea. The clinical diagnosis is confirmed by tissue biopsy via flexible sigmoidoscopy or colonoscopy.

G. Gastroenteritis.

(see Chapter 19.2). Crampy abdominal pain with diffuse diarrhea is the hallmark of gastroenteritis. Although most cases are self-limiting; more persistent or severe cases may require stool studies or flexible sigmoidoscopy, or both, for diagnosis.

H. Pancreatitis.

(see Chapter 11.6). Pancreatitis may present as an acute or chronic illness. Approximately 80% of cases are secondary to either cholelithiasis or alcohol use. The diagnosis can usually be made by history and physical examination, in conjunction with serum amylase and lipase determinations. CT of the abdomen is important in determining the presence or absence of pancreatic pseudocysts.

I. Gynecologic causes of abdominal pain.

Common pelvic sources of abdominal pain include recurrent urinary tract infection, ovarian cyst, ovarian torsion, PID, endometriosis, and mittelschmertz.

J. Less common causes of abdominal pain.

Clinically important, but less common, causes of abdominal pain include chronic hepatitis, intra-abdominal abscess, somatization, nephrolithiasis, porphyria, Henoch-Schönlein purpura, diabetic ketoacidosis, drug ingestion, and food hypersensitivity.

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2.7
JAUNDICE

Carolyn L. Frymoyer

Jaundice is a yellowish discoloration of the skin, sclerae, and mucous membranes caused by an accumulation of bilirubin to levels over 2.5–3.0 mg/dL. Other causes of yellowish pigmentation are excessive ingestion of foods rich in carotene (carrots) or lycopene (tomatoes) or certain drugs (quinacrine or busulfan). Based on the history, physical examination, and basic laboratory studies, the suspected etiology of jaundice can be divided into hemolysis, bilirubin conjugation or transport defect, hepatocellular disease, extrahepatic cholestasis, or intrahepatic cholestasis. Additional specific tests are indicated for each category.

I. History.

Toxins and drugs can induce hepatocellular damage or cholestasis, or both. Among the many agents known to cause jaundice are acetaminophen, certain antibiotics, chemotherapeutic agents, psychotropic medications, cholesterol-lowering agents, anticonvulsants, sex hormones, nonsteroidal anti-inflammatory drugs, inhalation anesthetics, thiazide diuretics, oral hypoglycemics, certain antihypertensives, certain antiarrhythmics, salicylates, cimetidine, warfarin (Coumadin), colchicine, allopurinol, penicillamine, gold, sulfa derivatives, and solvents. Alcohol use suggests intrahepatic cholestasis or hepatocellular injury. Hepatocellular injury due to viruses is associated with blood transfusions, intravenous drug use, sexual contact, travel to endemic areas, ingestion of contaminated foods, or contact with jaundiced persons. A history of gallstones, biliary surgery, previous episodes of jaundice or inflammatory bowel disease, acholic stools, sudden-onset jaundice, and right upper quadrant pain suggest extrahepatic cholestasis. Family history of jaundice suggests an inherited defect in conjugation or bilirubin transport, Wilson's disease, α_1-antitrypsin deficiency, hemochromatosis, or benign idiopathic cholestasis. Generalized pruritus suggests cholestasis. Recent nonbiliary surgery suggests hepatocellular injury.

II. Physical examination.

Presence of palmar erythema, spider angiomas, or ascites is suggestive of chronic liver disease. Kayser-Fleischer rings are seen in Wilson's disease. Xanthelasma is seen with chronic cholestatic liver disease, especially primary biliary cirrhosis. Hepatosplenomegaly, abdominal tenderness,

mass lesions, and cachexia are suggestive of inflammatory or neoplastic disease. Courvoisier gallbladder (a nontender, palpable gallbladder) is a sign of pancreatic cancer. Hepatic bruits or rubs suggest hepatocellular carcinoma.

III. Laboratory tests.

Initial laboratory tests should include transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, alkaline phosphatase, and albumin. Three patterns emerge, as delineated below.

A. Normal transaminases, alkaline phosphatase, and albumin suggest hemolysis or a defect of bilirubin conjugation or transport.

Fractionate the bilirubin into direct (conjugated) and indirect (unconjugated) bilirubin.

1. Elevated unconjugated bilirubin (>80%-85% of total) is seen with hemolysis or hereditary conjugating defects. Obtain a complete blood count (CBC), blood smear, reticulocyte count, and lactate dehydrogenase (LDH). If hemolysis is suggested, see Chapter 18.1, Chapter 18.2 and Chapter 18.3 . If laboratory results are not consistent with hemolysis, suspect a defect in conjugation, especially if the total bilirubin is less than 6 mg/dL and conjugated bilirubin is normal. Gilbert's syndrome is the most common conjugating defect (7% of population): bilirubin is usually less than 3 mg/dL but increases with fever, fasting, or stress; patients are asymptomatic and have normal liver histology. Crigler-Najjar syndrome is rare. Type I has bilirubins up to 50 mg/dL and results in death in infancy. Type II has bilirubin values as high as 20 mg/dL but no severe sequelae except jaundice.
2. Elevated conjugated bilirubin (>50% of total) suggests a congenital defect in conjugated bilirubin transport. These conditions appear in childhood or adolescence with bilirubin levels up to 25 mg/dL, but have no clinical sequelae. They follow an autosomal recessive inheritance pattern. Rotor's syndrome patients demonstrate visualization of the gallbladder on oral cholecystogram (OCG). With Dubin-Johnson syndrome the gallbladder is not seen on OCG; pathognomonic black pigment is found on liver biopsy.

B. Predominant elevation of transaminases suggests hepatocellular injury.

(see Chapter 11.5). Acute or chronic viral hepatitis can be diagnosed by viral hepatitis screens. Alcoholic hepatitis clinically resembles viral or toxic hepatitis, but AST is usually greater than ALT (a reversal of the usual ratio); diagnosis is based on a history of heavy alcohol intake, absence of other causes of hepatitis, and liver biopsy. Hereditary liver diseases include Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency. Wilson's disease is confirmed by low ceruloplasmin levels and Kayser-Fleischer rings or liver biopsy. Hemochromatosis is suspected in patients with a history of hepatomegaly, idiopathic cardiomyopathy, skin pigmentation, loss of libido, diabetes mellitus, or arthritis; elevated transferritin saturation and ferritin levels are suggestive of the diagnosis, which is confirmed by genetic testing or liver biopsy. α_1-antitrypsin deficiency is associated with pulmonary disease and confirmed by decreased α_1-antitrypsin levels. Congestive and ischemic diseases, including right-sided congestive heart failure, constrictive pericarditis, Budd-Chiari syndrome (hepatic vein or inferior vena cava obstruction), portal vein thrombosis, veno-occlusive disease, and hypotension, are causes of jaundice and hepatocellular injury; diagnosis is based on other physical findings. Liver diseases in pregnancy that cause hepatocellular injury are acute fatty liver of pregnancy and toxemia. Drug-induced hepatitis can be confirmed by drug levels (e.g., acetaminophen), agent-specific patterns of hepatotoxicity, and, occasionally, liver biopsy. Autoimmune hepatitis is suspected when antinuclear antibodies, smooth muscle antibodies, or antimitochondrial antibodies are seen; liver biopsy is helpful.

C. Predominant elevation of alkaline phosphatase suggests cholestasis.

5′-Nucleotidase and gamma-glutamyltransferase are usually elevated; if not consider a bone source. (Transaminases may also be elevated.)

1. If extrahepatic cholestasis is suspected based on history and physical examination, possible causes are choledocholithiasis, malignancies (pancreatic, bile duct, lymphoma, metastases), biliary stricture, sclerosing

cholangitis, chronic pancreatitis, biliary atresia, and other rare conditions (Asian cholangiohepatitis, ascariasis, hemobilia). *Extrahepatic biliary obstruction requires prompt surgical, endoscopic, or radiologic relief of obstruction.* Obtain ultrasound or CT scan to look for dilated intrahepatic bile ducts. Ultrasound is usually preferred due to lower cost, better detection of gallbladder stones, and avoidance of radiation exposure. CT gives better visualization of the pancreas and should be chosen if pancreatic pathology is suspected. If obstruction is confirmed, proceed to therapeutic intervention for relief of obstruction. Since ultrasound or CT scan can fail to detect up to 40% of intraductal stones, perform endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography if suspicion is high.

2. If intrahepatic cholestasis is suspected based on history and physical examination, order specific laboratory tests. Consider ultrasound to rule out extrahepatic obstruction. Acute and chronic hepatitis (viral, alcohol, and drug-induced) can be diagnosed by viral hepatitis screening (see Chapter 11.5) and by withdrawal of toxins. Cirrhosis is most commonly caused by long-term alcohol use and viral infections, especially hepatitis C. Rarer causes include genetic and metabolic diseases (Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency) and autoimmune diseases (primary biliary cirrhosis, primary sclerosing cholangitis, and lupoid hepatitis). Liver biopsy may be helpful if the diagnosis or cause is unclear. Chronic cholestatic syndromes include primary biliary cirrhosis and primary sclerosing cholangitis. Primary biliary cirrhosis is usually seen in middle-aged women; antimitochondrial antibodies are elevated in more than 90% of patients; liver biopsy confirms the diagnosis. Primary sclerosing cholangitis may be seen as an isolated finding or in association with inflammatory bowel disease, other fibrosclerosing syndromes, or AIDS; diagnosis is confirmed by ERCP or magnetic resonance cholangiogram. Benign recurrent intrahepatic cholestasis is diagnosed by recurrent episodes, family history, and absence of obstruction on cholangiography. Cholestasis of pregnancy is usually seen in the third trimester and often recurs in subsequent pregnancies or in association with estrogen use (see Chapter 13.6). Cholestasis can also be seen with sepsis, parenteral nutrition, postoperative state, or neoplasm.

2.8
EDEMA

Michael M. Herbst

Clinically apparent interstitial fluid accumulation is termed *edema*. It is the result of pathologic alteration of one or both of the Starling forces:

- The pressure differential across the capillary endothelium
- The oncotic force differential between plasma and the interstitial fluid

An increase in the capillary-tissue pressure differential results from increased venous pressure or decreased lymphatic return of interstitial fluid. The former is usually due to cardiac or venous disease, whereas the latter is usually due to lymphatic obstruction.

A decrease in the oncotic force differential results from a decrease in the serum protein concentration or an increase in the interstitial fluid protein concentration. The former may result from nutritional deficiencies, liver disease, or protein losing states. The latter usually results from increased endothelial permeability and occasionally from impaired clearance of lymph.

Each of these disturbances of the Starling forces may be the end result of many different pathologic mechanisms. Edema is therefore a common manifestation of many different disease entities. Because edema is a nonspecific manifestation of disease, diagnosis of its underlying cause is essential to proper treatment. Except for allergic reactions, edema itself is rarely of primary clinical importance. Often, however, it is the presenting complaint of a serious underlying disease.

The most common error in dealing with edema is to treat the patient empirically without considering an adequate differential diagnosis. In the elderly, for instance, edema is often assumed to be due to congestive heart failure (CHF) or venous insufficiency. The physician making this assumption will fail to recognize serious and potentially treatable diseases, such as deep venous thrombosis, hepatic disease, or renal disease. This error may literally be fatal.

I. Diagnosis.

A. General concepts.

Edema may be regional or systemic, and this distinction is the first key to diagnosis. Symmetrical edema is usually systemic in origin, and asymmetrical edema is usually due to regional disease. However, this correlation does not always hold. A systemic type of edema combined with local factors (e.g., mild CHF and unilateral varicose veins) may cause a primarily systemic edema to present asymmetrically. A regional cause of edema, such as a pelvic malignancy, may appear to be symmetrical. Table 2.8-1 lists the most important causes of each type of edema.

Systemic edemas
- Drugs
  - Hormones, especially steroids
  - Antihypertensives
  - Non-steroidal antiinflammatory drugs
- Cardiovascular disease
  - Cardiomyopathies
  - Congestive heart failure
  - Constrictive pericarditis
  - Vena caval obstructions
- Renal disease
  - Nephrosis
  - Chronic renal failure
  - Nephritis
- Liver disease
- Cirrhosis due to alcoholism, chronic viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, and others
  - Hepatic failure
- Nutritional
  - Anorexia nervosa
  - Malabsorption syndromes
  - Malnutrition
- Vasculitis
  - Systemic allergic reactions (e.g., angioedema)
- Miscellaneous
  - Cyclic edema
  - Orthostatic edema

Regional edemas
- Venous
  - Deep venous thrombosis
  - Venous insufficiency
  - Extrinsic compression (e.g., by tumor)
- Lymphatic
  - Inflammatory and infectious
  - Obstructive (e.g., carcinomatous)
  - Postsurgical (e.g., radical mastectomy)
  - Idiopathic
- Musculoskeletal
  - Acute trauma
  - Overuse syndromes (e.g., tenosynovitis)
  - Baker's cyst (popliteal vein compression)
- Miscellaneous
  - Reflex sympathetic dystrophy
  - Peripheral neuropathy
  - Arteriovenous malformations
  - Local allergic reactions
  - Thyroid disease (myxedema)

Table 2.8-1. Differential diagnosis of edema

B. History.

1. Inquire as to the **onset** and **duration** of the edema and any precipitating events (e.g., trauma or surgery), provocative or ameliorative factors (dependency or elevation), or **associated symptoms** (pain or redness.) These issues, while always pertinent, are especially important in regional edemas. For example, the edema of venous insufficiency typically improves overnight, whereas lymphedema does not; however, a systemic edema, such as cyclic edema, may vary with the menstrual cycle.
2. In systemic edemas, the physician must be especially careful to ask about any history or symptoms of cardiac, renal, hepatic, or malabsorptive diseases and about all medications. Patients should always be asked about the symptoms of CHF (see Chapter 9.4). Remember that it is as important to rule out CHF as it is to rule it in.

C. Physical examination.

1. Assess the **distribution** of edema: dependent edema, hand or facial edema, or total-body edema (anasarca). Discriminate between **pitting** and **nonpitting** (brawny) edema. The latter is more likely to be due to lymphedema or to chronic, organized edema. To assess pitting, apply thumb pressure for 5–10 seconds over the tibia or some other bony prominence. The degree of edema is usually (and somewhat loosely) classified as trace, mild, moderate, or severe, or one to four plus. Dependent edema is also often described by the level to which it is observed, for instance, to the knees.
2. Observe for **signs of inflammation** in the affected part and for the chronic skin hyperpigmentation of venous insufficiency (stasis dermatitis) (see Chapter 16.8). Observe for the cutaneous signs of chronic liver disease and cirrhosis (see Chapter 11.5).
3. Perform a careful **cardiac examination**, observing for cardiac enlargement, valvular heart disease, rhythm disturbances, and signs of pericarditis. Evidence of CHF must be carefully sought, with special attention to the jugular venous pulsations.
4. Perform an **abdominal examination,** observing for ascites, splenomegaly, and hepatomegaly.
5. Pelvic **examination** may be very important, especially when considering lower extremity lymphedema due to the lymphatic spread of carcinoma.
6. Examine the patient for **lymphadenopathy**, especially in regional or inflammatory edema.

D. Laboratory tests and imaging.

1. The laboratory may be very useful in difficult cases. All patients with unexplained edema should have the following tests performed:
   - Serum proteins
   - Liver function tests
   - Thyroid function tests
   - Blood urea nitrogen and creatinine
   - Urinalysis
2. A 24-hour urine protein excretion is useful for assessing the degree of nephrosis when that diagnosis is suspected. When infection is suspected, appropriate cultures and smears may be obtained. Stool studies may reveal malabsorption.
3. Imaging studies may be required when vascular obstruction, lymphatic obstruction, or hepatic, renal, or cardiac disease is suspected.
   a. *Deep venous thrombosis* (see Chapter 9.7). Deep venous thrombosis is common, frequently missed, potentially deadly, and treatable. If there is any reasonable suspicion of this disease, diagnostic testing should be performed. This can be done via impedance plethysmography, venography, or venous Doppler ultrasonography. The choice of modalities depends on their availability and the likelihood of the disease.
   b. *Tumor or lymphatic spread of carcinoma.* Computed tomography (CT) or magnetic resonance imaging (MRI) or, rarely, lymphangiography of the pertinent region may be indicated.
   c. *CHF and pericarditis.* Chest radiography, electrocardiography, echocardiography, radionuclide cardiography, and even cardiac catheterization may be necessary to diagnose these disorders.
   d. *Hepatic and renal disease*. Ultrasonography and MRI or CT may be useful in these diagnoses.

II. Treatment.

A.

The treatment of edema is always directed to the underlying pathophysiology. Avoid empirical treatment with diuretics unless the only likely diagnoses clearly justify their use.

B.

Most dependent edema, regardless of cause, may be safely treated with elevation of the legs and elastic compression stockings. Elastic stockings should fit well and develop the proper pressure gradient, which almost always requires custom fitting. Stockings that do not fit properly may worsen the patient's condition by acting as a tourniquet. Active patients are often reluctant to elevate the affected part or to wear compression stockings, but they should be vigorously encouraged to do so if only to prevent disease progression.

2.9
PELVIC PAIN

Karen M. Wildman

Pelvic pain can be caused by gynecologic, gastrointestinal, urologic, musculoskeletal, psychological, or neuropathic dysfunction. Although there may be overlap, acute and chronic pelvic pain will be considered separately in this chapter.

I. Acute pelvic pain

lasts for hours to weeks and is well defined in time, location, and quality. It is usually associated with a distinct pathologic process and often responds to treatment.

A. History

includes the location, duration, quality, and radiation of the pain, as well as any association with sexual activity, urination, bowel movements,

eating, or menstrual cycle. Question the patient regarding sexual activity, dyspareunia, contraception, and previous surgeries or infections. Obtain information about bowel habits, urinary complaints, fever, chills, vaginal discharge or irritation, or previous similar symptoms. Always consider pregnancy in any woman with childbearing potential.

B. Physical examination

should be thorough, with focus on the abdomen, back, pelvis, and rectum.

1. **Abdomen and back.** While palpating for tenderness of underlying structures, also note any musculoskeletal tenderness or spasm.
2. **Speculum examination.** Note any external genital lesions. Check for pain with insertion of the speculum and look for vaginal or cervical discharge, erythema, lesions, or bleeding. Collect cervical specimens for chlamydia, gonorrhea, wet mount, and potassium hydroxide (KOH) preparations.
3. **Bimanual examination.** Palpate for tenderness or masses at the introitus, urethra, bladder trigone, and vaginal cul-de-sac. Check for cervical motion tenderness and uterine size, contours, and tenderness. Note any adnexal masses or tenderness.
4. **Rectal examination.** Examine to confirm the findings of the pelvic examination. Also note rectal tenderness or masses, and check for blood.

C. Laboratory tests include urinalysis, genital cultures, vaginal wet mount, and KOH preparation.

Obtain a pregnancy test in all women of childbearing age. A complete blood count (CBC) or Gram's stain of vaginal discharge may be helpful. Ultrasonography is useful for pelvic masses or complications of pregnancy. Plain films, computed tomography (CT), or ultrasonography may be helpful in evaluating an acute surgical abdomen.

D. Differential diagnosis and treatment

1. **Pregnancy-related complications** include ectopic pregnancy and spontaneous abortion. Diagnosis is made by examination, positive pregnancy test result, and possibly ultrasound findings. Treatment is usually surgical (dilation and curettage, or laparotomy/laparoscopy). Medical management of early, unruptured ectopic pregnancies with methotrexate should be considered (see Chapter 14.5).
2. **Pelvic inflammatory disease** is characterized by the triad of lower abdominal pain, adnexal tenderness, and cervical motion tenderness (see Chapter 13.5). Associated findings may include fever, elevated white blood cell (WBC) count, elevated sedimentation rate, laboratory documentation of *Neisseria gonorrhoeae* or *Chlamydia trachomatis,* abnormal vaginal or cervical discharge, or pelvic mass on examination or ultrasonography.
   a. Inpatient treatment is indicated for patients who have fever and peritoneal signs or in cases of pregnancy, HIV infection, or suspected abscess. Consider hospitalization for noncompliant patients and those unable to take oral medications. One regimen is cefotetan 2 g IV every 12 hours, plus doxycycline, 100 mg IV or PO every 12 hours. An alternative, if anaerobic infection or abscess is suspected, is clindamycin, 900 mg IV every 8 hours, plus gentamicin, 2 mg/kg IV or IM loading dose followed by 1.5 mg/kg every 8 hours. Continue parenteral antibiotics until the patient has shown improvement for at least 48 hours, and follow with doxycycline, 100 mg orally twice daily, or clindamycin, 450 mg orally qid, to complete a course of 14 days (1). Pelvic or tubo-ovarian abscesses may need surgical drainage after initial antibiotic therapy.
   b. Outpatient treatment is appropriate for many patients. One treatment choice is ofloxacin 400 mg bid for 14 days plus metronidazole 500 mg bid for 14 days (1).
3. **Menstrual causes** of pain are cyclic, worse in the premenstrual and menstrual period, and often associated with normal physical examination and laboratory tests (2).

a. **Endometriosis** is caused by ectopic implants of endometrial tissue, commonly in the pelvis or lower abdomen. Pain often increases during the menstrual cycle. Untreated endometriosis can lead to adhesions, infertility, and chronic pelvic pain. Treatment is guided by symptom severity and the patient's future childbearing wishes. Medical management includes oral contraceptives continuously for 6–12 months without withdrawal, danazol 200–400 mg orally bid for up to 6 months, or gonadotropin-releasing hormone (GnRH) analogues, such as nafarelin acetate nasal solution (Synarel), one spray in one nostril bid for up to 6 months. Surgical treatment can involve lysis of adhesions, ablation of endometrial implants, hysterectomy, and oophorectomy. Consultation with a gynecologist is advised when treating these patients.

b. **Primary dysmenorrhea** is cramping pain with menses not associated with other pathology. Nonsteroidal anti-inflammatory medications (NSAIDs), such as naproxen sodium (Anaprox), 275–550 mg PO bid, may be given during menses for symptomatic relief. Oral contraceptives may be helpful when NSAIDs alone are inadequate.

c. **Mittelschmerz** is pain associated with ovulation, usually noted midcycle. Pain control can be achieved with NSAIDs. Oral contraceptives may help by suppressing ovulation.

4. **Ovarian cysts** are associated with adnexal tenderness, adnexal mass on examination, and findings consistent with a cyst on ultrasound. Cysts are common and usually asymptomatic, but large cysts (>5 cm) can cause significant pain and complications. Ruptured cysts can cause a sudden increase in pain. They occasionally cause intraperitoneal hemorrhage and require surgical treatment. Most intact cysts are best managed with pain medications and close observation through one to two menstrual cycles. Oral contraceptives may aid in resolution by causing ovarian suppression. Persistent large simple cysts, complex cysts on ultrasound, and cysts in postmenopausal or perimenopausal women should be evaluated by a gynecologist because of their malignant potential.
5. **Ovarian torsion** causes sudden onset of severe lower abdominal or pelvic pain, often localized to one side. Exquisite pain on palpation of the ovary is present. The patient may also have peritoneal signs, nausea, vomiting, and diaphoresis. This problem requires emergent surgical treatment to restore blood supply to the affected ovary.
6. **Leiomyomata (uterine fibroids)** are benign tumors of uterine smooth muscle. Examination reveals an enlarged, irregular uterus, with possible uterine displacement and tenderness. Pelvic ultrasonography can be diagnostic. Patients often report painful menses and increased flow. Large leiomyomata, heavy bleeding, or severe pain warrants surgical evaluation and treatment. Otherwise, symptomatic treatment is acceptable.
7. **Appendicitis** causes pain and tenderness localized to the right lower abdominal quadrant, but the pain can also radiate into the pelvis (see also Chapter 2.6). Fever, elevated WBC count, peritoneal signs, and anorexia are variably present. Differentiating between appendicitis, pelvic inflammatory disease, and ruptured ovarian cyst can sometimes be difficult. Treatment is surgical.
8. **Diverticulitis** is caused by inflammation of diverticula of the colon. Findings may include abdominal tenderness, nausea, vomiting, fever, and bloody stools. Diverticula may also rupture, causing development of peritonitis or abscess. Diverticulitis usually requires inpatient intravenous antibiotics. Perforated diverticula require surgical treatment as well as antibiotics.
9. **Irritable bowel syndrome** is a dysmotility syndrome of the gastro intestinal tract (see Chapter 11.8). Patients have alternating diarrhea and constipation and may have cramping pain, pain with defecation, abdominal bloating, and passage of mucus per rectum. Stress often exacerbates symptoms. Long-term control can be achieved by stress management,

dietary changes (elimination of caffeine, increased fiber, and elimination of milk products in lactose-sensitive patients), and fiber supplementation with over-the-counter psyllium products. Acute exacerbations can be managed with antispasmodic agents, such as dicyclomine hydrochloride (Bentyl), 10–20 mg PO qid.

10. **Miscellaneous causes.** Vaginitis, cervicitis, cystitis, urethritis, pyelonephritis, urinary tract stones, and lumbar disc disease can rarely cause acute pelvic pain and should be considered in the differential diagnosis.

II. Chronic pelvic pain

is defined as pelvic pain lasting longer than 3–6 months. It may have its basis in an organic problem, but it shares the unrelenting nature of other chronic pain syndromes. Chronic pelvic pain is positively associated with depression and a history of sexual or physical abuse, or both. Successful treatment often involves a multidisciplinary approach, with recognition of the chronic nature of the process and a clear definition of the treatment goals (3).

A. History

is as described in acute pelvic pain. Also question the patient about sexual or physical abuse, her current psychological state, and social history. Obtain records from previous evaluation and treatment of pelvic pain. Some practitioners obtain formal psychological testing.

B. Physical examination

and laboratory tests are the same as in acute pelvic pain, with the addition of a Pap smear. It is important to note the patient's emotional reaction to the examination.

C. Treatment

for chronic pelvic pain is complex. Patients should be treated as previously described for specific conditions such as endometriosis, irritable bowel syndrome, or pelvic infection. Many patients also need treatment for chronic pain syndrome. Treatment often involves coordination with other health care providers. Goals of treatment are pain control (not necessarily elimination) and optimization of lifestyle, with recognition by the patient of the chronic nature of the problem as well as the impact of stress, emotions, physical activity, and medications on the disease. Long-acting NSAIDs are often helpful for pain relief. Other helpful medications include low-dose tricyclic antidepressants [e.g., amitriptyline (Elavil), 10–50 mg at bedtime], and antiseizure medications [e.g., gabapentin (Neurontin) 300–600 mg PO tid, or carbamazepine (Tegretol) 100–300 mg bid]. Narcotics should not be routinely given. All medications for pain should be given on a scheduled basis, not as needed, as this decreases the patient's focus on her pain.

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2.10
BACK PAIN

Katherine L. Margo

Thomas D. Masten

Back pain, particularly low back pain, affects virtually everyone at some time. The etiology is often obscure, but once a serious medical problem has been eliminated the management is usually straightforward.

I. Low back pain

A. Etiology.

Causes include musculoligamentous injuries; disk herniation with nerve impingement; sacroiliac (SI) joint derangements; degenerative changes

of the bone, disk, or facet joint; spinal stenosis; severe spondylolisthesis or scoliosis; underlying systemic diseases, such as cancer, infection, rheumatologic disease; and visceral diseases, such as aortic aneurysms or kidney disease. The first task for the clinician is to rule out a serious nonorthopedic problem. Thereafter, defining a specific lesion is less important.

B. Diagnosis.

1. **History.** Serious conditions are found most frequently in patients older than 50 years. To rule out a potentially serious condition, ask about a history of trauma, cancer, unexplained weight loss or fever, failure of pain relief with bed rest, saddle anesthesia, bladder or bowel dysfunction, or a history that would indicate a risk of infection (e.g., HIV-positive status, intravenous drug use, and immune suppression).

   Inquire about the onset of pain. Disk problems tend to occur suddenly, whereas other mechanical pain often comes on gradually. Information about the duration of the pain and previous episodes of back pain, as well as identification of precipitating situations at work or during exercise can be helpful. Pain below the knee, paresthesias, and weakness of the lower leg are consistent with nerve compression, usually due to a disk protrusion or herniation. Patients with unilateral low back and buttock pain that gets worse with standing in one position may be suffering from an SI joint derangement. A history in older patients of exacerbation of pain with walking that is relieved by leaning forward is suggestive of neural claudication due to spinal stenosis. It is important to assess current functional limitations, the employment history, and the psychosocial situation when planning a course of treatment. Chronic pain is defined as pain lasting longer than 12 weeks. The management for chronic low back pain is different from that for acute low back pain.

2. **Physical examination.** Observation of the patient's posture and demeanor as you enter the room will assist you in assessing the severity of pain. Examine the spine for acute deviation, which is a sign of a disk derangement. Testing the range of motion of the spine looking for asymmetrical motion can also help identify disk problems. The walk test is performed by the examiner's positioning his or her thumbs over the patient's posterior superior iliac spines while the patient is standing and then watching to see if the thumbs move symmetrically when the patient's hips are flexed. Asymmetry of movement indicates an SI problem.

   Straight leg raising and extension of the knee while sitting (flip test) are tests for dural impingement usually from a disk; these tests are considered positive when pain is produced in the back or leg as the leg is extended. Pain on the contralateral side is a strongly positive test result.

   Every back examination should include a neurologic examination that includes muscle testing, sensory examination, and testing of deep tendon reflexes, especially in the L4 to Sl distribution, because 95% of lumbar disk herniations occur at L4 to L5 or L5 to S1. Palpation for tenderness over the lumbar spinous processes and between L4 and the iliac crest over the ileolumbar ligament completes the examination.

3. **Laboratory and radiographic studies.** In the evaluation of nontraumatic low back pain, laboratory or radiologic studies are not usually necessary during the first 4 weeks of the onset of back pain unless there are signs of a serious condition. Computed tomography (CT) and magnetic resonance imaging (MRI) can be misleading because of their high false-positive rate. Sixty-four percent of asymptomatic people have either a bulge or a protrusion of a disk on MRI (1). Even after 4 weeks, these tests should be reserved for the case in which surgery is contemplated. Blood tests are not indicated for the first 4 weeks unless there is a fever or other sign of systemic illness.

C. Management.

1. **Patient education.** Because 90% of patients recover within 4 weeks despite method of treatment, patient education regarding the natural history of acute low back pain is an important aspect of a successful outcome.

Contemporary management of acute low back pain, as expressed in the Agency for Health Care Policy and Research (AHCPR) Task Force report, moves beyond exclusively addressing pain control and bed rest to emphasis on improved activity tolerance and an early return to work. Taking time to discuss specific exercises and prevention by improving general fitness is also important. This also serves to avoid developing a disability mindset.

2. **Activity level.** Bed rest should be avoided except in the most extreme cases, and even then patients should be put on bed rest for only 1 or 2 days. Usual activities should be instituted as soon as possible. However, all lifting and bending probably should be avoided temporarily. Exercise classes are useful for people with nonspecific low back pain after 1 month (2).
3. **Medication.** One well-designed study has shown that patients treated with fewer pain medications and less bed rest than other therapy have lower costs and equal functional improvement after 1 and 12 months (3). Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen should be used as first-line agents. Muscle relaxants are frequently used but have not been shown to be any more effective than NSAIDs, and no study has shown use of both NSAIDs and muscle relaxants to be better than either one alone. AHCPR guidelines suggest that opioids taken for longer than 2 weeks, oral steroids, and colchicine should be avoided altogether.
4. **Physical treatment methods.** Manipulation by physical therapists, physicians, or chiropractors can be helpful during the first month of symptoms. It can also be used for the SI joint problems that are common in pregnancy. Standard traction, biofeedback, and physical modalities (e.g., heat and cold packs, corsets) have not been reported as helpful.
5. **Injections.** Epidural injections can be helpful in radicular pain and in spinal stenosis. Trigger point injections are also used but have not been thoroughly investigated.
6. **Surgery.** Cauda equina syndrome requires immediate surgery; otherwise only 5%–10% of symptomatic disk herniations require surgery. In fact, sciatica due to a herniated disk can resolve spontaneously in 9–12 months. Consider referral if a patient has persistent and severe sciatica and clinical evidence of nerve root compromise after 1 month of conservative care.
7. **Psychosocial factors.** A poor social situation can alter a patient's reaction to pain, especially if there is job dissatisfaction. Other factors, such as pending litigation, can complicate or prolong the treatment. Assessment by a psychiatrist or other mental health professional may be helpful if the psychological issues are complex.

II. Chronic low back pain.

Low back pain lasting longer than 12 weeks is considered chronic and carries with it a worse prognosis. The longer the pain lasts, the less the likelihood of recovery. The goal of treatment should be to improve functional capacity despite the pain. Passive modality treatments should be avoided. An active exercise/reconditioning program with experienced therapists can be helpful. Ongoing psychosocial support is also crucial. Ligament injections are advocated by some physicians. Surgery is best avoided unless there is a proven source of pain. Many alternative therapies are available to these patients; unfortunately, few have been studied scientifically. Most do not cause harm and may be worth trying for selected patients.

III. Cervical pain.

A. Diagnosis

1. **History.** A history of trauma, particularly that related to motor vehicle accidents, should be obtained. Pain down the arm with paresthesias in the distribution of C4 to C5 or below indicates nerve compression, often caused by disk protrusion. A story of waking up with a painful, deviated neck is consistent with an acute torticollis.

2. **Physical examination.** Range-of-motion testing of the neck should be performed, including side flexion, rotation, forward flexion, and extension. A complete neurologic examination of both upper extremities should be performed, including motor, sensory, and reflex testing.
3. **Laboratory and radiographic studies.** Unless there is a reason to suspect a systemic illness causing the pain or there is a history of trauma, no radiographs or other radiologic studies are necessary on initial evaluation.

B. Management.

When needed, immobilization with a soft or hard cervical collar should be limited to just a few days. The patient should start gentle range-of-motion exercises immediately. If the pain persists for more than 1 week, the patient should be referred for physical therapy. Medications should be limited to a mild analgesic, and a muscle relaxant should be added only if there is no response to the analgesic alone. Surgery is reserved for fractures or radiculopathy with disabling pain.

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III. EMERGENCY PROBLEMS IN AMBULATORY CARE

3.1
ANAPHYLAXIS

Susanne R. Dillon

Anaphylaxis is a clinical syndrome and medical emergency affecting multiple organ systems at varying intensities, from benign to life threatening. It is the result of a type 1 immunologic reaction causing activation of mast cells or basophils. Anaphylactoid reactions resemble anaphylaxis and are treated identically.

I. Diagnosis

A. Clinical presentation.

Regardless of cause, the clinical manifestations of anaphylaxis are similar. The onset of symptoms is usually rapid: 85% within 15 minutes and nearly all within 6 hours. Severity is directly related to rate of onset. A short prodrome of itching or burning of soles, genital area, lips, ears, or scalp may occur. Mild reactions involve the skin and may involve warmth, pruritus, flushing, and generalized urticaria. Moderate reactions involve other organ systems and may include angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness, upper and lower airway obstruction, weakness, dysphagia, dysarthria, and uterine contractions. Severe reactions may include hypotension, respiratory distress, cyanosis, shock, supraventricular or ventricular arrhythmias, myocardial infarction, and death. Nonfatal reactions typically resolve within 48 hours. Occasionally, biphasic reactions occur, in which symptoms return after 8–12 hours.

B. History.

It is important to be aware of the diverse causes of anaphylaxis (Table 3.1-1).

Venoms
Hymenoptera
Apids
Honeybees, bumblebees
Vespids: wasps, yellow-jackets, hornets
Formicids: fire ants, harvester ants
Others: Crotalids (pit vipers), Tabanidae (horseflies, deerflies)
Medications
Protein-based (hormones)
Non–protein-based (antibiotics, vitamins, succinate esters of hydrocortisone and methylprednisolone, nonsteroidal antiinflammatory drugs, opiates, muscle depolarizers)
Immunotherapy
Allergen extracts
Chemicals
Formaldehyde, ethylene oxide gas
Foods
Nuts, milk, shellfish, legumes, citrus fruits, bananas, chocolate, fish, eggs, grains
Foreign proteins
Vaccines (pertussis, typhoid, egg embryo)
Horse serum (antivenin)
Seminal plasma globulins (human, horse, rodent)
Antitoxins
Rubber and plastics
Radiocontrast material
Exercise
Idiopathic

Table 3.1-1. Causes of anaphylactic reactions

C. Laboratory.

Confirm by skin test, radio allergosorbent test (RAST), or basophil histamine release test.

II. Patient assessment

A. History.

Patients should be questioned about past attack severity, including causes, allergies, and symptoms of orthostatic hypotension or dyspnea.

B. Physical examination.

Vital signs should be monitored frequently. Inspiratory and expiratory stridor, hoarseness, and choking indicate upper airway obstruction. Wheezing indicates lower airway obstruction. Continuous oxygen monitoring is beneficial in initial evaluation and for treatment efficacy.

C. Laboratory studies.

1. **Arterial blood gases.** Mismatching of ventilation and perfusion secondary to airway obstruction results in an increased alveolar-arterial oxygen tension difference, or $P(A\text{-}a)O_2$. Arterial carbon dioxide tension ($PaCO_2$) is often low because patients hyperventilate to increase arterial oxygen tension (PaO_2). PaO_2 may be normal or low.
2. **Continuous cardiac monitoring** is indicated in patients with underlying heart disease, chest pain, hypotension, shock, concurrent use of ß-blockers, arrhythmias, and use of intravenous epinephrine or vasopressors.
3. **Chest radiography** is indicated in patients with localized physical findings or poor response to treatment of bronchospasm.
4. **Complete blood count** and electrolyte determinations are indicated if treatment is prolonged or if the patient is hospitalized.

III. Treatment.

The immediate goal of therapy is maintenance of the ABCs (airway, breathing, and circulation). The drug of choice is epinephrine, 1:1,000. See Table 3.1-2 for all medication dosing regimens.

Generic name	Trade name	Route	Adult dosing	Pediatric dosing
Albuterol 0.5% (in 2.5 mL saline)	Proventil, Ventolin	Neb	0.5–1.0 mL	Age <2 yr: 0.03 mL/kg Age >2 yr: 0.5–1.0 mL
Aminophylline	Phyllocontin	IV	Load with 6 mg/kg over 30 min, then 0.5–0.7 mg/kg per hour	Load with 5.6 mg/kg over 30 min, then 1 mg/kg per hour
Atropine	—	IV, endotracheal	0.3–0.5 mg q5–10min prn to total of 2 mg	0.02 mg/kg to a max of 0.5 mg and 1 mg for adolescent; may repeat once
Chlorpheniramine 2 mg	Chlo-Amine	PO	4 tabs	Age <6 yr: 1 tab Age 6–12 yr: 2 tabs
Cimetidine	Tagamet	IV, PO	300 mg q6–8h	5 mg/kg q6–8h
Diphenhydramine	Benadryl	PO, IM, IV	50 mg q6–8h	1mg/kg up to 50 mg q6–8h
Dopamine	Dopastat, Intropin	IV	2–20 µg/kg per minute	2–20 µg/kg per minute
Epinephrine 1:1,000	—	SC, IM	0.3–0.5 ml q15–20min prn	0.01 mL/kg to 0.3 mL q15–20min prn
Epinephrine 1:1,000	—	IV	1 µg/min titrate, up to 4–10 µg/min	0.025–0.100 µg/kg per minute titrate
Glucagon	—	IV	5–15 µg/min	1–2 mg/kg
Hydroxyzine	Atarax	PO	25 mg tid–qid	Age <6 yr: 50–100 mg/d in divided doses Age >6 yr: 50–100 mg/d in divided doses
Isoproterenol	Isuprel	IV	2–10 µg/min	0.1–1.0 µg/kg per minute
Metaproterenol 5% (in 2.5 mL saline)	Metaprel, Alupent	Neb	0.3 ml q20min prn	Age <2 yrs: 0.1 mL q20min prn Age >2 yr: 0.3 mL q20min prn
Methylprednisolone	—	IV	1–2 mg/kg q6h prn	1–2 mg/kg q6h prn
Norepinephrine	Levophed	IV	2–4 µg/min	0.1–1.0 µg/kg per minute
Prednisone	Pediapred, Deltasone	PO	1–2 mg/kg q8h prn	1–2 mg/kg q8h prn
Racemic epinephrine 2%	—	Neb	0.5–0.75 mL	0.25–0.5 mL
Terbutaline	Brethine	SC	0.25 mg q20min prn	0.01 mL/kg q20min prn
Terfenadine	Seldane	PO	60 mg bid	Age ≥12 yr: 60 mg bid

IM, intramuscular; IV, intravenous; Neb, nebulizer; PO, by mouth; SC, subcutaneous.

Table 3.1-2. Medication used to treat anaphylaxis

A. General therapy.

1. Epinephrine 1:1,000 SC or IM for adults is given at the rate of 0.3–0.5 mL. It may be repeated in 5 minutes if no response and then every 15–20 minutes prn. The higher dose is indicated in asthmatics. Children receive 0.01 mL/kg every 15–20 minutes to a maximum of 0.3 mL per dose.
2. Stabilize the airway and, if dyspneic, administer oxygen (may require endotracheal intubation or cricothyrotomy).
3. Obtain intravenous access with at least an 18-gauge needle for volume replacement and medications. Two intravenous lines are recommended if hypotension exists.
4. Decrease allergen absorption when appropriate (venoms, vaccines, injections) by placing a proximal tourniquet. Epinephrine 1:1,000 in a dose of 0.15 mL can be injected at the site. In case of an insect sting, remove any remaining stinger and venom sac by scraping it off. Do not pinch or squeeze the venom sac.
5. Assess vital signs frequently.
6. Hospital admission is recommended in all severe reactions.
7. Corticosteroids are often administered when symptoms are prolonged or to prevent biphasic reactions. Use methylprednisolone or prednisone.

B. Cutaneous symptoms.

Apply general therapy (previously mentioned) as indicated. H**1** antagonists are useful and in mild symptoms may be used primarily. Diphenhydramine, hydroxyzine, and terfenadine are examples. Cimetidine, an H**2** antagonist, does not appear to be helpful but may be added. (Caution should be used because cimetidine can cause bronchospasm.)

C. Airway obstruction.

Apply general therapy first.

1. For upper airway obstruction, add aerosolized racemic epinephrine 2%. Endotracheal intubation is indicated if the patient does not respond promptly.
2. For mild bronchospasm, add a nebulized ß-adrenergic agent, such as metaproterenol.

3. For severe bronchospasm, in addition to nebulized ß-adrenergics, add aminophylline. Terbutaline may be useful and may be repeated once in a 4-hour period.
4. For persistent symptoms, administration of an intravenous corticosteroid may be beneficial (see Section III.A).

D. Hypotension.

Apply general therapy first.

1. Increase central blood volume by placing the patient in Trendelenburg's position. Application of a military antishock trousers (MAST) suit can buy time for other treatments to act.
2. Intravenous fluid replacement with normal saline or colloids should be rapid. Large volumes may be required.
3. Pressor agents may be required for persistent or recurrent symptoms. Titrate to maintain systolic blood pressure in the 80- to 100-mm Hg range. Start with intravenous epinephrine. If the patient does not respond, consider continuous infusion of norepinephrine or dopamine.
4. Central venous pressure monitoring may be beneficial.

E. Special circumstances.

1. Concurrent use of ß-blockers diminishes the heart's natural inotropic response. Administration of intravenous glucagon can be beneficial. Consider atropine or an isoproterenol drip, or both.
2. Arrhythmias should be treated with standard antiarrhythmic agents.

IV. Patient counseling and prevention is extremely important

A. Avoidance techniques.

As much as possible, individual causes should be avoided (see Chapter 8.6). In hymenoptera allergy, it is important to curtail high-risk outdoor activities (e.g., mowing grass, trimming hedges, gardening). The patient should avoid areas with food attractants (e.g., picnics, garbage disposal areas, fruit trees) and scented preparations (e.g., shampoos, hair gels and sprays, perfumes) and wear protective clothing (e.g., drab colors, long sleeves, shoes, helmets, gloves).

B. First aid.

After appropriate instruction in use, epinephrine kits should be obtained and kept readily available.

1. Epinephrine 1:1,000 is available as Ana-kit (Miles, Inc., West Haven, CT; two 0.3-mL doses in syringe plus four 2-mg chlorpheniramine tablets), EpiPen (Center Laboratories, Port Washington, NY; 0.3 mL), and EpiPen Jr. (0.3 mL of epinephrine 1:2,000=0.15 mg) with an autoinjector.
2. Antihistamines. Diphenhydramine or chlorpheniramine should be taken.
3. Decrease absorption when appropriate (see Section III.A).
4. Seek medical attention

C. Immunotherapy.

may be indicated to desensitize patients. Before consideration, sensitivity should be confirmed by a positive skin test result, radioallergosorbent test, or basophil histamine release test at least 2–4 weeks after the anaphylactic reaction.

1. **Hymenoptera.** All adults and children with a history of moderate to severe reactions should be considered. Treatment for adults with cutaneous symptoms only is controversial and for children is not recommended.
2. **Medications or vaccines.** Consider only if there is compelling indication for use of the drug.

D. Medical alert identification tags are always indicated.

E. Pretreatment protocols for radiocontrast sensitivity are available.

V. Differential diagnosis

A.

Sudden loss of consciousness includes causes of syncopal episodes (e.g., vasovagal, seizures, arrhythmias, hypoglycemia) and cerebrovascular accidents.

B.

Respiratory distress includes asthma, chronic obstructive pulmonary disease, epiglottitis, and foreign body obstruction.

C.

Angioedema includes hereditary angioedema.

D.

Skin symptoms include systemic mastocytosis, carcinoid syndrome, serum sickness, Chinese restaurant syndrome, scromboid toxin, and side effects of medications.

E.

Psychiatric symptoms include factitious anaphylaxis and malingering.

3.2
DRUG OVERDOSE

Jerome E. Schulz

Suicide attempts, poisonings, pediatric accidental ingestion, and illicit drugs are the most commonly encountered drug overdoses (see also Chapter 5.7). Initially assess patients for the presence of life-threatening complications. Treatment should focus on the elimination of the drug and specific antidote and drug therapy.

I. Emergency treatment and evaluation

A. Stabilization.

In comatose or severely compromised drug overdose patients, establish an airway and ventilate the patient immediately. In lethargic or obtunded patients, check the gag reflex and, if it is not present, intubate the patient. If no blood pressure or pulse is present, begin cardiopulmonary resuscitation (CPR). Patients should be monitored for cardiac arrhythmias, and a large-diameter intravenous line should be placed.

B. Generalized treatment.

During the initial treatment of drug overdose patients, empirically treat unconscious patients for possible hypoglycemia with 50 mL of 50% dextrose intravenous (IV). Before glucose is given, patients should receive 100 mg of IV thiamine to prevent an acute Wernicke's syndrome in those with alcoholism. For potential narcotic overdoses, give naloxone (Narcan) to any patient with respiratory depression, 0.4 mg IV; if there is no response in 1–2 minutes, give 2 mg IV, and keep repeating the dose to a maximum of 10–20 mg IV.

II. History.

Question the patient, the patient's family or friends, and the paramedics about any drugs the patient is taking and whether any empty bottles or drug paraphernalia were found in the house. The approximate time of ingestion helps determine whether to use agents to increase the elimination of the drug. A past medical history helps to determine whether the patient has other significant diseases that may complicate the overdose.

III. Physical examination.

A quick physical examination should focus on blood pressure, pulse, respirations, and pupils. Examine the skin for sweating, a cold or clammy feeling, and needle marks. Rales in the lungs point to pneumonia or pulmonary edema. Check the abdomen for an enlarged liver, and smell the breath for any distinctive odors. The neurologic examination should include level of consciousness, presence of nystagmus, the gag reflex, and deep tendon reflexes.

IV. Laboratory assessment.

The laboratory is of limited value in the initial evaluation of overdose patients, and waiting for the results of toxicology screens can be life threatening. False-negative or false-positive drug screen results can be misleading. Baseline laboratory studies should include a complete blood count, electrolytes, urinalysis (including a check for hemoglobin to detect rhabdomyolysis), blood sugar, and blood urea nitrogen. Any patient with impaired respirations should have an arterial blood gas measurement, chest radiography, and electrocardiography. Do a toxicology screen on the blood, urine, and any gastric contents.

V. Specific drug overdose treatment

A. Cocaine and amphetamines.

1. **Clinical presentation.** Patients with stimulant drug overdoses present with chest pain, cardiac arrhythmias, hypertension, strokes, paranoia, seizures, severe agitation, and triggering or worsening of asthma attacks. Severe cocaine intoxication may present as bradycardia and hypotension. Death is caused by cardiac arrhythmias, status epilepticus, cerebral hemorrhage, or hyperthermia. Suspect cocaine overdose in young patients presenting with chest pain and screen the urine and serum for benzoylecgonine (a metabolite of cocaine) (1). Simultaneous ingestion of alcohol increases the production of cocaethylene, which causes prolonged drug toxicity. Smugglers may swallow large bags of cocaine to prevent detection, a practice known as "body packing." Rupture of the bags causes severe cocaine intoxication.
2. **Treatment.** Treat hypertension with diazepam (Valium), 5–10 mg IV no faster than 5 mg/min. If severe hypertension persists, start a sodium nitroprusside infusion, 0.5–10 µg/kg per minute. ß-Blockers are contraindicated because they may cause a paradoxical increase in blood pressure and increase the mortality rate in cocaine overdose patients. Hyperthermia needs to be aggressively treated with rapid cooling to prevent rhabdomyolysis and subsequent renal failure. Treat myocardial ischemia with nitroglycerin and aspirin. Consider thrombolytic therapy and/or coronary catheterization in acute myocardial infarctions. Treat body packers with activated charcoal (50–100 g in adults) and a cathartic. Amphetamine psychosis, seen after "speed runs," can be managed with diazepam, 0.1–0.2 mg/kg IV or, in severe cases, haloperidol (Haldol), 5–20 mg IM or PO (but this may cause hyperthermia and a lowered seizure threshold).

B. Tricyclic antidepressants.

1. **Clinical presentation.** Tricyclic antidepressants are frequently used in suicide attempts. Patients present with anticholinergic signs, including tachycardia, elevated temperature, confusion and delirium, decreased gastrointestinal motility, hyperreflexia, and dilated pupils. Patients presenting with arrhythmias, altered mental status, seizures, respiratory depression, or hypotension are at high risk, requiring close monitoring and usually admission to the hospital. Think of tricyclic antidepressant overdose if the patient has a QRS interval longer than 0.12 second with right axis deviation on the electrocardiogram (2).
2. **Treatment.** Because antidepressant overdoses decrease gastrointestinal motility, do gastric lavage and give activated charcoal every 4 hours. Treat cardiac toxicity and hypotension with sodium bicarbonate, 1–2 mEq/kg IV bolus, until the arterial pH is 7.45–7.55. If this does not control arrhythmias, give lidocaine. Glucagon (10 mg IV) has been used to treat severe hypotension in tricyclic overdoses (3). As a preventive measure, selective serotonin reuptake inhibitors should be used in high-risk suicide patients.

C. Ethanol and benzodiazepines.

1. **Clinical presentation.** Patients frequently use alcohol to "get the courage" to attempt suicide with other drugs. Adolescents may present with isolated alcohol intoxication due to experimental binge drinking. Symptoms include nystagmus, ataxia, hypoglycemia, vomiting, and coma. A blood level of 300 mg/dL causes coma in a "novice" drinker (see also Chapter 5.3). In patients with severe coma and respiratory depression or arrest, consider the possibility of concomitant γ-hydroxybutyrate (GHB, one of the "date rape" drugs) ingestion.
2. **Treatment.** When managing ethanol overdoses, do a urine toxicology screen to determine which, if any, other drugs have been ingested. Flumazenil (Romazicon, formerly Mazicon), 0.2 mg IV over 30 seconds, and repeated if needed in 1–2 minutes, can reverse the sedation and respiratory depressant effects in benzodiazepine overdoses (4), but it is rarely needed and can cause serious side effects (seizures if the patient is taking concomitant tricyclic antidepressants, and severe withdrawal effects and seizures if the patient is dependent on benzodiazepines). Temporary intubation and ventilatory support may be necessary in GHB overdoses or to prevent aspiration in sedative-hypnotic overdoses.

D. Opiates.

1. **Clinical presentation.** Opiate overdose is characterized by respiratory depression, pupil constriction [may not be seen with meperidine (Demerol) or diphenoxylate (Lomotil) overdose], central nervous system depression, and low blood pressure and pulse. In severe overdose patients, apnea and pulmonary edema may occur. If alcohol has been ingested,

opiate toxicity is increased. Fentanyl is not detected in standard urine toxicology screens.

2. **Treatment** (see above). In propoxyphene (Darvon) overdoses, large doses of naloxone are needed. Treat cardiac arrhythmias caused by propoxyphene with IV sodium bicarbonate (5). Because the effect of naloxone is shorter than that of most opiates, treat patients with repeated doses every 2 hours.

E. Hallucinogens.

1. **Presentation.** Lysergic acid diethylamide (LSD) is the most commonly abused hallucinogen. LSD causes sympathetic stimulation with tachycardia, hallucinations, paranoia, fear, dilated pupils, sweating, and fever. It can be difficult to differentiate hallucinogen intoxication from acute schizophrenic symptoms. Patients who have taken hallucinogens usually have no history of mental illness, know that the symptoms are drug related, and have visual instead of auditory hallucinations. Patients who have been at a "rave" dance club commonly ingest LSD, methylene dioxymethamphetamine (ecstasy or MDMA), or methylenedioxyamphetamine (Eve or MDA).
2. **Treatment.** Hallucinogens are rapidly absorbed into the bloodstream, and lavage and activated charcoal only increase agitation. Quiet reassurance helps patients to "come down." In severe cases, diazepam or lorazepam helps to quiet patients. MDMA can cause hyperthermia and muscle rigidity that can lead to rhabdomyolysis if untreated (cool the patient and use benzodiazepines for rigidity).

F. Phencyclidine.

1. **Clinical presentation.** Treatment of phencyclidine (PCP) overdose patients is dreaded by most health care professionals. Patients' behavior ranges widely, from quiet sedation to severe violence. PCP is frequently used as an adulterant in other illicit drugs, and patients may not know that they have ingested PCP. In mild intoxication, patients are lethargic, euphoric, and have hallucinations. In more severe intoxication, patients have hypertension, muscle rigidity, sweating, seizures, and coma. Suspect PCP intoxication in any patient with nystagmus and rapidly changing behavior.
2. **Treatment.** Because enterohepatic recirculation slows elimination, the effects of PCP last up to 24 hours. Decrease sensory input and administer activated charcoal to decrease reabsorption. Avoid the use of restraints, which can increase the risk of rhabdomyolysis. Treat violent behavior with benzodiazepines. Haloperidol may be used cautiously but it may increase muscle rigidity. Increased diuresis is advocated by some authors (6).

VI. Prevention.

Physicians play a critical role in preventing *prescription* drug overdoses. Evaluate all patients for their overdose potential. Give low-toxicity drugs to patients with a history of depression, substance abuse, previous suicide attempts, or overdoses and to those who may be more sensitive to drugs, such as the elderly, young, pregnant, or patients on other drugs. Female patients are more likely to overdose than male patients. Give high-risk patients smaller amounts of the drug with more frequent refills. This is especially true in patients with seizure disorders requiring barbiturates. Barbiturates are ten times more toxic than the benzodiazepines (7). In pain management, remember that propoxyphene is much more toxic in overdoses than other narcotics. For every written prescription, physicians should ask themselves:

- What is the overdose potential of this patient?
- Are there equally effective drugs that have less overdose toxicity?

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3.3
EPISTAXIS

Marc W. McKenna

Epistaxis, defined as bleeding from the nasal mucosa, is a common problem seen by and cared for by the primary care physician. Although more than 90% of nosebleeds are self-limiting and easily managed, the clinical spectrum includes life-threatening situations that require emergency intervention. Epistaxis is usually an isolated phenomenon but may be a herald of systemic disease (1).

I. Types

A. Anterior.

Bleeding from the anterior nasal mucosa is by far the most common source of epistaxis and the easiest to treat. Anterior bleeds are usually the result of cracks in dry nasal mucosa, mild local irritation, or trauma. The bleeding site is typically from the vessel-rich area called Kiesselbach's plexus.

B. Posterior.

Posterior bleeds are less common and potentially more serious. Posterior bleeds tend to occur in older patients and are associated with the presence of hypertension, diabetes mellitus, atherosclerosis, and bleeding disorders. The bleeding site is usually posterior to the inferior turbinate, and blood comes from the sphenopalatine artery.

II. Causes of epistaxis

A. Local.

- Dry nasal mucosa
- Infection
- Allergy
- Trauma
- Foreign body
- Tumor
- Nose picking

B. Systemic.

- Hypertension (see also Chapter 9.1)
- Atherosclerosis
- Alcohol
- Bleeding disorders (see also Chapter 18.3)
- Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
- Medications: aspirin, warfarin, dipyridamole, antihistamines, nasal steroids, diuretics

III. Assessment

A. History.

Immediate assessment of the patient's overall medical condition, hemodynamic stability, and the need for resuscitation is essential. If stable, the patient should be asked to describe the amount, severity, and duration of the bleeding. Inquiry into which side of the nose is involved should be made. Initial dripping of blood in the pharynx is more commonly an indication of a posterior nosebleed. The patient should also be questioned as to other medical conditions, present medication usage, history of trauma, and any previous episodes of epistaxis.

B. Physical examination.

Initial physical examination must include vital signs and assessment of the need for stabilization. If possible, the patient is best examined sitting up and leaning forward. Examination with a nasal speculum or otoscope should be performed to localize the site of bleeding. If bleeding is profuse, suction is needed. Topical application of 0.5%–1.0% phenylephrine (Neo-Synephrine) or oxymetazoline (Afrin) promotes vasoconstriction. Topical 2% pontocaine (Tetracaine) or 4% lidocaine (Xylocaine) can be used for anesthesia. A 4% cocaine solution provides both anesthesia and vasoconstriction. Topical agents can be applied with a cotton-tipped applicator or with a soaked cotton pledget.

C. Laboratory studies.

Pertinent laboratory analyses include a complete blood count, platelet count, prothrombin time, and partial thromboplastin time. A bleeding time may be helpful if there is a history of bleeding disorders.

IV. Treatment

First stabilize the patient. Try to relieve anxiety, and control the blood pressure.

A. Anterior bleed.

1. Initial treatment includes having the patient sit up and pinch the soft part of the nose for a full 5 minutes. If this is not successful, topical vasoconstrictors and anesthetics, as described in Section III.B, should be applied. Oxidized cellulose (Oxycel), microfibrillar collagen (Avitene), or absorbable gelatin sponge (Gelfoam) can be placed on the bleeding site. These adherent materials can help with hemostasis. They also have the advantage of not having to be removed because they dissolve over the next few days. If these interventions are successful, the patient should be discharged with instructions for increasing humidification of the nasal mucosa with frequent use of saline drops or at least nightly application of petroleum jelly to the friable nasal mucosa.
2. **Cautery.** If there was a significant amount of bleeding, if the bleeding has been recurrent, or if there are prominent septal vessels, many physicians cauterize the bleeding site. A moistened silver nitrate stick can be used to cauterize the area. Be cautious not to treat a larger area than necessary. If some bleeding is still present, electric cautery tends to be more effective but requires deep local anesthesia (2). Too aggressive electrocautery can lead to perforation of the septum. Gelfoam, Oxycel, or Avitene can also be used after cautery. Antibiotic ointment (such as Neosporin) can then be applied to the nasal mucosa, and the patient may be sent home. Once again, increased humidification of the nasal mucosa is necessary.
3. **Packs.** If bleeding persists, packing is necessary. A compressed nasal tampon (Merocel) can be placed in the nares. As it swells with hydration, it provides hemostasis. Another option is the use of bayonet forceps to place a full anterior pack. Half-inch petroleum jelly (Vaseline) gauze is used to fill the entire nasal cavity. Layer the pack into the anterior nasal cavity in tightly packed, accordion-type pleats that provide enough pressure to control the bleeding. Both the Merocel and nasal packing need to be impregnated with antibiotic ointment. Both are removed in 2–3 days. The patient should be treated with antistaphylococcal antibiotics while the packing is in place to decrease the risk of a sinus infection. The nasal tampon may need to be rehydrated to facilitate its removal. The disadvantage of packing is that it can be uncomfortable for the patient (3).

B. Posterior bleed.

True posterior bleeds that do not respond to anterior packing require posterior packing. Posterior packs exert pressure on the posterior pharynx with either a Foley catheter balloon or gauze, with traction coming from pressure at the anterior nares. These traditional packs are cumbersome and have been replaced by specially designed balloon catheters. These double-balloon catheters are lubricated with antibiotic ointment, and the tip is advanced to the nasopharynx. The nasopharyngeal balloon is inflated and pulled anteriorly until it fits snugly. Then the anterior balloon is filled to occupy the nares. Complications from posterior packs include hypoxia, increased vagal tone, hyperventilation, arrhythmias, and sinusitis (4). Patients must be hospitalized and closely monitored for arrhythmias and hypoxia. The packs are left in place for 3 days. Prophylactic antibiotics are recommended. Ear, nose, and throat consultation is the norm for all posterior bleeds. Persistent bleeds may require endoscopic cautery, vessel ligation, or vessel-specific embolization (5).

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3.4
SYNCOPE

Carole Nistler

Syncope is the temporary cessation of cerebral blood flow causing loss of consciousness and postural tone followed by spontaneous recovery, not requiring resuscitation. Presyncope is the sensation of light-headedness or faintness that may precede syncope or may represent an unrelated disorder.

Syncope is a symptom of one or more underlying causes. Cardiac causes, related to mechanical obstruction or arrhythmic disruption of cardiac output, should be identified early in the workup of syncope because these factors are associated with a 1-year mortality of 20%–30% and an increased incidence of sudden death (1,2). Syncope should be distinguishable by history from other conditions that cause altered consciousness, such as seizure, vertigo, amnesia, concussion, migraine, hypoglycemia, drug or alcohol intoxication, narcolepsy, or coma. These conditions either are associated with other distinctive symptoms or do not cause an abrupt loss of consciousness followed by a spontaneous recovery.

I. Causes of syncope

A. Cardiovascular.

(Table 3.4-1)

Cardiovascular
Reflex or circulatory
Neurally mediated or vasovagal attack
Situational (e.g., micturition, swallowing, defecation, pain)
Orthostatic (drugs, hypovolemia, infection, autonomic dysfunction, pregnancy)
Carotid sinus hypersensitivity (tight collar, shaving, elderly)
Cardiac
Mechanical or obstructive (aortic or pulmonic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, pulmonary embolism, tetralogy of Fallot, atrial myxoma, myocardial infarction, prosthetic valve malfunction)
Arrhythmia (sick sinus syndrome, atrioventricular block, supraventricular or ventricular tachycardia, long QT syndrome, pacemaker malfunction)
Noncardiovascular
Neurologic
Primary autonomic dysfunction (e.g., Shy-Drager syndrome)
Secondary autonomic dysfunction (e.g., alcoholic or diabetic neuropathies, pernicious anemia, cancer)
Vertebrobasilar transient ischemic attack
Subclavian steal syndrome
Vertebral artery compression (e.g., cervical rib)
Normal-pressure hydrocephalus
Psychiatric
Panic disorders
Hysteria
Depression
Unexplained

Table 3.4-1. Causes of syncope

1. Reflex or circulatory syncope is due to abnormal cardiovascular reflexes that disrupt or reverse the normal compensatory autonomic response to standing or any other situation that reduces venous return to the heart. Parasympathetic activity in the ventricular wall overrides the normal increase in sympathetic output of the heart and blood vessels, resulting in

peripheral blood pooling and right-sided heart underfilling. Neurally mediated syncope or vasovagal attack is diagnosed when no other cause is identified and is the most common cause of syncope among people without heart disease. A vasovagal cause of recurrent syncope may be confirmed with tilt-table testing (3,4).

2. Cardiac syncope is due to decreased cardiac output from either mechanical obstruction or arrhythmia. Obstructive causes are typically associated with exertion. Arrhythmias often cause abrupt unconsciousness, not related to exertion, and may be secondary to underlying structural heart disease, drugs, or electrolyte abnormalities. Ventricular tachyarrhythmias associated with underlying heart disease may be life threatening (see Chapter 9.6).

B. Noncardiovascular.

1. Neurologic syncope is an infrequent cause. Although tonic-clonic movements may be associated with syncope, seizure disorders should be distinguishable from true syncope by the presence of warning auras, urinary or fecal incontinence, and postictal states (see Chapter 6.4). Many neurologic disorders can cause autonomic dysfunction, which in turn leads to orthostatic causes of syncope. Although vertebrobasilar insufficiency, not carotid, may cause loss of consciousness, it is usually associated with brain stem or focal neurologic deficits.
2. Psychiatric syncope may be associated with hysteria, panic disorder, or major depression. Its management consists of treatment of the psychiatric disorder (see Chapter 5.1 and Chapter 5.2).

C.

Unexplained syncope may occur in 38%–47% of patients undergoing evaluation (5).

II. Diagnosis and management

A.

History should include a description of the syncopal event by the patient and, if possible, a witness; any preceding or residual symptoms (postictal state, neurologic deficit); any relationship to micturition, defecation, cough, swallowing, acute pain, postural change, exertion, shaving, increased neck pressure, or stretching. Medications that may cause syncope are nitrates, calcium channel blockers, ß-blockers, angiotensin-converting enzyme inhibitors, phenothiazines, tricyclic antidepressants, monoamine oxidase inhibitors, barbiturates, diuretics, and drugs that cause prolonged QT syndrome, such as quinidine, terfenadine, trimethoprim-sulfamethoxazole, and the macrolides.

B.

Physical examination should focus on the detection of cardiovascular or neurologic disease. Measurement of orthostatic changes (at least a 20 mm Hg decrease in systolic pressure on standing after a supine period of at least 5 minutes) may be diagnostic, if they occur in conjunction with syncopal symptoms. Carotid sinus pressure for 5 seconds in a supine patient may be attempted, with cardiac monitoring and intravenous access, to detect a cardiac pause of 3 seconds or a 50 mm Hg decrease in systolic blood pressure.

C.

Initial diagnostic tests should include blood urea nitrogen, creatinine, electrolytes, glucose, calcium, hematocrit, and, if appropriate, a pregnancy test (6). Cardiac enzymes, arterial blood gases, or drug screens may be indicated by the clinical picture. More importantly, an electrocardiogram (ECG) should be obtained to help rule out cardiac causes. If cardiac obstructive causes are suspected, an ECG and possibly cardiac catheterization may be indicated.

D.

Arrhythmia detection, suggested by an abnormal ECG (atrioventricular block, tachyarrhythmias, Wolff-Parkinson-White syndrome), should prompt further testing. Twenty-four-hour or 72-hour Holter monitoring lacks the sensitivity and specificity to detect arrhythmic causes of syncope. The continuous-loop ECG monitor, which can be worn for several weeks and which records the immediate past 5 minutes of cardiac rhythm when the patient pushes a button, may provide a better method. Signal-averaged electrocardiography is a noninvasive method of detecting the propensity for ventricular tachycardia. Electrophysiologic studies are indicated for patients with evidence of underlying heart disease whose diagnosis has not yet been identified through noninvasive tests.

E.

Tilt-table testing is indicated (a) in patients with recurrent syncope but without evidence of heart disease and (b) in patients with heart disease in whom no arrhythmia is detectable by noninvasive or invasive tests. Patients are placed on a table with electrocardiography and blood pressure monitors and are suddenly brought to an upright position of 40–90 degrees for 45–60 minutes. Syncopal symptoms represent a positive test result and provide 89%–100% specificity for neurally mediated syncope (4).

F.

Psychiatric evaluation should be considered for patients with recurrent, noncardiac syncope.

III.

Therapy is not required for noncardiac, nonrecurrent syncope; otherwise, it is directed at the underlying disorder.

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3.5
CEREBRAL CONCUSSION

Kim Edward LeBlanc

I. Introduction

A.

Any physician may be called on to evaluate someone with a concussion.

1. The treating physician must maintain objectivity.
2. Several sets of guidelines have been proposed (1,2,3,4 and 5).
3. It must be recognized that there are no universally accepted standards.

II. Definition

A.

There is no universally accepted definition of “concussion.”

1. The terms *concussion* and *mild traumatic brain injury* are used interchangeably.

B.

In 1966 the Committee on Head Injury Nomenclature of the Congress of Neurological Surgeons proposed the following definition of concussion: “a clinical syndrome characterized by immediate and transient posttraumatic impairment of neural functions, such as alterations of consciousness, disturbance of vision, equilibrium, etc., due to brain stem involvement.”

C.

A simple definition is often used: “Concussion is a trauma-induced alteration in mental status that may or may not involve loss of consciousness.”

III. Pathophysiology

A.

Concussion is usually the result of rotational forces applied to the head.

1. Acceleration or inertial effects to the brain occur as result of mechanical input.
2. The primary injury mechanism is a rotational acceleration force.

B.

Neuronal injury occurs with no visible lesion to the brain.

1. A diffuse brain insult results in widespread cerebral malfunction.
2. It represents a shearing injury generally proportional to severity of the blow.
3. Prolonged amnesia or unconsciousness is more serious than a simple “ding.”

IV. Symptoms

A.

The most common manifestations of concussion are:

1. Confusion
2. Disorientation
3. Amnesia

B.

Subtle manifestations may not be easily recognized. Examples include:

1. Slower responses to questions; difficulty following instructions
2. Disjointed speech patterns, vacant stares, deficits of memory
3. Emotional lability

C.

Symptoms usually seen in the first few minutes or hours include:

1. Nausea and/or vomiting; dizziness and/or vertigo
2. Headache, inattentiveness, occasional problems with speech or vision

D.

Examples of late symptoms that may also occur (may not be apparent for days or weeks) include:

1. Light-headedness, persistent mild headache, inability to concentrate
2. Lack of energy, frustration, intolerance to loud noises or bright light
3. Sleep disturbances; memory dysfunction

V. Recognition

A.

The unconscious patient should be presumed to have a cervical injury until proven otherwise.

B.

Differential diagnosis includes:

1. Subarachnoid hemorrhage
2. Hematomas: epidural, subdural, intracerebral
3. Intracerebral contusion
4. Second-impact syndrome

C.

Particular attention should be paid to signs of neurologic deterioration

1. Serial neurologic examinations should be performed at least every 5 minutes
2. Once the patient's immediate needs have been met, the physician may begin grading the severity of the concussion.

VI. Grading the severity of concussion

A.

Cantu's system

1. It is the most frequently used grading system among sports medicine physicians.
2. In addition, it is recommended by the American College of Sports Medicine.
3. This system divides concussion severity into three grades.
4. Grade is determined by loss of consciousness (LOC) and/or posttraumatic amnesia (PTA) (Table 3.5-1).

Symptom	Grade 1	Grade 2	Grade 3
PTA	<30 min	>30 min <24 hr	>24 hr
and/or LOC	None	<5 min	>5 min

LOC, loss of consciousness; PTA, posttraumatic amnesia.

Table 3.5-1. Grade is determined by LOC and/or PTA

B.

The American Academy of Neurology (AAN) has proposed another system:

1. This system is more conservative than Cantu's.
2. It is similar to that proposed by the Colorado Medical Society.
3. It changes Cantu's grade 1 into grades 1 and 2 according to a 15-minute time frame.
4. It also converts Cantu's grades 2 and 3 to a single grade 3.
5. There is some concern that profound memory impairment represents a more serious degree of brain insult than a brief LOC. This is not reflected in the guidelines proposed by the AAN.

   Grade 1. No LOC, with symptoms lasting *less* than 15 minutes

   Grade 2. No LOC, with symptoms lasting *more* than 15 minutes

   Grade 3. Any loss of consciousness

VII. Neuroimaging

A.

Determination of which concussions require neuroimaging studies should be based on the severity of the injury and clinical judgment of the clinician.

B.

Grade 1 concussions rarely require neuroimaging studies.

1. If symptoms are worsening or are persisting beyond 24 hours, neuroimaging is recommended.
2. Magnetic resonance imaging is considered to be more sensitive than computed tomography.
3. Electroencephalograms are generally useless in the evaluation of concussion.

C.

Grade 2 concussions, particularly on the second or third occasion, require neuroimaging studies (but not necessarily that same day).

D.

All grade 3 concussions require neuroimaging studies that same day.

1. In addition, consultation with a neurologist and/or a neurosurgeon should be sought.
2. It is imperative to rule out an ominous ongoing process with the cranium.

E.

Management is dictated by results of clinical and neuroimaging studies.

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3.6
FRACTURES REQUIRING SPECIAL CONSIDERATION

Jeffrey G. Jones

Eric Douglas Poplin

I. Fracture basics

A. Classification of fractures.

Complete fractures disrupt the entire cortex, whereas incomplete fractures involve only one side. Fracture location is usually related to anatomical landmarks or is described as involving the proximal, middle, or distal thirds of long bones. Closed (simple) fractures have no skin disruption that communicates with the bone, as compared with open (compound) fractures, which do disrupt the skin. Complicated fractures are those with associated soft-tissue injuries. Avulsion fractures occur when a tendon or ligament pulls away from the bone with an attached fragment. Alignment refers to the relationship of the longitudinal axis to the fracture fragments. Abnormal alignment is described by degrees of angulation. Position describes the relationship of the fragments to their normal location. Displacement describes the abnormal position of the fracture fragments. Impacted fracture fragments are pushed together, whereas distracted fracture fragments are pulled apart. Direction of fracture lines is indicated by the terms *transverse, oblique, comminuted,* and *spiral*. Transverse fracture lines are perpendicular to the axis of the bone, and oblique fracture lines cross the axis of the bone at an angle. Comminuted fractures have more than two fragments. Spiral fractures result from a torsional force.

B. Clinical diagnosis of fracture.

The diagnosis of fracture should be considered any time there is a history of significant acute or chronic trauma to a bone resulting in the complaint of pain. Signs of fractures include localized pain, tenderness, ecchymosis, and edema. Gross deformity, decreased function, abnormal mobility, and crepitus may also be present. Do not dismiss the possibility of a fracture because it cannot be immediately visualized on a radiograph. A careful examination for associated injuries to viscera, tendons, nerves, and blood vessels should always be included.

C. Imaging techniques.

Most fractures are adequately visualized on plain radiographs, but some fractures require special imaging techniques for prompt diagnosis and optimal treatment. Radionuclide bone scanning is a very sensitive but nonspecific tool in the evaluation of fractures. It is most commonly employed to evaluate suspected occult or stress fractures that are not apparent on plain radiographs. Tomography is used to evaluate suspected fractures in bones that are frequently obscured by overlying structures. Computed tomography (CT) scanning is particularly helpful in confirming fractures of the pelvic and facial bones. Magnetic resonance imaging (MRI) is useful to diagnose associated injuries to cartilage, ligaments, and tendons.

D. Treatment generalities

1. Stability. Stable fractures tend to maintain their position and alignment; unstable fractures tend to displace. Unstable fractures require early immobilization to prevent this result. If there is doubt about the stability of a particular fracture, it should be treated as unstable until consultation is obtained.
2. Associated injuries must be considered in the evaluation of any fracture. A detailed examination for damage to viscera, nerves, blood vessels, tendons, and overlying skin must be performed. The management of traumatized viscera usually takes precedence over fracture management. Neurovascular injuries should be recognized early and referred for repair. Most tendon ruptures also require surgical treatment. Open fractures require special consideration because even a small skin defect that communicates with the fracture greatly increases the patient's chances of developing osteomyelitis. These wounds should generally be debrided in the operating room and the patients given prophylactic antibiotics.
3. Reduction is the procedure that returns displaced fracture fragments to acceptable position and alignment. What constitutes acceptable position and alignment varies with the fracture location and type, patient age, and the functional demands placed on the bone. A neurovascular examination should always be repeated after reduction.
4. Immobilization of fractures is initially achieved by splinting to provide pain relief and to prevent further displacement, associated injuries, and the fat emboli syndrome. Definitive immobilization can be achieved through internal or external fixation. Internal fixation requires a surgical procedure. External fixation is provided by splinting or casting. Choosing the correct type and length of immobilization is critical for optimal healing. Inadequate immobilization can result in displacement, delayed union, or nonunion of fracture fragments. Prolonged or improper immobilization can result in stiffness and functional impairment. Consultation should be obtained if there is doubt about the appropriate type and length of immobilization.

II. Regional listing of the most common fractures

A. Skull

1. **General.** Indications for obtaining a computed tomography (CT) scan after head trauma include the following:
   - Focal neurologic deficits or altered mental state (including memory deficits)
   - Headache
   - Physical evidence of head trauma, including palpable bony abnormality or penetration injuries
   - Unreliable history or intoxication with drugs or alcohol
   - Age greater than 60 years

   If you are worried about a significant risk of skull fracture, worsening neural functioning, or other serious neurologic findings (such as seizures), obtain a consultation in addition to a CT scan or magnetic resonance image. If the patient is unconscious due to head injury, assume neck injury also. If the clinical examination indicates a strong possibility of central nervous system (CNS) injury, obtain a neurosurgery consultation rapidly. If there is blood behind the tympanic membrane (hemotympanum), cerebrospinal fluid (CSF) otorrhea, or CSF rhinorrhea, assume skull fracture regardless of radiographic findings. Be somewhat conservative in admitting patients for observation.

2. **Nasal.** Fractures are common and commonly missed. They become important if displaced or opened. In all cases involving nasal trauma, view the septum to rule out hematoma (if present, obtain an immediate ear, nose, and throat consultation). If there is a history of significant trauma to the nose, obtain nasal views (skull views are not adequate for visualizing detail). Do not miss anterior nasal spine fractures (small projection

just above the upper lip). Cartilaginous deformity may not be associated with radiographic abnormality but nonetheless requires referral, either immediately or in 3–5 days. Use cold compresses frequently to control swelling. If fracture is associated with open wounds, treat with anti-*Staphylococcus* drugs.

3. **Blow-out or orbital floor** fractures typically occur after blunt trauma to the eye or eyelids that is transferred to the weak floor of the orbit. This allows for the contents of the orbit to herniate through the floor, which may cause limitations in eye motion. The damage to the infraorbital nerve may cause anesthesia of the upper lip and gingiva. There is usually marked local swelling, which may make it difficult to appreciate the subtle enophthalmos (backward displacement of the eye.) A Waters' view of the orbit or a CT evaluation is generally diagnostic. If eye movement is limited, urgent ophthalmologic referral is required. If there are no ophthalmologic findings, the patient should be referred after starting on an antibiotic and being told to avoid blowing the nose.
4. **Mandible.** Patients with mandible fractures often present with malocclusion, which is a sensitive finding that should prompt a panoramic radiographic evaluation of the mandible. Because of the structure of the mandible, there is often more than one fracture. If there is a history of significant trauma, dislocation of the mandible must also be ruled out. If fracture is present, the patient will generally need to be admitted for observation and fixation.

B. Neck.

The family physician's role in evaluating neck trauma begins with a decision about whether radiographs are warranted. It is generally safe *not* to get films if there is no midline cervical tenderness, no focal neurologic deficit, normal alertness, no intoxication, and no coexisting injury, the pain of which could distract the patient from feeling the pain caused by the neck injury. If these criteria are not met, a lateral cervical radiograph that adequately demonstrates all seven cervical vertebrae is appropriate. To interpret films comfortably, remember the normal curves of the cervical spine (Fig. 3.6-1): Anterior and posterior vertebral body lines should form a smooth, continuous, lordotic curve, and the posterior cervical line should be a straight line connecting the bases of C1, C2, and C3. If the bases miss the line by more than 2 mm in either direction, suspect a pathologic process. Careful observation of these lines, along with the odontoid, can help the clinician rule out cervical fractures.

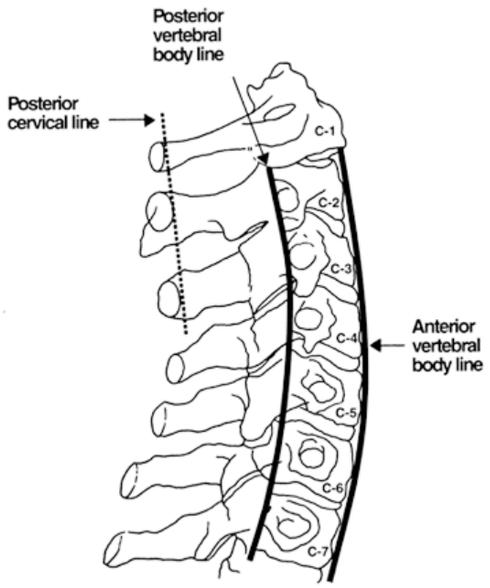

FIG. 3.6-1. Normal landmarks of the cervical spine.

The mechanism of injury can also be helpful in terms of indicating what type of fracture to look for. In relatively pure compression injuries, C1 (Jefferson's) fracture is common. Flexion injury fractures include anterior wedge compression fractures, clay-shoveler's fracture (an avulsed spinous process of C6 or C7), and teardrop burst fractures. Extension injuries predispose to the hangman's fracture (bilateral neural arch fractures of C2). Fracture of the odontoid is extremely dangerous because of its high level, proximity to the cord, and intrinsic instability. If there is any doubt about the possibility of a significant cervical injury after viewing the cervical films, proceed with neurosurgical consultation while maintaining immobilization.

C. Thoracolumbar.

Common mechanisms of injury and corresponding fractures include hyperflexion injury causing a compression fracture of the vertebral body; direct blow or violent muscular contraction often produces transverse and spinous process fracture; vertical compression results in compression fracture; rotation trauma causes shearing fractures through the posterior elements; and hyperextension often results in acute or stress fractures of the pars.

Plain radiographs are generally adequate to make the diagnosis, although a CT scan may be required. A radionuclide bone scan may be useful for sorting out the acuity of findings and detecting subtle compression fractures. Patients found to have acute spine fractures generally require hospital admission for further evaluation, treatment, and control of symptoms. They will

benefit from bed rest (for at least 24 hours, longer in more significant fractures), analgesics (often liberal use of narcotics is necessary to control pain), careful and serial neurologic reassessment, and, especially in the presence of neurologic deficit, emergent neurosurgical or orthopedic consultation.

D. Thoracic cage

1. **Rib fractures.** Fractures of the first or second ribs generally result from serious trauma, and attention should be directed to injury to the great vessels, cervical spine, head, and brachial plexus. These patients usually need to be admitted, and emergent angiography should be obtained if there is concern about vascular integrity.

   Other rib fractures, if at multiple levels, may result in a flail chest. This diagnosis is made by observing the paradoxical inward movement of the chest during inspiration. This flailing may not be obvious if there is shallow breathing or if the patient is splinting the chest due to pain, so one must also look for local pain due to palpation and crepitus. Initial treatment includes oxygen and positioning the patient with the injured

side down on the bed. Radiographic evaluation of the chest is necessary to confirm the injury as well as to rule out pneumothorax and hemothorax. If inadequate ventilation is a possibility, be prepared to intubate the patient. In these cases, admission to an intensive care unit and monitoring of oxygenation status are warranted.

Uncomplicated rib fractures are treated conservatively, provided that pneumothorax, hemothorax, and flail chest have been ruled out. Thus, a chest radiograph is generally required if the diagnosis of rib fracture is entertained. Rib detail films are of questionable usefulness because approximately half of the nondisplaced fractures cannot be seen in plain films, and treatment is the same for rib contusions and fracture.

Other visceral injuries may be associated with rib trauma, and further evaluation of the liver, spleen, and kidneys may be indicated, depending on results of the physical examination. Local crepitus may be present around a fracture site. In both fracture and contusion, there may be a pleural component to the pain. Chest wall supports should be used cautiously, if at all, because they impair the mechanics of ventilation and the clearance of pulmonary secretions, leading to atelectasis and pneumonitis. Analgesics and antitussives may cause the same problems and should be used at the lowest possible doses. Children represent a special case because their rib cages are so flexible that significant visceral injury may take place without rib fractures. Patients should be instructed on using a pillow for splinting and in taking deep breaths on a regular basis. Healing usually takes 4–6 weeks.

2. **Sternal fractures** are usually associated with significant trauma and are commonly the result of steering wheel impact in motor vehicle accidents. They are often associated with injuries to the heart, lungs, great vessels, head, and diaphragm. The mortality for people with these fractures is high. Chest radiographs with lateral views of the sternum generally demonstrate the fracture. An electrocardiogram (ECG) should be obtained in these patients because cardiac contusion is commonly associated with this fracture. Admission to an intensive care unit is often warranted.

E. Shoulder girdle

1. **Clavicle.** Fractures of the clavicle are common, and fractures of the middle third are the most common variety. Most patients have palpable swelling and tenderness at the fracture site and generally carry the affected arm in the adducted position, resisting motion of the arm. Because these fractures may be associated with neurovascular injuries, a meticulous examination should be done and documented. An anteroposterior (AP) and apical lordotic view usually demonstrates the fracture. There is tremendous remodeling capacity of the clavicle in children, and treatment for the greenstick and nondisplaced fracture is the use of a sling until symptoms resolve. If displacement is present, a figure-of-8 brace can be fashioned from a piece of tubular stockinette. In adults, a sling is also appropriate for the nondisplaced fracture.

   Displaced fractures can usually be reduced with the application of a commercially available figure-of-8 splint. Instruct the patient to pull the shoulders back as if “at attention,” and then the splint should be applied and tightened in this position. The patient should be made aware of possible signs and symptoms of neurovascular compromise. The patient should take measures to avoid maceration of the skin under the splint, usually by applying powder. A repeat film a week later is needed to ensure adequate positioning of the fracture; if adequate positioning is not achieved, referral to an orthopedic surgeon is usually warranted.

   Fractures of the medial and distal third of the clavicle are relatively rare and are associated with complications. Consultation with a specialist is suggested for these fractures.

2. **Scapulae.** Scapular fractures are relatively rare because the scapula is protected by a thick layer of muscle, which also helps to prevent displacement of scapular body and spine fractures. Carefully rule out coexisting pneumothorax, rib fractures, and other neurovascular injuries. Management of fractures of the body and spine includes immobilization with a sling (or sling and swathe), ice and analgesics, with early range-of-motion (ROM) exercises. Acromial, neck, and glenoid fractures generally require referral because of the propensity for complications (especially chronic bursitis or arthritis). Coracoid process fractures tend to do well with conservative care and early ROM exercises, providing there are no associated clavicular, acromial-clavicular, or brachial plexus injuries.
3. **Humerus.** Proximal humerus fractures may involve the surgical neck, anatomical neck, lesser tuberosity, and greater tuberosity. Most of these fractures are seen in the elderly. A minimally displaced neck fracture can be treated with a sling. Orthopedic referral is generally recommended for other neck fractures because of the likelihood of joint adhesions, malunion, avascular necrosis, and myositis ossificans. Greater tuberosity fractures, if displaced, are associated with longitudinal tears of the rotator cuff, in addition to the other complications listed previously. Initial treatment involves sling and swathe. Lesser tuberosity fractures are less common and often associated with posterior shoulder dislocations. In all proximal humerus fractures, but especially those involving the shaft, carefully assess and document the neurovascular status. Early mobility is also critical for successful treatment of all these proximal humeral fractures.

F. Arm and forearm fractures

1. **Humeral middle and distal fractures**
   a. Midhumeral fractures usually result from a direct blow. Displacement occurs frequently, and associated injuries to the radial nerve and brachial artery are common. Because of the risk of complications, these patients should be splinted and referred to an orthopedist.
   b. Distal humeral fractures result from a fall on the flexed elbow or outstretched arm. Associated injuries to the median nerve and brachial artery are common. Uncomplicated, nondisplaced intercondylar and medial epicondylar fractures can be treated by posterior splinting for 2–3 weeks followed by a sling and ROM exercises. Other distal humeral fractures should be splinted and referred.
2. **Forearm and elbow fractures**
   a. Elbow fractures require special consideration because of the complexity of the joint and the frequency of occult fractures of the radial head. The injury mechanism is usually a fall on the outstretched arm or on the tip of the olecranon. Patients with olecranon fractures have increased pain with elbow extension, whereas the pain of radial head fractures is usually aggravated by supination. Associated ulnar nerve injuries are not uncommon. The radiographic evaluation should include AP, lateral, and oblique views. It is important to look for the presence of a posterior fat pad or a displaced anterior fat pad. These signs may be the only radiologic abnormalities in nondisplaced radial head fractures. Suspected occult or nondisplaced radial head fractures can be treated with a posterior splint for 2 weeks followed by a sling and ROM exercises. Patients with displaced fractures of the radial head and fractures involving more than 30% of the joint surface should be referred to an orthopedist, as should those with olecranon fractures.
   b. Mid-forearm fractures are usually the result of a direct blow. Associated radioulnar joint dislocations are common. The radiographic evaluation should include views of the elbow and wrist in addition to AP and lateral views of the forearm. Nondisplaced complete fractures, torus fractures, and greenstick fractures with less than 15 degrees of

angulation should be treated with a long arm cast. Patients with other types of fracture should be splinted and referred to an orthopedist.

c. Distal forearm fractures are commonly seen in the primary care setting. The mechanism of injury is usually a fall on the outstretched hand. In the more common extension type (Colles') fracture, maximal tenderness is on the dorsal aspect. The flexion-type (Smith's) fracture has more volar tenderness. The neurovascular examination is particularly important because of commonly associated median nerve and radial artery injuries.

Nondisplaced fractures can be treated with a long arm cast. All other cases should be referred for reduction and fixation. Uncorrected dorsal angulation results in decreased wrist function.

3. **Wrist fractures.** Their small size, large number, and close proximity complicate the evaluation of the carpal bones. Occult fractures are common. Scaphoid fractures are the most common and complicated carpal fracture. They are usually caused by a fall on a hyperextended wrist. Patients present with tenderness over the scaphoid in the anatomical snuffbox and pain with radial deviation of the wrist and axial compression of the thumb. The radiographic evaluation should include AP, lateral, oblique, and scaphoid views. Remember that nondisplaced scaphoid fractures frequently have negative acute radiographs. Suspected occult fractures should be immobilized in a thumb spica splint or cast and reevaluated in 2 weeks. Healing of the scaphoid is hindered by its poor blood supply. Accordingly, avascular necrosis and nonunion are common complications. Persons with confirmed fractures should be referred to an orthopedist because of the high incidence of complications.
4. **Hand fractures.** Fractures of the hand are among the most common types of fracture encountered in primary care. Many hand fractures can be adequately treated without referral, but seemingly minor hand fractures can result in significant disability. A meticulous examination and careful management must be employed to avoid a poor outcome.
   a. Distal phalangeal fractures are usually the result of a direct blow. Loss of distal interphalangeal joint motion suggests a possible tendon avulsion. Nondisplaced tuft fractures can be treated with a protective splint for 2–4 weeks. Small subungual hematomas (<25% of the nail bed area) should be drained. Larger hematomas are suggestive of a significant nail bed laceration and should be repaired for optimal cosmetic result. Tuft fractures with associated subungual hematomas should be considered open fractures, and prophylactic antibiotics should be employed. Significantly displaced fracture fragments should be reduced to avoid nonunion and chronic pain. All patients with flexor tendon avulsion fractures and extensor tendon avulsions involving more than 25% of the articular surface should be referred to an orthopedist. The distal interphalangeal joint can be splinted in extension for 6 weeks to treat smaller extensor tendon avulsion fractures (mallet finger).
   b. Proximal and middle phalangeal fractures result from direct blows or axial compression. The physical examination should focus on ruling out the presence of rotational deformity and tendon avulsions. If the hands are held palm up and the fingers flexed, they should point toward the scaphoid. Any overlap suggests a rotational deformity. Extensor tendon avulsion fractures of the proximal interphalangeal central slip result in a boutonniere deformity. Decreased active ROM accompanies tendon avulsions. Nondisplaced extra-articular fractures and volar plate fractures involving less than 15% of the joint surface can be splinted in flexion for 3 weeks followed by 3 more weeks of dynamic splinting. Other fracture types should generally be referred.

c. Metacarpal fractures result from direct blows or compression with a clenched fist. Ruling out rotational deformities and associated injuries is the focus of the physical examination. Nondisplaced shaft fractures and mildly angulated neck fractures can be treated with a gutter splint. Up to 20 degrees of volar angulation is acceptable for the first and fourth metacarpal necks. The fifth metacarpal can tolerate up to 45 degrees of volar angulation. The second and third metacarpal necks require precise reduction. All other metacarpal fractures should be managed by an orthopedist.

G. Pelvis and hip

1. **Pelvic fractures.** These fractures may result from a wide range of forces, such as a motor vehicle accident or a simple fall. Serious pelvic fractures, namely, those that are unstable or that include displacement of the pelvic ring, are often associated with serious injuries. Significant hemorrhage is common, and the patient may present in shock. In these patients, hospital admission with appropriate specialty consultation is advised. The mortality of patients with pelvic ring fractures is high.

   Single pubic or ischial ramus fractures are the most common fractures of the pelvis. They may be due to acute trauma (e.g., falls in the elderly) or chronic trauma (e.g., stress fractures in athletes or during pregnancy). Acute fractures are often associated with injury to the urethra or bladder; therefore, hematuria and inability to void should be ruled out. Pain is deep in the groin and is exacerbated by hamstring stress. Bone scanning may be necessary to demonstrate a stress fracture. Treatment includes bed rest with progression to ambulation with crutches. A cushion for sitting may help relieve pain. Iliac wing fractures usually result from acute trauma, and the treatment is similar to that listed for single pubic or ischial ramus fractures.

   Coccyx fractures result from falls in which the individual lands in the seated position. Localized pain to palpation and pain with sitting or defecation characterize such fractures. The diagnosis can usually be confirmed by rectal examination, and radiographic results are often negative. Treatment generally involves bed rest, sitz baths, laxatives, and cushions for sitting.

2. **Hip fractures.** These fractures may involve the femoral head, neck, intertrochanteric area, trochanter, or subtrochanteric area.

   Because of the disturbance of blood supply that is often associated with the fracture and the fact that these fractures occur more frequently in frail patients, treatment tends to be complex, and the morbidity and mortality are relatively high. The primary care doctor should look for these fractures, using standard views of the hip, in patients with a history of falling and in patients complaining of groin or medial thigh pain that is worsened by leg motion. Leg shortening and external rotation may be present. Do not be misled by a finding that the patient is ambulatory.

H. Lower extremity

1. **Distal and mid-femur fractures.** The mid-femur is a strong bone with excellent blood supply, a characteristic that predisposes patients with femoral shaft fractures to significant potential for hemorrhage. The muscles surrounding the femoral shaft frequently cause a deformity and displacement of any fracture there. Patients generally present with severe pain, a shortened leg, and a swollen thigh. Routine films generally demonstrate the fracture. The extremity should be immobilized, and orthopedic consultation should be urgently obtained. Current therapy uses plating or intramedullary rodding for fixation.

   Distal femoral fractures are uncommon and may be intra-articular or extra-articular. They are usually the result of direct trauma, and these patients present with pain, swelling, and deformity of the knee. Because of the close proximity of this area of the femur to the peroneal nerve and the extensive vascular supply, it is essential that the neurovascular status

of the leg be evaluated and documented early in the assessment of the patient. Initial treatment includes analgesics, immobilization, and emergent referral.

2. **Tibia and fibula.** Tibial fractures are the most common of long-bone fractures. They may be intra-articular or extra-articular. Fractures of the tibial plateau (the medial and lateral tibial condyles) are easy to miss on standard radiographic films and are more readily seen on a tibial plateau view. Dislocations and fractures of the fibular head may appear innocuous but are often a marker for more significant knee injury. Displaced fractures of the tibia are often associated with displaced fractures of the fibula. Orthopedic consultation is recommended for tibial and fibular fractures because of the frequently associated injuries (ligamental, meniscal, and vascular) and the frequently seen complications, which can result in chronic pain, knee dysfunction, and degenerative arthritis.
3. **Patella.** Patellar fractures most commonly result from direct trauma, but a violent contraction of the quadriceps may cause an avulsion fracture. Transverse fractures are most common, followed by stellate and longitudinal types. Local tenderness and swelling are the most common presenting complaints. Active extension should be evaluated because the extensor mechanism can be disrupted. The AP, lateral, and skyline views of the patella are usually sufficient to define any fractures. Because bipartite and tripartite patellae are relatively common and usually bilateral, comparison views may be helpful. In the nondisplaced transverse fracture, aspiration of the hemarthrosis (helpful in lessening pain) and application of a long leg posterior splint or well-fitted long leg cast, with the leg in full extension, are the usual treatment choices. Attention must be paid to maintaining quadriceps tone with exercises. Consideration should be given to specialist consultation because of the possibility of traumatic chondromalacia and avascular necrosis. In other types of patellar fractures, consultation is recommended.
4. **Ankle.** Ankle fractures and ligamental injuries often coexist. It is useful to think of the ankle as a ring enclosing the talus and composed of the tibial plafond, medial malleolus, deltoid ligament, calcaneus, lateral ligaments, lateral malleolus, and the interosseous membrane. Disruption of the ring at only one place generally results in a stable ankle injury that can be treated by conservative means (posterior splinting, non-weight bearing, and edema control). If two or more disruptions of the ring are present, the ankle is not stable, and treatment is oriented to immobilization and emergent referral. The standard radiographs (AP, lateral, and mortise views) are usually adequate. Special attention should be paid to the malleolar-talar space. Search carefully for multiple injuries. Unilateral avulsion fractures of the distal tip of the malleolus are often treated like second-degree sprains. If there is any doubt about optimal management, discuss the case with an orthopedic specialist. The risk for complications of ankle fractures (traumatic arthritis, chronic talar instability, chronic pain and swelling, and osteochondral fractures) is high.
5. **Hindfoot fractures.** The calcaneus and talus have multiple articular surfaces and absorb a great deal of force. Although standard films may demonstrate fractures here, it is not unusual for CT scanning analysis to be required for adequate visualization of injuries. Also, occult fractures are common in this area. For this reason, the clinical examination is critical in making decisions about splinting and reassessment or the use of additional studies. Although full ankle motion may be present, heel pain with weight bearing after the appropriate trauma is common. Generally, the undisplaced fracture is treated with compression, non-weight bearing, elevation, and analgesics until swelling subsides, when a well-molded walking cast may be used. Partial weight bearing is generally needed for at least 8 weeks. Because of the high likelihood of posttraumatic arthritis and chronic pain and stiffness, patients bearing these fractures are

often referred to an orthopedic specialist. If any displacement is present, prompt referral is recommended.

6. **Midfoot fractures.** Navicular, cuboid, and cuneiform. Although normally relatively nonmobile, the midfoot is susceptible to fractures resulting from forced extremes of foot motion and crush injuries. Combinations of fractures and dislocations are common here. Examination of the foot reveals marked tenderness, pain, swelling, and, possibly, abnormal bony prominences. Standard radiographic views are generally adequate to reveal fractures. Small, nondisplaced chip fractures of the navicular are usually treated with a compressive dressing for several weeks. Other nondisplaced navicular fractures can often be treated conservatively with a well-molded walking cast. Displaced navicular fractures often require open reduction and are best referred. Cuboid and cuneiform fractures are often associated with tarsometatarsal dislocations that have spontaneously reduced, so the threshold for early referral should be kept low.
7. **Forefoot fractures.** Metatarsal, phalangeal, and sesamoid. Metatarsal and phalangeal fractures usually result from direct crush injuries. Because of the large forces to the second and third metatarsals during the push-off phase of walking or running, this is also an area that is prone to stress fractures. Standard foot radiographic views are generally adequate to demonstrate fractures (with the exception of early stress fractures). A secondary ossification center in the base of the fifth metatarsal may sometimes be confused with a fracture, but this area generally has smooth, bilateral sclerotic margins. Early stress fractures may require a bone scan to visualize the problem.

   Nondisplaced metatarsal neck fractures generally require ice, elevation, and analgesics during a period of 24–48 hours, after which swelling should subside. At this point, a short leg walking cast can be used for 4–6 weeks. Displaced neck fractures generally require orthopedic referral for reduction. Nondisplaced shaft fractures of the first metatarsal require a non-weight bearing cast for 3–4 weeks, followed by a walking cast for an additional 1–3 weeks. Nondisplaced shaft fractures o metatarsals 2–5 generally do well with conservative measures for 24 hours, followed by the use of a postoperative shoe or metatarsal pad plus crutches. Weight bearing may be permitted as tolerated. Displaced shaft fractures generally require orthopedic consultation for reduction. Fractures of the bases of the metatarsals can be problematic. Fractures of the base of the second metatarsal are pathognomonic of further tarsometatarsal joint disruption and should be carefully evaluated. The base of the fifth metatarsal is the most common metatarsal fracture, and an avulsion fracture and a transverse fracture of the base should be differentiated. The avulsion fracture can usually be treated with a compressive dressing and non-weight bearing initially, followed by a postoperative shoe or short leg walking cast as the patient can bear more weight without pain. An arch support is helpful. The transverse fracture of the base of the fifth metatarsal is more prone to delayed union or nonunion and has a more guarded prognosis. For this reason, orthopedic consultation is recommended.

   Most phalangeal fractures are caused by direct injury, such as a crush. Nondisplaced phalangeal fractures of toes 2–5 can usually be adequately treated with buddy taping (dynamic splinting). With this technique, the broken toe is taped to the adjacent toe, with a little padding between the toes to prevent skin maceration. An open-toe shoe may also be useful during this time. Fractures of the first toe are not adequately immobilized by dynamic splinting, and a walking cast is usually necessary. Displaced phalangeal fractures may require orthopedic consultation for reduction or fixation if they are not readily reducible by the primary care physician. Sesamoid fractures can usually be treated with arch supports for 2 months. However, if symptoms are severe a short leg walking cast can also be used.

III. Fractures of abnormal bone.

Any fracture that results from insignificant trauma should be considered pathologic, meaning that the broken bone has preexisting disease that has resulted in a loss of structural integrity. The patient may complain of pain that existed even before the fracture, and the actual fracture site may not be especially tender. The radiograph may have an altered appearance in that the trabecular patterns of the bone near the fracture can be disrupted. The most common causes of bone disease are osteoporosis, myelomas, and metastatic lesions (think of cancer of the thyroid, breast, prostate, bronchus, kidney, bladder, uterus, ovary, testicle, and adrenals.) Less common—but more benign—causes include enchondromas (also called chondromas), solitary bone cysts, and giant cell tumors. Malignant primary bone tumors may also present with pathologic fractures, which generally require specialist evaluation and treatment.

IV. Fractures unique to children.

There are several unique factors about the diagnosis and treatment of fractures in children. These include the presence of the epiphyseal plate, the tendency to suffer incomplete fractures, and the evaluation for signs of child abuse (see Chapter 20.5).

A.

Epiphyseal plate injuries are common because this site is the weakest portion of the immature skeleton. Injuries that would result in a ligamentous strain in adults frequently fracture the epiphyseal plate in children. The physical examination reveals tenderness and edema over the epiphysis. The radiographic evaluation may be difficult, and comparison views should be considered. Epiphyseal plate fractures are most commonly classified by the Salter-Harris system (Fig. 3.6-2):

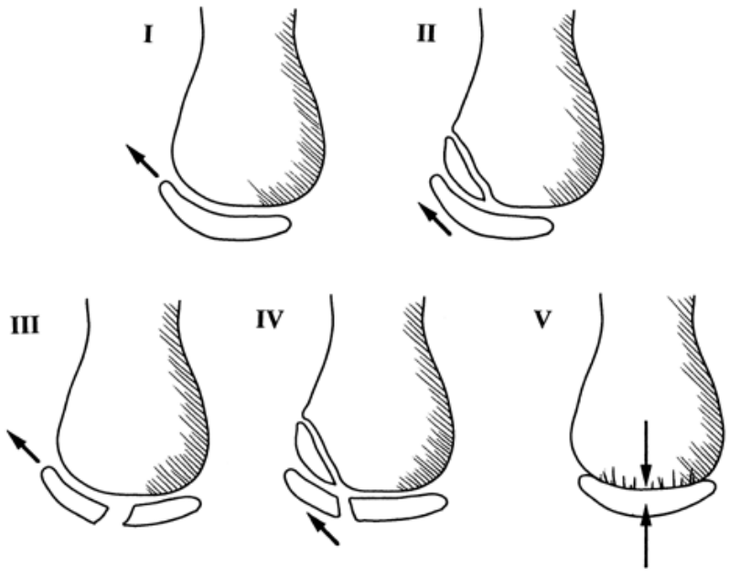

FIG. 3.6-2. The Salter-Harris system is used to classify epiphyseal plate fractures.

- Fracture through the epiphyseal plate
- Epiphyseal plate fracture with an associated metaphyseal fragment
- Fracture through the epiphysis onto the articular surface
- Fracture through the distal metaphysis, epiphyseal plate, and epiphysis
- Impaction of the epiphyseal plate

Types I and II are treated with casting, often after closed reduction, and enjoy a good prognosis. Types III and IV have a higher risk of growth disturbance and should generally be referred. Type V is often diagnosed in retrospect, after a growth disturbance has occurred.

B.

Incomplete fractures include torus fractures and greenstick fractures. Torus fractures occur when there is a buckling of one side of the cortex. They are usually caused by a compression force. Torus fractures occur commonly in the forearm after a fall on the outstretched hand. They are treated with a long arm cast for 4–6 weeks. Greenstick fractures occur when a long bone is bowed, resulting in a break in only the convex side of the cortex. These are generally stable fractures that most commonly occur in the forearm. Forearm greenstick fractures with less than 15 degrees of angulation should be casted for 4–6 weeks. Patients whose fractures show more than 15 degrees of angulation should be referred to an orthopedist.

C.

Physical abuse is a significant cause of early childhood fractures. Suspicion should be raised by an inconsistent or implausible explanation and by inappropriate parental behavior. The classic radiologic evidence of child abuse is multiple fractures in various stages of healing. Suspected victims should be evaluated with a skeletal survey, followed by the appropriate completion of forms and referrals to protective agencies.

IV. PROBLEMS OF INFANTS AND CHILDREN

4.1
DEVELOPMENTAL PROBLEMS IN CHILDREN

Dennis J. Baumgardner

Developmental problems of children include intellectual and special sensory deficits, motor dysfunction, and psychosocial disorders caused by nonprogressive central nervous system (CNS) dysfunction (behavioral problems are discussed in Chapter 4.9). Although more than 10% of children have developmental problems, diagnosis is often delayed due to overreliance on normal variation as explanations of subtle findings, inattention to specific milestone delays when the child is otherwise normal, reliance on strictly clinical impressions in deference to cumbersome screening devices, and the physician's or parents' reluctance to discuss their fears. This problem is best approached by ongoing surveillance in the context of a continuing relationship with the family (1,2,3 and 4).

I. Diagnosis

A. History

should include open-ended questioning of the parents regarding their child's physical, cognitive, and sensory development, and any prior professional concern or workup. The medical history should document established developmental risk, such as known sensory deficit, chromosomal abnormality, myelomeningocele, and HIV infection. For example, children with conditions such as cleft lip or palate may be otherwise unaffected or may experience physical or psychological developmental problems resulting from the cleft, and perhaps additional problems if the cleft is part of a syndrome.

B. Risk factor assessment

builds on prenatal care assessment. Biologic risk factors may be summarized as significant maternal disease, hazardous exposure, obstetric complication, congenital infection and malformation(s), and significant neonatal, infant, or childhood neurologic, cardiopulmonary, infectious, somatic, or metabolic disease. Family history may reveal risk factors, such as familial developmental or sensory deficits or chromosome abnormalities. Psychosocial risks include mental retardation; serious emotional disturbance, substance abuse, or lack of parenting skills in caregivers; limited social or financial support; and stress, violence, or a history of abuse or neglect in the family.

C. Physical examination

is essential for detection of risk, or workup, of developmental delay. Attention should be paid to growth abnormalities (including abnormal head circumference), congenital anomalies, skin findings (e.g., neurofibromatosis, Sturge-Weber syndrome), eye findings (e.g., retinal pigmentation of Tay-Sachs), organomegaly (neurodegenerative disorders), postural and transition movement disorders, as well as the neurologic examination. Key physical findings have been summarized by Levy and Hyman (3). Facies may be indicative of a specific syndrome (e.g., fetal alcohol) or may lead to erroneous conclusions. Many facially dysmorphic children have normal intelligence, whereas children deemed attractive may have any degree of cognitive impairment or autism.

D. Developmental surveillance

should be performed at each well-child visit by the use of milestones. This may be done “on the fly,” along with immunizations, in children who are only presented for episodic care. The milestones in Table 4.1-1 were selected on the basis of objectivity, ease of parental recall or demonstration in the office, and uniformity (e.g., crawling is omitted because some children never demonstrate this prior to walking). All four major streams of development (gross motor, fine motor, language, and personalsocial) are represented. The personal-social stream is deemphasized, as it may not always reflect cognition due to significant contribution of the environment as well as emphasis and practice at home. Developmental delay is defined as actual development that is 25% or more behind the expected rate in any or all of the four major streams.

1 mo
Raises head when lying prone (GM)
Retains a ring or rattle (FM)
Gives alerting response (1 wk) (A/L/C)
Regards face in direct line of vision (Vis, FM)
2 mo
Raises chest when lying prone (GM)
Social smiling (6 wk) and cooing (A/L/C)
Follows moving object across midline (Vis, FM)
3 mo
Up on elbows when prone (GM)
Hands unfisted more than half of time (FM)
Blinks to visual threat (Vis)
4 mo
Up on hands when prone (GM)
No head lag when pulled to sitting (GM)
Brings hands together (FM)
Orients to voice (A/L/C)
Symmetrical corneal light reflexes and normal eye cover testing (Vis)
5 mo
Sits with support (GM)
Transfers objects (FM)
Laughs (A/L/C)
6 mo
Sits with minimal support (GM)
Has unilateral reach (FM)
Babbles (A/L/C)
7 mo
Sits without support (GM)
Takes pellet (crude grasp) (FM)
Searches for dropped object (A/L/C)
8 mo
Comes to sitting position (GM)
Has immature pincer grasp (FM)
Says dada/mama (inappropriate) (A/L/C)
9 mo
Stands holding on (GM)
Bangs blocks together (FM)
Plays peek-a-boo (A/L/C)
12 mo
Walks with minimal assistance (GM)
Has mature pincer grasp (10 mo) (FM)
Releases voluntarily (FM)
Says dada/mama (appropriate) and two other words (A/L/C)
Searches for hidden object (A/L/C)
Follows simple verbal commands (with gestures) (A/L/C)
Drinks from cup (PS)
15 mo
Walks alone well (GM)
Puts in and takes out (pellets in a bottle) (FM)
Follows simple verbal commands (without gestures) (A/L/C)
Has three- to six-word vocabulary (A/L/C)
18 mo
Climbs (GM)
Stacks three or four blocks (FM)
Knows three body parts (A/L/C)
Imitates housework (A/L/C)
Uses spoon (PS)
2 yr
Runs (GM)
Stacks four or five blocks (FM)
Has 50-word vocabulary (A/L/C)
Uses some two- to three-word sentences (A/L/C)
Enjoys being read to, points to objects in book (A/L/C)
3 yr
Walks up and down stairs, alternating feet (GM)
Balances on one foot for 1 sec (GM)
Stacks nine blocks (FM)
Copies a circle (FM)
Knows own name and sex (A/L/C)
Uses three- to four-word sentences (A/L/C)
Dresses self except for buttons (PS)
4 yr
Hops on one foot (GM)
Throws a ball (GM)
Copies a circle and a cross (FM)
Counts to 4 (A/L/C)
Recognizes three or four colors (A/L/C)
5 yr
Walks heel-to-toe or skips (GM)
Balances on one foot for 5–10 sec (GM)
Builds a stairway or building with blocks (FM)
Copies a square (FM)
Counts to 10 (A/L/C)
Follows three commands (A/L/C)

A/L/C, auditory/linguistic/cognitive; FM, fine motor; GM, gross motor milestone; PS, personal/social; Vis, visual.

Table 4.1-1. Developmental milestone[a]

Key points regarding milestones include the fact that development should occur in an orderly, predictable, intrinsically controlled fashion, although often in spurts. Parents and providers may focus on growth in the first 8–10 months, disregarding gross motor delay. Similarly, gross motor surveillance may overshadow that of fine motor development, the latter often being the earliest indicator of motor disability (hypertonia or primitive reflexes may mimic normal gross motor development in cerebral palsy). Warning flags are abnormal head size and failure to have hands unfisted at least 50% of the time by 3 months. The presence of handedness earlier than 18 months may represent an opposite-side hemiplegia. Gross motor achievement may be falsely reassuring because it does not indicate intelligence. Language development is the best predictor of intellectual potential and is therefore combined with cognitive development in Table 4.1-1 . Fine motor skills combine visual maturation, hand function, and problem solving, and are the second best indicator of future intelligence.

Linguistic capacity develops in sequential, critically timed phases and depends on the adequacy of stored utterances (receptive vocabulary) in infancy. A common pitfall is to ignore a language milestone delay until age 2. Another cognitive warning flag is lack of appreciation of object permanence by the end of the first year. The average age of diagnosis of congenital deafness is 2 years; the pitfalls are parents' failure to seek the alerting response to sound in the nursery, and confusing the child's response to vibrations or to gestures as indicative of hearing. Expressive skills that are advanced in comparison with receptive skills may be a sign of a pervasive developmental disorder. Articulation problems are often not identified by the parents.

Follow-up of milestone delay should include formal developmental testing (by referral if necessary) using one of the many available instruments. The common tests have been reviewed. A revised, expanded Denver Developmental Screening Test II addresses concerns of insensitivity of the original instrument.

E. Further assessment.

There is no routine laboratory workup. The results of state screening for certain inborn metabolic disorders must be known, and testing augmented if there is plateau or loss of milestone skills, vomiting and lethargy, movement or cutaneous disorders, failure to thrive, unusual body odor, or suggestive family history. Thyroid disorders must always be ruled out in developmental delay. Children with abnormal muscle tone should be screened with creatinine phosphokinase and aldolase. Neuroimaging or electroencephalography, or both, is indicated for children with focal neurologic findings, abnormal head growth (confirmed by magnetic resonance imaging, MRI), craniofacial anomalies, many genetic syndromes, seizures, sensory impairments, and other unexplained findings. Appropriate lead screening must be undertaken because relatively low-level toxicity can lead to impairment (see Chapter 1.1). Children with major or multiple anomalies suggestive of a syndrome should have karyotyping (done best in consultation with a geneticist). Chromosomal mosaicism may present subtle findings and be missed by amniocentesis. DNA testing for fragile X syndrome should be considered in boys with mental retardation and autism. Learning disabilities are confirmed by neuropsychometric testing.

II. Specific syndromes and management

A. Learning disabilities

(75 in 1,000 children) may be specific or global, and etiologic factors are often unknown. Learning disabilities are associated with increased comorbidities, including depression, anxiety, substance abuse, and sleep and eating disorders. Dyslexia is the most common disability, and it may affect written language and mathematical skills development. Sensory deficits must be ruled out. Preschool diagnosis is often difficult, and problems may not arise until adolescence and persist or even present in adulthood. Treatment should be individualized, with the focus on educational therapy. Retention is rarely useful and may negatively affect self-esteem and socialization.

B. Mental retardation

(25 in 1,000 children) is defined as a deficit resulting from disease, injury, or abnormality that existed prior to age 18, IQ of 70–75 or below, and deficits in at least 2 of the following 10 areas of adaptation: communication, self-care, home living, social skills, community use, self-direction, health and safety, functional academics, leisure, and work. Mild retardation may be isolated, but severe retardation is often accompanied by associated deficits that also affect prognosis. Fetal alcohol syndrome, fragile X syndrome, Down's syndrome, and DiGeorge's syndrome (deletion of chromosome 22) are the common identifiable causes of severe retardation. Specific medical problems, such as gastroesophageal reflux or aspiration pneumonia, may also be present. Linguistic deficits are due to the cognitive deficits and contribute to the emotional and behavioral disorders that often occur.

C. Cerebral palsy

(2.5 in 1,000 children) is a collection of disorders that manifest as abnormal motion and posture caused by early CNS injury (most commonly during intrauterine development). The Swedish classification involves four types: spastic (abnormalities of the pyramidal tract including quadriplegia, diplegia, and hemiplegia), dyskinetic (choreoathetosis with variable tone or rigidity and dystonia), ataxic (broad-based gait, truncal titubation, and dysmetria), and mixed. Approximately two thirds of affected children have associated mental retardation; most of those with normal intelligence have perceptual problems that may result in learning disabilities. Treatment may include neurosurgery or orthopedic surgery or devices; medical treatment for seizures, spasticity, constipation, and gastroesophageal reflux; and appropriate therapies.

D. Autism and related disorders

(1.5 in 1,000 children). This division includes a spectrum of brain-based developmental disabilities with multiple etiologic factors, involving impaired reciprocal social interactions, communication, and imaginative activity. There are often associated global cognitive deficits but not motor deficits (except for clumsiness). About 25% of patients manifest seizures. Children who demonstrate social interest and some degree of empathy and sustained interactions are considered to have pervasive development disorder rather than autism. Often those with better socialization and very strong language skills are diagnosed with Asperger syndrome. Educational, language, and behavioral therapy and highly predictable daily routines and preparedness are treatment mainstays. New medications are being tested.

E. Hearing impairment

(6 in 1,000 children). Prompt recognition and habilitation, including early sign language instruction, can maximize language skill development and social and emotional growth. Risk factors for hearing loss include family history, congenital infections, craniofacial anomalies, birth weight less than 1,500 g, severe hyperbilirubinemia, bacterial meningitis, asphyxia, ototoxic medications, mechanical ventilation for 5 or more days, and suspected syndromes that may include hearing loss. One third of cases will be missed by these criteria, and the Joint Committee on Infant Hearing has endorsed universal hearing screening by age 3 months. The effect of recurrent or chronic otitis media on development is unclear as causality is difficult to prove. Delayed milestones should not be dismissed based on otitis media.

F. Visual impairment

(0.5 in 1,000 children) is present in many of those with developmental disorders. Conversely, an increased prevalence of developmental problems is seen in the visually impaired. Prompt diagnosis and referral to an ophthalmologist skilled in the care of children is essential.

G. Down's syndrome

(1 in 1,000 children), or trisomy 21, is a common cause of mental retardation and may serve as a prototype for other chromosomal abnormalities with a wide range of medical, developmental, sensory, and emotional manifestations. Specific Down's syndrome growth charts should be used along with screening for heart defects, hypothyroidism, atlantoaxial instability, and other associated conditions. Frequent office visits and provider education are required to anticipate and manage the various problems of children with any chromosomal abnormality or syndrome (see Chapter 14.3).

H. Failure to thrive

(unexplained weight loss or poor weight gain) is particularly common in low-income families and may be caused by a variety of psychosocial, environmental, neurologic, and anatomical factors and their interactions. An excellent review is available (5). There is evidence for a sensitive period for mental development that is mitigated by poor postnatal somatic growth, placing these infants at risk for cognitive delay.

I. Neurodevelopmental abnormalities due to HIV infection

are a spectrum of motor, cognitive, communication, social, and behavioral problems that may ultimately be seen in infected children. Appropriate antiviral and medical treatment and therapy and mainstream school settings for as long as possible are indicated (see Chapter 19.4).

J. Comprehensive primary care for children with developmental delay includes coordination and management of a team of medical and sometimes surgical and dental specialists, counselors (genetic, parental, family), habilitation or rehabilitation therapists, medical device services, and special educators.

Goals must be agreed on between physician, family, therapists, and educators and written progress reports shared. Knowledge of community and social services as well as advocacy for the child and family are essential.

K. Advice for the parents begins with frank, factual, unhurried, and compassionate discussions as soon as the diagnosis of delay is entertained.

Avoid speculation regarding intelligence and unnecessary pessimism.

Expectations often affect outcomes: Low expectations may be a self-fulfilling prophecy. Helpful advice for rearing a child with special needs includes setting realistic goals, avoiding hours spent finding the “perfect educational toy,” and following the baby's or child's own agenda (not feeling like one has to be teaching the child every minute to “catch up”). Maximizing communication in children with language disorders and helping parents foster special strengths of their child should help minimize the child's frustration and consequent additional emotional, behavioral, or social disturbances. Sports activities, including Special Olympics, are often helpful for weight management, fitness, development of physical coordination, and improvement of self-esteem. Often activities involving gross motor skills are most appropriate, with attention to specific instances that increase the risk of injuries (e.g., atlantoaxial instability in Down's syndrome).

Consistent discipline, appropriate for the level of understanding, is important for the child, particularly in the context of his or her siblings (the child with special needs should not “get away with anything” at a given developmental age if the siblings did not). Parents should avoid allowing undesirable behaviors, such as chewing on a book, because this is “progress,” only to have to work very hard later to extinguish the behavior.

III. Prevention

involves optimization of preconceptual, prenatal, and postnatal care (see Chapter 14.4 and Chapter 14.11). The latter includes not only avoidance of untoward exposure; early identification of toxic, metabolic, and medical disorders; appropriate therapy; and optimization of neurologic outcome, but also providing a nurturing environment. For the very premature, this should include careful restriction of stimuli and protected rest time. For the child in an at-risk home environment, a combination of social services, parental counseling and support groups, and an interested provider may improve outcome. Early diagnosis of visual or hearing loss should be made. Finally, whereas the efficacy of early intervention is debatable, early identification of developmental delay or risk affords the best chance for affecting developmental change via a still malleable nervous system. It also empowers the family to be proactive in maximizing the child's abilities, perhaps avoiding secondary emotional and physical disability.

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4.2
FEVER IN INFANCY AND CHILDHOOD

Sanford R. Kimmel

Fever is the elevation of body temperature above normal. Normal core body temperature is 37°C (98.6°F) ± 1°C, whereas a temperature of 38°C (100.4°F) or higher represents a fever. Rectal temperature most accurately reflects core temperature, especially in infants. Oral or tympanic temperatures are suitable for older children but can be inaccurate.

Fever in children is usually the result of an underlying infection but occasionally is due to collagen vascular disease, malignancy, or metabolic disorder, such as hyperthyroidism. Salicylate or anticholinergic poisoning as well as excessive environmental temperature also produce fever.

I. Diagnosis

A. History.

Febrile children may be sleepier or crankier than usual. Respiratory symptoms include rhinorrhea, sore throat, otalgia, and cough. Vomiting and diarrhea occur in gastrointestinal infections as well as other illnesses. Dysuria and frequent urination are suggestive of urinary tract infection (UTI) in older children but are often absent in infants. Pronounced lethargy or irritability is a red flag for a serious bacterial illness (SBI).

B. Physical examination.

Observation of the older infant or child is very helpful in determining the index of suspicion for an SBI. A pink, alert, wellhydrated, smiling, or easily consoled infant is much less likely to have an SBI than a pale, lethargic, dehydrated, dull, or irritable child. These variables are quantitated in the Yale Acute Illness Observation Scales (1). Table 4.2-1 lists physical findings that may be indicative of specific diseases (2).

Body region or system	Physical finding	Potential disease
Skin	Petechial rash	Meningococcemia
	Maculopapular rash, followed by petechial rash	Rocky Mountain spotted fever
Head	Bulging fontanelle, nuchal rigidity	Meningitis (later manifestation in child under 2 yr of age)
Eyes	Conjunctivitis	Associated otitis media, Kawasaki's disease, or measles with cough, coryza
Ears	Red, dull, nonmobile tympanic membrane	Otitis media
	Swelling and tenderness behind ear	Mastoiditis
Nose	Purulent rhinorrhea	Sinusitis
	Nasal flaring	Pneumonia or any condition producing respiratory distress
Throat	Stridor	Laryngotracheobronchitis (croup)
	Stridor with drooling, dysphagia, or aphonia	Epiglottitis
	Petechiae on soft palate and uvula	Streptococcal pharyngitis
	Vesicles or ulcers on soft palate and tonsillar pillars	Herpangina
	Vesicles or ulcers on tongue, lips, and buccal mucosa	Herpes stomatitis
	Strawberry tongue	Streptococcal pharyngitis or Kawasaki's disease
Chest	Tachypnea, retractions, decreased breath sounds, rales (may not be present)	Pneumonia
	Rhonchi	Bronchitis
	Wheezing	Bronchiolitis, asthma (inhaled foreign body or other causes)
Heart	Murmur	Subacute bacterial endocarditis, rheumatic fever (or normal due to increased cardiac output)
Abdomen	Local tenderness worsening with movement	Appendicitis or condition producing peritoneal irritation
Rectal	Fluctuant mass	Ruptured appendix or perirectal abscess
Musculoskeletal	Refuses to bear weight or use extremity	Septic arthritis or osteomyelitis, especially in the hip

From SR Kimmel, DW Gemmill. The young child with fever. *Am Fam Physician* 1988;37:202, with permission.

Table 4.2-1. Physical clues to infectious causes of fever in children

C. Screening laboratory tests.

No test can detect every SBI in all febrile children, but the following values in infants older than 28 days deserve further investigation:

1. White blood cell (WBC) count of 15,000/μL or more or WBC count of less than 5,000/μL
2. Absolute band count of 1,500/μL or higher
3. Presence of toxic granulation or vacuolization in neutrophils

D. Specific diagnostic studies

1. **Chest radiography** is indicated in the presence of pulmonary symptoms, such as tachypnea. Rales are not always heard in young children with pneumonia.
2. **Urinalysis with culture** should be considered in male infants younger than 6 months of age, older uncircumcised male infants, and female infants younger than 2 years old when fever does not have a source.

3. **Blood culture** should be considered in the child younger than 36 months who is at high risk for SBI, as indicated by physical examination, fever of 39°C or higher, or WBC count of 15,000/µL or greater.
4. **Lumbar puncture** should be performed in the presence of symptoms or signs suggestive of meningitis, such as excessive irritability or lethargy, seizures, or bulging fontanelle.
5. **Stool smear** of bloody or mucoid diarrhea demonstrating five or more WBCs per high-power field (hpf) suggests bacterial enteritis warranting stool culture for *Salmonella, Shigella, Campylobacter, Yersinia,* or pathogenic *Escherichia coli*.

II. Management of the febrile child at risk for a serious bacterial infection

A. Infants younger than 28 days

should undergo a sepsis workup in the hospital and receive parenteral antibiotics pending culture results.

B. Infants 28–90 days old

who are toxic or at high risk should be admitted for sepsis workup and treatment. Infants who are nontoxic and at low risk (see Section II.C) may be evaluated and treated as outpatients **provided they have reliable caretakers and follow-up.** Following cultures of the blood, urine, and cerebrospinal fluid (CSF), ceftriaxone (Rocephin), 50 mg/kg IM, up to 1 g maximum, should be administered. The child must be reevaluated within 24 hours (3).

C. Low-risk criteria

apply to those previously healthy term infants who appear generally well (nontoxic) and have no focal bacterial infection except otitis media (OM). Laboratory studies include total WBC of 5,000–15,000/µL, absolute bands less than 1,500/µL, urinalysis less than 5 WBCs/hpf or negative Gram's stain result, and stool with less than 5 WBCs/hpf. These criteria do not exclude all infants with SBI but have a negative predictive value of about 98%–99% (4).

D. Nontoxic infants aged 3–36 months with a temperature less than 39°C

should have fever treated symptomatically (see Section IV.A). Focal symptoms should be addressed but the child reexamined if he or she appears worse or the fever lasts longer than 48 hours.

E. Nontoxic infants aged 3–36 months with a temperature of 39°C or higher

should have screening WBC count and blood culture if there is no obvious focus for infection. Girls younger than 2 years and boys younger than 6 months (or older if uncircumcised) should have a urine culture. Chest radiography, lumbar puncture, or stool specimen should be obtained if clinically appropriate. Empirical antibiotic treatment with ceftriaxone or amoxicillinclavulanate (Augmentin), 40 mg/kg per day of amoxicillin divided in three doses, may be considered (5), especially if the WBC count is 15,000/μL or greater. Oral cefixime (Suprax) 16 mg/kg on day 1 followed by 8 mg/kg per day for a total of 14 days may be used to manage urinary tract infection (UTI) (6).

III. Follow-up of infants and children with fever without source

A. Infants 28–90 days old

must be rechecked within 24 hours. A second dose of ceftriaxone may then be given. OM or UTIs may be treated on an outpatient basis in afebrile, nontoxic, and nonbacteremic children. The afebrile wellappearing child with *Streptococcus pneumoniae* bacteremia may also be treated with oral antibiotics. Children who are still febrile, appear ill, or have a positive CSF culture result or bacteremia other than antibiotic-sensitive *S. pneumoniae* should be admitted for sepsis workup and treatment.

B. Children 3–36 months old

should be rechecked in 24–48 hours. If the child is afebrile and nontoxic, antibiotics can be discontinued after 48 hours. Oral antibiotics should be given for OM, UTIs, or antibiotic-sensitive *S. pneumoniae* bacteremia. Children who are still febrile, appear ill, or have a positive CSF culture result require further evaluation or parenteral antibiotic treatment, or both.

C. Structural evaluation of the urinary tract

should be performed on boys and young girls after their first documented UTI.

IV. Treatment of fever and febrile seizures

A. Avoid fever phobia

by educating parents that fever is a symptom of an underlying illness and is itself seldom dangerous (7). The primary reason to treat fever is to make the child more comfortable. Fever of 38.9°C (102°F) or higher may be treated with acetaminophen, 10–15 mg/kg per dose q4h up to maximum of 5 doses per day, or ibuprofen, 5–10 mg/kg per dose q6–8h in children 6 months or older. The child may subsequently be sponged with lukewarm water if the temperature exceeds 40°C (104°F). The child should be encouraged to drink liquids and may be covered with a light blanket.

B. Febrile seizures

occur in 2%–5% of febrile children between the ages of 6 months and 5 years. Seizures that are complex, occur upon arrival in the emergency department, or are accompanied by abnormal neurologic findings are a red flag that causes such as meningitis should be investigated (also see Chapter 6.4). Lumbar puncture should be strongly considered in infants younger than 12 months presenting with their first febrile seizure (8).

- **Simple seizures** are generalized tonic-clonic events that last less than 15 minutes and do not recur within 24 hours (8).
- **Complex seizures** last longer than 15 minutes, demonstrate focal signs, or recur within 24 hours or in a flurry (8).

1. **Assuring adequate airway, breathing, and circulation** is all that is usually required for a short febrile seizure. Intravenous lorazepam (0.05–0.1 mg/kg over 2–5 min) may be used for prolonged seizures or those compromising the child's cardiorespiratory status. If necessary, lorazepam may be repeated but the clinician should be prepared to assist the child's ventilation. Rarely, intravenous phenytoin (15–20 mg/kg) is given slowly (1 mg/kg per minute) for persistent seizure. Rectal diazepam (0.5 mg/kg to maximum dose of 5 mg) is 80% effective in controlling febrile seizures (9).

2. **Recurrent febrile seizures** may occur in 50% of children younger than 12 months and 30% of children older than 12 months at the time of their first simple seizure. Recurrent seizures are also more likely if seizures were complex, multiple, or occurred in children with underlying neurologic abnormalities or a history of afebrile seizures (10). Epilepsy may develop in 1%–2.4% of children with simple febrile seizures (see Chapter 6.4).
3. **Prophylaxis of febrile seizures** is rarely indicated for simple seizures but may be used for frequent or severe seizures. Phenobarbital at a blood level of 15 µg/mL is effective but causes behavioral side effects in 20%–40% of children. Valproic acid is effective in children but can cause fatal liver failure in addition to thrombocytopenia, gastrointestinal disturbances, and pancreatitis in those younger than 3 years. Oral diazepam given at the time of fever reduces the risk of febrile seizures but can cause lethargy and ataxia that could mask a CNS infection (10).

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4.3
INSPIRATORY STRIDOR, CROUP, AND EPIGLOTTITIS

Neil S. Skolnik

Inspiratory stridor is a syndrome of upper airway obstruction, characterized by a harsh sound on inspiration. Etiologic factors include croup, epiglottitis, retropharyngeal abscess, peritonsillar abscess, foreign body, extrinsic laryngeal compression (tumor, cyst, hematoma), angioedema, laryngeal webs, vascular rings, bacterial tracheitis, acquired or congenital subglottic stenosis, and laryngomalacia.

Viral croup, often considered synonymous with laryngotracheobronchitis, is the most common form of upper airway obstruction in children aged 6 months to 6 years. It is caused by inflammation and edema of the subglottic region of the larynx. Epiglottitis is a bacterial infection of the epiglottis that causes acute upper airway obstruction. It is usually caused by *Haemophilus influenzae* type b infection and has been nearly eradicated since the introduction of routine immunization with *H. influenzae* vaccine (see Chapter 1.1).

I. Croup

A. Clinical presentation.

The mean age of children presenting with croup is 18 months, with age ranging from 3 months to 6 years. Croup is most common in early fall and winter, and usually, but not always, is preceded by a couple of days of upper respiratory symptoms followed by hoarseness, low-grade fever, and a "croupy" or barking cough (1).

Illness may progress no further or may go on to cause inspiratory stridor, flaring of the ala nasi, and suprasternal and intercostal retractions. The lungs are generally clear but about 5% of the time there is associated wheezing.

B. Diagnostic studies.

Usually no diagnostic studies are needed, and the diagnosis of croup can be made on clinical grounds. White blood cell (WBC) counts are usually normal or mildly elevated but are greater than 15,000/mm^3 approximately 20% of the time. Lateral neck radiography shows widening of the hypopharynx. Posteroanterior radiographs may show a narrowed subglottic region known as a steeple sign. Classic signs of croup on radiography are seen only about half the time.

C. Treatment.

The first decision in the treatment of croup is whether a child should be treated on an outpatient or inpatient basis. This decision is made based on the degree of stridor, severity of retractions, pulse rate, respiratory rate, and evidence of cyanosis. Many physicians believe that stridor at rest is an indication for hospital admission. A helpful algorithm for treatment is shown in Figure 4.3-1 .

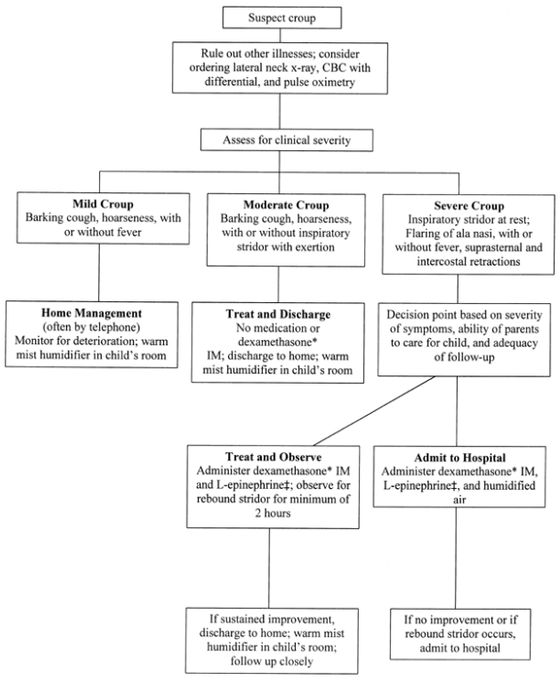

FIG. 4.3-1. An algorithm for the treatment of croup. *, dosage 0.6 mg/kg; ‡, dosage l-epinephrine 1:1,000, see text for dose. (From Skolnik NS. Croup. *J Fam Pract* 1993; 37:168, with permission.)

1. **Humidified air.** Provision of humidified air, either by having the parent hold the child in his or her arms in the bathroom at home with the shower turned on to generate steam or by using a croup tent in the hospital, is reasonable, although the efficacy of this time-tested treatment is unproved and varies a great deal.
2. **l-Epinephrine** (1:1,000) at a dose of 0.5 mL/kg diluted in 3 mL normal saline (maximum doses: <4 yrs: 2.5 mL/dose; >4 yrs: 5 mL/dose) administered by nebulizer can be given to acutely decrease the upper airway obstruction seen in croup. l-Epinephrine has been shown to have equivalent potency and safety when compared to the much less available racemic epinephrine (2). Epinephrine works through α-adrenergic effects, which lead to mucosal vasoconstriction that results in decreased edema in the subglottic region of the larynx. Time of onset of action is less than 10 minutes and duration of action is less than 2 hours. Treatment is very effective, but all children who receive racemic epinephrine must be observed for at least 2 hours because of the possibility of rebound stridor, and all such children should receive corticosteroid treatment (3).
3. **Adrenal corticosteroids.** Dexamethasone, 0.6 mg/kg IM or PO, is effective in decreasing airway obstruction, but it has a slow onset of action and often does not take effect for up to 6 hours. Prednisone, 3 mg/kg PO, is also probably effective but has not been studied as extensively. Adrenal corticosteroids should be administered to all children with severe croup, and many children with moderate croup (3).
4. **Nebulized budesonide.** Budesonide is a highly potent topical steroid that can be administered by nebulizer. It has a short onset of action and is effective in decreasing inspiratory stridor (4, 5). It is not yet available in the United States.

II. Epiglottitis

A. Clinical presentation.

Epiglottitis tends to occur in children who are older (3–7 years) than the croup age group with no history of a preceding upper respiratory infection. The disease is of sudden onset, and there is a high fever. The child is often sitting up, leaning forward and drooling without a cough, and appears toxic (6).

B. Diagnostic studies.

Lateral neck radiography shows a swollen epiglottis, classically referred to as the “thumb sign.” If the clinical presentation of a child suggests epiglottitis, the physician should not waste time getting a lateral neck radiograph. Visualization of the epiglottis should be performed as soon as possible in a controlled setting with facilities available for intubation and tracheotomy. Epiglottitis is confirmed by visualizing a cherry-red epiglottis. Blood cultures should be obtained because this is usually a bacteremic disease.

C. Treatment.

Treatment is twofold. First, the airway must be secured to ensure adequate ventilation. This is usually accomplished through endotracheal intubation done in a controlled setting where tracheostomy can be performed if necessary. Second, intravenous antibiotics effective against *H. influenzae* type b should be started (cefuroxime, 75 mg/kg per day divided into q8h, or ceftriaxone, 100 mg/kg per day divided into ql2h).

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4.4
REACTIVE AIRWAY DISEASE IN CHILDREN

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Michael T. Kernan

Airway hyperresponsiveness—the tendency of airways to constrict and cause obstruction due to inflammation-characterizes both asthma and wheezing respiratory illnesses in children.

I. Diagnosis

A. History

1. The most common symptoms include cough, wheezing, shortness of breath, and chest tightness. Determine if respiratory distress has happened before and when (e.g., seasonally, with upper respiratory infections, or nocturnally).
2. Associated diseases, including allergic rhinitis and atopic dermatitis, are common (see Chapter 8.6 and Chapter 16.5).
3. Aggravating factors, such as smoke, animals, exercise, upper respiratory infections, and drugs, should be identified.
4. A family history of allergies or asthma is common.

B. Physical examination

1. Obtain vital signs, including respiratory rate, temperature, pulse, and weight.
2. Observe the child's color and degree of respiratory distress and anxiety. Fatigue and cyanosis signal a severe attack, and the clinician should be prepared for respiratory failure.
3. Stridor indicates an upper airway problem, such as croup or foreign body (see Chapter 4.3).
4. Check if the wheezing is bilateral and document retractions as well as the ratio of inspiration to expiration (I/E). In children without wheezing or who have normal respirations, check for a posttussive wheeze. Lack of wheezing and presence of a normal chest examination do not exclude asthma.
5. Hydration status should be evaluated.
6. A complete ear, nose, and throat examination should be performed with a focus on infections, nasal polyps (pathognomonic for cystic fibrosis), and signs of allergies.

II. The differential diagnosis

includes the following conditions:

A. Asthma

is characterized by recurrent episodes of cough, dyspnea, and diffuse wheezing (see Chapter 10.1).

B. Bronchiolitis

is characterized by the insidious onset of wheezing, tachypnea, and chest wall retractions associated with a 2- to 3-day history of rhinorrhea, cough, and low-grade fever in a child younger than 2 years (1).

C.

Other conditions include **cystic fibrosis, bronchopulmonary dysplasia, gastroesophageal reflux, congestive heart failure, and pneumonia.**

D. Large airway obstruction

can be caused by foreign bodies, vascular rings, tracheomalacia, tumors, and laryngeal webs.

III. Diagnostic tests

A. Reversibility of airway obstruction

is diagnostic of asthma and can be evaluated with epinephrine or adrenergic aerosols.

B. Complete blood count and chest radiographs

are useful only with fever, to evaluate for pneumonia, or if congestive heart failure is suspected.

C. Pulmonary function tests

are usually reliable by age 5–6 years and are most useful for monitoring chronic asthma; they are not required for the diagnosis. If done to evaluate cough, provocation with methacholine might be needed (1).

D. Sinus radiographs, pulmonary function tests, studies for reflux, and specific IgE antibodies or skin testing

(75% of asthmatics have environmental allergies) are indicated for patients whose asthma is resistant to the usual treatment or to evaluate for suspected inciting factors.

E. Oximetry

is useful for determining severity of respiratory compromise but is not helpful in the differential diagnosis (2).

IV. Treatment

A. Prevention.

Warm-blooded animals should be removed from the home. Exposure to dust mites should be minimized by washing bedding and stuffed animals two times per week in water at least 130°F. Wipe off surface dust frequently using a damp cloth. Carpeting and upholstered furniture should be removed. The humidity level should be kept below 50%. Mattresses and box springs should be encased in airtight plastic covers with tape over the zipper. Regularly wash damp areas, such as shower stalls, basements, and window sills. Avoid environmental irritants. Do not allow smoking. Do not use wood stoves. Avoid strong odors or sprays. Do not clean when the patient is present. Reduce exposure to infections. Avoid day care settings if possible, and vaccinate appropriately. If symptoms are severe or systemic and steroids are needed regularly, immunotherapy may be necessary.

B. Pharmacologic therapy(3)

1. **Cromolyn sodium (Intal aerosol spray) and nedocromil sodium (Tilade)** are overall the safest medicines in asthma. They are antiinflammatory medicines and have no bronchodilator effect. The dosage is two puffs of multidose inhaler (MDI) 3–4 times per day or one unit dose via nebulizer mixed with a ß-agonist. The treatment may be decreased to 2 times per day with adequate clinical response.
2. **ß-Adrenergic agonists** are bronchodilators effective in treating early asthmatic responses and exercise-induced asthma. Selective ß-agonists are preferred due to fewer cardiac side effects. The ß-agonists are available as MDIs, nebulizer solutions, oral preparations, and parental preparations.
3. **Corticosteroids** are very potent anti-inflammatory medicines. Anti-inflammatory agents are the most important medicine in chronic recurrent asthma. They reduce inflammation, edema, and mucous secretions and restore ß-adrenergic responses. The topical agents are quickly metabolized and rarely cause systemic symptoms. Inhaled steroids and cromolyn are best given 10 minutes after inhaled ß-agonists.
4. **Theophylline** is a bronchodilator whose use has markedly decreased in recent years due to side effects and lack of an anti-inflammatory component.
5. **Anticholinergics** function as bronchodilators in most asthmatics. Ipratropium bromide (Atrovent) is poorly absorbed and has few systemic side effects. It is particularly useful in cold air-induced, irritant-induced, and emotionally induced asthma.
6. **Leukotriene receptor antagonists:** montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo). Montelukast is approved for age 6 and above, zafirlukast is approved for age 7 and above, and zileuton is approved for age 12 and above. Leukotriene antagonists work on the inflammatory cascade in asthma.

C. Management

1. "Step-care" management strategy of asthma, in which the number of medications and frequency of use are increased as symptoms worsen, is recommended by the National Heart, Lung and Blood Institute (3).
   a. Severe persistent
      1. Long-term control—*Daily* anti-inflammatory: high-dose inhaled corticosteroid *and* long-acting bronchodilator *and* corticosteroid tablets or syrup (2 mg/kg per day; do not exceed 60 mg/d).
      2. Quick relief—Short-acting bronchodilator; inhaled ß-agonists as needed.
   b. Moderate persistent
      1. Long-term control—*Daily* anti-inflammatory: inhaled corticosteroid, medium dose, *or* inhaled corticosteroid low-medium dose with long-acting bronchodilator, especially for nighttime symptoms. *If needed:* anti-inflammatory: medium-high dose inhaled corticosteroids *and* long-acting bronchodilator, especially for nighttime symptoms.
      2. Quick relief—Short acting bronchodilator; inhaled ß-agonists as needed.
   c. Mild persistent
      1. Long-term control—*Daily* anti-inflammatory: either low-dose inhaled corticosteroid or cromolyn or nedocromil (children usually begin with trial of cromolyn or nedocromil)
      2. Quick relief—Short-acting bronchodilator; inhaled ß-agonists as needed.
   d. Mild intermittent
      1. Long-term control—No daily medication needed.
      2. Quick relief—Short-acting bronchodilator; inhaled ß-agonists as needed.
   e. Second-line treatment for ³12 years: Leukotriene modifiers as alternative to high-dose inhaled glucocorticoid therapy or as an addition to therapy (taking advantage of different mechanisms of action).
2. Peak flowmeters, which measure peak expiratory flow rate (PEFR), are essential to manage asthma properly. The following are interpretations of flowmeter readings.
   a. The green zone is defined as a PEFR of 80%–100% of personal best: No symptoms are present; the patient can engage in full activity, and no change in medication is needed.
   b. The yellow zone is defined as a PEFR of 50%–80% of personal best: The patient is at increased risk of asthma attacks; treatment should be applied per the step-care management strategy (see Section IV.C.1).
   c. The red zone is defined as a PEFR of less than 50%. Call the physician; *emergency care is necessary*.

V. Indications for admission

are continued wheezing an hour after administration of ß-agonist in association with any sign of respiratory distress, persistent tachypnea, Pco greater than 40, Pao_2 less than 70, O_2 saturation less than 95%, and altered level of consciousness.

VI. Indications for consultation

are required multiple hospital admissions, continuation of symptoms, PEFR less than 90% of predicted and never returning to baseline, and poor status following intubation.

VII. Resources for patient education

A.

National Asthma Education Program, DHHS, Pub. No. 97-4051, 1997.

B.

American Lung Association, (800) 586-4872, http://www.lungusa.org/.

C.

Asthma and Allergy Foundation of America, (800) 727-8462, http://www.aafa.org/.

D.

Allergy and Asthma Network/Mothers of Asthmatics, Inc., (800) 878-4403, www.podi.com/health/aanma.

E.

National Asthma Education and Prevention Program, (301) 251-1222, www.nhlbi.nih.gov/nhlbi/nhlbi.htm.

F.

American Academy of Allergy, Asthma, and Immunology, (800) 822-2762, http://www.aaaai.org/.

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4.5
VIRAL EXANTHEMS OF CHILDREN

Jeffrey T. Kirchner

Viral exanthems of children are a common clinical problem encountered by the family physician. Numerous viral agents can produce a similar rash and other clinical symptoms, which makes the diagnosis challenging. A careful evaluation that includes age, immunization status, history of infectious diseases, exposures, medication use, type of prodromal period, features of the rash, and the presence of pathognomonic signs is helpful in establishing a diagnosis. Laboratory testing may be available to confirm the diagnosis but often is not acutely useful due to the time delay in obtaining viral cultures or serologic antibody titers. The increasing availability of polymerase chain reaction (PCR) testing should improve the ability to diagnose many infectious illnesses. Treatment in most cases is supportive.

I. Measles

A. Causative agent.

Measles is caused by an RNA paramyxovirus that belongs to the genus *Morbillivirus.* Infected individuals are contagious up to 7 days after the onset of symptoms.

B. Clinical manifestations

may initially include fever, cough, conjunctivitis, and Koplik's spots (an enanthem). Rash appears on the third or fourth day and begins as a purple-red maculopapular eruption along the hairline, forehead, and face. By the third day it spreads to the feet and it fades in the order of appearance. Acute encephalitis occurs in 1–2 per 1,000 reported cases and may be fatal.

C. Diagnosis.

This is usually made on clinical grounds, but viral cultures of body fluids or serologic testing is confirmatory. Specific IgM antibody is usually detectable by 72 hours after onset of the rash (1).

D. Treatment

of uncomplicated infections is supportive.

II. Rubella (German measles)

A. Causative agent.

Rubella is caused by a single-stranded RNA virus of the family Togaviridae.

B. Clinical manifestations

may include low-grade fever, postauricular adenopathy, headache, and myalgias. Rash consists of pink-red lesions that are discrete and do not coalesce. They appear first on the face and spread rapidly downward to the neck, arms, trunk, and lower extremities. The total duration is 3–4 days, with occasional brawny desquamation. Complications are rare but may include joint manifestations, thrombotic thrombocytopenia purpura, and encephalitis.

C. Diagnosis

is clinical but may be confirmed with serologic antibody testing for specific IgM antibody or paired sera for IgG antibody (2).

D. Treatment

is symptomatic and supportive.

III. Roseola infantum (exanthem subitum; sixth disease)

A. Causative agent.

Roseola is caused by the human herpesvirus type 6 (HHV-6). It is the most common viral exanthem in children younger than 2 years.

B. Clinical manifestations

include abrupt onset of fever, commonly 40–40.6°C, which persists for 3–5 days with a rapid decline. Rash appears after defervescence. The lesions are pink macules or maculopapules 2–3 mm in diameter that blanch with pressure. They appear first on the trunk and then spread to the neck, face, and upper and lower extremities. The total duration is 1–2 days.

C. Diagnosis

is clinical. Serologic testing for HHV-6 IgM is not routinely available; however, paired sera for IgG antibody obtained 2–3 weeks apart confirms the diagnosis.

D. Treatment

is symptomatic and supportive.

IV. Erythema infectiosum (fifth disease)

A. Causative agent.

Erythema infectiosum is caused by the human parvovirus B19. It is moderately contagious, with outbreaks occurring in families, day care centers, and classrooms.

B. Clinical manifestations

include fever and myalgias. Potential complications include erythrocyte aplasia, arthropathy, and fetal hydrops. Rash has a sudden onset on the face, with marked erythema (“slapped cheek” appearance). This is followed by a generalized lace-like rash on the trunk and extremities that may persist for several weeks. Heat, local irritation, or sunlight may cause a flare-up of the rash.

C. Diagnosis

is clinical but may be confirmed by serologic testing for parvovirus IgM antibody. IgG antibody is helpful for determining past infection and immunity.

D. Treatment

of uncomplicated cases is supportive. Immune globulin intravenous has been used with some success for immunocompromised patients with persistent infection and anemia (3).

V. Enteroviral infections

A. Causative agent or agents.

The enteroviruses consist of numerous strains of echoviruses, Coxsackie viruses, and polioviruses. They tend to cause infections in the summer and fall.

B. Clinical manifestations

are varied and include fever, gastroenteritis, respiratory disease, meningitis, and myocarditis. Rash consists of exanthems that are often rubella-like in appearance. They tend to be generalized, maculopapular, and nonpruritic. Petechial lesions are sometimes seen with type 9 echovirus and Coxsackie virus type A. The duration varies with age and viral type, lasting from a few days to 2 weeks.

C. Diagnosis

is clinical but may be difficult and often becomes one of exclusion. Serologic testing is available but is usually not acutely helpful.

D. Treatment

of uncomplicated cases is symptomatic and supportive.

VI. Kawasaki's disease (mucocutaneous lymph node syndrome)

A. Causative agent.

Kawasaki's disease remains one of unknown cause; it predominantly affects children under the age of 4 years.

B. Clinical manifestations

include fever, conjunctival infection, erythema and fissuring of the lips, induration of the hands and feet, enlarged lymph node mass, and rash. This is deeply erythematous and polymorphic and most commonly manifests as pruritic plaques that vary from 2 to 10 mm. They may resemble urticaria or the target lesions of erythema multiforme. Distribution is variable and may be diffuse, truncal, or limited to the extremities. It slowly fades with resolution of clinical illness.

C. Diagnosis

is clinical and must include five of the six clinical manifestations mentioned in Section VI.B . “Atypical Kawasaki's disease,” which is becoming increasingly recognized, is attributed to children who do not meet the case definition but have compatible laboratory findings and no other explanation for their illness. They are treated the same as patients with classic Kawasaki's disease (4).

D. Treatment

includes intravenous γ-globulin (2 g/kg as a single 10- to 12-hour infusion) and aspirin (100 mg/kg per day until afebrile or 14 days into the illness; decrease to 5–10 mg/kg per day until erythrocyte sedimentation rate and platelet count normalize).

VII. Infectious mononucleosis in children

A. Causative agent.

Mononucleosis, which is caused by the Epstein-Barr virus (EBV), occurs in children but is most commonly seen in adolescents and young adults (see Chapter 19.3).

B. Clinical manifestations

usually include fever, tonsillopharyngitis, cervical lymphadenopathy, and splenomegaly. The rash with EBV infection occurs in 10%–15% of patients and is usually on the trunk and arms. It is erythematous, macular and papular, or morbilliform. It appears during the first day or two of clinical illness and disappears by day 6 or 7. Inappropriate administration of amoxicillin results in a diffuse copper-colored rash.

C. Diagnosis

is made by serologic testing for EBV antibody, most commonly the Monospot test although other more specific EBV antibody testing is available (5).

D. Treatment

is symptomatic and supportive for uncomplicated cases.

VIII. Primary varicella (chickenpox)

A. Causative agent.

Varicella is caused by the varicella-zoster virus (VZV) and is one of the most contagious of childhood viral illnesses.

B. Clinical manifestations

include fever, headache, and malaise. Rash is characterized by the rapid evolution of macule to papule to vesicle. The vesicles, which resemble dewdrops, are 2–3 mm in diameter, pruritic, and rupture easily. The lesions appear in crops involving the face, extremities, and trunk. A unique feature of the rash is that the lesions in all stages may be found in the same anatomical area. They crust over by the seventh to tenth day.

C. Diagnosis

is clinical, although serologic testing for VZV antibody is routinely available.

D. Treatment

is usually symptomatic and may include antipyretics and antihistamines. Oral or intravenous acyclovir is sometimes used in complicated cases or for immunocompromised children. A highly effective live attenuated vaccine that prevents primary varicella infection has been available since 1996.

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4.6
MUSCULOSKELETA PROBLEMS OF CHILDREN

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John P. Fogarty

I. Scoliosis.

Scoliosis is a lateral deviation of the spine. Curves greater than 11 degrees are present in 2%–3% of adolescents at the end of their growth period. Approximately 65% of curves are due to idiopathic scoliosis, and 35% are secondary to underlying conditions, such as infection, neoplasms, metabolic disorders, upper and lower motor neuron disease, syrinx, tethered cord, spondylolysis, herniated disk, and myopathies.

A. Idiopathic adolescent scoliosis.

This is the most common spinal deformity evaluated by primary care physicians, present in 2%–3% of the general population. The most common curve pattern is a right thoracic apex, followed by right thoracic-left lumbar, thoracolumbar, double thoracic, and left lumbar curves. Patients with other curve patterns or curves associated with pain or stiffness that are likely due to underlying pathology should undergo expedient evaluation, be referred to an orthopedic surgeon, or both (1).

1. **Clinical presentation.** Children generally present with cosmetic concerns or are referred through school screening programs (see Chapter 1.1 and Chapter 1.2). Pain is suggestive of an underlying tumor or inflammatory process and is not part of idiopathic adolescent scoliosis.
2. **Physical examination.** The physical examination reveals varying asymmetries in shoulder and iliac crest height, asymmetrical scapular prominence, and a flank crease. The forward bending test is the most sensitive and should reveal a right thoracic and possibly a left lumbar prominence. The neurologic examination and gait should be normal. A scoliometer is useful for measuring the thoracic prominence (“rib humps”) and for follow-up.
3. **Radiographs.** Patients with a scoliometer reading greater than 5 degrees or who are otherwise suspected of a significant curve can be screened with a single, standing, 36-inch anteroposterior (AP) film. The vertebral levels with the greatest tilt are identified and measured by the Cobb method. Curves greater than 15 degrees are significant.
4. Risk factors for progression
   a. Spinal immaturity (Risser grades 0–2). Spinal growth correlates with ossification of the iliac apophysis from anterior to posterior. The Risser grading system is shown in Table 4.6-1 .

Grade 0: No ossification
Grade 1: Ossification of 0% to 25%
Grade 2: 25% to 50%
Grade 3: 50% to 75%
Grade 4: 75% to 100%
Grade 5: Fusion to ilium

Table 4.6-1. The Risser grading system for spinal maturity

   b. Girls, especially between the onset of the pubertal growth spurt (age 10–12) until cessation of spinal growth (Risser 4), are at risk for progression of scoliosis.
   c. Delayed puberty and menarche. Hypoestrogen status delays maturation of osseous growth centers and allows an accentuated curve.
   d. Family history imparts an 11%–27% risk of involvement.
5. Risk of progression
   a. >10 degrees: 2%–3%; >20 degrees: 0.3%–0.5%; >30 degrees: 0.1%–0.3%; >40 degrees, <0.1%.
   b. Girls have a tenfold higher risk of progression than boys.
6. Treatment
   a. Curvature of 0–10 degrees is normal.
   b. For curvature of 10–15 degrees, follow up every 6 months for clinical recheck with forward bending test and scoliometer test to check for progression.
   c. For curvature of 15–20 degrees, repeat radiographs every 3–4 months in a growing child with a larger curve. For smaller curves or near the end of growth, repeat radiographs in 6–8 months.
   d. For curves greater than 20 degrees, refer to a specialist for consideration of bracing and close follow-up.

II. Spondylolysis and spondylolisthesis.

Spondylolysis is a bony defect of the pars interarticularis. It is generally considered to be a fatigue (stress) fracture due to repetitive lumbar hyperextension and is most common at L5 to S1. The pars defect is present in 5%–6% of North Americans and more than 50% of Alaskan Native Americans or in those with a family history of spondylolysis. It is four times more common in gymnasts than in the general population. Nonathletes may be genetically predisposed to pars breakdown with minimal stress, whereas athletes likely place undue stress on a normal pars. In 47% of athletes with back pain, spondylolysis is the cause. Spondylolisthesis is forward slippage of the cephalad vertebral body on the caudad one. Grade I spondylolisthesis is slippage of 0%–25%; grade II, 25%–50%; grade III, 50%–75%; grade IV, 75%–100%; and grade V indicates slippage greater than 100%, which means no overlap of the two vertebral bodies.

A. Clinical presentation.

Low back pain develops in late childhood and early adolescence and is generally mild. Pain is aggravated with activities requiring lumbar hypertension, such as gymnastics, football (linemen), and ballet. The pain is midline or slightly lateral and may be referred to the buttocks or thighs. Radicular pain is unusual except in grade III slips or greater.

B. Physical examination.

Patients may have a stiff-legged gait due to tight hamstrings. Excessive lumbar lordosis is often present and there may be tenderness of the lumbar paraspinous muscles. Forward flexion does not aggravate the pain, whereas back hyperextension does.

Single-leg hyperextension test. The patient stands, grasps one knee, and hyperextends the low back. Back pain on the weight-bearing side suggests an ipsilateral pars interarticularis defect.

C. Radiographs.

Posteroanterior, lateral, and right and left obliques of the lumbosacral spine are usually sufficient to make the diagnosis, with the most common site of involvement between the fifth lumbar and first sacral segment. The pars interarticularis is best visualized on the oblique views, which show a lucent or sclerotic line known as the “collar of the Scottie dog.” The lateral view demonstrates the amount of slippage in spondylolisthesis. If radiographs are normal and suspicion remains, a bone scan or single photon emission computed tomography (SPECT) scan is indicated. SPECT is the most sensitive test and should be done if the plain bone scan is normal. Magnetic resonance imaging (MRI) inadequately visualizes the pars in up to one third of cases and should not be relied on to rule out the diagnosis.

D. Treatment

1. **Spondylolysis.** Any activity that causes pain should be restricted and the patient started on an antilordosis program of rehabilitation (abdominal and back strengthening, hamstring and hip flexor stretching). If pain persists in spite of conservative treatment, the patient should be placed in an antilordosis brace, such as a Boston overlap brace with 0 degree lordosis. The brace is worn during waking hours or up to 23 hours per day. For the first 2–3 weeks the patient performs only hamstring stretches. After 2–3 weeks or when pain subsides, lumbosacral stretches and abdominal strengthening out of the brace is added. Sporting activity while the brace is worn can be resumed when asymptomatic. Bracing can be weaned after 4 months if the individual is pain free with full sporting activity in the brace. The brace is tapered off by decreasing wear by 1 hour per day each week. Total bracing time is generally 6–9 months. Patients should be followed radiographically every 4–6 months for possible progression to spondylolisthesis. Patients with persistent pain should be referred.

2. **Spondylolisthesis.** Patients with slippage greater than 30% can be treated initially similarly to spondylolysis. Patients with slippage greater than 30% or with pain resistant to conservative treatment should be managed by an orthopedic surgeon.

III. Juvenile kyphosis (Scheuermann's disease)

Scheuermann's disease is an idiopathic condition resulting in anterior wedging of the thoracic vertebrae and a kyphotic deformity greater than 45 degrees. It occurs in approximately 4%–8% of the population, is equally common in male and female adolescents, and affected individuals are likely genetically predisposed.

A. Diagnosis.

Patients generally present at the onset of puberty (12–13 years) with a concern of a progressive “round back” deformity occasionally associated with pain. Pain is generally mild and activity related, but is not activity limiting or associated with easy back fatigability. The round-back deformity is accentuated by forward bending but does not fully correct with extension. Thoracic Scheuermann's (type I) has an apex at T7 to T9 and thoracolumbar Scheuermann's (type II) has an apex at T11 to T12 and is more commonly associated with pain. Approximately one third of patients have associated scoliosis. Excess lumbar lordosis is common and predisposes to spondylolysis at L5 to S1. Severe kyphosis may be associated with cord compression, extradural cysts, thoracic disk herniation, or restrictive lung disease, but these manifestations are rare.

B. Radiographs.

Complete evaluation requires full-length standing AP and lateral spine films. The lateral view shows irregularity of the involved vertebral end plates and anterior wedging of three or more contiguous vertebrae by 5 degrees or more. Kyphosis between T4 and T12 measured by the angle of Cobb is greater than 45 degrees. Only one or two vertebral bodies may be involved with thoracolumbar disease. The radiographs should also assess for associated scoliosis, lumbar hyperlordosis, and spondylolisthesis. Lateral hyperextension views are helpful in determining the flexibility of the deformity.

C. Treatment

1. **General.** Treatment is based on the severity of deformity, presence of pain, and the patient's age. Curves of 45–60 degrees with no evidence of progression are treated with observation, an exercise program to correct lumbar lordosis (abdominal strengthening, increasing hip flexor and hamstring flexibility), and thoracic spine hyperextension exercises. Recheck every 3–4 months.
2. **Bracing** is indicated with significantly painful curves greater than 50 degrees, progressive deformity, or curves that are cosmetically unacceptable (2). A modified Milwaukee brace is most commonly used in conjunction with exercises, is best if initiated before skeletal maturity, and generally requires 12–18 months of treatment. Consider referral to an orthopedist.
3. **Surgery** is indicated with severe deformities (generally >75 degrees) or persistent back pain unresponsive to conservative treatment.

IV. Flatfoot (pes planus)

Flatfoot is broadly categorized as either physiologic flexible flatfoot or pathologic flatfoot. Pathologic flatfoot in infants can be secondary to the common but benign calcaneovalgus foot or a more ominous congenital vertical talus. Older children may have a tarsal coalition, hypermobile flatfoot with tight heel cords, or neurogenic flatfoot.

A. Flexible flatfoot

1. **Etiology.** The normal arch is not present at birth and slowly develops around 5 years of age. Excessive laxity of the joint capsule and plantar ligaments allows the developing arch to flatten out while bearing weight. In young children, a fat pad may further obscure the arch.

2. **Clinical presentation.** Children are generally brought to the family practitioner by the parents with a concern about potential problems related to the flatfoot. There is no complaint of pain by the child.
3. **Physical examination.** The child's foot flattens with weight bearing but develops an arch while the child stands on tiptoe or actively dorsiflexes the great toe. Observed from behind, the calcaneus is in valgus position while the child is standing and inverts when the child stands on tiptoe. The child's ability to stand on the heels indicates adequate heel cord flexibility. The child should be able to stand both on the inner and outer borders of the feet indicating good muscular control and adequate subtalar motion.
4. **Radiographs.** Radiographs are not needed unless other pathology is suspected.
5. **Treatment.** Reassure parents that no treatment is necessary because there is gradual improvement with growth, generally by age 5 years. Arch supports do not make a difference in radiographic or clinical outcome. The occasional child who develops symptoms associated with the flatfoot should be given medial longitudinal arch supports or a medial heel wedge, or both.

B. Pathologic flatfoot.

Pathologic flatfoot is characterized by limited ankle motion and, frequently, foot or ankle pain. Ankle motion may be limited in dorsiflexion by a tight heel cord and in inversion and eversion by subtalar pathology.

1. Hypermobile flatfoot with tight heel cord
   a. **Etiology.** A tight heel cord combined with a flexible flatfoot forces the calcaneus into a valgus position during ambulation. This compensatory hindfoot valgus allows for more ankle dorsiflexion. The resultant abnormal foot biomechanics lead to pain.
   b. **Clinical presentation.** Patients complain of foot or ankle pain.
   c. **Diagnosis.** The patient has a flattened arch and calcaneal valgus when standing. Observation from the side shows early heel lift-off during the gait and an arch that develops as the toes dorsiflex. Subtalar motion (calcaneal inversion and eversion) is normal but ankle dorsiflexion is limited to neutral or less.
   d. **Treatment.** Patients with mild symptoms can be initially treated with aggressive heel cord stretching and a medial longitudinal arch support with a medial heel wedge. Those with more severe symptoms can be treated with a short leg walking cast, with the ankle neutral for 4 weeks followed by heel cord stretching. Surgery for heel cord lengthening and correction of heel valgus may be necessary if conservative treatment fails.

C. Congenital vertical talus.

Vertical talus is a congenital deformity whereby the head of the talus projects into the plantar aspect of the foot, producing a convexity on the sole.

a. **Clinical presentation.** The deformity is present at birth and, it is hoped, will be identified early on by the physician or parent. The infant has a rigid calcaneovalgus flatfoot and the arch has a convex or “rocker bottom” appearance.
b. **Diagnosis.** Lateral foot radiographs reveal the vertical position of the talus and a talonavicular dislocation.
c. **Treatment.** Surgical repositioning of the talus (approximately 6 months of age).

D. Tarsal coalition

a. **Etiology.** Tarsal coalition refers to failure of separation of one or more of the tarsal bones during development. This results in limited subtalar motion with pain secondary to an abnormal transfer of forces in the foot. Calcaneonavicular coalitions become clinically apparent between ages 9 and 13, and talonavicular coalitions between age 12 and 16. Coalitions are present in 1% of the population and approximately 50%–60% are bilateral.

b. **Clinical presentation.** Patients complain of vague midfoot, hindfoot, or ankle pain, worse with activity. There may be a history of frequent ankle sprains due to the limited subtalar motion.

c. **Diagnosis.** The foot is flat with weight bearing, and the calcaneus is in a valgus position. The calcaneus fails to invert when the patient stands on tiptoe and an arch does not necessarily form. There is little to no motion in the subtalar joint with passive calcaneal inversion and eversion, and pain is deep in the dorsolateral foot region. The peroneal tendon is occasionally tender and the muscle in spasm (peroneal spastic flatfoot).

d. **Radiographs.** Plain radiographs are often normal as many coalitions are cartilaginous or fibrous. A 45-degree oblique foot radiograph may show a calcaneonavicular bony bridge or an abnormal articulation. Talocalcaneal coalitions are best evaluated with an axial or Harris view to make visible the middle facet of the subtalar joint. Fine-cut (5 mm) computed tomography (CT) scanning is generally necessary to evaluate the subtalar joint fully and is the imaging study of choice.

e. **Treatment.** Painful conditions should be initially treated with a short leg walking cast and nonsteroidal anti-inflammatory drugs for 4 weeks. If pain resolves, the patient can be given foot orthoses to support the medial foot and heel. Failure to respond to casting and/or a recurrence of symptoms is an indication for surgery. **Many calcaneonavicular fusions fail conservative treatment, and early referral should be considered.**

V. Bowlegs (genu varus).

Varus angulation of the knee can be normal, secondary to metabolic disease, severe physiologic bowing, or osteochondrosis deformans tibiae (Blount's disease).

A. Normal development.

Children are born with genu varum, become maximally bowlegged by 6 months, and begin to straighten by 18–24 months. Genu valgum or “knock-knee” develops during the second to third year and peaks by the fourth year. Development then progresses back to the normal adult alignment of slight valgus by age 7–8 years (3). **Bowlegs should be fully evaluated if they have not corrected by age 2.**

B. Metabolic etiology.

Parents should be questioned regarding diet, and the child's growth curve should be reviewed. Rickets, abnormal calcium or phosphorus metabolism, and renal disease should be considered. If a generalized disorder is suspected, screening laboratory tests should be ordered, including serum calcium, phosphorus, alkaline phosphatase, creatinine, and hematocrit.

C. Severe physiologic bowing and Blount's disease

1. **Clinical presentation.** The child has a painless bilateral genu varus that is of concern to the parents. Growth and development is otherwise normal.
2. **Diagnosis.** Standing posteroanterior radiographs must be obtained while the child's feet are together or shoulder width apart and patellae directly forward. A tibiofemoral angle of more than 20 degrees is abnormal.
   a. **Severe physiologic bowing.** This is characterized by medial metaphyseal beaking of the distal femur and proximal tibia, medial cortical thickening, and no pathologic changes of the proximal medial tibial epiphysis.
   b. **Blount's disease.** This disorder is characterized by angulation under the posteromedial proximal tibial epiphysis, tibial metaphyseal irregularity, beaking of the proximal tibia, and wedging of the proximal epiphysis.
3. Treatment
   a. **Severe physiologic bowing.** Spontaneous correction generally occurs by age 7–8 years. Surgery may be indicated if the deformity persists past age 8.

b. **Blount's disease.** Patients should be referred for consideration of surgery once the diagnosis is made or suspected.

VI. Intoeing

A. General.

Intoeing affects a large number of infants and children and is a major source of concern for parents, leading to consultation and questions. Understanding the primary cause of concern is helpful in counseling the parents of the child with intoeing. Knowledge of what is normal and what will self-correct with normal growth and development will prevent unnecessary treatment, identify the rare causes that need intervention, and reassure most parents that the condition will resolve over time with normal growth.

B. Rotational profile.

The parents' attention focuses on the child's feet, but the source of intoeing can be anywhere in the lower extremities. Certain definitions are needed to facilitate evaluation of the gait and the lower extremities (Fig. 4.6-1).

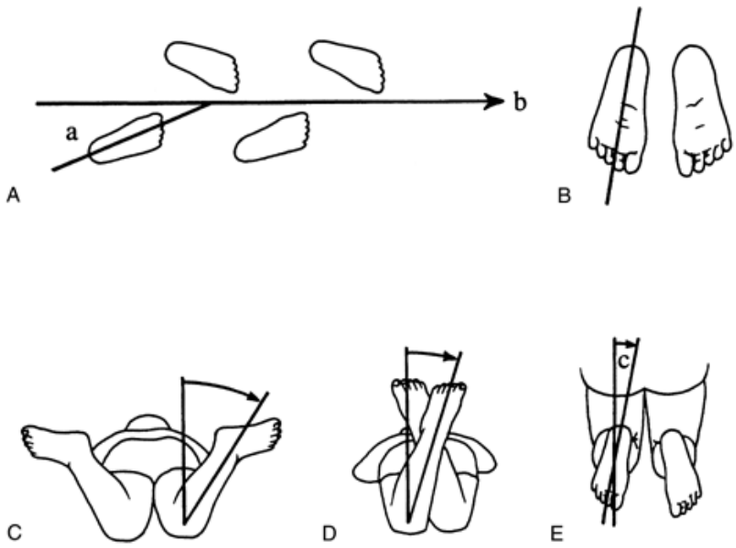

FIG. 4.6-1. Rotational profile. **A:** The angle between the line of progression (b) and the foot axis is the foot progression angle (a). **B:** Foot axis. **C:** Internal (medial) femoral rotation. **D:** External (lateral) femoral rotation. **E:** Thigh-foot angle (c) is formed by the foot axis and the longitudinal axis of the femur.

1. **Line of progression** is an imaginary line indicating the path of movement of the body while walking.
2. **Foot axis** relates to metatarsus adductus. An imaginary line bisects the long axis of the foot from the mid-heel through the middle of the metatarsal heads.
3. **Foot progression angle** is the angle of the intersection between the foot axis and the line of progression.
4. **Internal and external femoral rotation** are indices of femoral version. The child lies prone with the knees flexed at 90 degrees. The pelvis is stabilized and the angle of gravity-assisted internal and external rotation of each leg is measured.
5. **Thigh-foot angle** indicates tibial torsion. An imaginary line through the long axis of the foot is measured against the long axis of the femur, measured with the child in the prone position and the knees flexed at 90 degrees.

C. Metatarsus adductus

1. **Clinical presentation.** This is the most common cause of intoeing seen in the first year of life, either alone or combined with tibial torsion. Presentation may be unilateral or bilateral.
2. **Physical examination.** The foot is convex laterally and concave medially, with possibly a prominence at the base of the fifth metatarsal. With the heel held in neutral position and pressure directed laterally at the first metatarsal head, a flexible deformity corrects to neutral but does not overcorrect (as do normal feet). Flexible deformities may self-correct if the lateral border of the foot is stroked. Rigid metatarsus adductus does not allow either active or passive correction of the deformity.
3. **Treatment.** This condition resolves spontaneously by age 1 year in more than 90% of cases. Treatment of flexible metatarsus adductus involves having the parents passively correct the deformity with each diaper change. Referral for sequential casting is necessary for rigid metatarsus and is most effective if started early, preferably in the first month of life.

D. Medial tibial torsion

1. **Clinical presentation.** Parents are concerned about the appearance of asymptomatic unilateral or bilateral intoeing, generally in their 1- to 2-year-old.
2. **Physical examination.** Determine the thigh-foot angle by gazing along the axis of the lower leg with the child prone and the knee flexed (Fig. 4.6-1). Be sure there is no evidence of metatarsus adductus. Normal values of the thigh-foot angle are as follows:
   - Birth: 5 degrees medial to 5 degrees lateral version
   - 12 months: up to 10 degrees lateral version
   - Adults: 10–20 degrees lateral version
3. **Treatment.** Correction is almost always spontaneous, and braces, splints, cables, and special shoes have not been shown to be effective. The condition usually corrects by age 3–4. The child may habitually sit with the feet turned in toward the buttocks. Although not harmful, this may slow natural correction. Getting the child his or her own chair or encouraging sitting with the legs crossed “Indian style” in front may help while the child grows.

E. Femoral anteversion (medial femoral torsion)

1. **Clinical presentation.** A congenital inward twist of the femur causes turning in of the knee, leg, and foot and commonly presents between 3 and 7 years of age.
2. **Physical examination.** With the child prone and the knees bent at a right angle, the degree of internal rotation of the thighs is greater than that of external rotation. Medial rotation is normally less than 70 degrees for girls and 60 degrees for boys. Mild anteversion is 70–80 degrees, moderate is 80–90 degrees, and severe is greater than 90 degrees.
3. **Treatment.** Medial femoral torsion tends to correct spontaneously with growth. Special braces are not necessary because it is impossible to “brace” the femur into external rotation. Rarely, patients may need surgical derotation in their teen years if there is a severe torsion resulting in significant cosmetic or functional problems. Discouragement of children from sitting in the “W” position (with their lower legs outside of their thighs) may help natural correction.

VII. Common hip problems

A. Congenital hip dysplasia.

Developmental dysplasia of the hip in the infant represents a spectrum from subtle hip laxity to frank dislocation. It is 4 times more common in females and 3 times more common in the left hip than in the right. Newborn screening for this condition has greatly diminished the negative outcomes and is essential for early diagnosis and treatment.

1. **Physical examination.** Under optimal circumstances the infant will be relaxed during the examination and only one hip examined at a time.

a. **Barlow's test.** One hand stabilizes the pelvis with the infant supine and the other hand holds the hip to be examined with the thumb in the groin and the forefinger over the greater trochanter. The hip is flexed to 90 degrees and gentle pressure is exerted posteriorly with the web space of the examiner's hand while lateral pressure is exerted with the thumb. With this maneuver the unstable hip can be felt to dislocate from the acetabulum.
b. **Ortolani's test.** After Barlow's maneuver, the hip is abducted and gently lifted. Relocation of the dislocated femoral head is felt in a positive Ortolani's reduction test. It is important to note that “clicks” or “pops” are not diagnostic of this condition but rather indicate a palpable femoral head leaving the acetabulum.
c. Older children (>3 months) may be more difficult to examine, but signs to consider include tight or limited hip abduction; shortening of the leg; uneven gluteal, groin, or thigh folds; uneven knees when the child is supine with the hips flexed; or a limp or waddled gait.

2. **Imaging tests.** Plain radiographs are unreliable before 6 weeks of age. Radiographs may show proximal and lateral migration of the femoral head or poor acetabular development. Because of the dependence on positioning of the hips during examinations, there are many false-positive and negative results. Dynamic ultrasonography is the procedure of choice in the infant (4).
3. **Treatment.** In the 0- to 6-month age group, treatment is generally by Pavlik harness for the reducible hip and traction, closed reduction or spica cast for the unreducible hip or older child. Avascular necrosis develops in 2.5 of 1,000 infants referred for treatment prior to 6 months and 109 of 1,000 of those referred later. Orthopedic consultation is advised prior to any treatment.

B. Legg-Calvé-Perthes disease.

Also known as avascular necrosis of the femoral head, this is a mysterious disease with an unclear etiology. It occurs with a peak incidence at 4–8 years of age, a male-to-female ratio of 5:1, and is bilateral in 10%.

1. **Clinical presentation.** The patient usually presents with a limp, which is painless at first and then becomes painful only after activity. Pain becomes more constant and is frequently referred to the thigh or knee. Symptoms can be variable, and this entity must be considered in any child with a limp and/or groin, thigh, or knee pain.
2. **Physical examination.** The child may favor the hip and be unwilling to bear weight on it for any length of time. There may be slight limb shortening, and there is generally a decreased range of motion of the hip joint, especially in internal rotation and abduction.
3. **Radiographs.** Films are usually normal for the first 3–6 weeks of the disease but may later show flattening or irregularity of the femoral head. Technetium bone scanning or MRI is useful to confirm early disease.
4. **Treatment.** In younger children with early disease, treatment mainly consists of activity limitation and therapy to regain motion of the hip. The painful hip may require traction, crutches, Petrie cast, or abduction brace. Children identified after 8–9 years of age have a poorer prognosis. Recovery is more likely with disease diagnosed before age 5–6 (5). Orthopedic referral is recommended in all cases.

C. Slipped capital femoral epiphysis

1. **Clinical presentation.** This is the major hip disorder of older children, usually presenting in 11- to 14-year-old subjects and twice as often in boys as in girls. It occurs more commonly in obese children and in blacks, and is bilateral in 20% of cases. The most common presentation is a chronic limp, although patients can present with vague activity-related pain in the thigh, hip, or knee. These symptoms warrant high suspicion and an immediate evaluation.

2. **Physical examination.** The child is generally overweight (80th–100th percentile). Range of motion is limited in hip flexion, abduction, and internal rotation, and forced internal rotation causes groin or knee pain. Obligatory external rotation of the femur with passive hip flexion is a pathognomonic sign.
3. **Radiographs.** Widening of the growth plate is an early visible sign on the supine AP view, but it may be more obvious on the frog-leg lateral view as the hip slips further posteriorly than medially. Technetium bone scanning or MRI is useful in diagnosing preslips and questionable cases.
4. **Treatment.** Once identified, this merits prompt orthopedic referral. Treatment consists of avoiding any weight bearing and obtaining immediate orthopedic evaluation. Surgical pinning is the usual treatment, and it is essential to recognize this condition early to avoid the complications of hip osteonecrosis and cartilage erosion.

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4.7
ENURESIS

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Enuresis, or involuntary urination, is a common problem among children and can be divided into two main groups. First, enuresis can be either primary or secondary. Primary describes a pattern of never having achieved control; secondary enuresis occurs in an individual who had achieved control for at least 3 months but subsequently lost control. Each group can be subdivided into nocturnal (nighttime) or diurnal (daytime) enuresis.

Primary nocturnal enuresis (PNE), sometimes simply referred to as enuresis, is the most common group (80%). PNE is more prevalent in boys, although the age at which children obtain control at night varies widely. A few may be dry both day and night at age 2 years, but 20% of 5-year-olds still wet at night (1). Primary diurnal enuresis in older children and secondary enuresis are much less common and may represent a more serious underlying cause.

Enuresis can be disruptive to normal family life and can generate stress between parents and child. There may be anxiety about such events as sleepovers and campouts, and there are significant costs in lost time, laundry, and bedding, as well as the potential for guilt and loss of self-esteem (2). These concerns may offset the inherent costs of treatment. The decision to intervene is contingent on weighing such factors and on consideration of the degree of frustration in either the child or parents.

I. Diagnosis

The presentation varies by group.

A. Clinical presentation.

Whereas primary enuresis may or may not be perceived as a problem by parent or child (or physician), secondary enuresis is often problematic regardless of age. Infectious causes can be accompanied by dysuria, frequency, or urgency.

B. Urinalysis

is a helpful screen for infection and is a red-flag item in cases with urinary symptoms, but the urine is usually normal in most other instances. Other laboratory studies (below) should not be done routinely.

II. Assessment

A. History.

Key questions should include periods of dryness, stress in the family, family history of enuresis [80% have a relative with enuresis (3), bowel control (encopresis may signal stress or neurologic defect), peer interactions, and emotional changes. Do not forget to ask about urinary infectious symptoms (frequency, volume, stream, retention, urgency, dysuria). Also inquire about age and results of previous efforts at bowel and bladder training, previous therapy (if any), and other health problems and medications, particularly any psychotropic or other drugs with sedative or autonomic effects. Voiding history questionnaires are useful and may be obtained from the National Kidney Foundation on the internet (4).

B. Physical examination.

The physical examination is often unrevealing but helps to exclude less common anatomical or neurologic defects. Genitalia should be examined for hypospadias, fistula, or other congenital anomalies. Gait, rectal tone, perianal sensation, and anal reflex are rarely abnormal but can be screened to avoid overlooking the possibility of neurologic etiologies.

C. Laboratory studies

should be done selectively, depending on the history.

1. **Urine dipstick and microscopic analysis** are done to screen for infection, diabetes, and urinary tract abnormality.
2. **Urine cultures** may be obtained when indicated by urine microscopy.
3. **Ultrasonography of the kidneys, ureters, and bladder** (prevoid and postvoid) may yield clues to anatomical or functional abnormalities.
4. **Intravenous pyelography** may be necessary when greater anatomical detail is desired or if ultrasonography fails to yield an adequate image.
5. **Voiding cystourethrography** can be considered when an anatomical defect or physiologic dysfunction is suspected, such as when there is a history of daytime frequency, small stream caliber, or recurrent infection.

III. Treatment

A. Education.

Patient and parent education are paramount when choosing a treatment plan. Helpful information may be obtained from the National Kidney Foundation (4).

B. Expectant management.

Enuresis resolves spontaneously in 15% of children with enuresis each year (5). In some cases the best treatment may be to monitor the child's progress. Either a parent or the child can record in a log the number of wet or dry nights per week. A review of the log at 6 months may indicate progress toward resolution.

C. Behavioral therapy.

Behavioral techniques include arousal training, dry bed training, hypnotherapy, and the use of alarm systems (6). Enuresis alarms give excellent results provided that the parents and child are motivated. One parent often needs to wake the child and ensure that he or she rises to void. Success has been estimated at as high as 80% and relapse as low as 5% (7). The importance of parent compliance cannot be overemphasized.

Advantages of the alarm system include its relatively low cost and high success rate. Disadvantages include the need for active parental participation to help wake the child (a major factor in failure), the potential inability of the alarm to awaken the child or parents, and the presence of external hardware (8).

D. Desmopressin.

One to two sprays of desmopressin in each nostril at bedtime has a peak effect in 2–3 hours and may be effective the first night. The maximum dose is 40 µg (four sprays total). In tablet form, the initial dose is 0.2 mg orally 30–60 minutes prior to bedtime; 0.4 mg may be more effective and the dose may be titrated to a maximum of 0.6 mg as indicated (9). Success occurs in approximately 50% of patients, but relapse rates can be as high as 50%. No long-term studies have been done to assess treatment longer than 12 months (10). Advantages include the potential for immediate results, ease of administration, and some possible long-term improvement in decreased wetting frequency even if relapse occurs. Disadvantages are desmopressin's relatively high cost and high relapse rate. Side effects, such as hyponatremia and water intoxication, are rare when the drug is used in the recommended dosages and patients are advised to avoid excess water ingestion (11).

E. Imipramine

is usually given in lower doses than those used in childhood depression, and its onset of action is rapid where its antidepressant effect is delayed. The initial dose is 10–25 mg at bedtime. Doses can be increased by 10–25 mg every 1–2 weeks, up to a maximum dosage of approximately 1–2 mg/kg per day. Its success rate is as high as 50% but its relapse rates reaches 60% (12). Advantages include low cost, ease of administration, and, as with desmopressin, possible long-term improvement in reduction in wetting frequency after relapse. The main disadvantages are the high relapse rate and the risk of overdose. An important issue is informing parents about imipramine's potential toxicity and ensuring that they have a good understanding of the importance and techniques of proper dosing.

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4.8
COMMON POISONING IN CHILDREN

Jason Chao

Poisoning is a common medical emergency in children. Although 85% of pediatric poisonings can be managed at home, every year thousands of children suffer moderate or severe complications from poisoning.

I. Presentation

A.

Acute poisoning is usually brought to medical attention shortly after the event.

B.

Delayed effects of some poisons may not occur for hours to days. Remember to consider poisoning in the differential diagnosis of a child with serious unexplained symptoms or altered level of consciousness. Chronic poisoning may occur with few overt symptoms, especially with environmental toxins.

C.

More than 40% of ingestions involve cosmetics and personal care products, cleaning substances, or plants and are generally low-risk poisonings.

D.

Half of all poisoning deaths are due to medications, both prescription and over-the-counter. For ingestion of a substance of unknown toxicity, contact the local Poison Control Center.

E. Common toxic syndromes

1. **Anticholinergic syndrome** (atropine, antihistamines, tricyclic antidepressants, etc.) symptoms include mydriasis, dry skin, dry mouth, flushing, fever, urinary retention, ileus, tachycardia, hypertension, agitation, confusion, hallucinations, and seizures.
2. **Cholinergic syndrome** (organophosphate and carbamate pesticides, certain mushrooms, etc.) symptoms include salivation, lacrimation, bowel and bladder incontinence, miosis, bronchospasm, and bradycardia (see also Chapter 21.2).
3. **Sympathomimetic syndrome** (amphetamines, cocaine, theophylline, etc.) symptoms include mydriasis, sweating, fever, tachycardia, hypertension, agitation, confusion, hallucinations, seizures, nausea, vomiting and diarrhea.
4. **Sedative syndrome** (opiates, barbiturates, clonidine, ethanol, benzodiazepines, etc.) symptoms include lethargy, hypotension, bradycardia, respiratory depression, miosis, hypothermia, and hyporeflexia.

II. General management

A. Stabilization

1. **Establish the ABCs: airway, breathing, and circulation.** Perform a brief screening examination, including vital signs, mental status, and pupils, to identify the measures necessary in the first several minutes to prevent further deterioration of the patient.
2. Lethargic patients should receive glucose if immediate blood glucose testing is not available. Naloxone (Narcan) should be added for young children who may have ingested a narcotic. Use 0.1 mg/kg up to 2 mg IV. The dose may be repeated every 2 minutes if there is no response, to a total dose of 10–20 mg (1).

B. Decontaminate skin and eyes with copious rinsing.

Eyes should be irrigated with lids open using normal saline. Avoid contamination of health care workers.

C. Complete patient evaluation

is directed to identifying the type and amount of the toxic substance as well as the timing of the exposure, evaluating the severity of its clinical effects, and searching for associated complications and trauma.

D. Syrup of ipecac

may have a role in home management of poisoning to provide early gastric evacuation, if rapid transport to the emergency department is not available. However, the efficacy of syrup of ipecac is unproved.

1. It is indicated in the emergency room for agents too large to pass through a lavage tube, if ingestion is significant and has occurred within 30–60 minutes. However, it is rare to require ipecac in the emergency department.
2. Avoid ipecac in patients with caustic ingestion, age younger than 6 months, expected to deteriorate rapidly, with a depressed mental status, with a need for rapid gastrointestinal (GI) evacuation, or who have ingested a substance with substantial morbidity if aspirated (hydrocarbons).
3. Dosage. Give 15 mL for children 1–12 years old, 30 mL for older children and adults. If vomiting is not produced in 20 minutes, dosing may be repeated once. Infants of age 6–12 months may be given 5–10 mL in a single dose.
4. Persistent vomiting for more than 2 hours suggests toxicity from the substance ingested.

E. Gastric lavage has not been shown to improve clinical outcome

1. Gastric lavage may be considered if (a) the quantity of substance ingested is potentially life threatening and likely to pass through the lavage tube, and (b) a gag reflex is present. Lavage should be initiated within 60 minutes of ingestion.

2. Restrain the patient in a left lateral decubitus Trendelenburg's position. Use a large-bore (2–32 French) single-lumen tube via the orogastric route. Instill aliquots of 10–15 mL per kilogram of saline and aspirate back until aspirated contents are clear. Large volumes may be required. Protect the airway to prevent aspiration.

F. Activated charcoal

1. Oral activated charcoal decreases systemic absorption of many drugs, including aspirin, acetaminophen, barbiturates, phenytoin, theophylline, and tricyclic antidepressants. Substances not well absorbed include alcohols, caustics, lithium, cyanide, potassium, hydrocarbons, minerals, and metals (including iron).
2. Give charcoal after vomiting induced by ipecac, following gastric lavage, or alone. A newer method for severe ingestions involves charcoal, lavage, more charcoal. Protect the airway to prevent aspiration.
3. Dosage. Base dose on how much toxin must be adsorbed in a 10:1 activated charcoal/drug ratio, or give 1 g/kg to a maximum of 50 g. Can be mixed with chocolate or fruit syrup to increase palatability, or administered via gastric tube if not swallowed quickly.
4. Multiple-dose activated charcoal, given every 2–4 hours, may be used when large amounts or delayed-release drugs are ingested (2). Avoid dehydration if the activated charcoal is mixed with sorbitol.

G. Improve elimination of the toxin

1. Extracorporeal hemodialysis or hemoperfusion may be used in cases involving significant methanol, ethylene glycol, lithium, salicylate, or theophylline ingestion.
2. Polyethylene glycol-electrolyte lavage solution (whole-bowel irrigation) may be considered for substances not absorbed by activated charcoal. Dose: age 9 months–5 years, 500 mL/h; age 6–12 years, 1 L/h [3].
3. Cathartics, such as sorbitol or magnesium citrate, are generally used only in conjunction with activated charcoal. Sorbitol is available premixed with activated charcoal. Stool output should be closely monitored if given.

III. Individual poisons have a specific effective antidote in less than 5% of poisonings(3).

A. Acetaminophen

1. Emesis within 90 minutes of ingestion can decrease absorption by 50%.
2. Draw serum levels starting 4 hours after ingestion.
3. Acetylcysteine (Mucomyst) is indicated if the history suggests ingestion of more than 140 mg/kg or if plasma acetaminophen level falls on or above the line on a Rumack-Matthew nomogram (http://www.vh.org/Providers/ClinRef/FPHandbook/Chapter01/figures01/fig1-9.html; www.ashp.org/public/pubs/ajhp/vol56/num11/6a-tu.pdf). It is most effective if given within 8 hours of ingestion. The loading dose is 140 mg/kg either orally or by lavage tube after gastric lavage. Starting 4 hours after the loading dose, give 70 mg/kg every 4 hours for 17 doses. It may be diluted with a soft drink to a 5% solution.

B. Tricyclic antidepressants

1. Signs such as cardiac arrhythmia (QRS > 100 milliseconds), hypotension, or seizures may occur soon after poisoning.
2. Gastric emptying and activated charcoal decrease absorption. Avoid syrup of ipecac.
3. Avoid quinidine-like drugs and dopamine, which may exacerbate dysrhythmias.

C. Antihistamines

1. Cardiac monitoring, intravenous access, and lavage followed by activated charcoal are indicated for potentially significant ingestion.
2. Acetaminophen and aspirin are frequently combined with antihistamine preparations, and levels for these drugs should be obtained.
3. Physostigmine (Antilirium) is a specific antidote for significant anticholinergic toxicity and is given under close cardiac rhythm monitoring.

D. Insulin or oral hypoglycemic overdose

(see also Chapter 17.2)

1. Hypoglycemia is the effect of overdose with these substances. Ethanol, aspirin, and ß-blockers may also produce hypoglycemia.
2. Glucose as 25% glucose in water is given intravenously. Push 1 g/kg slowly.

E. Hydrocarbons

1. Provide supportive therapy for hypoxia and respiratory failure. Coughing, gasping, or choking that persists is indicative of aspiration.
2. Decontaminate skin with water, followed by soap or shampoo.
3. Gastric emptying and/or charcoal is not indicated unless the hydrocarbon product is a substance known for its systemic toxicity, including camphor, halogenated hydrocarbon, aromatic hydrocarbon, metal, or pesticide.

F. Iron

1. Induce emesis early with syrup of ipecac, or use whole-bowel irrigation because adult pills are too large for most lavage tubes, and activated charcoal is not effective.
2. Deferoxamine (Desferal) is reserved for significant ingestions (4). Give intravenously at no more than 15 mg/kg per hour until the child is no longer ill or the urine is no longer colored. If given intramuscularly, the dose is 90 mg/kg to a maximum of 1 g.

G. Lead

1. Succimer (DMSA) is given orally, 10 mg/kg every 8 hours for 5 days, followed by 10 mg/kg every 12 hours for an additional 2 weeks for moderately severe lead intoxication (50–69 µg/dL). The capsules can be mixed with juice, applesauce, or ice cream. Rebound increase in lead level is to be expected, and a repeat course of DMSA may be prescribed. Iron supplementation for iron deficiency anemia may be given concomitantly with DMSA.
2. Symptomatic patients or severe lead poisoning should be admitted and treated with parenteral dimercaprol (British antilewisite, or BAL) and edetate calcium disodium (EDTA).

H. Salicylates

1. Activated charcoal plus cathartic is effective in reducing absorption.
2. Intravenous sodium bicarbonate 1–2 mEq/kg every 3–4 hours enhances renal elimination.

I. Theophylline

1. Avoid use of syrup of ipecac unless ingestion took place less than 1 hour before arrival because protracted vomiting may occur.
2. Gastric lavage may be attempted, but tablets may be difficult to remove. In significant ingestions, repeated doses of activated charcoal should be administered, along with a cathartic.
3. Transfer to a facility with charcoal hemoperfusion or hemodialysis should be considered early, before the patient becomes too unstable for transfer.

IV. Continuing care and prevention

A.

Consider child neglect or abuse in poisoning under the age of 12 months. After the age of 5 years, unintentional ingestion is unusual, and poisoning is due to stress, suicidal gesture or attempt, or drug-seeking behavior.

B.

An adequate observation period should be established after diagnosis and initial treatment. Poison prevention education or social work assessment can be begun at this time. A referral source should be identified for follow-up treatment.

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4.9

BEHAVIORAL PROBLEMS OF CHILDREN

Elizabeth Steiner

Well-child and problem-focused visits offer opportunities for parents to raise questions about behavior concerns. Family physicians (FPs) should actively elicit such concerns either through directed questioning during the visit or by using standardized behavioral assessment questionnaires, such as the Child Behavior Checklist or the Pediatric Symptom Checklist (1), completed by the parents. FPs should always review questionnaires with the parents during the visit to augment the information provided and to normalize the discussion of behavioral concerns. FPs are well positioned to assess behavioral problems of children and offer advice because they generally care for multiple members and generations within a family. Consequently, they can tailor advice to the specific needs and abilities of the child's family.

I. Prevention of behavioral problems.

FPs have many opportunities to anticipate and intervene in behavioral problems. Prenatal visits, well-child visits for both the child in question and for siblings, and preventive care and problem-focused visits for the parents all offer occasions to discuss problems and offer guidance. Factors that predispose children to behavioral problems include mismatch between parental and child temperaments (e.g., quiet, low-activity child with high-energy parent), parental mental health problems (including post-partum depression), poor parental self-esteem, attachment difficulties between parent and child, inconsistency of parental response to the child, unrealistic parental expectations regarding the child's behavior, and developmental delay, especially speech-language delay, which contributes to frustration for both parent and child. In addition, conflict between the parents, the absence of a parent, and parental abuse of drugs or alcohol are risk factors for behavioral problems. FPs should watch carefully for signs of any of these problems and intervene as appropriate. FPs can both assess for potential problems and teach the parents about normal developmental stages and the behaviors associated with those stages. Anticipatory guidance is a critical component of well-child care—one that has a key role in both reassuring parents about their child's behavior and preventing unnecessary conflict about normal behavior.

II. Stages of behavioral assessment and intervention.

A. Clarify parental concerns.

The BATHE technique (see first edition, Chapter 45) is useful for this (2).

B. Assess parental knowledge

regarding normal developmental stages. Many parental concerns about behavior stem from unrealistic expectations regarding their child's behavior relative to his or her developmental stage.

C. Assess for family stresses

that may affect the child's behavior. Many behavioral problems stem from or are exacerbated by external stressors.

D. Take a full medical and developmental history,

including prenatal course, if the child is not well known to the practice. Prenatal alcohol and drug use, early childhood illnesses, and developmental delay can all lead to behavioral problems.

E. Ask what interventions parents have tried

to change the behavior. This gives important information regarding parenting style and the parents' ability to respond to the individual nature and needs of the child.

F. Counsel parents

about possible interventions for behavioral problems.

III. Principles of behavioral intervention.

A.

Children deserve and respond to respect from caregivers. Behavioral interventions will not be successful if parents treat the child disrespectfully.

B.

Consistency of response is critical. Behavioral change only occurs in the context of consistent and predictable responses.

C.

Positive reinforcement for desired behavior generally works better than negative reinforcement for undesirable behavior. Positive reinforcement includes active education of the child about expected behavior and its beneficial consequences rather than simply stating what the child should not do. When negative reinforcement is necessary, it should be age and behavior appropriate.

D.

Reassure parents that children need and want parents to exert consistent, reasonable controls on their behavior. Children are frightened when boundaries of acceptable behavior are not well defined and will often accelerate the problem behavior in order to elicit a parental control response.

E.

Tailor the plan to the child and the family. “One size fits all” does not apply to behavioral intervention, even in the same family. Plans must be specific—and communicated clearly to the child.

F.

Reassess progress on a regular basis and adjust the plan as needed.

IV. Specific techniques for intervention.

Many parents lack specific knowledge about acceptable, effective interventions to promote behavioral change. Too often, parents resort to punishments far more severe than the behavior warrants. FPs can help break cycles of ineffective discipline by educating parents about effective methods of intervention (3).

A. Time out.

Separate the child from desirable activities for a brief period (1–2 minutes for preschoolers, up to 15 minutes in school-aged children). “Grounding” adolescents for a day or two may help.

B. Extinction.

Ignore the undesirable behavior, especially if it has previously elicited attention.

C. Rewards/positive reinforcement.

Offer small rewards (inexpensive toys, increased time with one or both parents, increased privileges) for positive behavioral change. For example, if the problem behavior relates to bedtime, reward the child for conflict-free completion of the bedtime routine.

D. Discussion of consequences of and alternatives to the behavior.

Respect for children includes teaching them the consequences of and alternatives to unacceptable behaviors. For example, even fairly young children can understand simple explanations of how biting hurts and be encouraged to use words instead of physical aggression. As children get older, reasoning plays an increasing role in behavior modification.

V. Major mental health concerns.

Behavioral problems in children can generally be divided into three categories: (a) problems that are normal for the child's developmental stage and will resolve spontaneously as the child matures; (b) problems that began as a normal developmental phase, but have been exacerbated by external stresses and will require some level of intervention to resolve; and (c) problems that indicate a more serious underlying mental health problem. FPs must be aware of the prevalence of and diagnostic criteria for the common major mental health problems that can present in children.

Depression in children is generally underdiagnosed, in part because physicians fail to screen for it with the same rigor they would apply to adults (see also Chapter 5.2). Criteria for depression in children are virtually identical to those in adults, with minor modifications relevant to usual daily activities. Five or more of the following criteria must be present for at least 2 weeks in order to diagnose depression: depressed mood, anhedonia, sleep disturbance (hypersomnolence or disruption of normal sleep pattern), change in weight or appetite (>5% change in body weight over 1 month and/or failure to make expected weight gains), psychomotor retardation or agitation, low energy, feelings of worthlessness or guilt, decreased concentration and increased indecisiveness, or recurrent thoughts of death or suicide (see also Chapter 5.2). Children with depression may require medication, and this should generally be done in conjunction with a child mental health professional.

A. Anxiety disorder.

Virtually every child experiences some level of anxiety at various stages of life. Up to 50% of children may experience anxiety to the extent of true anxiety disorder that adversely affects their daily lives (3). Anxiety disorders may present as multiple somatic complaints, a marked increase in nervous habits (e.g., nail biting or thumb sucking), or stereotyped behaviors (e.g., head banging or other repetitive behaviors). Often, identifying and correcting external stresses, in combination with teaching the child simple coping skills, will correct the problem. Occasionally, especially when anxiety disorder is comorbid with depression, medication and more intensive psychotherapy may be required (see also Chapter 5.1) (4).

B. Conduct disorder

represents the extreme end of the spectrum of oppositional behavior. It is defined as a persistent pattern of behavior (more than -6 months) that violates the basic rights of others, including acts of aggression against people or animals, property destruction, theft, repetitive lying or other deceptions, and serious violations of rules in multiple environments (e.g., home and school). Attention-deficit/hyperactivity disorder (AD/HD) and learning disorders (see Chapter 4.11) are often comorbid with conduct disorder, and early identification of these problems may help prevent development of some aspects of conduct disorder. Children and adolescents with conduct disorder require prompt identification, aggressive intervention, and substantial support to their families (5).

VI. Common behavioral concerns seen in family practice.

A. Feeding problems

are among the most common concerns. Parents worry about adequate weight gain and spitting up (reflux) in infants, nutrition, food avoidance, and mealtime behaviors in preschoolers, and obesity in school-aged children. Generally, educating the parents about normal behavior at these stages is sufficient to address their concerns. It is important to remind parents that when food becomes a control issue between parent and child, this confrontation can lead to long-term unhealthy eating habits. Parents should offer a diverse range of nutritious foods, supplement with a multivitamin if necessary, demonstrate healthy eating habits, and avoid using food as a reward for other behaviors.

B. Oral habits,

such as nail biting, bruxism, digit sucking, and pacifier use, are common in preschool-aged children. Some authors hypothesize that these and other stereotyped behaviors are actually serving an important function in the child's development by serving as early coping mechanisms or self-calming techniques during stressful times or negative mood states (6). Increases in these behaviors often reflect new external stresses in a child's life. Identifying and addressing stresses, combined with positive reinforcement of behavioral change and work with the child to develop alternate coping skills, is generally the most successful intervention for these behaviors.

C. Sleep disorders

include trained night-waking, bedtime struggles, nightmares and night terrors, and sleepwalking (see also Chapter 5.6). *Trained night-waking* (i.e., the child awakens at a consistent time during the night) and *bedtime struggles* are best addressed by a consistent approach to bedtime that does not involve the parent staying with the child until the child falls asleep, and extinction (i.e., delayed response or no response at all to the child when he or she awakens during the night or protests at bedtime). *Nightmares* occur in virtually all children and are generally indicative of developmental issues and fears. Giving the child reassurance is usually sufficient. *Night terrors* may have their onset in early childhood all the way to early adolescence. Parents note that the child makes loud vocalizations and excessive movements, and appears terrified or panic stricken. The child is usually unresponsive to parental reassurance because he or she is not truly awake during the night terror. Treatment of night terrors is limited, and such episodes usually cease spontaneously by late adolescence. *Sleepwalking* occurs in approximately 15% of children. It too has its onset in early childhood and generally resolves spontaneously in adolescence. Parents should provide a safe environment so that the child does not sustain injury during sleepwalking episodes. Both night terrors and sleepwalking have strong familial histories, with 80%–95% of children with these disorders having a positive family history.

D. Stereotyped behaviors,

such as tics, head banging, body rocking, or other repetitive movements, can be disconcerting to parents. Many toddlers and preschoolers display these behaviors, and stress, negative mood, and fatigue generally exacerbate them. These behaviors usually resolve spontaneously and rarely cause injury to the child. Treatment involves reassurance of the parent, teaching other coping mechanisms to the child, and patience.

E. Masturbation

begins as early as 12 months in many children and is completely normal. Parents should use the behavior as an opportunity to begin discussion with the child about private behaviors and sexuality. In families with strong religious prohibition against masturbation, parents should tell children that “our family/religion does not believe in that behavior” rather than stating that the behavior is bad, which risks the development of unhealthy attitudes about sexuality.

F. Enuresis

is discussed in Chapter 4.8 .

G. Separation anxiety,

including school phobia, occurs in many children at various stages of life. Prevention includes giving the child accurate, age-appropriate information about expected separations and consistency in daily patterns of separation. School phobia often presents as multiple somatic complaints, only present on school days, and affects 5% of school-aged children. Parents should elicit information from children and teachers about learning problems, conflicts with teachers or classmates, boredom, or stresses directly due to separation from parents. Treatment involves diminishing stress and establishing firm guidelines about appropriate reasons for missing school.

H. Disruptive behavior

occurs over a spectrum of behaviors, including various manifestations of limit testing, temper tantrums, oppositional defiant disorder, and conduct disorder. Early identification of and intervention for these problems is critical for prevention of long-term mental health problems (7). *Limit testing* occurs at every stage of childhood and adolescence. Physicians should remind parents of the need to set and maintain firm, age-appropriate boundaries on behavior. *Temper tantrums* are common (75%) in children aged 3–5, and their incidence tails off to 4% in children aged 9–12. Extinction, limit setting, and time out are all effective treatments. Oppositional defiant disorder (ODD) represents a pattern of markedly defiant, negative, and hostile behavior lasting for at least 4 months and occurs in 2%–16% of children. Children with this disorder frequently lose their tempers, argue with adults, defy rules, blame others for problems, and have poor social relationships due to anger, resentment, and spitefulness. Like *conduct disorder* (see above), ODD often occurs in the context of comorbidities such as AD/HD or learning disabilities, which should be assessed and treated aggressively. Treatment of ODD rests in the domain of behavior modification and often requires family and individual psychotherapy to assist with resolution.

I. Alcohol, tobacco, and other drug use

should be screened for routinely during most visits with children over the age of 8 years. Prevention is essential, and involves open discussion with parents and children about risk factors, including genetic predisposition (family history of drug misuse), peer pressure, low self-esteem, and poor resiliency to external change and stress. Prevention also includes educating children in age-appropriate ways about the adverse effect of using tobacco, alcohol, and other drugs. FPs can participate in the very effective Tar Wars program through the American Academy of Family Physicians. Early identification of the problem is critical to effective treatment, which involves close parental supervision, appropriate positive and negative reinforcement, and counseling to address underlying issues.

VII. Working with other health care professionals: when to refer and to whom.

Some children and families will require intervention and treatment beyond the scope of practice of most FPs. Children who require medication for management of depression, tics caused by Tourette's syndrome, or AD/HD should be comanaged with a qualified specialist (e.g., psychiatry or neurology). Parents often will benefit from more extensive information about effective parenting skills. FPs should be aware of parenting resources, such as classes and hotlines within their communities, as well as a range of books on parenting that reflect different acceptable approaches to parenting. In the case of serious mental health disorders, major life stresses within a family, or significant mismatch between parental and child temperament, parents will also benefit from counseling by a child or family mental health professional. FPs should also be aware of useful

internet sites and national support networks available to parents, especially in communities where local mental health resources are limited due to geographic or insurance constraints.

Early recognition of and intervention in behavioral problems can promote a child's self-esteem, which in turn helps prevent later difficulties related to drug use, violence, school difficulties, and early sexual activity. FPs must include behavioral assessment and education during well-child visits.

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4.10
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

James E. Nahlik

Attention-deficit/hyperactivity disorder (AD/HD) is a psychological syndrome characterized by inability to focus attention enough to complete tasks. The diagnostic criteria for AD/HD were published by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (*DSM-IV*) in [1]. The punctuation of AD/HD in the *DSM-IV* is distinct, and the slash signifies the plus-or-minus nature of the hyperactivity component in the patient with deficits in his or her attention span. According to DSM-IV, AD/HD is seen in 3%–5% of school-aged children. It was previously thought to disappear at puberty, but this is not the case. Many adults display the characteristic behaviors and require interventions. Because AD/HD is inherited, the family physician may see the disorder twice at a glance as parent and child sit and fidget side by side in the office.

I. Diagnosis

A. Clinical presentation.

Patients typically display a persistent pattern of inattention or hyperactivity-impulsivity, that is more severe than is typically observed in their peers. The vast majority of AD/HD children come to the physician's attention during their primary grades. The task for the physician is to elicit a history from the patient, parents, and teachers that supports the diagnostic criteria. Then the physician must perform a physical examination and possibly laboratory studies that may demonstrate underlying organic problems. Physical examination of the AD/HD patient is important to rule out other causes of hyperactivity, but *no* specific features are uniformly noted with AD/HD.

1. One goal in the physical examination is to note multiple minor injuries, such as scratches, bruises, and scars, because these patients are “accident-prone.”
2. Occasionally, it may be noted that the tags have been cut from the patient's shirt or underwear. This phenomenon occurs because AD/HD individuals cannot tolerate the extra stimulus of a tag touching their skin.

B. Diagnostic criteria.

Table 4.10-1 summarizes the current diagnostic criteria for AD/HD (2).

1. At least six of the following symptoms of either inattentiveness or hyperactivity–impulsivity must be in evidence for 6 months or longer:
   - Inattention
     - Lack of attention to details or careless mistakes in schoolwork, work, or other activities
     - Difficulty sustaining attention to tasks or play activities
     - Impression of not listening when spoken to directly
     - Failure to follow through on instructions or finish schoolwork or duties
     - Difficulty organizing tasks and activities
     - Avoidance or dislike of tasks that require sustained mental effort, such as schoolwork or homework
     - Tendency to lose things necessary for tasks or activities, such as toys, school assignments, pencils, books, or tools
     - Distractions by extraneous stimuli
     - Forgetfulness in daily activities
   - Hyperactivity/Impulsivity
     - Fidgeting with hands or feet or squirming in seat
     - Not remaining seated when expected
     - Running about or climbing excessively (or subjective feelings of restlessness in older persons)
     - Difficulty engaging in leisure activities quietly
     - Often “on the go” or “driven by a motor”
     - Excessive talking
     - Tendency to blurt out answers before questions have been completed
     - Difficulty awaiting turn
     - Tendency to interrupt or intrude on others (e.g., butting into conversation or games)
2. Some of the above symptoms must be present before age 7
3. There must be significant problems in two or more environments, such as at school and at home
4. The history confirms that the symptoms do not occur exclusively during a different documentable mental disorder, such as schizophrenia, anxiety disorder, or a personality disorder

From Nahlik J. New thoughts on attention-deficit/hyperactivity disorder. *Hosp Pract (Office Edition)* 1995;30:49, with permission.

Table 4.10-1. Common symptoms of attention deficit/hyperactivity disorder

II. Assessment

A.

Office screening test. The test for AD/HD is described in a definitive article (3). The test takes about 5 minutes to complete and can be repeated with follow-up during which response to treatment can be assessed.

B.

Assessment can also be done with progress reports by teachers and parents.

C.

Standardized questionnaires (e.g., IOWA, Conners, and others) are useful.

D.

No laboratory tests are diagnostic, but normal serum thyroid-stimulating hormone levels can rule out hyperthyroidism as a cause.

III. Diagnosis of AD/HD

A.

The diagnosis is secured by fulfillment of the diagnostic criteria (see Table 4.10-1). Physicians should apply the *DSM-IV* criteria in the context of the clinical visit. The consistent use of these criteria will ensure a more accurate diagnosis and avoid over or under diagnosis.

B.

Pitfalls in securing diagnosis:

1. Not enough history is available in many instances.
2. Problem behavior may not always be observable in the office.
3. Laboratory tests and radiographic tests are of little assistance.
   a. Only about 5% of children with AD/HD have abnormal electroencephalograms (EEGs).
   b. Computed tomography (CT) scans are generally normal; magnetic resonance imaging (MRI) scans similarly have no abnormalities.
4. Reliance on parents' and teachers' reports is not always possible.
   a. Some parents have a hidden agenda to have their child diagnosed with AD/HD because additional school resources are then made available.
   b. Conversely, some people wish to avoid the stigma of the “hyperactive” label, and it can be considered a preexisting condition for insurance plans.
5. The syndrome is imprecisely defined in *DSM-IV*. The word *often* is used in each criteria, and its definition varies from physician to physician.
6. Presence of comorbid disorder is a challenge. These patients have more than their share of other problems. Over 30% of patients have another psychological syndrome or a learning disability.

IV. Behavioral therapy for AD/HD

A.

Educate the patient and the family about the disorder.

1. Inform patient and family that the disorder is usually inherited rather than the result of bad parenting.
2. The patient must not expect to outgrow AD/HD in adolescence.
3. Let the patient and family know that effective treatment is available.

B.

Behavior modification is mandatory. The parents or the patient should target one or two behaviors for modification and give rewards to the patient if behavior modification is successful.

1. Completion of school assignments is often a good target for behavior modification.
2. List making is an important behavior to encourage in children and adults.

C.

It is often helpful to recommend special accommodations in school.

1. A federal law, Section 504 of the Rehabilitation Act, requires public schools to permit extra preparation for tests, as well as other aids. An Individual Education Plan (IEP) can be requested.
2. Encourage participation in individual activities, such as martial arts, gymnastics, or scouting.
   a. The child receives immediate recognition of his or her accomplishments.
   b. The child builds self-esteem as he or she progresses.
   c. Team sports are sometimes problematic because the patient's chances for failure depend on the team's abilities and not solely on individual efforts.
   d. Many behavioral methods are described in *Attention Deficit Disorder: Strategies for School-Age Children* by Clare Jones (4).

V. Pharmacologic treatment

usually starts with a stimulant. The postulated ability of the stimulant is to “wake up” the frontal lobes, which in turn regulate activity level. Specifically the stimulants block the reuptake of dopamine and norepinephrine into the presynaptic neuron, and increase the release of these monoamines into the extraneuronal space. The efficacy of stimulant use is usually evident within 1–2 weeks.

A.

Methylphenidate (Ritalin, Methylin, Metadate, Concerta) appears to benefit 70%–80% of AD/HD children.

1. Peak effects on behavior occur in the first 2 hours after ingestion and diminish in 4–6 hours. The stimulants have demonstrated efficacy in a dose-dependent manner on a wide spectrum of abnormal behaviors commonly associated with AD/HD, including impulsive behavior, noisiness, noncompliance, disruptiveness, and improvement in maternal-child interactions (5).
2. Typical dosing starts children with 5–10 mg of methylphenidate in the morning.
   a. If this is only partially successful, the dose is repeated at approximately noon.
   b. In schools, the second dose is problematic, and so the 12-hour-release Concerta can be used.
3. Problems with methylphenidate
   a. It is unavailable in liquid form.
   b. In most states it is a schedule II drug requiring a written prescription each month.

B.

Medications are summarized in Table 4.10-2 .

Medication	Brand name	Initial dose	Maximum dose	Side effects of drug class
Stimulants				
Methylphenidate	(Ritalin) (Methylin) (Metadate)	5 mg bid-tid	60 mg/d	Tachycardia Hypertension Insomnia
Methylphenidate OROS (Oral Osmotic Release)	(Concerta)	18 mg qd	54 mg/d	Anorexia Headache Precipitation of tics
Dextroamphetamine	(Dexedrine) (Adderall)	2.5 mg bid-tid	40 mg/d	Irritability
Pemoline	(Cylert)	18.75 mg qd	75 mg qd	
Tricyclic antidepressants (given at bedtime)				
Imipramine	(Tofranil)	25–50 mg/d	5 mg/kg/d	Sedation Dry mouth
Desipramine	(Norpramin)	25–50 mg/d	5 mg/kg/d	Urinary retention Constipation Blurry vision
Amitriptyline	(Elavil)	25–50 mg/d	5 mg/kg/d	Hypertension Arrhythmias
Central acting antihypertensive				
Clonidine	(Catapres)	0.05 mg/d	0.008 mg/kg	Hypotension Dry mouth Dizziness Constipation Headache Drowsiness

From Searight HR, Nahlik JE, Campbell DC. Attention-deficit/hyperactivity disorder. *J Fam Pract* 1995;40:3, with permission.

Table 4.10-2. Pharmacotherapy for attention deficit/hyperactivity disorder

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V. HUMAN BEHAVIOR AND PROBLEMS OF LIVING

5.1

ANXIETY, PANIC DISORDERS, AND AGORAPHOBIA

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Not only are anxiety disorders important because of the distress they cause; they are also associated with "excessive" suicide-related mortality (1). Although recognition of anxiety disorders by private practitioners results in a shorter duration of illness and a greater frequency of mental health treatment, only 50% of patients with anxiety disorders are diagnosed by their physician (2).

I. Generalized anxiety disorder

A. Clinical presentation.

The hallmark of generalized anxiety disorder (GAD) is excessive worry out of proportion to existing problems. Patients with GAD present with multiple nonspecific complaints, including fatigue and muscular pain (3).

B. Diagnosis of GAD

is based on *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (*DSM-IV*) criteria (4). The patient must experience excessive anxiety and an inability to control his or her sense of worry for at least a 6-month period and have at least three symptoms related to motor tension, autonomic hyperactivity, and vigilance and scanning. GAD can be diagnosed only when the anxiety is unrelated to the focus of other anxiety disorders, such as panic attacks. If the patient has depression, the anxiety must be present when the depression is not (see also Chapter 5.2). Organic factors known to be associated with anxiety must not be responsible for initiating *and* main taining the anxiety. Hence, hyperthyroidism, substance abuse with such drugs as cocaine and amphetamines, and use of general stimulants, such as caffeine and tyramine (e.g., generally found in red wines and cheeses), must be excluded as the underlying cause of the anxiety. GAD differs from adjustment disorder with anxious mood in that in adjustment disorder a psychosocial stressor is present and the duration of disorder is less than 6 months.

C. Therapy

1. **Behavioral therapy.** Progressive relaxation, stress management, and assertiveness training with or without hypnosis are useful (5), as are family and group counseling as well as other forms of supportive psychotherapy. Cognitive behavioral therapy, in which anxious thoughts are identified and then changed, may be superior to other forms of behavioral therapy (6).
2. **Drug therapy**
   a. **Venlafaxine** is indicated for GAD with starting doses of 37.5 mg bid. It may be more effective than buspirone (7).
   b. **Benzodiazepines.** Response to benzodiazepines (Table 5.1-1) is more likely if (i) a precipitating stress exists, (ii) significant depression is lacking, (iii) the patient is aware of the psychological nature of his or her symptoms, (iv) there has been a prior response to benzodiazepines, and (v) the patient expects recovery. Responders notice improvement within the first week of therapy. Unfortunately, benzodiazepines frequently decrease alertness and performance. Although patients with GAD without prior substance abuse rarely abuse benzodiazepines, physical dependence frequently develops. Tapering the dosage by 10% per week can be tried after 2 months of therapy. Relapse is common, requiring reinstitution of the benzodiazepine or an attempt at intermittent therapy. Tricyclic antidepressants may reduce the chance of relapse.

Drug	Rate of onset	Usual daily dosage (mg)	Half-life (hr)
Alprazolam	Intermediate	0.5–4.0	12–15 (Xanax)
Chlordiazepoxide	Intermediate	15–100	5–30 (Librium)
Clonazepam	Intermediate	1–10	30–60 (Klonopin)
Clorazepate	Rapid	7.5–60.0	30–200 (Tranxene)
Diazepam	Rapid	2–40	20–100 (Valium)
Lorazepam	Intermediate	2–6	10–20 (Ativan)
Oxazepam	Intermediate	30–120	5–15 (Serax)
Prazepam	Slow	20–60	30–200 (Centrax)

Table 5.1-1. Commonly used benzodiazepines

   c. **Buspirone.** Patients with respiratory disease, dementia, prior substance abuse, or those on central nervous system (CNS) depressants may benefit from buspirone (BuSpar). Beginning with 5 mg tid,

patients usually require 20–30 mg/d. Twice-a-day dosing may be as effective as thrice-a-day dosing. Adequate dosing for 2–3 weeks is usually needed before patients note a response. Because there is no physical dependence, buspirone need not be tapered once therapy is completed.

d. **Other medications.** Tricyclic depressants may be of benefit in patients with GAD (6). In the management of GAD with major depression, venlafaxine is the drug of choice. However, tricyclic antidepressants and selective serotonin reuptake inhibitors also correct both disorders. Buspirone is an alternative. Because benzodiazepines may worsen depression, they should not be first-line agents in patients with GAD and depression. Although hydroxyzine is superior to placebo in GAD (8), ß-blockers have no place in the management of GAD.

3. **Referral** should be considered in the presence of comorbid anxiety or depressive disorders when the physician is uncomfortable with management. Patients with concurrent substance abuse may also be referred. Patients requiring specific behavioral techniques unfamiliar to the physician may also be referred to appropriate mental health providers.

II. Panic disorder and agoraphobia

A. Clinical presentation.

Panic attacks typically begin with cardiopulmonary symptoms, peak rapidly, and dissipate within 1–2 hours. Although patients frequently use multiple health care sites, the most common sites of presentation are the family practitioner's office and the emergency room (9). Although anxiety is not a common presenting complaint in patients with panic disorder (PD), panic-related symptoms, such as chest pain, dizziness, palpitations, and dyspnea, often motivate help-seeking behavior. When patients associate their panic attacks with the situations in which they occurred, fear and avoidance of those situations may develop as the patient attempts to prevent another panic attack. When this phobic avoidance restricts the patient's life, agoraphobia develops. Up to two thirds of PD patients have some degree of phobic avoidance (10).

B. Diagnosis

(based on *DSM-IV criteria*)

1. **Panic disorder.** Panic attacks are intense periods of fear, peaking within 10 minutes of onset, and include at least four autonomic symptoms, such as palpitations, sweating, trembling, dyspnea, choking, chest pain, nausea, dizziness, depersonalization, paresthesias, hot or cold flashes, and fear of dying. Diagnosis requires recurrent panic attacks and 1 month of either secondary behavior change or persistent worry about additional attacks or their consequences (e.g., “going crazy”). Panic attacks should not be due to a general medical problem or the direct effect of a substance (e.g., amphetamines) (see Chapter 5.7). Routine laboratory screening for general medical problems is probably inappropriate.

2. **Agoraphobia.** Diagnosis requires the presence of anxiety in situations where escape is difficult or help is unavailable. Such situations must either be avoided, endured with marked distress, or require a companion to be tolerated. Avoidance must not be explainable by the existence of another mental disorder.

C. Therapy.

An explanation of the role of neurotransmitters in psychiatric disease and the labeling of their symptoms as panic disorder frequently reassures patients. If an organic cause for the panic attacks is found, management begins with treatment directed at this condition. Dietary measures, such as the avoidance of caffeine and other stimulants, is helpful. In addition, patients should be encouraged not to use tobacco or marijuana (11). The goal of therapy is for the patient to be panic free. Unfortunately, the relapse rate following successful treatment is high.

1. **Behavioral therapy** Cognitive therapy in the PD patient is effective and results in few relapses. Applied relaxation is helpful, but individual psychotherapy and insight therapy are not. Systematic desensitization, in which the agoraphobic patient is progressively exposed to his or her situational fears, is effective when coupled with physician and family support. Increasing exposure to phobic situations should be encouraged in all patients with PD.
2. **Drug therapy.** Medications are helpful in preventing recurrent panic attacks in susceptible individuals. However, no medication is effective in aborting a panic attack once it has begun. Treatment should be continued until patients are panic free for at least 6–12 months. Medication should be tapered slowly to avoid withdrawal symptoms (12). Buspirone and ß-blockers are not effective in PD.
   a. **Selective serotonin reuptake inhibitors** are generally the drugs of choice in PD. Fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil) are effective, beginning with one-half tablet every morning and titrating up every 3 weeks as needed. Effective doses vary: fluoxetine, 20–40 mg/d; sertraline, 50–200 mg/d; and paroxetine, 20–60 mg/d.
   b. **Tricyclic antidepressants.** Imipramine (Tofranil), desipramine (Norpramin), and clomipramine (Anafranil) are effective in PD. The initial starting dose should be 25–50 mg at bedtime. The dosage may be increased up to 300 mg/day. Three weeks of treatment may be necessary before panic suppression is achieved. Imipramine is also effective in the treatment of agoraphobia.
   c. **Benzodiazepines.** Although neuroleptics are contraindicated in PD, certain benzodiazepines are highly effective. The high-potency benzodiazepines have efficacy similar to that of the tricyclics. The literature recommends high doses of benzodiazepines (alprazolam, 3–10 mg/d; lorazepam, 4–8 mg/d; or clonazepam, 2–6 mg/d), but experience in primary care settings suggests that lower doses are effective in primary care patients. The optimal dose of alprazolam may be 2–3 mg/d.
   d. **Monoamine oxidase inhibitors,** such as phenelzine (Nardil), may be even more effective than the tricyclics. Beginning with a dose of 15 mg at bedtime, the dose can be increased up to 60 mg/d. Due to the dietary restrictions, these drugs are not the first line of therapy.
3. **Referral** is appropriate if the physician is uncomfortable with using the indicated therapy. Referral is also considered in patients who are potentially suicidal or are actively abusing drugs or alcohol (see Chapter 5.3 and Chapter 5.7).

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5.2
DEPRESSION

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Major depression is a common disorder with a lifetime prevalence of 17% (1) and primary care practice prevalence of up to 21% (2). Depression is the most common cause (44% of patients) of high use of medical services (3). Depression may be fatal and is highly amenable to treatment by family physicians.

I. Diagnosis

A. Criteria.

The *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (*DSM-IV*) (4) criteria for the diagnosis of major depression must include one of the two major symptoms: anhedonia (loss of ability to experience pleasure) or dysphoria (feeling of depression). In addition, four minor symptoms must be present. These can be remembered as SIGECAPS, a mnemonic that is spelled out as follows:

- Sleep (early awakening or excessive sleep)
- Interest (motivation to take an action)
- Guilt (hopeless, helpless, worthless feelings)
- Energy (fatigue in morning, may improve in evening)
- Concentration (includes short-term memory problems)
- Appetite (overeating or undereating)
- Psychomotor agitation (irritability or anxiety) or retardation (slowed speech, movement, depressed affect)
- Suicidal ideation or planning

The symptoms must be present more days than not, for 2 weeks or longer, and not in association with mania, delusional or psychotic symptoms, normal grief, or concurrent disease (such as hypothyroidism; see Chapter 17.3).

B. Clinical presentation.

More than half of primary care depressed patients present with somatic complaints; only one fifth present with psychological symptoms (5). Persistent pain, such as headache or backache, is common. Major depression (and anxiety disorders) amplifies the symptoms of virtually any preexisting disease. Feeling anxious and having comorbid generalized anxiety, panic, or obsessive-compulsive disorder is common. In addition, the prevalence of depression increases as other medical problems (including anxiety) become more chronic.

The elderly tend to somatize more, express anhedonia more than dysphoria, and may have paranoia or agitation when depressed. In children and adolescents, school avoidance, separation anxiety, irritability or aggressiveness, promiscuity, drug abuse, or academic and/or behavioral problems in school are signals for possible depression.

The presence of substance abuse, alcoholism, coexisting anxiety (especially panic disorder), a history of mania, and being single increases the risk of suicide, which may occur in up to 15% of untreated depressed patients. Suicide attempts, threats, frank suicide plans, psychosis, mania, and treatment failure require an immediate consultation with or referral to a psychiatrist.

II. Treatment.

Treatment success is predicted by appropriate use of counseling, patient education, regular follow-up, proper diagnosis, and proper drug selection and dosage (see Table 5.2-1).

	Starting dose (mg/day)	Daily dose (mg/day)
Tricyclics		
Amitriptyline	25–50	100–300
Clomipramine	25–50	50–250
Desipramine	25–50	100–300
Doxepin	25–50	100–300
Imipramine	25–50	100–300
Nortriptyline	25	50–200
Protriptyline	10	15–60
Trimipramine	25–50	100–300
Selective serotonin reuptake inhibitors		
Citalopram	10–20	20–60
Fluoxetine	10–20	20–80
Fluvoxamine	25–50	50–300
Sertraline	25–50	50–200
Paroxetine	10–20	20–50
Heterocyclics		
Amoxapine	50	100–400
Bupropion SR	100–150	300–450
Maprotiline	50	100–225
Mirtazapine	15–30	15–45
Nefazodone	50–100	300–600
Trazodone	50	150–500
Venlafaxine XR	37.5	75–225

SR, sustained release; XR, extended release.
[a] SR and XR = long-acting preparations.

Table 5.2-1. Commonly prescribed antidepressants[a]

A. Medication.

All antidepressants are 60%–70% effective. Successful treatment of depression depends on the issues of medication selection, side effects, cost, dosing regimens, and proper follow-up.

Side effects are common. Most are pesky and go away with continued use or with dosage adjustments. An appropriate medication trial is 4–6 weeks. In patients older than 65, half of the usual dose and more gradual dose adjustments are the rules.

1. **Tricyclics.** Begin with one daily dose (usually at night) and increase by the same amount every 3–4 days until the target dose is reached or until side effects limit further adjustments. Common side effects include sedation, dry mouth, blurred vision, constipation, sexual dysfunction, hypotension (especially postural), and quinidine-like cardiac effects. Tricyclics

can be lethal in overdose with a one-week supply (6) and are relatively contraindicated in heart disease. Nortriptyline, desipramine, and imipramine may have less troublesome side effects.

2. **Heterocyclics.** Second- and third-generation antidepressants include bupropion, trazodone, nefazodone, maprotiline, amoxapine, mirtazapine, and venlafaxine. Bupropion SR is nonsedating and useful in resistant depression not associated with anxiety, must be taken twice daily, and, as with maprotiline, may lower the seizure threshold in susceptible patients. Trazodone is sedating and is usually taken at night, with side effects including stuffy nose, hypotension, daytime sedation, and, rarely, priapism. Venlafaxine XR has tricyclic-like action and efficacy without many tricyclic-like side effects and is taken twice daily. Nausea is a common side effect, and increases in blood pressure may occur. Amoxapine may cause tardive dyskinesia and is best reserved for psychotic depression. Nefazodone has significant anxiolytic and antidepressant properties and is taken once or twice daily. It may prolong the half-life of alprazolam and triazolam. Mirtazapine has fewer drugs interactions than most and is taken once or twice daily. Weight gain and sedation are common side effects. Bupropion, mirtazapine, and nefazodone are the least likely of all antidepressants to cause sexual dysfunction.
3. **Selective serotonin reuptake inhibitors (SSRIs).** The SSRIs are effective, well tolerated, and administered once a day. Common side effects include nausea, insomnia, headache, nervousness, and sexual dysfunction (anorgasmia and/or decreased libido in up to 43% of patients—more in some studies) (7).

B. Counseling.

Brief cognitive therapy is a successful counseling modality for family physicians. A patient's faulty negative beliefs can be challenged or “reframed” by the family physician and successfully reinforced by infrequent brief visits.

C. Treatment duration.

First episodes require treatment for 6–9 months and second episodes for at least a year. Third episodes define depression as chronic and indicate treatment for years, if not for life, to prevent relapse and/or treatment resistance.

D. Other treatment issues.

Many antidepressants are efficacious in anxiety disorders (also see Chapter 5.1). Medical literature supports the efficacy of some tricyclics (e.g., imipramine), the SSRIs, and nefazodone in the management of panic disorder (use lower starting doses); fluoxetine, fluvoxamine, and clomipramine in obsessive-compulsive disorder; and nefazodone and venlafaxine in generalized anxiety disorder coexisting with depression. Psychiatrists and knowledgeable family physicians may use carbamazepine, valproate, valproic acid, lithium, or monoamine oxidase inhibitors in treatment-resistant depressive patients. Buspirone, triiodothyronine, or lithium is sometimes added to tricyclics or SSRIs to augment the antidepressant action. Electroshock therapy is safe, rapidly effective, and especially useful in resistant, delusional, frankly suicidal, and withdrawn melancholic depressed patients.

Causes of treatment failure may include underdosing, inadequate treatment trial duration, concomitant use of depressing drugs (alcohol, benzodiazepines, barbiturates, narcotics, propranolol, methyldopa, reserpine, carisoprodol), the presence of other disease (e.g., hypothyroidism, pancreatic carcinoma), not switching to alternative medication or combination-therapy options, poor compliance, and failure to properly inform the patient.

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5.3
ALCOHOLISM

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Family physicians have the opportunity not only to treat but to prevent the physical and social consequences of alcohol abuse. Although alcohol use, cirrhosis rates, and alcohol-related traffic fatalities declined in the previous decade, there has been little improvement in other social consequences of alcohol abuse. Brief physician interventions with problem drinkers can decrease both alcohol use and the cost of health care (1). When treatment is necessary, the family physician's role may range from referral with follow-up to comprehensive rehabilitation, typically including the services of Alcoholics Anonymous and other support groups.

I. Basic principles.

The term *alcoholism* as used in this chapter is synonymous with alcohol dependence, as defined in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (*DSM-IV*) (2). Each individual is unique, but universally alcoholics have suffered misfortune associated with their drinking. Most do not recognize the link between their misfortune and drinking. They may drink intermittently or continuously. Some, especially those with a family history of alcoholism, develop problems soon after beginning drinking; others drink for decades before any problem is detectable. Heavy drinkers may demonstrate tolerance with behavior that appears normal, despite elevated blood alcohol levels. Diagnostically, the amount consumed is less important than the consequences of drinking.

II. Physiology.

Alcohol is metabolized at zero-order kinetics to acetaldehyde, then to acetate. Five to ten percent of alcohol is released unchanged in breath and urine. An adult male (of 70 kg) in good health can metabolize about 10 mL of absolute alcohol per hour. Neither the placental nor the blood-brain barrier offers protection from alcohol. Alcohol levels in alveolar air correlate with arterial blood alcohol concentration.

III. Screening.

A primary screen for alcohol-related problems may be done as part of the review of systems or as part of a routine visit. Patients who drink at all, no matter how infrequently, should be asked questions from the “CAGE,” a brief and practical primary screening tool for alcohol abuse. The term CAGE is an acronym for the key word in each of the four questions below (3). Any positive response justifies a more in-depth screen.

A.

Have you ever felt you should *cut* down on your drinking?

B.

Have people *a*nnoyed you by criticizing your drinking?

C.

Have you ever felt *g*uilty about your drinking?

D.

Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (“eye opener”)?
A slightly longer but more accurate alternative screening test is the Alcohol Use Disorders Identification Test (AUDIT) (Table 5.3-1) (4). AUDIT questions are provided below along with the scoring values. Typically, a total of eight points or more on the AUDIT is suggestive of alcohol dependence.

1. How often do you have a drink containing alcohol?
   (0) Never
   (1) Monthly or less
   (2) Two to four times a month
   (3) Two to three times a week
   (4) Four or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7 or 9
   (4) 10 or more
3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?
   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year
10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down?
    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Table 5.3-1. The AUDIT questionnaire

IV. General history.

A history sufficient to diagnose alcohol abuse or dependence should address the following topics, with collateral information being obtained from family members when possible: family history of alcohol problems; withdrawal history; frequency, volume, and type of alcohol consumed; time since last drink; memory gaps (blackouts); depression; marital dysfunction; sexual dysfunction; DWI convictions; repeated trauma; and use of other psychoactive substances.

V. Medical history and findings.

A variety of medical problems and physical signs are associated with acute and chronic alcohol abuse (Table 5.3-2).

Acute or recent	Chronic or prolonged
Hypertension	Hypertension and/or cardiomyopathy
Sudden muscle necrosis	Chronic alcoholic myopathy
Nausea, vomiting, gastritis, reflux	Chronic atrophic gastritis
Delayed gastric emptying	Pancreatitis, pseudocyst formation
Alcoholic hepatitis	Cirrhosis, alcohol ketoacidosis
Increased sputum production	Decreased platelet function
Hypothermia	Megaloblastic anemia
Hypoglycemia, lactic acidosis	Decrease in polymorphonuclear leukocytes
Nystagmus, diplopia	Decreased cell-mediated immunity and T cells
Ataxia, stupor, coma	Peripheral neuropathy, dementia
Loss of magnesium, zinc, phosphorus, calcium, potassium, thiamine, and/or folate	Males: breast enlargement, gonadal atrophy
Holiday heart syndrome: atrial or ventricular dysrhythmia associated with heavy drinking	Females: amenorrhea, anovulation
	Wernicke-Korsakoff syndrome (triad of confusion, ocular disturbance, and ataxia)

Table 5.3-2. Physical sign of alchol abuse

VI. Laboratory.

Laboratory tests are useful to screen, diagnose, and detect relapse. Typically, blood alcohol concentration (BAC), urine drug screen, bilirubin, prothrombin time, γ-glutamyl transpeptidase (GGT), electrolytes, and a complete blood count will suffice. Increases in bilirubin, GGT, and prothrombin time suggest liver dysfunction. Elevated mean corpuscular volume, mean corpuscular hemoglobin, and decreased red blood cell count suggest chronic heavy drinking.

Elevation of GGT suggests the possibility of alcohol abuse, although other conditions may also raise GGT values. High values on carbohydrate-deficient transferrin suggest moderate to heavy drinking for at least the preceding week or two and are useful in monitoring relapse.

VII. Diagnosis.

The implementation of *DSM-IV* criteria has standardized the diagnosis of alcohol use disorders, with the current emphasis on patterns of harmful consequences (Table 5.3-3).

Alcohol abuse	Alcohol dependence
For a diagnosis of alcohol abuse the patient must show one or more of the following related to alcohol, on a *recurrent* basis: 1. Failure to fulfill major role obligations 2. Use in physically hazardous situations 3. Legal problems 4. Continued use despite having persistent or recurrent social or interpersonal problems related to the alcohol use	For a diagnosis of alcohol dependence at least three of seven criterion items must be met: 1. Clinically significant tolerance 2. Clinically significant withdrawal 3. Recurrent failure of intent—drinks more or for longer duration than intended 4. Recurrent failure of control—persistent desire to stop or cut down usage 5. Preoccupation with alcohol 6. Predominance of alcohol-related activities 7. Continued alcohol use despite knowledge that the drinking contributes to a physical, social, psychological, or other problem

Table 5.3-3. Diagnosis of alcohol use disorders

VIII. Assessment of severity.

Alcohol abuse and alcohol dependence are progressive diseases, resulting in adverse consequences for the individual, family, friends, and co-workers, as well as society as a whole. As with diagnosis, consequences of use reflect severity. Deterioration in family life, friendships, and work performance; legal problems; poor self-esteem; personality changes; and financial difficulties indicate greater severity. Tolerance is a marker for severity. For example, being able to function well at 0.20% BAC indicates that the patient has developed substantial tolerance. Members of various cultural groups may be at increased risk due to genetics or isolation. Women typically demonstrate a more rapid progression of both alcoholism and its medical complications than do men with similar current drinking patterns. Pregnant women place their unborn child at risk for fetal alcohol syndrome. Lifestyle and socioeconomic issues place some individuals at higher risk, including the homeless, the chronically mentally ill, migrant workers, and rural residents. Adolescents are at greater risk because of their vulnerability to disruption of normal development.

IX. Acute intervention.

Risk of severe withdrawal is increased by advanced age (older than 45), poor physical condition, complicated withdrawal history, and the amount of alcohol consumed. Withdrawal begins as the blood alcohol level decreases, especially as it declines to below 75% of peak level. The first signs and symptoms include anxiety, restlessness, insomnia, and nausea. Blood pressure, pulse, and temperature increase. Hand tremor is the earliest reliable sign of alcohol withdrawal, but it can be masked by ß-blockers. Hallucinations, especially visual, may occur. Grand mal seizures, observed in about 5% of untreated withdrawal patients, typically occur about 48 hours after the last drink. Delirium tremens, a potentially fatal condition characterized by hallucinations, disorientation, trembling, drenching sweat, and electrolyte disturbances, may occur during the third through fifth day of withdrawal and occasionally as late as day 10. Detoxification is most often conducted on an outpatient basis in today's managed-care

environment, unless there are data to suggest the danger of impending complicated withdrawal. Table 5.3-4 gives several sample detoxification protocols.

Basic orders
Multivitamin 1–2 qd
Quiet room with even lighting
Folate, 1 mg PO qd × 3 d
Thiamine, 100 mg ASAP and qd × 3 d
PO fluids as tolerated; IV usually not required
Magnesium supplement 1–2 tablets PO stat and qd; may give deep magnesium sulfate IM for severe withdrawal risk (2 g q8h)
Oxazepam
Over age 55 or hepatic dysfunction. 15–30 mg PO qh until symptoms remit or sedation occurs, then repeat total dose q6–8h for first day, reducing this dosage by 25% each day. Most patients will be off medication by day 5.
Diazepam loading
Under age 55 and healthy liver. 10–20 mg PO qh until sedated. Usually no further medication is required.
Phenobarbital taper
Thirty mg PO qid × 3 d, 15 mg qid × 2 d, and 15 mg bid × 1 d. Augment with sodium phenobarbital, 130–260 mg IM, early in treatment for severe withdrawal. Early use of IM phenobarbital for moderate to severe withdrawal is the key to success with this regimen. Use phenergan or hydroxyzine for nausea.
Severe agitation
Haloperidol, 5–10 mg, may be given PO, IM, or IV for severe agitation, in combination with any above withdrawal regimen; repeat as needed.

IM, intramuscular; IV, intravenous; PO, by mouth.
The above and other detoxification protocols may be modified for use in conjunction with instruments such as the Clinical Institute Withdrawal Assessment (CIWA-Ar) to better relate medication administration to actual withdrawal signs and symptoms.

Table 5.3-4. Sample detoxification protocols

X. Maintenance of sobriety.

For good reason, most treatment programs emphasize active participation in support groups, especially Alcoholics Anonymous. Collateral groups, including Alanon, Alateen, and Adult Children of Alcoholics, provide support to family members. These groups are mainstays of sobriety maintenance.

A.

There is no “magic bullet” for alcoholism, but pharmacotherapy combined with a treatment program can improve outcomes. Pharmacotherapy generally consists of agents that provide aversive consequences for drinking, such as disulfiram (Antabuse), or agents that reduce the urge to drink. Disulfiram combined with a program to ensure compliance can reduce early relapse by diminishing impulsive drinking. Naltrexone (ReVia) when combined with supportive psychotherapy improves outcomes (fewer relapses); it appears to function by reducing the reward value of alcohol. It has been used for short-term treatment while monitoring of liver-associated enzymes takes place. Selective serotonin reuptake inhibitors may lower alcohol consumption and ameliorate depression, at least among alcoholics who suffer moderate to severe depression. Other medications, such as acamprosate (Campral) and ondansetron (Zofran) (5), show promise and are under active investigation.

B.

Depression and anxiety are frequently secondary to chronic alcohol use and remit after several weeks to months of abstinence. Early chemotherapy for anxiety and depression is therefore typically ill advised (see Chapter 5.1 and Chapter 5.2), except when there is evidence of a preexisting primary anxiety or depressive disorder. When alcoholism coexists with another disorder, such as preexisting depression or schizophrenia, usually both conditions are exacerbated and both must be treated. Treatment of comorbid conditions should be

marked by avoidance of addictive agents, especially those cross-tolerant with alcohol.

C.

Codependence is a serious relapse factor for the recovering alcoholic. Friends, family, and co-workers have frequently developed a pattern of “covering” for the impaired individual, allowing him or her to avoid the consequences of alcoholism and thereby perpetuating the disease. For this reason, most recovery programs strive to involve family members in the treatment program.

XI. Physicians' legal responsibilities and ethics.

The legal and ethical obligation of the physician to report instances of child or spouse abuse is well known. Households in which chemicals are abused are at substantially greater risk for both physical and sexual abuse (see Chapter 20.4 and Chapter 20.5). Legal guidelines govern the physician's obligatory actions in case of threat of suicide or assault, but danger to others may also take the form of an intoxicated patient planning to drive home from the emergency room. Such an intoxicated patient cannot be legally restrained unless he or she can be committed under state law; an exception is restraint by police. An individual who accepts treatment may still be restrained for medical reasons. If a patient is thought to be impaired, it becomes the hospital staff's duty to persuade the patient not to drive, to use a taxi, to call a friend or family member, and, if necessary, to contact the police and inform them of the situation. Public safety takes precedence over confidentiality, and if no such action is taken, the physician may risk liability should an injury result.

The ethical guidelines for physicians and other health care professionals articulate the provider's responsibility to report an impaired provider. The treatment success rate for impaired physicians is among the highest of any occupational group. Using the intervention services of treatment programs allows the impaired provider to maintain professional status, employment, and self-respect by receiving treatment while the program protects the public.

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5.4
SEXUAL DYSFUNCTION

John G. Halvorsen

Sexual problems are common. They occur in almost half of all marriages, in at least 75% of couples who seek marital therapy, and in more than half of all adults who visit primary physicians' offices.

I. Basic principles.

By definition, the sexual dysfunctions are disorders of sexual desire and of the psychophysiologic changes that occur during the sexual response cycle. The **Diagnostic and Statistical Manual of Mental Disorders,** 4th edition (**DSM-IV**) classifies them according to the following system (1).

A. Sexual desire disorders (SDDs)

1. Hypoactive sexual desire disorder is deficient (or absent) sexual fantasies and desire for sexual activity.
2. Sexual aversion disorder is extreme aversion to, and avoidance of, genital contact with a sexual partner.

B. Sexual arousal disorders

1. Female sexual arousal disorder is the inability to attain or maintain an adequate lubrication-swelling response of sexual excitement until sexual activity is completed.
2. Male erectile disorder (ED) is the inability to attain or maintain an adequate erection until sexual activity is completed.

C. Orgasmic disorders

1. Female or male orgasmic disorder is delayed or absent orgasm following normal sexual excitement.
2. Premature ejaculation (PE) is ejaculation with minimal stimulation before it is wanted, before, during, or shortly after penetration.

D. Sexual pain disorders

1. Dyspareunia is genital pain associated with sexual intercourse in either men or women.
2. Vaginismus is involuntary vaginal muscular spasm that interferes with sexual intercourse.

E. Sexual dysfunction due to a general medical condition

is sexual dysfunction that is fully explained by the physiologic effects of a medical condition.

F. Substance-induced sexual dysfunction

is sexual dysfunction that develops during or within a month of substance intoxication or when medication use is etiologically related.

II. Diagnosis (2,3 and 4)

A. Symptoms.

Physicians should routinely ask about sexual relationships with open-ended questions, pursuing positive responses with specific queries concerning various specific phases of the sexual response. A more complete history incorporates the following categories.

1. **Present history.** Pursue the presenting sexual concern with specific questioning, as one would further define any other problem.
2. **Sexual history.** Explore all current and past sexual experiences (including sexual abuse), relationships, attitudes, emotional reactions, knowledge, sexual identity, and body image.
3. **Developmental and family history.** Discuss family attitudes about sexuality, parental modeling, religious influences, relationships with parents and siblings, family violence, and level of family function in the couple's families of origin.
4. **Nature of current relationship.** Focus on the current relationship's development and stability, changes in feelings, unresolved conflict, loss of trust, and communication problems.

5. **Current stressors.** Inquire about intrafamilial stresses (e.g., death, illness, problems with children, normative individual and family life cycle development transitions) and extrafamilial stresses (e.g., financial, occupational, legal).
6. **Past medical history.** Identify any acute or chronic organic disease (diabetes mellitus is the most common organic cause), injury, or surgery that could affect sexual functioning. Inquire about psychological problems (depression and anxiety are most associated with sexual dysfunction). Many commonly used drugs also affect sexual function; examples are anticholinergics, antidepressants, antihistamines, antipsychotics, anxiolytics, hormonal contraceptives, narcotics, sedative-hypnotics, and drugs of abuse, including alcohol and tobacco.
7. **The International Index of Erectile Function (IIEF)** is a 15-item inventory that can help a busy clinician evaluate sexual functioning in men. Similar inventories for women are currently in the design and evaluation process.

B. Signs.

A comprehensive physical examination further defines concurrent acute or chronic illness and associated physical conditions.

1. **General.** Look for obesity, cachexia, and evidence of endocrine disease; determine vital signs.
2. **Cardiovascular.** Search for bruits (especially femoral), peripheral pulses, evidence of venous stasis, arterial insufficiency (especially in the lower extremities), or a pulsatile epigastric mass.
3. **Abdominal.** Look for pain, tenderness, mass, guarding, tympany, bowel activity, hernia, and evidence of prior surgery.
4. **Neurologic.** Examine gait, coordination, deep tendon reflexes, pathologic reflexes, sensation, motor strength, integrity of the sacral reflex arc (S_2 to S_4) with perineal sensation, anal sphincter tone, and bulbocavernosus (S_2, S_3), bulbo-anal (S_3, S_4), and anal (S_4, S_5) reflexes.
5. **Observe the male genitalia for testicular size and consistency, penile size, malformations, and lesions.** Examine the prostate for size, consistency, and tenderness. Obtain penile blood pressure measurements on any man with ED by inflating a 3-cm pediatric blood pressure cuff around the base of the penis and auscultating the central artery of the corpora cavernosa with a 9.5-MHz Doppler stethoscope as the cuff is deflated. The ratio between the penile systolic pressure and the brachial systolic pressure should exceed 0.75. Ratios less than 0.60 indicate penile vascular insufficiency.
6. **Female pelvic examination.** Search for the following findings (also see Chapter 13.1):
   a. **External genitalia.** Check for dermatitis, atrophy, vulvar inflammation, warts, episiotomy or other scars, and clitoral inflammation, or adhesions.
   b. **Introitus.** Look for hymeneal rigidity, tags, or fibrosis, urethral carbuncle, and Bartholin's gland inflammation.
   c. **Vagina.** Evaluate for spasm of the vaginal sphincter and adduction of the thighs with attempted vaginal examination, atrophy, discharge, inflammation, stenosis, relaxation of supporting ligaments, and tenderness along the vaginal urethra or posterior bladder wall.
   d. **Bimanual examination.** Check for cul-de-sac masses or tenderness and adnexal mass or tenderness. Determine the presence, position, size, mobility, and tenderness of the uterus.
   e. **Rectovaginal examination.** Examine for hemorrhoids, fissures, constipation, and tenderness.

C. Laboratory tests

1. **Laboratory evaluation for systemic disease** includes a complete blood count, fasting blood sugar level, urinalysis, tests for sexually transmitted diseases, lipid profiles, and tests of thyroid, liver, and renal function.
2. **Evaluation for SDD.** Obtain a 9 a.m. serum testosterone level in men. If levels are low or borderline, or if the low desire is associated with little or no sexual fantasy or masturbation history, obtain a serum prolactin level.
3. **Evaluation for female sexual arousal disorder.** Techniques are now available for measuring nocturnal clitoral and vaginal blood flow. They may become useful in the future to differentiate organic from psychogenic sexual disorders in women and to determine the role of arterial factors in affecting sexual arousal and orgasm.
4. **Evaluation for male erectile disorder**
   a. A 9 a.m. serum testosterone level screens for hypogonadism. If the level is low, obtaining follicle-stimulating hormone, luteinizing hormone, and prolactin levels can help to differentiate between primary testicular failure and secondary (pituitary-hypothalamic) failure. If hypogonadotropic hypogonadism is found, computed tomography (CT) or magnetic resonance imaging (MRI) can investigate the sella turcica for a pituitary tumor.

b. Nocturnal penile tumescence (NPT) evaluation helps differentiate psychogenic interference (erections occur during sleep) from organic interference (erections do not occur). Several techniques evaluate and quantify NPT.
    a. The snap gauge is a ring of opposing velcro straps connected by three plastic strips. It is wrapped around the penis before sleep, and, by noting whether 0, 1, 2, or 3 bands break during sleep, one can estimate the maximum erectile response.
    b. The Rigiscan is a small computer with two cables leading to rings that encircle the base and tip of the penis. The rings detect tumescence by passively expanding and detect rigidity by actively contracting. The Rigiscan records all erectile events and measures erection duration, tumescence, and rigidity.
    c. NPT monitoring is performed in a sleep laboratory where electroencephalographic tracings detect sleep cycles. Mercury strain gauges placed around the base and tip of the penis detect tumescence. Monitoring documents all erectile events; measures duration, tumescence, and rigidity (but not as well as the Rigiscan); and correlates erections with rapid eye movement (REM) sleep.
c. Duplex ultrasonographic scanning records blood flow in the cavernous arteries before and after a vasodilator [papaverine or prostaglandin E_1 (PGE_1, Alprostadil)] injection. Normal vessels should double in size, with an initial peak systolic flow velocity exceeding 30 cm/s.
d. Intracavernous injection of vasodilators (papaverine or PGE_1) helps screen for a vascular cause. Injections should cause an erection within 10 minutes that lasts for at least 30 minutes. Delays of longer than 15–20 minutes are suggestive of arterial insufficiency, and a normal erection that is lost quickly is suggestive of a cavernous leak.
e. Pudendal angiography. Selective internal pudendal angiograms can determine if an arterial block exists that could be corrected by penile revascularization.
f. Cavernosometry and cavernosography evaluate the veno-occlusive mechanisms of the corpus cavernosum. A vasoactive agent (20 µg PGE_1) is injected into a corpus cavernosum to cause an erection; this is followed by a heparinized saline infusion to maintain the erection. Radiographic contrast is then infused, and radiographs are taken to identify leaks in specific veins and the glans-spongiosal system.
g. Bulbocavernosus reflex latency tests measure the integrity of the sacral reflex arc (S_2 to S_4) by recording the time delay from stimulation of the glans by a pinch or squeeze to contraction of the bulbocavernosus muscle. Longer times suggest a neurologic cause for ED.
h. Somatosensory evoked potentials record wave forms over the sacrum and the cerebral cortex in response to dorsal penile nerve stimulation. They can help localize neurologic lesions to peripheral, sacral, or suprasacral locations.

5. **Evaluation for sexual pain disorders**
    a. Office laboratory procedures include saline and potassium hydroxide wet mounts of vaginal secretions to diagnose vaginitis or vaginosis; urinalysis, urine culture, and evaluation of prostatic secretions to diagnose associated genitourinary infections; and tests to diagnose chlamydial, herpes simplex, and gonococcal infections.
    b. Colposcopy may diagnose specific vaginal or cervical pathology, such as human papillomavirus infections (see Chapter 13.4).
    c. Pelvic ultrasound may diagnose adnexal, uterine, or cul-de-sac problems.
    d. Laparoscopy may diagnose, and in some cases treat, adnexal or intraperitoneal pathology.

e. Anoscopy or sigmoidoscopy may identify associated colorectal problems.

III. Treatment

A. Medical management (5)

1. Testosterone in the form of testosterone enanthate (200 mg IM every 2–3 weeks) is effective treatment for hypogonadal men with testosterone values less than 100 ng/dL. Transdermal preparations (AndroGel, Androderm, Testoderm) applied daily will also raise testosterone levels to normal in 90% of men. Testosterone has also been used to increase desire in women. Placebo-controlled studies are now in progress to evaluate the effectiveness and hazards of both oral and transdermal agents.
2. Bromocriptine mesylate (Parlodel) cures hyperprolactinemia. Doses begin at 1.25 mg every day and increase by 1.25 mg every 3–7 days until the serum prolactin level is normal.
3. Yohimbine (Aphrodyne) theoretically enhances penile erections by restricting penile venous outflow and increasing libido through a central nervous system effect. Dosage is 6 mg PO tid.
4. Sildenafil (Viagra) has become the drug of choice for most men with ED. The recommended dose is 50–100 mg taken 1 hour prior to sexual activity. It is contraindicated in patients taking organic nitrites because it potentiates their hypotensive effects. It is now being studied in women with arousal and orgasm disorders, and preliminary results indicate that it performs no better than placebo.
5. Oral phentolamine (Vasomax) 20–80 mg taken 15 minutes prior to intercourse improves erectile function in men with mild to moderate ED. It is not yet available in the United States.
6. Sublingual or transbuccal apomorphine (Uprima) in 2-, 4-, or 6-mg strengths reportedly improves erectile function in men with minimal organic disease. It is not yet available in the United States, and recently reported safety concerns may delay its approval by the Food and Drug Administration (FDA).
7. Intraurethrally inserted PGE tablets (MUSE) in strengths of 125, 250, 500, and 1,000 µg demonstrate effectiveness in 40% of men with ED from various causes.
8. Topical nitroglycerin (Nitrol) relaxes penile arterial smooth muscle, causing subsequent engorgement. Men with mild vascular, neurologic, or mixed arousal dysfunction may respond to 0.5–1.0 inches of 2% ointment applied to the penile shaft just prior to intercourse. The man must also wear a condom to avoid vaginal absorption by his partner. Topical 2% minoxidil solution (Rogaine) applied to the glans is reportedly as effective as nitroglycerin. Prophylactic analgesics help manage associated headache. Topical PGE_1 (Topiglan) is also under study in men with ED. Topical vasodilators may also enhance clitoral arousal and vaginal lubrication in women.
9. Intracavernous injection of vasoactive drugs. Patients may inject either papaverine or PGE into a corpus cavernosum with a 27-gauge needle to induce an erection. Men with neurogenic disorders, mild vascular problems, combined neurogenic and vascular disorders, and psychogenic problems for which psychosexual treatment has failed may respond well. Injections also benefit men with PE because sexual activity can continue despite the premature orgasm. Therapy begins with a low dose of either drug (10 mg papaverine; 2.5–5.0 µg PGE_1) that is gradually increased to provide an adequate erection that lasts 1–2 hours. This usually requires 30–60 mg papaverine or 5–20 µg PGE_1. Injections are limited to 3 per week and 10 per month. In difficult cases these drugs may be mixed and used in combination. Injecting vasoactive intestinal polypeptide (VIP) 0.025 mg mixed with phentolamine 2.0 mg (Invicorp) reportedly demonstrates efficacy in men who have failed other injection therapies. It is not yet available in the United States.
10. Tricyclic antidepressants in antidepressant doses may help manage PE because they inhibit the cholinergic component of ejaculation.

11. Thioridazine at standard antidepressant doses may also benefit men with PE.
12. Phenoxybenzamine (Dibenzaline) is used by men with PE in daily doses of 20–30 mg. It should not be used by men who wish to procreate because phenoxybenzamine inhibits seminal emission.
13. Clomipramine (Anafranil) may benefit PE by increasing the sensory threshold for genital stimuli. Doses start with 25–50 mg 3–5 hours prior to sexual activity and increase until the man achieves ejaculatory control, experiences side effects, or reaches maximal recommended doses.
14. Sertaline (Zoloft) 50–100 mg, Paroxetine (Paxil) 20–40 mg, and fluoxetine (Prozac) 20–60 mg taken 3–5 hours prior to sexual activity may also delay ejaculation.
15. A lidocaine-prilocaine cream formulation applied to the glans and covered with a condom 30 minutes prior to intercourse is also reported to help PE.
16. Water-based lubricating products (K-Y Jelly, Astroglide) applied directly to the genital area prior to intercourse may reduce discomfort associated with intercourse, and they do not increase infection or damage condoms like oil-based products.

B. Surgical management

1. **Arterial revascularization.** Successful surgery for proximal artery occlusion can improve blood flow through the hypogastric vessels. Success depends on whether the distal vessels are patent and whether surgery damages the autonomic nerves that travel over the vessels.
2. **Venous surgery.** Surgical procedures vary depending on where venous incompetence occurs. Ligating the affected veins provides added resistance to venous outflow and maintains erections.
3. **Penile prosthesis.** The penile prosthesis is the most reliable surgical option in the United States, with the inflatable prosthesis implanted most frequently. Prosthesis implantation is relatively uncomplicated, but most devices require replacement after 48–60 months.

C. Mechanical management.

Penile vacuum pumps (ErecAid) can also aid erections. Air is withdrawn from a lubricated cylinder that the man places over his penis to create a vacuum that draws blood into the corpora cavernosum. An elastic band around the penile base maintains the erection when the cylinder is removed. A device that creates suction over the clitoris (EROS-CTD) is now approved by the FDA. It increases clitoral blood flow, erection, and sensitivity, and reportedly enhances sexual arousal and orgasm in women.

D. Psychosexual therapy

1. Standard principles that undergird psychosexual therapy include the beliefs that people are responsible for their own sexuality; that growth in sexual attitudes, performance, and feelings results from behavioral change; that every person deserves sexual health; that physiologic relaxation is the foundation for sexual excitement; and that boundaries must be established with the nonsexual aspects of sexual dysfunction.
2. Cognitive-behavioral therapy that incorporates behavioral therapy into other treatments is the treatment choice for managing most sexual dysfunctions. Behavior therapists assume that sexual dysfunction is learned maladaptive behavior that causes patients to fear sexual interaction. Therapy inhibits the learned anxious response.
3. Sensate focus exercises heighten sensory awareness to touch, sight, sound, and smell. As patients focus on their own sensations they relax and overcome the barriers to their natural physiologic responses.
4. Hypnotherapy helps remove symptoms and alter attitudes by teaching patients to use relaxation techniques before a sexual encounter and to learn alternative ways of dealing with anxiety-provoking sexual situations.
5. Group therapy provides a strong support system to counteract sexual myths, correct misconceptions, and provide accurate information about sexual anatomy, physiology, and varieties of behavior.

6. Traditional marital therapy is also important to manage the marital or relationship problems that generate stress, fatigue, and dysphoria.

E. Specific sexual therapy techniques

1. Directed masturbation is the most effective treatment program to date for primary orgasmic dysfunction in women.
2. The stop-start technique of Semans and the squeeze technique modification of Masters and Johnson help manage PE.
3. Sexologic examination. The vaginal sexologic examination helps treat women with arousal and orgasmic disorders by assisting them and their partners to identify specific erotically sensitive vaginal and genital foci. The examination is performed with the sexual partner, after the woman's signed consent.
4. Systematic desensitization techniques successfully treat both dyspareunia and vaginismus.

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5.5
EATING DISORDERS

Cynthia G. Olsen

Eating disorders, which affect up to 7.5 million Americans (about 4% of the U.S. population), involve a disturbed eating behavior and distorted body image. Bulimia nervosa is three times more common than anorexia nervosa. The male-to-female prevalence of eating disorders is approximately 1:10. The mortality rates for each are significant, with that for anorexia nervosa being 2%–6%, mostly from starvation and suicide. The age of onset for anorexia begins at 13 years and that for bulimia is in later adolescence and young adulthood. Both are found predominately in industrialized societies, where ideals about body size and the acceptance of dieting are widespread.

I. Anorexia nervosa

A. Diagnostic criteria for anorexia nervosa (307.1) (1)

1. Refusal to maintain body weight at or above 85% normal weight for age and height
2. Intense fear of gaining weight or becoming fat
3. Disturbed perception of own body weight or shape, and denial of severity
4. Amenorrhea in postmenarchal female (at least three consecutive cycles)

B. Clinical presentation.

Anorexia nervosa tends to present after a stressful life event, such as a school change, and may be episodic, relapsing, or chronic. The behavior of the anorexic person includes impulse control problems and obsession with food. The two subtypes of anorexia nervosa include *restricting type* and *binge-eating/purging type.* Psychological features include issues of loss and separation, indifference or vigorous denial, perfectionism, dichotomous thinking, alexithymia, conflicting self-denial and hedonism, and delayed psychosocial development. The stress of starvation causes the person to appear irritable, dysphoric, anxious, and angry.

C. Differential diagnosis.

Psychiatric disorders that may mimic anorexia nervosa include major depressive disorder, schizophrenia, body dysmorphic disorder, substance dependency, obsessive-compulsive disorder, and social phobia. Medical conditions include colitis; carcinoma of brain, pancreas, or lung; AIDS; superior mesenteric artery syndrome; gastric outlet obstruction; and metabolic disorders such as Addison's disease, hyperthyroidism, or thiamine deficiency. The comorbidity of psychiatric and medical issues can make diagnosis and treatment challenging.

D. Symptoms and physical signs

The history is paramount in assessment and should include both the patient and family or friends. The clinician needs to verify body perception and weight loss behaviors. The anorexic patient may report aversion to meat, insensitivity to cold, other compulsive behaviors, exhaustion due to overactivity or overexercise, sleep disturbance, paradoxical satiety, constipation, nausea, abdominal pain, and bloating. Measurement of height, weight, and body mass index is important to assessment and monitoring of treatment. Clinical findings may include emaciation and decreased muscle mass, myopathy, lanugo of the trunk, peripheral edema, dry skin, petechiae, yellowed skin from hypercarotenemia, parotid gland hypertrophy, ketotic breath, bradycardia, hypothermia, and hypotension. Anorexic individuals who engage in binge/purge behavior may also have the findings of bulimia. Careful psychological assessment should focus on affective disorders, suicide risk, personality disorders, and substance abuse. In starving patients, depression may be the result of metabolic disturbance and can resolve with weight gain and correction.

Laboratory studies may reveal normochromic-normocytic anemia with leukopenia, electrolyte disturbance, hypothyroidism, low estrogen state with osteoporosis, diminished testosterone in males, increased liver functions due to fatty liver, hypercholesterolemia, increased growth hormone, renal insufficiency due to dehydration and hypokalemia, arrhythmias, and urine pH greater than 7. An electrocardiogram is important in severely underweight patients (>25% below baseline weight) and those using chemical purgatives, especially syrup of ipecac, to rule out a potentially life-threatening conduction disturbance. Magnetic resonance imaging usually reveals a decrease in brain size with ventricular dilatation.

II. Bulimia nervosa

A. Diagnostic criteria for bulimia nervosa (307.51) (1)

1. Recurrent binge eating, out of control, typically large amounts of food over a discrete time period (<2 hours)
2. Recurrent compensatory acts to prevent weight gain (vomiting, laxatives, diuretics, enemas, fasting, diet pills, excessive exercise)
3. Binge/purge cycle occurring twice per month for at least 3 months
4. Preoccupation with and criticism of body weight and shape

B. Clinical presentation.

Bulimia can be further subtyped into *purging* (more common) and *nonpurging* types. Bulimia is commonly found in families with a history of rigidity, substance abuse, sexual abuse, affective disorder, and obesity. Binge eating often begins after a period of dieting. The course may be chronic or intermittent with remissions, and long-term outcome is unknown. Bulimic individuals, unlike anorexic individuals, have normal or slightly above normal body weight, admit more readily to their behaviors, have more somatic complaints despite being healthier, and are more outgoing and expressive. Psychological features may include depressive disorders, emotional lability, low self-esteem, guilt and shame, negative self-criticism, dissociation during the binge/purge, substance abuse (one third), and personality disorders (one half). Behaviors include the consumption of sweets and

high-calorie foods, eating before and after parties, secrecy and attempts to hide behavior, manipulation of medications, and self-induced vomiting (the most common purge method, i.e., 80%–90%). Other common purge methods include regular use of laxatives, diuretics, diet pills, enemas, and syrup of ipecac. Unusual cases of medically ill patients withholding or abusing medical treatments for the purpose of weight loss have been reported (2).

C. Differential diagnosis.

Psychiatric disorders that may mimic bulimia include anorexia nervosa (binge-eating/purging type), major depression with atypical features, borderline personality disorder, and substance abuse. Mental illness comorbidity is high and can make diagnosis challenging. Neurologic conditions associated with abnormal eating features include Kleine-Levin syndrome, Klüver-Bucy-like syndromes, Parkinson's disease, migraine, temporal lobe epilepsy and other seizure disorders, brain tumors (posterior cranial fossa and pinealoma), post-concussive syndrome, and other conditions with increased intracranial pressure. Other medical entities include gastrointestinal carcinoma, pyloric obstruction, mesenteric artery syndrome, malignant hypertension, digitalis therapy, metabolic alkalosis, opiate withdrawal, and pilocarpine therapy.

D. Symptoms and physical signs.

Careful history for binge eating and compensatory behaviors is necessary. Patients may report abdominal distention and discomfort, constipation, frequent pharyngitis, “heartburn,” hematemesis, post-binge depression, and fluctuation of weight of 10 pounds in a month. Self-induced vomiting frequently results in dental damage with posterior erosion from acidity, caries, and chips. Russell's sign is abrasions and scarring on the dorsum of the hand (typically unilateral and the dominant side) caused by scraping on the teeth. Other findings include bilateral, painless parotid and submandibular gland hypertrophy, abdominal striae, anal tears and fissures, dehydration, electrolyte disturbance, myopathy (especially proximal muscles), cardiomegaly, and arrhythmia. Unlike anorexia patients, who experience amenorrhea, bulimia nervosa patients frequently have oligomenorrhea or irregular menses. Complications of purging can include gastric and esophageal rupture and tears, cathartic colon, aspiration and resulting pneumonitis, cardiac arrest, tonic-clonic seizures, carpopedal spasm, and hypokalemic nephropathy. Psychiatric assessment for comorbid conditions and suicide risk is necessary. Borderline personality disorder is a common comorbid condition that makes treatment difficult; it is characterized by self-destructive behavior, impulsive behavior, and poor interpersonal relationships.

E. Laboratory findings.

Abnormal laboratory findings may include occult blood in the stool, steatorrhea, hypocalcemia or hypomagnesemia, metabolic alkalosis, hypokalemia, impaired renal function, elevated serum amylase due to vomiting (30% of patients) and elevated liver enzymes, particularly aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase. Electrocardiographic abnormalities reflect electrolyte disturbance.

III. Management of eating disorders

A. Medical management.

Treating an individual with an eating disorder can be frustrating and generally requires a collaboration of providers, including any or all of the following: family physician, psychologist, psychiatrist, social worker, and nutritionist. Poorer outcome is associated with a history of sexual abuse, personality disorder, high pretreatment severity, and longer duration of illness. The first priority is to prevent serious complications; hospitalization is required for hemodynamic or metabolic disturbance, medication overdose, suicidal intent, and for the initiation of nutritional restoration. Psychiatric referral can help delineate the need for either outpatient or specialized inpatient care. Referral to a specialized program is prudent for anorexic patients with >25% loss of their previous weight. A nutritionist accesses lifetime dietary history and behavior and the patient's nutritional beliefs and values. Refeeding of the anorexic person begins by increasing the daily caloric intake by 300 calories and reducing activity by 50%. Refeeding syndrome, caused by overaggressive refeeding, results in fluid and electrolyte shifts, hypophosphatemia, congestive heart failure, hyper- and hypoglycemia,

diarrhea, myocardial dysfunction, and neurologic dysfunction, including seizures (3). An energy intake of 1,200 kcal/d is appropriate for the first few days in severely starved, emaciated patients. Weekly weight gain expectations should be between 0.5 and 1.5 kg, depending on the program. Most female adults require 3,000 kcal of energy per day to achieve full weight restoration (2). Total parental nutrition and tube feeding are invasive, remove responsibility from the patient, are often unsuccessful, and should only be used in dire situations. Appropriate eating behaviors include avoiding “dietary foods” aimed at weight loss, eating in company, and developing appropriate responses to both hunger and satiety. Bulimic patients at normal weight need to be educated about normal and relaxed eating behaviors, avoidance of restrictive practices, and tolerance of their body habitus.

Medical management of complications may necessitate hospitalization and referral. Cardiac monitoring of patients with electrolyte abnormalities, surgical consultation in the case of pneumothorax or Boerhaave's syndrome (25% mortality rate), or gastrointestinal specialist referral for cathartic colon, pancreatitis, or metabolic disturbance may be life saving. Pregnant patients have greater stress due to changes in body habitus, are at increased risk of hyperemesis gravidarum, and require close collaboration with an interested obstetrician.

Pharmacotherapy has included prokinetic drugs for delayed gastric emptying, estrogens for osteoporosis, trace minerals and vitamins for nutritional depletion, topical fluoride and sodium bicarbonate rinses for dental erosions, H_2 blockers for gastric reflux and bulk fiber supplements in constipation. Cyproheptadine (Periactin) is a sedating, serotonergic antagonist that may stimulate appetite but is usually not helpful.

B. Psychiatric treatment.

Psychiatric hospitalization is useful if the patient is depressed and suicidal, manifests behavior unresponsive to outpatient therapy, displays psychosis, or a recalcitrant denial in need of confrontation and family therapy. Treatment goals include reduction of weight loss and binge/ purge cycles and addressing unresolved psychological conflicts. Behavioral “prescriptions” and contracts are useful. Formal psychological testing is often performed. Psychotherapy (psychodynamic and cognitive-behavioral) in individual or group settings is essential. Family involvement is almost always needed for assessment and resolution of interpersonal and family conflicts. Aftertreatment plans and relapse prevention plans should be prepared upon discharge. The results of psychopharmacotherapy for anorexia are disappointing. Persons with distorted cognition do not respond to antipsychotic medications, which should be used only for the management of psychosis. Antidepressants, particularly selective serotonin reuptake inhibitors, are the primary therapeutic agents. Tricyclic antidepressants should be avoided in lower weight patients at risk of cardiovascular complications. Selective serotonin reuptake inhibitors with anxiolytic and antiobsessive properties are most useful.

In the absence of electrolyte disorders, bulimic patients are usually treated in an outpatient setting. Bulimic individuals have a better response to drug treatment than anorexic ones. Antidepressants can be helpful in reducing the number of binges, even in the absence of depression. The selective serotonin reuptake inhibitors (fluoxetine, paroxetine, and sertraline) are associated with low risk and low side effects, and are therefore well suited for these patients.

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5.6
SLEEP DISORDERS

Carol Cordy

Daytime fatigue is a common complaint of patients seen in primary care clinics. Primary insomnia is the most common cause of daytime fatigue, although insomnia secondary to other causes must be treated before this diagnosis can be made. Other common sleep disorders include obstructive sleep apnea (OSA), restless legs syndrome (RLS), and delayed and advanced sleep phase syndromes. Less common are narcolepsy, periodic limb movement disorder (PLMD), and sleepwalking and night terrors in young children.

When taking a sleep history, it is important to differentiate between fatigue due to a sleep disorder and sleep deprivation. Patients with sleep deprivation are tired because they stay up too late or are awakened frequently by children, a noisy bed partner, or an uncomfortable sleep environment. Adults need 6–9 hours of sleep nightly. Patients' sleep needs can be determined by allowing them to sleep as long as they can for several nights. The number of hours of sleep a patient needs by the third or fourth night of uninterrupted sleep in order to awaken refreshed is a good measure of that individual's sleep need.

Sleep deprivation, insomnia, and other sleep disorders can decrease a patient's ability to concentrate, cause irritability and depression, and increase traffic and industrial accidents.

I. Primary insomnia

A. Diagnosis

1. The patient usually complains of inadequate or poor-quality sleep secondary to difficulty initiating sleep, maintaining sleep, and/or nonrestful sleep.
2. The associated daytime fatigue causes impairment in daytime functioning.
3. The sleep disturbance is not secondary to another sleep disorder.
4. The sleep disturbance is not secondary to a psychiatric disorder, such as depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post traumatic stress disorder, or a somatoform disorder.
5. The sleep disturbance is not secondary to medications or drugs, such as steroids, antidepressants, decongestants, alcohol, nicotine, or caffeine.
6. The sleep disturbance is not secondary to a medical condition, such as asthma, allergy, pain, chronic obstructive pulmonary disease, congestive heart failure, or gastroesophageal reflux.
7. The sleep disturbance is not secondary to sleep deprivation, a noisy or uncomfortable sleep environment, hot flashes of menopause, poor sleep hygiene, jet lag, or shift work.

B. Diagnostic workup

1. The patient's bed partner can help rule out OSA, RLS, or PLMD.
2. Depression and anxiety inventories (Beck, Jung, and Hamilton) and PRIME-MD can be used to rule out psychiatric disorders.
3. A complete medical and drug history may identify causes of sleep disturbance.
4. Laboratory and imaging studies may rule out medical conditions and can be selected based on the patient's history and physical examination.
5. Unless there is a history suggestive of OSA, RLS, PLMD, or narcolepsy, referral to a sleep disorders clinic for sleep studies is rarely necessary.

C. Treatment

1. If insomnia persists after successful treatment of another sleep disorder, psychiatric disorder or medical condition, and medications and drugs that exacerbate insomnia have been stopped, treatment with behavior therapy and/or medication is appropriate.

2. Acute insomnia (less than 2 weeks) may be treated with proper sleep hygiene and a short course of hypnotic medication to help prevent chronic insomnia.
3. Chronic insomnia (more than 4 weeks) is treated with proper sleep hygiene as well as behavioral therapy and a short course of hypnotic medications.
    a. Proper sleep hygiene (not effective when used alone)
        a. Maintain a regular sleep/wake schedule and avoid daytime naps.
        b. Associate the bedroom with sleep and go to bed only when sleepy.
        c. Make the bedroom environment quiet, dark, and comfortable.
        d. Establish a bedtime ritual.
        e. Avoid caffeine, alcohol, and nicotine.
        f. Avoid heavy meals and do not exercise for at least 3 hours before bedtime.
    b. Behavioral therapies
        a. Stimulus control therapy helps patients associate the bedroom with rapid sleep onset. They leave the bedroom if they are not asleep within 15–30 minutes and return only when sleepy. This is repeated until the patient falls asleep.
        b. Sleep restriction therapy limits the time a patient spends in bed to their reported sleep time or a minimum of 4 hours. This creates a state of sleep deprivation, which promotes more rapid sleep onset and more efficient sleep.
        c. Less effective therapies include relaxation and cognitive therapies.
    c. Medications
        a. Benzodiazepine receptor hypnotics—Short-acting agents cause less daytime drowsiness. Intermediate- and long-acting agents cause less withdrawal and rebound insomnia. Do not use these agents in patients with sleep apnea or substance abuse. Use half doses in the elderly.
            a. Short-acting—triazolam (Halcion) 0.125–0.25 mg hs, oxazepam (Serax) 10–15 mg hs, zaleplon (Sonata) 5–10 mg hs, zolpidem (Ambien) 5–10 mg hs.
            b. Intermediate-acting—estazolam (Prosom) 1–2 mg hs, lorazepam (Ativan) 0.5–2 mg hs, temazepam (Restoril) 7.5–30 mg hs
            c. Long-acting—flurazepam (Dalmane) 15–30 mg hs, quazepam (Doral) 7.5–15 mg hs
        b. Sedating antidepressants are recommended only for patients with comorbid depression. Selective serotonin reuptake inhibitors and tricyclics may exacerbate RLS and PLMD.
            a. Trazodone (Desyrel) 25–100 mg hs may help with antidepressant induced insomnia.
            b. Amitriptyline (Elavil) 10–50 mg hs or doxepin (Sinequan) 25–100 mg hs may help depressed patients with comorbid insomnia. These drugs are contraindicated in the elderly and in patients who abuse drugs and alcohol or are suicidal.
            c. Citalopram (Celexa), mirtazapine (Remeron), nefazodone (Serzone), and paroxetine (Paxil) are less activating than other antidepressants for depressed or anxious patients with comorbid insomnia.
        c. Over-the-counter sleep aids contain diphenhydramine (Benadryl) or doxylamine (Unisom) and are not indicated for the treatment of insomnia.
        d. Melatonin 1–2 mg may help with jet lag, shift work, and delayed sleep phase syndrome, but there is little evidence to support its use in treating insomnia.
        e. Valerian and other herbals also have little evidence to support their use.

II. Obstructive sleep apnea

causes periodic nonbreathing episodes during sleep. It is most common in obese men and can cause hypertension, heart attack, congestive heart failure, and stroke.

A. Diagnosis.

Patients present with a history of loud snoring and may complain of morning headaches, unrefreshing sleep, daytime drowsiness, and waking gasping for breath.

B. Diagnostic workup.

Referral to a sleep disorders clinic is usually necessary.

C. Treatment

1. Patients should stop smoking and should avoid alcohol and sedating medications.
2. Comorbid conditions, including obesity, hypertension, and diabetes, should be treated.
3. Referral to a sleep disorders clinic for nasal continuous positive airway pressure and/or surgery is usually effective. Some patients may require tracheostomy.

III. Restless legs syndrome

causes dysesthesias and motor restlessness. It is usually idiopathic but may be secondary to anemia, uremia, neuropathy, or varicose veins.

A. Diagnosis.

Patients complain of “creepy, crawly” sensations while sitting or lying still.

B. Diagnostic workup.

If medical causes have been ruled out, there is no test for RLS. However, as many patients have comorbid PLMD, sleep studies may be appropriate.

C. Treatment

1. Clonazepam (Klonopin) 0.5–2.0 mg hs, triazolam (Restoril) 15–30 mg hs
2. Carbidopa-levodopa (Sinemet) 25/100 mg hs to twice nightly, pergolide (Permax) 0.25–1.0 mg qd to bid, bromocriptine (Parlodel) 5–10 mg qd to bid
3. Codeine (Tylenol No. 3) 1–2 tablets hs, hydrocodone (Vicodin) 1–2 tablets hs, oxycodone (Percocet) 1–2 tablets hs, propoxyphene (Darvon) 65–130 mg hs

IV. Delayed sleep phase disorder

is common in teenagers and young adults who often feel more awake and productive late at night and compensate for late hours by sleeping in. When school and work obligations interfere, they become sleep deprived. Advanced sleep phase disorder is common in the elderly who fall asleep early and awaken very early. Treatment consists of having the patient go to bed a little earlier (or stay awake a little longer) each night until the sleep pattern normalizes. Delayed sleep phase disorder usually resolves with age.

V. Narcolepsy

causes periods of excessive daytime drowsiness and a tendency to fall asleep at inappropriate times.

A. Diagnosis.

The patient complains of sleep attacks lasting minutes to hours sometimes associated with cataplexy (loss of muscle tone), paralysis, or hypnagogic hallucinations.

B. Diagnostic workup.

Referral to a sleep disorders clinic is usually necessary.

C. Treatment

1. Taking three or four short naps during the day can reduce daytime drowsiness.
2. Daytime drowsiness is treated with dextroamphetamine (Dexedrine) 5–30 mg bid to tid, methylphenidate (Ritalin) 10–30 mg bid to tid 30 minutes before meals, pemoline (Cylert) 37.5–75 mg qd to bid, or modafinil (Provigil) 200–400 mg each morning.
3. Cataplexy, sleep paralysis, and hallucinations are treated with fluoxetine (Prozac) 20–60 mg qd, paroxetine (Paxil) 20–60 mg qd, sertraline (Zoloft) 50–150 mg qd, clomipramine (Anafranil) 75–150 mg qd, imipramine (Tofranil) 75–150 mg qd, nortriptyline (Pamelor) 25–75 mg qd, or protriptyline (Vivactil) 10–40 mg qd.

VI. Periodic limb movement disorder

causes limb jerks that occur every 20–90 seconds for minutes to hours. It may be idiopathic or secondary to metabolic disorders, emphysema, rheumatoid arthritis, neurologic disorders, or medications.

A. Diagnosis.

The diagnosis is usually made by the patient's bed partner. The patient may complain only of daytime drowsiness.

B. Diagnostic workup.

The diagnostic workup may require referral to a sleep disorders clinic.

C. Treatment.

If medical causes have been treated and offending medications have been stopped but the condition persists, clonazepam (Klonopin) 0.5–2 mg hs or temazepam (Restoril) 15–30 mg hs may be helpful.

VII. Sleep terrors

differ from nightmares in that the patient does not remember the frightening dream and cannot be awakened during the terror. Sleep terrors and sleepwalking occur primarily in children. Treatment consists of ensuring the child's safety and reassuring the parents that the condition will resolve by early adolescence.

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5.7

DRUG MISUSE DISORDERS

Lisa Grill Dodson

Drug misuse has long been recognized as a medical and societal problem. These disorders are common, accounting for billions of dollars in medical costs, lost productivity, and years of life lost (1). Physicians are often in a position to first recognize the signs of drug abuse in patients presenting with other common problems. Patients suffering from drug use disorders may present with acute or chronic somatic complaints; psychiatric complaints; legal, occupational, or family problems; or drug-seeking behaviors. Physicians must maintain a high level of suspicion as well as a reasonable armamentarium of screening tools to recognize and treat these disorders. This chapter addresses both illicit and prescription drug abuse. Alcohol, tobacco, and drug abuse and overdosee are addressed separately.

I. Definitions.

Although any use of illicit substances and misuse of prescription or over-the-counter medications can be considered at-risk use, the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (*DSM-IV*) identifies specific diagnostic criteria for substance abuse and dependence. These are similar to the criteria for alcohol abuse and dependence outlined in Chapter 5.3 . Substance abuse is a *maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances* (2). Many substance users do not meet the criteria for either abuse or dependence. It is important to recognize that such labels may be damaging to the patient if incorrectly applied and to be accurate and judicious in the use of these diagnoses.

II. Recognition and screening.

The most important screening tool for the practicing physician is maintaining a high level of suspicion for the presence of drug use and abuse. Substance abuse affects all social and economic groups and ages. Although there are a number of signs and symptoms characteristic of substance

abuse, there is also wide variability in the manifestations of the disorder. In the earlier stages, the symptoms are primarily behavioral and psychological rather than physical. Complaints of depression, irritability, anxiety, paranoia, social withdrawal, poor memory, and poor concentration can be associated with drug use. Insomnia, loss of interest in activities, and marital, legal or occupational difficulties can also signal substance use. Physical health problems may not manifest until late in the disease course. Early recognition and intervention is associated with improved health and social outcomes (3).

A. Screening tools.

There are a variety of screening tools available for use in the office setting. The diagnostic standard for substance abuse is a careful diagnostic interview. Brief alcohol screening instruments, such as the CAGE questions below, can be modified to quickly assess drug use:

- “Have you ever felt that you ought to *c*ut down on your drug use”
- “Have you ever been *a*nnoyed by someone criticizing your drug use”
- “Have you ever felt *g*uilty about your drug use”
- “Do you ever use drugs in the morning as an *'e*ye opener?'”

The advantage of simple screening tools is ease of use and limited time commitment for the busy physician, but there are few data to suggest that these instruments offer advantage over other forms of history taking. One or more positive answers to CAGE or other drug screening questionnaires should prompt additional screening. There are a number of self-administered assessment tools, such as the Drug Abuse Screening Test (DAST), that have been validated for large populations and can be used for further screening. An adolescent-oriented version of DAST is also available. Alternatively, the patient can be referred to a specialist in substance abuse for more in-depth evaluation. Informing the patient of your level of concern about his or her drug use and offering advice regarding the consequences of drug use remains a powerful tool.

B. Laboratory testing.

Urinalysis remains the most commonly used and best validated method of laboratory testing for drugs of abuse. Advantages of urine testing include noninvasive collection of large sample volumes, well-established and cost-effective methodologies, and fairly standard excretion rates across populations. In addition, urine testing has been accepted for legal purposes. However, urine does not provide quantitative measures and is easily adulterated by addition of external substances or forced diuresis and dilution. Blood offers the advantage of quantitative and qualitative measurements but is limited by invasive collection procedures and the limited sample quantities available. Other body substances, including saliva, sweat, meconium, hair, breath, and breast milk, are potentially useful for identification of drug use, but each has advantages and disadvantages (4). Meconium may be of use in determining intrauterine drug exposure in high-risk infants but is not recommended for routine use.

III. Prescription drugs.

Prescription drug abuse, misuse, and diversion is a significant medical and social problem. Street values for commonly prescribed narcotics and other controlled substances is increasing. Fear of being “scammed” or fear of regulatory actions against physicians has had a deleterious impact on treatment of legitimate pain disorders and public confidence. Physicians should be concerned about their role in preventing misuse of prescription drugs. Prescribing practices that can help reduce the potential for misuse include:

- Maintaining high standards for charting, including flow sheets with prescription refills, next refill date, and diagnosis being treated
- Placing strict limits on after-hours prescribing
- Implementing prescription drug contracts with patients
- Exercising caution with brand-name-only narcotic prescriptions (brand name drugs frequently have a higher street value and may offer little or no advantage in efficacy)
- Insisting on obtaining medical records from previous and concurrent providers
- Restricting controlled-substances prescription to one pharmacy per patient
- Being knowledgeable about pharmacology, abuse potential, and drug interactions

- Knowing federal and state statutes regarding controlled substances prescribing
- Carrying out appropriate diagnostic tests
- Consulting with pain or other specialists when appropriate

Physicians can and should prescribe controlled substances appropriately while minimizing the risk of misuse or abuse.

IV. Treatment.

A.

Treatment of substance disorders is difficult and costly. Although full treatment of severe substance abuse may be outside the scope of many primary care physicians, the primary care physician may play a crucial role in assisting the patient in recognizing problems associated with their use and the need for treatment. Brief intervention, a method of short counseling sessions focused on changing a specific behavior, has been shown to be effective in decreasing drug use (3). The components of effective brief intervention include the following:

- Feedback to patient about effects of substance use
- Recommendations for behavioral change
- List of options to achieve behavioral change
- Discussion of patient reaction to feedback and recommendations
- Follow-up to monitor and reinforce behavioral change

B.

The level of intervention and treatment required may exceed the limits of what is possible in the office setting. Referral to inpatient, outpatient, or residential care may be required in advanced cases. Familiarity with the principles of treatment, as well as local resources available, allows the physician to remain involved in patient care and aids in transition following treatment. Characteristics of effective treatment programs include the following:

- An individualized treatment approach
- Treatment of multiple problems, not just drug use
- Adequate duration of treatment
- Use of behavioral methods combined with medication when appropriate
- Identification and treatment of coexisting mental disorders
- Monitoring for potential drug use while in treatment
- Multiple episodes and types of treatment as needed

C

Therapies include cognitive behavioral methods, such as relapse prevention therapy, individualized counseling, and motivational enhancement therapy. Twelve-step abstinence-based programs have been effectively adapted for a variety of substances and behaviors. The type of treatment that will be successful depends on a number of variables, including the motivation for entering treatment, social supports available, substance(s) of abuse, and age and gender. No one approach is universally successful. For example, adolescents, older adults, and pregnant women require substantially different approaches. Newer medications, such as naltrexone, bupropion, and selective serotonin reuptake inhibitors, are showing promise in reducing addictive behaviors when combined with psychosocial and behavioral therapies.

V. Confidentiality.

Federal statutes and regulations and many state laws require strict confidentiality surrounding medical records for drug abuse, screening, assessment, and treatment. Specific authorization for release of information is required; general medical consent is not sufficient.

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VI. DISORDERS OF THE NERVOUS SYSTEM

6.1
MIGRAINE HEADACHES

Anne D. Walling

Migraine syndromes are characterized by 4- to 72-hour episodes of headache plus other specific symptoms. The headache is usually unilateral (commonly around the eye or temple but often with extension to the occiput or neck), moderate to severe, “pulsating” or “throbbing,” and aggravated by activity. Accompanying symptoms and signs must include either nausea (with or without vomiting) or both photophobia and phonophobia for the diagnosis of migraine (1). Subtypes of migraine are based on specific symptom complexes prior to or during the headache, but the general diagnostic and management strategy is common to the entire group. Migraine is probably due to an inherited predisposition in the trigeminovascular system and its serotonin receptors (5-HT1), which can be activated by a variety of factors to precipitate an attack (2). Migraine is more common in women than men and is most prevalent in young adults. The frequency and severity of attacks diminish with age. Migraines may occur regularly with menstruation and commonly disappear during pregnancy.

I. Diagnosis.

Diagnosis is based on a history of typical attacks, from one or two per month to less than one per year, since early adulthood. An aura prior to the attack is useful in diagnosis but occurs in a minority of patients. Physical examination is usually normal and there are no confirmatory laboratory or radiologic tests.

II. Assessment.

A. History.

The key elements are being free of symptoms between attacks, having at least five attacks consistent with migraine without other disease that could explain the symptoms, and onset of attacks in adolescence or young adulthood. In addition to headache and gastrointestinal upset, a wide range of other symptoms may be reported. The severity of the attack may range from a level compatible with normal activities to complete prostration. A subgroup of patients experience specific prodromal features, especially visual symptoms (photopsia, scotoma, or “floaters” in the form of zig-zag lines), changes in mood, or, rarely, neurologic signs. Certain foods, such as red wine, tyramine, nitrites, and monosodium glutamate (MSG), or other factors (e.g., menstruation, relief of stress, tobacco smell, hunger) may precipitate attacks. It is characteristic behavior during the migraine attack to lie still in a dark, quiet room and apply cold or pressure to the painful area. Symptom relief on vomiting and termination of the attack by sleep are common. Most patients have a family history of migraine headache, and many give a personal history of childhood vomiting episodes (especially motion sickness).

B. Physical examination.

Between attacks, no physical abnormality is apparent. A thorough physical examination, with particular attention to the neurologic system, is necessary to eliminate other diagnoses and establish baseline data. During attacks, patients appear distressed, fatigued, and may be vomiting. Prominent, tender blood vessels may be detected on the affected side of the head, but the principal physical signs are in behavior and body positioning. Very dramatic presentations, particularly in new patients claiming allergy to injectable sumatriptan and ergotamine, should raise suspicions of narcotic abuse (also see Chapter 5.7).

C. Laboratory and radiology studies

are not indicated for diagnosis unless the presentation is highly unusual, the first attack occurs at an older age, attacks are associated with neurologic signs or symptoms, or there is a dramatic change in the migraine pattern. The diagnostic testing strategy must be targeted at the most probable alternative diagnosis based on the clinical picture and age of the patient. Investigations are most usually invoked to reassure the patient or the physician, or both.

III. Management principles.

Patients must be encouraged to take control of their migraine management with support from the physician. The goals are to relieve the severity and duration of symptoms, minimize the frequency of attacks, and prevent iatrogenesis, including maladaptive behaviors to this long-term condition. Patients should be encouraged to discover and avoid their own precipitating factors, including techniques for handling fluctuations in stress levels. Pharmacologic treatment strategies must be individualized and should be expected to change over time as the patient's migraine pattern evolves and newer agents become available.

IV. Management of acute migraine attacks.

All agents are most effective if taken early in the migraine process. Gastric stasis and vomiting limit the absorption of the effective dose of oral medication. The multiple migraine treatments may be grouped as follows:

A. Symptom-based treatments.

Analgesics, antiemetics, and sedatives alone or in combination are used to address the specific symptom complex of the patient. Choice of a first-line medication is based on patient experience, predominant symptoms, presence of or vulnerability to other medical conditions (particularly gastrointestinal bleeding), and issues such as cost and compliance. Narcotic medications are usually inappropriate for migraine therapy.

Aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs may all relieve pain, but the effective dose and route of administration must be determined based on experience for each patient. Caffeine is contained in many migraine remedies because it has both a direct effect (as a cerebral vasoconstrictor) and enhances other analgesics. Too much caffeine may prevent sleep and lead to rebound headache.

Antiemetics, often given as suppositories or by injection, may be the only treatment necessary. More commonly, they are combined with analgesics. All are sedating and some have central nervous system (CNS) side effects, such as anxiety. Metoclopramide (Reglan) has the advantage of promoting gastric emptying and enhancing the absorption of aspirin (3).

Sedatives are occasionally prescribed alone, but their major role is in combination medicines. Butabarbital and codeine have potential dangers of abuse in addition to contributing to migraine “hangover.” Butorphanol nasal spray has significant side effects of syncope and nausea and has been implicated in drug misuse.

B. Ergotamines.

These vasoconstricting agents can stop a migraine attack in some patients. Their use is limited by nausea and the danger of rebound headache. They should not be given during pregnancy or when vasoconstriction is contraindicated, as with coronary artery disease, hypertension, and peripheral vascular disease. Many currently available oral and rectal forms are combined with other agents, such as caffeine, pentobarbital, or belladonna. Ergotamines can be administered nasally, orally, sublingually, or rectally. Since the introduction of the triptans, there have been many changes in the commercial availability of the different ergotamines. Injectable dihydroergotamine (DHE 45), 0.5–l.0 mg IM, is highly effective, particularly if preceded by an antiemetic.

C. Triptans (5-HT 1B/1D receptor agonists).

This group includes sumatriptan (Imitrex, 6-mg SC injection; 25- and 50-mg oral tablets, 5- and 20-mg nasal spray), zolmitriptan (Zomig, 2.5- and 5-mg oral tablets), rizatriptan (Maxalt, 5- and 10-mg tablets), and naratriptan (Amerge, 1- and 2.5-mg tablets). The agents vary mainly in bioavailability, speed, and duration of action. They can provide significant relief if taken at any time during an attack but are not recommended during aura. Side effects include nausea, flushing, chest heaviness, and tingling. Because of concerns about hypertension and chest discomfort, medical supervision of the first injection or ingestion is advisable, and triptans are contraindicated in heart disease or in conjunction with ergotamines or monoamine oxidase inhibitors. Migraine may recur within 24 hours in up to 40% of patients (4).

D. A wide range of other agents,

including herbal remedies such as feverfew, have been recommended based on varying degrees of research evidence of efficacy.

V. Preventive therapy.

(5,6). Migraine cannot be completely eliminated. Preventive therapy may assist patients whose lives are disrupted by frequent, severe attacks. Patients seeking preventive therapy must have no contraindications to the specific agent or agents used, be compliant with daily medication, tolerant of drug-related effects, and be prepared to manage “breakthrough” migraines. Treatment may be necessary for several months to assess effectiveness. Many of the commonly recommended agents have not been approved for this indication by the Food and Drug Administration. Choice among the following multiple agents should be based on a realistic balance between benefit and risk for individual patients.

A. ß-Adrenergic blocking agents.

Propranolol (Inderal, 40–320 mg) and other agents that lack intrinsic sympathomimetic activity [nadolol (Corgard), atenolol (Tenormin), timolol (Blocadren), metoprolol (Lopressor)] can reduce the number of attacks in a significant proportion of migraine patients, but the optimum dose for each patient has to be determined by clinical trial. One agent in this class may succeed where another has not provided relief. Wheezing, hypotension, fatigue, and CNS effects may be encountered.

B. Antidepressants.

Certain antidepressants have a specific antimigraine effect, often at lower dosage than that required to treat depression. Amitriptyline (Elavil) is used alone or synergistically with a ß-blocker. The effective dosage may range from 25 to 175 mg daily, but side effects, such as sedation, dry mouth, and weight gain, limit its usefulness. Nortriptyline (Pamelor), 10–100 mg, doxepin (Sinequan), 10–150 mg, and (occasionally) protriptyline (Vivactil), 5–30 mg, are also reported to be useful in selected patients. Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac) and sertraline (Zoloft), have theoretical and anecdotal support as migraine prophylactic agents, particularly in patients who also have chronic tension headaches. Use of the monoamine oxidase inhibitor phenelzine (Nardil), 15–75 mg, is restricted to intractable cases. Its association with side effects, drug interactions, and potential hypertensive crises dictates that phenelzine be used with caution.

C. Nonsteroidal anti-inflammatory drugs.

Naproxen and related agents (Naprosyn, Anaprox), 3–1,100 mg, are used principally to reduce the probability of attacks during highly vulnerable times, as in menstrual migraine. Gastrointestinal bleeding is the major concern, but hepatic and renal problems, rashes, tinnitus, fatigue, and exacerbation of headache are also possible.

D. Calcium channel blockers.

Verapamil (Isoptin, Verelan), 90–240 mg, is the best documented of this group in modifying migraine. Delay in onset of action, constipation, and peripheral edema are possible.

E. Other agents.

Divalproex sodium (Depakote), 250–1,000 mg, and methysergide (Sansert), 2–8 mg, are principally used in research and specialized clinics.

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6.2
NONMIGRAINOUS HEADACHES

John W. Robinson

Headache (HA) is a common patient complaint, accounting for approximately 18 million outpatient visits per year (see Chapter 6.1). About 60% of HAs in men and 40% of HAs in women are nonmigrainous. Their intensity or chronicity may not be an indication of their seriousness. Unfortunately, many HA patients are treated without regard to diagnosis and are simply given pain medications. History is the single most important factor in the diagnosis, but every patient also deserves a careful neurologic examination. Certain signs and symptoms may indicate a serious headache: (a) sudden onset of a new type of headache; (b) progressive worsening of an existing headache; (c) headache accompanied by fever, nausea, and vomiting not attributable to systemic illness; and (d) headache accompanied by new neurologic findings (1). This chapter will discuss common and selected more serious types of HA.

I. General approach to workup of headaches.

A. History.

Ask questions to determine the status of the following factors: onset, location on head, frequency, duration, severity, character (especially throbbing versus constant), aura, associated symptoms, sleep habits, emotional factors, precipitating factors, family history, and past treatments.

B. Physical examination.

Determine the vital signs, condition of the skin, funduscopic status, neurologic status, and check for the presence of sinus tenderness, temporal artery tenderness, and carotid bruits.

C. Laboratory studies.

These are variable, from none to angiography.

II. Types of headaches.

A. Tension-type headaches

1. **Episodic tension headaches.** These are usually managed by the patient with over-the-counter analgesic medicines. If HA is too frequent or constant, see the discussion on chronic HA (Section II.A.2).
   a. **History.** HA pain is pressure and squeezing, which may radiate to the neck and shoulders. It is also called a muscle contraction HA. The HA is constant, usually not throbbing, and either bilateral or unilateral in location.
   b. **Physical examination.** This is usually normal, except for scalp "soreness."
   c. **Laboratory studies.** None.
   d. **Treatment.** Treat with over-the-counter analgesics, but if frequency increases see Section II.A.2.d .
2. **Chronic tension headaches.** These are also called chronic daily HA. Some patients claim that they are never without an HA. With nausea, photophobia, or phonophobia, it is called a daily mixed HA. If the pain is throbbing rather than constant, it is similar to a migraine.
   a. **History.** These HAs occur more than 15 days per month for at least 6 months and persist for 30 minutes to 7 days (2). Clinical characteristics are similar to the episodic tension HA. Family history of HA is common, and patients complain of sleep disturbance, anxiety, and depression. Analgesic overuse, especially aspirin, acetaminophen (Tylenol), and butalbital, may lead to rebound HA, thus continuing the chronic HA pattern.
   b. **Physical examination.** This is usually normal.
   c. **Laboratory studies.** Ordinarily, laboratory studies are not indicated unless initial onset is after age 35, onset occurs during exertion, or other red flag factors exist (see above) (3).
   d. **Treatment.** Withdraw the patient from daily analgesics. Symptoms may take 2 weeks to improve. The main treatment is antidepressants.

Start with amitriptyline (Elavil), 10–25 mg at bedtime, and slowly increase the dose if needed. Fluoxetine (Prozac), 10–20 mg PO daily, is an option. If the HA continues, try ß-blockers (propranolol, 20–40 mg PO tid), anticonvulsants (carbamazepine, 100 mg PO bid), calcium channel blockers (verapamil, 80–120 mg PO tid), or ergot preparations (dihydroergotamine [DHE 45]), 1 mg SC, repeated at 3-hour intervals up to a total of 3 mg, if HAs persist. Avoid use of narcotics.

B. Vascular headaches

1. **Migraine**(see Chapter 6.1)
2. **Cluster.** Cluster HAs are characterized by sudden onset of intolerable HAs that cluster around a period of days, weeks, or months.
   a. **History.** HA is a burning or boring sensation around one eye (always one sided). Duration is 15 minutes to 4 hours, and these HAs may occur several times in the same day (“clusters”). These HA sometimes wake the patient up from sleep. The male-to-female ratio is 5:1. There is no aura and rarely nausea and vomiting. The patient may have remissions (HA-free periods) lasting for months to years.
   b. **Physical examination.** The patient may have flushing of the involved side of the face, miosis, ptosis, conjunctival injection, and nasal congestion.
   c. **Laboratory studies.** These are usually not helpful, but consider tests to rule out glaucoma and vascular abnormalities (e.g., spontaneous dissection of carotid artery).
   d. **Treatment.** Treatment is similar to therapy for migraines except that oxygen (100% at 7 L for 15 minutes) may abort an attack, and prednisone (30 mg daily for 10–14 days) may prevent attacks during a cluster period (4).

1. **Hypertensive headache**(see also Chapter 9.1)
   a. **History.** Throbbing HA occurs, usually bilaterally.
   b. **Physical examination.** often reveals diastolic BP exceeding 120 mm Hg.
   c. **Laboratory studies.** Do a malignant hypertension workup. Consider doing computed tomography (CT) of the head to rule out a cerebral vascular accident.
   d. **Treatment.**Rapidly decrease the high blood pressure within 1 hour to a diastolic blood pressure of about 100 mm Hg. Try oral clonidine (0.2 mg) or intravenous drip of sodium nitroprusside.

C. Traction and inflammatory headaches

1. **Brain tumor**
   a. **History.** There is deep, dull, aching, steady pain, but pain is not excruciating. Initially it is intermittent and usually relieved by over-the-counter analgesics. HA is aggravated by Valsalva's maneuver, and it is worse in the early morning. Nausea and vomiting are variable.
   b. **Physical examination.** Look for localizing neurologic signs and mental changes.
   c. **Diagnostic studies.** Order contrast-enhanced head CT or magnetic resonance imaging (MRI).
   d. **Treatment.** Refer to neurosurgery.
2. **Subarachnoid hemorrhage**(see Chapter 6.6)
   a. **History.** HA is “the worst ever.” Associated symptoms are nausea, vomiting, and decreased mental status.
   b. **Physical examination.** Check for meningismus and focal neurologic signs.
   c. **Laboratory studies.** Order a head CT scan first; if the result is negative, do a lumbar puncture. Xanthochromic cerebrospinal fluid (CSF) indicates subarachnoid hemorrhage. If puncture is positive, then do cerebral angiography to confirm either ruptured aneurysm or arteriovenous malformation.

d. **Treatment.** Mortality is about 50%. Treatment options are to surgically clip the aneurysm, treat the high blood pressure, initiate nimodipine therapy, and give IV volume expansion.

3. **Meningitis**(see Chapter 6.3)
   a. **History.** The patient presents with severe, global, throbbing HA, accompanied by fever, nausea, vomiting, and photophobia.
   b. **Physical examination.** Check for stiff neck, rash, and altered mental status.
   c. **Laboratory studies.** Do lumbar puncture. Order CSF studies. If white blood cell (WBC) count exceeds 100 per high-power field and protein is greater than 45 mg/dL, then meningitis is likely. Culture is confirmatory (but do not withhold treatment while awaiting results).
   d. **Treatment.** Start treatment immediately, even if unable to obtain CSF. Empirical therapy for immunocompetent adult (<50 years) with community-acquired meningitis consists of three drugs: (i) cefotaxime (Claforan), 2 g IV q4–6h *or* ceftriaxone (Rocephin), 2 g IV q12h, plus (ii) dexamethasone 0.4 mg/kg IV q12h × 2d, plus (iii) vancomycin 15 mg/kg IV q6h—high dose (5).
4. **Temporal arteritis**
   a. **History.** The HA is dull, burning, and throbbing; the patient is older than 50 years.
   b. **Physical examination.** Check for tenderness, swelling, and erythema by temporal arteries. Decreased vision may lead to blindness and needs immediate treatment.
   c. **Laboratory studies.** Erythrocyte sedimentation rate is elevated (may exceed 100 mm/hr). Temporal artery biopsy is diagnostic.
   d. **Treatment.** Give prednisone, 40–60 mg PO each day for a month, then continue with several months of a slow tapering dose of prednisone. Recurrence of signs or symptoms or elevation in the erythrocyte sedimentation rate requires an increase in the prednisone dose.

III. Patient resources

a. **A.** National Headache Foundation: http://www.headaches.org/ 1-888-NHF-5552
b. **B.** American Council for Headache Education: http://www.achenet.org/ 1-856-423-0258
c. **C.** Headache Information Network: www.htinet.com/hin

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6.3
MENINGITIS

Navin M. Amin

I. Definition.

Meningitis is acute or subacute inflammation of meninges of the brain or the spinal cord. Acute meningitis (25% of cases) is an infection of less than 24 hours' duration, whereas subacute meningitis (75%) evolves over a period of 24 hours to 7 days. Bacterial meningitis has a mortality of 30%, which has not changed in the last two and a half decades.

II. Etiology of acute meningitis

The most likely pathogens causing acute bacterial meningitis depend on several factors as follows:

A. Patient's age

- 0–5 weeks: Group B streptococci, *Listeria monocytogenes*, Enterobacteriaceae (predominantly *Escherichia coli*), *Enterococcus*
- 5 weeks to 5 months: Group B streptococci, Enterobacteriaceae, *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*
- 5 months to 15 years: *S. pneumoniae, N. meningitidis, H. influenzae*
- 15–55 years: *S. pneumoniae, N. meningitides*
- Greater than 55 years: *S. pneumoniae, N. meningitidis, H. influenzae, L. monocytogenes*, Enterobacteriaceae, and other gram-negative organisms

B. Immunocompromised or neutropenic status.

Causative organisms in this patient group are *Staphylococcus aureus*; gram-negative pathogens, such as *E. coli, Pseudomonas, Serratia*, and fungi such as *Candida* and *Cryptococcus*.

C. With an intracranial shunt.

Patients with an intracranial shunt are likely to be infected with *Staphylococcus epidermidis, S. aureus,* and gram-negative organisms.

III. Etiology of subacute meningitis

A. Mycobacterial causes

include *Mycobacterium tuberculosis* and *M. avium-intracellulare* complex (in HIV patients) (also see Chapter 19.4).

B. Spirochetal organisms

causing subacute meningitis are *Treponema pallidum* and *Borrelia burgdorferi*.

C. Fungal causes

include *Cryptococcus neoformans, Coccidioides immitis*, and *Histoplasma capsulatum*.

D. Viral organisms

causing meningitis include echovirus, Coxsackie virus types A and B, herpesvirus types 1 and 2, *Enterovirus*, mumps, lymphocytic choriomeningitis, Epstein-Barr virus, cytomegalovirus, and arthropod-borne adenovirus.

E. Parasitic organisms

include *Naegleria* and *Angiostrongylus*.

IV. Clinical features

A.

The diagnosis of meningitis should be considered in every patient with fever and meningeal signs and symptoms. In bacterial meningitis, patients may have a precedent upper respiratory tract infection, otitis media, or pneumonia. Meningeal signs and symptoms include the following:

1. Generalized headache (new-onset), nuchal rigidity, vomiting, photophobia, seizures, and changes in mental status, from mild confusion and obtundation to lethargy, drowsiness, and coma, are signs of meningeal infection.
2. In the neonate, fever, decreased appetite, irritability, vomiting, or lassitude should alert the physician to consider meningitis. In the elderly, there may be only fever and a change in mental status.

B.

Clinical examination in acute bacterial meningitis may reveal an ill-looking, toxic, febrile individual with neck rigidity and a positive Kernig's or Brudzinski's sign. There may be impairment of mental faculties or cranial nerve palsies (particularly involving nerves III, IV, VI, and VII). Focal neurologic signs include hemiparesis, monoparesis, or hemianopia with or without papilledema. In subacute meningitis, these classic signs may be absent, and the patient may have fever and altered mental status only. In infections due to *N. meningitidis*, a rapidly developing, purplish skin rash may be seen.

V. Laboratory diagnosis

A. Cerebrospinal fluid (CSF) examination

1. Elevated opening pressure is found in acute bacterial meningitis.
2. Purulent fluid with high polymorphonuclear cell count, increased protein, and low glucose indicates acute bacterial meningitis. Do counterimmunofluorescence/latex agglutination and Gram's stain to identify the organism.

3. Lymphocytic CSF with a normal glucose level is commonly seen in viral meningitis or partially treated pyogenic bacterial meningitis.
4. Lymphocytic CSF with a low glucose level is commonly seen in tuberculosis and fungal meningitis.

B. Other laboratory tests.

Two blood cultures, complete blood count (CBC), serum electrolytes, and radiologic studies of the chest or computed tomography (CT) scanning of the sinuses may be needed in some situations to rule out the primary focus of infection. CT scanning of the brain is essential if there is associated papilledema and before a lumbar puncture is done.

VI. Treatment.

It is of vital importance that empirical antimicrobial therapy is started immediately, preferably within 30 minutes of diagnosis.

A. Empirical antibiotic treatment

1. Neonates (0–1 week) can be treated with ampicillin, 50 mg/kg IV q8h, and gentamicin, 2.5 mg/kg q8–12h, or cefotaxime (Claforan), 50 mg/kg IV q8h, or ceftriaxone (Rocephin), 100 mg/kg IV daily.
2. Children, adolescents, and adults (5 weeks to 55 years) may be treated with one of the following regimens:
   a. Cefotaxime for children: 150 mg per kilogram of body weight IV q6h.
   b. Cefotaxime for adults: 2 g q6h.
   c. Ceftriaxone for children: 100 mg per kilogram of body weight IV once or in two divided doses.
   d. Ceftriaxone for adults: 2 g IV daily.
3. Patients older than 55 years can be treated with ampicillin, 2 g IV q4h, and cefotaxime or ceftriaxone. In patients allergic to penicillin, chloramphenicol, 25 mg per kilogram of body weight IV q6h, or trimethoprim- sulfamethoxazole (Bactrim), 10–15 mg/kg per day in four divided doses with gentamicin, 5 mg/kg per day in three divided doses.

B. Adjunctive therapy.

Corticosteroids, such as dexamethasone, 0.15 mg per kilogram of body weight q6h for 4 days, are recommended for infants and children.

C. Specific therapy.

Once the specific pathogen is identified, specific cost-effective antibiotics should be substituted for empirical therapy.

1. ***S. pneumoniae***. For infection in adults, give penicillin 4 million U IV q4h. Children should receive 30,000 U/kg of body weight in divided doses. Alternatives are chloramphenicol or a third-generation cephalosporin. For penicillin-resistant pneumococci, give cefotaxime or vancomycin, 1 g IV q12h.
2. ***S. aureus***. For adults, give nafcillin, 2 g IV q4h. For children, give 100–300 mg per kilogram of body weight IV in divided doses.
3. ***L. monocytogenes***. Give penicillin or ampicillin plus gentamicin. Alternative therapy is chloramphenicol or trimethoprim-sulfamethoxazole plus gentamicin.
4. ***H. influenzae***. For ß-lactamase-negative infections, give ampicillin; for ß-lactamase-positive infections, give cefotaxime or ceftriaxone.
5. ***N. meningitidis***. Give penicillin or ceftriaxone, cefotaxime, or chloramphenicol.
6. ***E. coli or Enterobacteriaceae***. Give cefotaxime or ceftriaxone plus gentamicin.
7. **Tuberculosis.** Give a combination of isoniazid (INH), rifampin, pyrazinamide, and ethambutol, or streptomycin for 2 months, then INH and rifampin for an additional 7–10 months.
8. **Fungal etiology.** Give amphotericin B, 1 mg per kilogram of body weight IV, and 0.05–0.10 mg intrathecally with or without flucytosine (5-FC, Ancobon), 150 mg per kilogram of body weight daily in divided doses. An alternative is fluconazole (Diflucan), 400–800 mg PO or IV, in *Cryptococcus* or *Coccidioides* meningitis.

D. Duration of therapy.

Treatment of common bacterial meningitis continues for 7 days for *H. influenzae* and *N. meningitis*, 10–14 days for *S. pneumoniae*, 14–21 days for *Listeria* and group B streptococci, and 21 days for gram-negative bacilli (other than *H. influenzae*).

VII. Prevention

A.

Meningococcal meningitis. Contacts should be given rifampin, 600 mg PO q12h for 2 days, or ciprofloxacin, 750 mg PO once.

B.

H. influenzae meningitis. Children younger than 12 months should receive rifampin 20 mg per kilogram of body weight for 4 days.

6.4
SEIZURES

Donald B. Middleton

A seizure is an involuntary, transient, electrical discharge from the brain. Recurrent seizures, usually stereotypic, define epilepsy. A seizure can produce motor (convulsive), sensory, autonomic, cognitive, or combined signs.

I. Clinical presentation.

Generalized seizures abruptly produce alterations in consciousness, whereas partial seizures begin in a particular location and may remain localized (simple) or generalize, or adversely affect consciousness (complex). An inciting event (e.g., watching an electronic game screen), an aura (e.g., a peculiar smell), or a noxious exposure (e.g., trauma or infection) helps to distinguish seizures from nonepileptic paroxysms, such as cardiovascular syncope or hysteria. Interictal apnea, micturition, defecation, tongue biting, or injury is suggestive of seizure activity, as is postictal headache, lethargy, confusion, or Todd's paralysis.

A. Generalized seizures

1. **Tonic-clonic, tonic, or clonic epilepsy (grand mal)** is recurrent sudden loss of consciousness with major motor activity without an aura, but often with an initial cry. Postictal drowsiness is common. The majority of these common seizures are idiopathic, but many are secondary to reversible abnormalities, such as electrolyte imbalance.
2. **Atonic seizures** reflect sudden loss of muscle tone and therefore often result in severe trauma.
3. **Myoclonic seizures** are characterized by repetitive jerks of a single muscle group, usually affecting the trunk or an extremity, usually with preservation of consciousness. Examples are benign myoclonus of infancy and juvenile myoclonic epilepsy, affecting adolescents. Myoclonic seizures occur in syndromes such as infantile spasms, which carries a poor prognosis.
4. **Absence seizures**
   a. Typical spells (**petit mal**) usually last 5–10 seconds, may be accompanied by minor facial twitches or lip smacking, and have no postictal state. Onset is after age 4 years. Most petit mal seizures resolve by early adulthood.
   b. Atypical spells are accompanied by postictal abnormalities and are common in the Lennox-Gastaut syndrome of childhood, associated with developmental delay.
5. **Febrile seizures** may be generalized or focal, affect infants or toddlers, and reflect coexistent infection (see Chapter 4.2). These seizures require no treatment unless multiple or recurrent.
6. **Toxemia of pregnancy** can produce seizures reflective of hypertensive encephalopathy (see Chapter 14.8).
7. **Drug-related seizures** can be due to lowering of the seizure threshold, as with antihistamines or phencyclidine, or withdrawal, as from alcohol or barbiturate (see Chapter 5.7).

B. Partial seizures

are always focal in onset but often spread to become generalized; therefore, a careful history is required to detect an aura in all generalized seizure cases.

1. **Simple spells** do not cause loss of consciousness.
   a. Motor seizures frequently occur with a jacksonian march, aphasia, chewing, or postural change. Todd's paralysis occurring postictally is suggestive of partial seizure.
   b. Sensory spells are visual, auditory, gustatory, somatic, or vertiginous.
   c. Autonomic attacks start with nausea, vomiting, or diaphoresis.
   d. Benign childhood epilepsy occurs primarily during sleep in 4- to 13-year-old subjects and is self-limited. Consciousness is usually preserved.
2. **Complex spells** alter consciousness or cognitive functioning. Patients may develop amnesia, déjà vu or hallucinations. Temporal lobe (psychomotor) epilepsy is distinguished from absence spells by the presence of aura and postictal confusion.

II. Diagnostic evaluation

varies according to clinical presentation, but in general the following tests are helpful:

A. Electroencephalography.

This most useful test is not fully diagnostic in all patients. Hyperventilation, sleep, photic stimulation, ambulatory recordings, or videotaping may enhance accuracy. In absence seizures, generalized 3 per second spike-and-wave patterns help to rule out partial complex seizures, which usually show a focal abnormality on the electroencephalogram.

B. Blood tests.

Serum electrolytes (especially sodium), calcium, magnesium, blood urea nitrogen, glucose, liver function tests [bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamate oxaloacetate transaminase)], complete blood count, and, when indicated, toxin screens and alcohol level are often diagnostic.

C. Imaging studies.

Magnetic resonance imaging (MRI) is the preferred study, but computed tomography (CT) can be done emergently to rule out intracranial hemorrhage or trauma (see Chapter 6.6). Patients older than 60 years and with definite focal neurologic abnormalities are most likely to benefit from scans to eliminate the possibility of brain tumor.

D. Lumbar puncture

is indicated if infection or subarachnoid hemorrhage is suspected.

E. Anticonvulsant levels

are needed when control of seizures is poor, when drug toxicity is suspected, and 2 weeks after drug dosage is changed or potentially cross-reacting drugs are added.

III. Treatment.

Proper classification of the seizure is critical. Eyewitness accounts, history, neurologic assessment, and laboratory data point to the specific therapy most likely to succeed.

A.

Correction of blood chemistry abnormalities and combating inciting agents, such as drugs or infections, is essential.

1. **Hyponatremia.** Seizures or coma occur only if serum sodium is less than 110 mEq/L. Rarely, 3% saline is needed for active convulsions [number of milliequivalents patient's weight (kg) × 0.6 × (desired serum sodium - current serum sodium)]. Slow correction at the rate of 12 mEq/d avoids central pontine myelinolysis.
2. **Hypocalcemia** requires one or two ampules of calcium gluconate (90 mg/ ampule), IV over 5–10 minutes.

B.

Agents for epilepsy control are presented in Table 6.4-1 ; intravenous dosages are given in Section IV.B (1,2). Drugs of choice are listed in Table 6.4-2 .

Drug	Route	Adult (mg) SD	Adult (mg) UDD	Pediatric (mg/kg) SD	Pediatric (mg/kg) UDD	#DD	Therapeutic level (μg/mL)	1/2 T (hr)	Dosage forms (mg)	Seizure type GM	PM	SPS	CPS	MYO	FS	MIX	ADJ only	Special uses
Valproic acid (Depakene)	PO	500	1000–2000	10–15	30–60	2–4	50–120	4–12	250 C 250/5 mL S	x	x	x	x	x	x	x	—	Rectal: dilute 8 1:1 with H_2O; retention enema; 17–20 mg/kg initial, then 10–15 mg/kg, Q8 hr, prn
Divalproex sodium (Depakote)	PO	Same as above		Same as above		2–4	SAME	4–18	125 CSP 125,250,500 TrDR; 500 T (ER)	x	x	x	x	x	x	x	—	
Valproate sodium (Depacon)	IV	Same at ≤20 mg/min		Same at ≤20 mg/min		—	SAME	4–18	100/mL I	x	x	x	x	x	x	x	—	
Carbamazepine (Tegretol, others)	PO	200	400–2,000	5–10	10–30	2–4	4–12	8–17	100 CT 200 T 100/5 mL S 100,200, 400 TrXR) 200,300 CSP	x	—	x	x	—	—	x	—	
Phenytoin (Dilantin, others)	PO IV	200 15–20 mg/kg at ≤50 mg/min (up to 1,500 loading)	200–700	5 15–20 mg/kg at ≤50 mg/min (up to 1,500 loading)	5–15	1–3	10–20	12–48	30,100 CXR) 30,100 C 50/mL I 125/5 mL S 50 CT	x	—	x	x	—	—	x	—	Does not follow linear kinetics; adjust dose in small steps; commonly used for posttraumatic (surgical, etc.) prophylaxis
Fosphenytoin (Cerebyx)	IV, IM	10–20 PE 20 mg/kg at 150 mg/min	4–6	10–20 PE 20 mg/kg at 150 mg/min	4–6	1–3	10–20	12–48	75/mL (2,10 mL VIAL)	x	—	x	x	—	—	x	—	75 mg equivalent to 50 mg phenytoin; loading dose given in phenytoin equivalents (PE); water soluble
Phenobarbital (Luminal, others) (other similar agents include mephobarbital)	PO, IV	60	60–240	4 PO 10–20 IV	4–8	1–3	15–40	40–140	16 C 15/5 mL E 20/5 mL E 30/mL I 60/mL I 65/mL I 130/mL I 120 PI 8,15,16,30, 32,60,65, 100 T	x	—	x	x	—	x	x	—	Use is very limited due to effects on personality
Primidone (Mysoline)	PO	250	250–1,500	10	10–30	3–4	5–12 (primidone)	10–12 (primidone) 40–140 (phenobarbital)	250/5 mL S 50,250 T	x	—	x	x	—	—	—	—	Also can cause behavior change
Clorazepate (Tranxene)	PO	3.75	22.5–60	0.5	0.5–1.0	2–3	1–2	18–36	3.75,7.5, 15 T 11.25,22.5 TrXR)	x	—	x	x	—	—	x	—	For children age 10 yr or older and adults; serum levels usually NOT monitored
Gabapentin (Neurontin)	PO	300	900–3,600	300 mg	900–3,600 mg	3	2 and up	4–10	100,300, 400C 600,800T	x	—	x	x	—	—	x	x	Therapeutic monitoring unnecessary; for children age 12 yr and older and adults
Lamotrigine (Lamictal)	PO	50–100	100–400	0.15–0.6	1–5	1–2	2–4	15–60	25,100,150, 200 T 5,25 CT	x	x	x	x	—	—	x	x	Initial dose lower when on valproic acid; monotherapy for PS; for children age 2 yr and older and adults
Ethosuximide (Zarontin)	PO	500	750–2,000	10–20	10–40	1–2	40–100	30–60	250 C 250/5 mL S	—	x	—	—	x	—	x	—	Useful for akinetic seizures
Methsuximide (Celontin)	PO	300	600–1,200	10	10–25	2–4	10–40	24–50	150,300 C	—	x	—	x	—	—	—	—	Adjunct for CPS
Clonazepam (Klonopin)	PO	1	1.5–20	0.01–0.03	0.05–0.2	2–3	20–80 ng/mL	19–50	0.5,1.2 T	x	x	—	—	x	—	x	—	Useful for akinetic seizures
Felbamate (Felbatol)	PO	400	1,200–4,800	15	15–45	3–4	30–130	15–24	400,600 T 600/mL S	—	—	x	x	—	—	x	x	Dangerous toxicity
Topiramate (Topamax)	PO	50	400–1,600	1–3	5–9	2	Not established	21	15,25 CSP 25,100, 200T	x	—	x	x	—	—	x	x	Age 2 yr and older
Tiagabine (Gabitril)	PO	4	4–56	4 mg	4–32 mg	2–4	Up to 550 ng/mL	7	4,12,16,20T	—	—	x	x	—	—	—	x	Age 12 yr and older
Levetiracetam (Keppra)	PO	500	500–3,000	—	—	2	Not established	6–10	250,500, 750T	—	—	x	x	—	—	—	x	Age 16 yr and older
Oxcarbazepine (Trileptal)	PO	300	600–2,400	8–10	600–1,800 mg	2	Not established	9	150,300, 600T	—	—	x	x	—	—	—	x	Children age 4 to 16 yr and adults (may serve as monotherapy)
Zonisamide (Zonegran)	PO	100	300–600	—	—	1–3	20	50–70	100 C	—	—	x	x	—	—	—	x	Age 16 yr and older
Vigabatrin (Sabril)	PO	—	—	500 mg	2,000–4,000 mg	2	Not established	5–8	500 mg	—	—	—	—	—	—	—	—	For infantile spasms; reported visual loss; rarely used in adults

SD, starting dose; UDD, usual daily dose; #DD, number daily doses; 1/2 T, half-life; GM, grand mal; PM, petit mal; SPS, simple partial seizures; CPS, complex partial seizures; MYO, myoclonic seizures; FS, febrile seizures; MIX, mixed seizure disorder; ADJ, adjunct only; C, capsule; T, tablet; CSP, capsule sprinkles; I, injection; S, syrup; T (DR), tablet (delayed release); CT, chewable tablet; T (XR or ER), tablet (extended release); C (XR), capsule (extended release); E, elixir; PI, powder for injection; PE, phenytoin equivalent.

Table 6.4-1. Drugs for seizures

Type	Seizure	First choice	Alternatives (adjuncts)
Generalized	Grand mal	Valproate Carbamazepine Phenytoin	Primidone, phenobarbital, clonazepam, clorazepate; (gabapentin, lamotrigine, topiramate)
	Petit mal (absence)	Ethosuximide Valproate	Methsuximide, clonazepam; (lamotrigine, acetazolamide)
	Myoclonic	Valproate	Primidone, phenobarbital, clonazepam; (phenytoin, carbamazepine)
Partial	Simple or complex	Carbamazepine	Valproate, phenytoin; (gabapentin, lamotrigine, zonisamide, oxcarbazepine, levetiracetam, tiagabine, topiramate); rarely felbamate, clonazepam, clorazepate
	Febrile seizures	Rectal diazepam	Valproate rectally

Table 6.4-2. Drugs of choice for seizures

C.

Acetazolamide (Diamox), pyridoxine, adrenocorticotropic hormone (ACTH), biotin, or a ketogenic diet is useful under special circumstances.

D.

During pregnancy, the drug that has controlled the seizures should be continued. Folate and vitamin D supplements may reduce birth defects (see Chapter 14.6).

E.

Rectal diazepam or valproic acid are useful to achieve rapid seizure control, even in the home environment, especially for febrile convulsions.

F.

Vagal nerve stimulation can achieve seizure control without drug side effects.

G.

Surgery offers some intractable seizure victims excellent outcomes.

IV. Status epilepticus

is defined as continuous or repetitive convulsions lasting for 30 minutes or more and uninterrupted by consciousness.

A.

Evaluation is done as in Section II, except that lumbar puncture is usually deferred unless bacterial meningitis is suspected.

B.

Treatment includes correction of abnormal findings and administration of the following drugs:

1. Thiamine, 100 mg IV, is given when alcoholism or malnutrition is possible.
2. Dextrose, 25<-50 g IV, is given for adults; 2–4 mL/kg of 25% solution for children.
3. For adults and as a second choice for children phenytoin (Dilantin), 15–20 mg/kg IV infusion, is given at less than 50 mg/min, maximum 1 g in 20 minutes. A therapeutic level of 10–20 μg/mL is attainable within a few minutes. An alternative is fosphenytoin (20 mg/kg) given IV or IM with fewer side effects at 150 mg/min (equivalent to 100 mg/min of phenytoin).
4. If recommendations in Section IV.B.3 are not effective in adults or in children, one of the following two courses is taken:
    a. A benzodiazepine is the drug of choice in children and may be used in adults. Either diazepam (Valium), 0.3 mg/kg IV, maximum 20 mg, or lorazepam (Ativan), 0.1 mg/kg IV, maximum 4 mg, may be given over 2–5 minutes. A repeat dose may be given. If the chosen drug fails, give midazolam (Versed), 0.2 mg/kg IV, at 1 mg/min, followed by a 0.2 mg/kg per hour infusion.
    b. A barbiturate, phenobarbital (Luminal), 10 mg/kg IV, is given over 10 minutes and repeated once if needed. If this drug fails, give pentobarbital (Nembutal), 2–8 mg/kg IV, at 25 mg/min, followed by a 0.5–5.0 mg/kg per hour infusion.
5. Propofol (Diprivan) can be added for continued seizures.

V. Drug side effects.

are common but often controllable with serum levels. Periodic complete blood count and liver function tests are often required.

A.

Phenytoin (Dilantin) can produce stomach upset, rash, gum hyperplasia (preventable with teeth cleaning), ataxia, nystagmus, folate deficiency, drowsiness, hirsutism, sedation, and osteomalacia.

B.

Carbamazepine (Tegretol) can produce rash, sedation, hepatitis, bone marrow suppression, and hyponatremia.

C.

Valproic acid (Depakene) can produce hepatitis, pancreatitis, sedation, hemorrhage, and hair loss.

D.

Benzodiazepines, including oxcarbazepine, can cause sedation and respiratory depression.

E.

Ethosuximide (Zarontin) can cause gastrointestinal upset, ataxia, sedation, hepatitis, and generalized seizures.

F.

Phenobarbital and primidone (Mysoline) can cause sedation, irritability, learning disability, rash, osteomalacia, and anemia.

G.

Gabapentin (Neurontin) can cause sedation, ataxia, and nystagmus.

H.

Lamotrigine (Lamictal) can cause rash, sedation, blurred vision, headache, ataxia, and vomiting.

I.

Topiramate (Topamax) can cause sleepiness, ataxia, psychomotor slowing, and kidney stones.

J.

Tiagabine (Gabitril) can produce dizziness and somnolence.

K.

Levetiracetam (Keppra) can cause dizziness and somnolence.

L.

Zonisamide (Zonegran) can produce ataxia, sleepiness, fatigue, and kidney stones.

VI. Prevention

is aimed at avoidance of head trauma (e.g., with seat belts and bicycle helmets), infection (e.g., vaccines), drug abuse (e.g., drug education), stroke (e.g., blood pressure control), and cancer (e.g., smoking prevention). People with

epilepsy should not swim alone or climb unassisted. Some states require that notification be made to driver's license authorities.

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6.5
TRANSIENT ISCHEMIC ATTACKS

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K. Patricia McGann

I. Definition.

A transient ischemic attack (TIA) is defined as a focal neurologic deficit lasting less than 24 hours. Most TIAs last less than 1 hour, with an average length of 2–15 minutes.

II. Prognosis.

The risk of stroke after TIA is high, estimated to be 8% within the first month, 12% within the first year, and 30% at five years (1). Evaluation and management of TIA is focused on the prevention of these subsequent strokes (see also Chapter 6.6).

III. Pathogenesis.

A TIA results from temporary interruption of cerebral or retinal arterial blood flow. Ischemic events are most common and are usually thromboembolic in origin. Stenotic carotid arteries increase the incidence of occlusion. Atherosclerotic disease leads to abnormal activation of coagulation, fibrin deposition,

formation of platelet thrombi, and ultimately to vessel occlusion. Symptoms depend on the region deprived of blood flow.

IV. Diagnosis.

Immediate history and physical examination should support the acute onset of focal motor or sensory loss, visual disturbance, cognitive change, or disequilibrium. Because symptoms have abated or are resolving upon presentation, diagnosis of TIA is primarily clinical. Conditions that may mimic TIA include complicated migraine, tumor, hypoglycemia, postepileptic paralysis, Bell's palsy, and drug overdose.

V. Evaluation.

Goals are to evaluate for a remediable cause and to assess modifiable risk factors. Immediate evaluation should include complete blood count with platelets, prothrombin and activated partial thromboplastin time, sedimentation rate, syphilis serology, glucose, and electrocardiogram. Further workup for a patient with a solitary event may be safely delayed for a few days if the following conditions are met: initial test results are negative, there is no suspicion of cardiac emboli as a source, and the neurologic deficit has resolved. Patients with multiple recent TIAs or those with symptoms that are increasing in severity (crescendo TIA) should be considered for immediate anticoagulation as they are at greater risk of early stroke.

In spite of their limitations, carotid duplex studies are needed to identify and treat critical stenosis. Cerebral arteriography augments ultrasonography when assessing severe (>70%) stenosis or complete occlusion. It evaluates possible dissection, vasculitis, or aneurysm. Transcranial ultrasonography can reveal information about the medial and posterior circulation, but rarely alters treatment.

Transthoracic or transesophageal echocardiography should be performed in patients with known or suspected arrhythmias or valvular disease. Echocardiography should also be considered in young patients without major risk factors or in whom no identifiable source of TIA has been found. Transesophageal echocardiography supersedes transthoracic echocardiography as the test of choice only when detection of a left atrial thrombus would alter management.

Ambulatory electrocardiographic monitoring is indicated only for patients with suspicious palpitations temporally related to the TIA.

The modifiable risk factors for future stroke (hypertension, diabetes, smoking, cardiac disease, hyperlipidemia, sedentary lifestyle, and heavy alcohol consumption) must be investigated and treatment initiated.

VI. Imaging.

The diagnosis of TIA should be questioned and cranial computed tomography (CT) considered if symptoms have not resolved at the time of evaluation. If symptoms have resolved, a CT is not necessary. Magnetic resonance imaging (MRI) for initial evaluation of TIA is not warranted (2).

VII. Treatment

A. Immediate treatment.

If a cardiogenic TIA is suspected, the patient should be anticoagulated, either as an outpatient or in the hospital, and further evaluation completed immediately. If the TIA is not thought to be cardiogenic and the patient is stable from both a cardiovascular and neurologic standpoint, antiplatelet therapy can be started on an outpatient basis.

B. Risk factor modification.

Aggressive treatment of hypertension is the long-term goal, but caution applies in the acute setting. Patients with significant carotid stenosis may have a hemodynamic basis for the TIA. Lowering the blood pressure too much or too quickly in these patients may precipitate further symptoms. Generally, unless systolic blood pressure is greater than 220 mm Hg or mean arterial pressure is greater than 130, antihypertensive medication should be withheld until definitive evaluation is complete. The long-term goals for hypertension treatment are a systolic of less than 140 and a diastolic of 90 or less (see also Chapter 9.1).

The use of statin drugs to lower cholesterol decreases risk of stroke and total mortality, although the antistroke effects may be separate from the lipid lowering properties.

Alcohol consumption has a J-shaped relationship with stroke risk. Heavy consumption elevates risk for hemorrhagic stroke while light consumption confers a protective effect for ischemic stroke (3) (see also Chapter 5.3).

Physical activity is associated with a reduced risk of ischemic stroke and has a dose-dependent effect. Walking at a pace of 3 or more miles per hour for 4 or more hours per week is associated with significant reduction in the risk of stroke (4).

C. Platelet inhibition and oral anticoagulation.

Every patient having a TIA should receive antiplatelet therapy unless there is a contraindication. Aspirin is the initial recommended choice at a dosage of 50–325 mg/d. Alternative therapies include long-acting dipyridamole and aspirin in combination (Aggrenox), clopidogrel (Plavix), or ticlopidine (Ticlid). Patients with atrial fibrillation should receive long-term anticoagulation with a target international normalization ratio (INR) of 2.0–3.0. Many clinicians alter aspirin dose or change to an alternative therapy for patients who have a TIA on aspirin. Since these patients have a high risk for subsequent stroke, such a change seems logical. It is not evidence based that an increase in aspirin dose is beneficial. There is evidence that the combination of aspirin and long-acting dipyridamole is more effective than aspirin alone.

D. Surgery.

Carotid endarterectomy should be considered for patients with TIA in the carotid distribution who have ipsilateral carotid stenosis determined by arteriography to be 70%–99%. The surgery is not beneficial for those patients with 0%–29% stenosis, and there is uncertainty about the potential benefit of endarterectomy for symptomatic patients with 30%–69% stenosis (5).

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6.6
STROKE

Elise M. Coletta

Stroke is a permanent, focal, nonconvulsive loss of brain or retinal function of vascular origin. It is a major cause of death and disability in the United States.

I. Types of stroke.

A. Ischemic.

Eighty percent of all strokes are ischemic in origin. One third of these are embolic (vessel-to-vessel or cardioembolic). Thrombotic events can involve large or small cerebral vessels. Those involving the small vessels are termed *lacunar events.*

B. Hemorrhagic.

Seventy percent of hemorrhagic events occur in brain tissue (intracerebral hemorrhage). Remaining events occur beneath the arachnoid covering of the brain (subarachnoid hemorrhage).

II. Causes of stroke.

A. Ischemic.

The majority of ischemic stroke events are due to underlying atherosclerosis. Nonatherosclerotic causes (e.g., vasculitis, arterial dissec

tion, antiphospholipid antibodies) should be considered in children, adults younger than 45 years, and individuals without risk factors for atherosclerosis. Atrial fibrillation (AF) is an important cause of cardioembolic stroke (see Chapter 9.5).

B. Hemorrhagic.

Intracerebral hemorrhage (ICH) is most often secondary to underlying hypertension; other important causes include a bleeding disorder, aneurysm, arteriovenous malformation, or tumor. Cerebral amyloid angiopathy should be considered in elders. Seventy to eighty percent of nontraumatic subarachnoid hemorrhages (SAHs) are secondary to aneurysm.

III. Assessment.

The evaluation of a stroke patient should confirm the diagnosis, identify causal or contributing conditions, and identify factors that may affect initial management or the development of complications. Presenting symptoms and signs are useful for determining the location, cause, and type of stroke. The clinical presentation of stroke depends on the vascular distribution affected. The majority of ischemic events occur in the carotid system. Hemorrhage can involve cerebral tissue of more than one vascular distribution.

A. History.

Hemorrhagic and embolic infarctions characteristically develop suddenly. Thrombotic strokes may have a slow or stuttering onset and often develop during sleep. Severe headache, vomiting, mental status change, and nuchal rigidity are more common with hemorrhagic events. The presence of atherosclerotic or cardioembolic disease or risk factors is important.

B. Physical examination.

Anterior circulation signs include amaurosis fugax, aphasia, hemisensory loss, and hemiparesis. Ataxia, binocular blindness, drop attacks, and severe dysarthria are more associated with vertebrobasilar insufficiency.

C. Laboratory assessment

1. **Neuroimaging.** An initial noncontrast computed tomography (CT) scan differentiates between ischemic and hemorrhagic events in 95% of cases (1). A repeat scan 48 hours after an initial negative study often reveals the ischemic defect. If the CT scan result is negative, magnetic resonance imaging (MRI) may be helpful if brain stem infarction or hemorrhage is suspected. Unless clearly related to hypertension, a patient with ICH should be evaluated for an underlying lesion with contrast CT or MRI. Cerebral arteriography definitively diagnoses underlying aneurysm or arteriovenous malformation after ICH or SAH.
2. **Electrocardiography and chest radiography.** Stroke can occur coincident with myocardial infarction (MI). Patients at risk for AF should have cardiac monitoring. A chest radiograph is helpful for evaluation of cardiac status and may reveal an associated aspiration pneumonia.
3. **Blood tests.** Complete blood count (including platelet count), prothrombin and partial thromboplastin time, electrolytes, glucose, blood urea nitrogen, creatinine, cholesterol, and hepatic enzymes are obtained routinely (1). Serial cardiac enzymes should be obtained if an MI is suspected. Arterial blood gas analysis is required if hypoxia is suspected. Patients with a presumed nonatherosclerotic cause of stroke require an erythrocyte sedimentation rate, syphilis serology, drug screen, and evaluation for a prothrombotic state.
4. **Lumbar puncture.** Cerebrospinal fluid (CSF) analysis is indicated if SAH is suspected but not confirmed by CT. Gross blood or xanthochromia and high CSF pressure are seen with SAH. Lumbar puncture is contraindicated for the ICH patient.
5. **Other.** A lateral cervical spine film is necessary for patients with coma of unknown cause and those with neck pain or cervical spine tenderness. An electroencephalogram is useful if seizure is suspected. Duplex carotid imaging can determine the severity and location of carotid atherosclerosis but may not accurately differentiate between vessel occlusion and very-high-grade stenosis. Transthoracic echocardiography is useful in the presence of clinical evidence of heart disease or a high suspicion of cardioembolism.

IV. Acute management of stroke

A. Ischemic

1. **General.** Meticulous supportive treatment positively affects functional recovery from stroke. First, basic cardiopulmonary stability is established. Patients with large infarcts are at risk for the development of cerebral edema and should have restriction of fluids to 1,500 mL/d. Intravenous fluid should be 0.9% saline. Hypoxia is sought, evaluated, and treated, as are hypovolemia, elevated temperature, hypotension, and hyperglycemia. Vital signs and neurologic status are monitored. Prophylaxis against deep venous thrombosis is prudent for all but the most minor cases of stroke.
   a. **Blood pressure.** Acute antihypertensive treatment is not recommended unless mean arterial pressure [sum of systolic blood pressure (SBP) +2 (diastolic blood pressure) ÷ 3] is greater than 130 mm Hg or SBP exceeds 220 mm Hg (1). Lower blood pressure elevations may require treatment in the setting of acute MI, congestive heart failure, acute renal failure, dissection of the thoracic aorta, or ICH. Oral treatment is preferred with agents such as captopril (Capoten). Sublingual nifedipine (Procardia) may precipitously lower blood pressure and increase the neurologic deficit. Parenteral agents include labetalol (Normodyne) and enalapril (Vasotec). The goal of treatment is to reduce mean arterial pressure by 15% in the first 24 hours (see also Chapter 9.1).
   b. **Swallowing and bladder and bowel function.** The initial 25%–45% incidence of dysphagia suggests that NPO ("nothing by mouth") status should be maintained until swallowing is evaluated. Elevating the head of the patient's bed to 20 degrees may prevent aspiration. Urinary retention and incontinence, constipation, fecal impaction, and fecal incontinence can all occur after a stroke and should be sought, evaluated, and treated (2).
   c. **Mobilization.** Daily passive range-of-motion joint exercises should begin promptly, followed by more active exercises. Proper joint positioning is also necessary to prevent contracture. Because early head movement may precipitate neurologic deterioration, bed rest is maintained for 24 hours or until the patient is neurologically stable. Twenty-five percent of stroke patients deteriorate neurologically during the first 2 days. No clinical or laboratory parameter is useful to predict who will progress.
2. **Pharmacology.** Tissue-type plasminogen activator (0.9 mg/kg, maximum 90 mg) is effective in reducing acute ischemic stroke damage in selected patients when administered within a 3-hour symptom window by an experienced clinician (3). However, this is at the expense of a tenfold increase in risk of ICH (3). Heparin (to maintain the partial thromboplastin time between 1.5 and 2.5 times baseline) has proven useful in the management of acute cardioembolic stroke (1). Uncontrolled hypertension or a large infarct is a contraindication to early anticoagulation. No direct data support the use of antiplatelet or anticoagulant medications acutely.

B. Hemorrhagic stroke

1. **General** (see Section IV.A.1). After SAH, careful lowering of blood pressure to prehemorrhage levels is necessary. Aggressive reduction may precipitate cerebral vasospasm.
2. **Pharmacology.** Seizure prophylaxis is commonly used for SAH patients. Prophylactic use of nimodipine (60 mg q4h for 21 days) prevents cerebral vasospasm in SAH patients. SAH patients with cerebral edema are treated with corticosteroids.
3. **Surgery.** The decision to evacuate a hematoma surgically in an ICH patient is individualized. Early surgery has significantly improved outcome only for patients with large cerebellar infarcts or hemorrhages. Patients with SAH should be promptly diagnosed and quickly moved to centers with neurosurgical expertise. The timing of aneurysm surgery depends on multiple factors.

V. Rehabilitation.

The functional approach to care consists of two phases.

A. Acute phase.

Early assessment of functional status (activities of daily living [ADLs], mobility, instrumental ADLs, and psychological and social resources) is necessary to ensure proper identification of all stroke-related disability. Maximal patient outcome is obtained through attention to functional problems along with the more traditional aspects (e.g., pharmacologic therapy) of early stroke care (2). Stroke is an immobilizing illness. Stroke-related disability occurs secondary to the actual neurologic impairment and the development of immobility-related medical complications (e.g., deep venous thrombosis, pressure ulcers). The latter are often preventable with prompt attention to mobilization after a stroke, along with other preventive measures (4). The elderly patient who has had a stroke may develop immobility-related medical problems after as little as 3–5 days of inactivity.

B. Recuperative phase.

Most stroke patients benefit from a formal rehabilitation program. The locale for provision of such services (e.g., hospital rehabilitation unit, skilled nursing facility) is dictated by availability and an assessment of the patient's rehabilitation potential and social supports.

VI. Chronic care of the stroke patient.

Half of stroke patients surviving their initial event are alive 7 years later. Forty percent of these individuals survive with no dysfunction. An equal number have only mild impairment (defined as deficits in two or fewer ADLs).

A. Shoulder pain.

The causes of shoulder pain after stroke include frozen shoulder (adhesive capsulitis), shoulder subluxation, tenosynovitis, subacromial bursitis, rotator cuff injury, brachial plexus traction injury, and reflex sympathetic dystrophy (RSD).

RSD is a poorly understood phenomenon characterized by burning or aching limb pain, hyperesthesia, vasomotor skin changes, and distal extremity edema leading, ultimately, to a contracted and trophic extremity. RSD is treated with range-of-motion exercises and paravertebral sympathetic ganglion block. Proper shoulder positioning and avoidance of arm edema may prevent RSD and other shoulder problems.

B. Depression.

Clinically significant depression occurs in 30%–60% of stroke survivors. This problem may not develop until after acute hospital discharge and can present several years after the neurologic event. Post-stroke depression can be effectively treated through supportive techniques and the judicious use of antidepressant medication (see Chapter 5.2).

C. Sexuality.

Stroke-related impairment, comorbid disease, medication effects, performance anxiety, relationship stress, and other psychological issues may all affect sexual functioning. General education and specific suggestions tailored to the patient's situation can be helpful (see Chapter 5.4).

D. Family issues.

The stroke patient's caregiver and family unit may also show signs of stress and depression. Family adjustment is enhanced through psychological support, proactive education, and the provision of instrumental assistance (e.g., home health aide).

VII. Prevention

A. Primary.

Risk factors for stroke include older age, male sex, hypertension, cigarette use, hyperlipidemia, diabetes mellitus, heavy alcohol use, obesity, inactive lifestyle, AF, atherosclerosis, black race, and oral contraceptive use.

1. **Lifestyle modification.** Treatment of hypertension, increasing physical activity, and cessation of cigarette use reduce the risk of stroke (see Chapter 9.1). Post-myocardial infarction and unstable angina patients with average or high cholesterol levels show a reduction in subsequent stroke rate with statin treatment. In diabetic patients, strict blood pressure control, but not glucose control, has been proven to reduce stroke risk.
2. **Pharmacology.** Aspirin is only effective for patients at high stroke risk. Warfarin (to maintain the international normalized ratio [INR] at 2–3) is effective in patients with AF (see Chapter 9.5). Aspirin (325 mg/d) is more modestly effective but should be used when warfarin is contraindicated and in AF patients at low stroke risk (i.e., those with lone AF).

3. **Surgery.** Asymptomatic, highly selected (i.e., excluding high risk), patients with carotid diameter stenosis greater than 60% have a reduced 5-year stroke rate with carotid endarterectomy (plus 325 mg aspirin per day) when treated in centers with perioperative morbidity and mortality below 3% (5). However, 45% of strokes are attributable to small-vessel or cardioembolic disease in this population, thereby significantly reducing the benefit of surgery (6).

B. Secondary.

Transient ischemic attacks (TIAs) are a major risk factor for subsequent stroke (see Chapter 6.5).

1. **Lifestyle modification.** Based on primary-prevention data, it is believed that control of hypertension and avoidance of cigarettes decreases the recurrence of stroke.
2. **Pharmacology.** Warfarin (to maintain the INR at 2–3) significantly reduces the risk of recurrent cardioembolic stroke in patients with AF (7). Aspirin (325 mg/d) is less effective. No good data support the use of warfarin for symptomatic or asymptomatic patients with large artery stenosis. Aspirin (50–1,300 mg/d) is effective in reducing the recurrence of nonfatal stroke, MI, and vascular death in patients who have suffered a TIA or minor stroke (8). Adding extended release dipyridamole to aspirin therapy reduces the risk of secondary stroke and vascular events. Clopidogrel (75 mg qd), with its better side effect profile, has replaced ticlopidine for patients who are aspirin intolerant or for whom aspirin has failed to provide the needed effect.
3. **Surgery.** After exclusion of high-risk patients and in centers with perioperative stroke and death rates of less than 6%, carotid endarterectomy reduces the risk of subsequent stroke for patients who have had a TIA or minor stroke and have carotid diameter stenosis of 70%–99% (9). However, up to 20% of symptomatic patients with this degree of stenosis will develop a stroke unrelated to underlying carotid disease. Hence, surgery does not eliminate the risk of subsequent stroke (10). The absolute benefit of surgery in patients with moderate (50%–69%) stenosis is relatively small.

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6.7

PARKINSON'S DISEASE

Eduardo C. Gonzalez

I. Overview.

Parkinson's disease (PD) is a chronic progressive neurologic disorder characterized by resting tremor, rigidity, bradykinesia, and postural instability. Pathologically, it is associated with a loss of the dopaminergic substantia nigra resulting in a loss or decrease in dopamine. PD affects more than 500,000 individuals in the United States, with about 50,000 new cases each year. It occurs more commonly in men than in women, and with no racial predilection. The incidence of PD peaks at the age of 60 years. The majority of persons affected with PD die of the same causes as the general population (1,2).

II. Clinical manifestations.

The diagnosis of PD is purely clinical. The classic signs of tremor, rigidity, bradykinesia, and postural instability help to narrow the differential. The presence of two of the four classic signs and a definite response to an adequate dose of levodopa is a very good indicator of PD (2,3).

A. Tremor

is the most common symptom in PD and usually the first observed. The tremor occurs at rest and is most frequently seen in the hands, often involving the thumb and forefinger (pill-rolling tremor). In the initial stages it is usually unilateral, then progresses bilaterally and to other parts of the body, such as legs and eyelids. The tremor disappears with purposeful movement and sleep, and increases with anxiety and when concentrating on a task. Tremor is absent in 10%–15% of individuals with PD. It is often confused with an essential tremor (Table 6.7-1). Of the classic symptoms of PD, it is often the least disabling (2,3).

Characteristic	Parkinsonian tremor	Essential tremor
Family history	Usually negative	Positive in 50%
Age at onset	Mid-adulthood	Any age
Tremor type	Resting	Postural
Body part affected	Hands, legs	Hands, head, voice
Rigidity, bradykinesia	May be present	Never present
Disease course	Progressive	Slowly progressive, long static periods
Alcohol	No effect	Marked reduction
Levodopa	Effective	No effect
Propranolol (Inderal)	May decrease tremor	Effective
Primidone	No effect	Effective

From Hopfensperger K, Koller WC. Recognizing early Parkinson's disease. *Postgrad Med* 1991;90:49, with permission.

Table 6.7-1. Comparison of parkinsonian tremor and essential tremor

B. Rigidity

is a result of an increase in muscle tone of the agonist-antagonist muscles (e.g., triceps fail to relax when biceps flex). Rigidity is more prominent in large joints and, when accompanied with a tremor, is called “cogwheel rigidity” (3).

C. Bradykinesia

is the difficulty in initiation of movement, which results in difficulty in getting out of a chair and initiating gait (shuffling gait), expressionless (masked) facies, drooling (due to reduced ability to swallow), and lack of arm swing when walking (3).

D. Postural instability

is usually a late sign of PD. It is due to flexor muscles being more rigid and resistant to relaxation than extensor muscles and results in patients' walking and standing with trunk bent forward and possibly leaning to one side (3).

E. Changes in speech and handwriting

occur, with speech becoming very soft and monotonous, and written letters becoming progressively smaller(micrographia) (3).

F. Sleep disturbance

has been found to affect 74%–98% of patients with PD. The cause may be related to problems with sleep initiation due to tremors and dystonias (3).

G. Depression

occurs in up to 40% of PD patients, possibly due to the limitations of the disease as well as the disease itself (3). Antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), are most useful due to the low incidence of side effects in the elderly. Use caution when using selegiline and monoamine oxidase inhibitors (MAOIs) with SSRIs (2).

H. Dementia

may occur in up to 30% of PD patients (3).

I. Other clinical findings

commonly seen in PD include orthostatic hypotension, constipation, urge urinary incontinence, sexual dysfunction, dysphasia, pedal edema, seborrheic dermatitis, and eye irritation (due to decreased blinking) (3).

III. Management

A. A general approach to all patients with PD should include both education and a methodical use of medication.

This involves educating both patient and family about the disease, using physical and occupational

therapy to teach skills that will maintain and enhance the patient's ability to continue with activities of daily living (ADLs). With the use of medications, providers should try to avoid prescribing drugs that can exacerbate PD (e.g., neuroleptic agents and certain antiemetics), and initiate any medication in low doses and gradually increase and withdraw as indicated to avoid side effects and acute exacerbations (1,2,4).

B. Drug therapy.

For the patient whose symptoms do not significantly limit ADLs, drug therapy should be initiated with selegiline (Eldepryl), 2.5–5.0 mg PO every day for a week, then 5 mg at breakfast and at lunch. Some studies have suggested that selegiline may slow the rate of symptom development and delay the need for carbidopa-levodopa (2,4). Whether this is through a neuroprotective mechanism or just a function of the medication is still unclear. Other agents should be delayed until symptoms significantly limit the patient's ADLs due to potential tolerance and side effects that may occur.

1. Amantadine (Symmetrel) is best used as a short-term monotherapy for 6–12 months in the early management of mild to moderate PD in patients younger than 60 years who are experiencing akinesia and rigidity; the drug confers less benefit for tremor. Initially, administer 100 mg/d, up to 300 mg/d in twice-daily doses, adjusting the dose for renal-impaired individuals. The risk of cognitive side effects is significant, so it is best reserved for younger patients (1).
2. Anticholinergics are considered for early monotherapy in patients younger than 60 years with tremor-predominant PD who are not significantly disturbed by akinesia (5). Trihexyphenidyl (Artane) is initiated at 0.5–1.0 mg PO bid and increased gradually to a dose of 2–3 mg PO tid. Benztropine (Cogentin) is given in doses 0.5–1.0 mg PO bid. If the patient does not respond to one agent, it is reasonable to try another. Dementia and advanced age are risk factors for adverse effects (1,4).
3. Dopamine agonists are most beneficial when used as monotherapy or as an adjunct to levodopa when levodopa requirements exceed 600 mg/d, instead of increasing levodopa for worsening symptoms. Dopamine agonists are divided into two classes: ergot-derived [bromocriptine (Parlodel) and pergolide (Permax)] and non-ergot-derived [pramipexole (Mirapex) and ropinirole (Requip)]. The two classes differ in their selectivity for dopamine receptors, half-lives, and protein binding (2). Bromocriptine (Parlodel) is initiated at 1.25 mg PO daily and titrated slowly according to the response to a daily level of 10–25 mg. It should be administered three to five times per day. Pergolide (Permax) is initiated at 0.05 mg PO

daily and titrated slowly over several weeks to 2–4 mg/d given tid. Pramipexole (Mirapex) is initiated at 0.125 mg PO tid for one week, and then increased by 0.125 mg weekly to a maximum dose of 3–4 mg/d, or until a therapeutic response is seen or side effects occur (4). Ropinirole (Requip) is initiated at 0.25 mg PO tid and titrated weekly by 0.25–0.50 mg/dose until a therapeutic response is seen or side effects occur. Doses up to 8 mg PO tid have been used. In general, the latter three agents appear to be superior to bromocriptine (Parlodel). With the use of all of the dopamine agonist, one may need to decrease the dosage of levodopa as the dopamine agonist is titrated upward, to reduce dopamine toxicity (4).

4. Catechol-*O*-methyltransferase (COMT) inhibitors are medications that block the breakdown of dopamine by inhibiting the COMT enzyme. These drugs are used only as adjunct therapy to levodopa. Their use may necessitate a reduction of the levodopa dose. They should not be used in combination with MAO inhibitors such as selegiline (Eldepryl). Entacapone (Comtan) is initiated at 200 mg daily taken with the levodopa dose. The dose may be increased to a maximum dose of 8 tablets per day. Tolcapone (Tasmar) is initiated at 100 mg PO tid. It can be titrated to a maintenance therapy range of 300–600 mg daily. Tolcapone has been associated with fulminant liver failure. It should be avoided in patients with liver disease and be discontinued if the patient has no response within 3 weeks. Liver monitoring is recommended at baseline, every 2 weeks for the first year, every 4 weeks for the next 6 months, and every 6 weeks thereafter. Entacapone (Comtan) has not been associated with hepatotoxicity and does not require liver monitoring (1).
5. Levodopa (Sinemet) is the most effective symptomatic drug available for treatment of PD. It should be withheld until significant limitations in ADLs and job performance appear (5). Initiate sustained release carbidopa-levodopa at 25/100 mg or 50/200 mg PO bid, given early morning and early to mid-afternoon, with food to limit nausea. Maintain a relatively low dose of 200–400 mg of levodopa until progressive disabling symptoms require an increase in dosage or dosing frequency. Once a daily dose of 600 mg of levodopa is reached, the addition of a dopamine agonist is favored over further increases in levodopa. If there is a delayed onset of effect or lack of sufficient peak effect, then fast-release carbidopa-levodopa may be added to the regimen. Excessive levodopa most often manifests as dyskinesias and confusion (1).
6. **Surgical intervention.** Several surgical interventions have been studied for the treatment of PD in patients refractory to medical therapy. These include fetal dopamine neuron transplantation in the putamen, thalamotomy, and bilateral posteroventral pallidotomy. Fetal tissue transplantation has shown significant improvement in patients but is still experimental. Thalamotomy and bilateral posteroventral pallidotomy have demonstrated improvement in tremor, and rigidity and tremor, respectively. Thalamic electrical stimulation is also being studied as an alternative to thalamotomy (6).

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6.8
ALZHEIMER'S DISEASE

Gregg Warshaw

Alzheimer's disease (AD) is a progressive dementia. Although it occurs rarely in middle age, the prevalence increases in old age to more than 20% in adults 80 years and older (1). Loss of short-term memory is typical of the clinical syndrome of a progressive dementia. Other symptoms include impaired judgment, mood disorders, loss of insight, aphasia, visual spatial impairment, flattening of affect, and change in personality. The cognitive changes result in a progressive loss of functional ability. As the illness progresses, early symptoms are commonly followed by additional behavioral symptoms (delusions, hallucinations, and agitation) and difficulty swallowing, controlling bladder and bowel functions, and maintaining mobility.

The diagnostic criteria for AD include the following (modified from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition) (2):

- Multiple cognitive deficits become apparent, including memory impairment and aphasia or apraxia or agnosia or disturbance in executive functioning (e.g., planning, organizing, sequencing, abstracting).
- Decline in social or occupational function, or both, occurs.
- Gradual onset and progressive course are seen.
- Other causes are excluded.
- Symptoms exist in the absence of delirium or major depression.

I. Differential diagnosis.

A. Causes

of progressive dementia in older adults include AD (more than 50% of cases), followed by vascular dementia, alcohol-related dementia, dementia with Lewy bodies, Parkinson's disease, Pick's disease (frontal lobe and speech disturbances predominate), and AIDS-related dementia. Extreme caution is required when diagnosing a confused older adult as having a nonreversible dementia. Delirium should always be excluded. There is also a long list of potentially reversible conditions that can present as a chronic deterioration of cognitive function, including adverse effects from medications and alcohol, depression, thyroid disease, hypoxemia, subdural hematoma, normal-pressure hydrocephalus, and intracranial neoplasia (3).

B. Risk factors

for AD include advancing age, family history, and the presence of Down's syndrome. By age 90, about half of the first-degree relatives of AD patients develop a dementia. Recent studies suggest an association between alleles of the apolipoprotein E gene locus on chromosome 19 and increasing risk for late-onset AD (apoE4). ApoE genotyping is not a reliable screening test for the risk of developing AD (4).

II. Evaluation.

A. A thorough patient history

and a careful physical examination (emphasizing the neurologic examination) are essential for determining the possible cause for chronic confusion. The diagnosis of AD is made by exclusion; no clinical feature or commonly available diagnostic test can confirm the diagnosis. The most important historic information is the duration of symptoms. A steady, slow, subtle progression of disease is characteristic of AD, whereas a dramatic clinical course or wide fluctuation in symptoms would not be consistent with AD. Focal neurologic findings, seizures, and gait disturbances are rare features early in the course of AD. Interviewing a family member or friend who is familiar with the patient's symptoms is essential.

B.

It is helpful to use an **objective test for mental status** (5). However, well-educated, intelligent adults can score near normal on a screening test and still have a progressive dementia. A measure of functional capacity should also be obtained from family or friends. When office cognitive testing and

family observations are discordant, more formal neuropsychological testing may be required.

C. Laboratory assessment

should include a complete blood count (CBC), general serum chemistries, thyroid-stimulating hormone, and a vitamin B level. Further testing in individual cases can include a toxicology screen, serologic tests for syphilis and human immunodeficiency virus (HIV) antibodies, a chest film, and a spinal fluid analysis. An electroencephalogram (EEG) is seldom helpful. A computed tomography (CT) scan with contrast is indicated if there is a history of rapid symptom onset (<1 year), sudden deterioration, abnormal neurologic examination, or head trauma. Magnetic resonance imaging (MRI) of the brain seldom adds additional useful information.

III. Management.

A. Specific treatment of memory loss

associated with AD is currently limited to the use of tacrine (Cognex) rivastigmine (Exelon) and donepezil (Aricept), acetylcholine agonists. The frequent daily dosing (qid) and the risk of hepatotoxicity with tacrine has made donepezil [once-daily dosing, no requirement for alanine aminotransferase (ALT) measurement] or rivastigmine the better alternatives. About one third of patients who take donepezil 5–10 mg/d obtain some benefit from this medication. Dramatic responses are rare. Initial dosing is 5 mg/d, and the dose can be raised to 10 mg/d if the side effects are tolerated (e.g., nausea, diarrhea, dizziness, headache, myalgia, and ataxia). Rivastigmine is prescribed at 1.5 bid for two weeks, with slow increases, as tolerated, up to a maximum dose of 6 mg bid. The efficacy of proposed treatments to delay disease progression (e.g., α-tocopherol, selegiline, *Ginkgo biloba*) remains disappointing (6).

B. Chronic management

of AD includes office visits at 4- to 6-month intervals. Each visit should include time with the patient's primary caregiver. Recognition and treatment of coexisting acute and chronic disorders can help maintain optimal function. At each visit, the physician should attend to a careful review of medications that could further impair the patient's function, hearing and vision evaluation and rehabilitation, weight and nutrition, exercise activity, dental care, bladder and bowel continence, fall and accident prevention, and driving safety.

Associated depression can be treated with a low-anticholinergic antidepressant (e.g., desipramine, selected serotonin reuptake inhibitors) (see Chapter 5.2). Anxiety and agitation can usually be managed through environmental adjustments and the avoidance of caffeinated beverages. Benzodiazepines should be used cautiously. Hallucinations or delusions respond to low-dose neuroleptics (e.g., haloperidol, 0.5–3.0 mg/d) or, if extrapyramidal side effects occur, a more expensive atypical neuroleptic can be tried [e.g., risperidone (Risperdal) 0.25–2.0 mg/d]. Insomnia may respond to exercise, avoidance of naps, the addition of night lights, and reassurance. Sundowning (evening agitation) may be amenable to increased lighting, reorientation, or low-dose neuroleptics. All new behavioral problems in AD patients should be evaluated carefully because they may represent the onset of a delirium from a new infection, a drug reaction, or other illness (7).

C. Families and caregivers of AD patients can benefit from regular counseling.

For example, early in the illness, advice about the cause of the cognitive problems, advance directives, and legal and financial planning are helpful. In the middle stages of disease, respite through home care or day care programs, as well as help to recognize anger and guilt in caregivers, can be helpful. In the later stages, patients and families may need advice about nursing homes, planning for terminal care, and planning for the surviving family. Excellent materials describing the impact of AD are available (8). The Alzheimer's Association has local chapters throughout the United States providing information and support (800-272-3900; http://www.alz.org/).

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6.9
PERIPHERAL NEUROPATHY

John M. Wilkinson

Peripheral nerves may be damaged by many different disease processes, toxic insults, and injuries. The long and often vulnerable axons of the peripheral nervous system may contain motor, sensory, and autonomic fibers, alone or in combination. Peripheral neuropathies vary widely in their presentation, depending on the specific fibers involved, as well as on whether the axon itself or only the myelin sheath is affected.

I. Diagnosis.

A. Signs and symptoms.

In the early stages of many peripheral neuropathies, patients may experience only pain or other subjective symptoms; measurable sensory deficits are much less common. Motor dysfunction, if present, may range from mild weakness to complete paralysis, usually more pronounced distally. Decreased tendon stretch reflexes are the earliest objective sign of motor dysfunction; stumbling, tripping, or clumsiness of either hands or feet may also be reported, often out of proportion to the degree of measurable weakness. Autonomic dysfunction is most often associated with diabetes (see Chapter 17.2).

B. Approach to the patient.

If particular symptoms are thought to represent a peripheral neuropathy, the identification of treatable causes or underlying medical conditions, particularly diabetes, alcoholism, and nutritional deficiencies, should be the first priority. Ask about recent viral illnesses or any new medications. Work and hobbies should be reviewed for activities that cause repetitive nerve trauma as well as for any potential toxic exposures. Hereditary neuropathies are not uncommon; in previously unrecognized or longstanding distal neuropathies, a detailed family history is often helpful. Neurologic consultation and electrodiagnostic testing often help to further define the basis for symptoms; nonetheless, it is often not possible to make a specific diagnosis (1,2).

II. Mononeuropathies.

are usually due to entrapment, compression, or other physical injuries of peripheral nerves deep to fibrous bands, where they pass through bony openings or arch across bony prominences. Repetitive work or cumulative trauma may also be implicated. Treatment is generally conservative, including work or activity modification. Surgical exploration should be reserved for more chronic mononeuropathies that have begun to show evidence of weakness or atrophy. **Mononeuropathy multiplex** results from multifocal involve

ment of individual peripheral nerves; the clinical picture is highly variable and potentially confusing. Ischemic diabetic neuropathy, as well as vasculitides and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), accounts for most cases.

A. Trigeminal neuralgia

(tic douloureux) is relatively common and usually idiopathic. It is characterized by brief paroxysmal attacks of severe, lancinating facial pain in the maxillary or mandibular divisions of the trigeminal nerve; the ophthalmic division is rarely involved. Many patients report trigger points sensitive to even mild stimuli, such as chewing, teeth brushing, shaving, or talking. Carbamazepine (Tegretol) 200–300 mg tid is usually effective. Start with 100 mg at bedtime and increase by 100 mg every 1–3 days until symptoms are relieved; some patients may require doses of up to 400 mg tid. Phenytoin (Dilantin), 300–600 mg daily, or baclofen (Lioresal), 5–20 mg tid, may be a useful alternative or, less frequently, an adjunct to carbamazepine.

B. Bell's palsy

(idiopathic facial paralysis), an acute onset of isolated facial nerve paralysis, is common, occurs at any age, and is presumed to be inflammatory. The prognosis, with or without specific treatment, is excellent; almost all patients have spontaneous recovery in 1–3 weeks. However, approximately 15% of patients, particularly those who are older or more severely affected, may show some residual weakness for several months or even permanently. Bilateral Bell's palsy is rare and potentially more worrisome; consider Lyme disease, HIV infection, leukemia, syphilis, infectious mononucleosis, or sarcoidosis (see Chapter 19.3, Chapter 19.4, Chapter 19.5, and Chapter 19.10).

1. **Clinical presentation.** Symptoms typically develop overnight and the patient notices a facial droop on awakening. Many patients recall sitting in a draft or report a recent viral illness. The degree of impairment is widely variable, ranging from mild weakness and a delay in blinking to complete paralysis and inability to close the eye. Forehead muscles are involved in Bell's palsy; frontal sparing indicates a central nervous system (CNS) lesion. Corneal sensation is usually intact. Food may catch in the cheek on the affected side.
2. **Therapy.** Prednisone, 60–80 mg daily, tapered over 10–14 days may be helpful, especially if started within the first 2 or 3 days. Careful eye care is essential; the eye should be kept moist and lubricated with artificial tears or an ophthalmic ointment (Lacrilube). It may also be necessary to protect the eye with a shield or to tape it shut during sleep.

C. Brachial plexus neuropathies

are usually due to blunt or penetrating trauma. Any injury that penetrates the axilla or that forcibly stretches the head and shoulder may result in numbness and paresthesias of the arm and diffuse weakness of the arm and shoulder. Direct extension of apical lung tumors (Pancoast's tumor), or metastatic brachial plexopathy, particularly from breast cancer, is not uncommon. Late-onset impairment caused by radiation therapy may also cause similar symptoms.

D. Carpal tunnel syndrome

(CTS) is the most common of all entrapment neuropathies. Any process that encroaches on the median nerve, either intrinsically or extrinsically, can cause a CTS. CTS is discussed in Chapter 15.5 .

E. Ulnar nerve entrapment

in the ulnar groove or about the cubital tunnel is the most common ulnar neuropathy. Young athletes involved in overhand activities, particularly pitching, as well as patients who lean on their elbows at work or who have had prolonged elbow pressure after coma or general anesthesia are particularly susceptible. Patients experience intermittent paresthesias in the fourth and fifth fingers, as well as the dorsoulnar aspect of the hand and forearm. They may also experience generalized weakness of grasp and clumsiness of the hand and fingers, especially with fine manipulation. The ulnar nerve may also be compressed at the wrist (ulnar tunnel or Guyon's canal syndrome) in individuals with certain occupations or in long-distance bicyclists; motor symptoms are more pronounced, with few, if any, sensory symptoms.

F. Radial nerve injuries

most commonly occur as a result of pressure in the axilla, such as might occur after a drunken sleep with the arm draped over

the back of a chair (Saturday night palsy) or from an ill-fitting crutch. Patients have a wrist-drop and paralysis of the finger extensors; there may also be weakness of extension at the elbow as well as of supination of the forearm. Entrapment of the posterior interosseus nerve (radial tunnel syndrome) at the level of the supinator muscle may be confused with “tennis elbow”; advanced cases show weakness of finger extensors without a wrist-drop.

G. Lumbosacral neuropathies

1. **Meralgia paresthetica** is a compression neuropathy of the lateral femoral cutaneous nerve of the thigh, most commonly seen in obese or diabetic individuals. Patients experience increasingly severe numbness, pain, paresthesias, and decreased sensation of the anterolateral thigh; there is no objective weakness.
2. **Femoral neuropathy** is most commonly due to a diabetic vascular mononeuropathy; it results in weakness of leg extension and paresthesias of the anteromedial thigh and the medial aspect of the lower leg and foot.
3. **Peroneal neuropathy** may be caused by pressure at the level of the fibular head exerted by an ill-fitting cast, trauma, or improperly positioned delivery room stirrups. Diabetic, vasculitic, and hereditary neuropathies may also affect the peroneal nerve, leading to foot-drop and sensory changes of the dorsum of the foot and ankle.
4. **Tibial neuropathy** (tarsal tunnel syndrome) most often is attributable to compression of the tibial nerve in the tarsal tunnel at the medial ankle, resulting in burning and paresthesias of the sole of the foot; this may be aggravated by walking or prolonged standing.

III. Polyneuropathies

are characterized by diffuse, bilateral, usually symmetrical damage, generally producing a distal, stocking or glove pattern of paresthesias and sensory loss, later followed by decreased tendon reflexes and muscle weakness.

A. Diabetic neuropathy

is the most commonly encountered polyneuropathy; some form of neuropathy develops in one third to one half of all diabetics, although it is most often mild and self-limited (also see Chapter 17.2). It usually develops only after many years, although it may occasionally be the presenting feature of diabetes. Rigorous and early glycemic control prevents or delays the development of neuropathy; early recognition of diabetic neuropathy may decrease the incidence of lower extremity complications (3).

1. **Clinical presentation.** Most commonly, diabetic patients experience a distal, symmetrical polyneuropathy with predominantly sensory involvement and only mild motor signs. Initially, the patient may not perceive pain, thus initiating a cascade of events that may ultimately lead to development of diabetic ulcers with the potential for infection or amputation. Later, the patient may also experience severe burning discomfort or dysesthesias, particularly of the plantar surfaces of the feet. Involvement of large myelinated fibers may cause decreased joint position sense, leading to both sensory ataxia and secondary arthropathy (Charcot's joints). Some diabetic patients may have purely autonomic signs and symptoms. Postural hypotension is probably most common, but gastrointestinal (diabetic gastroparesis, intestinal hypomotility, and constipation or diarrhea) and genitourinary (impotence and atonic bladder) symptoms may also occur. Myocardial infarction is commonly silent in diabetic patients because of loss of small pain fibers in the cardiac sympathetic system. Diabetics frequently develop single as well as multiple mononeuropathies; these patients are more prone to both ischemic as well as entrapment neuropathies.
2. **Therapy.** Optimal glycemic control is most important for both prevention and treatment. For pain control, the tricyclics, especially amitriptyline, 10–150 mg at bedtime, may be helpful; either desipramine or nortriptyline, 75–150 mg, may be a useful alternative in patients unable to tolerate amitriptyline. Gabapentin, 300–1,800 mg daily, carbamazepine, or phenytoin may also be used. The mild opioid analgesics, used

judiciously, may also be helpful. Topical capsaicin 0.075% applied once daily may also help relieve diabetic neuropathy (4).

B. Inflammatory neuropathies

1. **Herpes zoster**(shingles) is caused by the reactivation of latent varicella virus in the distribution of the affected nerve (see Chapter 19.8). The characteristic vesicular eruption is unilateral and most often involves a thoracic dermatome. Herpes zoster of the trigeminal nerve usually arises in the ophthalmic division. Vesicles on the tip of the nose may indicate ophthalmic zoster; if there is eye pain, redness, or photophobia, refer the patient to an ophthalmologist. Involvement of the geniculate ganglion of the facial nerve may result in an acute facial nerve paralysis, accompanied by an eruption on the ear and within the ear canal (Ramsay Hunt syndrome). Weakness or paralysis, especially of the facial nerves, or disseminated zoster is more likely to occur in elderly individuals or in patients immunocompromised by HIV or malignancy.

   High-dose acyclovir (Zovirax) 800 mg 5 times daily for 7 days, valacyclovir (Valtrex) 1,000 mg tid, or famciclovir (Famvir) 500 mg tid, also for 7 days, have been shown to decrease both the duration and severity of acute symptoms if started early. Their benefit in preventing postherpetic neuralgia, which may be particularly debilitating in elderly patients, remains equivocal; nonetheless, start treatment within the first 72 hours of symptoms in all patients older than 50 years. There is no good evidence that the addition of corticosteroids is beneficial. For established postherpetic neuralgia, nonspecific measures, including treatment with carbamazepine, phenytoin, tricyclic antidepressants, gabapentin, topical capsaicin 0.075%, or topical lidocaine 5% have all been recommended. There is no good evidence for the efficacy of corticosteroids (5).

2. **Lyme disease.** Bell's palsy, which may be bilateral, or a polyradiculopathy may be seen in the early disseminated phase of Lyme disease (see Chapter 19.9).
3. **Leprosy.** Despite its low incidence in the United States, leprosy remains the most common cause of treatable peripheral neuropathy in the world. Leprosy must be included in the differential diagnosis whenever a patient from a high-risk group presents with a peripheral neuropathy. As leprosy and its attendant skin lesions progress, increasing anesthesia, with the potential for breakdown and injury, occurs in the lesions. Some degree of sensory loss is always present in leprosy; it is not unusual for symptoms of neuropathy to occur long before other manifestations of the disease.
4. **Acute inflammatory demyelinating polyradiculopathy** (AIDP) or **Guillain-Barré syndrome** (GBS). GBS is a syndrome of symmetrical, rapidly progressive, ascending muscle weakness with decreased or absent tendon stretch reflexes; it is an uncommon sequel to several common infections. *Campylobacter jejuni* gastroenteritis is most frequently the antecedent infection; various viral illnesses may also trigger GBS. Early confirmation of *C. jejuni* infection, as well as the measurement of antiganglioside antibodies, will guide treatment decisions and has important prognostic value. All patients should be hospitalized to carefully monitor their respiratory status and ability to handle secretions, for neurologic consultation and testing, and to initiate either plasmapheresis or immunoglobulin therapy. Although more rapid progression of muscle weakness or evidence of axonal involvement is worrisome, the overall prognosis is excellent, with most patients making a full recovery (6).
5. **CIDP.** This disorder is a relatively common neuropathy that often goes unrecognized. Clinical and electrophysiologic diagnostic criteria have been established, allowing clinicians to distinguish CIDP from other acquired neuropathies. The usual clinical picture is of a predominantly motor neuropathy with an elevated CSF protein value. Specific, highly effective immunotherapies are available for CIDP; therefore, it is im

portant that this disorder be carefully distinguished from the hereditary neuropathies.

6. **HIV** (see Chapter 19.4). The initial presentation of HIV infection may be as GBS or CIDP; HIV testing is indicated in these patients. In later stages, secondary opportunistic infections of the peripheral nervous system, primarily by herpes zoster or cytomegalovirus, may occur. Patients withlate-stage HIV infection may have a particularly painful neuropathy.

C. Nutritional neuropathies

are all related to B-vitamin deficiencies. These generally occur in combination with one another, primarily in chronic alcoholics. Patients with anorexia or bulimia, patients with malabsorption, and food faddists may also experience B-vitamin deficiencies. A symmetrical distal polyneuropathy is common to all the nutritional neuropathies.

1. **Alcoholic neuropathy** is clinically indistinguishable from nutritional neuropathies due to vitamin deficiencies. In a few alcoholic patients, a neuropathy may occur despite an adequate diet. The prognosis for ultimate, but slow, recovery is good for patients who are able to stop drinking and resume a proper diet with multivitamin supplements (see Chapter 5.3).
2. **Vitamin B_1 (thiamine) deficiency**, or beriberi, most commonly occurs in chronic alcoholics. Although its primary form is a Wernicke-Korsakoff encephalopathy, a typical distal polyneuropathy may also occur. Both entities are treated with IM injection of thiamine 100 mg every 12 hours the first day, followed by 100 mg daily PO.
3. **Vitamin B_6 (pyridoxine) deficiency** is caused by certain drugs that interfere with pyridoxine metabolism, notably isoniazid and dapsone. Inasmuch as they are used in the treatment of leprosy, which in itself causes a sensory neuropathy, the clinical picture is potentially confusing. Pyridoxine supplements, 50 mg tid, may prevent this complication. However, excessive amounts of pyridoxine (>500 mg daily) may also cause a severe sensory neuropathy.
4. **Vitamin B_{12}deficiency** may present initially with only vague paresthesias without objective signs. Because hematologic abnormalities may not be apparent until the neurologic complications have become irreversible, it is important to measure serum vitamin B_{12} levels in patients being evaluated for distal polyneuropathies.

D. Toxic neuropathies

develop over several weeks to months as a result of continued exposure to certain drugs, industrial toxins, or heavy metals. A progressive, symmetrical, ascending polyneuropathy is most frequently seen with occupational exposures. The most commonly implicated drugs include anticancer agents, particularly cisplatin and vinca alkaloids, as well as isoniazid, dapsone, and amiodarone. Rare incidents of arsenic poisoning, either intentional or resulting from insecticide exposure, may cause a late-onset progressive polyneuropathy. Chronic lead exposure causes a predominantly motor neuropathy, typically beginning in the upper limbs, with an asymmetrical radial neuropathy and wrist-drop. A toxic neuropathy often improves gradually when the exposure is discontinued, if not immediately, then within several weeks. A neuropathy that continues to progress must be due to some other cause; this point has important medicolegal implications in the evaluation of neuropathies that are thought or claimed to be occupationally related. Fluctuating symptoms may be due to intermittent exposures.

E. Hereditary neuropathies,

generally showing a slowly progressive and indolent course, are more common than has been previously recognized. They are typically associated with high-arched feet (pes cavus) and hammertoe deformity, as well as slowly progressive weakness and wasting of peroneal muscle groups. There is no specific treatment for any of these disorders; the ultimate prognosis is fairly good, with a manageable degree of disability.

F. Miscellaneous.

Patients with peripheral neuropathies are occasionally found to have one of the dysproteinemias, most often monoclonal gammopathy of unknown significance; multiple myeloma only rarely causes a polyneuropathy.

Monoclonal proteins may be detected by serum protein electrophoresis; plasma exchange may be an effective therapy. Patients with distant, often occult, malignancy may present with a carcinomatous peripheral neuropathy, predominantly associated with small-cell tumors of the lung. Antineuronal nuclear antibodies may serve as useful serologic markers of these paraneoplastic syndromes, preceding detection of cancer by months or even years.

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VII. EYE PROBLEMS

7.1
CONJUNCTIVITIS AND OTHER CAUSES OF A RED EYE

John E. Sutherland

Richard C. Mauer

The most common causes of "red eye"—conjunctivitis, trauma, allergies, subconjunctival hemorrhage, and lid problems—are usually benign. However, some conditions presenting with a red eye require urgent evaluation and treatment. These include keratitis, episcleritis, scleritis, uveitis, orbital cellulitis, and acute angle-closure glaucoma. Symptoms requiring immediate referral to an ophthalmologist are pain, proptosis, perilimbal injection, photophobia, tenderness, and decreased vision.

I. Infectious conjunctivitis (bacterial or viral) is the most common cause of red eye.

A. Diagnosis.

Bacterial conjunctivitis presents with burning, irritation, and a purulent discharge that usually becomes bilateral within 2 days. *Viral conjunctivitis* discharge shows a more watery discharge and burning or gritty sensation and is often epidemic. *Chlamydial conjunctivitis,* more common in younger patients, shows a mucopurulent discharge, often is associated with urethritis or vaginitis, and tends to be subacute.

1. **Laboratory studies.** Immunofluorescent tests on ocular scrapings for *Chlamydia trachomatis* and culture for *Neisseria gonorrhoeae* are required. Bacterial cultures should be obtained in neonates and patients who have severe inflammation or chronic or recurrent conjunctivitis. Results most commonly reveal *Staphylococcus epidermidis, Staphylococcus aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae.* Viral studies are rarely performed. Urethral or cervical cultures may be indicated.
2. **Physical findings.** Vision should be recorded and is normal unless the cornea is involved with keratitis. Hyperemia is highly diffuse. Staining of the cornea with fluorescein should be performed, using topical anesthetic drops, cobalt blue filter, sterile irrigation fluid, and magnification with an ophthalmoscope or slit lamp. The cornea should be examined for a poor surface light reflex, infiltrate, ulcer, or ciliary or perilimbal injection. The presence of small papillae is common with viruses, and lid vesicles suggest herpesvirus infection. In herpes simplex, corneal involvement is usually dendritic (1,2).

B. Treatment

1. **Bacterial conjunctivitis (topical).** Antibiotic drops or ointment are given every 2–4 hours. It is best to choose an antibiotic with adequate gram-positive coverage. Choices include tetracycline (Achromycin), bacitracin, ciprofloxacin (Ciloxan), ofloxacin (Ocuflox), chloramphenicol (Chloroptic, Ophthochlor), sulfacetamide (Bleph-10, Sulf-10, Isopto Cetamide, Sodium Sulamyd), gentamicin (Garamycin), tobramycin (Tobrex), and erythromycin (Ilotycin, Ak-Mycin), or combinations, such as neomycin- polymyxin B-bacitracin (Neosporin), trimethoprim- polymyxin B (Polytrim), and polymyxin B-bacitracin (Polysporin). Neomycin preparations are more likely to invoke a hypersensitivity reaction.
2. **Bacterial conjunctivitis (systemic)**
   a. ***H. influenzae***. Topical and systemic treatment is needed because of the risk of meningitis. Trimethoprim-polymyxin or quinolone eye drops are used for topical therapy. Systemic therapy choices are amoxicillin-clavulanate (Augmentin) or rifampin (Rifadin), or both.
   b. ***N. gonorrhoeae*** in adults. Ceftriaxone (Rocephin), 1 g IM or IV one time and frequent topical saline irrigation in endemic areas of penicillin-resistant gonorrhea are used, or penicillin G, 10 million U daily for 5 days, with frequent topical irrigation in nonendemic areas. In penicillin-allergic patients, ciprofloxacin, 500 mg PO single

dose, or ofloxacin, 400 mg PO single dose, may be given (see also Chapter 19.6).

c. **Chlamydial follicular inclusion and chronic bacterial conjunctivitis.** This is usually treated with oral tetracycline or erythromycin, 250–500 mg qid, or doxycycline, 100 mg bid, or clarithromycin, 250–500 mg bid for 3 weeks (2,3) (see also Chapter 19.7).

3. **Viral conjunctivitis (systemic and topical)**
   a. **Adenoviral conjunctivitis.** This is extremely contagious for up to 14 days and may not resolve for up to 3 weeks. Treatment is supportive and includes ice-cold compresses, artificial tears, and naphazoline (Albalon, AK-Con, Vasocon, Naphcon) or naphazoline-pheniramine (Naphcon-A) qid if itching is severe.
   b. **Herpes zoster.** Referral is indicated for corneal involvement. If the trigeminal nerve is involved, treat with oral acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex) for 7 days.
   c. **Acute hemorrhagic.** This is caused by an enterovirus or coxsackievirus, both highly contagious and epidemic but self-limited. Treatment is supportive.
   d. **Molluscum contagiosum.** Removal of the central core of the lesion present on the eyelid is sufficient to cure the conjunctivitis.
   e. **Others.** Infectious mononucleosis, influenza, Lyme disease, cat-scratch fever, mumps, rubella, pharyngoconjunctival fever, and vaccinia viruses may be etiologic agents, and these are all treated supportively (2).

II. Neonatal conjunctivitis.

It is imperative to make a specific etiologic diagnosis. Chemical irritation presents within 24 hours and most commonly is caused by prophylactic erythromycin, tetracycline, or silver nitrate. Chlamydial, gonococcal, and other bacterial infections are next, in that order. The presence of herpes simplex type 2 infection requires consultation (4).

A. Diagnosis.

A detailed maternal history is important. Physical examination should assess for systemic illness.

B. Laboratory studies.

Gram's stain, Giemsa stain, immunofluorescent antigen detection, Papanicolaou's stain, and specific cultures may be necessary.

C. Treatment.

Topical therapy includes gentamicin for gram-negative and erythromycin for gram-positive organisms. Pseudomonal infection requires consultation. Systemic therapy for chlamydial infection is erythromycin syrup, 50 mg/kg per day qid for 14 days. For gonococcal infections, use ceftriaxone (Rocephin), 25–50 mg/kg qd IV or aqueous penicillin G 100,000 U/kg qd × 7 days. Supportive treatment only is needed for chemical conjunctivitis.

III. Allergic conjunctivitis.

Acute allergic conjunctivitis (AAC) is a common immediate hypersensitivity reaction. Vernal and atopic keratoconjunctivitis are more severe and may lead to sequelae.

A. Diagnosis

1. **History.** AAC is characterized by bilateral itching, tearing, and mild eyelid swelling. *Vernal keratoconjunctivitis* occurs in children and adolescents with more severe symptoms, including photophobia. This is most frequently seasonal and associated with other hay fever symptoms (see also Chapter 8.6) Atopic keratoconjunctivitis is associated with dermatitis and cataracts.
2. **Physical findings.** A stringy discharge, mild redness, and edema occur in hay fever, whereas in atopic disease corneal involvement and blepharitis are common. Giant papillae are found on the conjunctiva in the vernal disorder and in contact lens-associated conjunctivitis.

B. Treatment

1. **Vasoconstrictors and pheniramine.** These topical agents are instilled once daily. The combination of naphazoline and pheniramine (Naphcon-A) is more effective than a drug of either category alone, as is the new antihistamine, levocabastine (Livostin) qid or olopatadine (Patanol) 0.1% bid.

2. **Mast cell stabilizers.** Lodoxamide 0.1% (Alomide) qid, nedocromil 2% (Alocril) bid, or cromolyn 4% (Crolom) qid are effective in treatment during peak exposure. Ketotifen 0.025% (Zaditor) bid is a combination H_1 antagonist and mast cell stabilizer.
3. **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Ketorolac 0.5% (Acular) or diclofenac (Voltaren) qid may be effective.
4. **Corticosteroids.** Prednisolone (Pred Forte, Ak-Pred, Pred Mild), dexamethasone (Decadron, Maxidex, Ak-Dex), fluorometholone (FML or Flarex), loteprednol (Alrex, Lotemax), or rimexolone (Vexol) 2–4 times per day is highly effective. Corticosteroids may cause cataracts or glaucoma with long-term use and should be administered under the direction of an ophthalmologist.

C. Nonpharmacologic treatment.

Cold compresses, saline irrigation, and ocular lubricants 4–8 times daily may provide relief. Elimination or reduction of the allergen exposure should be attempted. In severe cases, desensitization or systemic steroids, or both, may be needed (2,3,5).

IV. Keratitis

A. Diagnosis.

Keratitis presents with decreased vision, pain, tearing, and photophobia.

1. **Laboratory studies.** With a break in the corneal epithelium, corneal cultures are taken. *Staphylococcus aureus*, *Pseudomonas*, and *Klebsiella* are the most common organisms found, but gonococci may be seen and may perforate the cornea within 24 hours. Discharge is usually yellow to green.
2. **Corneoscleral.** Visual acuity is often decreased. A red flag is perilimbal injection or redness at the cornea scleral limbus. In *immunologic keratitis*, there are less intense symptoms, but there may be associated blepharitis. *Herpes simplex keratitis* presents with moderate eye pain, watery discharge, slightly decreased visual acuity, and a dendritic staining pattern to the cornea.

B. Treatment.

Keratitis is a potentially serious vision-threatening inflammation. Immediate referral to an ophthalmologist is imperative (1,6). Antiviral therapy with trifluridine (Viroptic, 1% drops) or vidarabine (Vira-A, 3% ointment) is available.

V. Episcleritis.

Episcleritis is a common, nonserious, non-vision-threatening inflammation of the synovial membrane covering the eye. It is usually attributed to engorgement of the episcleral vessels.

A. Diagnosis.

Diagnosis often must be made at the slit lamp. Episcleritis usually presents with mild or minimal ocular discomfort and usually is unilateral without discharge.

1. **Laboratory studies.** Usually no tests are needed.
2. **Physical findings.** Fiery red inflammation of the episcleral tissue with tenderness is a common finding. Neo-Synephrine 10% used topically blanches the vessels and renders the eye white. The injection is mobile with finger manipulation, with only minimal tenderness and no discharge. Visual acuity is usually unaffected. Nodular episcleritis, with only a focus of inflammation, may last for 2 weeks to 2 months.

B. Treatment.

Usually no treatment is needed to resolve this condition, unless there is ocular irritation. Oral NSAIDs can also be used as initial therapy. Artificial tears, topical vasoconstrictor-antihistamines, or mild steroids may be used for 2 weeks. Referral to an ophthalmologist may be required to rule out uveitis.

VI. Scleritis.

Scleritis is a destructive inflammatory process involving the outer scleral wall, with severe systemic and visual consequences often following. Forty percent of patients have some immunologic disorder diagnosed during workup. Scleritis may lead to globe perforation or loss of function of an eye.

A. Diagnosis.

Scleritis usually presents as a slowly progressive unilateral ocular pain with injection, which can become very severe and debilitating. No discharge is seen, and tearing is prominent.

1. **Laboratory studies.** A thorough evaluation is necessary because there is a high frequency of associated rheumatologic disorders. Workup should

include a complete blood count (CBC), sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, serologic testing for syphilis, and radiographic examination to rule out ankylosing spondylitis.

2. **Physical findings.** Tenderness of the globe is very common. Inflammation can be diffuse, nodular, or necrotizing, quite intense with a very injected scleral surface ranging from fiery red to violaceous blue. Neo-Synephrine 10% does not blanch the vessels.

B. Treatment.

Therapy with NSAIDs, immunosuppressive agents, or massive oral or IV corticosteroids is required. The best course is referral to an ophthalmologist (2,6).

VII. Acute angle-closure glaucoma.

Acute angle-closure glaucoma presents as an acute, usually unilateral perilimbal injection, with moderate to severe eye pain, nausea, decreased vision, and often a fixed mid-dilated pupil (see Chapter 7.2).

VIII. Uveitis.

Uveitis can be localized to the anterior or posterior segments of the eye, but in severe cases it presents as a panophthalmitis. It is typically thought of as an immune disorder. Treatment is urgent because severe consequences, such as anterior-angle scarring with glaucoma, may result.

A. Diagnosis.

Acute anterior uveitis usually presents over 1–3 days of increasing, usually unilateral, ocular pain with mildly decreased vision in the early stages and severe visual consequences in more advanced disorders. Photophobia is usually the most prominent symptom associated with this condition.

1. **Laboratory studies.** A workup is usually not necessary, and the results are often negative. If repeated episodes occur, a systemic workup similar to that for scleritis should be done.
2. **Physical findings.** The redness is in the perilimbal area, which is immediately around the cornea. Tearing is present without discharge. The eye is usually moderately tender to palpation. A sluggish, miotic pupil is invariably present.

B. Treatment.

Referral to an ophthalmologist results in treatment with topical, and occasionally systemic, corticosteroids, as well as cycloplegics (1,2,6,7).

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7.2

EYE PROBLEMS OF AGING: CATARACTS, GLAUCOMA, AND MACULAR DEGENERATION

Jon O. Neher

Vision problems are common in the elderly, and more than 90% of the community-dwelling elderly wear eyeglasses. Readily correctable refractive errors, such as progressive farsightedness (presbyopia), are an important source of visual impairment. However, more severe forms of visual loss in the elderly are usually the result of longstanding

diabetes or age-associated eye diseases: cataracts, chronic open-angle glaucoma, and macular degeneration (1). Vision loss is associated with decreased longevity, decreased mobility, and increased falls with injury (2). Complaints about vision should always prompt a focused history, a thorough examination of the eyes (including lids, conjunctiva, cornea, anterior chamber, iris, lens, and optic fundus), and testing of visual acuity with either a Snellen chart or a Rosenbaum pocket vision screener. This evaluation is usually sufficient to allow the family physician to arrive at a presumptive diagnosis and determine a proper disposition.

I. Cataracts

A. Presentation.

Small opacifications in the lens of the eye are clinically insignificant. More extensive opacification produces gradual, painless visual loss over months to years. The degree of visual loss depends on both the density and the location of the cataract. Frequently, patients complain of glare or halos from bright lights before becoming concerned about worsening acuity. Problems with far vision are more common than complaints about near vision. Monocular diplopia, though rare, has been described.

B. Evaluation.

Physical examination demonstrates some loss of ability to clearly visualize the macula with direct ophthalmoscopy. Denser cataracts lend a brown or milky discoloration to the lens and are easily seen by looking into the pupil while shining an ophthalmoscope into the eye at an oblique angle. Visual acuity testing results are variable but are reduced for denser cataracts and for those nearer the center of the lens. Incidental cataracts are a common finding because only half of patients with cataracts on examination complain of vision problems.

C. Management

1. **Referral.** Patients who have limited their nighttime activities, complain of halos around bright lights, or have reduced visual acuity should be referred to an ophthalmologist for evaluation. In general, asymptomatic lens opacification does not require referral.
2. **Surgery and postsurgical care.** The definitive treatment for cataracts is surgery. However, surgery is delayed until the patient's visual impairment causes a significant restriction of daily activities. Earlier surgery is indicated only if other eye pathology, especially glaucoma or macular degeneration, is present or suspected. During surgery, the natural lens is removed and replaced with a prosthetic lens. Usually the posterior capsule of the natural lens is left in place to support the prosthesis. This native tissue may eventually opacify (50% of treated eyes at 3–5 years) and produce a secondary reduction of vision. Laser surgery is generally sufficient to remove the offending tissue from the visual axis and is well tolerated.
3. **Medical management.** Patients wishing to avoid or delay surgery may be helped by improvement of illumination, pupil dilation to enhance light transmission, wearing tinted glasses to block wavelengths of light scattered by the cataract, and avoiding nighttime activities (especially night driving).
4. **Prevention.** Cataract formation is promoted by prolonged ultraviolet light exposure, diabetes mellitus, and the use of topical or systemic steroids. The use of sunglasses by people who work in bright outdoor environments is a prudent preventive measure. Oral and ocular steroids should be used only with firm indication. Diabetics should receive annual eye examinations. Although some have advocated the use of antioxidant medications or vitamin therapy to prevent or retard the progression of cataracts, the benefit of such treatment has not been proven.

II. Chronic open-angle glaucoma

A. Presentation.

The term *glaucoma* is used when the pressure within the globe damages the eye's internal structures. Although there are several rare types of glaucoma, 90% of cases in the United States involve chronic open-angle glaucoma. The only symptom is gradual, painless loss of peripheral

vision. Most patients remain unaware of this loss until the disease has progressed significantly. Without treatment, the visual field becomes a gradually constricting tunnel until finally central vision is lost and complete blindness results.

B. Evaluation

1. **Screening** for glaucoma remains controversial. However, current expert opinion favors periodic screening for patients over 65 and those in certain high-risk groups (2). In most communities, glaucoma screening should be conducted by an ophthalmologist. However, in certain settings, family physicians will need to screen for glaucoma themselves using intraocular pressure (IOP) testing. The IOP may be readily measured with an applanation or pneumatic tonometer. A normal IOP is 10–21 mm Hg. Above this pressure, the lifetime risk of glaucoma increases rapidly.
2. **Physical findings** suggestive of the retinal and optic nerve damage of glaucoma may be found on direct ophthalmoscopy. These include (a) an optic cup diameter greater than half the optic disk diameter, (b) marked asymmetry of optic cup size, (c) optic nerve pallor, and (d) hemorrhage. A significant reduction of peripheral vision may be noted with confrontational field testing. These physical findings are suggestive of advanced disease and are rare in most primary care settings.

C. Management

1. **Referral to an ophthalmologist** is indicated when there is peripheral vision loss or suggestive funduscopic findings. More commonly, family physicians should consider referring patients with risk factors for glaucoma—the elderly, blacks older than 40 years, diabetics, and those with a history of eye trauma, eye surgery, or ocular steroid use—to an eye specialist for routine evaluation. IOP criteria for referral include an IOP in either eye of 21 mm Hg or more, or a difference in IOP of 5 mm Hg or more between the eyes. A definitive diagnosis of early glaucoma requires sensitive visual field testing and funduscopy by the ophthalmologist.
2. **Medical management.** The key to glaucoma treatment is the reduction of IOP to reduce damage to the eye. Ophthalmologists also treat some patients with isolated IOP elevation (without evidence of eye damage) in order to prevent the development of frank glaucoma. Topical medications, delivered in the form of eye drops, are first-line therapy. When successful, these medications may need to be continued indefinitely. Family physicians will therefore frequently encounter patients using these medications and need to be aware of their more common side effects and drug interactions (3).
   a. ß-Adrenergic blockers (e.g., timolol maleate drops) may cause the worsening of congestive heart failure or reactive airway disease and acute delirium.
   b. Miotics (e.g., pilocarpine drops) are generally well tolerated but may cause headache. In overdose they cause excessive sweating, salivation, abdominal cramping, and diarrhea.
   c. Carbonic anhydrase inhibitors (e.g., dorzolamide drops or oral acetazolamide), when given orally, can cause metabolic alkalosis with paresthesias and malaise. As sulfonamides, all forms can induce hypersensitivity reactions.
   d. Prostaglandins (e.g., latanoprost drops) may produce permanent darkening of the iris or transient headaches.
   e. Sympathomimetics (e.g., brimonidine), as a class, have variable side effects. Brimonidine cannot be used in conjunction with monoamine oxidase inhibitors.

   Techniques that the patient can implement to reduce systemic absorption of eye drops include refrigeration of the medication to increase viscosity and occlusion of the nasolacrimal duct at the medial canthus with finger pressure for 5 minutes after instillation.

3. **Surgical management.** When medication fails to adequately lower IOP, the patient is typically treated with laser surgery of the aqueous outflow tract. Laser surgery is highly successful but may need to be repeated in 5–10 years. Other options for refractory disease include open trabeculectomy and destruction of the ciliary body.

III. Macular degeneration

A. Presentation.

Macular degeneration is an idiopathic process that disrupts the normal microarchitecture of the retina. Most patients experience a gradual, painless loss of central vision that over many years progresses to legal blindness (acuity of 20/200 or worse). Often, patients first seek help when they can no longer read small print. The peripheral vision is relatively spared, however, so that the patient can still move about his or her environment even with advanced disease. A small percentage of patients with macular degeneration develop subretinal neovascularization with hemorrhage or retinal detachment. This causes abrupt vision loss, visual field cuts (scotomata), or distortion of objects in the central visual field.

B. Evaluation.

On direct ophthalmoscopy of patients with macular degeneration, an examiner may note a mottled appearance to the macula, yellowish spots (called *drusen*), or areas of hyper- or hypopigmentation. Not infrequently, these changes exist hidden behind cataracts. Office testing reveals that visual acuity is significantly impaired.

C. Management

1. **Referral.** Patients suspected of having macular degeneration should be referred to an ophthalmologist for definitive diagnosis. An urgent referral is indicated if the patient has had a recent, acute worsening of vision because prompt intervention may be helpful.
2. **Surgical management** is helpful in only a small minority of patients. Subretinal neovascularization may be treated with laser surgery if caught early. Unfortunately, even in these cases, the progressive nature of the underlying disease is not altered. In addition, neovascular damage reoccurs in about 50% of treated eyes in 2 years. Nonlaser light can also be used to treat neovascularization when used in conjunction with photosensitive drugs that are given intravenously (so-called photodynamic therapy).
3. **Medical management.** Ongoing management of macular degeneration focuses on the early diagnosis of treatable complications and on maintaining function as visual acuity gradually diminishes. Ophthalmologists commonly ask patients—especially those who have already become legally blind in one eye from macular degeneration—to look at an Amsler grid daily. The Amsler grid is a standardized pattern of lines that helps the patient to recognize when a sudden change in central vision has occurred. Any such change warrants immediate reevaluation of the retina. Because peripheral vision is relatively spared, patients benefit from devices that magnify and allow small images to cover healthier retina. For example, bright lighting, large-print books, computer screens, and projectors are helpful to patients who wish to read. In counseling patients, it must be stressed that although loss of sharp central vision will occur, preservation of peripheral vision allows many patients with macular degeneration to retain high levels of independence and self-sufficiency.
4. **Prevention.** Modifiable risk factors for macular degeneration include smoking, low dietary intake of antioxidant vitamins and zinc, and sun exposure (4). Smoking cessation and the use of sunglasses are prudent but unconfirmed preventive measures. Studies of vitamin and mineral supplementation to prevent macular degeneration are ongoing.

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7.3
OCULAR INJURIES

Michael L. Tuggy

Direct trauma, foreign body, and chemical injury are the most common causes of eye injuries. The significance of the injury varies greatly depending on the mechanism and extent of injury. The goal of the initial evaluation is to identify any injuries that could permanently affect vision and to relieve pain common to these injuries. Most patients are able to provide clear histories of the event, making the diagnosis simple and leaving the physician to rule out serious sequelae. Athletic facilities and industrial work sites are common places for eye injuries to occur. Physicians should emphasize the importance of protective eye equipment in patients who frequent such sites.

I. General considerations.

A. Any ocular injury

requires a thorough history and examination to determine the nature of the injury, the effect of the injury on visual acuity, and the risk of possible penetration of the globe. All patients with eye injuries must have visual acuity testing with careful examination of the globe, cornea, fundus, pupillary responses, and extraocular movements.

B. Slit-lamp examination.

If a slit lamp is available, a slit-lamp examination should be performed in cases of suspected abrasion, burn, or direct trauma.

C. Medications and special equipment

1. Topical anesthetics (proparacaine or tetracaine) to facilitate removal of foreign bodies.
2. Fluorescein dye with an ultraviolet light source.
3. Antibiotic suspensions or ointments for prophylaxis.
4. Sterile cotton-tipped swabs and 25-gauge needle to aid in removal of superficial foreign bodies.
5. Mydriatics: atropine, 1%, or homatropine, 5% for relief of ciliary spasm.

II. Specific ocular injuries

A. Corneal abrasion and foreign body

1. **Presentation.** Corneal abrasion is the most common urgent eye complaint seen in the primary care setting. The most common mechanism of this injury is wind-driven particulate matter entering and being trapped under the eyelid. These small particles are sensed acutely by the patient, who subsequently complains of constant pain in the eye. Marked tearing and injection of the eye usually accompany the pain of the abrasion.
2. **Diagnosis**
   a. Corneal abrasions are best detected with fluorescein staining of the cornea. Use of topical anesthetics is not mandatory before staining of the eye. Fluorescein-tipped applicator paper is placed on the medial canthus of the eye and the patient is instructed to close the eye. Within 15 seconds, normal tearing will disseminate the stain across the cornea and scleral conjunctiva. Under ultraviolet light, patches of fluorescein that adhere to the denuded epithelium identify abrasions.
   b. The upper lid should be inverted to rule out the presence of a foreign body. If a superficial foreign body is present, then local anesthesia

should be applied and the foreign body removed with a cotton-tipped applicator or 25-gauge needle.

3. **Treatment**
   a. Patching of the affected eye in no longer recommended because it may increase the risk of infection. Topical anesthetics should be avoided if no foreign body is present (1).
   b. Atropine, 1%, or homatropine, 5%, 2 drops in the affected eye may be used to reduce pain symptoms from ciliary spasm. Oral nonnarcotic analgesics or topical nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used for pain relief (2).
   c. Application of topical antibiotic solution reduces the risk of secondary infection and is recommended for all abrasions. Corticosteroid suspensions are contraindicated.
4. **Follow-up.** If symptoms resolve in 48 hours, no follow-up is necessary. If symptoms persist, reexamination is indicated to rule out retained foreign body or infection.

B. Hyphema

1. **Presentation.** Hyphema results from a direct blow to the eye or orbit, and is often related to sports activities. The patient has pain in the eye, decreased visual acuity, and injection of the globe.
2. **Diagnosis.** The finding of blood in the anterior chamber confirms the diagnosis. This finding may be delayed for hours to days following injury if bleeding is gradual.
3. **Treatment.** Strict bed rest with head elevated at least 20 degrees.
   a. Bilateral eye patches to minimize eye movement.
   b. Instill atropine, 1%, 2 drops bid to reduce ciliary spasm.
   c. If an ophthalmologist is not readily available, intraocular pressure should be reduced by the use of oral acetazolamide or mannitol.
   d. Appropriate pain medications that are free of aspirin.
4. **Follow-up.** Immediate ophthalmologic referral is indicated in all cases of hyphema (3).

C. Penetrating injuries to the globe

1. **Presentation.** Penetrating injuries to the eye are often caused by high-velocity missiles or severe blunt trauma to the orbit and globe. Vision is markedly decreased in the affected eye. Small projectile injuries may be very difficult to locate within the eye.
2. **Diagnosis.** Direct examination may reveal collapse of the anterior chamber or protrusion of the iris through the open cornea. Minute penetrations of the cornea may be made apparent by the seeping out of aqueous fluid through the cornea of a fluorescein-stained eye. Limit examinations of the eye to a minimum before an ophthalmologist is present.
3. **Treatment.** Strict bed rest with head elevated at least 20 degrees.
   a. Apply bilateral eye patches to minimize eye movement. An eye shield should be placed over the injured eye.
   b. Do not put any medications into the eye.
   c. Give anti-emetic such as chlorpromazine 25 mg IM every 4–6 hours to prevent emesis.
   d. Morphine 2–4 mg IV as needed for pain
4. **Follow-up.** Urgent ophthalmologic consultation is required for surgical repair.

D. Orbital and lid injuries

1. **Presentation.** Orbital contusions or lacerations may have associated bony orbital injury. Many patients with orbital fracture complain of diplopia or increased pain with certain ocular movements due to entrapment of the extraocular muscles. Retro-ocular hematoma causes proptosis and requires urgent consultation for evacuation (4).
2. **Diagnosis.** Careful palpation of the orbit reveals point tenderness and a palpable step-off if a displaced fracture is present. Restricted extraocular movements or proptosis should be ruled out. A Water's view is the

best radiographic study to identify orbital rim or orbital floor injuries in the office setting.

3. **Treatment**
   a. The eye should be shielded but not patched after the examination is completed.
   b. Lid lacerations should be repaired by an ophthalmologist. It is important that the lacrimal ducts and cartilage of the lid be aligned properly at closure.
   c. Orbital fractures are be treated with analgesics and local measures (ice) until the swelling is reduced. Even with some restriction of extraocular muscles, some patients will not require surgical intervention if the entrapment resolves within 2 weeks.
4. **Follow-up.** Patients should be referred to an ophthalmologist within 12 hours.

E. Chemical and thermal burns

1. **Presentation.** Chemical burns are grouped by their relative pH values. Alkali burns are potentially the most serious as bases are more difficult to clear, though acid burns may cause more rapid destruction of tissue (4). There is usually considerable pain and injection of the eyes with loss of visual acuity. The classification for thermal burns is similar to that for burns of the skin.
2. **Diagnosis.** History of chemical or thermal exposure followed by eye pain is adequate for the diagnosis of a burn injury. The cornea may appear eroded or hazy from edema.
3. **Treatment**
   a. Topical anesthetics should be applied for pain relief during irrigation or examination.
   b. All alkali and acid burns should be copiously irrigated with 2 L of normal saline. Do not attempt to neutralize the agent. Careful inspection after irrigation is important to prevent further injury with particulate matter.
   c. Alkali and thermal burns should have a mydriatic applied (atropine or homatropine).
4. **Follow-up.** Patch the affected eye and refer the patient to an ophthalmologist.

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VIII. EAR, NOSE, AND THROAT PROBLEMS

8.1
ACUTE OTITIS MEDIA

Richard Joseph Breuner

Cora Collette Breuner

Acute otitis media (AOM) is a short-lived suppurative infection of the middle ear. The emergence of drug-resistant *Streptococcus pneumoniae* has led to two changes in treatment recommendations: fewer patients should receive antibiotics, and many of those treated will require higher-dose amoxicillin. Careful distinction should be made between AOM and otitis media with effusion (OME) because AOM may merit antibiotic treatment whereas OME does not. AOM affects both children and adults, and the clinical presentation varies according to age group (1,2,3,4,5 and 6).

I. Clinical presentation.

Ear pain with or without fever in the setting of upper respiratory infection is the most common presentation in both children and adults. Anorexia, nausea, vomiting, diarrhea, and headache are less common. In children younger than 2 years, disturbed sleep, irritability, and anorexia are common, and may be the only symptoms. Adults complain of hearing loss, ear fullness, and ear pain. Discharge from the ear canal represents either ruptured tympanic membrane in the setting of AOM or otitis externa (see Chapter 8.3). Rupture of the eardrum usually relieves ear pain.

II. Diagnosis

A. Children and adults.

AOM is defined as the presence of fluid in the middle ear in association with erythema or injection, opacity, or a bulging tympanic membrane. The injected eardrum is hyperemic, darker, and redder than the normal white or gray tympanic membrane (2). Care should be taken during the exam to keep the child calm, as crying will cause the same injection of the eardrum. Infants may be fed during the exam for this purpose. The presence of middle ear effusion can be detected by an increased light reflex from the tympanic membrane and should be confirmed by failure to move the tympanic membrane with pneumatic otoscopy (3). Middle ear effusion alone without local inflammation is indicative of OME and should be managed without antibiotics (see Chapter 8.2).

A tympanic membrane rupture is visible as a defect in the drum, unless the ear canal is filled with pus. In that case, the patient must be treated as if the membrane were ruptured.

B. Infants.

The presence of fever greater than 38°C in an infant younger than 3 months requires comprehensive evaluation (see Chapter 4.2). The presence of a red tympanic membrane in the febrile infant should not influence the extent of the evaluation. Diagnosis and treatment of AOM in a neonate may require tympanocentesis.

III. Treatment

A. Efficacy.

In multiple randomized controlled trials comparing treatment of AOM with antibiotics versus placebo, antibiotics improve outcomes, but the treatment effect is small (1). Approximately 80% of untreated children have clinical resolution by 7–14 days, compared with 95% of those treated with antibiotics. The treatment effect of antibiotics is more pronounced when outcomes are assessed at 2–3 days. This treatment effect may disappear following effective universal childhood vaccination for *Pneumococcus*. In contrast, otitis media with effusion requires no treatment unless it persists for more than 3 months (3) (see Chapter 8.2). Decongestants, antihistamines, and steroids are not indicated for AOM (6).

B. Organisms.

The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, and group A β-hemolytic *Streptococcus*. In 30%–50% of AOM, no bacteria can be cultured from the middle ear; these infections are presumed to be viral.

C. Antibiotics.

Amoxicillin remains the drug of choice despite the fact that all but the lowest risk patients will require high-dose treatment. The increasing incidence of drug-resistant *S. pneumoniae* infections has led the Centers for Disease Control and Prevention to recommend higher dose amoxicillin in patients who are at increased risk for such relative resistance (4). Those risk factors include age younger than 2 years, antibiotic exposure during the previous 3 months, or attendance at a day care facility. Patients with no risk factors and AOM should receive amoxicillin 40 mg/kg per day to a maximum of 750 mg/day divided for dosing every 8–12 hours. Patients with one or more risk factors should receive amoxicillin 90 mg/kg per day to a maximum of 1,500 mg/day divided for dosing every 8–12 hours. Patients who are allergic to amoxicillin should receive either sulfamethoxazole-trimethoprim (trimethoprim 8 mg/kg per day divided for dosing every 12 hours) or Pediazole (50 mg/kg per day divided for dosing every 6–8 hours). Adults who are allergic to amoxicillin should receive either double-strength sulfamethoxazole-trimethoprim twice a day or second-generation cephalosporins, dosed as follows: cefaclor 250 mg bid; cefprozil 500 mg once a day; ceforoxime 250 mg bid; or loracarbef 400 mg bid.

D. Membrane ruptures.

The same antibiotic choices are appropriate, but dry-ear precautions should be prescribed.

E. Treatment duration.

Five- to seven-day courses of antibiotics are as effective as longer courses and will decrease selection pressure for resistant organisms. Patients who are younger than 2 years with a perforated tympanic membrane or chronic or recurrent AOM should have 10-day treatment courses, but all others may be adequately treated with 5- to 7-day courses (1).

F. Treatment failure.

Fever, ear pain, and fussiness should resolve within 2–3 days. If not, the patient should be reexamined. Continued effusion alone is to be expected in successfully treated AOM. Effusion and erythema or opacity signifies treatment failure, and the patient should be treated with amoxicillin-clavulanate, 80–90 mg/kg per day of amoxicillin and 6.4 mg/kg per day of clavulanate to a maximum of 1,500 mg/d of amoxicillin in divided doses every 8 hours or cefuroxime 30 mg/kg per day to a maximum of 500 mg/d in divided doses every 12 hours (4).

G. Recurrence.

OME is common for 30–60 days following the successful treatment of AOM. Consider counseling parents about this during initial treatment. Routine “ear checks” are no longer recommended. If AOM recurs within 90 days of initial treatment, the patient should be treated with a broader spectrum antibiotic for 10 days (as above, under treatment failure). AOM recurring more than 90 days from the previous episode should be treated as an initial episode.

H. Prophylaxis.

A meta-analysis summarizing antibiotic prophylaxis concluded that antibiotic treatment resulted in an average decrease in the number of episodes of AOM of 0.11 episode per patient per month, or slightly more than one episode per year (5). This benefit must be weighed against the risk of promoting resistant pneumococci. Consider alternatives to antibiotic prophylaxis such as eliminating smoking in the home, reducing day care attendance, eliminating pacifiers, or giving influenza vaccine (1). Candidates for prophylaxis should have three episodes of AOM in 6 months, or 4 episodes in 1 year. These episodes should be documented in your office or the emergency room. Patients younger than 2 years or in day care settings are more likely to benefit because their recurrence risk is higher. Use amoxicillin 20 mg/kg per day or sulfamethoxazole 50–75 mg/kg per day, both in a single dose.

I. Referral.

The following are guidelines for specialty referrals.

1. **Audiology.** Audiology evaluation is indicated for three episodes of AOM in 6 months or four episodes in 12 months, or OME lasting longer than 3 months.
2. **Ear, nose and throat specialist.** Referral is indicated for any child with a hearing deficiency, especially if the hearing loss is bilateral.
3. **Speech and language evaluation.** Referral is recommended in any child with speech delay or hearing deficit (6).

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8.2
CHRONIC OTITIS MEDIA

Russell G. Maier

Chronic otitis media (COM) encompasses a broad area of ear disease that is discussed as three main clinical entities: otitis media with effusion (OME), chronic suppurative otitis media (CSOM), and COM. OME is defined as the presence of fluid in the middle ear without signs or symptoms of infection. Controversy exists regarding the diagnosis and treatment of OME. OME is one of the few areas in medicine that has been studied by an evidence-based panel that developed objective treatment recommendations (1). Much of the discussion on OME is based on the panel's recommendations and findings, although they primarily discuss children aged 1–3 years. CSOM is defined as chronic (6-week) otorrhea through a non-intact tympanic membrane. COM is defined as a perforation lasting longer than 1 month without drainage.

I. Otitis media with effusion

A. Clinical presentation.

In children and adults, the presentation is the same. Commonly there are no complaints, and the diagnosis is made on a screening examination. If symptoms are present, they include behavioral changes, parental or patient complaints of diminished hearing, or a fullness or discomfort in one or both ears. Historically, the most common cause of OME is a prior ear infection (also see Chapter 8.1).

B. Risk factors.

Risk factors for OME include recurrent acute otitis media (AOM), group child care, passive smoke exposure, absence of breast-feeding as an infant, craniofacial abnormalities, and allergies.

C. Clinical examination.

The diagnosis of OME is primarily clinical. There are few useful tests and no laboratory studies that aid in the diagnosis.

1. **Physical examination.** The patient is afebrile. On examination, the external auditory canal should be normal. The drum may appear normal or thickened. The diagnosis depends on middle ear fluid being present. This may be noted as an air-fluid level, bubbles, or serous or serosanguinous fluid in the middle ear. If fever, a bulging erythematous eardrum, or drainage is present, the diagnosis of OME cannot be made. The definition of OME is fluid without infection.
2. **Additional tests**
   a. **Pneumatic otoscopy.** If the diagnosis is uncertain, pneumatic otoscopy following the otoscopic examination is imperative. A drum that

appears normal may have fluid behind it. For pneumatic otoscopy to be accurate, a complete seal must be obtained in the ear canal. When slight positive and negative pressure is applied to the tympanum, it should move briskly back and forth. An effusion inhibits this movement.

b. **Tympanometry.** If following clinical examination and pneumatic otoscopy the clinician is still unsure about the diagnosis, tympanometry provides a useful adjunct. An effusion produces a flat, type B tympanogram.

D. Treatment.

Treatment for adults and children is primarily medical but varies depending on the examination and underlying illnesses.

1. **Child with an abnormal examination.** Although less common in primary care than in a specialist setting, children sometimes have abnormal findings upon examination. Treatment should be initiated with consultation with or referral to (or both) an ear-nose-and-throat (ENT) physician for a child with a craniofacial abnormality, OME in the only hearing ear, or unilateral OME with worrisome findings on examination, such as an ipsilateral neck mass.
2. **Normal child with otitis media with effusion for less than 3 months**
   a. **Watchful waiting.** In a variety of studies, the spontaneous resolution of OME ranges from 60%–90% in 3 months. Given that approximately two thirds of all children improve without any treatment and with no risk to the child, many recommend this treatment course. Follow-up visits are recommended at 3- to 6-week intervals after the initial diagnosis.
   b. **Antibiotics.** In the past, antibiotics have been an option for treatment during the first 3 months. Given the increasing difficulties and risks with resistant organisms, watchful waiting is now the preferred course (2).
   c. **Steroids.** In the first 3 months, steroids are not recommended because they show no benefit in this early period (3).
   d. **Risk factor reduction.** In all patients, there are several modifiable risk factors that contribute to OME. The child should not be exposed to any secondary smoke. Any smoking by family members or relatives should be done outside of the home or car, not in a different room. Group child care is a risk factor that rarely can be modified.
3. **Otitis media with effusion for 3 months or more**
   a. **Hearing evaluation.** At 3 months, all children with bilateral effusions should receive a hearing evaluation. If the hearing loss is 20 decibels (dB) or worse, the options of watchful waiting or medical treatment need to be considered. Surgery is now an option.
   b. **Watchful waiting.** Spontaneous resolution continues to occur such that within 6 months 85% of symptoms have resolved.
   c. **Antibiotics.** If a course of antibiotics is to be tried, amoxicillin or trimethoprim-sulfamethoxazole would be first-line treatment, with amoxicillin does at 40–80 mg/kg per day in three divided does. If a second course is used, a ß-lactamase-stable antibiotic is recommended.
   d. **Steroids.** Although the Agency for Health Care Policy and Research (AHCPR) panel does not recommend steroids, many clinicians do recommend a trial of steroids in OME present longer than 3 months. There is no benefit to a course of steroids alone. Prednisone, 1 mg/kg per day in two divided doses, is given for 7 days concurrent with a 14- to 21-day course of antibiotics. If treatment is successful, it is followed by prophylactic antibiotics for 3 months, amoxicillin, 20 mg/kg per day, or sulfisoxazole, 75 mg/kg per day, because of a high relapse rate following treatment with combined steroids and antibiotics (4). Recent exposure to varicella and concurrent varicella, sinusitis, or other acute infection is a contraindication to steroids. If the child is

already on steroids, the medication must be stopped. Acyclovir should be considered for children infected with varicella.

e. **Surgery.** Surgery is an option in a child with a documented hearing loss of 20 dB or worse. Myringotomy or tonsillectomy provides no benefit over watchful waiting. Thus, surgical options include tympanostomy tubes in children younger than 4 years and adenoidectomy in children older than 4 years. There are no data to show benefit of adenoidectomy in children younger than 4 years (5).

f. **Patient education.** An excellent reference for patients is the *Parent's Guide to Middle Ear Fluid in Young Children* (in English and Spanish), and for clinicians, the *Quick Reference Guide to Managing Otitis Media with Effusion in Young Children*. Both publications are available by calling (800) 358-9295 or through AHCPR Publications Clearinghouse, PO Box 8547, Silver Spring, MD 20907.

II. Chronic suppurative otitis media and chronic otitis media

A. Clinical presentation.

CSOM often presents with drainage from an ear. Usually the individual feels fine or otherwise appears healthy. The patient may complain of otalgia, state that he or she is “out of sorts,” or complain of hearing loss or difficulty hearing from the affected ear. COM is usually painless.

B. Risk factors.

Risk factors include recurrent AOM, immune impairment (e.g., from diabetes or chronic illness), allergies, craniofacial abnormalities, and an increased prevalence in certain subpopulations, including Eskimos and Native Americans. The use of tympanostomy tubes results in an approximately 1.6%–3.0% incidence of chronic otorrhea.

C. Physical examination.

Clear otorrhea is unusual, and a cerebrospinal fluid leak should be suspected. Especially in children, one needs to rule out a foreign body with secondary otitis externa as the cause of otorrhea. In adults as well, a careful examination and possibly a therapeutic trial must be done to rule out otitis externa as the cause of otorrhea. Once the external auditory canal has been cleaned, the tympanic membrane should be examined. Often a large central perforation is seen, with an abnormal middle ear noted. Marginal perforations are more often associated with cholesteatomas and other severe complications. If a cholesteatoma is noted, the patient should be referred to an ENT physician. CSOM with cholesteatoma is primarily a surgical disease.

D. Laboratory studies.

If possible, cultures should be obtained. Material from the middle ear is most helpful. Drainage from the external auditory canal is acceptable, but the canal should be sterilized and the culture obtained from reaccumulated fluid. Culture should include both aerobes and anaerobes.

1. **Tympanometry.** If a perforation is suspected but not seen, a tympanogram will show a large canal volume but flat tracing or will fail to make a seal.
2. **Audiologic evaluation.** Because many patients complain of hearing abnormalities, it is helpful to document this finding so as to follow it during treatment. A conductive hearing loss of more than 30 dB is suggestive of disruption of the ossicular chain.
3. **Imaging studies.** The diagnosis of CSOM and COM is primarily clinical. If a cholesteatoma is suspected, if the diagnosis is uncertain, or if intracranial extension is suspected, computed tomography should be performed (6).

E. Immediate referral.

Patients with a facial palsy, labyrinthitis, or suspected intracranial suppuration should be referred immediately.

F. Treatment

1. **Chronic suppurative otitis media.** Initial management involves removing the debris. If the practitioner does not have an operating microscope or suction, treatment may be better referred to an ENT physician. Following removal of debris, empiric antibiotic treatment with oral agents that cover *Streptococcus pneumoniae*, *Haemophilus influenzae*, Moraxella

catarrhalis, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and anaerobes is recommended (7). Amoxicillin clavulanate, 20–40 mg/kg per day in children or 500 mg every 8 hours in adults (not tid) or 850 mg bid to minimize diarrhea, may be prescribed. In conjunction with systemic therapy, topical otic suspension, such as neomycin, polymyxin B, and hydrocortisone (Cortisporin) or gentamicin otic drops, can be initiated. In adults, oral ciprofloxacin, 500–750 mg bid, can be added for pseudomonal coverage. The use of fluoroquinolones is contraindicated in children. If the combination of antibiotics and debridement does not stop the drainage, there are two other options.

a. **Aggressive medical management.** For CSOM refractory to conservative measures there are good data to support either inpatient or outpatient aggressive medical therapy: frequent suctioning and intravenous antibiotics for 6 weeks (8,9). The primary care physician should refer the patient to an ENT physician for this care.
b. **Surgery.** If aggressive medical management fails (after 2 weeks of intravenous therapy there is no improvement), tympanomastoid surgery should be considered as the next step.

2. **Chronic otitis media.** A dry, uninfected middle ear does not require acute treatment other than being kept dry. Definitive repair is done electively in adults or at age 9–12 years in children.

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8.3
OTITIS EXTERNA

Paul Evans

Otitis externa is an inflammatory condition, usually self-limiting, of the external auditory canal (EAC). It is commonly seen in primary care because it affects all age groups. Summertime increases in incidence are due to water exposure in swimming and related activities that reduce cerumen protection (1). Otitis externa can be diffuse or circumscribed, acute or chronic, or can have eczematous features. Rarely, it can progress to

necrotizing or “malignant” otitis externa in diabetics or other immunocompromised patients, leading to serious illness, cranial nerve palsies, or death. Risk factors include trauma to the external auditory canal, swimming or moisture exposure, use of a hearing aid (2), and predisposing skin disorders, such as eczema, seborrhea, or psoriasis.

I. Clinical presentation

A. Symptoms.

The most frequently described symptoms are itching, purulent discharge, otalgia, plugging of the ear, mild hearing loss, ear fullness, and tinnitus.

B. Signs.

On examination, there is pinnal tenderness, an erythematous and edematous external auditory canal, and a discharge. Pinnal eczema is often present.

II. Diagnosis

A. Acute otitis externa.

It is usually infectious in origin, with *Staphylococcus aureus* or *Pseudomonas aeruginosa* being the most common isolates. Fungi such as *Aspergillus*, *Candida*, and others have also been implicated. (3). Anaerobes may also play a role. Cultures in acute otitis should be reserved for therapeutic failures because most patients respond to first-line therapy. Non-infectious causes, such as contact dermatitis, eczema, psoriasis, or trauma, should be sought.

B. Chronic otitis externa.

Chronic otitis is defined by symptoms lasting longer than 2 months. Causes similar to acute otitis externa are seen, but chronic otitis may be the result of failure to correctly diagnose and treat the pathogen initially. Predisposing factors remain important.

C. Necrotizing or “malignant” external otitis.

This is a rare but important infection seen most commonly in elderly diabetics. Severe ear pain and systemic signs and symptoms may be present along with cranial nerve palsies. If not detected early and treated aggressively, this condition may progress to skull base osteomyelitis with possible erosion to the central nervous system. *Pseudomonas* is the most common pathogen (4).

III. Management

A. Acute otitis externa

1. Clean out exudates and debris by gently suctioning or swabbing. Use of irrigation is controversial.
2. Initial culture is not necessary (3).
3. Topical drops that contain a mild acid (e.g., Domeboro Otic, 4–6 drops q2–3h) or antibiotics and a steroid [e.g., neomycin, polymyxin B sulfates, and hydrocortisone (Cortisporin Otic suspension), 3–5 drops qid] are effective agents. Acidification lowers pH to inhibit *Pseudomonas* growth. Therapy should be used for about 7–10 days with sufficient quantity to contact all involved EAC tissues. If infection spreads to the concha or to the preauricular or infra-auricular area, systemic antibiotics should be considered. If a fungal etiology is suspected, topical nystatin and clotrimazole have been successful first-line agents.
4. Cotton wicks for a severely swollen EAC assist in reducing swelling and more effectively getting topical therapy to targeted tissue. After 48–72 hours, the wick can usually be removed, with continuation of drops for the full 7–10 days.
5. Pain control with a topical anesthetic [e.g., benzocaine, antipyrine, and dehydrated glycerin (Auralgan), 2–4 drops q1–2h as required], acetaminophen, or ibuprofen is usually successful. Occasionally, short-term narcotic analgesics may be necessary.

B. Chronic otitis externa.

1. Maintain cleanliness of the EAC.
2. Because initial treatment has failed for 2 months or longer, bacterial and fungal cultures should now be done. A screening potassium hydroxide (KOH) preparation can rapidly detect fungal elements, which indicates otomycosis.
3. Reexamine for other conditions, such as chronic purulent otitis media with perforation, furunculosis, eczema, seborrhea, or psoriasis.

4. Carefully evaluate for contact dermatitis due to prior therapies. Common sensitivities to neomycin and other agents in topical preparations must be kept in mind.
5. If compliance has been ensured with an appropriate regimen for the cultured pathogen, a change to another antibiotic is indicated. Mixed bacterial and fungal infections may require multiple drug therapy. Addition of topical steroids reduces inflammation and the accompanying symptoms.
6. If all medical therapy fails, surgical consultation is appropriate for consideration for conchomeatoplasty or another procedure as a last resort.

C. Necrotizing or malignant otitis externa.

This rare condition requires early and aggressive therapy including consultation with an otolaryngologist. Hospitalization with antipseudomonal parenteral antibiotics (e.g., ceftazidime and gentamicin), careful debridement, and computed tomography (CT) or magnetic resonance imaging (MRI) to delineate the extent of bony or soft-tissue erosions are recommended (4). All elderly diabetics with external otitis should be monitored for this serious complication.

IV. Prevention

A. Infectious causes

Because most of the bacterial and fungal organisms thrive on moist tissues, attention to drying the EAC and lowering the growth of pathogens with a mildly acidic environment is important. Over-the-counter preparations for preventing swimmer's ear that contain a drying agent and a mild acid are effective; similar home remedies can be made with a mixture of 50% isopropyl alcohol and 50% vinegar (5% acetic acid). When applied after moisture exposure, such a mixture is both efficacious and cost effective (5).

B. Noninfectious causes.

Maintaining good aural hygiene and getting early treatment of dermatologic problems lowers the incidence of otitis externa. Use of topical steroids for eczematous conditions as well as for allergic or contact dermatitis is helpful. Patients who use occlusive EAC devices, such as hearing aids, earpieces, or stethoscopes, must maintain a high level of attention to cleanliness to avoid bacterial or fungal contamination.

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8.4
PHARYNGITIS AND STREPTOCOCCAL THROAT INFECTION

Thomas P. Ehrlich

David B. Callahan

I. Etiology.

Pharyngitis in both adults and children is caused by a variety of organisms. These include groups A, C, and G streptococci, *Neisseria gonorrhoeae, Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Corynebacterium diphtheriae*, *Corynebacterium haemolyticum,* and *Candida* species. Many cases are viral. Acute mononucleosis may present as pharyngitis (see Chapter 19.3).

Pharyngitis is almost always a self-limited disease. The major task of the clinician is to detect and treat infection by group A ß-hemolytic streptococci (GABHS) so as to prevent the occurrence of acute rheumatic fever. It is also important to diagnose patients with abscess formation and to provide symptomatic treatment for those with self-limited disease (1).

II. Diagnosis

A. Clinical history and examination.

This may be nonspecific, but the following guidelines are sometimes helpful:

1. GABHS infection often results in tonsillar exudate, anterior cervical adenopathy, and palatal petechiae. In children, impetiginous lesions on the face and around the nose are also commonly seen. Children often complain of headache and stomachache.
2. Peritonsillar abscess can present with trismus, deviation of the uvula, bulging of either tonsillar pillar, and the classic “hot potato voice.”

B. Cultures.

Appropriate culture is the standard for diagnosing GABHS. Both for culture and for rapid testing, adequate swabbing technique is essential to prevent false-negative results. Both tonsils and tonsillar pillars as well as the uvula should be swabbed. Visible exudate should be obtained.

C. Rapid tests.

Rapid assays for GABHS are accurate and cost effective, but they are not all alike in terms of sensitivity. In general, treatment can be based on a positive rapid test result without follow-up culture. Depending on the sensitivity of your particular rapid test, treatment may be withheld based on a negative rapid test result. Backup culture with treatment of patients showing growth of GABHS may be considered (2).

III. Management

A. Antibiotic treatment for GABHS pharyngitis.

Primary treatment should be with penicillin (PCN, Pen-Vee K). An acceptable alternative for penicillin-allergic patients is erythromycin. Amoxicillin may be used in children who will not tolerate the taste of penicillin suspension (Pen-Vee K). Beware of the use of amoxicillin and ampicillin in infectious mononucleosis; the combination may cause a rash. Azithromycin and cephalexin may also be used but are not thought to be superior.

1. The adult dose of penicillin V is 500 mg bid for 10 days. The children's dose is 40 mg/kg divided bid for 10 days.
2. Adult dose is erythromycin base (ERYC, PCE, others), 500 mg bid for 10 days. For children, give erythromycin estolate (Ilosone), 40 mg/kg per day divided bid for 10 days (supplied as 125 and 250 mg/5 mL) or erythromycin ethylsuccinate, 40–50 mg/kg per day divided bid-qid for 10 days (supplied as 200 and 400 mg/5 mL).
3. When compliance is an issue, for children weighing 27 kg (60 lb), give one dose of 600,000 units of penicillin G benzathine IM. For a child or adult weighing more than 27 kg (60 lb), give 1.2 million units IM.
4. Children may return to school and adults to work 24 hours after starting antibiotics if they are afebrile and feeling better. For patients with allergy to primary medications or for treatment failure, cephalosporins, azithromycin, or amoxicillin-clavulanate (Augmentin) are commonly used. Do not use sulfonamides, tetracyclines, trimethoprim, or chloramphenicol. Treatment failure is usually due to colonization or coinfection with ß-lactamase producing organisms, which can inactivate the antibiotic given. GABHS remains uniformly penicillin sensitive.

B. Symptomatic management of pharyngitis

includes administration of nonsteroidal anti-inflammatory drugs or acetaminophen. Prednisone, 1–2 mg/kg per day, can be used for severe tonsillitis with airway obstruction secondary to infectious mononucleosis (see Chapter 19.3).

C. Empiric treatment.

Many clinicians will empirically treat siblings of GABHS culture-positive or rapid test-positive children if they complain of sore throat with fever.

D. Peritonsillar abscess.

Treatment includes aspiration, incision, and drainage. Antibiotics effective against GABHS and anaerobes should also be given. Augmentin or clindamycin is commonly used.

IV. Prevention.

Prophylaxis for acute rheumatic fever (secondary prevention) for patients who have rheumatic heart disease should be for life. Patients without heart disease should receive prophylaxis until (a) they are over the age of 21 and (b) 5 years has elapsed since the last attack (3). The following are acceptable regimens:

- Penicillin G benzathine, 1.2 million units IM every 3–4 weeks (preferred regimen), or penicillin V, 250 mg PO bid
- Sulfadiazine, 500 mg PO every day for patients weighing less than 27.3 kg (60 lb), or 1 g PO every day for patients weighing more than 27.3 kg (60 lb)
- Erythromycin, 250 mg PO bid (used if patient is allergic to penicillin and sulfonamides)

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8.5
SINUSITIS

Lyle J. Fagnan

I. Introduction.

Rhinosinusitis, or the common cold, is a leading cause of visits to the family physician's office. The average adult has 2–3 colds per year, and children experience 6–8 colds each year (1,2). This represents 50% of all adult illnesses and 75% of illnesses in children. These are self-limited illnesses. The challenge to the family physician is to develop a diagnostic and treatment plan that is both consistent with the current evidence regarding the natural course and treatment and acceptable to the patient or parent.

Indiscriminate use of antibiotics for upper respiratory infections (URIs) has resulted in an increase in the penicillin-resistant pneumococci resistance rate from 4% in the 1980s to 37% in 1997 (3). Clinicians diagnosed sinusitis or bronchitis in 66% of all patients with URI symptoms and prescribed antibiotics for 98% of sinusitis diagnoses (4).

The frontal, ethmoid, and maxillary sinuses drain through the osteomeatal complex. Impaired mucociliary clearance and osteomeatal obstruction contributes to sinusitis (Table 8.5-1).

Allergic rhinitis
Anatomical variations
Barotrauma
Dental infections, procedures, trauma
Hormone factors
Immunodeficiency disease
Inhalation of irritants
Mechanical ventilation
Nasal dryness
Nasotracheal and nasogastric tubes
Upper respiratory infections

Table 8.5-1. Predisposing factors for sinusitis

II. Epidemiologic factors

A. Etiologic agents

Sinusitis is a part of the spectrum of an upper respiratory illness. Up to 0.5% of URIs in adults develop into acute sinusitis (5). Five to ten percent of pediatric URIs are complicated by sinusitis (6). Seventy percent of community-acquired acute sinusitis in adults and children is caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Branhamella (Moraxella) catarrhalis* causes 25% of pediatric acute sinus infections.

B. Related diseases.

Chronic sinusitis is secondary to irreversible damage of the osteomeatal complex and requires otolaryngology consultation and functional endoscopic sinus surgery (FESS) to restore the physiology of sinus aeration and drainage. Fungi, which are normal commensals of the upper airway, may lead to chronic sinusitis in diabetics or immunocompromised patients.

III. Presentation.

One half to two thirds of patients with sinus symptoms who visit the family practice office are unlikely to have bacterial infection (7,8).

A. History and physical examination.

In the office, clinicians rely on the patient history and physical examination to diagnose sinusitis. No single symptom or sign is both sensitive and specific for acute sinusitis. Among the signs and symptoms used to increase the likelihood of diagnosing acute sinusitis are a “double sickening” (biphasic illness), pain with unilateral prominence, purulent rhinorrhea by history, purulent secretions in the nasal cavity, a lack of response to decongestants, pain in the eyes on leaning forward, and maxillary toothache. With a double sickening, the patient reports starting with a cold and then starting to improve, only to have the congestion and discomfort return (Table 8.5-2) (9,10 and 11).

A “double sickening”
Unilateral pain
Pain above or below the eyes on leaning forward
Maxillary toothache
Purulent rhinorrhea by history
Purulent secretions in the nasal cavity on examination
Poor response to decongestants or antihistamines

Table 8.5-2. Clinical indicators of acute sinusitis

In children the symptoms of sinusitis are less specific than in adults. Symptoms include persistent nasal congestion and cough lasting more than 10 days, high fever, and purulent nasal discharge. Children are less likely to present with facial pain or headache (6,12).

The differential diagnosis of acute sinusitis includes protracted URI, dental disease, nasal foreign body, migraine or cluster headaches, temporal arteritis, tension headaches, and temporomandibular disorders.

B. Diagnostic studies

1. Results of blood studies, such as elevated sedimentation rate and C-reactive protein, are nonspecific indications of sinusitis (10,11).
2. Nasal cultures are of limited value because the mixed flora does not correlate with bacteria aspirated directly from the sinuses.
3. Plain sinus films are usually reserved for patients presenting with recurrent symptoms. A single Waters view of the sinuses has a positive predictive value of 87%–90% in both children and adults for diagnosing maxillary sinusitis when compared with three- or four-view sinus series (13,14).
4. Sinus computed tomography (CT) has a high sensitivity but low specificity for demonstrating acute sinusitis. In one study, 40% of asymptomatic patients and 87% of patients with community-acquired colds had

sinus abnormalities on sinus CT (15). Limited sinus CT studies are useful in delineating the osteomeatal complex in anticipation of an otolaryngology consultation and FESS to evaluate and treat chronic sinus inflammation.

IV. Therapy.

Recent studies of antibiotics for acute sinusitis have raised questions regarding efficacy. Of patients receiving placebo medication for sinusitis, 40%–60% will experience resolution of symptoms at 2 weeks, compared with 60%–80% of patients receiving antibiotics (16,17).

Few randomized controlled trials exist concerning the effectiveness of ancillary treatments, such as hot fluids, saline nasal rinses, decongestants, mucolytic agents, antihistamines, and topical nasal steroids.

A. Antibiotics.

Although the incidence of ß-lactamase-producing organisms causing sinusitis is greater than 25% in some communities, there has been no superior outcome in using broad-spectrum antibiotics over amoxicillin. The first-line antibiotics for acute sinusitis are amoxicillin and trimethoprim-sulfamethoxazole. These two drugs are relatively inexpensive (Table 8.5-3).

Antibiotic	Usual adult dose (10-d course)	Cost ($)[a]
First-line therapy		
Trimethoprim-sulfamethoxazole, double-strength (Bactrim DS)	160/800 mg bid	25 8 (generic)
Amoxicillin	500 mg tid	12 (generic)
Second-line therapy		
Amoxicillin-clavulanate (Augmentin)	500/125 tid or 875/125 bid	94
Cefuroxime (Ceftin)	500 mg bid	132
Clarithromycin (Biaxin)	500 mg bid	65
Doxycycline	200 mg on day 1, then 100 mg on days 2–10	2–6

[a] Estimated cost to the pharmacist at the usual adult dose, based on average wholesale prices in *Redbook*. Montvale, NJ: Medical Economics Data, 1998. Cost to the patient will be higher, depending on prescription filling fee.

Table 8.5-3. Approximate cost of antibiotic treatment for community-acquired acute sinusitis

The standard duration of treatment for acute sinusitis has been 10–14 days, although one study noted benefit from a 3-day course of antibiotics (18).

B. Ancillary treatments.

Adjunctive treatments are prescribed to improve ciliary function and decrease edema. Most of the treatments are unproved; however, a number of modalities are inexpensive, uncomplicated, and have a low incidence of side effects.

1. Sipping of hot tea or chicken soup increases mucociliary clearance for up to 30 minutes.
2. Saline rinse with a normal saline solution (¼ teaspoon of salt to 7 oz. of warm water) removes crusts and moistens mucous membranes.
3. Vasoconstrictor nose drops and sprays may provide temporary relief of nasal congestion when used for no longer than 48–72 hours. The short-acting α_1 agonists, such as phenylephrine, are preferred over the longer acting imidazoline derivative oxymetazoline.
4. The mucolytic agent guaifenesin has been prescribed for thin secretions and shown not to be effective.
5. Although first-generation antihistamines may decrease the duration and severity of sneezing, rhinorrhea, and nasal congestion associated with the common cold, they are not beneficial in treating the symptoms of acute sinusitis.

6. Although topical steroids are effective in management of allergic rhinitis, their benefit in treating acute sinusitis is not supported and they are expensive.

C. Patient education.

Concerns about antibiotic resistance, drug side effects, and efficacy regarding treatment efficacy have led to the publication of guidelines by the U.S. Centers of Disease Control and Prevention (CDC) and the American Academy of Pediatrics. The guidelines promote two principles for judicious use of antibiotics in patients with URIs: (a) an antimicrobial should not be given for the common cold, and (b) mucopurulent rhinitis (thick, opaque, or discolored nasal discharge) is not an indication for treatment unless it persists for more than 10–14 days. The CDC has developed useful patient education handouts and tools for health providers that include the advice: "When parents request antibiotics for rhinitis or the 'common cold,' give them an explanation, not a prescription for antibiotics." The handouts can be downloaded from the CDC website at www.cdc.gov/ncidod/ar/. An order form can be completed at the site to have copies of materials mailed. Included with the order is a prescription pad providing parents with an explanation of the viral illness along with a checklist for treatment recommendations.

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8.6
ALLERGIC RHINITIS

Denise K. C. Sur

I. Introduction.

Allergic rhinitis is a common condition affecting approximately 20% of the U.S. population and ranking as the sixth most prevalent chronic illness in the United States. Patients with this condition can be severely restricted in their daily activities and spend excessive time away from work and school.

II. Diagnosis

A. Clinical presentation

1. **History.** The history is the major diagnostic tool in recognizing allergy as a cause of rhinitis. The most common symptoms of allergic rhinitis are paroxysms of sneezing, rhinorrhea, nasal and palatal pruritus, ocular symptoms, and nasal obstruction. Allergic rhinitis can be either seasonal or perennial, with the seasonal type primarily related to pollen and the perennial type related to indoor allergens.

   Other types of rhinitis include eosinophilic nonallergic rhinitis, vasomotor rhinitis, and rhinitis medicamentosa. Patients with eosinophilic nonallergic rhinitis or vasomotor rhinitis usually do not experience pruritus or paroxysms of sneezing. Patients with rhinitis medicamentosa usually have a history of repetitive topical decongestant use.

   Nasal congestion associated with headache, purulent postnasal discharge, and halitosis suggests sinusitis (see also Chapter 8.5). Persistent unilateral obstruction suggests the presence of polyps or other structural obstructions.

   Of note is that some studies have linked the early introduction of foods to infants and the exposure of infants to cigarette smoke to the early development of allergic rhinitis.

2. **Physical examination.** Patients with allergic rhinitis, whether seasonal or perennial, often have pale, bluish, boggy mucosa and clear secretions. Children may have darkening under the eyes and a nasal crease resulting from rubbing the nose. Conjunctivitis may or may not be present. The nonallergic patient, especially the vasomotor rhinitis patient, is more apt to have red mucosa with secretions of any color or consistency.

B. Laboratory testing

1. Nasal smears for eosinophils are not diagnostic for allergic rhinitis but can be predictive of a favorable response to topical corticosteroids.
2. Skin testing or epicutaneous (prick) testing with appropriate antigens and positive and negative control substances is the most useful procedure for detection of allergic triggers in allergic rhinitis. Skin testing is specific and sensitive, and can assist in management by either avoidance or immunotherapy. It is important to note that food allergies need not be routinely tested because they rarely play a role in allergic rhinitis.
3. A specific serum immunoglobulin E (IgE) radioallergosorbent test (RAST) should be used in lieu of skin testing only when the patient has severe eczema or dermatographism.

III. Management.

Three approaches may be used: avoidance, medication, and immunotherapy.

A. Avoidance.

Avoidance of allergen exposure is always indicated, although it may be difficult to achieve. Measures that help control indoor allergen exposure include placement of dust-proof covers over pillows and mattresses, frequent dusting of surfaces and floors with a damp mop, maintenance of an indoor humidity below 50%, and avoidance or frequent bathing of indoor pets if the patient is sensitive to animals. Measures that help control outdoor allergens include closing of windows, running of air conditioners, and avoidance of lawn mowing and leaf raking.

B. Medications

1. **Antihistamines.** These medications relieve sneezing, itching, and rhinorrhea but not congestion. Their most common adverse effects are sedation, performance/learning impairment, and anticholinergic effects (dry mouth, constipation, urinary retention, and abdominal pain). Compared with first-generation antihistamines, second-generation medications are equally or more effective, have fewer adverse effects, and are generally more expensive. Of the second-generation antihistamines, both loratadine and fexofenadine have Food and Drug Administration labeling as nonsedating, whereas cetirizine does not because it produces a higher incidence of somnolence and fatigue than placebo. Unlike early second-generation antihistamines, loratadine, cetirizine, and fexofenadine have not been linked with arrhythmogenic potential when administered with other medications. Azelastine, an intranasal antihistamine preparation, offers acute symptomatic relief with minimal sedation. Its main drawback is that it leaves a bad taste in the mouth.

   Commonly used antihistamines are listed in Table 8.6-1 .

Antihistamine	Usual dosage
First-generation antihistamines	
Chlorpheniramine maleate (Chlor-Trimeton)	4 mg PO q4–6h
Clemastine fumarate (Tavist)	1.34–2.68 mg PO q12h
Diphenhydramine (Benadryl)	25–50 mg PO q4–6h
Promethazine (Phenergan)	12.5 mg PO q12h
Second-generation antihistamines	
Cetirizine (Zyrtec)	5–10 mg qd
Loratadine (Claritin)	10 mg PO qd
Fexofenadine (Allegra)	60 mg PO bid

PO, by mouth.

Table 8.6-1. Commnoly used antihistamines

2. **Decongestants.** Oral decongestants are α-adrenergic agonists. They have been shown to be effective but can cause side effects, including nervousness, insomnia, irritability, headache, palpitations, and urinary obstruction. Their effects on blood pressure are still in dispute. They are contraindicated in glaucoma and during monoamine oxidase inhibitor therapy. Nasal decongestants should be used for only 2–3 days because prolonged use can lead to rebound congestion and rhinitis medicamentosa.

   Commonly used decongestants are phenylpropanolamine (Propagest), 20–25 mg PO q4h; and pseudoephedrine (Sudafed), 60 mg PO q4–6h.

3. **Inhaled steroids.** Topical nasal corticosteroids are the most potent medical treatment currently available for allergic rhinitis. They have been proved safe for long-term use but can occasionally cause nasal irritation, burning, and bloody nasal discharge. Rare reports of septal perforation have been made. Nasal corticosteroids are approved for use in adults and children older than 12 years. Regular prophylactic use is much more effective than as-needed use.

   Commonly used inhaled steroids are listed in Table 8.6-2 .

Steroid	Dosage
Beclomethasone	1 spray each nostril bid-qid
Budesonide (Rhinocort)	2 sprays each nostril bid or 4 sprays each nostril qd
Flunisolide (Nasalide)	2 sprays each nostril bid
Fluticasone propionate (Flonase)	2 sprays each nostril qd or 1 spray each nostril bid
Triamcinolone acetonide (Nasacort)	2 sprays each nostril qd
Mometasone furoate	2 sprays each nostril qd
Dexamethasone sodium phosphate	2 sprays each nostril bid-tid
Antihistamine	
Azelastine	1 spray each nostril bid
Mast cell stabilizers	
Cromolyn (Nasalcrom)	1 spray each nostril tid-qid

Table 8.6-2. Commonly used inhaled agents

4. **Inhaled cromolyn.** Nasal cromolyn sodium (Nasalcrom) has been shown to be beneficial in treating allergic rhinitis and is approved for use in both adults and children. Its full effect may take up to 3–4 weeks, and adherence may be decreased secondary to need for use 4–6 times a day, but its use may eliminate the need for antihistamines and decongestants in the long term. Based on its human and animal safety profiles, cromolyn should be the first drug considered for the management

of allergic rhinitis in pregnant women and in children. The usual dosage is one spray in each nostril three or four times per day.

5. **Inhaled antihistamines.** One topical antihistamine, azelastine, is now available. It is shown effective in placebo-controlled studies and, like oral antihistamines, can cause sedation.

C. Immunotherapy.

Immunotherapy is the subcutaneous administration of increasing doses of allergens to which the patient is sensitive. It is indicated when severe symptoms are present that do not respond to avoidance or medication. Allergy injections given over a 3- to 5-year period may reduce symptoms in approximately 85% of cases (1).

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IX. CARDIOVASCULAR PROBLEMS

9.1
HYPERTENSION

Kevin A. Pearce

Systemic hypertension (HTN) in adults is defined as systolic blood pressure (SBP) of 140 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher, based on the average of at least three readings taken over at least three visits (1). Risk factors for developing HTN include obesity, a family history of HTN, African-American heritage, type II diabetes mellitus, low socioeconomic status, and increasing age. Although common, it is not normal for BP to increase with age in adults, but the absolute health risks from HTN increase with age. The most common sequelae of HTN are myocardial infarction (MI), stroke or cerebrovascular accident (CVA), congestive heart failure (CHF), and death. Control of HTN reduces the incidence of CVA, MI, and CHF, and prolongs life (1, 2, 3). Optimal treatment regimens consist of lifestyle alterations and medication to achieve a target BP of 120–130/60–85 mm Hg while minimizing side effects (Tables 9.1-1 and Table 9.1-2) (1,2,3 and 4).

Generic name (trade names)	Recommended starting dose[a]
Diuretics	
Thiazides	
Bendroflumethiazide (Naturetin)	10 mg qd
Benzthiazide (Exna)	50 mg qd
Chlorthalidone (Hygroton, others)	25 mg qd
Chlorothiazide (Diuril, others)	500 mg qd
Hydrochlorothiazide (HydroDIURIL, others)	25 mg qd
Hydroflumethiazide (Saluron, others)	50 mg qd
Indapamide (Lozol)	1.25 mg qd
Methyclothiazide (Enduron, others)	2.5 mg qd
Metolazone (Zaroxolyn)	2.5 mg qd
Polythiazide (Renese)	2 mg qd
Quinethazone (Hydromox)	50 mg qd
Trichloromethiazide (Diurese, others)	2 mg qd
Potassium sparing	
Amiloride (Midamor)	5 mg qd
Spironolactone (Aldactone)	50 mg qd
Triamterene (Dyrenium)	50 mg bid
Loop	
Furosemide (Lasix)	20 mg bid
Torsemide (Demadex)	5 mg qd
β-Blockers	
Without ISA	
Atenolol (Tenormin)	50 mg qd
Betaxolol (Kerlone)	10 mg qd
Bisoprolol (Zebeta)	5 mg qd
Carvedilol (Coreg)	6.25 mg bid
Metoprolol (Lopressor)	100 mg qd
Nadolol (Corgard)	40 mg qd
Propranolol (Inderal)	80 mg qd[b]
Timolol (Blocadren)	10 mg bid
With ISA	
Acebutolol (Sectral)	200 mg bid
Carteolol (Cartrol)	2.5 mg qd
Penbutolol (Levatol)	20 mg qd
Pindolol (Visken)	5 mg qd
α,β-Blocker	
Labetolol (Normodyne, Trandate)	100 mg bid
α_1-Blockers	
Doxazosin (Cardura)	1 mg at bedtime
Prazosin (Minipress)	1 mg bid
Terazosin (Hytrin)	1 mg at bedtime
Angiotensin-converting enzyme inhibitors	
Benazepril (Lotensin)	10 mg qd
Captopril (Capoten)	25 mg tid
Enalapril (Vasotec)	5 mg qd
Fosinopril (Monopril)	10 mg qd
Lisinopril (Prinivil, Zestril)	10 mg qd
Trandolapril (Mavik)	1 mg qd
Quinapril (Accupril)	10 mg qd
Ramipril (Altace)	2.5 mg qd
Calcium channel blockers	
Dihydropyridines	
Amlodipine (Norvasc)	5 mg qd
Felodipine (Plendil)	5 mg qd
Isradipine (DynaCirc)	2.5 mg bid
Nisoldipine (Sular)	20 mg qd
Nicardipine (Cardene)	30 mg bid[b]
Nifedipine (Procardia, Adalat)	30 mg qd[b]
Diltiazem (Cardizem, others)	120 mg qd[b]
Verapamil (Calan, others)	180 mg qd[b]
Central α_2-agonists	
Clonidine (Catapres)	0.1 mg bid
Guanabenz (Wytensin)	4 mg bid
Guanfacine (Tenex)	1 mg qd
Methyldopa (Aldomet)	250 mg bid
Peripheral antiadrenergics	
Guanadrel (Hylorel)	10 mg qd
Guanethidine (Ismelin)	10 mg qd
Reserpine (Serpasil)	0.1 mg qd
Direct vasodilators	
Hydralazine (Apresoline)	10–25 mg qid
Minoxidil (Loniten)	5 mg qd
Angiotensin receptor blockers	
Candesartan (Atacand)	16 mg qd
Irbesartan (Avapro)	150 mg qd
Losartan (Cozaar)	50 mg qd
Telmisartan (Micardis)	40 mg qd
Valsartan (Diovan)	80 mg qd
Parenteral drugs for hypertensive crisis	
Labetalol (Normodyne)	20–40 mg IV q10min
Methyldopa (Aldomet)	250–500 mg IV q6h
Hydralazine (Apresoline)	10–40 mg IV q1–2h nonpregnant 5–10 mg IV q20min in pregnancy
Diazoxide (Hyperstat)	50–150 IV q15min
Enalaprilat (Vasotec IV)	1.25 mg IV q6h
Nitroprusside (Nipride)	0.2–10 μg/kg/min IV (use low dose in pregnancy)

ISA, intrinsic sympathomimetic activity.
[a] Review of full prescribing information is strongly advised.
[b] Sustained-release formulations recommended.

Table 9.1-1. Antihypertensive drugs

	Coexisting medical condition									
Drug	Pregnancy	CAD	CHF	LVH	↓ HR	DM	COPD	Gout	↑ Lipids[a]	CRI
Diuretics										
Thiazide	—	—	Yes	—	—	—	—	No	No	No
Loop	—	—	Yes	—	—	—	—	No	—	Yes
Potassium-sparing	—	—	Yes	—	—	—	—	—	—	No
β-blockers[b]										
Without ISA	—[c]	Yes	Yes[c]	—	No	—	No	—	No	—
With ISA	—[c]	—	—	—	—	—	No	—	—	—
Labetalol	—	—	No	—	No	—	No	—	—	—
ACE inhibitors	No	Yes	Yes	—	—	Yes	—	—	—	Yes[d]
Calcium blockers[b]										
Diltiazem	—	—	No	—	No	—	—	—	—	Yes
Verapamil	—	—	No	—	No	—	—	—	—	Yes
Dihydropyridines	—	—	—	—	—	—	—	—	—	Yes
α_2-Agonist	—	—	—	—	—	—	—	—	—	—
Methyldopa	Yes	—	—	—	—	—	—	—	—	—
Angiotensin blocker	No	—	Yes	—	—	—	—	—	—	Yes[d]

A thiazide diuretic, β-blocker, or ACE inhibitor is recommended if coexisting conditions do not suggest otherwise.
Yes = drug is preferred; No = drug is relatively contraindicated; —, drug is acceptable but evidence is insufficient to rank treatment options.
ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; DM, diabetes mellitus; ↓ HR, bradycardia; ISA, intrinsic sympathomimetic activity; ↑ Lipids, dyslipidemia; LVH, left ventricular hypertrophy.
[a] Effects on lipids are modest.
[b] Long-acting formulations are recommended.
[c] Combine with diuretic and ACE inhibitor for systolic CHF.
[d] ACE inhibitors and angiotensin blockers are contraindicated in bilateral renal artery stenosis, or if serum creatinine is >3.0 mg/dL.
[e] Avoid β-blockers in first-trimester pregnancy.

Table 9.1-2. Guidelines for choosing initial drugs for essential hypertension

I. Diagnosis and classification

A. Diagnosis.

Diagnosis depends on accurate readings that reflect the patient's *usual* BP. Readings taken when a patient is acutely ill or in pain should not be used to diagnose HTN.

1. Routine BP measurements should be taken with the patient seated, after at least 5 minutes of rest, with the arm supported at the level of the heart (supine readings are acceptable). Note the index marks on the BP cuff to ensure proper placement and fit. SBP should be recorded at the onset of sounds and DBP at their disappearance. The recommendation is that at least two readings be taken at each visit. Falsely elevated readings may occur if the BP cuff is too small or if severe atherosclerosis is present. If the radial artery is still palpable as a “cord” after inflating the cuff until the pulse is obliterated, then systolic readings are probably not reliable.
2. Home BP measurements are typically about 5–10 mm Hg *lower* than those taken in the medical office. They are of limited diagnostic value but can enhance patient compliance. A consistent and significant discrepancy between BP levels at home and in the medical office may warrant further investigation, including ambulatory BP monitoring.
3. Automatic ambulatory BP monitoring improves diagnostic and prognostic accuracy. However, for reasons of practicality, it should be reserved for patients in whom a significant “white-coat” response is highly suspected, or for patients with symptoms of paroxysmal hypotension or paroxysmal hypertension (1).

B. Classification.

HTN is classified according to severity as stage 1 (SBP 140–159 or DBP 90–99 mm Hg), stage 2 (SBP 160–179 or DBP 100–109 mm Hg), stage 3 (SBP ≥180 or DBP ≥ 110 mm Hg. Classification is defined by *either* SBP *or* DBP, whichever falls into the higher stage (1). High-normal BP is defined as SBP 130–139 or DBP 85-89 mm Hg, and should be lowered, if possible, to less than 130/85 mm Hg. This is especially important in patients with CHF, diabetes, or chronic renal insufficiency (1).

II. Evaluation

A. Detection of a reversible cause,

or exacerbating condition, rests on history and physical examination, followed by a few well-chosen tests (5). Although lifestyle factors, such as alcohol abuse, may exacerbate HTN, only about 5% of patients have a solely secondary cause. Secondary causes to consider include alcohol or drug abuse, sleep apnea, pregnancy, renal artery stenosis, hyperthyroidism or hypothyroidism, primary renal disease, panic disorder, primary hyperaldosteronism, and medication effects (e.g., oral contraceptives, corticosteroids, stimulants). Unless the history and physical examination suggest

otherwise, diagnostic laboratory testing can be limited to the following: serum electrolytes, glucose, blood urea nitrogen (BUN) and creatinine, complete blood count, and urinalysis.

B. Risk stratification

includes assessment of target organ damage (TOD) and other major cardiovascular risk factors, including diabetes and hyperlipidemia. Their presence and severity increase both the clinical risk from HTN and the importance of its control. TOD due to HTN includes left ventricular hypertrophy, coronary artery disease, hypertensive retinopathy, CHF, renal insufficiency, peripheral arterial disease, and CVA. *Symptomatic* TOD can usually be detected through the history and physical examination. *Asymptomatic* TOD should be screened for through history and physical examination,

standard electrocardiography, serum BUN and creatinine, and urinalysis. In addition to history and physical examination, laboratory screening for hyperlipidemia and diabetes is indicated (see also Chapter 17.2 and Chapter 17.4). Control of all modifiable cardiovascular risk factors should be stressed.

C. Assessment of comorbid conditions

is necessary for a comprehensive and safe approach to the treatment of HTN. Some coexisting medical conditions and/or their treatments lead to special indications or contraindications for certain antihypertensive drugs (Table 9.1-2). The physician should always check drug interactions before prescribing.

III. Treatment

A. Nonpharmacologic treatment

should be included in the treatment of all hypertensive patients. It can suffice as the *sole* therapy for asymptomatic patients with stage 1 HTN who have no evidence of TOD or diabetes, if BP can be kept lower than 140/90 mm Hg. *If the lifestyle changes suggested below do not control BP after 6 months, drug therapy should be added for most patients* (1). For patients with no TOD and no other cardiovascular risk factor, allowing up to 12 months for lifestyle changes is reasonable. Most patients with TOD or diabetes will require antihypertensive medication to achieve target BP, which should be ≤ 130/85 mm Hg. Pushing diastolic BP to ≤ 80 mm Hg appears to benefit diabetics (4). Nonpharmacologic treatment can be expected to lower BP on the order of 4–10/2–5 mm Hg. The same lifestyle alterations are also recommended for the primary prevention of HTN (1).

1. **Weight loss.** Patients who are at least 10% above ideal body weight, or whose body mass index exceeds 27, should be placed on a regimen of diet and exercise that can be sustained indefinitely. Gradual and maintained weight loss is the goal.
2. **Low-sodium diet.** The average American consumes 4–5 g of sodium (9.5–12 g of salt) daily, mostly in processed foods. Limiting dietary sodium to less than 2 g/d is recommended. Patients should be taught to use food labels and to make healthy choices in restaurants.
3. **Moderation of alcohol to less than two standard drinks per day** is recommended. One drink equals 12 ounces of beer, 5 ounces of wine, or 2 ounces of liquor. Some patients (especially women) may be sensitive enough to alcohol that further restriction is necessary.
4. **Regular aerobic activity** lowers BP and overall cardiovascular risk independently of weight loss. It also reduces overall cardiovascular risk by other mechanisms. A regular walking routine is a reasonable exercise regimen for most patients.
5. **A diet rich in potassium** should be maintained and can usually be achieved through 4–5 daily servings of fresh fruits (bananas, citrus), juices (orange, tomato), and/or vegetables (broccoli, squash, green leafy vegetables).

B. Pharmacologic treatment.

Grouping the drugs available for the treatment of HTN into ten major classes, as shown in Table 9.1-1, aids in therapeutic choices. Preparations containing two drugs are also available. For most patients, each medication should be started at the lowest recommended dosage and titrated upward, if necessary, at 2- to 8-week intervals, depending on the severity of the HTN. Elderly patients may require even lower doses. Begin with a single-drug or a low-dose combination.

1. **First-line antihypertensive drugs.** Diuretics and ß-blockers have been recommended as initial treatment for all patients who do not have a contraindication to their use because for many years these medications were the only antihypertensive agents proven to reduce cardiovascular risk among uncomplicated patients (1). Angiotensin-converting enzyme inhibitors (ACEIs) and dihydropyridine calcium channel blockers (CCBs) have now also been shown to reduce MI and stroke risk (2,3 and 4). ACEIs have been shown to be especially beneficial in diabetics and patients with CHF, and the evidence supporting them is more extensive than that for CCBs. The other acceptable (but unproven) first-line alternatives are:

angiotensin receptor blockers and the α–ß blocker labetolol (Normodyne). α_1-Adrenergic blockers have fallen out of favor because one (doxazosin) was recently shown to be inferior to the diuretic chlorthalidone for cardiovascular risk reduction.

2. **Choosing the initial drug or drugs.** Start with a thiazide diuretic, ACEI, or ß-blocker unless contraindicated due to another medical condition or a negative experience by the patient. Consider evidence that a certain drug will provide special benefit (e.g., ß-blocker after an MI, or ACEI for CHF). If these are eliminated as first choices, choose an alternative based on coexisting medical conditions, potential drug interactions, dosing schedule, cost, and, finally, the age and race of the patient (African Americans and the elderly may respond better to diuretics and CCBs than to ACEIs and ß-blockers) (1). Pay special attention to the drugs' inotropic and chronotropic effects on the heart and to their effects on serum potassium. Table 9.1-2 summarizes relative indications and contraindications for the frequently used classes of antihypertensive drugs with respect to common coexisting medical conditions.

C. Hypertensive crises

are rare clinical emergencies in which high BP must be lowered immediately to prevent or limit a morbid complication. The situation, not the BP level alone, constitutes the emergency. Examples include acute pulmonary edema, acute MI, hypertensive encephalopathy, eclampsia, and dissecting aortic aneurysm. In these situations, a controlled reduction of BP by 20%–25% over a few minutes to a few hours is indicated. Hypertensive urgencies are situations in which BP should be lowered to 160–170/100–110 mm Hg within 24 hours to prevent complications. These include severe perioperative hypertension and accelerated malignant hypertension (BP greater than 220/ 120 mm Hg and rising). Precipitous decreases in BP should be avoided. The goal is clinical stabilization, not normalization of BP. Relatively short-acting parenteral (intravenous, IV) antihypertensives, followed by oral therapy usually work best. Suggested IV drugs and doses are listed in Table 9.1-1 . If IV therapy is not an option, oral captopril (Capoten) 25 mg, clonidine (Catapres) 0.1–0.2 mg, or labetalol (Normodyne) 200–400 mg can be used; each has a hypotensive effect within 1 hour. Sublingual administration is not more effective than oral. In the setting of acute CVA, HTN should generally not be treated unless SBP is greater than 220 mm Hg or unless there are signs of progressive intracranial bleeding. Quiet bed rest often results in a significant decrease in BP (1,6).

D. Follow-up.

Patients with stage 3 HTN should be seen every 1–4 weeks until the BP is less than 180/110 mm Hg. Those with stage 1 or 2 HTN should be seen at 1- to 3-month intervals until the BP is at target level. Thereafter, elderly patients and those with TOD or high cardiovascular risk should see their doctor at least annually. Laboratory tests at follow-up are determined by the type of therapy, other conditions, and the baseline values. If treatment goals have not been met at the prescribed follow-up intervals, the medication dose should be changed, a different class of drug should be tried, or a second drug from another class should be added (Table 9.1-1). Combining two first-line drugs from different classes at low to moderate doses is often effective, and inclusion of a diuretic is desirable (1). Avoid unwanted drug interactions, especially those that have cardiac and electrolyte effects. Central sympatholytics, α_1 blockers, and peripheral antiadrenergics are best reserved as second-line drugs (except in pregnancy, as discussed below). Direct vasodilators are useful for patients failing treatment with first- and second-line drugs but should be combined with a diuretic.

IV. Hypertension in pregnancy

A. Definitions and diagnosis.

During pregnancy, HTN is diagnosed if SBP has risen by 30 mm Hg or more from prepregnancy or first-trimester values, or if SBP is 140 mm Hg or greater, or if DBP has increased by 15 mm Hg or greater or is 90 mm Hg or higher. Preeclampsia is HTN accompanied by edema and

proteinuria, with onset after the 20th week of gestation. Transient HTN of pregnancy (gestational hypertension) develops during pregnancy without proteinuria or edema. By definition, chronic HTN must have been observed before the 20th week of gestation. Preeclampsia can be superimposed on chronic HTN. Preeclampsia should be the presumptive diagnosis if it cannot be excluded because it has the most immediate and serious consequences for the mother and fetus (7) (see also Chapter 14.6 and Chapter 14.8).

B. Treatment.

In preeclampsia, pharmacologic antihypertensive treatment has no proven benefit for mother or fetus. Therefore, use antihypertensive drugs in preeclampsia only if the BP seriously threatens the mother before the problem is cured by delivery (i.e., SBP greater than 160 and DBP greater than 110 mm Hg are reasonable treatment thresholds, but consider clinical status). In such cases, methyldopa (Aldomet), 250–500 mg PO tid, is recommended prenatally. Severe HTN during labor or delivery can be safely controlled with labetalol (Normodyne) 10–20 mg IV every 10–15 minutes. An alternative is hydralazine (Apresoline), 5–10 mg IV every 20–30 minutes (7). Bed rest is the only nonpharmacologic antihypertensive treatment recommended in pregnancy, despite its unproven efficacy. In some cases, delivery of the fetus is the only way to prevent progression to eclampsia (see also Chapter 14.6).

Stage 1 chronic HTN can be simply followed during pregnancy without drugs because antihypertensive therapy is not supported by evidence of significant benefit for the mother or fetus (7). Note that weight loss, aerobic exercise, and sodium restriction are not recommended for the pregnant patient with HTN. Drug treatment is recommended by most authorities for DBP exceeding 100 mm Hg, but it is unproved whether control of stage 2 or 3 chronic HTN prevents preeclampsia or improves fetal outcome. Methyldopa is the drug of choice because it has the longest history of use with little evidence of adverse fetal effects. *ACEIs and angiotensin receptor blockers disrupt uterine and fetal circulation and are contraindicated in pregnancy. B-Blockers should be avoided in the first trimester*. All the other oral antihypertensive drugs are classified as Food and Drug Administration category B or C for use in pregnancy, so they can be used as alternatives to methyldopa. Dosing is the same as for nonpregnant adults (Table 9.1-1). Transient HTN of pregnancy appears to be benign but should be managed in the same way as chronic HTN. It will resolve after delivery, by definition.

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9.2
ISCHEMIC HEART DISEASE

Lee A. Green

Management of acute cardiac ischemia [unstable angina and myocardial infarction (MI)] is based on the principles of rapid evaluation, risk stratification, and prompt initiation of therapy. Diagnostic and management decisions must be made rapidly and implemented immediately because the efficacy of many of the available treatments declines rapidly with time from onset of ischemia.

I. Rapid evaluation

A. Time frame

is crucial: Patients should be classified as having probable noncardiac pain, stable angina, acute ischemia (unstable angina or MI), or infarction meeting thrombolysis criteria very swiftly. An electrocardiogram (ECG) should be obtained within 10 minutes of presentation, and thrombolysis candidates should begin receiving lytic agents within 30 minutes.

B. History

is the most important information in the decision process for chest pain patients. It should include the following:

1. The location, character, and time course of the pain. Chest or left arm pressure or pain of a steady, dull nature is classic for cardiac ischemia. Occasionally, pain may be present only in the jaw or scapular area. Sharp or pleuritic pain weighs against the diagnosis, as does pain that can be localized with one finger.
2. History of ischemic cardiac disease.
3. The classic epidemiologic risk factors, such as smoking, high cholesterol, hypertension, obesity, and family history, are of limited diagnostic utility in the acute setting (1).
4. The patient's sex is often misused as a diagnostic cue (2) and should in general not be strongly influential in the decision making process.
5. Diabetes is a long-term risk factor of little direct diagnostic utility in the emergency department, but bear in mind that diabetic patients often lack the characteristic pain of acute ischemia (see Chapter 17.2).

C. Electrocardiography

is the other cornerstone of diagnosis and risk stratification. Crucial features that are predictive of acute ischemia include the following:

1. Q waves of 1 mm or greater in at least two contiguous leads and not known to be previously present.
2. ST segment changes, either 0.5 mm or more elevation or 1 mm or more depression, in at least two contiguous leads.
3. T-wave changes, either hyperacuity (≤ 50% of maximum QRS amplitude) or inversion (excluding lead aV_1), in at least two contiguous leads.
4. New conduction disturbances and arrhythmias.

D. Physical examination

should be expeditiously conducted and directed to key findings, which include pulmonary edema, particularly sudden or “flash” edema; mitral valve murmur, particularly if of new onset; hypotension or shock; confusion or other mental status changes; and hypoxia.

E. Chest radiography

should not delay evaluation of potential ischemia and initiation of anti-ischemic therapy.

F. Laboratory testing

1. Creatine kinase (CK) is measured every 6–8 hours until MI is diagnosed or excluded. In the low-risk patient with normal ECG this may be a single measurement at 8 hours. MB isoenzyme fractions of 0.40 or greater are diagnostic of MI. In some centers MB subform analysis has replaced isozyme determination and is more specific. CK-MB can be indicative of reinfarction; the length of time troponins remain elevated makes them unsuitable for that purpose.

2. Cardiac troponins T and I are more than 90% sensitive and similarly specific at 8 or more hours from the onset of pain (3). Either or both may be assayed, generally for levels greater than 0.1 ng/mL. Positive troponins with normal ECG and normal or borderline CK-MB can identify patients with non-Q-wave MI or unstable angina who are at increased risk for infarction or sudden death, and may benefit from intensive therapy or revascularization.

G. Differential diagnosis.

Patients presenting with chest pain and related complaints have acute cardiac ischemia in a minority of cases: approximately 30% in the emergency department setting (4) and less than 5% in the primary care physician's office setting (5) (see Chapter 2.5). Other high-probability diagnoses that should be considered are panic attack, gastroesophageal reflux disease, musculoskeletal pain, and pleurisy. Panic attack and gastroesophageal reflux disease are often close mimics of angina, and both are more common than angina in primary care settings. Both can result in morbidity, if misdiagnosed as angina, from inappropriate cardiac workups and from failure to manage the patient's real condition.

II. Risk stratification

A. Thrombolysis criteria

1. Patients with ischemic symptoms plus acute Q waves, or ST-segment elevation of at least 1 mm in at least two contiguous leads, or acute left bundle-branch block are thrombolysis candidates. Patients with ST-segment depression in leads V and V suggestive of posterior MI may receive some benefit.
2. Patients not meeting these criteria should not receive thrombolytic therapy (6) as it exacerbates outcomes. Thrombolysis is contraindicated for ST-segment depression other than that associated with posterior MI.
3. Thrombolytic therapy should be initiated as early as possible, although it still offers some benefit at up to 12 hours from symptom onset.
4. Contraindications are active gastrointestinal and genitourinary bleeding (but not menses), abdominal or thoracic surgery within 1 month, head trauma, recent stroke, hypertensive crisis, aortic dissection, and pancreatitis. Age is not an absolute contraindication, but mortality among patients 75 years and older may be increased rather than decreased by thrombolysis (7), and alternative strategies should be considered for them.
5. Emergent catheterization with balloon angioplasty is an optional alternative in centers equipped and staffed to provide it, and it may be more cost effective in some circumstances (8).

B. High-risk patients

not meeting thrombolysis criteria

1. High-risk features include rest pain, acute ST-segment elevation, new or worsening murmurs, CHF symptoms including S_3, and hypotension.
2. This category includes both MI and severe unstable angina patients. They may be impossible to distinguish, and initially they are treated in an identical fashion.

C. Intermediate-risk patients

include those with prolonged (= 20 minutes) rest pain now resolved, ST depression or T-wave changes, and new or recently (≤ 2 weeks) accelerated chronic angina of Canadian Cardiovascular Society class III (pain on one flight of stairs or one to two blocks walking) or class IV (pain with minimal activity), or those 65 years of age or older. Intermediate-risk patients are typically observed in the hospital until MI has been ruled out (or confirmed) and angina brought back under control.

D. Low-risk patients

lacking the intermediate-risk and high-risk features mentioned previously may be observed in the hospital in some cases but will typically be treated primarily as outpatients.

III. Treatment of MI

A. Initial medical therapy

1. Aspirin is one of the most effective mortality-reducing interventions available.

a. All high- and intermediate-risk patients and most low-risk patients lacking absolute contraindications should receive aspirin, 325 mg chewed stat, followed by 160–325 mg orally daily or 325 mg every other day (9).
b. True contraindications are clear history of severe hypersensitivity, currently active major hemorrhage, or recent (≤ 2 weeks) bleeding ulcer disease or hemorrhagic stroke.
c. Ticlopidine (Ticlid), 250 mg bid, or clopidogrel (Plavix), 75 mg once daily, may be considered as alternatives to aspirin in patients with true aspirin hypersensitivity.

2. ß-Blockers also substantially improve survival and should be employed unless clearly contraindicated.
a. Asthma, chronic obstructive pulmonary disease, bradycardia, and CHF require cautious initiation, at one half to one quarter the usual doses and titrated upward to normal doses if tolerated, but they are not absolute contraindications to treatment.
b. Marked (PR interval more than 0.24 second) first-degree atrioventricular block, any second- or third-degree block, cardiogenic shock, bradycardia less than 60 beats/min, or hypotension with systolic blood pressure less than 90 mm Hg are contraindications until resolved.
c. Acute IV loading is indicated for high-risk patients; others may begin oral dosing in the first 24 hours.
d. Metoprolol (Lopressor) and atenolol (Tenormin) are most frequently employed due to their favorable side effect profiles. Esmolol IV (Brevibloc) is an ultrashort-acting agent minimizing risk for asthma, chronic obstructive pulmonary disease, CHF, or bradycardia patients. Atenolol is initiated with 5 mg IV over 10 minutes, then repeated over 5 minutes. If tolerated, 50 mg is given orally stat and bid, then 50–100 mg daily after the acute episode. Metoprolol is initiated with 5 mg IV every 2 minutes for three doses, then 50 mg PO bid beginning 15–60 minutes after the third IV dose and continuing for 48 hours. Fifty to 100 mg PO daily is used after the acute episode. Esmolol is initiated IV at 0.1 mg/kg per minute and then titrated upward by 0.05 mg/kg per minute every 10–15 minutes until effect is achieved or 0.2 mg/kg per minute is reached.
e. Blood pressure and heart rate should be monitored during initiation, along with frequent auscultation for pulmonary edema or bronchospasm.

3. Heparin may or may not add benefit to aspirin alone or to thrombolysis followed by aspirin (10,11).
a. Full-dose heparinization is required if heparin is to be used.
b. Low molecular weight heparin (LMWH) is at least equal and some studies find it superior to unfractionated heparin (UFH), and LMWH offers a lower risk for bleeding complications. It is administered subcutaneously in either fixed or weight-dependent dose according to the specific preparation chosen (see package inserts or institutional protocols). Coagulation parameters are not monitored or dose adjusted for LMWH.
c. Administration of UFH may be IV or SC, in any of the several clinical protocols commonly used, to maintain activated partial thromboplastin times of 1.5–2.5 times the control.
d. Heparin is continued for 3–5 days or until revascularization if the patient is to receive such therapy acutely.

4. Platelet glycoprotein (GP) IIb/IIIa inhibitors may be of benefit in patients having MI but without ST-segment elevation, who have high-risk features or refractory ischemia and are not at increased risk of bleeding complications. Tirofiban (Aggrastat), eptifibatide (Integrilin), and abciximab (ReoPro) are the currently available agents.

They are administered by intravenous bolus followed by infusion, on protocols specific to the agents. Package inserts or institutional protocols should be read before initiation. All are administered with heparin; eptifibatide and abciximab are also combined with aspirin. Thrombocytopenia, recent (less than 30 days) active internal bleeding, recent major surgery, recent stroke, recent major trauma, history (ever) of intracranial hemorrhage, existence of atrioventricular malformation, aneurysm, severe hypertension, intracranial malignancy, or suspicion of aortic dissection contraindicates the use of GP IIb/ IIIa blockers.

5. Nitroglycerin (NTG) relieves symptoms, although it probably does not affect complications or mortality.
   a. Initial treatment is up to three sublingual tablets of NTG over 15 minutes; if symptoms are not relieved, NTG IV should be initiated.
   b. NTG IV is initiated at 5–10 µg/min and titrated upward by 10 µg/ min every 5–10 minutes until relief is achieved, or until the occurrence of headache or systolic BP below 90 mm Hg (or 30% below baseline systolic blood pressure in significantly hypertensive patients); 100 µg/ min or more may be needed.
   c. Patients who benefit should be switched to oral or topical therapy once they are free of symptoms for 24 hours.
6. Angiotensin-converting enzyme (ACE) inhibitors
   a. Patients with even transient clinical evidence of CHF or evidence of left ventricular (LV) dysfunction will have reduced mortality if ACE inhibitors are tolerated without hypotension (12,13). There is no clear benefit to patients with normal LV function.
   b. Although optimal timing of initiation has not yet been defined, within 24 hours of hemodynamic stabilization appears prudent at this time (12).
   c. Agents include lisinopril (Prinivil, Zestril), fosinopril (Monopril), and quinapril (Accupril) initiated at 5 mg daily and titrated upward to 20 mg/d (lisinopril) or 30 mg/d (other agents) as CHF symptoms require; enalapril (Vasotec) initiated at 2.5 or 5.0 mg/d titrated up to 40 mg/d in single or divided (bid) dose; ramipril (Altace) initiated at 2.5 mg bid up to 5 mg bid; trandolapril (Mavik) initiated at 1 mg/d titrated up to 4 mg/d single dose; and captopril (Capoten) 12.5–25.0 mg tid (occasionally up to 50 mg tid if necessary). All agents should be initiated with follow-up of blood pressure for hypotension.
7. Morphine is effective at relieving pain as well as anxiety when used intravenously in adequate doses (0.05–0.1 mg/kg), repeated as needed (often much more frequently than 3 hours). Inadequate dosing is common. Other narcotics and mixed agonist-antagonists offer no advantage over morphine.
8. Oxygen is typically administered at 2 L/min by nasal cannula.
9. Anxiolytics, such as diazepam (Valium), are seldom indicated if pain relief is adequate. Morphine is also readily reversible if necessary.
10. Calcium channel antagonists do not improve outcomes and can increase mortality in patients with LV dysfunction or pulmonary edema (9). They are used for atrial arrhythmias, variant angina, or hypertensive urgencies. Nifedipine (Procardia) should be avoided in coronary artery disease patients not in full ß blockade.
11. Prophylactic antiarrhythmic agents, such as lidocaine (Xylocaine and others), are not effective in improving outcome and increase mortality in the hospital. They should not be employed (14).

B. Thrombolytic therapy

1. Hospitals offering thrombolysis usually do so according to written protocols. The reader is urged to consult her or his institution's protocol for details of administration.
2. Usual agents and regimens are streptokinase (1.5 million U IV over 1 hour) or recombinant tissue plasminogen activator (15 mg IV in 2 minutes, then 0.75 mg/kg for 30 minutes, then 0.5 mg/kg for 60 minutes,

not to exceed 100 mg total). Recombinant tissue plasminogen activator offers a small (approximately 1%) absolute mortality risk reduction and fewer allergic reactions, but its cost is approximately ten times that of streptokinase.

3. Thrombolytic therapy is accompanied by aspirin and ß-blockers and may be followed by IV heparin while the patient is in the hospital.

C. Complications,

such as arrhythmias, CHF, high-grade block, and hypoxemia, are common, and monitoring should anticipate them. Hypotension may be severe and can require pressor agents or intra-aortic balloon pumping. Ventricular aneurysm and myocardial rupture may occur approximately one week after MI.

D. Continuing treatment

1. ß-Blockers are beneficial for at least 5 years after MI (9). The duration of benefit of aspirin use is undefined but exceeds 2 years. ACE inhibitors are beneficial for at least 15 months.
2. Noninvasive testing (see Section VI) is recommended before discharge for those not undergoing angiography acutely. Patients whose results suggest uninfarcted myocardium remaining at risk are candidates for coronary angiography and potential revascularization as soon as feasible.

IV. Treatment of unstable angina

A. High-risk patients

(see Section II) are treated as for MI, except that unstable angina patients are not candidates for thrombolysis. Troponins may be useful in risk prognostication and subsequent treatment decisions.

B. Intermediate-risk patients

(see Section II) typically require in-hospital observation and electrocardiographic monitoring while symptoms are controlled and MI ruled out, and they will benefit in reduced mortality and morbidity from aspirin and ß-blocker therapy as outpatients unless contraindicated.

C. Some low-risk patients

may require hospital monitoring, but most may be urgently treated as outpatients and followed up within 24–72 hours. Treatment is similar to that of stable angina (Section V).

V. Treatment of chronic stable (effort-induced) angina

A. Aspirin,

160–325 mg/d, reduces mortality and nonfatal MI. Angina patients should be taking aspirin unless contraindicated (see Section III.A.1). If the contraindication is hypersensitivity (not bleeding risk), ticlopidine or clopidogrel should be considered.

B. ß-Blockers

are effective antianginal therapy and also reduce mortality; therefore, they should be the first choice for patients able to tolerate them (see Section III for specific agents and regimens).

C. Nitrates

are useful orally in several preparations or topically (as paste or patches) for symptom control in patients for whom ß-blockers alone do not suffice or who cannot tolerate them.

1. Sublingual tablets (0.4 mg) are effective within 90 seconds for brief attacks.
2. Oral and topical nitrates should be given with a 6- to 8-hour nitrate-free interval daily, typically at night, to prevent attenuation or disappearance of therapeutic effect.
3. Several brands of topical nitrate patches are available that are very convenient for patients. Sites should be shifted with each application to prevent skin complications.
4. Oral agents include isosorbide dinitrate (Isordil, Sorbitrate, and others) and isosorbide mononitrate (Ismo, Imdur) in both regular and sustained-release preparations. Regular-release isosorbide dinitrate is initiated at 5–20 mg every 6 hours for 3 doses daily, titrated upward to 10–40 mg per dose. Sustained-release dinitrate is initiated at 40 mg/day, titrated upward to 40–80 mg 1–3 times daily. Regular-release isosorbide mononitrate is dosed at 20 mg on arising and repeated 7 hours later; sustained-release mononitrate is initiated at 30–60 mg in the morning, titrated upward to 120–240 mg/d in steps of 30–60 mg, with 3 days at each step.

D. Calcium channel antagonists

are appropriate in few situations. They are not reviewed in detail here due to their limited utility in ischemic heart disease.

VI. Noninvasive testing

A. Graded electrocardiographic exercise testing

under graduated protocols, using a treadmill or bicycle ergometer and 12-lead electrocardiographic monitoring, is the first-choice noninvasive test for diagnosing coronary artery disease and evaluating risk for patients with unstable angina (9). Submaximal stress testing is used for post-MI patients evaluated prior to discharge.

B. Stress testing

is recommended at discharge (typically 12–24 hours from admission) for patients who are ruled out for MI or unstable angina on short-stay protocols.

C. Pharmacologic stress testing

is reserved for patients with orthopedic or other disabilities that preclude reaching an adequate exertion level on graded exercise testing.

D. Thallium scintigraphy imaging

is useful for patients whose ECGs are difficult to interpret due to bundle-branch blocks, pacemaker effects, or other preexisting anomalies. It adds few data to graded exercise testing results for the majority of patients. Stress echocardiography is not generally recommended as a first choice (especially in patients with prior MIs who have preexisting wall motion abnormalities) but is used in some institutions; its test characteristics are still under study.

VII. Revascularization

A. Medical therapy versus revascularization

1. Patients with multiple comorbid conditions of poor prognosis are seldom candidates for revascularization. However, age alone is not a contraindication.
2. Significant likelihood of improved survival with revascularization is demonstrated for patients with 50% or greater left main coronary artery stenosis, three-vessel disease and diminished LV function, and two-vessel disease involving the left anterior descending artery.
3. Symptom improvement may be achieved for patients with any degree of coronary artery disease who have lifestyle-limiting anginal symptoms that are not adequately controlled with medical therapy.
4. Patients with severe LV dysfunction, especially those requiring intra-aortic balloon pumping, should be evaluated by a consultant for candidacy for emergency revascularization.

B. Angioplasty versus coronary artery bypass grafting (CABG)

1. Left main coronary lesions are considered inappropriate for angioplasty due to the high rate of emergency CABGs.
2. Patients with diabetes who are on insulin or oral agents have lower mortality with CABG than with angioplasty (15) and should receive CABG in preference to angioplasty. This is not true for diabetics who do not require medication (see Chapter 17.2).

C. Stenting

1. Stent placement after angioplasty, when combined with suitable antithrombotic therapy (particularly platelet GPIIb/IIIa blockers), may improve outcomes. This area is under active research, and recommendations are changing rapidly.

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9.3
MURMURS AND VALVULAR HEART DISEASE

Eric M. Walsh

IV. Overview.

Approximately 3.4% of adults have valvular heart disease (1). Of those with valvular heart disease, the vast majority (73%) have mitral regurgitation. Most of the other patients with valvular heart disease (27%) have aortic stenosis, with a smaller percentage presenting with aortic insufficiency and mitral stenosis. A tiny percentage of adult patients with valvular heart disease have right-sided murmurs, ventricular septal defects (VSDs), or other pathology. The incidence of valvular heart disease in children is more difficult to estimate because some pathologic murmurs, such as a small VSD or a patent ductus arteriosus (PDA), may disappear. For each of the common types of valvular heart disease it is important to know the essentials of diagnosis, natural history, medical interventions, complications, and timing of surgery. Other areas of importance include murmurs in pregnant women, murmurs in athletes, and murmurs in infants and children.

V. Basic diagnostic tools

A. History and physical examination.

History suggesting valvular heart disease is directed at symptoms potentially related to dysfunction of a valve. These symptoms can be thought of as relating to diminished forward flow (fatigue and decreased exercise tolerance) and symptoms relating to pulmonary congestion (paroxysmal nocturnal dyspnea and orthopnea). The physical examination focuses on the location, timing, duration, and quality of the murmur.

In addition to these cardinal elements, various provocative maneuvers can cause changes in the murmur, changes that aid diagnosis. Valsalva's maneuver and standing decrease preload. Squatting or raising the legs increases preload. Handgrip increases afterload. There is no maneuver that decreases afterload. The beat after the long pause associated with a premature beat may also give clues to the etiology of a murmur by causing increased filling of the left ventricle.

B. Electrocardiogram (ECG).

The ECG is not a specific tool for the diagnosis of valvular heart disease. Findings such as atrial enlargement or left ventricular hypertrophy (LVH) often occur late in the course of valvular heart disease.

C. Chest x-ray (CXR).

Like the ECG, the CXR does not offer early or specific diagnostic clues to valvular heart disease. Radiographic evidence of cardiomegaly or pulmonary congestion is a late finding.

D. Echocardiogram.

The echocardiogram is the definitive indicator that rules in or rules out the presence of valvular heart disease. It should be used when there is moderate clinical suspicion of valvular heart disease (2).

VI. Mitral regurgitation

A. Essentials of diagnosis.

Mitral regurgitation causes a holosystolic murmur best heard at the apex. It typically includes S_2, although late in the course of the disease, when left atrial pressure is high, the murmur will end earlier. The murmur of mitral regurgitation may become louder with increased afterload (handgrip). It usually does not change with increased preload (squatting and leg-lift) or with the beat after a compensatory pause for a premature contraction.

B. Prognosis and medical management.

Mitral regurgitation is the most indolent and benign of the valvular lesions. Patients often do well on medical management for years after the development of symptoms. Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors is the mainstay of treatment. More advanced disease can also be treated with diuretics and digoxin as a way of postponing or avoiding surgery.

C. Complications of the disease and timing of surgery.

The most common complication of mitral regurgitation is atrial fibrillation, which is often difficult to restore to sinus rhythm. Congestive heart failure is a late complication. Timing of surgery is controversial, but clear indications include LV failure, decreased cardiac output, and a rapid increase in ventricular size of more than 2 cm/yr as defined by echocardiogram or CXR. It is important to realize that a normal ejection fraction does not mean a normal cardiac output because a portion of the ejection fraction of the left ventricle is going into the left atrium and not into the systemic circulation.

D. Mitral valve prolapse (MVP).

MVP is an exceedingly common condition that is sometimes a cause of mitral regurgitation. Patients may present with symptomatic arrhythmia, atypical chest pain, or exaggerated autonomic symptoms. Physical examination reveals a click and sometimes a murmur, which move toward S_2 with increased preload and increased afterload. The click and murmur move toward S_1 with decreased preload. The click and the murmur are often evanescent. The degree of pathology is related to the degree of mitral regurgitation, which often must be confirmed by echocardiogram. ß-Blockers can be used for symptomatic treatment of chest pain or arrhythmia.

IV. Aortic stenosis

A. Essentials of diagnosis.

The murmur of aortic stenosis is described as a harsh and diamond-shaped systolic murmur. It is best heard at the second right intercostal space. It gets softer with increased afterload, and usually does not change with maneuvers that affect preload. The murmur will often be noticeably louder in the first beat after the compensatory pause for a premature contraction. Symptoms occur late in the course of the disease and are a very ominous sign.

B. Prognosis and medical management.

Presymptomatic management is directed at defining the rate of progression, namely, the gradient across

the valve and the progression of LVH. There is no benefit in medical management with regard to symptoms or prognosis.

C. Complications of the disease and timing of surgery.

The development of congestive heart failure, syncope, or angina carries a prognosis worse than that of many kinds of aggressive cancer. Surgery should be considered immediately when any symptoms occur. Presymptomatic surgery can be considered when there is ventricular enlargement, frequent ectopy, wall motion abnormalities, or severe electrocardiographic abnormalities, such as LVH, repolarization abnormalities, or left bundle-branch block. New research has shown that the speed of the blood flow through the stenotic valve, even in asymptomatic patients, may be a good indicator of which patients require surgery (3).

VI. Subvalvular aortic stenosis

A. Essentials of diagnosis.

Subvalvular stenosis has several names. It is called idiopathic hypertrophic subaortic stenosis (IHSS), asymmetric septal hypertrophy, or hypertrophic obstructive cardiomyopathy. The murmur of IHSS is similar to the murmur of aortic stenosis. Differences are that any maneuver that will make the left ventricle larger in diastole will make the murmur softer. These maneuvers include increased preload (squatting, lifting the legs), increased afterload (handgrip), or a post-extrasystolic beat. A smaller left ventricle (decreased preload: standing, Valsalva) will make the murmur louder. Peripheral pulses are extremely brisk.

B. Prognosis and medical management.

Recent work suggests that the degree of septal hypertrophy is directly related to the prognosis (4). Medical management is with ß-blockers or calcium channel blockers with negative inotropic effect. Arrhythmia or syncope is an ominous sign.

C. Complications of the disease and timing of surgery.

IHSS is sufficiently rare and unpredictable in its course that comanagement with a cardiologist is recommended. There is not good agreement on guidelines for when surgery (septoplasty) should be considered.

VII. Aortic insufficiency

A. Essentials of diagnosis.

Aortic insufficiency is often missed clinically for many years. The diastolic murmur is soft and easy to overlook. Aortic insufficiency should be suspected with a loud systolic flow murmur (secondary to increased stroke volume from regurgitation), bounding pulses, or a wide pulse pressure. A high-pitched blowing, decrescendo, diastolic murmur is best heard at the left sternal border with the patient sitting and in holding his or her breath in expiration. The murmur may get louder with increased afterload (handgrip).

B. Prognosis and medical management.

With a normal ECG, normal blood pressure and no cardiomegaly on CXR, 96% of patients with aortic insufficiency are alive at 15 years without surgery. Even with two to three ECG abnormalities and cardiomegaly, the prognosis is good; 70% of patients are alive at 15 years without surgery. The mainstays of medical management are afterload reduction with ACE inhibitors and, secondarily, diuresis.

C. Complications of the disease and timing of surgery.

Surgery can be put off until clinical symptoms (fatigue, dyspnea on exertion) develop or until certain objective findings occur. These findings include pulse pressure greater than 100 mm Hg, LVH and/or ST-T changes on ECG, cardiothoracic ratio greater than 60% on CXR, echocardiographic findings of end-systolic diameter greater than 50 mm, or end-diastolic diameter greater than 70 mm.

VIII. Mitral stenosis

A. Essentials of diagnosis.

Mitral stenosis, the rarest left-sided valve pathology, is the most difficult to diagnose clinically. The diastolic murmur, with pre-systolic accentuation, is best heard at the apex. Although S_2 is classically described as being loud, it can also be normal or soft at the disease progresses. Changes in preload and afterload do not usually change the murmur.

B. Prognosis and medical management.

Fifty-eight percent of patients with mild symptoms and 85% of patients with moderate symptoms are dead at 10 years without surgery. The only medical options for mitral stenosis are

the use of diuretics and attempting to maintain sinus rhythm (which can be very difficult). If there is atrial fibrillation, rate control to 50–60 beats/min is essential. Symptoms are directly related to valve area, becoming obvious and potentially disabling below a valve area of 2.5 cm^2. Medical management does not improve outcome.

C. Complications of the disease and timing of surgery.

Workup for surgery should begin before symptoms begin. Age and anticoagulation risk affect the decision as to what type of surgery should be done. Often, the decision of artificial valve versus commisurotomy cannot be made until the time of surgery.

IX. Valvular heart disease in the athlete

A. Preparticipation physical.

The preparticipation physical should focus on a family history of heart disease; sudden death; personal history suggesting syncope, near syncope, or arrhythmia; and evaluation of heart murmurs in supine, sitting, standing, squatting, and post-squatting positions.

B. High-risk murmurs.

Most common causes of serious valvular heart disease in athletes causing sudden death are mitral prolapse and IHSS (5).

C. Risk assessment.

The main issue with mitral valve prolapse is the degree of ectopy present, especially with exercise. In IHSS, the most significant problem is the degree of outflow obstruction, which is usually related to the thickness of the septum.

X. Valvular heart disease in pregnancy

A. Etiology.

Most murmurs in pregnancy are physiologic.

B. Preexisting disease.

Preexisting valvular heart disease often is exacerbated by pregnancy.

C. Contraindications to pregnancy.

Valvular disease causing New York Heart Association (NYHA) class III or class IV heart failure, severe left to right shunt, hypoxemia, or hemoglobin greater than 18 is a contraindication to pregnancy.

XI. Valvular heart disease in infants and children

A. Congenital versus valvular disease.

The physician must consider valvular heart disease as a subset of congenital heart disease. In diagnosis of murmurs in infants and children, think of congenital problems and then rule in or out a valvular etiology.

B. A taxonomy of pediatric murmurs

1. Left to right shunts, e.g., VSD or atrial septal defect (ASD).
2. Obstructive lesions, such as aortic stenosis, pulmonic stenosis, coarctation of the aorta.
3. Valvular insufficiency

C. Age-dependent risk of a pathologic murmur

1. A murmur heard in the first 24 hours of life carries a 1 in 12 risk of being due to congenital heart disease.
2. A murmur heard at 6 months has a 1 in 7 chance of being due to congenital heart disease.
3. By 1 year, the odds drop to 1 in 50 and continue to decline through childhood and adolescence.

D. Relative frequency of pathologic murmurs in infants.

Sixty-three percent of murmurs in congenital heart disease are caused by the six most common congenital defects:

1. VSD—32%
2. Pulmonic stenosis—9%
3. PDA—8%
4. ASD—7%
5. Coarctation of the aorta—4%
6. Aortic stenosis—4%

E. Signs and symptoms of valvular disease in infants and children

Findings more common in infants and children than in adults include grunting, poor feeding, sweating, poor weight gain, wheezing, decreased exercise tolerance, cough, and squatting after exercise (to increase preload). Cyanosis and edema are very late findings.

F. Referral strategies.

Pediatric cardiologists do not order echocardiograms in about 50% of patients seen in referral for murmur. This makes the strategy of referring all questionable murmurs to a pediatric cardiologist more cost effective than ordering echocardiograms and referring only the pediatric patients with positive findings on echo.

G. Timing of surgery

1. Children who have congenital heart disease that might require surgery should be treated with input from a pediatric cardiologist.
2. Reasons not to operate include the fact that some structural problems, such as VSD and PDA, sometimes resolve on their own. Other reasons not to operate include the fact that younger children are poorer operative candidates and that artificial valves will need to be replaced as the child grows.
3. Reasons not to wait too long include irreversible processes (such as pulmonary hypertension) and irreversible structural damage (such as dilatation or hypertrophy of the ventricles).

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9.4
HEART FAILURE

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I. Overview.

Heart failure (HF) affects 4.8 million persons in the United States. HF is the only cardiovascular disorder whose incidence and prevalence are increasing, especially in the elderly and in women. This diagnosis accounts for 11 million outpatient visits *and 3 million hospitalizations* annually, with costs exceeding $20 billion. Despite medical therapy, the morbidity and mortality from this disorder remains unacceptably high, averaging 10% mortality at 1 year and 50% mortality at 5 years.

HF occurs when the heart is unable to generate a cardiac output sufficient to meet and maintain the metabolic requirements of the body, either at rest or on demand. This definition does not address whether there is primary systolic (pump related) or diastolic (compliance related) ventricular dysfunction, or a combination of both. The term *congestive* is applicable only when there are signs or symptoms of pulmonary or systemic volume overload, typically due to avid sodium and water retention, reflecting the neurohormonal activation characteristic of HF.

The most frequent cause of HF in the 1990s was coronary artery disease (see Chapter 9.2). Hypertensive or valvular heart disease and primary cardiomyopathy (familial or idiopathic) are also common entities. Further, myocardial dysfunction can be secondary to infectious, metabolic, endocrine, nutritional, or toxic causes (notably alcohol and anthracyclines); connective tissue or pericardial diseases;

neuromuscular or autoimmune disorders; as well as infiltrative diseases (amyloidosis, hemochromatosis, sarcoidosis) or undiagnosed congenital heart disease. This chapter does not address the special category of high-output HF (due to thyrotoxicosis, sepsis, severe anemia, beriberi, Paget's disease, myeloma, pregnancy, or significant arteriovenous shunting). Diastolic (lusitropic) HF is characterized by a stiff, noncompliant left ventricle usually resulting from antecedent hypertension or coronary artery disease, or both (1,2). Systolic function is generally preserved, but left ventricular (LV) filling pressures are increased, relaxation is impaired, and stroke volume is diminished. Diastolic dysfunction as the cause of HF symptoms is suggested by the clinical history. Although the prevalence of diastolic failure in a primary care setting is not known with certainty, studies based on patients seen in referral centers suggest that up to 40% of patients with HF may have primarily diastolic dysfunction.

II. Diagnosis

A. History and symptoms.

It is important to recognize that ventricular dysfunction can be asymptomatic, yet early diagnosis and treatment reduces morbidity if not mortality. Symptoms of chronic HF due to insufficient cardiac output can include fatigue, reduced exercise capacity, and decreased concentration or mental function. Symptoms suggesting congestion include orthopnea, exertional dyspnea, paroxysmal nocturnal dyspnea, abdominal bloating, nausea, and fluid retention (ascites, edema). The acuity of onset and tempo of progression of HF should also be determined. The cause of ventricular dysfunction should be sought, and provocative and exacerbating factors reviewed.

The New York Heart Association (NYHA) classification system is widely used to categorize patients by symptoms, although it is not objective and therefore is subject to criticism. Class I patients have no symptoms with normal activities and no limitation of their physical activity. Class II patients have symptoms of HF with slight or moderate activity. Class III patients have marked limitation of activity but are comfortable at rest. Class IV patients have symptoms of HF at rest—and the worst prognosis.

B. Physical examination.

Signs of “left-sided HF” include a resting tachycardia or tachypnea and an abnormal apical impulse (enlarged, diffuse, displaced, dyskinetic, or sustained). In systolic HF, you may detect an S_3 gallop, diminished carotid upstroke volume (low pulse pressure), and cool extremities. In diastolic HF, you might note hypertension and an S_4 gallop. Typically, bibasilar rales are noted if filling pressures are acutely elevated. However, in chronic HF it is common to find clear lung fields with coarse breath sounds or reduced respiratory diaphragmatic excursion. Pleural effusions, when present, are bilateral or typically right more than left.

Signs of biventricular or “right-sided” HF include an elevated jugular venous pressure, a right ventricular (RV) lift or subxiphoid tap, a loud P_2 (pulmonary hypertension), RV gallop, hepatojugular reflux, pulsatile or tender hepatomegaly, ascites, and peripheral (dependent) edema. Signs of right-sided HF without signs of LV dysfunction should direct your attention to primary or secondary pulmonary vascular diseases.

The greater the number of symptoms and signs observed in a given patient, the more reliable is the diagnosis of HF. The most specific physical findings are an elevated jugular venous pressure, an S_3, a laterally displaced apical impulse, pulmonary rales that do not clear with cough, and peripheral edema not due to venous insufficiency (2).

C. Diagnostic testing

1. **Electrocardiography.** Assess for signs of infarction, arrhythmia, conduction delays, chamber enlargement, or hypertrophy. Nonspecific electrocardiographic abnormalities are common.
2. **Chest radiography.** Look for an increased cardiothoracic ratio, specific chamber enlargement, pulmonary vascular redistribution or edema, Kerley's B lines, or pleural effusions. A normal chest radiograph does not rule out HF.

3. **Blood tests.** Perform a complete blood count (CBC), serum electrolytes, creatinine, albumin, liver function tests, and urinalysis. Include thyroxine and thyroid-stimulating hormone if the patient is older than 65 years, has atrial fibrillation, or has signs or symptoms of thyroid disease. Perform other laboratory screening tests as indicated by history and physical examination only.
4. **Assess ventricular function.** HF is most cost effectively diagnosed by the measurement of ejection fraction (EF) either by radionuclide imaging (radionuclide ejection fraction or multiple gated acquisition) or echocardiography with Doppler. An EF of 0.40 or less reflects significant systolic dysfunction; the EF may be low, normal, or supranormal in diastolic dysfunction. Each method has its own inherent advantages and limitations; one should consider cost, availability, and expertise of the laboratory in choosing which test to order. Echocardiography is usually more widely available and less expensive. Furthermore, the echocardiogram can indicate chamber dimensions, ventricular wall thickness, and valvular abnormalities and provide a screen for the presence of focal wall motion abnormalities, which imply underlying coronary disease. Doppler echocardiography can provide a noninvasive estimation of intracardiac hemodynamics and demonstrate diastolic relaxation abnormalities.
5. **Holter monitors.** Holter monitoring is typically not indicated for screening for arrhythmias or ischemia in the absence of symptoms.
6. **Exercise testing.** If the patient is stable, exercise testing can provide objective evidence of functional impairment or screen for ischemic heart disease. *About 60% of patients with HF have underlying coronary artery disease.* Use nuclear or stress echocardiography techniques if the electrocardiogram is not interpretable.

III. Prognosis.

Each of the following are easy-to-measure, independent variables suggestive of a poor prognosis.

- Ejection fraction: Systolic dysfunction with EF less than 0.30; concomitant RV dysfunction or enlargement
- Functional class (NYHA class IV): 30%–50% mortality at 1 year
- Hemodynamics: concomitant pulmonary hypertension, right HF
- Chest radiograph: increased cardiothoracic ratio
- Exercise capacity: inversely related to work achieved (age dependent)
- Doppler echo: pattern of mitral valve inflow velocity
- Arrhythmias: atrial or ventricular
- Neurohormonal activation: plasma catecholamine elevation, hyponatremia

IV. Management of chronic systolic HF.

For HF refractory to standard therapy or HF with multiple adverse prognostic indicators, consider referral to an HF center or cardiologist for further evaluation. Routine anticoagulation is not recommended unless indicated for atrial fibrillation or valvular disease.

A. Vasodilators.

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of the pharmacologic management of systolic HF, and contemporary therapy of systolic HF mandates an ACE inhibitor unless contraindicated. In the Survival and Ventricular Enlargement Trial (3), Cooperative North Scandinavian Enalapril Survival Study (4), Veterans Administration Cooperative Vasodilator-Heart Failure Trial (5), and Studies of Left Ventricular Dysfunction (6) trials of the late 1980s and early 1990s, ACE inhibitors were shown to improve hemodynamics by afterload reduction, attenuate neurohormonal abnormalities, and improve symptoms and quality of life, although they increased EF by only 1%–2%. The progression of HF is slowed by ACE inhibitor therapy, providing a survival benefit and reducing hospitalizations. In the SOLVD prevention arm, ACE inhibitor use delayed the onset of HF symptoms related to “silent” LV dysfunction. Side effects of ACE inhibitor therapy include symptomatic orthostatic hypotension, hyperkalemia, hyponatremia, cough, angioedema, and worsened renal function. Some of these may be obviated by the use of angiotensin II receptor blockers, such as losartan,

although survival benefits have not been conclusively proved with these new agents. In initiating an ACE inhibitor in a patient at high risk for hypotension (low jugular venous pressure and systolic blood pressure less than 90 mm Hg), it is prudent to start with a small dose of a short-acting agent, such as captopril, 6.25–12.5 mg, and observe the patient for up to 2 hours. Once this is tolerated, changing to an agent with daily or twice-daily dosing may enhance compliance. Increase the dose every 1–2 weeks until side effects are noted or the dose reaches the equivalent of those used in the HF trials: captopril, 50 mg tid, or enalapril, 10–15 mg bid (Table 9.4-1). Recheck electrolytes and creatinine after every dose increase or after addition of other medications. Recent data from the Atlas Study Group demonstrated that high-dose lisinopril (30 mg/d) was more effective than low-dose lisinopril (2.5 mg/d or 5 mg/d) in reducing the combined end points in patients with systolic HF of all-cause mortality, cardiovascular (CV) hospitalization, HF hospitalization, and combined CV and HF mortality (7). Therefore, the benefit of ACE inhibitors may be dose related in a positive fashion.

	Initial dose (mg)	Target dose (mg)	Recommended maximal dose (mg)
Thiazide diuretics			
Hydrochlorothiazide	25 daily	As needed	50 daily
Chlorthalidone	25 daily	As needed	50 daily
Loop diuretics			
Furosemide	10–40 daily	As needed	240 bid
Bumetanide	0.5–1.0 daily	As needed	10 daily
Ethacrynic acid	50 daily	As needed	200 bid
Thiazide-related diuretic			
Metolazone	2.5 (test dose)	As needed	10 daily
Potassium-sparing diuretics			
Spironolactone	25 daily	As needed	100 bid
Triamterene	50 daily	As needed	100 bid
Amiloride	5 daily	As needed	40 daily
ACE inhibitors			
Enalapril	2.5 bid	10 bid	20 bid
Captopril	6.25–12.5 tid	50 tid	100 tid
Lisinopril	5 daily	20 daily	40 daily
Quinapril	5 bid	20 bid	20 bid
Benazepril	10 daily	20 daily	40 daily
Ramipril	2.5 daily	10 daily	20 daily
Fosinopril	10 daily	20 daily	40 daily
β-Blockers			
Carvedilol	3.125 bid	25 bid	25 bid
Bisoprolol	1.25 daily	10 daily	10 daily
Metoprolol CR/XL	12.5 daily	200 daily	200 daily

ACE, angiotensin-converting enzyme.
From Konstam M, et al. *Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction.* Clinical practice guideline No. 11. AHCPR Publication No. 94-0612. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, 1994, with permission.

Table 9.4-1. Duiretics, angiotensin-converting enzyme inhabitors, and ß-blockers used for chronic heart failure

For patients who cannot tolerate an ACE inhibitor, the currently accepted alternative regimen is the combination of hydralazine and isosorbide dinitrate (Table 9.4-1). The mortality benefits are not as great as those of ACE inhibitors but are significantly better than those of placebo or vasodilatory α-blockers (prazosin). Side effects (headache, nasal congestion, hypotension, palpitations) are significant with this regimen; up to 25% of patients will discontinue one or both. Recent data also suggest that the newer dihydropyridine calcium channel blockers, such as amlodipine, may be another option.

Angiotensin II receptor blockers may be used if the patient is intolerant of ACE inhibitors or the combination of isosorbide and hydralazine. However, the angiotensin II receptor blockers have not supplanted the ACE inhibitors as the cornerstone of HF therapy.

B. ß-Blockers.

ß-Blocker therapy should be added to standard therapy in all patients with mild to moderate (NYHA class II-III) systolic HF who are clinically stable. Currently, insufficient data exist to make firm recommendations about the use of ß-blockers in patients with severe (NYHA class IV) systolic HF or those who are asymptomatic (NYHA class I). Well-performed clinical trials have demonstrated a mortality benefit and fewer hospitalizations with the use of carvedilol (8,11) bisoprolol (12), and metoprolol CR/XL (13). Studies are ongoing comparing different ß-blockers, but currently no data convincingly support the use of one drug over another.

Regardless of the choice of ß-blockers, similar recommendations can be made regarding their addition to standard therapy. First, the patient should be carefully evaluated for clinical stability. Patients with worsening edema, dyspnea, or other manifestations of HF should first be stabilized for a period of at least a week before ß-blockers are instituted. ß-Blockers should be started at low doses (Table 9.4-1) and titrated upward no more frequently than every 2 weeks. Patients should be followed carefully for signs of decompensation (fluid retention, bradycardia, heart block, and hypotension). Patients who manifest worsening HF should have their other medications adjusted or the ß-blocker dose reduced or the drug withdrawn. With careful observation the majority of patients can tolerate ß-blocker therapy and achieve target doses (Table 9.4-1). In general, patients who are on chronic ß-blocker therapy at a stable dose who experience decompensation can be continued on their ß-blocker. In most cases the decompensation in these patients is attributable to another cause. However, careful clinical evaluation is mandatory in all such cases.

C. Digitalis.

Digoxin remains a useful drug in systolic HF two centuries after its initial use. The Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme Study (14) of digoxin withdrawal in patients with HF clearly demonstrated the efficacy of digoxin. Exacerbated HF requiring treatment, hospital admission, and reduced exercise capacity and quality of life scores occurred with higher frequency in patients who were withdrawn from digoxin. In the Digitalis Investigation Group trial (15), digoxin had a neutral effect on mortality but was beneficial in decreasing hospitalizations for HF. Aside from increasing EF by 4%–5% due to its inotropic effects mediated by sodium-potassium pump inhibition, digoxin improves rest and exercise hemodynamics, and is sympathoinhibitory, attenuating the neurohormonal and baroreceptor abnormalities seen in chronic HF. This latter role as neurohormonal antagonist has been recently described and may be the more important mechanism of action.

Digoxin therapy can be limited by renal insufficiency and conduction abnormalities (heart block, slow atrial fibrillation) but is generally well tolerated, with few side effects at normal doses. Its use should be considered if symptoms remain after ACE inhibitor titration or if the EF is less than 0.40. In stable outpatients, loading doses are unnecessary. The elderly or small persons should be started on 0.125 mg daily, all others on 0.25 mg daily. Nomograms are available to determine the digoxin dose for patients with renal dysfunction. Measurement of digoxin levels is generally useful only (a) to verify suspected noncompliance, (b) to evaluate signs or symptoms of

toxicity, (c) to ensure safe levels in view of worsening renal or cardiac function, and (d) when other medicines are added that have potential drug interactions [verapamil, quinidine, amiodarone, spironolactone (Aldactone), some antibiotics] or that can worsen renal function (nonsteroidal anti-inflammatory drugs, including high-dose aspirin).

In patients with HF and atrial fibrillation whose ventricular rate is not controlled with digoxin 0.25 mg daily, addition of a ß-blocker or amiodarone is generally preferable to an increased dosage of digoxin.

D. Diuretics.

Diuretic therapy should only be initiated when patients have symptoms or signs of systemic congestion due to volume overload. Diuretics relieve congestive symptoms by promoting excretion of excess sodium and water. However, they do not increase cardiac output and may even reduce it. They can exacerbate the hypotensive response to ACE inhibitor therapy, further activate the renin-angiotensin-aldosterone system, and can be limited by the development of diuretic resistance or refractoriness. Thiazide diuretics should be used if fluid retention is mild, but they are effective only when the glomerular filtration rate is greater than 30 mL/min. Loop diuretics are the mainstay of diuretic therapy in HF when congestion is moderate. When fluid retention is extreme or the patient has become refractory to loop diuretics, intravenous administration of a loop diuretic or the addition of the thiazide-like agent metolazone (1–5 mg 30 minutes to 1 hour prior to loop agent), or both, can dramatically increase natriuresis (Table 9.4-1). Electrolytes, including magnesium, require close attention when diuretics are used. Hypokalemia can exacerbate digoxin toxicity or arrhythmias. Chronic loop diuretic use can also result in folate depletion. Potassium-sparing diuretics should be used with caution in patients on ACE inhibitor therapy.

The RALES Trial (16) demonstrated a beneficial effect on mortality from progressive HF with low-dose spironolactone in patients with severe HF on standard therapy. Normokalemic patients with adequate renal function (creatinine less than 2.5 mg/dL) and severe systolic HF should receive spironolactone 12.5–25 mg daily. The serum potassium level should be checked at one week, frequently thereafter, and at any time there is a change in dosage of any medication that may influence potassium balance. Strong consideration should be given to lowering or eliminating supplemental potassium when spironolactone is added to the regimen.

V. Management of chronic diastolic HF.

Diastolic HF is common and can be notoriously difficult to treat. The etiologic factors in coronary artery disease and hypertension should be sought and treated, if present. Calcium channel blockers, ß-blockers, and ACE inhibitors have all been shown to be useful and may promote regression of ventricular hypertrophy. Diuretics are often necessary for congestive symptoms, but excessive preload reduction (nitrates, diuretics) can impair cardiac output and exacerbate symptoms and should be used cautiously.

VI. Evaluation of exacerbating or provocative factors.

Assess for medication or dietary noncompliance (sodium, alcohol, excess fluids), drug abuse, medication additions (diltiazem, nonsteroidal anti-inflammatory drugs, and other agents), uncontrolled hypertension or diabetes, decreased renal or hepatic function, thyroid abnormalities, anemia, infection, ischemia or infarction, arrhythmias, pulmonary embolism, new valvular dysfunction, and sleep apnea.

VII. Adjuncts to therapy: education.

Discuss with the patient and family the diagnosis and reason(s) for the development of HF, including prognosis and intended treatment plan. Advance directives should be discussed. Symptoms referable to HF should be reviewed and patients instructed to call if symptoms are noted or increased, including rapid weight gain. Emphasize sodium restriction to 3 or preferably 2 g/d, avoidance of alcohol, and the importance of good nutrition. Vaccinations should be updated. Exercise prescriptions (walking, biking, swimming) are generally safe in compensated HF of class III or less and may improve clinical status. Exercise testing may give patients more confidence in beginning a

moderate exercise program or in resuming more of their normal activities, including sex. Educational materials are useful, as is a home nursing evaluation to reinforce education and look for pitfalls to the therapeutic plan.

The clinical practice guideline of the Agency for Healthcare Research and Quality (AHRQ), *Heart Failure: Evaluation and Care of Patients with Left Ventricular Systolic Dysfunction* (Publication No. 94-0612), is a useful and informative resource for the primary care physician caring for patients with HF and can be ordered by calling the AHRQ Publications Clearinghouse at 800-358-9295.

VIII. Prevention

A. Primary prevention.

Family physicians must vigorously detect and treat cardiac risk factors in patients early, ideally by developing good health behaviors in children and adolescents. Cardiac risk factors include (but are not limited to) smoking, hypertension, dyslipidemia, obesity, diabetes, and sedentary lifestyle.

B. Secondary prevention.

All patients discovered to have an EF of less than 0.40 should be treated with an ACE inhibitor. Patient education is mandatory. For refractory failure, referral to a transplantation or HF cardiologist should be considered.

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9.5

ATRIAL FIBRILLATION AND OTHER SUPRAVENTRICULAR TACHYCARDIAS

Jim Nuovo

I. Atrial fibrillation

(AF) is one of the most common cardiac dysrhythmias. It is important to appreciate the variety of cardiac and systemic conditions that can cause this problem. The treatment involves assessment of the underlying cause, control of the rate, consideration of electric or pharmacologic conversion, and anticoagulation. (Other supraventricular arrhythmias are discussed in the second half of this chapter.)

A. Diagnosis

1. **Clinical presentation.** Symptoms are often vague and include fatigue, dizziness, palpitations, effort intolerance, and breathlessness. Palpitations are more likely to be described for paroxysmal attacks. Many patients have no specific symptoms. Patients with severe symptoms may describe angina or dyspnea.
2. **Physical examination.** The cardiovascular examination provides the essential features to diagnose this condition. The examination should reveal an irregularly irregular pulse. The rest of the examination should include an assessment for evidence of the precipitating causes of AF and for complications from AF. It should include the following: an assessment for a murmur consistent with valvular disease, assessment of stigmata of ethanol abuse, an assessment for signs of hyperthyroidism (see Chapter 17.3), and for evidence of adverse events from the AF (hypotension, pulmonary edema, and peripheral edema).
3. **Laboratory studies: electrocardiographic findings.** AF is characterized by chaotic electrical activity on the electrocardiogram (ECG) that demonstrates an irregularly irregular rate and rhythm. This is manifested by constantly changing R-R intervals. The QRS complexes are narrow unless there is aberrant ventricular conduction. There will be no discernible P waves before the QRS complex and no flutter waves (a saw-tooth appearance of atrial activity). The fibrillation waves are best seen in leads II, III, aVF, and V. The fibrillation pattern may be fine or coarse. A few patients have fine AF with little evidence on the ECG. The irregular ventricular pattern should allow determination of AF. Some patients have coarse fibrillation waves, making it difficult to distinguish from atrial flutter. Coarse AF can be distinguished by the erratic ventricular response. One of the most challenging problems is distinguishing aberrant intraventricular conduction and ventricular ectopy, particularly ventricular tachycardia (VT) in the presence of AF. Features favoring the presence of VT include QRS duration greater than 0.14 second, left axis deviation, and QRS complexes with a right bundle-branch block configuration (1).

B. Evaluation for etiology.

Many conditions can cause AF. Laboratory tests should be prudently selected to search for these underlying causes.

1. **Systemic causes.** Systemic abnormalities that predispose a person to AF include hypertension, hyperthyroidism, binge drinking, hypoxemia, and hypokalemia.
2. **Cardiac causes.** Cardiac causes include valvular heart disease (e.g., mitral valve stenosis or regurgitation, aortic stenosis or regurgitation), left ventricular hypertrophy, congestive heart failure, cardiomyopathy, pericarditis, coronary artery disease (e.g., 18% of patients with myocardial infarction develop AF), atrial abnormalities secondary to right or left ventricular overload, and the Wolff-Parkinson-White syndrome.
3. **Lone AF.** When no underlying cause is found, the condition is called lone AF. This may occur in as many as 10% of patients with AF.

C. Therapy for atrial fibrillation

1. **Unstable AF.** Unstable AF is defined in patients who experience angina, congestive heart failure, or hypotension with the episode. For these patients, immediate cardioversion is indicated.
2. **High-risk situations.** Some patients, although not requiring immediate electrical cardioversion, are at greater risk of an adverse outcome. Older patients, particularly those with multiple medical problems or those with mitral or aortic stenosis or hypertrophic cardiomyopathy, should be strongly considered for inpatient management.
3. **Stable AF.** For those who do not have an unstable presentation, the issues include a search for the underlying cause (as described), rate control, conversion to a normal sinus rhythm, and anticoagulation.
   a. **Rate control.** In stable patients, ventricular rate control with an atrioventricular (AV) nodal blocking agent is recommended. Digoxin has been the mainstay for many years. However, patients treated with digoxin increase their sympathetic tone and often end up with problems of breathlessness or fatigue due to rapid ventricular response. It is frequently necessary to have high doses of digoxin to achieve adequate rate control. This increases the risk of toxicity, particularly in the elderly. Other medications, such as ß-blockers (propranolol, atenolol, metoprolol, sotalol, and esmolol) or calcium channel blockers (verapamil and diltiazem), are becoming the preferred choice to control rate because the onset of action is relatively fast. Two new antiarrhythmic drugs currently under investigation include dofetilide and azimilide. Table 9.5-1 outlines these drug options.

Drug	Intravenous dose	Oral dose
Propranolol	1 mg/min; maximum dose 0.1 mg/kg	20–80 mg bid–qid
Metoprolol	5 mg q5min; maximum dose 15 mg	25–100 mg bid
Atenolol	5–10 mg over 5 min	25–100 mg daily
Verapamil	2.5–5.0 mg over 2 min; 5–10 mg in 15–30 min if necessary	40–80 mg bid–qid
Diltiazem	20–45 mg over 2 min	30–120 mg tid–qid
Adenosine	6 mg rapid bolus; 12 mg in 2 min if necessary	
Quinidine gluconate		324 mg tid–qid
Procainamide	Initially, 20–50 mg/min to maximum of 15 mg/kg; stop with hypotension, with QRS widened >50%, or with arrhythmia suppressed; maintenance dose is 2–4 mg/min	500–1,000 mg qid
Digoxin	Initially, 0.25 mg q6h for 4 doses	0.125–0.25 mg/d

[a] Disopyramide, amiodarone, and bretylium may also be used.
From EP Havranek EP. The management of atrial fibrillation: current perspectives. *Am Fam Physician* 1994;50:959, with permission.

Table 9.5-1. Frequently used drugs in the treatment of atrial arrhythmias[a]

   b. **Conversion to sinus rhythm.** After ventricular rate is controlled, conversion should be considered. Patients with AF benefit from conversion to sinus rhythm. Conversion reduces the risk of stroke, increases exercise capacity, and eliminates the need for anticoagulation. The duration of AF before cardioversion correlates strongly with the likelihood of recurrence of AF.

1. **Electrical conversion.** Electrical transthoracic cardioversion is often an effective procedure with a response rate of approximately 85%. Synchronized cardioversion with low energy levels (100 J) should be tried first. Progressively higher levels may be necessary (200, 300, or 360 J). If this fails, antiarrhythmic agents can be administered in loading doses and the procedure repeated. An alternative is to begin antiarrhythmic drug therapy and perform electric cardioversion several days later, when the serum levels are in the therapeutic range. Prior to conversion, anticoagulation is recommended. All patients with AF for more than 3 days should be anticoagulated to an international normalized ratio of 2–3 for 3 weeks. If the clinical situation is more urgent, the patient may be placed on heparin. It remains uncertain how long the patient requires this regimen before conversion. After cardioversion, warfarin should be continued for 3–4 weeks as the atrium requires this time to return to normal.
2. **Pharmacologic cardioversion.** An alternative to electrical cardioversion is pharmacologic conversion. Despite its long-term use for this problem, digoxin does not increase the rate of conversion. Effective drugs include quinidine, ß-blockers, and procainamide. Others less often considered include disopyramide, amiodarone, and propafenone. Conversion is achieved in 25%–50% of patients treated with procaine, quinidine, sotalol, or amiodarone. The best choice for a particular patient is contingent on comorbid illnesses. For example, patients with chronic obstructive pulmonary disease should not receive ß-blockers. Recent association of torsades de pointes with the newer agents (sotalol and dofetilide) is worrisome and suggests that they should be started in the hospital with continuous cardiac monitoring. The risk of ventricular arrhythmias is greater in patients with left ventricular dysfunction (2). Specific regimens are listed in Table 9.5-1 .
3. **Maintenance therapy.** After conversion, 75% of patients revert to AF if not treated with an antiarrhythmic agent. AF of less than 12 months is less likely to recur. Half of patients on quinidine, sotalol, or procainamide remain in normal sinus rhythm up to 12 months later.

c. **Anticoagulation.** Patients with AF have an increased risk of thromboembolism in comparison to those with sinus rhythm. Those with rheumatic valve disease have a 17-fold increase in risk; nonrheumatic disease has a 6-fold increase. Risks for stroke in nonrheumatic AF include a history of stroke or transient ischemic attack, diabetes mellitus, hypertension, congestive heart failure, angina, myocardial infarction, and advanced age.
   1. **Indications.** Current recommendations from the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy are to provide anticoagulant therapy to all patients with AF who are eligible for anticoagulation except patients younger than 60 years with lone AF (3). Anticoagulation for patients with AF must be done for the following conditions: valvular heart disease, dilated cardiomyopathy, ischemic heart disease, hypertensive heart disease, and before elective cardioversion of AF even if the AF has been present for a few days. A recent analysis of nonrheumatic AF trials resulted in the following recommendations:
      a. Patients younger than 60 years with lone AF need not be anticoagulated.
      b. Patients aged 60–75 years with lone AF may be treated with one aspirin (325 mg) per day; however, some physicians recommend anticoagulation.

c. Patients younger than 75 years with one risk factor for stroke benefit from oral anticoagulation.

d. Patients older than 75 years, even without other risk factors, benefit from warfarin because of the high risk of stroke with increased age (3) (see Chapter 6.6).

2. **Safety.** The complications of anticoagulation increase with age. The safety of anticoagulation in older patients with AF is still a topic of controversy. Recent data suggest that to achieve optimal levels of anticoagulation with the lowest risk, the target value for the international normalized ratio should be set at 3.0, and values below 2.0 and above 5.0 should be avoided (4). Once stable anticoagulation is reached, patients can be followed at intervals of 8–10 weeks (5). Recent literature indicates that many patients at risk for ischemic stroke are still not receiving warfarin therapy (6).

II. Supraventricular tachycardia (SVT)

refers to arrhythmias with three or more complexes at a rate exceeding 100 beats/min. The focus originates in the AV junctional area above the bundle of His. Reentry phenomena account for the majority of these dysrhythmias.

A. Diagnosis

1. **Clinical presentation.** Patients often describe sensations such as heart pounding or racing. They have regular or skipping beats and generally become anxious. There is generally no association with activity. Episodes are usually well tolerated in young people in the absence of any coexistent heart disease. In the elderly and in those with diseases such as ischemic heart disease, pulmonary edema or ischemia may be aggravated by the accelerated rate.
2. **Physical examination.** A complete physical examination should be undertaken with emphasis on the cardiovascular system. Evaluation is identical to that described for AF.
3. **Laboratory studies**
   a. **Electrocardiographic findings.** Patients in whom SVT is suspected should have a 12-lead ECG with a rhythm strip lasting at least 2–3 minutes. If P waves are difficult to distinguish due to the rate of the tachycardia, leads aVF and V_1 may be helpful.
   b. **Ambulatory 24-hour electrocardiographic monitoring (Holter monitoring).** A Holter monitor or event monitor may be considered if the resting ECG is normal and the history is suggestive of a dysrhythmia.
   c. **Additional studies.** Laboratory studies may also include the following, depending on the clinical situation: electrolytes, calcium, magnesium, hemoglobin, arterial blood gases, thyroid function, toxic screen, and drug levels.

B. Classification of SVT.

SVT may be classified by the regularity of the rhythm, the width of the QRS complex, and the relationship of the P waves to the QRS complex.

1. **Regular rhythm SVT**
   a. **Narrow QRS complex.** The QRS duration is 100 milliseconds or less. The specific classification is based on the relationship of the P wave to the QRS complex. If the P waves occur simultaneously with or shortly after the QRS complex, this is called short RP tachycardia. If the P waves precede the QRS complex with a normal PR interval, this is called long RP tachycardia (7). Identification of the specific type of SVT assists in therapy.
      1. **Short RP tachycardia.** The most common forms of short RP tachycardias include the following:
         a. **AV nodal reentrant tachycardia.** This is usually an abrupt-onset tachycardia lasting seconds to hours; it accounts

for 50%–60% of all regular narrow QRS tachycardia. The P wave is identified in the ST segment or is buried in the QRS complex.

b. **AV reentrant tachycardia.** This is usually an abrupt-onset tachycardia lasting seconds to hours; it accounts for 40% of all regular narrow QRS tachycardias. The P wave is usually negative in lead I.

2. **Long RP tachycardia.** The most common forms of long RP tachycardias include the following:
   a. **Sinus tachycardia.** This is identified with a normal P wave that precedes the QRS complex. Typically it does not exceed 170 beats/min. Onset and termination are gradual. It is often a reflection of extracardiac abnormalities, such as infection, hypovolemia, anxiety, pain, hyperthyroidism, acute severe anemia, and fecal impaction.
   b. **Atrial tachycardia.** In atrial tachycardia, an atrial source outside the sinoatrial node activates the atria. Accordingly, P-wave morphology varies depending on the site of the source. Paroxysmal atrial tachycardia with block is usually seen in patients with digitalis toxicity.

b. **Atrial flutter.** Atrial flutter is often a regular, narrow QRS tachycardia. It is a rhythm characterized by an atrial rate of 240–350 beats/ min, commonly with variable AV block (2:1, 3:1, or 4:1) causing a ventricular response of 70–150 beats/min. The characteristic flutter waves (saw-tooth) are best seen in leads II, II, aVF, and V.

c. **Wide QRS regular tachycardia.** This form of SVT with aberrant conduction results in a wide QRS complex (more than 0.12 second). It is often difficult to differentiate this from the more dangerous dysrhythmia, VT. Features that favor VT are stated in Section I.A .

2. **Irregular rhythm SVT**
   a. **Atrial fibrillation** (see Section I)
   b. **Multifocal atrial tachycardia.** This is an irregular tachycardia characterized by three or more different P-wave morphologies. Frequently, PR intervals are variable. It is usually associated with advanced cardiac or pulmonary diseases. Previously mentioned metabolic abnormalities (e.g., hypokalemia and hypoxemia) may also precipitate this dysrhythmia.

C. Treatment

1. **Acute irregular rhythm SVT**
   a. **Vagal maneuvers.** Carotid sinus massage, Valsalva's maneuver, gagging, and a baroreceptor reflex may be tried. If carotid sinus massage is used, auscultation should be performed first. If a bruit is present, the maneuver should not be done. Massage should not exceed 10 seconds and should be done unilaterally.
   b. **Pharmacotherapy.** Adenosine is very effective in the treatment of SVTs (excluding AF and atrial flutter). It is given by rapid (1–3 seconds) IV push (6 mg). If this is not successful, a 12-mg dose may be given in 1–2 minutes and repeated in 1–2 minutes. An alternative regimen is verapamil given 2.5–5.0 mg IV, with a repeat dose of 5–10 mg in 15–30 minutes if necessary.
   c. **Electroconversion.** For patients who do not respond to pharmacotherapy or vagal maneuvers and who are unstable (i.e., hypotensive), synchronized cardioversion is recommended. Electrical conversion recommendations are identical to AF (see Section I.C.3.b).
2. **Chronic irregular rhythm SVT.** Class I medications (e.g., quinidine, procainamide, and disopyramide) and class III medications (e.g., amiodarone and bretylium) may be used.

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9.6
VENTRICULAR DYSRHYTHMIAS

Dan Brewer

I. Introduction.

The care of patients with ventricular dysrhythmias has undergone dramatic changes since the publication of the Cardiac Arrhythmia Suppression Trial (CAST) (1) in 1981. It is clear that ventricular dysrhythmias [premature ventricular contractions (PVCs), sustained and nonsustained ventricular tachycardias (VTs)] are markers for increased mortality in patients with ischemic cardiovascular disease, but the CAST trial showed that the potential for harm in managing these rhythm disturbances with antiarrhythmic medications is also great. Recent trials have begun to show a clear advantage of implantable cardioverter defibrillators (ICDs) over antiarrhythmic medications in the treatment of high-risk patients with ventricular dysrhythmias (2). The general trends have been to move away from prophylactic and empirical treatment of ventricular dysrhythmias, to search for and correct underlying etiologic factors such as ischemia, and to treat those at highest risk with either ICD or amiodarone, which is the only currently available antiarrhythmic agent that has not been shown to cause excess mortality with treatment (3).

All family physicians should

- be familiar with the Advanced Cardiac Life Support (ACLS) protocols for caring for patients with emergency dysrhythmias,
- have an appreciation for common drugs that may cause ventricular dysrhythmias,
- be comfortable with the initial evaluation of a patient with palpitations and/or syncope, and
- be able to recognize ventricular dysrhythmias on an electrocardiogram (ECG).

Many family physicians will also want to participate actively in the care and decision making of patients who have heart disease that includes ventricular dysrhythmias.

II. Emergency care.

Patients who present with ventricular dysrhythmias in an emergency setting [cardiac arrest, sustained VT with or without hemodynamic compromise] should be treated according to current ACLS protocols (4). Physicians who care for patients in such settings should be familiar with these guidelines.

A. Hemodynamically unstable patients.

Patients with cardiac arrest or VT/ ventricular fibrillation (VF) and hemodynamic instability should be electrically

defibrillated without delay. The current (2000 revision) protocol calls for three consecutive defibrillations at 200, 300, and 360 J as needed to reestablish spontaneous circulation. There should be no delay for cardiopulmonary resuscitation (CPR) or pulse checks during these rapid “stacked shocks.” If this sequence is unsuccessful, rescuers should proceed to the CPR/epinephrine/cardioversion sequence and then to antiarrhythmic medications if necessary.

Patients with polymorphic ventricular tachycardia (torsades de pointes) should be given an intravenous infusion of 1–2 g of magnesium.

B. Patients with wide-complex tachycardia but adequate blood pressure.

Patients with a wide-complex tachycardia who maintain an adequate blood pressure should be treated as though they have VT unless it is known with certainty that the rhythm is supraventricular. There are many guidelines that attempt to distinguish between VT and supraventricular tachycardia (SVT) with aberrant conduction on the basis of electrocardiographic criteria, but *physicians caring for patients in emergency situations should ignore this distinction* and manage all wide-complex tachycardias as if they are VT (4). The most important error to avoid is giving verapamil to a patient with VT, which can be fatal.

ACLS guidelines before 2000 recommended use of lidocaine followed by procainamide, bretylium, and electrical cardioversion for stable VT. The International Guidelines 2000 now recommend treatment with intravenous procainamide, sotalol, amiodarone, or beta-blockers. The algorithm on stable VT shows how the specific choice of agent is based on considerations of baseline cardiac function and QT interval.

If a supraventricular dysrhythmia is strongly suspected, two doses of adenosine (6 and then 12 mg rapid IV push) can be given after the second dose of lidocaine. This may terminate SVTs and generally will not harm a patient with VT. It is particularly important to remember to go immediately to electrical cardioversion if the patient's hemodynamic status begins to deteriorate or if the rhythm deteriorates to ventricular fibrillation.

III. Initial diagnosis

A. History

1. **Palpitations.** Patients frequently present to family physicians complaining of palpitations. A very small minority of these will have a serious ventricular dysrhythmia as the underlying cause. Historical features that make an underlying cardiovascular cause more likely include corresponding chest pain or dyspnea, a known history of coronary disease, or multiple risk factors for atherosclerosis.

   In a patient with palpitations, a careful history of the character, timing, and associated symptoms should be taken. A history of prescription and over-the-counter drugs, caffeine intake, alcohol and tobacco use, and anxiety is often very helpful. Illicit drugs such as amphetamines and cocaine may cause palpitations.

2. **Syncope.** A careful history of any syncopal episode may give a clue to the underlying cause. In general, syncope of cardiac origin is more likely to be sudden and associated with an injury at the time of the fall, whereas vasovagal syncope is usually preceded by warning symptoms of nausea, warmth, or light-headedness. In vasovagal syncope, protective reflexes usually remain intact during the fall. Vasovagal syncope is much more common than syncope on the basis of VT/VF.

   Exercise-induced syncope in a young person should prompt an investigation for hypertrophic cardiomyopathy. This is the most common cause of sudden death in young athletes.

3. **Review of systems/past medical history/family history.** When taking a history from a patient with syncope or palpitations, clues to underlying heart disease should be sought. Any history compatible with ischemic heart disease or cardiomyopathy makes the subsequent evaluation more urgent. A family history of sudden cardiac death or syncope

may be a clue to one of the inherited syndromes of prolonged QT, ventricular dysplasia, or hypertrophic cardiomyopathy. These syndromes may have other associations, such as hearing loss. Patients who have had surgical correction of congenital heart disease, especially tetralogy of Fallot or transposition of the great vessels, may also be at risk for VT/VF.

4. **Medication/drug use.** Overdose with tricyclic medications can cause VT/VF. Digoxin toxicity (often made worse by low serum levels of potassium or magnesium) can create pleomorphic ventricular dysrhythmias. Any medication that prolongs the QT interval can increase the risk of ventricular dysrhythmias (Table 9.6-1). If the patient is on such a medication, any drug that interferes with hepatic metabolic enzymes (such as erythromycin or ketoconazole) may precipitate dysrhythmia by decreasing the metabolism and raising the serum level of the offending drug.

Phenothiazines, especially chlorpromazine
Tricyclic antidepressants
Class IA cardiac drugs
Quinidine, procainamide, disopyramide
Class IC cardiac drugs
Flecainide, encainide, sotalol

Table 9.6-1. Some common drugs that lengthen the QT interval

5. Several drugs, including astemizole, terfenadine, and cisapride, have been removed from the market due to their effect of lengthening the QT interval. The U.S. Food and Drug Administration has begun to require manufacturers to look more thoroughly for QT prolongation in new drugs that are in the process of approval.

B. Physical examination.

Physical examination in the patient who is suspected of having VT/VF should focus on evidence of heart failure, ventricular outflow obstruction, and atherosclerotic vascular disease. Patients with VT/ VF and heart failure are at much higher risk of serious adverse events. This examination should include careful palpation and auscultation of the heart searching for an S_3 gallop. The regularity of the cardiac rhythm should be assessed. The pulmonary examination may show evidence of pulmonary edema (rales in the dependent fields). The general examination should include evaluation for jugular venous distention and dependent peripheral edema. The character of peripheral arterial pulses should be assessed.

C. Electrocardiography

1. **General.** An office ECG during an asymptomatic period may give important clues to the diagnosis of palpitations and syncope but cannot rule out serious disease. The tracing should be examined for signs of ventricular irritability (PVCs), pre-excitation (a delta wave of early ventricular depolarization), ventricular hypertrophy, and ischemic disease. PVCs are characterized by premature wide complexes (more than 120 milliseconds) followed by a compensatory pause before the next ventricular beat. Patients with a preexisting bundle-branch block pattern or Wolf-Parkinson- White syndrome may have a wide complex SVT, so prior tracings should be examined if they are available.
2. **Distinguishing ventricular from SVTs.** If the ECG shows a wide complex (QRS 120 milliseconds) tachycardia, a systematic approach may be taken to determine if the tachycardia is of supraventricular or ventricular origin (an example of VT is shown in Figure 9.6-1):

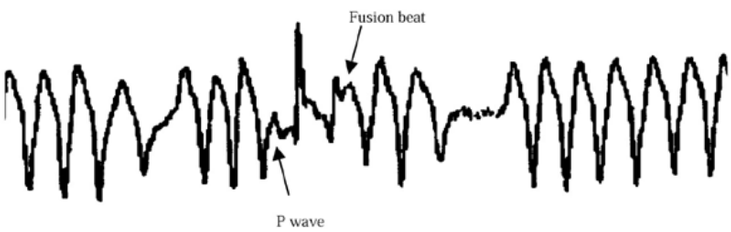

FIG. 9.6-1. Ventricular tachycardia.(Courtesy of Freeman Rawson, M.D., University of Tennessee, Knoxville.)

   a. Is there an absence of RS complex in all precordial leads?

b. If there is an RS complex, is the RS interval greater than 100 milliseconds in any precordial lead?
   - This is measured from the start of the R wave to the nadir of the S wave.

c. Is there AV dissociation?
   - Evidenced by independent P waves or fusion beats.

d. Does morphology of lead V_6 favor VT?
   - qR or QS pattern.

e. Are any of the three morphologic criteria for VT present in leads V1, V2?
   - R wave longer than 30 milliseconds in V1 or V2. Notched S wave.
   - More than 60 milliseconds to nadir of S wave.

An affirmative answer to any of the five questions suggests VT rather than SVT with aberration.

3. **Characterizing VTs.** VTs are characterized by their morphology and duration.
   a. **Morphology**
      1. **Monomorphic VT.** Each ventricular beat is identical.
      2. **Pleomorphic VT.** More than one pattern of monomorphic VT is present.
      3. **Polymorphic VT.** The shape of the ventricular beat changes from beat to beat.
   b. **Duration**
      0. **Salvos:** 3–5 beats.
      1. **Nonsustained VT:** More than 6 consecutive beats, less than 30 seconds.
      2. **Sustained VT:** More than 30 seconds or any time period with hemodynamic compromise.

D. Other investigations

1. **Electrolytes.** Electrolyte disturbances can cause VT/VF. Hypokalemia is the most common abnormality, but hypocalcemia and hypomagnesemia have also been implicated in causing this problem.
2. **Drug levels.** Any patient who takes digoxin should have drug level and electrolytes checked. Digoxin toxicity most commonly causes pleomorphic VT, and this is much more common in the presence of hypokalemia. Theophylline toxicity can also cause VT.
3. **Metabolic.** Hypoxemia and metabolic acidosis can cause or aggravate ventricular dysrhythmias, particularly in very ill patients.

E. Risk stratification

(Fig. 9.6-2). The results of these initial investigations are used to “risk-stratify” the patient with potential ventricular dysrhythmias. Many patients can be reassured without further evaluation. Individuals with PVCs or nonsustained VT and no structural heart disease have a benign

long-term prognosis and should not be exposed to the potential toxicity of antiarrhythmic drugs. The most important prognostic factor for a patient with PVCs or nonsustained VT is the ejection fraction: those with severely depressed left ventricular function are at highest risk of death from dysrhythmia.

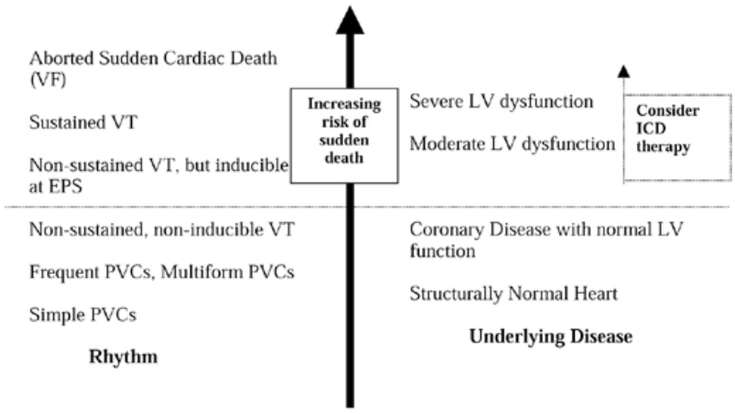

FIG. 9.6-2. Risk stratification of patients with ventricular dysrhythmias

IV. Advanced diagnosis

A. Holter monitor/event monitor.

Holter monitoring is often the first step in evaluation of palpitations. This test creates a continuous electrocardiographic recording for 24 hours and allows the physician to see the cardiac rhythm that is present at the time of the patient's symptoms. It is important that the patient fill out the diary of symptoms that occur during wearing of the monitor. A normal Holter tracing at the time of symptomatic palpitations has an excellent negative predictive value (it nearly rules out serious VT/VF as the cause). On the other hand, PVCs are a very common finding on a Holter monitor, and minor abnormalities, especially if the patient is asymptomatic, should not be “overinterpreted.”

If the patient's symptoms are infrequent and there is concern that they will not occur during the time a Holter monitor is worn, an event monitor can be used. This device is triggered at the time the patient's symptoms occur and provides a continuous ECG. This increases the likelihood of capturing a symptomatic episode, but event monitoring is significantly more expensive than Holter monitor testing.

B. Critical care telemetry monitoring.

Many serious ventricular dysrhythmias are diagnosed in the hospital while monitoring a patient in the first few days after a myocardial infarction. Routine monitoring of continuous ECGs for such patients is now standard and the immediate treatment of VT/VF in the postinfarct period has been a major part of the reduced mortality of myocardial infarction since the introduction of coronary care units. Patients with acute myocardial infarction should have routine continuous electrocardiographic monitoring in the initial stage of their hospital care.

C. Echocardiography.

Some measure of left ventricular function is required in assessing the patient with VT/VF who is potentially at high risk for complications. The most commonly used and readily accessible test in most settings is the calculated ejection fraction obtained from an echocardiogram. The echocardiogram can also evaluate possible valvular heart disease and show focal wall motion abnormalities suggestive of ischemic cardiac disease.

D. Evaluation for ischemia.

A majority of patients with VT/VF in the United States have ischemic cardiac disease as the underlying etiologic factor (see Chapter 9.2). For this reason, most patients should undergo an evaluation for reversible ischemic disease. The specific test (exercise stress test, exercise or pharmacologic stress with nuclear imaging or echocardiography, cardiac catheterization or positron emission tomography) should be chosen on the basis of the patient's level of risk, ability to exercise, and baseline ECG as well as the expertise and preference of the performing physician.

E. Cardiac catheterization.

Cardiac catheterization is often required to delineate the extent of coronary disease. The cardiac output and pressure measurements obtained at the time of catheterization are generally considered to be the most accurate measurements of left ventricular function available. Cardiac catheterization and electrophysiologic study (EPS) can be performed at the same time.

F. EPS.

The gold standard for evaluating a patient with known or suspected VT/VF is an EPS. This is an invasive test similar to a cardiac catheterization in which multiple electrical leads are threaded to the endocardium to map electrical impulses and to induce dysrhythmias with applied electrical impulses. VTs are characterized as inducible or noninducible and suppressible or nonsuppressible (with medication) at the time of EPS. Inducible sustained VT is an indication of increased risk for sudden death in patients with reduced ejection fraction. Some VTs can be cured by ablation at the time of EPS.

V. Treatment

A. Non-pharmacologic.

Patients with palpitations should be instructed to reduce caffeine and eliminate smoking. They should discontinue any medications that may be contributing to the symptoms if possible. Such medications include theophylline and sympathomimetic agents such as pseudoephedrine.

Patients with ischemic heart disease and VT/VF may benefit from revascularization (either angioplasty or bypass surgery) to correct the ischemia.

B. Drugs

1. **Beta-blockers.** Beta-blockers have significant anti-arrhythmic properties and have been shown to reduce mortality for patients with ischemic heart disease and congestive heart failure. The benefit of beta-blockade increases with the patient's risk for adverse events.

   Beta-blockers also may have the effect of decreasing symptomatic palpitations in low risk patients. They should be the first pharmacologic treatment considered for both symptomatic palpitations in patients with structurally normal hearts and for patients with life-threatening ventricular dysrhythmias. All patients with known coronary disease and/or congestive heart failure should receive beta-blockers unless there is intolerance or a specific contraindication.

2. **Anti-arrhythmics.** Patients whose dysrhythmias are not controlled with beta-blockers may be candidates for amiodarone. Amiodarone is a type III anti-arrhythmic and is the only anti-arrhythmic other than beta-blockers that has not been shown to cause excess mortality in clinical trials.

   There are many other anti-arrhythmic medications that are available, but they all have potential for pro-arrhythmic effect and may cause increased mortality in treated patients. For this reason, their use has fallen out of favor. These should be used only with caution in carefully selected patients. The classification of anti-arrhythmics is shown in Table 9.6-2 .

Type 1A: Quinidine, disopyramide, procainamide
Type 1B: Lidocaine, tocainide, mexiletine, phenytoin
Type 1C: Flecainide, encainide
Type II: β-Blockers
Type III: Amiodarone
Type IV: Calcium channel antagonists

Table 9.6-2. Classification of antiarrhythmic drugs

C. Implanted cardiac defibrillators.

ICDs are used in the treatment of patients with life threatening ventricular dysrhythmias who are at high risk for sudden death (5). These devices are physically similar to pacemakers. They have an implanted power source beneath the skin of the chest and electrical leads connected to the heart, which can sense VT/VF and deliver electrical defibrillator shocks in response to sustained dysrhythmias. In clinical trials that have randomized patients to ICDs or antiarrhythmic drugs, the ICDs have

consistently been better at improving survival in high-risk patients. ICDs have been shown to be better even in patients who appear to have adequate suppression of their dysrhythmias with medication.

The disadvantages of ICDs are that they are invasive, expensive and occasionally may give shocks to patients who are still conscious.

VI. Summary.

Patients with frequent PVCs or nonsustained VTs but no other evidence of heart disease should be reassured that they have an excellent prognosis. If treatment is needed for symptomatic palpitations, ß-blockers should be used.

Patients with diminished ventricular systolic function and either sustained VT or inducible VT (on EPS) are at high risk for cardiac death. They should be investigated for reversible ischemia and other factors that may exacerbate their rhythm disturbances. These patients should all receive ß blockade if tolerated. Those at highest risk should receive EPS and consideration of an ICD. Empirical therapy with antiarrhythmic medications is almost never appropriate because of the increased mortality associated with these agents.

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9.7
VENOUS THROMBOSIS AND THROMBOPHLEBITIS

Mitchell S. King

Linda R. Bigi

Deep venous thrombosis (DVT) and subsequent embolism of clot to the pulmonary circulation, termed pulmonary embolism (PE), are potentially life-threatening conditions that require prompt diagnosis and treatment to limit the associated morbidity and mortality. Prophylaxis against development of DVT in hospitalized patients and in high-risk outpatients can lower the incidence of this disease. Superficial thrombophlebitis,

although generally not life threatening, can pose a risk for development of DVT and causes considerable patient discomfort.

I. Deep venous thrombosis

A. Clinical presentation.

A high index of clinical suspicion is necessary for the diagnosis of DVT.

1. **The history** may include lower extremity aching, swelling, or feeling of warmth. A search for risk factors, such as obesity, trauma, surgery, recent hospitalizations or travel, family history or personal history of DVT, congestive heart failure, pregnancy, and oral contraceptive pill (OCP) use, should be included.
2. **The physical examination** may be normal or may include findings of lower extremity swelling, tenderness, warmth, or palpable venous "cords."

B. Diagnostic testing

1. **Laboratory findings**
   a. A complete blood count (CBC), prothrombin time (PT), and partial thromboplastin time (PTT) should be obtained in anticipation of starting anticoagulant therapy.
   b. In patients younger than 40 years, without apparent risk factors, or with recurrent or family history of DVT, consider assessment for protein C deficiency, protein S deficiency, antithrombin III deficiency, lupus anticoagulants, hyperhomocysteinemia, and the genetic mutations for factor V Leiden and prothrombin 20210. Interpretation of these laboratory results must take into account current usage of heparin, warfarin (Coumadin), or OCPs as well as the presence of renal or liver disease, disseminated intravascular coagulation, pregnancy, and acute arterial or venous thrombosis (1).
2. **Venous imaging**
   a. Noninvasive testing may include duplex scanning or impedance plethysmography (IPG). Duplex venous scanning has become the test of choice to assess the patient for DVT. IPG is also acceptable, but it is probably less sensitive and specific than duplex scanning. These tests are noninvasive, and they are less sensitive for calf vein thrombi, which are not thought to be clinically significant unless they propagate proximally, which occurs approximately 20% of the time. Serial testing over several days can be done to evaluate the patient for the possibility of proximal propagation of calf vein thrombosis (2).
   b. Venography is the standard by which the other tests are measured, but it is invasive and carries with it a risk of contrast sensitivity and of developing DVT as a result of the procedure. Consider using venography in the setting of a high clinical suspicion when the noninvasive test results are negative or when the clinical suspicion is very low and the noninvasive test results are positive.

II. Pulmonary embolism

A. Clinical presentation

1. **History.** A patient with PE may present with nonspecific symptoms, such as dyspnea, palpitations, and a sense of impending doom, or with more classic symptoms of chest pain, cough, hemoptysis, symptoms consistent with DVT, or cardiovascular collapse.
2. **Physical findings** are also nonspecific. The most common physical findings are tachypnea, tachycardia, and signs consistent with DVT.

B. Diagnostic testing

1. **Laboratory findings**
   a. Arterial blood gases should be obtained and may reveal a low or normal po_2 and pco_2.
   b. A CBC, PT, and PTT should be ordered in anticipation of use of anticoagulants.
   c. See Section I.B.1.b for workup of the hypercoagulable state.

2. **Imaging**
   a. **Chest radiography** findings with PE are nonspecific and may show effusions, atelectasis, localized infiltrates, or decreased vascular markings, or they may be normal.
   b. **Ventilation-perfusion (V/Q) scanning** is the test of choice in diagnosing PE. Findings are reported as normal, low, intermediate, or high probability of PE based on the presence or absence of mismatched wedge-shaped perfusion defects. If the findings are nonconfirmatory or discordant with the level of clinical suspicion, duplex scanning may help to confirm the diagnosis, or invasive testing with pulmonary arteriography may be indicated.
   c. **Pulmonary arteriography** is the gold standard test for diagnosing PE, and, if positive, shows clot obstruction of one or more pulmonary arteries. This invasive test exposes the patient to contrast material and may be less readily available, depending on the availability of personnel.
   d. **Computed tomography (CT) scanning and magnetic resonance imaging (MRI)** are being studied for their role in diagnosing PE. Spiral CT scan has been most studied, and is sensitive for emboli in the main, lobar, and segmental, but not the subsegmental, pulmonary circulation. At present, it may have a role in helping to define indeterminate V/Q scans but does not displace pulmonary arteriography as the definitive test (3).

III. Treatment of DVT and PE.

Oxygen, intravenous fluids, ventilator support, and other supportive measures should be provided as indicated by the clinical status of the patient.

A. Anticoagulants

1. Heparin is the immediate drug of choice for treating DVT and PE and should be started when the diagnosis is suspected, unless there are contraindications to its use, such as increased risk of bleeding or heparin sensitivity.
   a. It is critical to achieve a therapeutic PTT (1.5–2.5 times control) within 24 hours of diagnosis to minimize the chances of recurrent DVT and to prevent clot propagation and PE (4). Algorithms have been developed to assist with attaining this goal (Table 9.7-1).

PTT	Drip rate	Bolus
<1.2 × control	Increase 200 U/h	Rebolus 80 U/kg
1.2–1.5 × control	Increase 100 U/h	Bolus 40 U/kg
1.5–2.5 × control	Maintain current	
2.5–3.0 × control	Decrease 100 U/h	
>3.0 × control	Decrease 200 U/h	Hold infusion for 1 h

PTT, partial thromboplastin time.
[a] Initial bolus 80 U/kg. Initial drip at 18 U/kg.

Table 9.7-1. Nomogram for adjustment of intravenous herparin dosing[a]

2. Duration of use. Heparin is generally continued for 5–7 days and is overlapped with the initiation of warfarin therapy.
3. Laboratory monitoring
   1. A PTT should be obtained initially every 6 hours until therapeutic and a stable PTT has been attained, after which a PTT may be obtained every 12–24 hours.
   2. While the patient is on heparin, a CBC should be obtained every 2–3 days to monitor for thrombocytopenia. Mild degrees of thrombocytopenia (more than 100,000 platelets per high-power

field) occur commonly with heparin therapy. More severe degrees of thrombocytopenia may be associated with arterial thrombosis and may require cessation of heparin therapy.

3. During pregnancy, patients need long-term heparin therapy, generally subcutaneously beginning with a dosage of 17,500 U q12h, after initial intravenous therapy. The PTT should be monitored with the goal of attaining a value of 1.5–2.0 times normal. CBC, potassium, and liver enzymes should be monitored. With long-term heparin therapy, there is a risk of promoting osteoporosis. To minimize this, supplemental calcium should be given during pregnancy (5).

4. Low molecular weight heparin (LMWH), rather than intravenous heparin, can also be used for the management of DVT and PE. Enoxaparin 1 mg/kg q12h has been approved for this indication. No laboratory test other than a CBC is needed. This allows for outpatient therapy of selected patients with DVT.

5. Warfarin can be started 24 hours after initiating LMWH or attaining a therapeutic PTT on intravenous heparin. An initial loading dose of 10 mg is given, and subsequent doses are based on the prothrombin international normalized ratio (INR) value, as shown in Table 9.7-2 (6).

INR	Warfarin dose (mg)
<1.3	10
1.4–1.8	7.5
1.9–2.3	5.0
2.4–2.8	2.5
>2.8	Hold

From Hull R, et al. A standardized prescriptive warfarin sodium nomogram. *Clin Res* 1994;42: 185A, with permission.

Table 9.7-2. Warfarin dosing nomogram based on prothrombin time international normalized ratio(INR)

a. Laboratory monitoring. PT should be obtained daily initially. After a therapeutic value has been achieved, PT times may be obtained twice weekly until stabilized and thereafter weekly to monthly.

b. Warfarin must be administered for 3 months, except in cases of recurrent DVT, in which case it may have to be continued for 6–12 months, or possibly for lifetime in cases of factor deficiencies and resistance.

c. Complications of warfarin use. Bleeding and warfarin-induced skin necrosis are the two major complications. With initiation of warfarin therapy, a hypercoagulable state is temporarily created because of the more rapid depletion of protein C levels. This protein C depletion is thought to be a cause of the skin necrosis that can rarely occur, with the risk being greater in patients with protein C deficiency. Many drugs interact with warfarin and can affect PT values.

d. Pregnancy. Warfarin is contraindicated in pregnancy.

B. Other treatments

1. Greenfield filters may be indicated in patients with recurrent DVT or PE despite adequate anticoagulation or in patients in whom the use of anticoagulants is contraindicated.

2. Thrombolytics, followed by heparin and warfarin, may have a role in treating patients with massive PE or in select patients with extensive iliofemoral DVT to effect prompt dissolution of clot. To treat PE, recombinant tissue plasminogen activator has been suggested as the agent of choice, with dosages and contraindications as for treatment of acute

myocardial infarction. Use of localized catheter infusion of recombinant tissue plasminogen activator has been recommended for treatment of iliofemoral thrombosis [7].

3. Pulmonary embolectomy should be considered in unstable patients with massive PE who may not be candidates for thrombolytics.

IV. DVT prophylaxis

A. Risk factors

for development of DVT include obesity, trauma, surgery (particularly lower extremity orthopedic surgery), prior history of or family history of DVT, OCP use, congestive heart failure, malignancy, and pregnancy. Identifying risk factors and assessing the degree of risk for the patient are the first steps in providing appropriate prophylaxis (Table 9.7-3).

Surgery (esp. lower-extremity orthopedic surgery)
Personal or family history of deep venous thrombosis
Trauma
Obesity
Congestive heart failure
Malignancy
Pregnancy
Medications (e.g., oral contraceptives, tamoxifen and related medications)

Table 9.7-3. Risk factors for deep venous thrombosis

B. Recommendations

are shown in Table 9.7-4 . For high-risk patients, consideration should be given to evaluating for DVT prior to hospital discharge or to empirically continuing anticoagulant therapy for 6 weeks (8).

Low-risk medical and surgical patients	Gradient stockings alone or with SC heparin 5,000 U q8–12h, starting 2 h preoperatively or on hospital admission. Therapy may continue until patient is ambulatory or discharged
Moderate-risk medical and surgical patients	Pneumatic compression stockings placed in the operating room and continued until patient is ambulatory, with SC heparin (as above) or low molecular weight heparin (e.g., Lovenox 30 mg SC q12 h)
Neurosurgery and ocular and genitourinary surgery patients	Pneumatic compression stockings
High-risk patients (includes knee and hip surgery)	Low molecular weight heparin (enoxaparin, 30 mg SC q12h) or oral anticoagulants (see Section III.A.2 and Table 9.7-2), treatment of deep venous thrombosis and pulmonary embolism for dosing) along with gradient or pneumatic compression stockings

SC, subcutaneous.

Table 9.7-4. Recommendations for deep venous thrombosis prophylaxix

V. Superficial thrombophlebitis

generally occurs in the lower extremity in association with trauma, infection, or varicose veins. It manifests as a tender cord or knot with some surrounding erythema. In the upper extremity, it is most commonly seen with intravenous cannulation. In the absence of inciting causes,

consideration should be given to evaluation for malignancy or an underlying hypercoagulable state. Treatment involves use of heat, elevation, and nonsteroidal anti-inflammatory medications. If the process appears to be extending to the thigh and the saphenofemoral junction, anticoagulation and ligation or excision of the vein may be necessary. If extension into the deep system is a concern, duplex scanning should be performed to assess the need for additional anticoagulant therapy.

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9.8
PERIPHERAL ARTERIAL DISEASE

Karen M. Bolton

Peripheral arterial disease encompasses acute and chronic arterial occlusions of the lower and upper extremities, gut, and neck. Causes of acute arterial occlusion include thrombosis, embolism, and trauma. The arteries most often identified with chronic atherosclerotic disease, in order of incidence, include femoropopliteal-tibial, aortoiliac, carotid and vertebral, splanchnic and renal, and brachiocephalic (1).

I. Chronic extremity arterial insufficiency.

A.

Risk factors include cigarette smoking, diabetes mellitus, hyperlipidemia, hypertension and abnormalities of blood viscosity, and hyperhomocystinemia.

B.

Claudication is pain of the lower extremity that is predictable with exercise and relieved by rest without a change in position.

1. **Clinical presentation** of claudication is most commonly calf pain (associated with superficial femoral occlusion), but it can present as thigh, hip, or buttock pain as well (aortofemoral or internal iliac occlusion).
2. **Differential diagnosis** of claudication includes arthritis, intervertebral disk disease, spinal stenosis, peripheral neuropathy, restless legs syndrome, deep venous thrombosis, arterial embolus, and Buerger's disease.
3. Claudication usually stabilizes or improves with time with the development of collateral circulation (2).

4. Claudication is associated with a significantly increased incidence of coronary artery disease, stroke, and other peripheral artery diseases (2).

C. Physical findings.

of chronic arterial insufficiency include atrophic skin with hair loss, brittle nails, dependent rubor, elevation pallor, coolness to touch, ischemic tissue ulceration, and gangrene. Femoral, posterior tibial, and pedal pulse diminution or absence before or after exercise represents significant disease.

D. Diagnostic studies

1. Segmental blood pressure measurements in arm, thigh, calf, and ankles at rest or during exercise are quite helpful. The ratio of ankle to arm systolic pressure, called the ankle-brachial index (ABI), is abnormal if less than 0.9, indicating the possibility of significant disease. A ratio of less than 0.5 indicates severe disease.
2. Duplex ultrasonographic scanning provides a noninvasive method of measuring the presence, location, and degree of arterial obstruction.
3. Computed tomography and magnetic resonance angiography can also be helpful.
4. Angiography is the standard test for measuring arterial atherosclerosis, but it carries risks and should be reserved for patients with suspected significant disease who are considering an interventional procedure.

E. Medical management

involves intervening with risk factor modification and preventing, identifying, and treating associated diseases, such as coronary artery disease and stroke.

1. **Risk factor modification.** Smoking should be discouraged. Hypertension and hyperlipidemia should be adequately treated with the usual appropriate pharmacologic and nonpharmacologic methods, watching for vasoconstriction as an adverse effect of hypertensive medication (see Chapter 9.1 and Chapter 17.4). Diabetics tend to have the disease more distally and in smaller vessels and have an increased risk for severe atherosclerotic disease. Aggressive management of diabetes is appropriate (see Chapter 17.2).
2. **Exercise** is beneficial in improving the pain-free walking distance in patients with claudication.

F. Pharmacologic treatment

1. Pentoxifylline (Trental) is used in dosage of 400 mg tid. Clinical improvement in claudication is variable.
2. Cilostazol (Pletal) is used in dosage of 100 mg bid to improve symptoms of claudication.
3. Aspirin (325 mg daily) is often used to modify a patient's risk for stroke and myocardial infarction.

G. Interventional procedures,

such as percutaneous transluminal angioplasty and vascular reconstruction, should be considered for the few patients having symptoms that interfere with lifestyle, who have failed to improve with usual medical management, and who have developed ischemic rest pain, ulcers, or gangrene.

II. Acute peripheral arterial occlusion.

A. Clinical presentation

of acute occlusion is heralded by the “5 P's”: pain, pallor, paresthesias, paralysis, and pulselessness. The pain may be dramatic and severe, starting distal to the obstruction, then gradually migrating proximally toward the level of occlusion. Numbness and paresthesias may mask all other presenting symptoms.

B. Embolism.

The heart is the most common source of emboli from left atrial fibrillation and left ventricular fibrillation in a patient with a myocardial infarction. Peripheral embolization is produced from thrombi in arterial walls that may be present in aneurysms or on atherosclerotic plaques. Therapy for acute embolic occlusion consists of anticoagulation and prompt embolectomy.

C. Thrombosis.

The most common cause of acute thrombosis is progressive atherosclerosis. Treatment requires arteriography and surgery, or balloon angioplasty with adjunctive thrombolytic therapy and anticoagulation.

III. Other causes of peripheral arterial disease

A. Mönckeberg's medial calcific sclerosis

does not narrow the arterial lumen but creates a noncompressible artery that has little effect on circulation. It may be accelerated and severe in diabetics and in patients taking long-term corticosteroid therapy.

B. Buerger's disease, or thromboangiitis obliterans,

is a vasculitis of small and medium-size veins and arteries that occurs predominantly in middle-aged men. It starts distally and progresses cephalad, involving both upper and lower extremities. Tobacco use is the sole known etiologic factor.

C. Other arterial inflammatory diseases

that cause an arteritis can display arterial occlusion.

IV. Vasospastic diseases.

A. Raynaud's disease

is characterized by vasospastic attacks precipitated by exposure to cold or emotional stimuli; bilateral involvement of the extremities; absence of gangrene or, if present, limited to the skin of the fingertips; no underlying responsible disease; symptoms for at least 2 years; and normal pulses.

B. Raynaud's phenomenon

refers to vasospastic attacks like those in Raynaud's disease, which occur secondary to a systemic condition such as connective tissue disease, Buerger's disease, carpal tunnel syndrome, primary pulmonary hypertension, trauma, and use of vasoconstrictor drugs.

C.

Management of both the disease and the phenomenon consists of the use of pharmacologic vasodilators as well as plasmapheresis or sympathectomy.

V. Cervical carotid atherosclerotic disease.

Clinical syndromes of occlusive disease of the extracranial cervical carotid artery include amaurosis fugax, transient ischemic attacks, reversible ischemic neurologic deficit, and strokes (also see Chapter 6.5 and Chapter 6.6). Noninvasive duplex scanning has emerged as the screening test of choice. Treatment is carotid endarterectomy in patients who have a greater than 70% cross-sectional diameter reduction and a low surgical risk. Medical treatment involves anticoagulation with aspirin at 325 mg daily, ticlopidine (Ticlid) 250 mg bid, clopidogrel bisulfate (Plavix) 75 mg daily, or warfarin (Coumadin) when ulcerated plaques are present, keeping the international normalized ratio at 2–3.

VI. Aneurysmal disease.

Surgical resection of a thoracic aortic aneurysm is indicated when the aneurysm is symptomatic, when it measures 6 cm in diameter or larger or enlarges over time, or when it is accompanied by significant or poorly controlled hypertension. Abdominal aortic aneurysm is at significant risk for rupture when the aneurysm is 5 cm in diameter or larger, and repair should be considered before then.

VII. Visceral disease.

Acute embolic occlusion of the superior mesenteric artery, thrombotic occlusion of major visceral vessels, and nonocclusive mesenteric ischemia related to cardiac disease and low flow states all produce segmental bowel necrosis. The clinical presentation of acute embolic occlusion of the superior mesenteric artery includes sudden onset of severe abdominal pain and prompt bowel emptying after the onset of pain. Chronic intestinal ischemia (intestinal angina) is gradual in onset, with pain after eating, and is usually seen in female smokers with significant weight loss and a desire for smaller and smaller meals. Surgical consultation for revascularization should be considered.

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X. RESPIRATORY PROBLEMS

10.1
ASTHMA

Howard N. Weinberg

Asthma is a reversible lung disorder characterized by airway spasm, obstruction, and inflammation. Severity is highly unpredictable, ranging from mild illness to death. There is no predilection for age, sex, or race. Proper control of asthma requires prompt recognition of illness, excellent communication between physician and patient, and intense education.

I. Diagnosis

A. History.

1. **Triggers.** There are three principal triggers for exacerbations:
   a. **Allergens.** These include inhaled substances, such as molds, pollens, dust, animal danders, cosmetics, tobacco smoke, cockroaches, and household scents; and medications, especially ß-blockers and aspirin. Both selective agents and optical preparations of ß-blockers can aggravate asthma or cause death.
   b. **Infections.** Viral upper respiratory infections (URIs) are particularly problematic. In children, it is common for episodes to follow URIs.
   c. **Psychological factors.** These can play a significant role. Panic attacks can be misinterpreted as asthma.
   d. **Symptoms**
      a. Typical presentation includes dyspnea, cough, and wheezing in a range of mild to severe with onset over minutes or days.
      b. Atypical presentation. Some patients may be so tight that the usual triad of symptoms may appear only after initial treatment. At the other end of the spectrum, asthma may manifest only by chronic cough (also see Chapter 2.4). A persistent night cough is often the only symptom of asthma in children.
      c. Exercised-induced asthma (EIA) is a variant in which symptoms are seen only following exercise

B. Physical examination.

Auscultation reveals rhonchi and expiratory wheezes. Often there is a reversal of the normal 2:1 inspiratory-to-expiratory ratio. Respiratory rate is increased out of proportion to fever. Other signs include subcostal, intercostal, or supraclavicular muscle movements, nasal flaring, cyanosis, or change in mental status.

C. Laboratory findings

1. **Peak flowmeter.** This gives a readily obtainable objective guide to the severity of an episode. Peak flow should be measured as baseline and before and after interventions; measurement techniques should also be taught for home monitoring (1).
2. **Arterial blood gases.** These are of little value unless needed to determine admission to hospital.
3. **Chest radiography.** Radiography is not to be used routinely. It may be of value in newly diagnosed patients or when a complication is suspected.

II.Therapy

A. General principles

1. **Avoidance.** Avoidance is of critical importance. Be particularly aware of indoor factors, including pillows, flowers, scents, cosmetics, woodstoves, and kerosene heaters. Under no circumstance should anyone smoke in the house of an asthmatic adult or child.
2. **Immunotherapy.** Consider allergy desensitization (see Chapter 8.6). Patients should receive both pneumococcal and influenza vaccinations.
3. **Education.** Excellent source material has been prepared by the National Asthma Education Program for patients and for providers (2).

B. Maintenance drug therapy

(3)

1. **ß-Adrenergics.** These agents are generally considered first, especially when intermittent therapy is all that is needed. If usage becomes daily, switch to another medication with ß-adrenergics available for exacerbations (rescue).
   a. **Metered-dose inhaler (MDI).** Albuterol (Proventil, Ventolin), bitolterol (Tornalate), pirbuterol (Maxair) are all recommended at 1–2 inhalations q4h prn. Salmeterol (Serevent) is recommended at 2 inhalations q12h for prevention and does not preclude the usage of faster acting agents. Attention must be given to teaching proper technique. Many patients require a spacer device (InspirEase, Key Pharmaceuticals; or Aerochamber, Monaghan Medical).
   b. **Nebulizer.** Nebulizers are available for albuterol (2.5 mg q4h) and bitolterol (1.5–3.5 mg q6h). A new agent, levalbuterol (0.63 mg q6h), may have fewer side effects, but this remains to be seen. Nebulizers are useful in the home environment for acute situations or when the MDI cannot be mastered.
   c. **Oral medications.** These are recommended primarily in young children or for nocturnal asthma; otherwise, they offer no advantage but increase side effects.
2. **Anti-inflammatories.** Anti-inflammatory agents are now advised as the first line, especially when daily treatment is needed.
   a. **Inhaled corticosteroids.** These have few side effects and great potential to reduce morbidity. They require 4–8 weeks for full onset of action and are not effective for acute attacks. Commonly available are beclomethasone (Beclovent, Vanceril) 2–8 inhalations bid, budesonide (Pulmicort) 1–2 inhalations bid, flunisolide (AeroBid) 2–4 inhalations bid, fluticasone (Flovent 44, 110, and 220) 2–4 inhalations bid, and triamcinolone (Azmacort) 2–8 inhalations bid. Dosing may have to follow inhaled ß-adrenergic agonists. Flovent 220 should be avoided if possible due to potential adrenal suppression.
   b. **Oral steroids.** Try to avoid daily use. These may be very helpful in preventing severe episodes (see Section II.C.3).
   c. **Cromolyn (Intal) and nedocromil (Tilade).** These are unique agents that differ from corticosteroids and have few if any side effects. Onset of action is usually 2–4 weeks. Dosage is 2 inhalations qid, but this can be tapered to the minimum effective amount. Both agents are available as MDI, and cromolyn for nebulizer.
   d. **Leukotriene modifiers.** These are relatively new oral agents that show great promise: montelukast (Singulair) 10 mg every evening for patients older than 12 years, 5 mg for patients aged 6–12 years, 4 mg for patients aged 2–5 years; and zafirlukast (Accolate) 20 mg bid for patients older than 12 years, 10 mg for patients aged 6–12 years, 1 hour before meals or 2 hours after meals.
3. **Theophylline.** This is no longer considered the treatment of choice. It may be useful when the previous two classes of medication are not effective or in nocturnal asthma or in children who are too young to use MDIs.
4. **Anticholinergics.** These may also be tried when other medications are not effective. Ipratropium (Atrovent) is available as an MDI, 2 inhalations qid, for nebulizer, or in combination with albuterol (Combivent).
5. **Mucolytics and expectorants** are of no proven benefit.

C. Acute drug therapy

1. **Hydration and oxygen** are extremely important during an acute episode. Intravenous fluids may also be needed.
2. **ß-Agonists** are the initial treatment of choice. Nebulizer treatments may be given at 60-minute intervals as needed or a MDI used with a spacer at the rate of one inhalation per minute for 5 minutes. Subcutaneous administration is rarely indicated because it offers no advantage yet increases toxicity.

3. **Corticosteroids**
   a. **Oral.** Oral corticosteroids are recommended for most exacerbations, especially when the usual therapy has failed. Try a 6- to 10-day course in a tapering dosage, starting at 1–2 mg/kg per day in children or 40–80 mg/kg per day in adults, either bid or tid. Some patients with a history of exacerbation under certain circumstances, such as onset of a URI or exposure to an allergen, may benefit from prophylactic treatment.
   b. **Intravenous.** Intravenous corticosteroids are recommended for all resistant patients, especially when considering hospitalization. Give the treatment at least 4 hours to work before deciding on admission. Methylprednisolone is the agent of choice, given 0.5–1.0 mg/kg q6h. Controversy exists over optimal dosage, but 125 mg q6h is considered the upper limit.
4. **Theophylline.** Theophylline is of no benefit in the acute setting. Many experts still use aminophylline after admission. If aminophylline is used, serum levels must be closely monitored to avoid toxicity. Therapeutic range is 5–15 mg/L.
5. The admission decision ideally should not be made until adequate treatment (including steroids) has been given for 4–8 hours. Decision should be based on treatment failure or signs of impending respiratory failure.

III. Special issues

A. Exercise-induced asthma.

Exercise-induced asthma is very common and should never prohibit an individual from participating in physical activity. Acceptable and useful treatment includes pre-exercise ß-adrenergics or continual use of anti-inflammatories (see Section II.B.2.a and Section II.B.2.c).

B. Pregnancy.

Asthma can be a serious risk to the developing fetus. Use of ß-adrenergic agents, cromolyn, leukotriene modifiers, steroids, and theophylline is considered safe. Some antibiotics, live virus vaccines, and iodides must be avoided (see Chapter 22.2).

C. Breast-feeding

should be encouraged as a way to delay onset of allergies. The same medication considerations apply as in pregnancy (see Chapter 22.2).

D. Prevention.

Asthma cannot be prevented, but morbidity and mortality can be minimized. This involves complete avoidance of smoking, aggressive use of anti-inflammatory drugs, and early recognition of exacerbations, with rapid intervention, especially with steroids.

E. Psychosocial issues.

Much attention should be paid to the patient's and family's attitudes. Education is the key to effective control. Try to avoid labeling the patient as ill. Foster the attitude that this is a person with asthma, not an asthmatic person.

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10.2
ACUTE BRONCHITIS AND PNEUMONIA

William J. Hueston

I. Acute bronchitis

Acute bronchitis is one of the most common diagnoses made in primary care practices. Symptoms of acute bronchitis can mimic asthma in acute stages. For patients in the early stages of acute bronchitis, pulmonary

function tests may be indistinguishable from those of patients with asthma. As the bronchitis improves, patients are sometimes left with a lingering post-bronchitic syndrome that may resemble asthma or, more specifically, cough-variant asthma (also see Chapter 10.1).

A. Diagnosis

1. **Clinical presentation.** Patients with either acute bronchitis or pneumonia usually present with a productive cough but may also complain of pleuritic chest pain, shortness of breath, occasional hemoptysis, and fever (usually less than 101°F). In most cases, acute bronchitis symptoms are preceded or accompanied by symptoms of an upper respiratory tract infection. On physical examination, wheezes or diffuse rhonchi may be present. The presence of localized rales should raise the possibility of pneumonia.
2. **Laboratory or radiologic evaluation.** Unless the patient has an underlying chronic pulmonary disease or appears seriously ill, there is little benefit from evaluating arterial blood gases, white blood cell counts, sputum Gram's stains or culture, or routine chest radiograph.
3. **Differential diagnosis.** In addition to suspecting pneumonia in patients with a cough, one should consider sinusitis and asthma in patients presenting with a productive cough and wheezing. Particularly in younger patients, symptoms of recurrent or chronic bronchitis may be indicators of underlying asthma and warrant further evaluation.

B. Management of acute bronchitis

1. **Antibiotic use.** There is little evidence to support the use of routine antibiotics in previously healthy patients with acute bronchitis. Patients with underlying asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), or another illness that would predispose to immunoincompetence may benefit from antibiotic administration using such medications as erythromycin [e.g., erythromycin ethylsuccinate (EES)] 400 mg qid or 800 mg bid), trimethoprim-sulfamethoxazole (Bactrim, Septra) 1 double-strength tablet bid, or cephalexin (Keflex), 250 mg qid.
2. **Bronchodilators.** Because patients with acute bronchitis often present with wheezing and have reversible changes on pulmonary function tests, the use of aerosolized bronchodilating agents, such as albuterol (Proventil), 1–2 puffs qid for 7–10 days, may be useful for reducing the duration of symptoms and returning patients to their usual activity earlier.
3. **Post-bronchitic syndrome.** Patients who have experienced acute bronchitis may continue to cough for several months following their acute illness. This cough is usually unproductive and may be exacerbated by exercise, changes in temperature or humidity, or other factors that instigate airway reactivity. In these patients, continued treatment with albuterol or a similar ßagonist agent may help the airway reactivity and reduce the cough. Eventually, these symptoms subside totally and the bronchodilator can be discontinued.

II. Pneumonia.

Many bacterial organisms are responsible for pneumonia in ambulatory patients, although in most cases a specific bacterium is not found. The morbidity of pneumonia in patients with bacterial etiologies and the increased mortality among older patients and those with underlying pulmonary diseases make the timely diagnosis and proper management of pneumonia in ambulatory patients important.

A. Diagnosis

1. **Clinical presentation.** Patients with pneumonia present with a productive cough, sometimes with hemoptysis. Pleuritic chest pain, shortness of breath, tachypnea, and fever may also accompany the cough. Some patients, especially children and the elderly, may present without a cough and with vague, poorly defined symptoms, such as fever, nausea, or abdominal pain. Patients often have rales in the affected area, although with consolidation rales may not be present. With consolidation, the only physical

findings may be decreased breath sounds and egophony. Decreased breath sounds may also be noted in patients with associated pneumonic pleural effusions.

2. **Laboratory and radiologic evaluation.** The diagnosis of pneumonia is confirmed by chest radiography. Both posteroanterior and lateral views should be taken when possible to help localize the area of infiltrate. A sputum specimen for Gram's stain and culture can often be helpful in directing the selection of antibiotic. In patients with underlying pulmonary diseases, arterial blood oxygen concentration should be evaluated by blood gas analysis or pulse oximetry. For patients who appear ill, a white blood cell count and differential may be useful for following the progress of recovery, and a blood culture should be strongly considered.
3. **Presentation in the elderly.** Older patients may not exhibit any of the usual signs and symptoms of pneumonia. Many older individuals have nonspecific symptoms, such as anorexia, confusion, or falls, as early signs of pneumonia. Because of the high mortality in the geriatric population, pneumonia should be considered in all older patients who are exhibiting acute changes in their mental status or general health.

B. Management

1. **Individualizing management.** Many previously healthy individuals with acute pneumonia can be managed on an outpatient basis. However, based on the increased mortality from pneumonia among patients with certain risk factors, hospital admission should be strongly considered for patients with chronic pulmonary diseases, patients with cirrhosis, those showing significant hypoxia or hypotension, elderly patients, and those with impaired immunocompetence. In addition, patients with signs of compromise, such as tachypnea (respiratory rate over 30) or hypotension, should be hospitalized.
2. **Antibiotic selection.** The difficulty in obtaining sputum specimens from some patients makes empirical treatment with antibiotics the recommended management of all pneumonias encountered in the primary care setting. In addition, recent growth in the number of *Streptococcus pneumoniae* strains that are resistant to penicillin and other commonly used antibiotics makes antibiotic selection very important. The American Thoracic Society and the Infectious Disease Society have issued recent guidelines to assist with antibiotic selection for low- and high-risk patients (1).
    a. **Treatment with low risk for drug-resistant *Streptococcus pneumoniae* (DRSP).** Initial antibiotic selection should be based on Gram's stain results. In the absence of an adequate specimen, for previously healthy patients, antibiotics should be chosen to cover the most common community-acquired agents noted previously (see Section I.B.1). For ambulatory patients, empirical therapy with macrolides, such as erythromycin (e.g., EES), 400 mg qid or 800 mg bid, or azithromycin (Zithromax), 500-mg single dose followed by 250 mg daily, or a fluoroquinolone with enhanced pneumococcal activity (such as levofloxacin or ofloxacin) will be effective against the most common bacterial organisms as well as atypical agents. In heavy smokers and patients with underlying COPD, consideration should be given to using a drug that is also effective against *Haemophilus influenzae*, such as second-generation cephalosporins or clarithromycin (Biaxin, 500 mg bid), or a fluoroquinolone with enhanced pneumococcal activity (such as levofloxacin or ofloxacin), both of which are effective against *Mycoplasma, Streptococcus pneumoniae*, and *Legionella*. Patients with underlying chronic pulmonary disease or with other risk factors, such as institutional residence, alcoholism, or other debilitating illness, may require broader gram-negative coverage with a second- or third-generation cephalosporin, such as cefuroxime (Zinacef), 750 mg IV or IM q8h. In these patients, the addition

of a macrolide to cover *Legionella* and other atypical organisms should be considered. In cases where fever and symptoms persist, a follow-up chest film may be useful to evaluate for a potential empyema. In addition, patients who are not improving with empirical therapy should be suspected of having DRSP and should be treated accordingly (see below).

3. **Inpatient treatment with high risk for DRSP.** Risk factors for infection with DRSP include recent hospitalization; use of ß-lactam antibiotics in the previous 3 months; severe underlying illness such as malignancy, chronic renal failure, or advanced liver disease. In patients with higher risk for DRSP, initial therapy should be started with either a fluoroquinolone with enhanced pneumococcal activity (such as levofloxacin or ofloxacin) or, in critically ill patients, with vancomycin. Fluoroquinolones with enhanced *S. pneumococcus* activity demonstrate good activity against intermediate-resistance *Streptococcus* but not against highly resistant statins. Vancomycin should be used for highly resistant strains or in critically ill patients where resistance status is unknown.
4. **Follow-up.** In patients with lobar or segmental pneumonias that do not clear with antibiotic therapy, further evaluation with computed tomography may be advisable to evaluate for an obstructing tumor. In addition, because of the increased possibility of an underlying tumor associated with pneumonia in patients older than 40 years, a follow-up chest film is indicated in4–6 weeks in such individuals (see also Chapter 10.5).

C. Prevention.

Because of the increased morbidity associated with pneumonia in certain risk classes, patients with underlying asthma, COPD, and threatened immunocompetence (including prior splenectomy, cardiac or renal disease, or age greater than 65) should receive a pneumococcal vaccine and yearly influenza vaccinations (see also Chapter 1.4)

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10.3

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

John M. Heath

Joshua J. Raymond

I. Background

A.

Chronic obstructive pulmonary disease (COPD) involves symptomatic airflow obstruction due to long-term inhalation of inflammatory particles.

B.

COPD clinically manifests in two forms:

1. In *chronic bronchitis*, the predominant form of COPD, smooth muscle hypertrophy and excessive neutrophil secretions at the terminal bronchus level cause coughing with sputum production of at least 3 months duration and over two consecutive years.
2. In *emphysema*, the loss of distal lung elasticity and destruction of alveolar walls leads to progressive dyspnea.

C.

COPD effects 7% of the U.S. population and is among the top five causes of death. Worldwide, COPD mortality trends are increasing among population groups whose smoking prevalence is also increasing (1).

D.

Cigarette smoking causes 90% of COPD, though only 20% of smokers will develop obstructive lung symptoms. What predisposes an individual smoker to develop COPD may relate to the cellular response to oxidative stress, induced by inhaling smoke.

II. Symptoms

A.

The principal features of COPD are cough, sputum production, and dyspnea. Unlike asthma's episodic airway brochospasms, the more gradual and progressive dyspnea in COPD is caused by fixed changes in the airway parenchyma and is less reversible.

B.

The psychological aspects of COPD include those shared by many chronic diseases associated with progressive functional decline: withdrawal, isolation, and depression.

C.

Key symptoms are progressive breathlessness and productive cough.

III. Clinical findings

A.

Airflow limitation results in percussive hyperresonance. Prominent use of accessory respiratory muscles is accompanied by diminished breath sounds.

B.

Classic “blue bloater” and “pink puffer” presentations are in the late stages of COPD:

1. Right-side heart failure caused by hypoxemia and pulmonary hypertension leads to peripheral edema and cyanosis in chronic bronchitis.
2. Failing respiratory muscles and decreased lung support cause emphysema patients to make prolonged puffing efforts to maintain lung expansion.

C.

The clinical course of COPD varies widely due to the severity of exacerbations and frequency of comorbid conditions, which often are also smoking related.

D.

Key physical signs are prolonged expiration and decreased airflow.

IV. Laboratory tests

A.

Pulmonary function testing (PFT) demonstrates a characteristic pattern of reduced airflow with forced expiratory volume at 1 second (FEV_1) less than 70% of predicted.

1. The FEV_1 improvement with inhaled ß agonists is less in COPD than in asthma and is poorly correlated with symptoms during activity.
2. The progress of PFT deterioration in COPD can be improved by smoking cessation.

B.

Radiologic findings on chest x-ray include bullous dilation of the terminal airways, flattening of the diaphragm, and hyperlucency of peripheral lung fields.

C.

Arterial blood gasses can show hypoxemia and hypercapnia during exacerbations.

D.

The key determination is pulmonary function testing.

V. Differential diagnosis

A.

α_1-Antitrypsin deficiency can produce dyspnea, cough with wheeze, and should be suspected in a younger symptomatic nonsmoker.

1. PFTs reveal decreased carbon monoxide diffusing capacity.
2. Diagnosis is confirmed by low serum levels of α_1-antitrypsin.

B.

Cystic fibrosis is a genetic abnormality that presents at a younger age with obstructive airway symptoms and gastrointestinal disease.

VI. Treatment approach

A.

Smoking cessation is the only proven intervention to alter lung deterioration (2).

B.

The goals in COPD therapy are to relieve symptomatic airflow obstruction, reduce airway inflammation, and reverse hypoxemia (3).

VII. Medication, oxygen, and surgery

A.

Bronchodilator therapy with sympathomimetic agents such as $ß_2$-receptor agonists relaxes airway smooth muscles and relieves air hunger.

1. Long-acting preparations, such as salmeterol (Serevent), are given twice a day and decrease the frequency of COPD exacerbations.
2. Short-acting preparations, such as albuterol (Protentil, Ventolin), bitolterol (Tornalate), and pirbuterol (Maxair), provide immediate relief from acute bronchospasm and are used as “rescue” agents.

B.

Inhaled anticholinergic medications, such as ipratropium (Atrovent) and tiotropium (U.S. release pending), reduce airway inflammatory secretions and aid in bronchodilation. They can be dosed sequentially with ß agonists or as a combination product (Combivent).

C.

The preferred delivery method for both types of agents is by inhalation. Metered-dose inhaler (MDIs,) or "puffers," are most effective when used with a spacer device, which increase drug delivery into the lower airways. Nebulization is an alternative delivery route if patients are unable to handle an MDI device.

D.

Corticosteroids are a mainstay of therapy in acute COPD exacerbations but have not demonstrated improvement in chronic therapy. Steroids can be delivered by MDI, oral, or parental routes and are thought to decrease airway inflammation and enhance bronchial reactivity to ß-adrenergic stimulation.

E.

Methylxanthines such as theophylline are used as second-line agents for refractory patients and for those who are unable to use inhaled therapies.

F.

Antibiotics are often added empirically in acute exacerbations but remain controversial, as less than 50% of protected-tip, bronchoscopically obtained cultures in COPD patients reveal a predominant microorganism (4).

1. Macrolide antibiotics appear most effective against the most common respiratory pathogens: *Haemophilus influenzae, Moraxella catarrhalis*, and *Streptococcus pneumoniae*
2. COPD exacerbations complicated by comorbid illnesses may also involve gram-negative bacilli and require amoxicillin-clavulanate, fluoroquinolones, or upper-generation cephalosporin antibiotics.

G.

Alternative therapies, such as mucolytics and expectorants, are widely used, though without objective evidence of improvement from limited controlled studies.

H.

Oxygen is critical for patients with documented hypoxemia: Pao_2<60 mm Hg.

1. Dosed as a flow rate of liters per minute and titrated to relieve hypoxemia.
2. Duration of at least 18 hours per day is necessary to reduce mortality. Oxygen is supplied as a compressed gas or from liquid reservoirs, or from a room air concentrator and delivered by nasal cannuli, demand-flow device, or mask. A conserver device can sense and trigger oxygen flow during inhalation to minimize loss from reservoir sources.
3. Whereas daytime use provides symptomatic relief, use during sleep is critical because nocturnal hypoxemia is associated with cardiac arrhythmia and pulmonary hypertension.

I.

Surgical treatments include resection of bullous emphysematous areas to allow greater lung expansion and single-lung transplantation in end-stage emphysema patients.

J.

Influenza and pneumococcal vaccination is also recommended.

VIII. Diet

A.

Increased respiratory effort to overcome obstructive forces requires enhanced calories.

B.

Adequate hydration is critical to allow expectoration of mucus.

IX. Activity.

Pulmonary rehabilitation improves respiratory muscle tone and strength. Components include breathing against resistance and accessory respiratory muscle conditioning.

X. Patient education

A.

Smoking cessation is the single most important element in COPD management.

B.

Proper technique for inhaler use, self-monitoring of respiratory efforts, and facilitating expectoration can be accomplished with cross-discipline input from respiratory therapists.

C.

Close communication during the start of acute exacerbations with patient and caregiver may help to prevent unnecessary hospitalizations.

D.

End-stage disease management requires advance directive discussions about the use of mechanical ventilation as well as cardiopulmonary resuscitation.

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10.4
TUBERCULOSIS

Patrick T. Dowling

Michelle Anne Bholat

Tuberculosis (TB), a chronic, necrotizing infection caused by *Mycobacterium tuberculosis*, remains the leading infectious cause of death globally. In 1997, a World Health Organization (WHO) panel estimated that the global prevalence of TB infection was 1.86 billion people. After an unprecedented increase in reported cases in the United States that began in 1986, the disease has been brought under control (1,2,3,4 and 5). Although pulmonary disease is its most common clinical presentation, its infectious manifestations are protean. Approximately 15% of patients have an extrapulmonary form of disease, with involvement of the pleural spaces, bone, pericardium, meninges, genitourinary tract, lymph system, or peritoneum. Hematogenous spread may result in miliary TB, so named because of its characteristic millet-seed appearance on chest radiographs (CXRs). Patients with HIV infection have an extremely high rate of both pulmonary and extrapulmonary disease (4). Furthermore, extrapulmonary involvement tends to increase in frequency with worsening immune compromise.

Endogenous reactivation of latent tuberculosis infection (LTBI) as opposed to new primary infection (exogenous reinfection) accounts for the majority of cases of active disease in the United States (4,5 and 6). Individuals with advanced HIV infection are the exception to this because they have unusually high rates of primary infection. Chronic medical conditions, outlined in Table 10.4-1, as well as corticosteroid use and immunocompromised states are important predisposing factors for reactivation. Associated with poverty, TB is more likely to occur among the elderly, low-income blacks and Hispanics, immigrants from high-incidence countries, and those who reside in communities where TB is common.

Clinical condition	Relative risk (%)
Silicosis	30
Diabetes mellitus	2.0–4.1
Chronic renal failure/hemodialysis	10.0–25.3
Gastrectomy	2–5
Jejunoileal bypass	27–63
Solid-organ transplantation	20–74
Carcinoma of head or neck	16

Table 10.4-1. Relative risk for developing active tuberculosis by selected clinical conditions

I. Clinical findings of disease

A. Symptoms and signs.

Although some patients may be asymptomatic, most present with chronic nonspecific symptoms, such as cough, fever, night sweats, weight loss, lassitude, and hemoptysis. Extrapulmonary disease may present as a fever of unknown origin. On examination, patients often appear chronically ill with weight loss. Apical rales may be present.

B. Diagnostic studies.

Diagnosis depends on chest film findings and identification of the acid-fast bacillus (AFB) from the sputum.

1. **Radiographic findings.** Classically, the CXR reveals fibrocavitary lesions of the upper lobes (apical and posterior segments); however, a varied picture may be present, with infiltration, miliary nodules, or an effusion; or it may be normal, especially with disseminated disease. HIV-infected patients tend to have atypical CXRs. Cavitary and upper lobe lesions are rare. A significant number of patients have normal chest films as immune-suppressed individuals lack the cellular immune response that causes cavitation (4).

2. **Bacteriologic evaluation.** Sputum smears for APB with the Ziehl- Neelsen stain are available immediately but are limited by a sensitivity of 55% and a specificity of 99%. Cultures, which typically take 6–8 weeks, have a sensitivity of 81% and a specificity of 98%; this is lower with noncavitary disease. An enhanced broth-based culture detection technique (BACTEC) can provide culture results in 2 weeks; this period can be reduced further with nucleic acid probes. *M. tuberculosis* can also be cultured from the blood; bacteremia has been reported in 14% of patients with TB.
3. **Additional diagnostic tools.** Bronchoscopy with transbronchial biopsy can provide immediate diagnosis in smear-negative cases, but because of its risks and expense it should be reserved for selected cases (e.g., HIV-infected patients), primarily to exclude other diagnoses. Serodiagnostic techniques using enzyme-linked immunosorbent assay (ELISA) methods do not currently offer any clinical utility. New nucleic acid amplification tests (NAA) can enhance diagnostic certainty, but they do not replace clinical judgment (7).
4. **Tuberculin skin testing.** The Mantoux test, which involves the injection of 0.1 mL of intermediate-strength purified protein derivative (PPD) intradermally, is used in the diagnosis of TB. It cannot distinguish between past infections and current disease. The test is interpreted at 48–72 hours by measuring the degree of maximum *induration*, not *erythema*. A negative test result does not exclude the disease. Although anergy testing may provide prognostic information for immunocompromised individuals, it is no longer recommended for use in identifying tuberculosis infection, even in those who are HIV infected (4,5). *As there is no reliable method to distinguish a reaction caused by prior immunization with bacillus Calmette-Guerin (BCG) from those caused by natural infection, a positive reaction should be assumed to be secondary to exposure as opposed to the BCG, especially in those who are at increased risk* (4,5). Three cutoff levels for determining a positive tuberculin skin test reaction are based on sensitivity, specificity, and prevalence of tuberculosis in different groups:
   a. A ≤*5-mm* induration for HIV-positive individuals, recent contacts with persons with active TB, individuals whose CXR findings are consistent with old healed TB (fibrotic changes), and patients with organ transplants and other immunosuppressed patients receiving more than 15 mg/d of prednisone for more than 1 month.
   b. A ≤*10-mm* induration for recent immigrants (within the last 5 years) from high-prevalence countries; low-income minority populations; residents and employees of correctional facilities, nursing homes, and shelters; health care workers; injection drug users, individuals with chronic medical conditions (Table 10.4-1); and children younger than 4 years or infants, children, and adolescents exposed to adults in high-risk categories.
   c. A ≤*15-mm* induration for persons with no risk factors for TB.

II. Treatment of active tuberculosis.

Outpatient management of individuals suspected of having TB should be considered. Hospitalization is recommended if the patient is incapable of self-care or poses an infectious risk to others. Hospitalized patients suspected of having TB should be placed in respiratory isolation until smear results become available or they have completed 2 weeks of treatment with clinical response. Public health officials must be notified to trace contacts and to ensure compliance and follow-up.

A. Chemotherapy.

It is now recommended that all patients be treated with four drugs for 2 months daily. The drugs include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (ETH) or streptomycin. Adults should receive 50 mg of pyridoxine daily when treated with regimens containing INH to reduce neurotoxicity. Regimens must include at least two drugs to which the mycobacterium is susceptible to avoid resistance. Furthermore, the drugs must be taken regularly and for a sufficient period of time to be effective. Because compliance over long periods of time with several drugs is difficult, directly observed therapy (DOT) should be considered. The following are current national recommendations (8,9).

1. **Confirmed or suspected active tuberculosis cases.** These should be treated with a four-drug regimen until the results of mycobacterial cultures and sensitivities have been obtained. Administer daily INH-children, 10mg/kg; adults, 300 mg; RIF—children, 10–20 mg/kg per day; adults, 10 mg/kg per day to a maximum dose of 600 mg/d; PZA—children 20–30 mg/kg per day; adults, 25 mg/kg per day to a maximum of 2 g/d; ETH—children and adults, 15–25 mg/kg per day. Streptomycin should be substituted for ETH in very young children. If there is no resistance to INH and RIF, both PZA and ETH are discontinued after 2 months if repeat sputum cultures are negative and there is improvement in the patient's clinical condition. INH and RIF are continued for an additional 4 months for a total treatment course of 6 months. If the patient remains symptomatic, or if a follow-up smear or culture result remains positive after 3 months of therapy, consultation is indicated.
2. **HIV-infected patients.** Three possible regimens that include RIF-based treatments have been recommended by the U.S. Centers for Disease Control and Prevention. However, RIF is contraindicated when the patient is receiving protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). In its place are 6-month rifabutin-based treatments and 9-month streptomycin-based regimens, which may be used on such patients. The use of streptomycin is contraindicated in pregnant women. (Consult the local health department for recommendations.)
3. **Multidrug-resistant tuberculosis.** This is defined as disease that is resistant to both INH and RIF. Patients should be treated with a regimen that includes three or four drugs to which the tuberculosis isolate is susceptible.
4. **Extrapulmonary disease.** Treatment is the same as in Section II.A.1 but is continued for 9 months. Due to a paucity of data, the recommendation is that miliary TB, bone or joint TB, and TB meningitis in children and infants require 12 months of therapy.
5. **Pregnancy and lactation.** Use INH, RIF, and ETH for 9 months with pyridoxine, 25 mg/d. Streptomycin should be avoided because of ototoxicity to the fetus; PZA is not recommended because its teratogenicity is unknown. Lactating women who are taking antituberculous medication should breast-feed before ingesting their medication. Bottle supplementation should be used for the first feeding after dosing (9). For infants whose mothers were treated for active TB during pregnancy and who are themselves on INH for treatment of LTBI, bottle-feeding is recommended.

B. Monitoring for adverse reactions.

Liver enzymes, bilirubin, creatinine, and a CBC/platelet count should be obtained as baseline information before implementing the standard regimens. If PZA is to be used, uric acid should be obtained. If ETH is included in the regimen, obtain baseline and monthly visual acuity as well as red-green perception to detect drug-induced optic

neuritis. Patients should be seen monthly and monitored clinically for adverse effects. For individuals with abnormal baseline studies, follow-up studies are indicated. In those with normal baseline studies, follow-up laboratory testing should be done only if drug toxicity is suspected.

C. Evaluation of response to treatment.

Repeated sputum examinations, beginning with weekly smear quantitation, are desirable until sputum conversion is documented. More than 85% of patients on INH and RIF with positive cultures convert to negative after 2 months. If sputum remains positive after 2 months, drug susceptibility studies should be repeated, and DOT should be implemented. CXRs are less valuable than sputum examinations for evaluation and should not be routinely performed (10).

III. Targeted tuberculin testing and treatment of latent TB infection (LTBI)

A. Change in nomenclature.

Although the terms *preventive therapy* and *chemoprophylaxis* have been used for decades, usually in reference to the use of INH to prevent the development of active TB disease, they are confusing and inaccurate. To describe the intervention with a greater degree of accuracy, the new terminology is *treatment of LTBI* (5).

B. Recommendations for targeted tuberculin testing.

Targeted tuberculin testing is indicated to identify individuals at high risk for TB who would benefit by treatment of LTBI. These groups include individuals at risk for recent infection with *M. tuberculosis* and those who are at risk for progression to active TB. Interpretation of the three cutoff points for determining a positive tuberculin skin test reaction as noted under Section I.B.4 . According to new recommendations of the CDC, tuberculosis testing should only be performed in persons who belong to at least one of the high-risk groups noted below (5), as a decision to test is a decision to treat. Routine screening of other persons, including children not belonging to high-risk groups, is discouraged.

Anergic patients with HIV infection should be treated if they are close contacts, previously had a positive skin test, or are members of a group in which the prevalence of TB is at least 10%.

C. Reducing progression from LTBI to active disease.

Whereas 90% of active cases of TB in non-HIV-infected individuals are secondary to endogenous reactivation, treatment that diminishes or eradicates the bacterial population in “healed” or radiographically invisible lesions is an important means of reducing progression from infection to disease.

Since 1965, INH for 6–12 months has been the mainstay of therapy of individuals with LTBI infection, reducing the rate of reactivation by at least 70%. However, adherence to therapy has been problematic because of the long duration of therapy and concerns about toxicity (10). New “short course” regimens, initially developed for HIV-infected persons, are now among the four approved regimens for the treatment of LTBI. Anergic patients or those with a previous history of a positive PPD and HIV infection should be treated if they are close contacts. Before initiating treatment physicians must ensure that active disease is ruled out. Once active disease is excluded, the decision to treat hinges on an analysis of risks and benefits.

1. For pregnant, HIV-negative women, INH given daily or twice weekly for 6 or 9 months is recommended. For women at risk for progression of LTBI to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active TB is lower, some experts recommend waiting 3 months post partum. (Table 10.4-2)

			Rating[a]	
Drugs	Duration (mo)	Interval	HIV–	HIV+
INH	9	Daily	A	A
		Twice weekly	B	B
INH	6	Daily	B	C
		Twice weekly	B	C
RIF-PZA	2	Daily	B	A
	2–3	Twice weekly	C	C
RIF	4	Daily	B	B

INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.
[a] A, preferred; B, acceptable alternative; C, offer when A and B cannot be given. In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

Table 10.4-2. treatment regimens for latent tuberculosis infection

D. Risk of therapy.

Treatment of LTBI is usually indicated, regardless of age, in patients who belong to high risk groups. The U.S. Centers for Disease Control and Prevention makes no firm recommendations regarding the treatment of patients at lower risk. Use of INH is associated with hepatitis, the incidence of which is age related beginning after age 19 and increases significantly after age 35. Extensive use of alcohol may enhance this association. Fatal INH-associated hepatitis has been reported. The risk is highest among women, particularly black and Hispanic women; it may also be increased

during the postpartum period (5). Baseline studies are indicated in individuals at high risk for hepatotoxicity, such as those with HIV infection, alcoholism, chronic liver disease, pregnancy, or postpartum status (8). Patients should be monitored monthly and liver function tests obtained if clinically indicated. INH should be discontinued if liver enzymes reach three times the upper limit of normal levels in symptomatic patients or five times the upper limit of normal levels in asymptomatic patients (4). Because INH may increase the serum level of phenytoin (Dilantin), a decreased dosage of the latter may be necessary. Women receiving RIF and oral contraceptives should be advised to use a backup method of contraception to avoid pregnancy. Pyridoxine, 25–50 mg/d, is recommended in adults to reduce the risk of peripheral neuropathy.

IV. Nontuberculous mycobacteria.

Nontuberculous mycobacteria are ubiquitous and are responsible for producing cutaneous, pulmonary, lymphatic and disseminated disease.

A. Disseminated Mycobacterium avium complex (MAC) disease

is the most common bacterial infection in patients with AIDS, occurring in 20%–40%. It is rare with CD4 counts greater than 100; it should suspected in HIV-infected persons with CD4 counts below 50. The prognosis of patients with MAC, like other opportunistic infections, has improved significantly due to several factors, including the use of highly active antiretroviral therapy (HAART) regimens. Prophylaxis with a macrolide agent such as clarithromycin or azithromycin is indicated in patients with CD4 counts below 50 (11).

B. Mycobacterium kansasii,

the second most common nontuberculous mycobacteria pulmonary disease, presents with variable and nonspecific signs and symptoms. Diagnosis is based on clinical, radiographic, and bacteriologic criteria as well as measures to exclude other pulmonary disease, including TB. Pulmonary disease caused by *M. kansasii* responds to most TB regimens. Consultation with local health department experts is recommended (see Chapter 19.4).

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10.5
LUNG CANCER

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William T. Leslie

I. Epidemiology and pathology.

Cancer of the lung is the leading cause of cancer mortality in the United States in men and women, resulting in 89,300 and 67,600 estimated annual deaths, respectively, in 2000 (1). The overall 5-year survival rate is 13% for non-small cell lung cancer (2) and 2-year survival is 15%–40% for small cell cancer being managed with chemotherapy. More than 90% of lung cancer patients have a history of cigarette smoking. Lung cancer is divided into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). This categorization is useful in clinical staging, treatment, and prognosis. The incidence is SCLC 18%, squamous cell (epidermoid) 30%, adenocarcinoma 40%, and large cell carcinoma 12% (2).

II. Screening.

Currently no accepted mass screening is available. Patients with risk factors such as tobacco use or chronic obstructive pulmonary disease (COPD), individuals with a family history of lung cancer, roofers, asphalt workers, talc miners, uranium miners, and asbestos workers should be screened periodically. Low-dose computed tomography (LDCT) has been shown to be superior to standard chest radiography for early detection (3).

III. Diagnosis

A. History and clinical presentation.

The most common presenting signs and symptoms of lung cancer are cough, hemoptysis, dyspnea, wheezing, chest pain, dysphagia, hoarseness, and weight loss.

B. Physical examination.

A history (including risk factors) and physical examination is performed, with attention to lymph nodes and weight loss (see Chapter 2.1). Patients with cancer obstructing the bronchial passages often have fever, coarse rales, decreased breath sounds, and dullness to percussion over the obstructed area. Patients presenting with pleural fluid have a 45% chance of malignancy, 50% of which are lung cancer (4).

C. Special studies and recommended staging tests.

The purpose of staging NSCLC is to identify patients with surgically resectable disease. SCLC is usually surgically unresectable because of early metastasis, and staging is done only to determine if the patient has localized disease. An abnormal finding on chest film is followed by CT scanning that includes the liver and adrenal glands. Positron emission tomography (PET) scanning is reported to be more accurate than CT scanning and bone scanning in exposing occult metastatic disease (2). Patients with bone pain or elevated serum alkaline phosphatase should have a bone scan, and those with neurologic signs or

symptoms, including mental status changes, should have magnetic resonance imaging (MRI) of the brain. Patients with SCLC should have bone and brain scanning even in the absence of signs and symptoms because of the likelihood of early metastases to these areas. Fiberoptic bronchoscopy for central lesions and transthoracic needle aspiration for peripheral lesions can be used to make a histologic diagnosis. Presurgical mediastinoscopy is done to biopsy enlarged mediastinal nodes. Thoracentesis with cytology should be performed for pleural effusion. Positive results in the latter two tests may prevent unnecessary surgery.

IV. Complications of lung cancer

A. Complications due to tumor extension or metastasis.

Patients with the following complications are not candidates for surgical resection: superior vena cava syndrome; malignant pleural effusion; contralateral lung metastases; supraclavicular lymph node involvement; contralateral hilar or mediastinal lymph node involvement; tumors closer than 2 cm to the carina; distant metastases; a low pulmonary reserve that precludes lung resection; comorbid disease with unacceptable surgical risk; involvement of the pericardium, heart, esophagus, or great vessels; and SCLC unless discovered as an isolated pulmonary nodule. Patients who are candidates for lung surgery should have pulmonary function tests, including arterial blood gases. Those with borderline pulmonary function should have quantitative ventilation- perfusion scans to allow estimates of postsurgical function.

B. Paraneoplastic syndromes associated with NSCLC.

These syndromes result from substances produced by cancer cells. Fortunately, they are uncommon, but they can be life threatening.

1. **Hypercalcemia.** (see also Chapter 17.5). This is caused by diffuse skeletal metastases or ectopic production of a parathormone-related peptide. Hypercalcemia is most commonly associated with squamous cell carcinomas and least commonly with SCLC. Symptoms are polyuria, dehydration, constipation, and mental confusion. Treatment consists of vigorous saline hydration with furosemide (Lasix) to restore a urinary output of 2 L/d in patients with a normal cardiac status. Thiazide diuretics must be avoided. Pamidronate (Aredia) is given intravenously to rapidly lower the serum calcium.
2. **Hypertrophic pulmonary osteodystrophy.** Signs include clubbing of fingers, joint and bone pain, and alkaline phosphatase elevation. This condition responds to nonsteroidal anti-inflammatory drugs (NSAIDs) and surgical excision of the tumor.
3. **Deep venous thrombosis.** (see also Chapter 9.7). This is treated with intravenous heparin or subcutaneous low molecular weight heparin (Lovenox) 1 mg/kg q12h.
4. **Epidural spinal cord compression.** Pain is the most prominent symptom, followed by weakness and sensory loss. Treatment is initiated immediately with dexamethasone (4–6 mg IV q6h) to decrease edema. This treatment is usually followed by radiation or surgical decompression, depending on the cell type and clinical circumstances.

C. Paraneoplastic syndromes associated with SCLC

1. **Syndrome of inappropriate excretion of antidiuretic hormone (SIADH).** SIADH responds to antitumor treatment and fluid restriction. Demeclocycline (Declomycin) 150–300 mg qid is useful in refractory situations.
2. **Hypercortisolism.** Hypertension, hypokalemia, glucose intolerance, and proximal muscle weakness can be seen. Aminoglutethimide (Cytadren) or mitotane (Lysodren) can be used.
3. **Central nervous system and neuromuscular disorders.** A myasthenia-like syndrome (Eaton-Lambert syndrome), limbic encephalopathy, and sensorimotor neuropathy may occur.

V. Treatment

A. NSCLC.

Surgery is the treatment for NSCLC. Stage I disease (i.e., a tumor smaller than 3 cm and no regional lymph node involvement) has a 55%–70%

5-year survival. Stage II disease (i.e., tumor larger than 3 cm with localized atelectasis, and ipsilateral peribronchial or hilar node involvement) carries a 40% survival at 5 years. Stage IIIa disease (i.e., extension to chest wall, diaphragm, and pericardium; atelectasis; and ipsilateral mediastinal nodes) has a poor surgical survival. Stage IIIb (i.e., malignant pleural effusion, involvement of great vessels or heart, and contralateral hilar or supraclavicular node involvement) and stage IV disease (distant metastases) are inoperable. Combinations of surgery, radiation, and chemotherapy may be used to treat stage IIIa and IIIb cancers. Preoperative irradiation with or without chemotherapy may reduce a tumor's stage and make it operable.

B. SCLC.

Isolated nodules of SCLC (T1N0) have been treated successfully by surgical resection and chemotherapy. About 40% of patients present with unresectable stage III disease and 55% with extensive stage IV disease. Chemotherapy followed by mediastinal and prophylactic brain irradiation is the most effective treatment. Drug regimens containing cisplatin are currently used. Two-year disease-free survival in extensive disease is uncommon. Gene therapy for lung cancer is currently under intensive investigation (5).

VI. Follow-up.

Successfully treated patients may be followed by the schedule below:

A. Chest radiography

every 3 months for the first year, every 6 months for the second year, and then annually.

B. CT

of the chest every 6 months for the first year, then at 24 months.

C. History and physical examination

is done every 6 months for 2 years, then annually. Patients with SCLC should have a liver profile every 3 months for 3 years in addition to the above.

VII. Palliation.

Management of symptoms in incurable lung cancer is a vital role of the family physician. Respiratory symptoms, such as dyspnea and cough, may be treated with oxygen, cough suppressants, mucolytic agents, and aerosols. Nebulized opioids (morphine sulfate 5–50 mg) have been used in severe cases of dyspnea, exerting their effect by direct action on opioid receptors in the large airways (6). Painful metastases are treated with scheduled doses of long-acting morphine every 12 hours (MS Contin, Oramorph SR) and with short-acting morphine prn every 3–4 hours (MSIR, Roxanol). These doses must be increased as tolerance occurs. NSAIDs are useful for bony metastases. Transdermal fentanyl patches (Duragesic) are available for patients who are unable to tolerate morphine or oral medication. Oral transmucosal fentanyl (Actiq) is also available for break-through analgesia (q4–5h) in the form of a lollipop and, like Roxanol, can be absorbed directly through the oral mucosa. Most terminal patients have access to a hospice program that supplies medication, equipment, and nursing visits. Medicare and most private insurance cover these services.

VIII. Prevention.

Primary prevention consists of avoidance of carcinogens and is the most effective way to reduce mortality. Avoidance of tobacco would eliminate the vast majority of lung cancers. Family physicians should persist in efforts to dissuade their patients from smoking. Because of the long latency period associated with carcinogen exposure, the family physician needs to obtain careful work, family, and smoking histories. *Secondary prevention* entails early diagnosis at a curable stage. LDCT screening for high-risk patients may become the most effective way to achieve this.

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XI. GASTROINTESTINAL PROBLEMS

11.1
PEPTIC ULCER DISEASE AND GASTRITIS

Alan M. Adelman

Peptic Ulcer Disease

Peptic ulcers may involve any portion of the upper gastrointestinal (GI) tract, but most ulcers are found in the stomach and duodenum. Duodenal ulcers are approximately three times as common as gastric ulcers. *Helicobacter pylori* (HP) is the major cause of peptic ulcer disease (PUD). A rare cause of PUD is Zollinger-Ellison syndrome.

I. Diagnosis

A. Clinical presentation.

Although PUD may occur or recur in the absence of pain, epigastric discomfort is the most common presenting symptom. Associated symptoms may include fullness, belching, bloating, heartburn, food intolerance, nausea, or vomiting. Severity and description of the pain is variable and correlates poorly with size or number of ulcers. The clinical presentation of PUD overlaps with that of other causes of epigastric discomfort (gastroesophageal reflux disease, nonulcer dyspepsia, gastric cancer, and cholelithiasis).

B. General approach to the assessment of PUD

(1,2). First, patients with complications of PUD (bleeding, gastric outlet obstruction, perforation), patients with signs of systemic disease (anemia, significant weight loss), or patients with persistent or recurrent pain should be evaluated by upper endoscopy and managed immediately (see Chapter 11.3). Patients ≤ 45 years of age should also be considered for prompt endoscopy and management. Second, medications that can cause epigastric discomfort should be discontinued. In particular, patients should be questioned about the use of non-steroidal anti-inflammatory drugs (NSAIDs), both prescription and over-the-counter. All other patients should be tested for HP and, if positive, should be treated with HP-eradicating agents.

II. Assessment of PUD

A. Physical examination

usually reveals only epigastric tenderness. Findings such as a succussion splash (gastric outlet obstruction), abdominal rigidity (perforation), or heme-positive stools (bleeding) are suggestive of complications of PUD.

B. Laboratory studies

(3)

1. Testing for *H. pylori*. There are several ways to test for HP. Serologic testing offers the easiest way of testing for HP and avoids the need for an endoscopy. Finger-stick testing, quantitative serologic testing, and enzyme-linked immunosorbent assay (ELISA) testing are available. A stool sample can be tested with an immunoassay. A urea breath test can also be used to determine the presence of HP. If an ulcer is diagnosed endoscopically, a rapid urease test (Campylobacter-like Organism [CLO]; Delta West, Bentley, West Australia) is the quickest means to determine HP. To test for cure, a urea breath test (4 weeks after therapy), a falling ELISA titer (1, 3, and 6 months after therapy), or CLO at repeat endoscopy can be used.
   a. Quick serologic or finger-stick testing is a qualitative procedure for office use. Average sensitivity is 67%–94% and specificity is 74%–91%. Qualitative serologic testing cannot document eradication of HP.
   b. ELISA is a quantitative assay. Average sensitivity is 86%–94% and specificity is 78%–95%. Although a rapid decrease in the titer indicates cure, the titer may fall slowly over 12–18 months even in successfully treated patients.
   c. Stool testing has a sensitivity greater than 95% and a specificity greater than 90%.

d. Urea breath testing requires a breath sample. Average sensitivity is 90%–96% and specificity is 88%–98%. This test will probably become the test of cure when it is widely available.
e. Rapid urease testing requires a mucosal biopsy. Average sensitivity is 88%–95% and specificity is 95%–100%.
f. Histologic testing requires a biopsy specimen and special stains. Average sensitivity is 93%–96% and specificity is 98%–99%.
g. Culture requires a mucosal biopsy. Average sensitivity is 80%–98% and specificity is 100%. Culture and drug sensitivities are important when drug resistance is suspected.

2. Upper endoscopy should be performed as the initial study in patients with complications of PUD, patients with signs of systemic disease, patients 45 years of age or older, and patients who have failed empirical therapy. The main advantage of endoscopy is its capacity to obtain biopsy specimens for pathology and testing for HP.
3. Double-contrast upper GI studies can reliably diagnose both duodenal and gastric ulcers, but the false-negative rate can exceed 18%, whereas the false-positive rate is 13%–35%.

III. Therapy.

The therapy is determined by the presence or absence of HP. Antibiotic treatment is given to patients who are positive for HP. The addition of an histamine receptor antagonist (HRA) or proton pump inhibitor (PPI) hastens relief of pain. PPIs such as omeprazole (Prilosec) also have anti-HP action and are included in some anti-HP regimens. Patients with HP-negative ulcers are treated with traditional anti-acid agents alone. The value of treating nonulcer dyspepsia patients with *H. pylori* infection remains to be determined.

A. Regimens for *H. pylori*

(3). Several regimens have been shown to be effective. All regimens are given for 14 days.

1. Bismuth subsalicylate (Pepto-Bismol) 2 tablets qid, metronidazole (Flagyl) 250 mg qid, tetracycline (Achromycin or others) 500 mg qid, and HRA (ranitidine 150 mg bid or others). HRA is required for an additional 2 weeks. Ranitidine and bismuth are available as Tritec. Bismuth, metronidazole, and tetracycline are available as Helidac.
2. PPI (lansoprazole 30 mg qd), amoxicillin 1000 mg bid, and clarithromycin (Biaxin) 500 mg bid (available as Prevpac)
3. PPI (omeprazole 20 mg bid or lansoprazole 30 mg qd), metronidazole 500 mg bid, clarithromycin (Biaxin) 500 mg bid
4. HRA, bismuth 2 tablets qid, clarithromycin (Biaxin) 500 mg bid, and amoxicillin 1,000 mg bid or metronidazole 500 mg bid or tetracycline 500 mg bid
5. Bismuth 2 tabs qid, metronidazole 500 mg tid, tetracycline 500 mg qid, PPI (omeprazole 20 mg bid or lansoprazole 30 mg qd)

B. Traditional agents

1. H_2RA. Cimetidine (Tagamet) 400 mg bid, famotidine (Pepcid) 20 mg bid, nizatidine (Axid) 150 mg bid, and ranitidine (Zantac) 150 mg bid are equally effective. Cimetidine appears to be associated with the highest incidence of side effects and drug interactions.
2. Proton pump inhibitors. Omeprazole (Prilosec) 20 mg daily, lansoprazole (Prevacid) 15 mg daily, rabeprazole (Aciphex) 20 mg qd, and pantoprazole (Protonix) 40 mg qd are more potent acid inhibitors than HRA.
3. Sucralfate (Carafate), 1 g qid, is effective in healing peptic ulcers. There are no significant side effects, but the size of the tablet and frequency of administration are potential drawbacks.
4. Antacids. Antacids are effective in healing ulcers, but their use is limited by the number of doses required. Aluminum hydroxide/magnesium hydroxide/simethicone antacids (Maalox extra strength, Mylanta double strength), 2 tablets qid, is unlikely to produce constipation or diarrhea. Phosphate depletion can occur with antacid use in malnourished patients, and hypermagnesemia can result in patients with chronic renal failure.

5. Dietary therapy is limited to the elimination of foods that exacerbate symptoms, and the avoidance of alcohol and coffee (with or without caffeine). Both alcohol and coffee increase gastric acid secretion.
6. Cessation of cigarette smoking speeds ulcer healing. In HP-negative ulcers, smoking cessation decreases the risk of recurrence.
7. Combination therapy. There is no evidence that combination therapy of traditional agents (e.g., sucralfate and an HRA) hastens healing.

IV. Refractory or recurrent ulcers.

Eradication of HP reduces the rate of recurrence of peptic ulcers in individuals with HP-positive ulcers. In patients with a refractory or recurrent ulcer and documented HP, several issues should be considered. The use of NSAIDs should be discontinued. Compliance with medication should be reviewed. Resistant HP has been reported, necessitating retreatment with a different antibiotic regimen. In patients with a gastric ulcer, cancer should be considered. Zollinger-Ellison syndrome should be considered in patients with severe or multiple ulcers, large gastric mucosal folds, or unexplained diarrhea and steatorrhea.

V. Maintenance therapy.

Smokers, patients with recurrent non-HP ulcers, the elderly, and patients with a history of a bleeding ulcer should receive maintenance therapy with an HRA at half the usual dose at bedtime (e.g., ranitidine 150 mg hs).

Gastritis/Gastropathy

Gastritis/gastropathy is a collection of disorders characterized by damage to the gastric mucosa. Gastritis represents the presence of inflammation, whereas in gastropathy inflammation is absent. These disorders can be either acute (associated with acute injury secondary to NSAID use, stress, alcohol, bile acids) or chronic (autoimmune, *H. pylori*). Since gastropathy associated with NSAID use is the most common form encountered by physicians, this section will deal specifically with NSAID-related gastropathy.

I. Presentation.

Pain is much less common than in PUD. Usually patients are asymptomatic unless blood loss is appreciable. Life-threatening GI bleeding may be the initial presentation. Anorexia, nausea, or vomiting may be present, although dyspeptic symptoms do not correlate well with endoscopic findings.

II. Risk factors

for development of NSAID gastropathy include age older than 60 years, previous history of ulcers with or without complications, concomitant use of corticosteroids, high doses of NSAIDs, and extended use of NSAIDs. Other potential factors may include alcohol consumption and smoking. Concurrent use of anticoagulants increases the risk of GI complications.

III. Physical examination.

Physical findings are usually absent unless the patient presents with bleeding.

IV. Laboratory studies.

Anemia is usually the initial finding, prompting further radiologic or endoscopic evaluation.

V. Therapy(4)

A.

Discontinue use of NSAID, if possible, or consider use of a COX-2 inhibitor, such as rofecoxib (Vioxx) or celecoxib (Celebrex). If the NSAID cannot be switched or discontinued, reduce the dosage to the lowest effective amount. Reduce or discontinue other risk factors.

B.

Medication. HRA and PPI have been shown to be effective in healing gastric ulcers secondary to NSAID use. PPI is the drug of choice if the NSAID cannot be discontinued.

C.

If the patient has PUD and found to be positive for HP, then treatment for HP is recommended.

VI. Prevention.

Consider use of COX-2 inhibitor if patient has risk factors for NSAID-related gastropathy. If switch cannot be made, discontinue or reduce the dose of NSAID. Misoprostol is used in patients who have a history of ulcers, especially with bleeding as a complication. A PPI may be used as an alternative for individuals who cannot tolerate misoprostol.

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11.2
GASTROESOPHAGEAL REFLUX DISEASE

John P. Muench

Alexandra Verdieck

I. Introduction

A. Gastroesophageal reflux disease (GERD)

denotes the symptoms or pathologic changes in the esophageal mucosa that result from reflux of stomach contents. GERD is a very common, often chronic and relapsing condition. As many as 10% of U.S. adults have heartburn symptoms every day, and up to 44% have intermittent symptoms. Despite the fact that more than half of these patients have mild symptoms that can be self-managed with over-the-counter (OTC) antacids, GERD often adversely affects quality of life and can lead to serious complications (1).

B. Esophagitis.

Reflux esophagitis describes the subset of GERD associated with mucosal damage. Esophageal squamous epithelium is intolerant of chronic exposure to gastric acid (the duration of exposure generally predicts severity of damage). Epidemiologic data show a 3%–4% prevalence of esophagitis in the general population, but 65%–97% of patients with esophagitis have a mild or moderate form (2).

C. Esophageal complications.

Mild esophagitis can progress to erosions and ulcerations, which can in turn progress to esophageal complications such as strictures and metaplasia known as Barrett's esophagus. Barrett's is considered a premalignant condition. Patients with Barrett's have a 1% risk per year of developing esophageal adenocarcinoma (3). Severity of symptoms does not necessarily correlate with the severity of esophageal damage or presence of complications.

D. Extraesophageal complications.

Reflux can also contribute to extraesophageal complications due to regurgitation and aspiration. These include asthma, laryngitis, chronic cough, recurrent pneumonitis, nocturnal choking, chronic hoarseness, pharyngitis, subglottic stenosis, and dental disease (2).

II. Etiology

A. Anatomy/physiology.

Several factors contribute to the reflux of gastric contents into the esophagus. Normally, the lower esophageal sphincter (LES) and diaphragm form a physical barrier, and gastric contents that reflux are then quickly cleared by peristalsis. Thus, abnormal transient LES relaxation, esophageal dysmotility, delayed gastric emptying, and large hiatal hernia all may play a role in the pathophysiology of GERD.

B. Lifestyle and dietary factors

can also contribute as direct irritants or by affecting the LES. These include use of tobacco, alcohol, caffeine, chocolate,

citrus fruits, peppermint, tomato-based products, and possibly onions and garlic (1,4).

C. Some medications

can also exacerbate GERD. These include non-steroidal anti-inflammatory drugs (NSAIDs), theophylline, calcium channel blockers, nitrates, anticholinergics, potassium chloride, alendronate, iron, and tetracycline.

D. The role of H. pylori in the pathogenesis of GERD remains to be clarified

but some studies indicate that it may actually be protective (3).

III. Clinical presentation. Typical symptoms

of GERD are a retrosternal “heartburn” and/or regurgitation after a meal or alcohol use. The pain can be very severe and radiate to the jaw or arm. Symptoms are worsened by lying down or bending over and are relieved with antacids. **Atypical symptoms,** which might signal complications, include atypical chest pain, nausea, chronic cough, and hoarseness. **Alarm symptoms** that may represent severe GERD complications include dysphagia, odynophagia, weight loss, anemia, and gastrointestinal (GI) bleeding (see also Chapter 11.3).

IV. Diagnosis

(4)

A. Empirical diagnosis.

If a patient's history is typical for uncomplicated GERD, an initial trial of empirical therapy (including lifestyle modification) should be begun. If empirical therapy does not relieve symptoms, or if the patient experiences atypical or alarm symptoms, further diagnostic testing should be done.

B. Endoscopy.

This is the technique of choice for evaluating esophageal mucosa for esophagitis or complications in patients with refractory or atypical symptoms. Because the presence of Barrett's esophagus seems to be a function of the duration of reflux, some experts argue that older patients or patients with longstanding reflux symptoms should be considered for endoscopy regardless of treatment success. The diagnosis of Barrett's esophagus requires biopsy-proven metaplasia.

C. Other diagnostic modalities.

Barium swallow is not as sensitive or specific as endoscopy for evaluating GERD, but it can be used to detect large ulcers, strictures, motility disorders, and hiatal hernia if endoscopy is not available. Ambulatory pH testing can be helpful for confirming the reflux of GERD in patients who have refractory symptoms but normal endoscopy. Esophageal manometry is helpful in documenting effective peristalsis, especially in assessing patients in whom antireflux surgery is being considered.

V. Treatment options.

The purpose of treatment is to minimize the exposure of the esophagus to refluxate, thus alleviating symptoms and healing damaged tissue.

A. Lifestyle modifications

will improve symptoms in approximately 20% of patients who comply. These include:

- Elevating head of bed 6 inches
- Avoiding use of alcohol, tobacco, and caffeine
- Losing weight
- Avoiding the recumbent position for 3 hours after meals
- Avoiding large fatty meals
- Avoiding patient-specific symptom-provoking foods

B. Antacids.

Numerous OTC antacids are available. These include calcium carbonate (Tums), aluminum hydroxide (Gaviscon or Maalox), magnesium hydroxide (Mylanta), and many others. They are effective if used in appropriate doses after meals or with onset of heartburn.

C. Histamine 2 receptor antagonists (H_2RAs).

These are effective for treatment of mild to moderate GERD. More severe symptoms or esophagitis require the higher range of dosing. Generic cimetidine and ranitidine are the most cost effective medications.

- Cimetidine (Tagamet) 400 or 800 mg twice daily
- Famotidine (Pepcid) 20 or 40 mg twice daily
- Nizatidine (Axid) 150 or 300 mg twice daily
- Ranitidine (Zantac) 150 or 300 mg twice daily

All four of the H_2RAs are now available OTC at a dose that is usually half the lower prescription dose. While they do not act as quickly as antacids,

they provide longer symptom relief and are effective for prevention of GERD symptoms.

D. Proton pump inhibitors (PPIs).

These relieve symptoms and heal esophagitis in the highest percentage of patients. More than a decade of experience with these medicines has alleviated many of the concerns over their long-term side effects.

- Lansoprazole (Prevacid) 15 or 30 mg daily
- Omeprazole (Prilosec) 10 or 20 mg daily
- Rabeprazole (Aciphex) 20 mg daily
- Pantoprazole (Protonix) 40 mg daily

E. Promotility agents

are somewhat effective although limited by side effects. Cisapride (Propulsid) was removed from the market in 1999 because of its association with cardiac arrhythmias. Metoclopramide (Reglan 10–15 mg up to 4 times daily) remains on the market, but its use is limited because it may cause drowsiness, parkinsonism, and tardive dyskinesia.

F. Surgery.

Antireflux surgery, in which the gastric fundus is wrapped around the esophagus (fundoplication), helps prevent reflux by increasing LES tone. Laparoscopic approaches appear to be equal or be superior to open surgery. At the end of one 3-year trial, surgery was slightly superior to omeprazole 20 mg daily, but higher doses of the PPI were as effective as surgery (4). Fundoplication can be especially helpful in relatively young, healthy patients with severe GERD who have not been responsive to medications. While initially expensive, surgical costs can be less than that of chronic medication over the course of several years.

VI. Treatment strategies

A. Initial management

of GERD is directed by severity of symptoms, duration of symptoms, and presence of atypical symptoms. An approach of starting with conservative treatment (lifestyle changes and antacids or OTC H_2RAs) and then stepping up to higher doses or stronger medications is favored by most. Treatment should be continued for 8 weeks and then reassessed. Patients with longstanding severe GERD or complications will most likely require PPIs. If the patient remains symptomatic on high-dose PPIs, then the diagnosis should be reconsidered (1).

B. Maintenance.

Relapse rates are high with all forms of medical therapy. Many of these patients will benefit from a maintenance dose of a H_2RA or PPI at the lowest effective dose to maintain remission of symptoms or complications. Some may require lifelong therapy. The presence of Barrett's esophagus or strictures necessitates lifelong treatment with a PPI to prevent progression, although no treatment has yet been shown to cause remission in Barrett's esophagus patients.

VII. Referral.

Patients who have not responded to treatment in 12 weeks or those with atypical symptoms should be referred for endoscopy or other workup. Additionally, patients with longstanding GERD symptoms, especially those who are 50 years or older, should have at least a single endoscopy to screen for metaplasia. Patients with known Barrett's should undergo surveillance endoscopy every 2–3 years, and more frequently for higher grades of dysplasia (5).

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11.3

UPPER GASTROINTESTINAL BLEEDING

Mel P. Daly

Upper gastrointestinal (UGI) bleeding is a common clinical problem, causing 10,000–20,000 deaths each year in the United States. Most episodes (80%) are self-limited and require only supportive therapy, but if bleeding is continuous or recurrent, the mortality is 30%–40%. Surgery may be required in 15%–30% of patients.

I. Etiology of UGI bleeding

(table 11.3-1). Peptic ulcers, gastritis, esophageal varices, and gastroesophageal mucosal tears account for 90% of cases (see Chapter 11.1). Other causes include gastric tumors, esophagitis, hematobilia, hiatal hernia, aortointestinal fistula, vascular malformations, and Dieulafoy's lesion (submucosal arterial malformation) (1).

Common
Gastritis (erosive due to NSAIDs)
Peptic ulcer disease
Gastroesophageal mucosal tears
Cancer (carcinoma, lymphoma, polyps)
Rare
Infections (CMV, herpes, *Candida*)
GERD
Aortoenteric fistula
Blood dyscrasia
Vasculitis
Hemorrhagic telangiectasia
Pancreatic cancer
Uremia

CMV, cytomegalovirus; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug.

Table 11.3-1. Causes of upper gastrointestinal bleeding

A. Peptic ulcer disease (PUD)

is the most common cause of UGI bleeding. Duodenal or gastric ulcers caused by *Helicobacter pylori* are common causes of UGI bleeding. Although pain is the usual presenting symptom, 10% of patients present with UGI bleeding.

B. Gastritis

is associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol, severe systemic disease, major trauma, burns, and ventilator use. These conditions also increase the risk of bleeding from underlying PUD.

C. Esophageal varices

occur in patients with cirrhosis who have portal hypertension. Bleeding is more likely in patients with advanced cirrhosis and large varices. Concomitant PUD, gastritis, or Mallory-Weiss tears in alcoholic patients may also cause hemorrhage.

D. Gastroesophageal (GE) mucosal tears (Mallory-Weiss).

Hemorrhage results from mucosal laceration of the GE junction induced by retching or vomiting. Patients are often heavy alcohol users, and 30% use aspirin or NSAIDs. Tears may occur from coughing, severe asthma attacks, seizures, cardiopulmonary resuscitation, and straining at stool.

E. Other causes.

Blood dyscrasias, vasculitis, connective tissue diseases (CTDs), and hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease) may rarely be the cause of UGI bleeding. Hematobilia occurs secondary to trauma, injury, or vascular malformations of the liver or biliary tree. Aortoduodenal fistulas and large ectatic submucosal arteries (Dieulafoy's lesion) or AVMs may cause massive hemorrhage. Gastroesophageal reflux disease (GERD), cancer, and infections such as cytomegalovirus (CMV), herpes, or candida may cause UGI bleeding but more usually cause chronic blood loss. Rarely, large hiatal hernias may cause blood loss as a result of linear mucosal tears. Even more rarely, gastric cancer, lymphoma, polyps, and other tumors of the stomach or small intestine may cause UGI bleeding.

II. Clinical presentation

depends on the location, source, and acuity of the bleed.

A.

Acute UGI bleeding often presents with bloody vomiting. Blood from a recent bleed is usually bright red. Bleeding from varices is usually abrupt and massive. Melena (black, tarry, malodorous stools) usually is the result of UGI bleeding or lesions of the small intestine if GI transit time is prolonged.

B.

Chronic or unrecognized UGI bleeding may present with pallor, dizziness, dyspnea, iron deficiency anemia, or occult blood in stool.

C.

Physiologic responses to UGI bleeding

1. In acute UGI bleeding, the physiologic response depends on the rate and extent of hemorrhage.
   a. Blood loss less than 500 mL is usually asymptomatic, except in elderly patients with coronary artery or chronic lung disease.
   b. Rapid blood loss results in decreased cardiac output reflex, vasoconstriction, and increased peripheral resistance. Orthostatic hypotension indicates a reduction in blood volume of more than 20%.

Light-headedness, confusion, nausea, sweating, fainting, and thirst are commonly associated with blood loss.

c. When blood loss approaches 40% of blood volume, shock occurs, with tachycardia, hypotension, pallor, and cold clammy extremities.

2. Chronic blood loss may be asymptomatic or present with signs and symptoms of anemia, hyponatremia, and hypoalbuminemia as a result of retention of hypotonic fluid to replenish intravascular volume.

III. Diagnosis and treatment

always begins with resuscitation, restoration of intravascular volume, correction of hemoglobin loss, and treatment of pathophysiologic changes.

A. Resuscitation.

Vital signs should be monitored frequently and fluid replaced rapidly. Crystalloids (normal saline or Ringer's solution) or fresh frozen plasma should be used until blood is available. Military antishock trousers may be required to correct shock. For unstable cardiac patients, central venous or pulmonary wedge pressures should be measured, with a goal of keeping blood pressure and pulse stable and maintaining urinary output at more than 40 mL/h. Blood replacement is important in the elderly and those intolerant of hypoxia.

B. Gastric lavage through a nasogastric (NG) tube

localizes bleeding proximal to the ligament of Treitz. NG suction removes gastric fluid, blood, and swallowed air and can control nausea and vomiting. If the aspirate is clear, the tube should be left in place for several hours. If the aspirate is negative for blood during active bleeding, it is unlikely that bleeding is from the UGI tract. Lavage with room-temperature water is as effective as instilling levarterenol for vasoconstriction or using cold solutions. Aliquots of 100–500 mL are infused and removed by gravity drainage to prevent suction trauma to the mucosa. The pace of the diagnostic evaluation depends on the characteristics of the NG aspirate. A “negative,” clear, or bilious aspirate suggests that a more elective approach is indicated.

C. History and examination

identifies the cause in only 50% of cases.

1. **Prior history** of PUD or dyspepsia may suggest ulcer bleeding. A history of medication and alcohol use should be elicited. Symptoms of cirrhosis may suggest variceal bleeding. Bleeding from other sources (e.g., frequent nosebleeds, bruising) may suggest a coagulopathy.
2. **Examination.** Epigastric tenderness is suggestive of PUD. Hepatosplenomegaly may occur in liver disease or malignancy. A rectal examination may reveal melena, but stool may be normal in patients with minimal or recent bleeding.

3. **Laboratory studies.** If blood loss is rapid, the hematocrit may not reflect the magnitude of loss because equilibration with hemodilution requires 8 hours. The blood urea nitrogen may be elevated due to blood protein breakdown to urea by intestinal bacteria and reduced glomerular filtration rate. Histologic examination or culture of endoscopic specimens can be diagnostic for *H. pylori* infection. Serologic assays of *H. pylori*-specific IgG levels parallel the diagnostic accuracy of invasive tests. Urea-labeled breath tests may be equally accurate.

D. Esophagogastroduodenoscopy (EGD)

has replaced barium studies for diagnosing UGI bleeding because of its greater accuracy and the potential for therapeutic interventions (2).

1. In stable patients, EGD is usually indicated to locate the bleeding source but is not required if the diagnosis and therapy are clear from the clinical and laboratory data. In uncomplicated patients, empirical trials of treatment may be instituted.
2. Persistent UGI hemorrhage is an indication for immediate EGD. If bleeding is heavy, the source may not be identified. Patients with cirrhosis should have EGD because more than one source of hemorrhage may exist. Patients with visible vessels or varices are candidates for endoscopic treatment.
3. Angiography. If bleeding continues and EGD fails to reveal the source, angiography may be useful in diagnosing bleeding from varices, vascular ectasias, and aneurysms. Angiography also may be useful in the management of esophageal varices and Mallory-Weiss tears and in the embolization of bleeding ulcers or tumors in patients who are not surgical candidates.

IV. Specific therapeutic interventions

A. Peptic ulcer bleeding

1. Medications. Antacids should be initiated empirically. Intravenous H_2 blocker therapy (famotidine 20 mg IV q12h, ranitidine 50 mg, or a continuous infusion of ranitidine at 6.25 mg/h) is the regimen of choice. Famotidine (20 mg PO q12h) and nizatidine (150 mg PO q12h) are alternatives for stable patients (3). Gastric acid pump inhibitors, such as omeprazole (20 mg/d PO), lansoprazole (30 mg PO q12h), and pantoprazole (40 mg/d PO) are widely used. Cytoprotective agents, such as sucralfate (1 g PO before meals and bedtime) and prostaglandins (misoprostol 200 µg PO q6h), are helpful in treating PUD. Their use in acute bleeding has not been studied. If *H. pylori* infection is diagnosed, treatment with regimens that include bismuth, subsalicylate/omeprazole, clarithromycin/tetracycline, and metronidazole are usually effective (see Chapter 11.1).
2. Laser photocoagulation and electrocautery under direct endoscopic visualization may rapidly control active ulcer bleeding.
3. Infusion of vasopressin (pitressin) directly into the vessel supplying a bleeding lesion may be indicated if endoscopic hemostasis fails (4).
4. Surgery is indicated if hemorrhage is brisk or sustained for longer than 6–12 hours, or if shock is not controlled by resuscitation. Patients with rapidly bleeding or recurring gastric ulcers may be surgical candidates (5).

B. Gastritis and gastric erosions.

Antacids and H_2 receptor blockers reduce the incidence of hemorrhage from stress ulcers. Misoprostol is effective in preventing gastritis due to NSAIDs. Sucralfate and omeprazole are also effective for patients with prior UGI bleeding who require continued NSAIDs (6). Massive bleeding may be controlled by infusion of vasopressin into the left gastric artery. Laser and electrocautery under direct visualization may control persistent bleeding.

C. Variceal bleeding

may be completely controlled by intravenous vasopressin (100 units of vasopressin in 250 mL of 5% dextrose in water, which is 0.4 unit/ mL, to infuse at a rate of 0.3 unit/min for 12 hours, 0.2 unit/min for 24 hours, and 0.1 unit/min for 24 hours). Endoscopic sclerosis and banding often effectively control bleeding. Acute bleeding may be abated by balloon occlusion

with a Sengstaken-Blakemore tube followed by definitive therapy within 48 hours. Recurrent bleeding may be prevented by periodic endoscopic sclerotherapy (7). Propranolol given twice daily (at a dose that reduces the heart rate by 25%) decreases portal pressure, although the response is nonuniform. Surgical shunt procedures to decompress the portal system are associated with a high incidence of encephalopathy. Liver transplantation is the treatment of choice for healthy patients with end-stage disease.

D. Arteriovenous malformations,

when actively bleeding, are best treated with electrocautery. Mallory-Weiss tears usually stop bleeding spontaneously but may require cautery or injection therapy.

E. Stress gastritis.

Prophylaxis using antacids, H_2 receptor blockers, omeprazole, or sucralfate decreases the incidence of bleeding. Acid reduction therapy may allow for bacterial colonization of the respiratory tract and possible pneumonia. Sucralfate does not alter gastric pH and is associated with a lower rate of nosocomial pneumonia.

V. Prognostic indicators.

Bleeding from varices has a high recurrence rate and mortality (50%–70%). Peptic ulcers with visible vessels have a rate of rebleeding of up to 50%. Other prognostic indicators include severity of the initial bleed, age (older patients have a higher mortality), concomitant disease, ulcer diameter greater than 2 cm, and the requirement for emergency surgery (8).

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11.4
CHOLELITHIASIS AND CHOLECYSTITIS

Edward Christopher Vincent

Michael A. J. Purdon

The prevalence of gallstones in adults in Western industrialized nations averages 10%–15%. It is lower (5%) in Asians and Africans and higher (up to 70%) in Native Americans. Women are twice as likely as men to develop gallstones. Incidence increases with age; 25% of persons over age 65 and 50% over age 75 have cholelithiasis. A family history of cholelithiasis and a diet rich in carbohydrates and fats are additional risk factors for gallstone formation (1, 2 and 3).

I. Asymptomatic cholelithiasis

A. Diagnosis.

Typically, asymptomatic gallstones are discovered incidentally during abdominal sonography or laparotomy for nonbiliary tract disease.

B. Management.

Most persons with “silent” stones can be treated expectantly, as only 1%–2% become symptomatic each year (1,4,5). Cholecystectomy should be considered in patients with a calcified (“porcelain”) gallbladder or who undergo laparotomy for an unrelated condition. Diabetes is no longer considered an indication for elective cholecystectomy, but diabetics with symptomatic stones should be treated promptly (6,7 and 8).

II. Symptomatic cholelithiasis

A. Diagnosis.

An estimated one third of persons with gallstones will eventually develop symptoms. Of these, 30% will have acute or complicated cholecystitis (see Section III, Section V, and Section VI), 50% will have recurring pain typical of chronic cholecystitis (see Section IV), and 20% will have a single episode of pain (1,5).

A distinction should be made between gallstone pain (“biliary colic”) and abdominal pain in patients with gallstones. Typical biliary colic is a steady right upper quadrant (RUQ) or epigastric pain that lasts 1–5 hours and may be associated with nausea and vomiting. It commonly occurs at night, usually around the same time. Postprandial pain, dyspepsia, bloating, flatulence, and fatty food intolerance are not specific for gallstone-related pain. Physicians who encounter patients with these symptoms should consider other diagnoses (4,5,9).

B. Management.

Patients with acute, chronic, or complicated cholecystitis due to cholelithiasis should be offered surgical or medical intervention (see below). In uncomplicated cases, the clinician may adopt an attitude of watchful waiting because up to 20% of patients with symptomatic gallstones do not have recurring pain after their initial episode (4,5).

III. Acute cholecystitis

A. Diagnosis

1. **History.** Ninety to ninety-five percent of patients with acute cholecystitis have gallstones. Acalculous cholecystitis is usually associated with major surgery, trauma, severe infection, critical illness, advanced age, or total parenteral nutrition. Patients with acute cholecystitis usually complain of a rapid onset of severe, cramping RUQ abdominal pain, nausea, and vomiting (5,7).
2. **Physical examination** findings may include a low-grade fever, RUQ or epigastric tenderness, guarding, and Murphy's sign (pain on inspiration during palpation of the RUQ). The gallbladder may be palpable in up to 30% of patients (5,7).
3. **Laboratory tests.** A white blood cell (WBC) count of 12,000–15,000 cells/μL and mild increases in the serum transaminases, bilirubin, amylase, and alkaline phosphatase are common. Bilirubin greater than 4 mg/dL is unusual (5,7).
4. **Imaging studies.** Ultrasonography (US) is 95% sensitive and specific for diagnosing gallstones and has largely supplanted oral cholecystography (OCG). Computed tomography (CT) may identify gallstones when US cannot because of overlying fat or bowel gas. Radionuclide cholescintigraphy [hepatoiminodiacetic acid (HIDA) scanning] is the test of choice in patients without gallstones and patients who have an atypical presentation. Nonvisualization of the gallbladder in spite of normal visualization of the liver and bile ducts is 90%–95% sensitive and specific for acute cholecystitis. Abdominal plain films are rarely diagnostic of cholecystitis but are recommended to exclude other conditions (5,7).

B. Management.

Moderately ill patients with suspected cholecystitis are given nothing by mouth and hospitalized for intravenous fluid replacement and diagnostic evaluation. Intravenous antibiotics with activity against gram-negative, gram-positive, and anaerobic bacteria are usually indicated. One regimen is ticarcillin (Ticar), 4.0 g q6h, with metronidazole (Flagyl), 1.0 g loading dose followed by 0.5 g q6h. Mezlocillin (Mezlin) or piperacillin (Pipracil) may be used instead of ticarcillin.

Cholecystectomy should be performed within 24–72 hours in most patients with acute cholecystitis because complications are more likely with delayed surgery. Patients who are unstable or who have peritonitis should undergo immediate surgery (1,4,5,7,8,10,11).

Laparoscopic cholecystectomy is the procedure of choice for uncomplicated acute cholecystitis. Patients with pancreatitis, peritonitis, sepsis, coagulopathy, gallbladder cancer, or cholecystenteric fistula are usually best managed by open cholecystectomy. Male sex, advanced age, and a history of multiple painful attacks are additional factors favoring an open operation. US evidence of a stone more than 20 mm, gallbladder wall thickness more than 4 mm, or common bile duct (CBD) diameter more than 6 mm also increases the likelihood of converting to an open procedure. Cholecystostomy (percutaneous gallbladder drainage and stone removal) remains an option for patients who are poor surgical candidates (4,5,8).

C. Complications.

Mortality from cholecystectomy is only 0.2%. Most deaths occur in elderly or critically ill patients. Injury to the bile ducts is slightly more common with laparoscopic compared to open cholecystectomy (4,8,11).

Gallbladder perforation occurs in 3%–12% of patients with acute cholecystitis. Diabetics, the elderly, and immunocompromised patients or patients with systemic vascular disease are at higher risk for perforation. Elderly or diabetic patients are also more likely to develop emphysematous cholecystitis, a rare but serious condition with 15% mortality. Patients with large (usually greater than 2 cm diameter) stones who have cholecystenteric fistula may develop intestinal obstruction ("gallstone ileus") if the stone passes via fistula into the bowel (5,7).

IV. Chronic cholecystitis

A. Diagnosis

1. **History.** In contrast to acute cholecystitis, patients with chronic cholecystitis have a more indolent course. Fever is uncommon, and abdominal pain ("biliary colic"), nausea, and vomiting are less severe. Episodes are shorter in duration and recurrent.
2. **Physical examination** is frequently unremarkable and serves only to exclude other causes of abdominal pain.
3. **Imaging studies.** As with acute cholecystitis, US is the diagnostic modality of choice. OCG may be helpful in determining which patients are candidates for medical treatment (see Section IV.B.2).

B. Management

1. **Surgical.** As is true for acute cholecystitis, most patients with chronic cholecystitis should be offered laparoscopic cholecystectomy.
2. **Medical.** Medical management may be considered for patients who are poor operative candidates or who decline surgery.
   a. Ursodiol (Actigall, usual dosage 8–10 mg/kg per day divided bid or tid) is an oral bile acid that dissolves gallstones in selected patients. Optimal stones for dissolution are cholesterol rich, radiolucent, and less than 10 mm in diameter; they "float" when viewed by US or OCG. The gallbladder must be functioning as noted on OCG or HIDA scan. Because of these restrictions, only 30% of patients with chronic cholecystitis are candidates for ursodiol treatment. Complete dissolution rates average 30%–50%, depending on the size of stones. Gallstones recur within 5 years in 50% of successfully treated patients. Maintenance therapy with 4–5 mg/kg per day reduces the 5-year recurrence rate to 25%. Ursodiol is well tolerated but expensive (4,5,12).
   b. Contact dissolution employs methyl *tert*-butyl ether (MTBE), a lipid solvent that is infused into the gallbladder via a T-shaped tube, transhepatic catheter, or nasobiliary tube. As with ursodiol, candidates for MTBE must have a functioning gallbladder and radiolucent, floating stones. Most of these stones can be dissolved within 24 hours. Disadvantages include limited availability and experience as well as potentially serious side effects, such as intravascular hemolysis. Stone recurrence rates are similar to those for ursodiol treatment (4,5).

C. Extracorporeal shock wave lithotripsy (ESWL)

is an experimental, noninvasive, outpatient method of gallstone treatment. Experience is limited; in optimal patients, the efficacy is 70%–90%. Disadvantages include restricted applicability and availability, the need for concomitant oral dissolution therapy, a high incidence of biliary colic, and a stone recurrence rate similar to those for other nonsurgical methods (1,4,5).

V. Choledocholithiasis.

In patients with choledolithiasis, 10%–15% of those younger than 60 years and 30%–95% older than 60 years have CBD stones (1). If found, CBD stones should usually be removed due to a high complication rate (1,4,5,13).

A. Diagnosis

1. **History and physical examination** may be unremarkable, but usually patients with CBD stones present with some variation of Charcot's triad (jaundice, RUQ pain, and fever) (5,13).
2. **Laboratory tests.** Similar to that in patients with acute cholecystitis, results of serum liver tests [direct bilirubin, alkaline phosphatase, and γ-glutamyltransferase (GGT)] are usually elevated. However, the degree of elevation is typically greater than that encountered in patients with acute cholecystitis (5,13).
3. **Imaging and other studies.** A dilated CBD on US suggests choledocholithiasis; however, this finding is seen in only 50% of patients. For three decades endoscopic retrograde cholangiopancreatography (ERCP) has been the gold standard for diagnosing CBD stones. Advantages include a high sensitivity and specificity (up to 95%) with comparable success rates for stone removal. Disadvantages include a small but significant risk of complication (usually pancreatitis) and availability (mainly limited by operator skill). Magnetic resonance cholangiography (MRC), helical CT cholangiography (HCTC), and endoscopic US (EUS) are newer additions to the list of noninvasive tests. All are highly sensitive and specific (80%–100%) and are comparably safe. None are therapeutic, however, and may not be as widely available as ERCP (4,5,13,14).

B. Management

depends on operator availability and experience. Preoperative cholangiography or ERCP with endoscopic sphincterotomy is more than 90% successful in expert hands. Intraoperative cholangiography should be seriously considered in most young and all elderly patients who have not had either preoperative ERCP, MRC, HCTC, or EUS. Most CBD stones discovered at surgery should be removed via laparoscopic exploration, conversion to an “open” procedure, or postoperative ERCP (4,5,8).

C. Complications

include acute (“ascending”) cholangitis (see Section VI) and gallstone pancreatitis.

VI. Acute cholangitis

is a rare but potentially lethal infection of the biliary ductal system usually associated with obstructing choledocholithiasis (5).

A. Diagnosis.

Charcot's triad (see Section V.A.1) is seen in 60%–70% of patients. RUQ tenderness and diffuse peritonitis is common. Laboratory findings are similar to acute cholecystitis (see Section III.A.3). US may be diagnostic, but cholangiography is usually necessary for treatment planning.

B. Management

includes supportive care and use of broad-spectrum intravenous antibiotics (see Section III.B). Many patients are too ill to undergo extensive surgery but require immediate drainage of the CBD. These patients should be offered ERCP-guided sphincterotomy to remove the obstruction. If ERCP fails or is not available, drainage of the CBD may be tried percutaneously via US- or CT-guided transhepatic biliary intubation. Percutaneous cholecystostomy may help if the cystic duct is open and the CBD obstruction is distal. Open or laparoscopic cholecystectomy may be performed once the patient's condition has improved (5,8).

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11.5
VIRAL HEPATITIS

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Drugs, toxins, metabolic overload, pregnancy, infection, and countless other conditions may cause acute and chronic liver cell inflammation or hepatitis. This chapter discusses one common form of infectious hepatitis: viral hepatitis. This condition is caused by nonhepatotropic and hepatotropic viruses. The nonhepatotropic viruses infect many organs and are usually self-limited, except in immunocompromised hosts. These five nonhepatotropic viruses are all members of the herpes family of viruses: Epstein-Barr virus (EBV), varicella-zoster, herpes simplex virus (HSV) type 1 and type 2, and cytomegalovirus (CMV). The hepatotropic viruses may produce systemic symptoms but are highly liver specific. They include the following viruses: hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E. New hepatitis viruses have been identified and may explain what heretofore had been characterized as non-A-E viral hepatitis. Approximately 5%–20% of cases of acute and chronic hepatitis are not explained by A-E agents. (1).

When faced with a patient with presumed viral hepatitis, it is essential that the clinician makes the most precise diagnosis possible because prevention, patient education, prognosis, and treatment strategies vary considerably with the specific virus.

I. Nonhepatotropic viruses

A. Epstein Barr virus.

EBV is the etiologic agent associated with infectious mononucleosis, a viral syndrome occurring mostly in adolescents or young adults (see Chapter 19.3). EBV may also cause posttransplantation hepatitis. Clinical signs include exudative pharyngitis, periorbital edema, hepatosplenomegaly, and rash. Most cases show some elevation of the hepatic transaminase and between 5% and 10% of patients have jaundice. The diagnosis can be made in the office with a complete blood count showing a predominance

of atypical lymphocytes and a positive heterophile antibody test (Monospot test). This latter test can be negative in the first 7–10 days of the acute illness. The diagnosis can also be made by demonstrating a fourfold increase in the titer of immunoglobulin G (IgG) antibody against viral capsid antigen (anti-VCA) in cases of reactivation illness or of IgM anti-VCA in cases of primary infection. EBV is not thought to cause chronic hepatitis in patients without immune compromise. Treatment of persons with infectious mononucleosis is supportive. Upper airway compromise can be a concern in the acute phase of the illness.

B. Varicella (chickenpox).

Varicella (chickenpox) is primarily a disease of children, whereas zoster is usually a reactivation of the latent varicella infection. (see Chapter 4.6). Subclinical hepatitis is probably common in childhood but overt hepatitis can occur as part of a widely disseminated viremia usually in the setting of immune compromise. Acyclovir has been shown to be beneficial in childhood and should be administered to patients with disseminated varicella and associated hepatitis.

C. Herpes simplex virus.

HSV-1 and HSV-2 rarely cause hepatitis but can affect immunosuppressed patients undergoing a liver transplant. Fulminant hepatic failure associated with disseminated intravascular coagulation can occur in this setting. Prophylactic use of acyclovir can prevent this type of infection in liver transplant patients.

D. Cytomegalovirus.

CMV causes few symptoms in the average patient but is the most common opportunistic viral infection of the liver graft. Ganciclovir has reduced the severity of CMV infection in patients who underwent recent liver transplantation.

II. Hepatotropic viruses.

The hepatotropic viruses infect immunocompromised and nonimmunocompromised hosts. Five agents have been studied most completely, including hepatitis A, B, C, D, and E viruses. Two newer agents, hepatitis F and G virus, are currently being reviewed. These five agents are genetically unrelated and each can produce an acute illness of variable severity. These infections resulting from these different forms share a number of common clinical features but can be distinguished by serologic markers. The agents can be divided into enterically transmitted viruses (hepatitis A, E, and possibly a hepatitis F), and nonenterically transmitted viruses (hepatitis B, C, D, possibly G, and perhaps others not yet discovered), which produce acute and chronic syndromes. These chronic syndromes, thought to be associated primarily with hepatitis B, C, and possibly D, can lead to chronic hepatitis, cirrhosis of the liver, and the devastating hepatocellular carcinoma.

III. Enterically transmitted hepatotropic viruses

A. Hepatitis A virus (HAV).

HAV is a small, 27-nm, RNA virus, similar to the rhinovirus that causes the common cold and the polio virus. Inactivation of the virus from contaminated items can be achieved by immersion in boiling water for 1 minute, contact with formaldehyde and chlorine, or ultraviolet radiation. Geographic areas with high prevalence include North Africa and the Middle East. Moderate prevalence in found in Central and South America, southern Africa, and India. In the United States over the past several decades, the highest rates of HAV have occurred in a small number of states and counties (2). The highest prevalence is in the western region of the United States, with Missouri, Texas, Colorado, Arkansas, and Montana having the highest rates between 1987 and 1997. Despite these regional differences, about 50% of the U.S. adult population show evidence of past infection. HAV is transmitted primarily by fecal contamination and oral transmission through person-to-person contact or ingestion of contaminated water. Children have a major role in transmission. One study reports 52% of households having a child younger than 6 years for HAV-infected adults without obvious source (3). In the United States, communities with high rates of HAV infection are often relatively well defined either geographically or culturally and include American Indian, Alaskan native, and selected Hispanic or migrant communities. Communities with intermediate risk feature HAV disease that

persists for several years and often occurs at regular intervals are large, such as metropolitan areas, with the children with asymptomatic HAV infection composing the largest group. In communities with low rates of infection, most cases are reported among school-aged children, adolescents, and young adults. These rates reflect little year-to-year variation.

1. **Clinical course of HAV infection.** The illness caused by HAV infection usually has an abrupt onset of symptoms that include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. Diarrhea is more common in HAV infection than in other forms of viral hepatitis. The likelihood of symptoms from HAV infection correlates with age. Seventy percent of HAV-infected children younger than 6 years are asymptomatic. Signs and symptoms usually resolve within 2 months, but 10%–15% of symptomatic patients have prolonged or relapsing symptoms lasting up to 2 months. In infected persons, HAV replicates in the liver causing the hepatitis as manifested by serum aminotransferases (aspartate aminotransferase and alanine aminotransferase) increasing variably between 10 and 100 times normal. This rise precedes the rise in bilirubin but does not correlate with the extent of hepatocyte damage. Peak infectivity occurs during the 2-week period during the elevation of liver enzymes before the rise in bilirubin. During this time, concentration of virus in the stool is the highest and declines after jaundice appears (bilirubin higher than 2.5 mg/dL). Serum bilirubin rises to levels of 2.0–20.0 mg/dL. Children can shed HAV virus in their stool for several months after the onset of clinical disease. Chronic shedding of HAV in the stool does not occur, but adults with relapsing infection can shed for up to 6 months. Hypoglycemia, elevated prothrombin times, and persistent jaundice correlate with severe disease. The case fatality rate for acute HAV infection is 0.6% and is associated with fulminant hepatitis. Consumption of hepatotoxic chemicals, such as alcohol and acetaminophen, early in the illness and certain underlying conditions, such as glucose-6-phosphate dehydrogenase deficiency and sickle cell disease, are associated with the highest bilirubin levels.
2. **Diagnosis of HAV.** The diagnosis of HAV infection is made by finding IgM antibody to HAV (IgM anti-HAV) in the acute-phase or early-convalescence-phase serum. IgG antibody to HAV (IgG anti-HAV) can be detected in the convalescent phase of the disease and persists for life, conferring lifelong immunity. No specific treatment for HAV infection exists, but supportive care with attention to fluid and electrolyte balance is indicated in severe cases.
3. **Vaccination.** HAV infection is the most common vaccine-preventable illness reported in the United States. Widespread use of the hepatitis A vaccine licensed in 1995 would lower disease incidence considerably. In 1996, the Advisory Committee on Immunization Practice (ACIP) recommended that the vaccine be used primarily on individuals thought to be at high risk for infection, such as those who travel to countries with high or intermediate disease, men who have sex with men, intravenous (IV) drug users, persons with clotting factor disorders, children living in communities with high rates of disease, and persons with chronic liver disease who are at risk of acute liver failure with concomitant HAV infection. (4). During the past few years, review of the national epidemiologic data and results of community-based hepatitis A vaccine program indicates that the 1996 recommendations have had limited impact on the overall incidence of HAV disease in the United States. A reviewed ACIP recommendation in March 1999 called for routine vaccination of children in states, counties, and communities with rates of greater than or equal to 20 HAV cases per 100,000 population and consideration of routine vaccination in children in those areas with HAV infection rates greater than or equal to 10 but less than 20 HAV cases per 100,000 population (5). Immune globulin (IG) provides protection against HAV infection through possible

transfer of antibody. Persons who have been recently exposed to HAV and were not previously vaccinated should be administered a single intramuscular (IM) dose of IG (0.02 mg/kg) as soon as possible, but not more than 2 weeks after the last exposure. People vaccinated with at least one dose of hepatitis A vaccine more than a month prior to exposure do not need IG. However, IG is indicated for postexposure prophylaxis in the following situations in which the diagnosis of HAV is confirmed by IgM anti-HAV testing: (a) unvaccinated household and sexual contacts and anyone else with close personal contact such as baby-sitters; (b) unvaccinated staff and attendees of day care centers; (c) household contact of day care attendees in diapers; (d) common-source food handlers if a food handler in a restaurant has been diagnosed with HAV. Restaurant patrons are not routinely immunized unless excessive diarrhea was present in the food handler and extremely poor hygienic practices are discovered and the postexposure period is less than 2 weeks; (e) IG is not routinely indicated when a single case occurs in an elementary or secondary school or work setting. If hepatitis A vaccine is recommended for a person getting the IG, it can be given simultaneously at a separate site. Vaccine alone is not recommended for prophylaxis.

B. Hepatitis E (HEV).

The hepatitis E virus resembles HAV in transmission and cause. It is the major etiologic agent of enterically transmitted non-A, non-B hepatitis worldwide. It is thought to be spread via contaminated water with household transmission being rare. The highest rates of disease are in young to middle age adults. No evidence of chronic infection has been detected with hepatitis E. Virtually all cases of HEV in the US are reported in travelers returning from high HEV-endemic areas. HEV mortality is low except in pregnant women in which the case fatality rate may be as high as 10-30 percent. Both IgM and IgG antibody to HEV are elicited following HEV infection. No serologic tests for diagnosis of HEV infection are available in the United States, but several are available in research laboratories; enzyme immunoassays, Western blot assays that detect IgM and IgG anti-HEV in serum, polymerase chain reaction tests to detect HEV RNA in serum and stool, and other immunofluorescent antibody blocking assays to detect anti-HEV in the serum and liver. No treatment is available for HEV infection. Prevention relies primarily on the provision of clean water supplies and prudent hygienic practices with traveling. IG prepared from plasma collected in non-HEV endemic areas is not effective, and the value of IG from plasma collected in endemic areas is unclear. Prototype vaccines in animals have not been successful in preventing virus excretion in the stool.

IV. Nonenteric hepatotropic viruses

A. Hepatitis B virus (HBV).

HBV is the most important cause of acute and chronic liver disease worldwide. Forty-five percent of the world population lives in areas of high prevalence of chronic HBV infection [7%–8% of the population is hepatitis B surface antigen (HBsAg)–positive]; 43% of the world's population lives in areas with moderate prevalence (2%–7% HBsAg-positive), and 12% in low-prevalence areas (less than 2% HBsAg-positive). Lifetime risk of acquiring infection has been as high as 60% in the high-prevalence areas, 20%–60% in moderate-prevalence areas, and less than 20% in low-prevalence areas. HBV is a 42-nm double-stranded DNA that replicates by reverse transcription. The virus consists of an outer surface membrane containing HBsAg, which also circulates in the blood as 22-nm spherical and tubular particles. HBsAg is the primary component of hepatitis B vaccine; this antigen induces a protective neutralizing antibody that provides long-term immunity. The core of the hepatitis B virus contains hepatitis B core antigen (HBcAg), hepatitis Be antigen (HBeAg), DNA-dependent DNA polymerase, and a single molecule of partially double-stranded DNA. HBsAg is probably acquired as the virus passes through the hepatocyte cytoplasm. The HBcAg is found in the nuclei of hepatocyte of infected patients. HBeAg is thought to be a degradation product of the HBV core. HBsAg is found in serum 30–60 days after HBV

infection. The corresponding antibody (anti-HBs) is responsible for long-term immunity and develops after infection resolves or with immunizations. HBeAg, detectable in the serum of HBV-infected patients, correlates with viral replication and high infectivity. Antibody to HBeAg correlates with loss of viral replication and lower infectivity. An understanding of these markers for HBV infection is essential for proper management of HBV disease. This is summarized in Table 11.5-1 .

Test	Comment
HBcAg	No commercial test
HBsAg	Surface antigen of HBV, first serologic marker to appear
HBeAg	HBV replication and infectivity
IgM antiHBcAg	Marker of recent acute infection
Anti-HBs	Vaccine immunity or resolved infection
Anti-HBe	Antibody indicates low infectivity better outcome

HBV, hepatitis B virus.

Table 11.5-1. Test for markers for hepatitis B virus infection

1. **Transmission.** In the United States the most important route of HBV transmission is by sexual contact, either heterosexual or homosexual, with an infected person. Injection of illegal drugs is also an important route. Other percutaneous exposures include tattooing, body part piercing, and acupuncture. Medical personnel injured by sharp objects on the job are also at high risk. Chronically infected mothers can transmit HBV to their infants. This route has fallen during the 1990s since we have been screening all pregnant women prenatally for HBV infection, given hepatitis B immune globulin (HBIG) to infected newborns, and universally recommended that HBV vaccine be given to all infants born in America.
2. **Clinical course.** HBV develops insidiously with an incubation period averaging 120 days. Constitutional symptoms are more severe than with HAV infection. These include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. About 10%–20% of HBV-infected patients develop a serum sickness reaction with high fever (up to 40°C), rash, arthralgias, and arthritis during the incubation period. Most acute HBV infections resolve, but some patients develop a fulminant hepatitis, which may have a fatal outcome. Confusion in association with ascites as well as elevation of the bilirubin and prothrombin time is suggestive of hepatic failure. About 80% of patients who develop deep hepatic coma in the face of acute HBV infection die. With early and aggressive support, patients often survive without sequelae.
3. **Chronic HBV infection.** HBsAg positivity correlates with chronic HBV infection. It is therefore important to document the disappearance of this antigen from the serum after an acute HBV infection. Ten percent of HBV infected patients are HBsAg-positive after 6 months, but a full 50% of these become HBsAg-negative by 12 months. The younger a person is at the time of acute HBV infection, the more likely that person is to be HBsAg-positive. A neonate has a 90% chance of being HBsAg-positive for life unless the neonate receives HBIG. A child who contracts HBV at age 5 has a 25%–50% chance of being antigen-positive. If an adult patient with chronic HBV infection feels good and eats well, deterioration is unlikely. Twice-yearly transaminase testing allows assessment for hepatitis activity. Patients with chronic HBV infection also benefit from measurements of serum α-fetoprotein and liver sonography at 6- to 12-month intervals, screening for the development of cirrhosis and hepatocellular carcinoma. If signs of deterioration develop, liver biopsy is indicated to

assess disease activity. The treatment of HBV infection has been improved by the introduction of the nucleoside analogue lamivudine into clinical use. Interferon-α is ineffective if any cirrhosis is present and is poorly tolerated by many patients. Lamivudine has been intensively studied and is highly potent against HBV. This agent increases the loss of HBeAg and has brought about marked improvement in liver chemistries and liver histology. The major limitation has been the emergence of so-called escape mutants due to amino acid substitution in the viral reverse transcriptase leading to decreased antiviral potency. Recognition of these mutations has provided impetus for testing additional viral agents. Ineffective host immune response is thought to play a role in unresolved active HBV infection. Wright and colleagues gave adjuvant preparations to enhance expression of HBV antigens to limited numbers of patients with encouraging results (6). Liver transplantation in chronic HBV infection has been tried in the past but has been limited by the recurrence of HBV infection post transplantation. Studies involving the use of HBIG alone and in combination with lamivudine are ongoing and suggest improved survival and decreased reinfection rates post transplantation with the use of these agents. To prevent the consequences of chronic hepatitis B infection, which are cirrhosis and hepatocellular carcinoma, a comprehensive hepatitis B elimination strategy has been updated by the Advisory Committee on Immunization Practice. The overall goal is to eliminate HBV transmission. The hepatitis B elimination strategy includes the following:

a. Screen all pregnant women for HBsAg and provide HBIG and HB vaccine to all children born to these mothers.
b. Provide HB vaccine to all infants as part of their routine childhood vaccination schedule.
c. Provide catch-up vaccination for children in high-risk groups including Alaskan natives, Pacific islanders, and infants from countries with high prevalence of HBV.
d. Provide hepatitis B vaccine to adolescents, including all previously unvaccinated children at age 11–12 and adolescents in high-risk groups.
e. Vaccinate adults in high-risk groups including:
    - Adults with a STD history and who have > 1 sexual partner in the previous six months.
    - Household contacts of person with chronic HBV infection.
    - Health care and public safety workers who have exposure to blood in the workplace.
    - Clients and staff of institutions for the developmentally disabled.
    - International travelers spending more than 6 months in countries with high rates of HBV.
    - Injecting drug users.
    - Sexually active homosexual and bisexual men.
    - Recipients of clotting factor concentrates.

B. Hepatitis D (delta) virus.

HDV is a defective single-stranded RNA virus that requires the helper function of the HBV envelope protein or HBsAg to replicate. The HBsAg encapsulates the HDV genome and HDV cannot exist and replicate without a pre-existing chronic HBV infection or an acute HBV infection. Patients with acute HBV infection and concomitant HDV infection have a more severe acute illness with the risk of fulminant hepatitis about 2%–20%. Chronic HBV carriers who acquire HDV infection have a much higher incidence of cirrhosis, approaching 70%–80% compared with a 15%–30% chance of liver cirrhosis with chronic HBV infection alone. Modes of transmission for HDV are similar to those of HBV. Percutaneous exposure is most common with sexual transmission possible but less efficient than for HBV. Perinatal HDV transmission is rare. IgM and IgG antibody to HDV is

detectable in most patients with HDV infection but generally declines to undetectable levels after infection resolves. HDAg is detectable in about 25% of patients with HDV infection. It disappears as the HBsAg disappears following infection resolution.

Acute HDV coinfection can be prevented by pre- or postexposure prophylaxis for HBV. As no products exist to prevent HDV superinfection, prevention depends primarily on risk factor reduction through education concerning contaminated needles.

The geographic distribution of HDV is different from that of HBV, with South America having the highest HDV endemicity. The world seems to be enjoying a decrease in HDV infection from an epidemic that began in the 1970s, which is hopefully coming to an end (7).

C. Hepatitis C virus (HCV).

HCV is an enveloped single-stranded RNA virus. HCV has the ability to mutate within an infected host. Heterogeneous variants, called quasi-species, exist simultaneously in an infected person. At least six groups of genetically distinct HCVs have been isolated, each with a number of closely related subtypes. Patients infected with HCV mount an immune response to specific sites on the virus. Mutations in the viral genome are not recognized by preexisting antibodies. The mutant genome subsequently escapes detection and this appears to be the mechanism by which HCV maintains chronic infection (8). The diagnosis of HCV infection is made by the detection of anti-HCV antibody in the serum of infected persons. This antibody is detectable by 5–6 weeks in 80% of infected patients and by 12 weeks in 90%. Because this enzyme immunoassay (EIA) can be positive in other inflammatory conditions of the liver, false positives can be decreased through the use of a more specific, supplemental recombinant immunoblot assay (RIBA) antibody test for HCV. Although not widely available, the diagnosis of acute HCV disease can be made 1–2 weeks after infection through detection of HCV RNA using reverse transcriptase polymerase chain reaction (RT-PCR) techniques.

1. **Risk factors.** Percutaneous exposures from an infected blood or organ donor and injected drug use are the most efficient modes of transmission with an overall prevalence of 60% following these exposures. Hemodialysis and needlestick exposures and receiving untested blood products prior to 1990 are other significant risks. Sexual or household exposure to an HCV-positive contact, having multiple sex partners, and vertical transmission to an infant from an HCV-infected mother are other risk factors, but the magnitude of these risks has not been established.
2. **Clinical course.** The acute phase of HCV is often mild and the patient usually remains anicteric or even asymptomatic. The most important feature of HCV infection is its chronicity. Between 70% and 80% of infected individuals develop chronic active hepatitis or cirrhosis. Some go on to develop hepatocellular carcinoma. Prevention through risk factor reduction is clearly the most effective treatment. If a patient tests positive for HCV antibodies, serial alanine aminotransferase levels at 6- to 12-month intervals are helpful because negative enzymes do not prove inactive disease. All HCV positive patients with liver enzyme elevation should undergo liver biopsy. Treatment with interferon has resulted in normalization of serum transaminases in about 50% of HCV-positive patients. This normalization appears to be higher in patients with liver inflammation who have not yet developed significant cirrhosis. Some HCV genomes appear to be more sensitive to the therapeutic effects of interferon. Despite initial enthusiasm with interferon in some HCV patients, permanent remissions do not occur in more than 75% of treated patients and the side effect profile with interferon is quite high (9).

   Children and HCV patients treated early in the disease with interferon alone or in combination with ribavirin appear to do better than those treated later in the disease. Genotype testing may also be important. Those patients with HCV genotype non-1b have higher response rates.

Management of chronic HCV infection is a rapidly changing area. Combination of interferon and ribavirin is now approved by the U.S. Food and Drug Administration for patients who have relapsed following interferon treatment alone. Other treatments, including corticosteroids, ursodiol, and thymosin, have not been effective. High iron levels may reduce interferon efficacy. Phlebotomy prior to interferon has been studied but results are inconclusive. Patients are becoming more interested in alternative therapies for this challenging condition and physicians need to be prepared to address questions regarding these alternatives (10).

3. **Liver transplantation.** Chronic HCV infection is the most common indication for liver transplantation in the United States. Recurrence of HCV is almost universal because most patients are viremic at the time of transplantation. Research is ongoing to prevent infection and subsequent destruction of the transplanted organ. There is concern that interferon may hasten allograft rejection.
4. **HIV coinfection** (also see Chapter 19.4). Most studies of chronic HCV infection have excluded patients with HCV-HIV coninfection. Small research trials indicate that the effectiveness of treatment of HCV in such patients correlates directly with the activity of the HIV infection. Better response to interferon correlates with higher CD4 counts and a healthier immune system.
5. **Trends in HCV disease.** The incidence of HCV disease has declined considerably. From 1989 to 1993 it declined 75%. The decline started in the mid-1980s when the AIDS epidemic forced changes in blood donor selection practices. It continued in the early 1990s when HCV antibody testing became widely available and continues today. This latter drop is thought to be due to safer needle use practices among injecting drug users.
6. **Postexposure prophylaxis.** IG is not effective in the treatment of HCV infection. Patient education (particularly in patients who inject drugs), frequent testing in high-risk populations, ongoing surveillance of donated blood products, and rapid treatment when HCV infection with liver inflammation is diagnosed remain the cornerstones of therapy (11).

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11.6

PANCREATITIS AND PANCREATIC CANCER

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Pancreatitis

Pancreatitis is a common clinical disorder encountered in primary care. Yearly, there are more than 100,000 hospitalizations for this disease in the United States, with mortality between 2% and 30% (1).

I. Pathophysiology

A. Acute pancreatitis.

Four pathways are theorized as likely etiologic factors in the pathophysiology of pancreatitis:

1. Secretion against an obstructed duct
2. Bio-reflux into the pancreatic duct
3. Duodenal reflux into the pancreatic duct
4. Intracellular protease activation (2)

Cholelithiasis is the most common obstructive cause, whereas alcoholism—the most common cause overall—directly damages the acinar cell and induces changes in secretory function (see Chapter 5.3 and Chapter 11.4).

B. Chronic pancreatitis.

Whereas in acute pancreatitis, the pancreas heals and resumes normal function, persons with chronic pancreatitis have persistent damage with pain, malabsorption, and acute episodes superimposed intermittently (3). Again, alcoholism is the most common cause.

II. Diagnosis

A. History.

Pancreatitis usually presents with right upper quadrant pain, nausea, vomiting, and fever. A history of cholelithiasis, alcoholism, or lipid disorders, particularly familial hypertriglyceridemias, is also important. For any patient with prior pancreatitis with appropriate symptoms, chronic pancreatitis should be high on the differential diagnosis. Certain drugs, such as azathioprine, sulfonates, estrogens, tetracyclines, valproic acid, and thiazide and furosemide diuretics, can cause pancreatitis, as can blunt abdominal trauma.

B. Examination

1. **Physical.** On physical examination, patients with pancreatitis can have tender left upper quadrant, basilar rates from pleural effusion, erythematous skin nodules from fat necrosis, and Cullen's and Turner's signs. Abdominal rigidity, diminished bowel tones, and hypotension may also be present.
2. **Laboratory.** Ranson's criteria guide the clinician to laboratory evaluation and predict severity of the illness.

   Admission

   Age >55

   WBC >16,000/mm [4]

   Blood glucose >200 mg/dL

   Lactic dehydrogenase >350 IU/L

   Aspartate aminotransferase >250 S-F U/L

   Fluid sequestration >6 L (5,6)

Within 48 hours

Hematocrit decrease >10%

Blood urea nitrogen (BUN) increase >5 mg/dL

Calcium <8.0 mg/dL

PAo_2 <60 mm Hg

Base deficit >4 mEq/L

Mortality from acute pancreatitis is approximately 1% with fewer than three signs among Ranson's criteria, 15% with three to four signs, 40% with five or six signs, and nearly 100% with seven or more signs. Elevated serum amylase and lipase are almost always present and are also key laboratory results to follow serially because they fall in sequence with remission of the disease (7). Blood cultures should be drawn in the febrile patient to rule out bacterial infection.

C. Imaging.

Plain films of the abdomen may show ileus and possible pancreatic calcifications. Chest radiography may show pleural effusions. Ultrasonography may reveal gallstones or an enlarged, edematous pancreas, but computed tomography is more sensitive and best for locating a pseudocyst (8,9).

III. Treatment.

Treatment goals are mainly supportive because no specific medical or surgical therapy can directly limit the pancreatic autodigestion or inflammatory processes. Goals of therapy are aimed at relief of symptoms, prevention or correction of complications, and alteration of the clinical course of the disease. The mainstay of treatment is aggressive intravenous hydration; correction of electrolyte imbalances, particularly low serum calcium; and putting the pancreas at rest by decreasing gastric secretions. This is done by giving the patient nothing by mouth, using nasogastric suction, feeding by total parenteral nutrition in some cases, and using intravenous H_2-receptor blockers (10). Patients not responding to these supportive measures or those with pseudocyst formation should be considered for gastrointestinal or surgical specialist referral for further diagnostic tests and procedures, including endoscopic retrograde cholangiopancreatography, pseudocyst drainage, and cholecystectomy (11). Prognosis is excellent if underlying causes are alleviated.

Pancreatic Carcinoma

Pancreatic carcinoma is the fifth leading cause of cancer death in the United States, affecting more than 24,000 people each year (12). It has a very poor prognosis, with less than 20% survival 1 year after diagnosis and an overall survival rate of 3%.

I. Pathophysiology.

More than 90% of pancreatic malignancies arise from the exocrine pancreas and are histologically adenocarcinomas. Most of these arise from the pancreatic ductal system (13).

II. Diagnosis

A. History.

Abdominal pain, jaundice, anorexia, weight loss, and depression are most common. Dark urine, clay-colored stools, and gastrointestinal bleeding may also be present.

B. Examination.

Tender left upper quadrant, tender palpable gallbladder, splenomegaly, and varices may be noticeable.

C. Laboratory evaluation.

Tumor obstruction may cause elevated liver function tests and malnutrition may be evident by low protein and albumin. Dehydration may be present with elevations in BUN and creatinine. Complete blood count is often normal, and amylase may or may not be elevated.

D. Imaging.

Ultrasonography is useful for screening masses larger than 2 cm, especially in the head and body, but computed tomography is the most sensitive test overall and can double as a staging tool. Endoscopic retrograde cholangiopancreatography is also an important imaging method and may be therapeutic by stent placement to alleviate jaundice. Magnetic resonance imaging is of no advantage, but percutaneous fine-needle aspiration may be useful in some patients.

III. Treatment

A. Medical.

Medical efforts are aimed at giving supportive therapy and adequate pain control. Correction of metabolic imbalances and dehydration, as well as occasional nasogastric suction and total parenteral nutrition, may be necessary for the patient's comfort. Pain control is best obtained with morphine and its derivatives, whereas nausea control is best accomplished with prochlorperazine (Compazine) or ondansetron (Zofran).

B. Chemotherapy.

Chemotherapy is aimed at inhibition of tumor growth and spread, but it has not proved curative. Streptozocin and 5-fluorouracil have been used as adjuvant therapy, but to no proven benefit. Pharmacologic inhibition of hormonal effects using octreotide (Sandostatin) may be of some use in symptom palliation.

C. Surgery.

Surgical resection provides the only opportunity for cure. However, despite sophisticated staging methods, most patients with adenocarcinoma of the pancreatic head that appeared resectable preoperatively were subsequently found to have metastatic or locally invasive disease. The most common surgical treatment for carcinoma is Whipple's resection, which involves the gastric antrum, the entire duodenum and proximal 10 cm of jejunum, the head of the pancreas, the gallbladder, and the distal bile duct. Variations, such as the pylorus-preserving pancreatoduodenectomy, have been carried out but the mortality is similar.

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11.7
DIVERTICULAR DISEASE

Robert L. Buckley

Diverticulosis is a common condition, affecting approximately one third of people older than 45 years and two thirds of those older than 85 years. The majority of patients (80%) remain asymptomatic, and the condition is found incidentally. Patients with diverticulosis can present with painful diverticula, bleeding, or diverticulitis.

I. Painful diverticulosis

A. Diagnosis

1. **Clinical presentation.** Patients with painful diverticular disease tend to be younger than those with asymptomatic diverticula and present most frequently with colicky or aching left lower quadrant abdominal pain of short duration (see Chapter 2.6).
2. **Examination.** Patients with diverticulosis or painful diverticular disease have a normal examination, with no evidence of peritoneal irritation, mass, or inflammation.
3. **Laboratory and radiographic evaluation.** In the absence of diverticulitis, all laboratory studies are normal. Diverticula are frequently found incidentally on barium enema or endoscopy.

B. Treatment.

Treatment includes increasing dietary fiber. Prescribe bran (25 g/d) and psyllium hydrophilic mucoid [Metamucil; 1 teaspoon (3.4 g) 1–3 times daily], which decreases intraluminal pressure and may reduce symptoms as well as progression of the disease. Ninety percent of patients placed on a high-fiber diet remain symptom free (1). Propantheline (Pro-Banthine), 7.5–15.0 mg 30 minutes before meals and at bedtime, can be used for treatment of abdominal cramping.

II. Diverticular bleeding

A. Diagnosis

1. **Clinical presentation.** Bleeding from diverticula is usually painless, may be occult or massive, and occurs as a result of rupture of the vasa recta on the dome of the diverticulum.
2. **Examination.** The patient may appear normal or show evidence of hypovolemia, depending on the extent of bleeding. There is usually little or no abdominal tenderness. Rectal examination demonstrates hematochezia or stool that is positive for occult blood.
3. **Laboratory and radiographic evaluation.** The patient may show evidence of iron deficiency anemia, although in acute bleeding the serum hemoglobin may be normal. If bleeding is minimal, the patient may undergo colonoscopy to identify the source of bleeding and rule out other pathologic conditions, such as angiodysplasia or neoplasia. In patients with brisker bleeding and those who cannot tolerate colonoscopy, the site of bleeding may best be identified using a bleeding scan or by arteriography (arteriography requires a bleeding rate of 0.5 mL/min) (2).

B. Treatment.

In as many as 80% of patients, bleeding stops spontaneously with only supportive treatment, although the risk of rebleeding is 25%. Patients with severe bleeding may be treated with intra-arterial vasopressin for up to 24 hours, if the site of bleeding is known. Transcatheter embolization or endoscopic laser photocoagulation may also be tried. Patients who would be unable to tolerate continued bleeding, who fail medical management, or who suffer from repeated episodes of bleeding should be considered for surgery because up to 50% of patients with two episodes of bleeding will have additional rebleeding (2).

III. Diverticulitis

A. Diagnosis

1. **Clinical presentation.** Diverticulitis is a complication of diverticular disease that may result in diverticular rupture, generalized peritonitis, and fistula formation. In the United States, diverticulitis most often involves the sigmoid and descending colon (3). Patients present with abdominal pain (most often left sided) and may have dysuria, fever, chills, abdominal distention, nausea, anorexia, and, occasionally, vomiting. The differential diagnosis includes ischemic colitis, carcinoma of the colon, mesenteric venous thrombosis, inflammatory bowel disease, nephrolithiasis, and appendicitis.
2. **Examination.** Patients may present with relatively few findings if the inflammation is isolated to the pericolic fat, or they may present with

findings of acute peritonitis. In early diverticulitis, the temperature can be normal or a low-grade fever may be present. On abdominal examination, there are varying degrees of tenderness to palpation and rebound tenderness. In the presence of abscess or fistula, a mass may be palpable. Patients on immunosuppressive medications may show few findings on initial physical examination, even in the presence of overt perforation.

3. **Laboratory and radiographic evaluation.** The complete blood count (CBC) in mild or early disease is normal or may show an increase in white blood cells (WBC). Urinalysis can show microscopic hematuria and pyuria from irritation of the ureter or from vesicocolic fistula formation. Stool is positive for occult blood in up to 25% of patients. Plain film radiographs of the abdomen should be obtained to rule out free intraperitoneal air. Abdominal computed tomography (CT) is well tolerated and can provide evidence of inflammation of the pericolic fat and presence of an abscess or fistula formation. Ultrasonography can show thickened bowel. Water-soluble contrast enema is sensitive and specific for diverticulitis. Colonoscopy can be used to rule out other causes of the patient's symptoms after the acute episode has resolved (4).

B. Treatment.

A reliable patient with mild symptoms of diverticulitis can be managed on an outpatient basis. The patient should initially be started on a clear liquid diet. Antispasmodic medications and analgesics can be used to provide symptomatic treatment. Oral antibiotics that have been used for diverticulitis include amoxicillin-clavulanate (Augmentin), 250–500 mg every 6–8 hours, or the combination of metronidazole (Flagyl), 500 mg every 6 hours, and either ampicillin, 500 mg every 6 hours, tetracycline, 250–500 mg every 6 hours, trimethoprim-sulfamethoxazole (Septra, Bactrim), 1 double-strength tablet twice daily, or ciprofloxacin (Cipro), 500 mg twice daily. Oral antibiotics may be needed for up to 2 weeks (5).

Patients with more severe signs and symptoms, the immunocompromised, and frail elderly patients may require inpatient management. Patients admitted to the hospital should be placed at bowel rest and given intravenous hydration. Antibiotic coverage for gram-negative aerobes and anaerobes should be started. One antibiotic that can be used is cefoxitin sodium (Mefoxin), 4–6 g/d IV in four divided doses. An aminoglycoside can be added if there is a concern about antibiotic resistance or if *Pseudomonas* infection is suspected. Gentamicin, 1.7 mg/kg loading dose and 1.0–1.4 mg every 8 hours (corrected for patients with renal insufficiency), and clindamycin, 600 mg every 6 hours, in combination have also been shown to be effective. Other drug choices include piperacillin/tazobactam (Zosyn) 2–4 g every 6–8 hours, imipenem/cilastatin (Primaxin), 0.5–1.0 g every 8 hours, ticarcillin/clavulanate (Timentin), 3.1 g every 4–6 hours, and the combination of an aminoglycoside and metronidazole (Flagyl), 7.5 mg/kg every 8 hours (5).

Analgesics can be given as needed, but nonsteroidal anti-inflammatory drugs have been shown in some studies to be associated with a higher incidence of perforation and should be avoided. Patients who are septic, have fistulas, are immunocompromised, develop an abscess, fail medical management, or have signs of obstruction or recurring disabling attacks are candidates for surgery. In patients with abdominal abscesses, CT-guided needle drainage may delay the need for emergency surgery and allow the performance of a single-stage procedure.

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11.8
IRRITABLE BOWEL SYNDROME

Martin C. Schulman

Irritable bowel syndrome (IBS) is a functional disorder of the colon that is not caused by any anatomical, infectious, or inflammatory abnormality. As such, it is a diagnosis of exclusion because there is no diagnostic test for this disorder. Differential diagnosis includes inflammatory bowel disease, diverticulosis, giardiasis, lactose intolerance, oligosaccharide intolerance, other malabsorption syndromes, neoplasm, and intermittent partial small bowel obstruction. Functional bowel syndrome and spastic colon are acceptable alternative terms for IBS.

Diagnosis

Symptoms.

The classic symptoms of IBS are crampy abdominal pain and constipation or diarrhea. Many patients suffer from both constipation and diarrhea in an alternating fashion. The pain of IBS can be associated with the urge to have a bowel movement and relieved by having a bowel movement. Patients with IBS are typically never awakened by abdominal pain. Bloating and excessive intestinal gas are common complaints of patients who suffer from IBS. Mucus per rectum, although often suggestive of inflammatory bowel disease, can be due to IBS (see also Chapter 11.9).

Associated factors.

Patients with IBS frequently associate a flare of symptoms with stress, even acute stress. Similarly, IBS can be a somatic manifestation of an underlying anxiety disorder. If lactose intolerance is a possible factor, then trials of lactose avoidance or lactase supplementation (Dairy Ease, LactAid) should be considered. If oligosaccharide intolerance is a possible factor, then avoidance of the possible offending foods or a trial of α-galactosidase supplementation (Beano) should be considered.

Physical examination.

The abdominal examination of a patient with IBS is typically unremarkable, although abdominal tenderness and distention can be found.

Tests.

The need for tests is based on the examiner's level of suspicion of a diagnosis other than IBS. For instance, a patient with a worrisome symptom, such as hematochezia, melena, narrowed stool caliber, or weight loss, should have some diagnostic tests performed. Alternatively, a patient with only typical IBS symptoms may best be served by avoiding any diagnostic tests and proceeding directly to empirical therapy with a beneficial response serving as confirmation of the diagnosis. The following tests should be considered.

1. **Complete blood count.** Iron deficiency anemia suggests the possibility of chronic occult gastrointestinal blood loss, and eosinophilia suggests the possibility of a gastrointestinal parasite infection.
2. **Chemistry panel.** Chemical analysis may show liver or kidney dysfunction.
3. **Stool studies.** These studies look for occult blood, white blood cells, parasitic infection, bacterial infection, or excessive fecal fat. Because

microscopic diagnosis of giardiasis can be difficult, it is reasonable to consider empirical therapy for this when it is strongly suspected.

4. **Radiology.** Plain abdominal radiographs obtained during an episode of acute abdominal pain can expose a bowel obstruction. Results of a barium enema study can show evidence of diverticula, masses, and inflammatory bowel disease.
5. **Endoscopy.** Colon endoscopy can be done to look for diverticula, neoplasms, and inflammatory mucosa. Full colonoscopy has the advantage of looking at the entire colon, but this procedure requires sedation and is more expensive than sigmoidoscopy. The patient's awake state during sigmoidoscopy is an advantage in that patients with IBS often note that the discomfort caused by air insufflation mimics their usual abdominal pain. Some people believe that spasm during endoscopy is more likely to occur in those with IBS.

Treatment.

The mainstay of treatment is fiber therapy to increase the bulk of stools and regulate bowel movements, thus preventing the symptoms associated with IBS. Other dietary changes and stress reduction measures can be helpful as well. Antispasmodic and antidiarrheal medications are used for symptomatic relief until the measures described previously are effective and subsequently for breakthrough symptoms as needed.

Fiber.

Dietary fiber in an amount adequate to regulate bowel movements should prevent the pain and bloating associated with IBS. Dietary fiber must be accompanied by adequate fluid intake to be beneficial. Natural fiber sources include whole-grain breads and cereals, vegetable salads, fresh fruits, and unprocessed bran. If natural sources are inadequate, then fiber supplements should be used one to three times daily. These supplements include the following:

1. **Psyllium preparations.** This fiber source can be found in powders (Citrucel, Metamucil), granules (Perdiem), and wafers (Metamucil).
2. **Calcium polycarbophil (FiberCon, Konsyl).** This fiber source comes in tablet form.

Other dietary changes.

Carbonated beverages should be avoided because these increase intestinal gas. Chewing slowly can decrease aerophagia. Caffeine and nicotine should be avoided because these can stimulate colonic smooth muscle in an adverse way. A food and symptom diary can be helpful in monitoring response to treatment.

Stress and anxiety reduction.

Stress reduction measures, psychological counseling, and antianxiety medication when indicated can all be helpful in reducing IBS symptoms.

Antispasmodic medications.

These are used as needed to control the crampy pain of IBS.

1. Hyoscyamine sulfate (Levsin), 0.125–0.250 mg PO or SL every 4 hours prn.
2. Dicyclomine hydrochloride (Bentyl), 20–40 mg 4 times daily prn.

Antidiarrheal medications

. These should be used sparingly to control prolonged episodes of diarrhea associated with IBS. Care must be taken to avoid constipation secondary to these medications. Examples include the following:

1. Loperamide hydrochloride (Imodium). The initial dose is 4 mg followed by 2 mg after each loose stool, up to a maximal daily dose of 16 mg.
2. Diphenoxylate hydrochloride with atropine sulfate (Lomotil) is taken as 2 tablets or 2 teaspoons up to 4 times daily prn.

Serotonin receptor modulators.

These form a new class of medications specifically designed to treat the symptoms of IBS by affecting gastrointestinal motility and perhaps pain perception as well. Clinical effectiveness has so far been demonstrated only in women.

1. Alosetron hydrochloride (Lotronex) is a selective 5-HT3 receptor antagonist that was used to decrease symptoms in patients with diarrhea-predominant IBS. Constipation was an expected potential side effect

but serious side effects, such as ischemic colitis and impaction, caused the medication to be voluntarily withdrawn from the market on November 28, 2000.

2. Tegaserod (Zelmac) is a selective 5-HT4 receptor agonist that is awaiting U.S. Food and Drug Administration approval at a dose to be determined. It decreases symptoms in patients with constipation-predominant IBS. Diarrhea is an expected potential side effect.

11.9
INFLAMMATORY BOWEL DISEASE

Robert G. Ross

I. Overview.

The term inflammatory bowel disease (IBD) collectively includes the processes of Crohn's disease (CD) and ulcerative colitis (UC), which are chronic, relapsing, and remitting inflammatory conditions of the gastrointestinal (GI) tract. The incidence of IBD in developed countries is approximately 2–4/100,000 population, the prevalence 0.1%–0.2%. The most common age of presentation is from adolescence to 30 years with a smaller increase in incidence in the 50- to 80-year age group.

A. Pathology.

CD is characterized by a granulomatous, transmural inflammatory infiltrate located at any level of the GI tract from mouth to anus, most commonly found in the ileocecal area. CD is a patchy, noncontinuous process. UC is limited to the colon, usually involves only the superficial layers of the bowel, and is continuous in nature. UC virtually always involves the rectal mucosa.

B. Etiology.

The pathogenesis of IBD remains obscure. The prevailing belief is that IBD is heterogeneous, with several genetic and environmental factors playing a role. The final manifestation of the process is mucosal inflammation presenting with a wide variety of symptoms (1).

II. Clinical presentation

A. Crohn's disease.

The most common presentation is ileitis, which may manifest only as diarrhea and abdominal pain, or may include systemic features such as anorexia; fever; weight loss; anemia; and increased white blood cell count, erythrocyte sedimentation rate, and C-reactive protein levels. Bloody diarrhea usually indicates colonic involvement. The disease may also present as small bowel obstruction or localized peritonitis accompanied by fever, abdominal pain, and leukocytosis. This presentation is often mistakenly diagnosed as acute appendicitis or diverticulitis. Less common presentations include refractory oral ulceration, perianal fistula or abscess, gastroduodenal disease (dyspepsia, anorexia, nausea and vomiting, epigastric pain), intra-abdominal abscess, or symptoms of enterovesical fistula (urinary tract infection, fecaluria).

Alternative diagnostic considerations in CD include appendicitis, cecal diverticulitis, *Yersinia enterocolitica* infection, ileocecal tuberculosis, giardiasis, small bowel lymphoma, the vasculitis associated with Behçet's syndrome, and cecal carcinoma. CD confined to the colon may be confused with UC. In patients experiencing mainly weight loss and diarrhea, diseases associated with malabsorption (celiac sprue) are possibilities. In the female patient, gynecologic disease should be considered.

B. Ulcerative colitis.

Patients experience symptoms of proctitis, including rectal bleeding, urgency, and tenesmus. Occasional incontinence of stool is seen in more than half of patients. Rectal disease may cause constipation and hard

stools streaked with blood. Patients with severe colitis develop bloody diarrhea (more than 6–10 bowel movements per day), fever, weight loss, volume depletion, and anemia. At presentation in an adult, 55% have proctitis alone, 30% have left-sided colitis, and 15% have more extensive disease. In children, disease involvement is usually more extensive (2). The differential diagnosis of UC includes infectious colitis (discussed in the next section), ischemic or radiation-induced colitis, and CD limited to the colon. Irritable bowel syndrome (IBS) often mimics the presenting symptoms of UC and CD, but never causes rectal bleeding or a positive fecal occult blood test.

C. Physical examination.

The physical examination may reveal right lower quadrant tenderness or the sensation of a mass in patients with active CD. The presence of left lower quadrant tenderness in a patient with rectal bleeding should always raise the possibility of active UC. Patients with severe UC or toxic megacolon appear acutely ill with abdominal tenderness, dehydration, tachycardia, hypotension, and, often, fever. In the rare case of perforation, peritoneal signs and/or abdominal rigidity will be present. Rectal examination should be performed to check for rectal tenderness and the presence of blood. The perianal region and oral mucosa should be examined, as up to one third of patients with CD develop perianal disease, and many have oral ulcers.

D. Complications

1. **Local (GI).** UC can lead to toxic megacolon resulting in perforation and intra-abdominal sepsis. CD may cause fibrosis, stricture, intestinal obstruction, fistulas, and intra-abdominal abscesses, as well as perianal disease. Colonic mucosa that is involved with IBD is more likely to develop dysplasia and carcinoma, with more compelling evidence of malignant change in UC. The frequency of screening for carcinoma in IBD is controversial, but after 8 years of disease it is prudent to perform colonoscopy and biopsy regularly.
2. **Systemic.** Extraintestinal manifestations of IBD include ocular changes of episcleritis and uveitis, reactive arthropathy with ankylosing spondylitis seen in 5% of patients, and the dermatologic manifestations of erythema nodosum and pyoderma gangrenosum. A serious complication, seen most often in UC is sclerosing cholangitis.

III. Diagnostic tests

A. Laboratory testing and cultures.

Presently, there is no serum marker that is sensitive or specific enough to have any real clinical usefulness. The diagnosis rests with the analysis of the clinical presentation, the omission of infectious causes that may mimic IBD, and the choice of study that is most likely to confirm suspicion of IBD. The physician must obtain a complete history, including foreign travel, exposure to food-borne illness, and use of antibiotic agents. Stool samples should be obtained for culture of *Salmonella, Shigella, Campylobacter, Yersinia, Escherichia coli* O157:H7, and enteroinvasive *E. coli*; examination for ova, cysts, and parasites; and testing for *Clostridium difficile* toxin. In a patient who has rectal intercourse, rectal cultures for *Neisseria gonorrhoeae* and *Chlamydia* should be obtained. HIV testing should be considered, as opportunistic GI tract infections can cause diarrhea, weight loss, and abdominal pain (see Chapter 19.4) Stool testing for *Giardia lamblia* antigen may help determine the cause of chronic diarrhea and abdominal pain (see Chapter 19.11). In the acutely ill and toxic patient who is having moderate or severe rectal bleeding, diarrhea, and/or abdominal pain, complete blood count, electrolytes, albumin, amylase, and type and screening or cross-matching of blood products is mandatory.

B. Endoscopy.

Sigmoidoscopy is the first diagnostic test to perform in the patient with bloody diarrhea. Direct examination of the rectal and sigmoid mucosa with biopsy is possible. It is often difficult to determine the cause of colonic inflammation based on appearance, and the physician usually must wait until cultures and pathologic specimens are available before diagnosing

IBD. Caution is advised in performing sigmoidoscopy during severe colitis. However, biopsy is safe in this situation.

CD can be diagnosed by colonoscopy, especially if the ileocecal valve can be traversed (ileoscopy) and the terminal ileum examined. This is often the only method of diagnosing early ileal or colonic CD. Colonoscopy is also an effective method of assessing the extent of UC, which can be useful in determining if systemic or local therapy is appropriate. Colonoscopy is almost never warranted during bouts of severe colitis or in the patient with toxic megacolon, although there is debate about the safety of the examination in this situation. Typically, there is a cobblestone appearance of the colon in CD, with areas of normal mucosa between involved areas. In UC, inflammation is continuous with erosions and friability apparent. However, in about 10% of sufferers, the differentiation between CD and UC is impossible based on clinical presentation and extensive testing.

C. Radiography.

If severe colitis or obstruction is suspected, a three-position abdominal series should be obtained (upright chest film, abdominal decubitus and flat-plate or kidney-ureter-bladder views) to rule out perforation, obstruction, or toxic megacolon. Toxic megacolon is diagnosed when the diameter of the colon on the flat plate exceeds 5.5 cm. In CD, the terminal ileum is best viewed via a peroral pneumocolon exam, where the patient consumes a barium meal. Once the barium reaches the cecum, a rectal catheter is used to introduce air into the colon. This gives a double-contrast view of the ileum. Other studies include a single-contrast small bowel follow-through examination, and enteroclysis (small bowel enema) in which a catheter is introduced into the proximal jejunum, followed by air or methylcellulose. This is the procedure of choice if more proximal disease is suspected. In UC, the best test is the air-contrast barium enema (not during severe disease or toxic megacolon). If a complication, such as intra-abdominal abscess, is suspected, then abdominal computed tomography should be done. The role of magnetic resonance imaging is not well defined (3).

IV. Management

(See Table 11.9-1)

Agents	UC indications and dosage	CD indications and dose	Contraindications	Side effects
Local				
Hydrocortisone (HCT) enema (Cortenema) 100 mg	Enema (100 mg) Proctitis, sigmoid disease single agent in mild disease, supplement to systemic treatment 1 appl qhs × 21 d	For CD of lower colon/rectum, same doses as with UC	Obstruction, local abscess, perforation, peritonitis, recent anastomosis, fistulas; sensitivity to drug/class, infections	Local irritation, rectal bleeding Serious side effects not reported
HCT foam (Cortifoam) 90 mg	As with HCT enema 1 appl PR qd–bid × 2–3 wk, then qod	For CD of lower colon/rectum, same doses as with UC	See HCT enema	See HCT enema
HCT suppositories 100 mg	As with HCT enema	For CD of lower colon/rectum, same doses as UC	See HCT enema	See HCT enema
Mesalamine suppositories (Rowasa) 500 mg	As with HCT but more effective 500 mg PR bid	As with HCT but more effective 500 mg PR bid	Sensitivity to drug/class, obstruction, local abscess, perforation, peritonitis, fistulas	Local irritation, rectal bleeding
Mesalamine enemas (4 g/60 mL)	As with HCT but more effective 1–4 g/d PR Maintenance 1–4 g qod	As with HCT but more effective 1–4 g/d PR maintenance 1–4 g qod	See mesalamine suppositories	See mesalamine suppositories
Systemic				
IV steroids HCT (Solu-Cortef) Methylprednisolone (Solu-Medrol)	Effective for remission induction only HCT 300 mg/d Methylprednisolone 40–60 mg/d	Effective for remission induction only HCT 300 mg/d Methylprednisolone 40–60 mg/d	Drug sensitivity Relative with infections, caution if CHF, diabetes, TB, hypertension	Adrenal insufficiency, psychosis, immunosuppression, peptic ulcer, osteoporosis, others
PO steroids Prednisone (Deltasone)	As with IV steroids: prednisone 40–60 mg/d	As with IV steroids Prednisone 0.25–0.75 mg/kg/d	See IV steroids	See IV steroids
PO sulfasalazine (Azulfidine 500-mg tabs)	Remission induction 2–6 g/d (1 g qid). Maintenance 2–4 g/d. Administer with folate 0.4–1 mg/d	Effective in ileocolonic disease only, induction 3–5 g/d (1 g qid). Maintenance 3 g/d. Administer with folate 0.4–1 mg/d	Hypersenaitivity to drug/class/sulfa/salicylates, renal/hepatic dysfunction, porphyria, obstruction, caution G6PD deficiency	Poorly tolerated esp. at high doses (GI) rashes, Stevens–Johnson syndrome, hemolytic anemia, GI, headache, pancreatitis, hepatitis, sperm ab.
PO mesalamine 5-ASA (Asacol ileocolonic release 400 mg, Pentasa 250 mg, jejunum to colon)	Remission induction 4–4.8 g/d (Asacol 1,200 mg qid). Maintenance 400–800 mg qid, sometimes lower	Remission induction Asacol 1–1.2 g qid, Pentasa 1 g qid, better for proximal disease? Maintenance same as remission	Hypersenaitivity to drug/class, caution in impaired renal function	Anaphylaxis, confusion, headache, GI, pharyngitis, dizziness, asthenia, others
PO antibiotics metronidazole (Flagyl) ± ciprofloxacin (Cipro)	N/A	Effective in remission alone or in combination, first choice for perianal disease. Flagyl 250 mg qid ± Cipro 500 mg bid	Hypersensitivity to drug/class, pregnancy, caution with CNS disorder	GI, seizures, rash, photosensitivity, liver function test elevation, neuropathy and Antabuse reaction with Flagyl

ASA, acetylsalicylic acid; CD, Crohn's disease; CHF, congestive heart failure; CNS, central nervous system; G6DP, glucose-6-phosphate dehydrogenase; HCT, hydrocortisone; TB, tuberculosis; UC, ulcerative colitis.

Table 11.9-1. Inflammatory bowel disease: management options

A. Hospitalization.

With severe symptoms, abnormal vital signs, severe colitis, intra-abdominal abscess, or other complications, management should occur in the hospital setting. The patient should be given intravenous rehydration, left NPO, and receive intravenous therapy (usually with high-dose steroids) as soon as the diagnosis is made. In these cases it is prudent to seek consultation from a gastroenterologist and/or surgeon. Consultation is also advised in the case of a patient who does not respond to initial outpatient management or develops complications such as fistula, obstruction, or abscess.

B. Outpatient.

Local therapy of proctitis and sigmoid disease (mild to moderate) should be attempted prior to systemic treatment. Patients with CD should discontinue the use of oral contraceptives and smoking. UC patients conversely may benefit from the use of transdermal nicotine (Nicoderm, Habitrol). IBD sufferers should avoid the use of nonsteroidal anti-inflammatory drugs. Systemic agents effective in IBD include 6-mercaptopurine (6-MP, Purinethol), azathioprine (AZA, Imuran), methotrexate, cyclosporin (in UC only), and anti-tumor necrosis factor antibody [infliximab (Remicade)]. Infliximab is especially effective in patients with complications of CD. A variety of experimental treatment approaches (tacrolimus, interleukin-10, omega-3 diets) are being tested. If the use of newer systemic agents is considered or complex therapy is necessary, this is best undertaken after consultation. Once remission occurs, maintenance therapy should be considered. Sulfasalazine (Azulfidine), 6-mercaptopurine, and AZA are effective in maintaining remission in CD, and sulfasalazine is useful in UC as well. Better tolerated agents, such as mesalamine (Asacol, Rowasa, Pentasa) and olsalazine (Dipentum), are not as effective as sulfasalazine in UC but may be more appropriate in CD. Steroids, though useful in inducing remission, are not effective in maintenance

therapy (4). Symptomatic therapy for diarrhea (codeine, operamide, Imodium) is contraindicated in severe disease and megacolon.

V. Patient information.

An excellent source for patient information is the Crohn's and Colitis Foundation of America, 444 Park Avenue South, New York, NY 10016-7374, (212) 685-3440. Internet address http://www.ccfa.org/.

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11.10

ANORECTAL DISEASE AND HEMORRHOIDS

Thomas J. Zuber

Anorectal disease and hemorrhoids are problems frequently encountered in primary care practice. Approximately 80% of all U.S. adults experience hemorrhoidal disease at some time in their lives. This chapter reviews common anorectal problems and includes a table with important patient management recommendations.

I. Anal fissures

A. Definition.

A fissure is a crack or tear in the anal mucosa, possibly caused by the passage of hard stool or the development of ischemic mucosal injury in the posterior anal canal. Most fissures occur in the posterior midline, although up to 10% of fissures in women are in the anterior midline. Fissures off the midline should prompt consideration of other medical disorders such as Crohn's disease, anal carcinoma, AIDS, or syphilis (1).

B. Clinical course.

Fissures occur in the heavily innervated anoderm below the dentate line and generally produce severe pain. Bleeding is noted in up to 60% of patients. A small number of fissures will become chronic. Recurrent trauma from the passage of stool can deepen the fissure, producing muscle spasm and reducing mucosal blood flow. Edema from the nonhealing fissure can produce the diagnostic “sentinel skin tag” in the distal anal canal. Chronic fissures usually have produced symptoms for more than 2 months.

C. Medical management.

Acute fissures can be managed with local anesthetics (lidocaine hydrochloride 2% jelly), warm sitz baths, and efforts to promote soft stools (Table 11.10-1). Most fissures resolve spontaneously or with aggressive medical therapy within 6 weeks of the onset. Acute or chronic fissures can be managed with twice-daily application of topical nitrates. Early studies used 0.2% ointment; commercially available products in the United States (2% nitroglycerin ointment) should be diluted. Botulinum toxin 20 units injected in two divided doses into the internal anal sphincter on both sides of the canal appears even more effective. Only the rare patient who fails these pharmacologic interventions should be considered for surgical intervention.

1. Take nonprescription ibuprofen (three 200-mg tablets three times a day with food) and acetaminophen (two tablets every 6 h) if needed for discomfort. Avoid taking narcotics (such as codeine), which can produce further constipation.
2. A sitz bath (soaking in a tub of warm water) for 20 min several times a day can reduce discomfort and promote healing of the tissues.
3. Use stool softeners for at least 2 wk to promote softer stools and to allow the tissues to heal. Start with nonprescription docusate sodium (two 100-mg capsules two times a day) and increase the dosage if you remain constipated.
4. Drink at least 5–6 full glasses of water or fluid daily.
5. A daily stool bulking agent will promote softer stools and improved colon health. Psyllium or methylcellulose powder (1 tablespoon) can be taken in a glass of orange juice daily to make these substances more palatable. Most patients experience bloating, gas, or cramping with the bulking agents initially, but generally this resolves after 2 wk. You can use simultaneous stool softeners when starting the bulking agents.
6. Do not use enemas or place anything in the rectum for the next 2 wk. Local application of ointments, creams, or pads to the anal tissues is permitted.
7. The National Institutes of Health recommends at least five servings of fresh fruits and fresh vegetables daily. A proper diet can promote soft stools and reduce the chances of recurrent anal disease.
8. Because stool in the rectum rapidly becomes dried out, do not delay going to the bathroom when you feel the rectum fill. Do not sit for long periods on the toilet or strain on the toilet. Please remove all reading materials from the bathroom.

Table 11.10-1. Management recommendations for patients with fissures or hemorrhoids

D. Surgical management.

Lateral internal sphincterotomy is the procedure of choice. A small percutaneous incision is made into the internal sphincter, cutting muscle fibers without entering the anal canal. The technique is simple and effective, but the potential for permanent incontinence has led to more aggressive medical management as described above.

II. Anorectal abscesses and fistulas

A. Definition.

An abscess is a localized collection of pus, whereas an anal fistula is an abnormal connection from an abscess to the anal canal or external skin. Abscesses and fistulas are both part of the same disease process (2). Most anorectal abscesses develop from retrograde infections of the anal glands in the crypts at the dentate line. Acute infections produce an abscess, whereas chronic infections can develop into a fistula tract.

B. Clinical course.

As an abscess enlarges, the lesion can progress in many directions. Most abscesses extend down toward the skin to become a perianal abscess. Occasionally, the abscess grows upward into the fat of the ischiorectal fossa.

C. Management.

Anorectal abscesses should be surgically drained on discovery (2). A cruciate incision (in the shape of a plus sign) should be made as close to the anal orifice as possible. Direct compression of the tissues expresses the pus, and an iodoform gauze drain is placed in the abscess cavity for removal in 24 hours. Antibiotics should not be used in place of surgical drainage, and their use after drainage is controversial. Patients should be warned about possible fistula formation.

D. Complications of drainage.

About 40% of abscesses that drain spontaneously or following surgery develop into a fistula. Fistulas produce intermittent tenderness and drainage. Pus may be noted at anoscopy coming from the fistula into the anal canal. Physicians should not probe fistulas in the office setting. Fistulas often require complicated and extensive surgical procedures and are best referred to experienced rectal surgeons when they are encountered.

III. Anal warts, polyps, and neoplasms

A. Management of warts.

Anal condylomas are produced by the human papillomavirus (HPV). Anal intercourse is a causative factor in many (up to

80 %) but not all patients. As with all HPV lesions, there is a significant spontaneous resolution rate in nonsmokers with normal immune system function. Treatments that can be used to eliminate anal condylomas include topical podofilox, topical 5% 5-fluorouracil, interferon injections, cryosurgical destruction, electrosurgical ablation, surgical excision, or laser ablation. Anal Pap smears can be performed to examine for anal dysplasia associated with HPV (see also Chapter 13.4).

B. Management of polyps.

Anal polyps are common benign growths that may represent residual from prior hemorrhoids or fistulas. Condylomas or tumors also can appear as a polyp, and so uncertain lesions in the anal canal should be biopsied. Anal malignancies are less common, but basal cell carcinoma, squamous cell carcinoma, melanoma, or prolapsed rectal carcinoma all can occur.

IV. Pruritus ani

A. Definition.

Pruritus ani is excessive and often intractable anal itching from multiple causes. Men are more commonly affected in a ratio of 4:1 (3). Pinworms (*Enterobius vermicularis*) and chronic *Candida* infection are the most common infectious agents (see also Chapter 16.2 and Chapter 19.11). Local dermatitis can result from allergic reaction to scented or dyed toilet tissue, or from allergies to certain foods (e.g., coffee, tea, cola, beer, chocolate, or tomatoes).

B. Management.

Although poor hygiene may lead to pruritus ani, overzealous cleansing and application of medications also can produce itching. A program of gentle but effective hygiene should be promoted. Drying the anal skin can help, and patients may require frequent changes of cotton underwear during the summer months to prevent skin maceration and further itching. Some patients have been effectively treated with topical antifungals and low-potency steroids.

V. Anorectal infections.

Infectious proctitis can produce rectal discomfort, tenesmus, and rectal discharge. If a mucopurulent discharge is noted, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most common pathogens (see Chapter 19.6 and Chapter 19.7). Syphilis also can produce anorectal infection and should be tested for (see Chapter 19.5). Treatment can be initiated with acyclovir or famciclovir if the characteristic ulcers of herpesvirus infection are noted.

VI. External hemorrhoids

A. Clinical course.

External hemorrhoids occur external to the dentate line, which is the junction of the rectal mucosa and the specialized anoderm of the anal canal. When external hemorrhoids become thrombosed, patients may experience bleeding and extreme pain with defecation. Thrombosed external hemorrhoids typically resolve spontaneously over a 2-week period.

B. Surgical management of thrombosis.

Acutely swollen and tender thrombosed external hemorrhoids may be surgically removed if the physician encounters the lesions in the first 72 hours after onset (4). After 72 hours, the discomfort of the procedure probably outweighs the relief provided from the surgery. Historically, simple incision over the thrombus was performed to remove the clot. Simple incision often results in reformation of the thrombus. Many experts recommend that an elliptic excision be performed to unroof the hemorrhoid. Once the entire clot is excised, the physician can leave the wound open with gauze placed over the area to collect drainage. Alternately, the entire external hemorrhoid plexus can be excised and the wound closed with buried subcuticular absorbable suture.

C. External tags.

An external hemorrhoid shrinks as its blood supply is reduced, often leaving an external tag as the only evidence of the hemorrhoid. External tags are not routinely removed as they rarely produce symptoms and generally do not interfere with hygiene.

VII. Internal hemorrhoids

A. Definition.

The anal cushions are blood-filled sacs that reduce the effects of stool passing through the anal canal. With the chronic passage of hard stool or straining, the anal cushions can lose their fibrocollagenous support.

The cushions then dilate and prolapse into the anal canal, thus becoming hemorrhoids.

B. Clinical course.

Internal hemorrhoids occur above the dentate line. Because the rectal mucosa is not innervated above the dentate line, internal hemorrhoids generally do not produce pain. The major symptoms of internal hemorrhoids are bleeding and protrusion. Patients may report the sensation of a lump or complain of bright red blood on the tissue or in the toilet.

C. Presentation.

First-degree internal hemorrhoids do not protrude through the anal orifice and are seen in the lumen of the canal. Second-degree internal hemorrhoids protrude through the anus but spontaneously reduce. Third-degree internal hemorrhoids protrude and must be manually replaced into the rectum. Fourth-degree hemorrhoids protrude permanently and cannot be replaced. Primary care physicians most frequently encounter first- and second-degree internal hemorrhoids.

Internal hemorrhoids occur in three consistent positions in the anal canal. With the patient in the left lateral position, the physician usually examines the patient from the right side of the table with the patient's head to the left. The three locations for internal hemorrhoids are the right posterior position (10 o'clock position in the canal), right anterior position (2 o'clock position in the canal), and left lateral position (6 o'clock position in the canal). The slotted Ives anoscope (Redfield Corporation, Montvale, NJ) provides excellent visualization of hemorrhoids and the anal canal.

D. Surgical management.

Internal hemorrhoids are most often managed medically (Table 11.10-1). Patients who fail conservative treatment can be considered for surgical intervention. Surgical excision of internal hemorrhoids often is a painful and expensive intervention that can result in a prolonged recovery period. Surgical or laser excision of internal hemorrhoids has been largely replaced by other outpatient treatment modalities.

E. Rubber band ligation.

Rubber band ligation of internal hemorrhoids has been performed for many years. One or two small latex rings are placed at the base of the hemorrhoid, resulting in necrosis and sloughing of the hemorrhoid in the following week. The equipment for banding is inexpensive, but the procedure can produce moderate discomfort. Banding also rarely can produce pelvic sepsis, a life-threatening condition.

F. Infrared coagulation.

Infrared coagulation is a safe and effective office technique for first-, second-, and third-degree internal hemorrhoids. A 0.7-cm light tip applies the infrared energy to the superior aspect of the internal hemorrhoid. A 1.25- to 1.5-second pulse of energy is well tolerated by the patient while producing an eschar that tethers the hemorrhoid to the underlying tissues. Three to five exposures to each hemorrhoid generally reduces blood flow and shrinks the hemorrhoid.

G. Other treatment modalities.

Bipolar diathermy (electrosurgery) produces a similar effect on the hemorrhoid as the infrared treatment. A low-voltage galvanic probe also is used for office treatment of hemorrhoids. These office treatments produce similar healing rates and are well tolerated (5). Cryotherapy and sclerotherapy generally have been abandoned for these newer, and safer, modalities.

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11.11
COLORECTAL CANCER

Eugene Orientale Jr.

Thomas Agresta

Colorectal cancer (CRC), one of the most prevalent cancers in the Western world, is the second most common cause of cancer-related death in the United States. The disease has a high prevalence (4%–5% lifetime incidence), passes through a long asymptomatic yet detectable phase, and has a high cure rate when detected at an early stage (90% survival at 5 years). In addition,

CRC has a high mortality rate when advanced disease occurs (less than 10% at 5 years with metastatic disease). Thus, CRC is ideally suited to prevention and early detection programs (1).

I. Screening modalities

A. Digital rectal examination (DRE).

DRE is not considered a cost-effective means of detecting CRC. At age 40 years, DREs should be commenced as screening for prostrate disease, not CRC (see Chapter 12.5). DRE should precede a flexible sigmoidoscopy or colonoscopy. Stool guaiac testing has a high false-positive rate if performed with DRE and should be withheld.

B. Fecal occult blood testing (FOBT).

Annual screening of asymptomatic individuals after age 50 is effective (sensitivity 72%–88%, specificity 98%, and positive predictive value 10%–17%) and decreases CRC mortality by 15%–33% (1). FOBT is usually performed on stool specimens acquired on each of three consecutive bowel movements. Any positive test should prompt a diagnostic workup. False positives can be caused by consumption of red meat, turnips, horseradish, vitamin C, and certain medications (aspirin, nonsteroidal anti-inflammatory drugs), as well as benign conditions, such as diverticulosis or hemorrhoids.

C. Flexible sigmoidoscopy

(see Chapter 11.12). This office procedure, performed with a 60-cm scope, is capable of screening from the rectum to the splenic flexure. It can diagnose up to two thirds of colonic lesions and has been shown to reduce CRC mortality by 60%–80% at a fraction of the cost of colonoscopy (1). Patient acceptability and compliance are significant issues. The procedure is embarrassing for some patients and requires an uncomfortable bowel preparation that might involve a liquid diet, laxative, electrolyte purge solution, or enema prior to the procedure. Conscious sedation is not required and complications are uncommon, with intestinal perforation occurring about once in 5,000–10,000 examinations. The American Cancer Society currently recommends routine screening every 3–5 years after age 50. The combination of annual FOBT and periodic flexible sigmoidoscopy is a cost-effective means of CRC detection in the general population (2).

D. Air contrast barium enema (ACBE).

This radiologic procedure allows visualization of the entire colon. Patient compliance and acceptability is comparable to that of flexible sigmoidoscopy. It has limitations in evaluation of the rectum and sigmoid colon but can be useful for proximal lesions. ACBE has a sensitivity of only 50% for large adenomatous polyps (3) and 55%–85% for Dukes stage A and B cancers. Specificity ranges from 99% for large cancers to 90% for large polyps (1). There are no current recommendations to use ACBE as a routine screen for CRC. ACBE is twice the cost of flexible sigmoidoscopy and has a similar complication profile but can be useful in patients who refuse endoscopy.

E. Colonoscopy.

This method remains the final common pathway of all other positive screening tests. With adequate bowel preparation it is almost 100% specific and 95% sensitive for detection of neoplasm. Biopsy or polypectomy can be performed. A bowel preparation is always necessary, and conscious sedation improves patient acceptability (4). Use as a primary screening tool remains controversial, and high cost has precluded widespread implementation. Many family physicians are now acquiring skills in full colonoscopy, which ultimately may be a significant factor in the early detection of CRC.

II. Diagnosis

A. Risk factors.

These include advancing age, male sex, family history, cigarette smoking, inflammatory bowel disease, and familial genetic syndromes (familial polyposis and hereditary nonpolyposis colorectal cancer) (5). Diets that are low in fiber or high in fat or alcohol also correlate with increased risk for CRC.

B. Presentation.

There is a lack of correlation between duration of symptoms at diagnosis and survival. Early detection can be both elusive and challenging, with more than 65% of patients presenting with advanced disease.

1. Bleeding is most commonly occult, but patients also can present with melena or hematochezia.
2. Pain may be secondary to intestinal obstruction or metastasis.
3. Altered bowel movements range from diarrhea to obstipation. In the elderly, any change in bowel habits should prompt diagnostic consideration.
4. Constitutional complaints include fatigue, malaise, fever, and weight loss.
5. Metastatic disease may present with jaundice, pruritus, and ascites (liver); respiratory complaints (lung); or pathologic fracture (bone).
6. Weight loss, anemia, and a palpable mass is the triad associated with a proximal lesion.
7. Asymptomatic presentation is not uncommon.

C. Pathology

1. **Colonic polyps** are of two general types.
   a. Hyperplastic polyps sometimes cannot be distinguished from other polyps solely on the basis of endoscopic appearance. They are sessile, 10 mm or less, and tend to occur in the distal colon. A smooth and uniform appearance may uniquely distinguish these lesions. On gross inspection small (less than 5 mm) hyperplastic polyps are often referred to as “diminutive” and need not be biopsied or ablated.
   b. Neoplastic polyps are mucosal outgrowths that may be broadly based or pedunculated. Although most polyps do not undergo neoplastic transformation, most CRCs originate from polyps through a 10- to 15-year process. Polyps undergo metaplastic transformation approximately 40%–60% of the time (6). Three cell patterns are recognized.
   3. Adenomatous polyps (tubular or glandular cell pattern) are histologically arranged in densely packed tubular glands and are the least malignant adenoma.
   4. Villous (papillary cell pattern) polyps are arranged in fingerlike projections and are less common than tubular adenomas. A villous polyp has a higher malignant potential; if larger than 2 cm, it has a 50% chance of containing invasive cancer.
   5. Mixed adenomatous-villous polyps have mixed-cell patterns and are common in large tumors. The risk for malignancy depends on the size and percentage of the villous cell pattern.
   6. **Colorectal cancer**
      a. Histologic classification is of value for prognosis and treatment selection.
         1. Adenomatous CRC is the most common neoplasm and is further differentiated by grade (poorly, moderately, and well differentiated). As with other neoplasms, poor differentiation in histologic specimens is associated with worse prognosis.
         2. Mucinous CRC is an uncommon form that secretes abundant extracellular mucin and has a poor prognosis.
         3. Signet ring CRC (linitis plastica) is composed of cells distorted by intracellular mucin into a signet ring shape. It is typically associated with metastasis at the time of diagnosis.

4. The Dukes classification, though somewhat less precise than the tumor-necrosis-metastasis (TNM) scheme, is commonly used because of its simplicity (Table 11.11-1). Prognosis is directly related to depth of invasion (7).

Stage	Description	5-yr survival (%)
A	Confined to the bowel wall	90
B	Through the wall and locally invasive (no lymph node involvement)	60–80
C	Metastasis to regional lymph nodes	20–50
D	Distant metastasis (peritoneum, liver)	5

From Fry R, Fleshman J, Kodner I. Cancer of the colon and rectum. *Clin Symp* 1989;41:2, with permission.

Table 11.11-1. Dukes' classification scheme for colon cancer

III. Management

A. Polyps.

Because polyps have malignant potential, they should be biopsied or removed at the time of colonoscopy. Larger sessile polyps sometimes require either surgical or piecemeal colonoscopic resection. Polypectomy is performed with the use of wire snare or biopsy forceps technique, both of which may be accomplished with concomitant electrocautery.

B. Cancer.

Management varies according to histology, location, and stage.

1. Colonoscopy with polypectomy may obviate the need for surgery. In some cases, even large biopsy-proven cancerous lesions can be removed in piecemeal fashion.
2. Surgery is the general treatment for cancers beyond Dukes stage A. The goal is complete removal or destruction of neoplastic tissue with maximal preservation of surrounding tissues.
3. Adjuvant chemotherapy has been shown to be effective for Dukes stage B and C cancers. Current recommendation is fluorouracil with either levamisole or leucovorin (the latter for metastatic disease) (8).
4. Radiation can be of benefit in the management of rectal cancer and advanced CRC and in palliation for patients with unresectable disease.
5. Surveillance with cancer markers or colonoscopy has unfortunately not demonstrated any improvement in survival rate. Carcinoembryonic antigen (CEA) is nonspecific and thus not useful for screening. For existing CRC, CEA may be used as a marker for disease recurrence every 3 months for the first year after resection, and then every 6 months for 2 more years. Colonoscopy is generally performed at 6- to 12-month intervals and 2 years post resection.

IV. Prevention

A. Diet.

A low-fat, high-fiber diet reduces the risk of CRC. Additional supplementation with folate may further reduce risk.

B. Aspirin.

The daily use of aspirin has been shown to both decrease the incidence of CRC and and the occurrence of metastasis (9).

C. Screening.

Screening for adenomatous polyps in an aggressive and systematic manner has proved effective in the prevention of CRC (see Chapter 1.3 and Chapter 1.4). Family physicians with full colonoscopic skills may play an integral role in the containment of this common cancer (10).

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11.12
FLEXIBLE SIGMOIDOSCOPY

John L. Pfenninger

Clinical research has documented the value of screening flexible sigmoidoscopy (FS). In nonsmokers, colon cancer has the second highest incidence and is the second highest cancer killer in both men and women (see Chapter 11.11). Screening with FS and removal of precursor polyps could reduce colon cancer by 80% (1). Colonoscopy after a completed flexible sigmoidoscopy indicated that only 5% of patients had more proximal colonic neoplasia whether or not there were distal adenomas (2). All primary care physicians must either perform FS or incorporate a method of practice to ensure that their patients have regular colorectal cancer (CRC) screening, which has now also been recommended by the U.S. Preventive Health Services Task Force (3) and virtually all medical organizations.

I. Indications for flexible sigmoidoscopy

A. Screening.

American Cancer Society guidelines state that FS and annual hemoccults can be used alone but it is preferred that they be used together for colon cancer screening (1,4). A comparison of 22 different CRC screening strategies showed that the most effective strategy for white men was annual rehydrated fecal occult blood testing plus FS every 5 years from age 50 to 85 years. Colonoscopy was less effective (5). Others concur (6,7,8 and 9). Screening is recommended in the following situations:

1. Every 5 years in asymptomatic, nonrisk patients older than 50 years.
2. In at-risk patients older than 40 years, in conjunction with air contrast barium enema (ACBE) as an alternative to colonoscopy. At-risk individuals are defined as:
   a. Those with a first-degree relative who was younger than 60 years when diagnosed with colon cancer or adenoma (1,10,11)
   b. Individuals with a previous personal diagnosis of polyps or colorectal cancer (colonoscopy preferred)
   c. Individuals with two or more second-degree relatives with colorectal cancer. If there is a personal or family history of breast, ovarian, or uterine cancer, the risk of colorectal cancer is increased for an individual but no additional screening is recommended.

B. Symptoms.

Because of redundant loops of sigmoid colon and because the insertion tube that is used with a barium enema can obscure a lesion, FS is generally needed with most ACBEs. FS is indicated in addition to ACBE if the entire bowel must be visualized. Individual circumstances dictate whether FS alone or in conjunction with ACBE is indicated. Pertinent symptoms include:

1. Abdominal pain
2. Rectal bleeding (bright red or occult)
3. Constipation or diarrhea
4. Persistent change in usual bowel habits
5. Unexplained weight loss, fever, or anemia

6. Evaluation of radiographic abnormality or to confirm a radiographic finding with biopsy
7. Suspected inflammatory bowel disease or antibiotic-associated colitis
8. Anorectal symptoms (but note that hemorrhoids alone are not an absolute indication for FS or ACBE and must be put into the context of the entire patient history and examination. Medicine will no longer accept “hemorrhoids” as a justification for doing endoscopy.) (12)

II. Contraindications

A.

Acute abdomen

1. Suspected perforation
2. Peritonitis or intra-abdominal sepsis
3. Diverticulitis
4. Bowel infarct
5. Fulminant colitis

B.

Severe cardiopulmonary disease

C.

Inadequate bowel preparation

D.

Lack of subacute bacterial endocarditis (SBE) antibiotic prophylaxis when indicated (see Section IV.E) (13)

E.

Uncooperative patient

F.

Marked bleeding disorder

G.

Relative contraindications (require additional caution)

1. Pregnancy
2. Recent abdominal surgery
3. Distorted pelvic anatomy
4. History of pelvic irradiation
5. Recent barium enema (if still passing barium)

H.

When colonoscopy is indicated (such as in high-risk patients with inflammatory bowel disease who should receive a colonoscopy 8 years after the diagnosis was first made and every 5 years thereafter, for follow-up of colon cancer, and for patients with familial polyposis syndromes)

III. Equipment

A.

Flexible fiberoptic sigmoidoscope (at least 60 cm long; Figure 11.12-1)

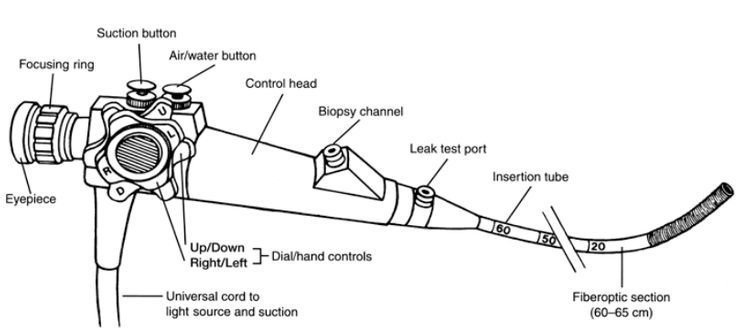

FIG. 11.12-1. Components of the 60-cm flexible sigmoidoscope.

B.

Light source

C.

Suction unit

D.

Biopsy forceps

E.

Lubrication jelly (e.g., KY jelly)

F.

4 × 4-inch gauzes

G.

Nonsterile gloves, shielded glasses

H.

Anoscope (Ive's slotted anoscope preferred)

I.

Basin of water (suction water through scope and immediately place scope into basin after procedure is completed)

J.

Formalin jars for any biopsies

K.

Nursing assistant

L.

Videotape unit and monitor if desired (not necessary for documentation)

IV. Patient preparation

A.

Informed consent

B.

Two Fleet enemas 2 hours prior to procedure (additional 1 or 2 may be necessary until clear return) (14,15)

C.

Laxative and/or magnesium citrate the evening before only if:

1. The patient usually takes it.
2. There is a history of constipation.
3. There was a previous attempt at the procedure with enemas alone without complete cleansing.

D.

Antianxiety agents (e.g., diazepam [Valium], 10 mg PO 1 hour prior) are rarely indicated.

E.

Antibiotic prophylaxis (13) (see Chap. 22.1)

1. Antibiotic prophylaxis is generally not recommended for endoscopy procedures with or without biopsy.
2. It is prudent to give prophylaxis where high risk exists, as with the following:

a. Prosthetic valves
b. History of bacterial endocarditis
c. Surgically constructed systemic pulmonary shunts or conduits

3. Give ampicillin, 2.0 g IV, combined with gentamicin, 1.5 mg/kg IV, 30 minutes before the procedure and 8 hours later, or a single oral dose of amoxicillin (3.0 g 1 hour before and 1.5 g 6 hours after the procedure) may be used instead. Vancomycin, 1.0 g IV, is a suitable substitute for patients who are allergic to penicillin.

F.

It is generally permissible to do the following:

1. Take fluids on the morning of the examination.
2. Take any usual medications.

V. Technique

(16,17)

A.

Perform an abdominal examination on the patient in the supine position.

B.

Turn the patient to the left lateral decubitus (Sims') position for FS examination.

C.

Lubricate the scope and anoscope with KY jelly.

D.

Perform a digital examination with lubricant.

E.

The operator inserts the scope gently until resistance is felt (usually 15 cm).

F.

Insufflate the bowel by covering the air button, which is the button closest to the patient. Covering the opening introduces air; depressing the button with sharp, intermittent strokes introduces water to clean the lens. Use enough air to open the lumen but not so much as to cause pain.

G.

Two methods of further insertion

1. The operator controls movement knobs with the left hand and inserts the scope with the right hand.
2. The operator controls the knobs and the assistant inserts the scope with directions from the operator or while watching a monitor. This method is often much easier and more practical, although it is frowned on by many “experts.” Those with smaller hands find it difficult to manipulate both knobs of the scope with the left hand, making the two-person technique more practical. Nursing assistants soon learn the feel of the scope and the operator's technique. After an operator and an assistant have worked together for a while, no words need be spoken; instead, gentle pressure on the scope by the operator lets the person inserting know what to do. Many find this method far superior to the single-person approach and are more successful in completing full insertion.

   Note: Ideally, the scope should be advanced only when the bowel lumen is visualized. If the patient experiences pain, stop. Reassess the position. If the scope is passing easily, without discomfort to the patient, even if the lumen cannot be completely visualized but the bowel wall can be seen “passing by,” it is safe to carefully continue inserting the scope.

H.

Difficulty in passage occurs at approximately 20 cm and at 35–40 cm coinciding with the sigmoid curves. When forward progress is halted by pain or inability to see lumen, stop. Be sure the bowel is adequately inflated. Torque the scope (turn the entire headpiece) to the right and gently withdraw. This straightens the sigmoid loop. Try insertion again, and repeat if necessary. Remember, when forward progress is impeded, withdraw.

I.

Other methods for advancement, including dithering, jiggling, alpha maneuver, and more aggressive torquing, are not covered here.

J.

Advance until the entire 60- to 70-cm scope is inserted.

K.

Thorough examination of the bowel occurs on withdrawal of the scope. All mucosal surface areas must be visualized, especially behind various “valves” and folds. Many will reinsert the scope a second time. It reinserts much more easily because the bowel is now straightened and facilitates a “second look” to ensure that no pathology is missed.

L.

Complete examination of the rectum is mandatory. Rectal lesions will be missed unless one of the two following procedures is done (18):

1. Retroflex the scope so that it turns back on itself. (You will actually see the scope in the anal canal.) Rotate the handpiece of the scope 360 degrees to view the entire area. Surprisingly, the patient experiences little discomfort.

2. Use Ive's slotted anoscope (or other acceptable anoscope) to view the entire area after the sigmoidoscope is withdrawn.

M.

Suctioning

1. If water and mucus obscure the exam, they must be suctioned using the suction button (the one closest to the operator).
2. Depress the button briefly and intermittently, moving the scope slightly in and out. Continuous suction creates a suction polyp by which mucosa is pulled into the suction port and becomes elevated, taking on the appearance of a polyp. Suction polyps can cause an unnecessary biopsy.

N.

Biopsy technique

1. Identify the lesion.
2. Insert the biopsy forceps into the biopsy port.
3. The assistant holds the operating handle of the forceps and follows the endoscopist's directions.
4. When the tip of the forceps is seen protruding from the scope in the bowel lumen, say “Open.”
5. Advance the forceps onto the lesion. Say “Close.”
6. Give a gentle, sharp tug on the forceps and withdraw.
7. Place the specimen in formalin container.
8. Observe the site. Generally, there is minimal bleeding. Obtain another sample if necessary.
9. Generally, any lesion can be biopsied unless it appears vascular or is located inside a diverticulum. The use of hot (electrical) forceps requires special precautions and a full bowel prep is needed to avoid methane gas explosions. Complications from biopsy are almost nonexistent.

O.

On completion of the examination, remove all air from bowel (intermittent suction, moving scope gently forward and back) as above. Ask the patient to tell you when it feels like all air is gone; then go a little longer. Immediately suction water through the scope. Place the entire scope in the basin of water.

P.

Patient is discharged home. No special follow-up is needed. Report excessive pain, fever, or bleeding.

VI. Significance of polyps

(19)

A.

Virtually all cancer starts in polyps.

B.

Hyperplastic polyps require no further follow-up. They are generally less than 5 mm.

C.

Adenomatous polyps (tubular, tubular villous, and villous) require a total-bowel examination (colonoscopy).

D.

Cancer risk increases in larger polyps (greater than 1 cm), when there are numerous polyps and in those with more villous content.

E.

All polyps should be biopsied, especially smaller ones. If the polyp is found to be hyperplastic, a colonoscopy can be avoided. Colonoscopy is indicated for all adenomatous polyps of any size (20,21).

VII. Cleaning and disinfection.

Proper cleaning of the scope is essential for patient protection and proper function. Most equipment problems occur because of inadequate cleaning. The company representatives provide cleaning instructions that require close, absolute adherence (22,23).

VIII. Complications

(24)

A.

Major complications (listed here) are extremely rare.

1. Bowel perforation.
2. Bleeding.
3. Missed pathology (up to 3%).
4. Bacterial endocarditis, but prophylaxis of all patients is not indicated.
5. Bacterial and hepatitis B virus transmission. No reports of HIV transmission.

B.

Minor

1. Abdominal pain or distention (usually secondary to air) common.
2. Vasovagal reaction.

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XII. RENAL AND UROLOGIC PROBLEMS

12.1
CYSTITIS AND BACTERIURIA

Evan A. Ashkin

I. Etiology

Cystitis and bacteriuria are caused by similar organisms in adults and children. In uncomplicated cystitis, two organisms are responsible for a majority of infections: *Escherichia coli* accounts for 70%–90% of cases, and *Staphylococcus saprophyticus* accounts for 5%–20% of infections. Complicated infections are still predominantly *E. coli* but are associated with a higher population of other Enterobacteriaceae, *Proteus mirabilis, Klebsiella* species, and *Serratia*. Other pathogens include *Enterococcus, Pseudomonas aeruginosa,* and *Candida* species. Urinary catheter-associated infections may be polymicrobial and account for 40% of all nosocomial infections (1). In 10%–15% of cases, standard culture methods do not detect bacteria. Fastidious organisms, such as *Ureaplasma urealyticum* and *Chlamydia hominis,* may have a role in these cases (2).

II. Diagnosis

A. Complicated versus uncomplicated.

For diagnostic and treatment purposes in adult females and young males, cystitis must be classified as either complicated or uncomplicated. A complicated infection is associated with a condition that increases risk for acquiring infection or failing therapy (2). Cystitis is considered complicated in diabetics, pregnant and postmenopausal women, patients with a genitourinary (GU) abnormality or renal calculi, and those with an atypical presentation or recent history of receiving GU instrumentation or antibiotics. In children and older men, urinary tract infection (UTI) is always treated as a complicated infection.

B. History and physical.

Cystitis generally presents with sudden onset of dysuria, urinary frequency, and urgency. Gross hematuria, when present, helps distinguish UTI from genital herpes simplex and vaginitis. Flank pain, fever, nausea, vomiting, and rigors are indicative of upper tract disease. Children often present with enuresis. Infants may present with poor feeding, irritability, vomiting, and diarrhea (3). A physical examination of the genitalia, abdomen, and flank is often helpful in establishing a diagnosis.

C. Urinalysis.

Pyuria is present in almost all cases of cystitis. Urinalysis of a mid-stream voided specimen, after careful periurethral washing, often establishes the presence of pyuria. Leukocyte esterase (LE) screening on a dipstick has a sensitivity of 75%–96% and a specificity of 94%–98% in detecting more than 10 leukocytes per high-power field (hpf) or more than 10^5 uropathogen colony-forming units (cfu) per milliliter of urine. In symptomatic patients where LE is negative, microscopic analysis is indicated to identify pyuria. Nitrite dipstick analysis and microscopic evaluation for bacteria are too insensitive to be recommended for screening; however, a positive nitrite dipstick is highly specific for the presence of gram-negative bacteria. In infants and pre-toilet-trained children, a urine bag may be acceptable for specimen collection unless the child is ill. Suprapubic aspiration or catheterization must be preformed on all ill-appearing children younger than 2 years or when the urine bag specimen is suggestive of UTI (4).

D. Urine culture.

In symptomatic women, significant bacteriuria has been recently redefined as 10^2 uropathogen cfu/mL, with a sensitivity of 95% and specificity of 85% for acute cystitis. UTI may be diagnosed in young men with 1,000 uropathogen cfu/mL with a sensitivity of 97%. Asymptomatic bacteriuria is defined as 10^5 uropathogen cfu/mL. In uncomplicated acute cystitis in women a urine culture is not necessary. A urine culture should be obtained in all children, in all men, and in women with complicated infections.

III. Treatment.

A short course of antimicrobial therapy may be used in women with uncomplicated cystitis. Three days of therapy with fluoroquinolones or trimethoprim-sulfamethoxazole in areas with less than 10% resistant strains of

E. coli may be used. Single-dose therapy is not reliably effective (2). Longer courses of treatment are recommended for all other infections.

A. Uncomplicated cystitis in women.

1. Three-day regimens. Trimethoprim-sulfamethoxazole (Bactrim DS, Septra) one double-strength tablet bid, trimethoprim (Priloprim) 100 mg bid, norfloxacin (Noroxin) 400 mg bid, ciprofloxacin (Cipro) 250 mg bid, ofloxacin (Floxin) 200 mg bid, levofloxacin (Levoquin) 250 mg daily, cefixime (Suprax) 400 mg daily, cefpodoxime (Vantin) 100 mg bid.
2. Seven-day regimens. Nitrofurantoin monohydrate (Macrobid) 100 mg bid, nitrofurantoin (Macrodantin) 100 mg qid; all drugs listed for *3-day regimens* may be used for 7 days.

B. Complicated UTI.

Treat for 10–14 days with any of the drugs listed for *3-day regimens.*

C. UTI in Young men.

Seven days of trimethoprim-sulfamethoxazole or fluoroquinolones as listed under *3-day regimens.*

D. Asymptomatic bacteriuria and cystitis in pregnant women

(all drugs listed are pregnancy category B) 7–10 day regimens of, cephalexin (Keflex) 250 mg bid-qid, nitrofurantoin 100 mg qid, nitrofurantoin monohydrate 100 mg bid, erythromycin 250–500 mg qid, amoxicillin-clavulanic acid (Augmentin) 500 mg bid (5).

E. UTI in children.

Seven to ten days of therapy is adequate if there is no evidence of upper tract disease. Amoxicillin 20–40 mg/kg per day in 3 doses, trimethoprim-sulfamethoxazole, 6–12 mg trimethoprim, 30–60 mg sulfamethoxazole per kilogram per day in 2 doses, cefixime 8 mg/kg per day in 2 doses, cefpodoxime 10 mg/kg per day in 2 doses, cefprozil (Cefzil) 30 mg/kg per day in 2 doses, cephalexin 50–100 mg/kg per day in 4 doses, loracarbef (Lorabid) 15–30 mg/kg per day in 2 doses (4). Increasing resistance of *E. coli* to amoxicillin make it a less reliable choice.

IV. Special circumstances

A. Children.

Workup of children with UTI is essential as recurrent upper tract infections can cause renal damage with long-term sequelae. Infants and children younger than 5 years should receive treatment or prophylactic antibiotics until imaging studies are done. Ultrasonographic imaging of the urinary system and either voiding cystourethrography or radionuclide cystography should be performed. In cystitis after age 5 years, workup is indicated after one or two infections. In such children, if urinary system ultrasonographic scan is normal no further evaluation is needed.

B. Pregnancy.

Pregnant women have a prevalence of asymptomatic bacteriuria of 10% and are at increased risk for UTI, which can cause intrauterine growth retardation, low birth weight, and increased risk for preterm birth. Routine screening and treatment is recommended by obtaining a urine culture at 12–16 weeks' gestation (5).

C. Recurrent cystitis in women.

Cystitis recurring during the first week following treatment should be considered as a relapse. Management should consist of pretreatment urine culture and antimicrobial sensitivity testing, followed by 7 days of fluoroquinolone therapy. Recurrences that occur after a week can be treated as uncomplicated cystitis. Women with more than three infections yearly may be managed by self-treatment with a 3-day regime, continuous prophylaxis for 6 months with nitrofurantoin 50–100 mg daily, trimethoprim-sulfamethoxazole half a double-strength tablet daily, norfloxacin 200 mg daily, cephalexin 250 mg daily, or trimethoprim 100 mg daily, or, if associated with intercourse, postcoital prophylaxis with trimethoprim- sulfamethoxazole half a double-strength tablet (1).

D. Catheter-associated UTI.

Symptomatic infections can be diagnosed with as little as 100 cfu/mL. Treatment should be with fluoroquinolones for 10–14 days. Patients with catheters who have asymptomatic bacteriuria should not be treated unless they are immunosupressed, at high risk for bacterial endocarditis, or about to undergo GU instrumentation (1).

E. Asymptomatic bacteriuria.

Defined as $\leq 10^5$cfu/mL, asymptomatic bacteriuria should only be treated in pregnant women, patients with renal transplants, and patients scheduled to undergo GU procedures.

V. Prevention.

In male infants circumcision may reduce the incidence of UTI. Voiding dysfunction in both children and adults leads to increased risk for UTI, and diagnosis and treatment can be preventative. In some women, voiding before and after intercourse and drinking cranberry juice may be effective in preventing cystitis. Urinary catheterization should be done sparingly. If needed for prolonged use suprapubic and condom catheters have lower rates of UTI. Aseptic technique in placing catheters and use of silver alloy catheters in patients at high risk for UTI is also beneficial.

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12.2
PYELONEPHRITIS

Garfield C. Pickell

Pyelonephritis is characterized by bacterial invasion of the renal parenchyma. Some combination of the following signs and symptoms is usually present, but in elderly or compromised patients, any or all may be absent: urinary frequency, urgency, dysuria, suprapubic pain, flank pain, costovertebral angle tenderness, fever, general malaise, nausea and vomiting, prostration, bacteriuria, pyuria, and hematuria. Cultures typically grow more than 10^5 organisms per milliliter, but, particularly with fastidious or nosocomial organisms, 10^3 organisms per milliliter may be consistent with renal infection. Bacteremia and sepsis complicate untreated pyelonephritis (more often when there is underlying pathology or debilitation) and necessitate early diagnosis and presumptive therapy.

I. Diagnosis

A. Subjective.

Adults typically present with fever, low back pain, costovertebral angle pain, general malaise, and, often, dysuria, nausea and vomiting, or diarrhea. A significant proportion of adults present only with lower tract symptoms: frequency, dysuria, urgency, and suprapubic discomfort. In infants, small children, and the aged, the presentation may be vague, with irritability, lethargy, altered mentation, anorexia, and, eventually, dehydration. Onset may be insidious, or acute—as, for example, following traumatic removal of an indwelling catheter over a chronically infected prostate—and may be associated with sepsis.

B. Objective.

Physical examination is normal in 50% of patients. Suprapubic tenderness, diffuse abdominal or flank tenderness, costovertebral angle

tenderness, flushing, tachycardia, hypotension, fever, and signs of dehydration may be present.

C. Investigations

1. **Urinalysis.** Unless the affected kidney is obstructed, there is pyuria (>10 white blood cells (WBC)/mm^3) usually bacteriuria, and often hematuria, white cell casts, and proteinuria.
2. **Hematology and chemistry**
   a. Leukocytosis with left shift is usually present.
   b. Elevated blood urea nitrogen (BUN), creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and electrolyte disturbances in more severe disease.
   c. **Bacterial cultures** (usually positive)
      a. *Escherichia coli*, other Enterobacteriaceae, *Staphylococcus saprophyticus*, and *Enterococcus* still account for more than 90% of cases.
      b. *Klebsiella, Enterobacter,* and *Proteus* are becoming more common.
      c. Sexually transmitted disease (STD) pathogens are common in at-risk populations.
      d. *Serratia, Pseudomonas,* and *Staphylococcus epidermidis,* as well as other unusual organisms, are primarily nosocomial (1).
   d. **Other investigations** (usually unnecessary)
      a. Ultrasonography (US) is indicated if obstruction, stones, or pyonephrosis suspected.
      b. Intravenous pyelography (IVP) is relatively contraindicated
      c. If US is nonspecific, consider computed tomography (CT). Obstructed pyelonephritis is a closed-space infection (abscess) and requires immediate urologic drainage.

II. Assessment of severity

A. Uncomplicated

1. Stable (only moderately ill and able to retain oral fluids)
   a. The patient is treated as an outpatient with initial oral or parenteral rehydration.
   b. Initial parenteral followed by oral antibiotics.
2. Unstable (dehydrated or unable to retain oral fluids). Hospitalize and treat with parenteral fluids and antibiotics.

B. Complicated.

Hospitalize all patients with renal insufficiency, uncompensated diabetes, prostration, urinary tract obstruction, nephrolithiasis, sickle cell disease, malignancy, cardiovascular instability, immunosuppressive disorder, congenital urinary anomalies, other concomitant serious disease, infants younger than 6 months, or unstable pregnant patients.

C. Septic patients.

Admit these patients, aggressively rehydrate, and administer parenteral antibiotics. Initiate anticipatory management of potential cardiorespiratory collapse (shock).

III. Treatment

A. Outpatient

1. Oral treatment
   a. A single agent, ofloxacin (Floxin), 400 mg bid, or levofloxacin (Levaquin), is as effective as standard two-drug parenteral regimens in patients able to retain oral fluids. In addition to common urinary pathogens, it is active against *S. aureus, Pseudomonas aeruginosa,* the gonococcus *Chlamydia, Trichomonas,* and *Ureaplasma*.
   b. Ciprofloxacin, levofloxacin, enoxacin, and ofloxacin appear to be equally effective, and oral therapy is as effective as intravenous therapy (2).
   c. Trimethoprim-sulfamethoxazole (TMP 160 mg + SMX 800 mg) bid is as effective in most circumstances at a fraction of the cost.
2. Parenteral treatment followed by parenteral or oral treatment. *Note:* Aminoglycosides are concentrated in renal tissue 5–40 times serum levels and persist for up to a year. Three days of standard-dose gentamicin or a single large dose (10 mg/kg) combined with 14 days of amoxicillin,

a quinolone, or TMP/SMX is as effective as 14 days of combined therapy, and far less toxic and expensive (3).

a. Gentamicin 10 mg/kg IV or ceftriaxone (Rocephin), 1 g IM, with 1 g probenecid PO initially (4). (Probenecid increases the half-life of ß-lactam antibiotics up to twofold without altering peak serum or renal parenchymal levels.)
b. Follow with 14 days of broad-spectrum oral coverage with a quinolone or TMP/SMX (TMP 160 mg and SMX 800 mg) bid.
c. A change in antibiotic is appropriate when culture and sensitivity testing are available in only 5% of cases; and blood cultures are not helpful (5).

B. Inpatient therapy.

Any of the following regimens may be used. (However, if renal function is impaired or undetermined, do not give a second dose of gentamicin.)

Gentamicin, 3 mg/kg per day IV for 3 or 14 days, or single dose 10 mg/kg IV, plus ampicillin, 1 g IV q6h; ampicillin/sulbactam (Unasyn), 2 g IV q6h; TMP, 4 mg/kg, and SMX, 20 mg/kg q12h IV; or ciprofloxacin, 400 mg IV bid alone or with gentamicin; or ceftriaxone 1 g q12h IV alone.

Aztreonam, 1 g/d IM or IV (useful in elderly, debilitated patients with recurring infections and multidrug gram-negative resistance; effective against all gram-negative bacteria, including *P. aeruginosa*)

C. Adjunctive treatment

1. Hydration
2. Pain relief
   a. Give oral or parenteral narcotics for the first 48 hours.
   b. For severe dysuria, give phenazopyridine (Pyridium), 200 mg tid PO.
   c. If severe pain persists after 48 hours, or fever after 96 hours, consider imaging. Pain and fever resolve more quickly with combination therapy
3. If nausea and vomiting are present, give PO or per rectum (PR) antiemetics.
4. If fever is present, give acetaminophen or nonsteroidal anti-inflammatory drug PO or PR.

IV. Complications

A. Treatment failure.

Initial failure of a patient to defervesce in 96 hours should be evaluated for complicating factors.

1. Diagnosis can usually be established by renal US and CT scan.
2. Treatment. If obstruction or perinephric abscess is present, surgical drainage and combination parenteral therapy with ß-lactam antibiotic and aminoglycoside are indicated.

B. Failure of bacteriologic cure.

In the case of failure of bacteriologic cure or early relapse within 1 month, take the following actions:

1. Diagnosis can be made via urinalysis, culture and sensitivity testing, and renal panel.
2. Treat with a 14- to 30-day treatment course with a culture-determined antibiotic.

C. Multiple recurring infections

1. Diagnosis can be made via US for anatomical abnormalities, by renal scan for differential function, or by IVP.
2. Treat with 3- to 6-month suppression therapy with nitrofurantoin, 50 mg/d (more than 50 years of use results in minimal resistance), or TMP/SMX, half a tablet per day, or norfloxacin (Noroxin), 400 mg/d. Suppression therapy often allows for restoration of normal defense mechanisms.

D. Children with recurring infections

1. Diagnosis. Evaluate for reflux or structural abnormalities with US and renal scanning or voiding cystourethrography.
2. Treatment. Suppression therapy (see Section IV.C.2) is appropriate if a minor degree of reflux or anatomical anomaly is present. Surgery may

be indicated but is usually unnecessary. The goal of treatment is prevention of symptoms, scarring, and stone formation.

E. Pregnancy

(also see Chapter 14.6)

1. Diagnosis. Evaluate for complications of pregnancy.
2. Treatment. Hospitalize if the patient is not clearly stable. Quinolones are not approved. If infection is recurrent, suppress with nitrofurantoin 100 mg/d.

F. Geriatric patients

1. Diagnosis
   a. Evaluate for stones, prostatic obstruction, or incomplete bladder emptying with urinalysis, catheterization for residual, and imaging as indicated.
   b. Review hygiene.
   c. Consider estrogen deficiency if the patient is postmenopausal.
   d. Consider chronic bacteriuria.
   e. Expect multiple and resistant organisms.
   f. Consider *Candida* infection in debilitated patients.
   g. Consider other predisposing factors, such as malnutrition, incontinence, immobility, and drugs.
2. Treatment. Treatment should be specific to the problem. Address underlying factors, and consider suppression for chronic bacteriuria if the patient has had an episode of pyelonephritis with uremia or sepsis.

G. Nosocomial infections.

Therapy should cover *P. aeruginosa, S. epidermidis* and *aureus*, and *Serratia marcescens*.

H. Sexually active patients.

For treatment, consider *Trichomonas vaginalis, N. gonorrhoeae, Chlamydia trachomatis*, and *Ureaplasma*.

I. In-dwelling catheters.

Treatment consists of removal of the catheter or suppression. Rotate suppression antibiotics every 6 months. Expect resistant organisms. Avoid long-term catheterization if possible. Suppression prevents sepsis but not bacteriuria.

J. Urosepsis

1. Diagnosis. Consider predisposing factors.
2. Treatment. Consider suppression if predisposing factors are not resolvable.

K. Prostatitis

(see Chapter 12.3)

1. Diagnosis is based on physical examination findings or demonstration of high concentration of bacteria in prostatic secretions or post-massage urine sample.
2. Treatment. Administer TMP/SMX or a quinolone for 1–3 months. If bacteria are not identified, treat with doxycycline, 100 mg bid, for 14–30 days.

L. Epididymitis

1. Diagnosis. Evaluate for STD.
2. Treatment. Requires 30-day treatment.

M. Stones.

To diagnose, follow closely for persistence of urea-splitting organisms, such as *Proteus mirabilis*.

N. Women with frequent recurrences.

Treat with a single dose of nitrofurantoin, 50 mg, or a half-tablet of TMP/SMX, or 100 mg of TMP on mornings after sexual intercourse.

O. Renal failure.

Use ceftriaxone, a quinolone, or aztreonam.

V. Education

A.

Instruct patients in appropriate prophylactic measures.

1. Fluid intake should be at least 1,500 mL/d to enhance recovery, avoid obstruction from urinary sediment, and reduce reinfection in patients with urinary tract abnormalities or catheters.
2. For proper hygiene, see Chapter 12.6 .

B.

Anticipate a preventive or suppressive program in the case of recurrence.

C.

For women, anticipate symptoms of candidal infections.

VI. Follow-up

A.

Urinalysis should be performed in 3–4 days.

B.

Urinalysis with culture should be performed if indicated 7–10 days after completion of treatment.

VI. Cost containment

A.

Administer outpatient treatment where appropriate.

B.

Antibiotic choice. Older, established drugs, such as gentamicin and TMP/ SMX, are as effective as newer, much more expensive drugs for the treatment of community-acquired infections. Oral therapy with any drug is invariably cheaper than parenteral therapy.

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12.3
EPIDIDYMITIS AND PROSTATITIS

Douglas S. Parks

Epididymitis and prostatitis are infections of the male urinary tract that usually are caused by extension of infection from the urethra or the bladder. These infections typically are caused by the usual urinary tract and sexually transmitted disease (STD) pathogens. It is possible to predict the more likely pathogen and start empirical therapy based on the patient's age.

I. Epididymitis

is a bacterial infection of the epididymis that is frequently caused by an ascending urethritis.

A. Clinical presentation.

The patient usually complains of a rapid onset of unilateral scrotal pain, which often radiates up the spermatic cord to the groin and possibly to the flank. This pain is typically followed within 3–4 hours by unilateral swelling, redness, and induration of the scrotum. The testis then swells to twice its normal size. The patient often has fever up to 40° (104°F). Frequently, there is a history of recent urethritis. Physical examination reveals an exquisitely tender, swollen epididymis, which early on is adjacent to a normal testis. Within a few hours, the testis also swells, and it is not possible to differentiate between epididymis and testis by palpation. A reactive hydrocele may develop. Elevating the scrotum above the symphysis (Prehn's sign) may reduce pain.

B. Diagnosis

is based mostly on the clinical presentation. If testicular torsion is missed in the differential diagnosis, the result may be loss of the testis within 6 hours. Torsion is uncommon in men older than age 25. It has an abrupt onset and frequently is accompanied by nausea and vomiting. There may be a past history of similar episodes with spontaneous resolution. On examination early, only the testis is tender. Swelling and edema develop quickly, which makes it impossible to differentiate testis from epididymis. Prehn's sign usually reveals increased pain in torsion. If there is any question of torsion, prompt surgical consultation is indicated to prevent loss of

the testis. Ultrasonography may be useful in determining whether swelling is in the testis or the epididymis. Technetium scans show increased uptake in epididymitis and decreased uptake in torsion.

C. Treatment

consists of appropriate antibiotics and supportive care. Supportive care includes bed rest, scrotal elevation, and pain control. Ice may help within the first 48 hours. For severe pain, consideration can be given to infiltration of the spermatic cord with local anesthetic, such as 1% bupivacaine or 1% lidocaine. Empirical antibiotics should be started promptly. In men older than 35, the most common pathogens are enteric organisms, such as *Escherichia coli*. After obtaining clean-catch urine for culture, antibiotics appropriate for cystitis (such as trimethoprim-sulfamethoxazole, a cephalosporin, or a quinolone) should be administered until culture results are available. In men younger than 35, sexually transmitted pathogens, including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are more common. Following urethral swabs for Gram's stain and culture or antibody testing, an appropriate antibiotic (such as ceftriaxone, 250 mg IM, followed by doxycycline, 100 mg bid for 10 days, or ofloxacin, 300 mg bid for 10 days) should be started.

Any antecedent history of urinary tract infection or urethritis helps in the selection of the best agent. Urethral instrumentation or unprotected insertive anal intercourse makes enteric bacteria more likely. A history of gonorrheal or chlamydial infection in a sexual partner makes these pathogens more common. In any case, improvement should be noted in 3 days. Lack of improvement should be cause for reevaluation of therapy. Any recent sexual partners (contact within 30 days) of men with STD epididymitis should be evaluated and treated (also see Chapter 19.6 and Chapter 19.7).

II. Prostatitis

is an inflammation of the prostate gland, which includes four subcategories. (Prostatic hypertrophy is discussed in Chapter 12.4 .) Acute bacterial prostatitis is an acute, usually gram-negative, bacterial infection of the prostate that typically accompanies an acute bacterial cystitis. Chronic bacterial prostatitis is an indolent infection of the gland and may be a cause of recurrent cystitis. Nonbacterial prostatitis is a chronic inflammation of the gland with no identifiable cause. Prostatodynia is a clinical diagnosis with irritative voiding symptoms and pelvic pain but no evidence of inflammation in prostatic secretions.

The National Institute of Diabetes, Digestive and Kidney Diseases has proposed another classification system which comprises Category I: Acute Bacterial Prostatitis; Category II: Chronic Bacterial Prostatitis; Category III: Chronic Pelvic Pain Syndrome which includes IIIA: Inflammatory (analogous to nonbacterial prostatitis in the traditional scheme) and IIIB: Noninflammatory (analogous to prostatodynia). There is also a Category IV: Asymptomatic Inflammatory Prostatitis, which refers to prostatitis that is asymptomatic but found incidentally on biopsy.

A. Clinical presentation.

The patient with acute prostatitis usually presents with a short history of perineal pain, dysuria, urinary frequency, hesitancy, urgency, and nocturia. Pain frequently radiates to the sacrum and down the penis and sometimes to the rectum. Urinary retention may occur. Hematuria may be present, as may a purulent urethral discharge. Fever is usually present, sometimes with chills and muscle aches. In severe cases the patient may be septic. On examination, the prostate is usually tender. In chronic prostatitis, these symptoms are minor and, except for intermittent exacerbations, may be totally absent. The only symptom of chronic prostatitis may be recurring cystitis. Nonbacterial prostatitis presents in the same way as chronic prostatitis, and prostatodynia presents mostly with pain and irritative symptoms, such as weak stream and frequent voiding.

B. Diagnosis

is based on the clinical presentation in acute bacterial prostatitis. Care should be taken to not massage the prostate in acute prostatitis because this may cause bacteremia and sepsis. Clean-catch urine should be obtained for culture, and urethral cultures should be done if there is evidence of urethritis. Blood cultures should be obtained if there is high fever or evidence of

sepsis. Chronic bacterial prostatitis is difficult to diagnose on clinical grounds alone; therefore, a high index of suspicion should be maintained. The prostate is usually soft and boggy. Urinalysis may be negative. Urine culture also may be negative, but expressed prostatic secretions or ejaculate may show more than 15 leukocytes per high-power field, and cultures are usually positive. Differential cultures may be necessary to differentiate chronic prostatitis from urethritis or cystitis. In this technique, the first 10 mL of urine in a void (VB_1), 10 mL from midstream (VB_2), expressed prostatic secretions (EPS) obtained by prostate massage, and 10 mL of urine following massage (VB_3) are obtained and examined microscopically and quantitatively cultured. If VB_1 shows the highest numbers of white blood cells (WBCs) and colonies on culture, urethritis is diagnosed. If VB_2 is highest, cystitis is more likely. If EPS or VB_3 (or both) are highest, chronic bacterial prostatitis is confirmed. Nonbacterial prostatitis shows WBCs, but culture results are negative. Prostatodynia shows neither WBCs nor positive culture results. A screen that can be done as an alternative in patients with no evidence of urethritis is the pre- and postmassage test. Urine specimens are obtained before and after prostatic massage and then compared for presence and amount of bacteria and leukocytes. This is analogous to comparing VB_2 and VB_3 and is nearly as accurate.

C. Treatment

is guided by the results of cultures. Most infections are due to common urinary pathogens, and empirical therapy can be selected on that basis. Severe acute prostatitis should be treated with parenteral antibiotics followed by 3–4 weeks of oral antibiotics. Less severe infections can be treated with oral antibiotics only. In the acute phase, nearly all antibiotics penetrate the inflamed prostate. Penetration of the gland is more of a problem in chronic bacterial prostatitis. Treatment should continue for a minimum of 4 weeks, and 6 weeks is more typical. Antibiotic choices include trimethoprim-sulfamethoxazole (double-strength bid), tetracycline (250–500 mg qid), norfloxacin (400 mg bid), ciprofloxacin (500 mg bid), or ofloxacin (200–400 mg bid). Following treatment, cultures should be repeated. Supportive treatment includes rest, analgesics (nonsteroidal anti-inflammatory drugs are often helpful), hydration, and stool softeners. Warm sitz baths also may provide relief. If urinary retention is a problem, suprapubic bladder drainage may be considered. A Foley catheter should not be placed because of an increased risk of sepsis.

Nonbacterial prostatitis, which unfortunately is the most common form of prostatitis, is notoriously refractory to treatment. A few patients respond to an empirical trial of an antibiotic that covers the atypical bacteria (e.g., *Ureaplasma* and *Chlamydia*), such as doxycycline, erythromycin, or a quinolone. Avoidance of caffeine, alcohol, and spices may be indicated, especially if the patient finds that these substances aggravate his symptoms. Otherwise, supportive measures are the only therapy currently available. Prostatodynia with annoying irritative symptoms may respond to an α-adrenergic blocking agent, such as prazosin (1–2 mg/d or bid) or terazosin (5–10 mg/d).

12.4

BENIGN PROSTATIC HYPERPLASIA

Robert M. Guthrie

Benign prostatic hyperplasia (BPH) is the most common benign tumor among men. Anatomical enlargement of the prostate begins in the fifth decade and increases progressively with age, so that nearly 85% of men at age 80 are afflicted with BPH (1). The symptoms of BPH are only weakly related to the size of the prostate. Symptoms

are instead affected mainly by dynamic factors that increase the smooth muscle tone in the prostate and urethra, particularly in younger men (2). In the 1990s, the advent of medical treatment has changed the status of BPH away from a surgical disorder to a primary care disorder, with transurethral resection of the prostate (TURP) surgery reduced by 43% from 1991 to 1995 (3).

I. Diagnosis

A. Clinical presentation.

The diagnosis of BPH is essentially clinical. The patient's history of BPH symptoms is crucial and is best obtained through the American Urological Association (AUA) BPH symptom index (Table 12.4-1). This seven-question, self-administered questionnaire is a quick, reliable, objective measure of a patient's symptoms, and it can be also used to screen patients for symptomatic BPH (4). Simply total the scores for the seven questions together. A score of 7 or lower signifies mild disease, not requiring treatment. A score of 8—19 represents moderate disease, and a score of 20–35 severe disease.

Question	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. During 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. During the last month or so, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
3. During the last month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. During the last month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. During the last month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. 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. 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?	None (0)	1 time (1)	2 times (2)	3 times (3)	4 times (4)	5 or more times (5)

[a] American Urological Association symptom score = sum of questions 1–7.
From Barry M, et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. *J Urol* 1992;148:1549, with permission.

Table 12.4-1. The American Urological Association symptom index [a]

B. Physical examination

should include a digital rectal examination to check for nodularity that might indicate prostate cancer and to evaluate the size of the gland (also see Chapter 12.5). A focused neurologic examination should be performed.

C. Laboratory tests

required are limited. A urinalysis for signs of infection and proteinuria, indicating possible renal disease, or hematuria, possibly indicating malignancy in the urinary tract, is important, as is a serum creatinine to assess renal function. A prostate-specific antigen (PSA) test is optional (5). Uroflowmetry and postvoid residual test are optional and not necessary in initial evaluation. Invasive studies, such as cystoscopy and intravenous pyelography, are not indicated.

D. Urologic referral

is required only when there are indications of cancer—prostate nodule, elevated PSA, or hematuria—or when there is severe obstruction that indicates surgery, including refractory retention, recurrent infection, significant hematuria, or renal insufficiency (5).

II. Treatment

in a patient for whom surgery is not mandated by obstruction or severe symptoms is based on the patient's AUA score and by patient choice. If the AUA score is 7 or lower, no treatment is indicated. If the AUA score is 8–19 (moderate) or 20–35 (severe), medical therapy or surgery should be presented to the patient as probably beneficial.

In previous years, patients with symptomatic BPH had only two treatment options: urologic surgery and watchful waiting. New medical options are now available. There are, at this point, no clear guidelines as to which therapy is best for any individual patient.

A. Watchful waiting

is a reasonable alternative for some patients with AUA symptom scores greater than 7. It should be presented as one therapeutic alternative for the patient to consider. Watchful waiting is inexpensive and without side effects. As many as 42% of patients have symptom improvement with watchful waiting (5).

B. α-Blockers

are excellent agents in the treatment of symptomatic BPH. Originally developed as antihypertensive agents, α-Blockers act through a reduction of smooth muscle tone. In addition to lowering elevated blood pressure, this effect reduces muscle tone in the prostatic area and reduces BPH symptoms. This reduces the “dynamic” component of BPH symptoms, which are related to the large number of α receptors in the prostate and bladder neck.

Still used as antihypertensive agents, two traditional α-Blockers, doxazosin (Cardura) and terazosin (Hytrin), are currently marketed in the United States for treatment of symptomatic BPH. Tamsulosin (Flomax), a new α-Blockers, is marketed for BPH symptoms but not for hypertension. All three appear to be extremely similar in effectiveness and side effects. In double-blind trials, each agent produced 60%–70% reductions in BPH symptoms and nearly 50% improvement in urinary flow rates (6,7 and 8).

1. Dosing of doxazosin and terazosin needs to be done correctly for maximum effectiveness and avoidance of side effects. Because starting at an advanced dose can produce dramatic symptoms (chest pain, tachycardia), dosing must be begin at the lowest dose, preferably at bedtime, with 1 mg of either terazosin or doxazosin. The dose should then be increased to 2 mg and higher every 1–2 weeks until the patient has improved significantly or the effective dose has been reached. It is important to increase the dose gradually until the effective dose is reached, namely, doxazosin, 4–8 mg, or terazosin, 5–10 mg. Tamsulosin can be initiated at the therapeutic dose of 0.4 mg without titration.
2. Patient monitoring for α-blocker use is quite simple. Several studies have shown that they do not lower blood pressure in normotensive patients (8,9,10 and 11), but baseline and follow-up blood pressure should be monitored. AUA symptom scales should be repeated at follow-up visits to determine the improvement in symptoms. Blood counts should be monitored periodically for reduction in white or red cell counts.
3. Side effects are mild and are usually well tolerated. Most common is malaise or fatigue, seen in 6%–12% of patients, along with dizziness in approximately 10%. Orthostatic hypotension and pedal edema are other side effects of doxazosin and terazosin. Using an evening rather than a morning dosing may reduce those symptoms and has been shown to produce the same effectiveness as morning dosing (9). Tamsulosin may have fewer orthostatic symptoms, but it produces ejaculation disorders in about 15% of patients (8).

C. Finasteride (Proscar)

inhibits the enzyme that converts testosterone to dihydrotestosterone, on which growth of the prostate is dependent. It had been hoped that reduction of an enlarged prostate would bring about an improvement in the BPH symptoms and urine flow rate. The effectiveness of finasteride, particularly in the primary care setting, remains unproven. A 5-mg dose produces significant reduction in the size of the prostate after 6 months. The improvement in BPH symptoms at 12 months is 20%–30%, however—about half that seen with α-Blockers. This has led to controversy, with Lepor arguing that there is only a subset of patients who benefit symptomatically from finasteride (12). Recent information confirms this, with finasteride producing reduction in BPH symptoms only when there are BPH symptoms **and the prostate is quite enlarged**

(13). Two recent studies showed that, while doxazosin and terazosin reduced symptoms, **the effect of finasteride was no different from that of placebo**, either used alone or when combined with the α-blocker (14,15). Combination therapy of finasteride and an α-blocker should not be used regularly in primary care. Finasteride has been shown to reduce urinary obstruction and prostate surgery, but only on men with BPH symptoms, decreased urinary flow rates, and enlarged prostate glands (patients not typical for primary care) (16).

1. Dosing of finasteride is simple. Patients are started on the 5-mg dose, and no dose titration is necessary. This dose should be continued for a full 12 months for a complete therapeutic trial.
2. Side effects of finasteride are mild and are primarily in the area of sexual functioning, including loss of libido (4.8%), impotence (5%), and ejaculatory disorders (3.5%). No specific laboratory monitoring is required. Finasteride does, however, reduce a patient's PSA, and this needs to be considered when following patients on finasteride (see Chapter 12.5).

D. Saw palmetto

is a popular plant extract marketed directly to consumers for BPH symptoms. Its effectiveness is unproven because of a lack of large, placebo-controlled trials. Two large recent studies show that it has symptom reduction similar to that of finasteride in short-term treatment (17,18). As finasteride was recently shown in these types of patients not to be an improvement over placebo, this implies that much, if not all, of saw palmetto's effect is placebo effect.

E. Surgical referral

has absolute indications (urinary retention, recurrent infection, obstructive uropathy, hematuria, and possible malignancy) and relative indications, including failure of nonsurgical therapy, patient or physician preference, and severe symptoms.

The vast majority of surgical procedures for prostate disease are TURPs. The TURP procedure is safe, with a mortality of only 0.2% and a postoperative morbidity of 18%, with infection, sexual dysfunction, and incontinence being the major complications (19). The necessity of a repeat TURP after many years is about 18%, but this statistic was generated before the availability of medical therapies (20). TURP is extremely effective in reducing BPH symptoms by about 80%–85% (21).

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12.5
PROSTATE CANCER

Richard G. Roberts

Prostate cancer is the most common nondermatologic neoplasm of the American man. In 1999, there were 179,300 new cases and 37,000 deaths from prostate cancer, making it the second most common cause of cancer death in men (1). The controversy around this most prevalent cancer centers on the fact that the vast majority of men with prostate cancer die with it, not of it; whereas 30% of men older than 50 years (and 90% of men older than 90 years) have microscopic prostate cancer, only 3% will die of it (2). Epidemiologic studies associating prostate cancer with cadmium exposure, vasectomy, and a high-fat diet await further confirmation. Family history raises a man's risk several times; black men are at four times greater risk of prostate cancer death than white men.

I. Clinical presentation.

Most men with prostate cancer have no symptoms.

A.

Asymptomatic men with prostate cancer are diagnosed through a screening program, during a routine physical examination, or as an incidental finding at the time of surgery for benign prostatic hyperplasia (BPH). About 10% of prostate cancers are discovered at the time of transurethral resection of the prostate (TURP) for BPH (3). The dramatic increase in prostate cancer rates is thought to be due to increased detection resulting from the more frequent use of prostate-specific antigen (PSA) testing and needle biopsy of the prostate (4).

B.

Local symptoms can mimic BPH, which is a common condition that will affect almost every man who lives long enough (see Chapter 12.4). Symptoms can include urinary frequency, hesitancy, intermittency, nocturia, dribbling, and weak stream. Rapidly progressing symptoms that develop over a few months are more indicative of prostate cancer; symptoms from BPH can remain stable for a number of years.

C.

Metastatic disease most often presents with bone pain, particularly in the spine.

II. Diagnosis

A. Digital rectal examination (DRE)

in the man with prostate cancer may be normal (stage A), reveal a hard nodule confined to the prostate gland (stage B), or demonstrate lateral extension from the prostate to the seminal vesicles (stage C). DRE has a positive predictive value of 0.24, i.e., there is a 24% probability that a man with an abnormal DRE suggestive of prostate cancer will have prostate cancer (5).

B. Prostate-specific antigen

is a serine protease secreted by the prostate that helps to liquefy the seminal coagulum. In serum, most PSA is complexed with α_1 -antichymotrypsin, with 5%–40% being free (6). PSA levels can be elevated (higher than 4 ng/mL) in prostate cancer, BPH, prostatitis, and following prostate biopsy. DRE does not appear to increase the PSA level. About one third of men with a PSA greater than 4 have a cause of the elevation other than prostate cancer; about one-fourth of men with prostate cancer have a PSA less than 4. The higher the PSA, the greater the chance that it is due to prostate cancer (7). An abnormal DRE, when combined with a PSA greater than 4, improves the positive predictive value to 0.49—about the same odds as flipping a coin. Several approaches have been proposed to improve the accuracy of PSA testing, including PSA density (PSA level divided by ultrasonographically estimated prostate volume), PSA velocity (rate of increase of PSA over time, said to be worrisome if more than 0.7 ng/mL per year), and age-specific PSA (an acknowledgment that the prostate enlarges with aging with PSA levels expected to increase such that a PSA higher than 2.5 is abnormal in a 49-year-old man but a PSA lower than 6.5 is normal in a 70-year-old

man) (8). The greatest enhancement to PSA accuracy appears to be with percent free PSA, with lower levels more likely to represent prostate cancer. For example, a free PSA level of less than 15% improves the positive predictive value to 76% and the negative predictive value to 53% that a man has organ-confined prostate cancer (9).

C. Transrectal ultrasonography

involves placement of an ultrasound transducer in the rectum. Transrectal ultrasonography is most commonly done to guide needle biopsy; it is not a very accurate screening or diagnostic tool for prostate cancer (10).

D. Needle biopsy,

usually guided by ultrasound, has made histologic sampling of the prostate relatively easy and safe. Major complications, usually bleeding, occur less than 2% of the time. Samples are taken from both lobes at four (quadrant) or six (sextant) sites.

E. Staging of prostate cancer

is intended to separate men with cancer localized to the prostate (stage A = nonpalpable or stage B = palpable), who are thought to have the best chance for cure, from men with spread beyond the prostate capsule (stage C = local extension or stage D = regional nodes or distant metastases), who are believed to be beyond cure and have treatment focused on palliation of symptoms (e.g., urinary obstruction, bone pain). Staging can often require evaluation of pelvic lymph nodes by laparoscopy, laparotomy, or imaging studies, such as computer tomography. Tumor aggressiveness is assessed using a Gleason score: The degree of histologic normalcy is estimated on a scale of 1 (well differentiated) to 5 (anaplastic). The two most dominant sections of the specimen are scored and their scores are added to determine the Gleason score. Tumors with Gleason scores higher than 7 are very aggressive and have a high probability of progression, regardless of treatment.

III. Management

of prostate cancer depends on its stage. The aim of managing early disease, localized to the prostate, is to achieve cure; the goal for management of advanced disease that has spread beyond the prostate capsule is palliation of symptoms.

A. Localized disease

is usually managed with watchful waiting, radical prostatectomy, or radiation therapy. The dilemma in deciding whether, or how, to treat localized disease is that there are no studies that demonstrate improved mortality with earlier detection or treatment of prostate cancer.

1. **Watchful waiting.** Men with low-grade, early-stage prostate cancer who are treated conservatively have life expectancy similar to men in the general population (11). A 10-year follow-up of men with localized disease showed no difference between men who underwent radical prostatectomy and men who were treated with watchful waiting (12). Invasive therapy may be of benefit for men younger than age 65 with localized tumors that are moderately or poorly differentiated (13).
2. **Radical prostatectomy.** Most advocates of aggressive therapy for localized prostate cancer do not recommend surgery if the man has less than a 10-year life expectancy, which is about 74 years for an otherwise healthy American man. Radical prostatectomy rates have increased dramatically and show marked geographic variation, with men in the western United States much more likely to have surgery than men in the eastern part of the country. A disturbing trend is that the rate of increase in radical prostatectomy is as great in men older than 75 as in younger men (14). Radical prostatectomy complications include death (1-2%), impotence (60%), some degree of urinary incontinence (63%), and urethral stricture (12%) (15,16).
3. **Radiation therapy** has traditionally been used for older men with higher grade, more advanced tumors. Radiation may be provided by external-beam irradiation or by interstitial implants (17). Risks of radiation treatment include death (0.2%), some degree of urinary incontinence (6%), bowel injury (11%), and impotence (41%).

B. Advanced disease

may require surgical resection (TURP, radical prostatectomy) for relief of urinary obstructive symptoms. Radiation therapy is often used for relief of pain from bony metastases. The mainstay of symptomatic advanced disease is hormone therapy with the options outlined below. The goal is symptom control, not cure. Side effects common to all the methods of androgen ablation include gynecomastia, hot flashes, and decreased libido and potency.

1. Orchiectomy reduces testosterone levels and can be done on an outpatient basis with use of local anesthesia. Its main advantage over drug therapy is that compliance with medication prescription is not an issue. No advantage is gained by adding estrogen after orchiectomy. Patient acceptance is the critical determinant of whether orchiectomy is indicated.
2. Estrogen therapy in the form of diethylstilbestrol (DES 1–3 mg/d PO) appears to be more effective when given earlier in the course of the disease. DES at higher doses increases the risk of thromboembolism and cardiovascular toxicity.
3. Gonadotropal releasing hormone agonists suppress luteinizing hormone and decrease testosterone levels over 2–3 weeks. Leuprolide (7.5 mg/mo IM) and goserelin (3.5 mg SC once a month) appear as effective as castration or DES but are expensive.
4. Flutamide (250 mg PO tid) is a nonsteroidal antiandrogen that blocks the binding of testosterone. Its advantage is that potency can be maintained. Disadvantages include cost as well as development of methemoglobinemia and hepatotoxicity.
5. Other agents have been used, such as progestins (megestrol 40 mg PO 2–4 times daily), ketoconazole (400 mg PO every 8 hours), and various chemotherapeutic agents (estramustine, vinblastine, suramin).

IV. Prevention and screening.

The cause of prostate cancer remains unknown; therefore, no methods of prevention have been identified. The theory behind prostate cancer screening programs is that early diagnosis and treatment will improve outcomes; this theory remains unproved. The American Cancer Society recommends annual PSA testing and DRE in men older than 50 years, and similar screening for men older than 40 years who are at high risk (family history, black). However, other authorities, such as the U.S. Preventive Services Task Force, do not recommend screening because of the lack of proven effectiveness and the risk of reduced quality of life resulting from the complications of therapy (18,19) (see Chapter 1.3 and Chapter 1.4). Given the often indolent nature of prostate cancer, no guidelines recommend screening for men with less than a 10-year life expectancy. Primary care physicians appear to be more aggressive about PSA testing and referral for biopsy than are recommended by the most aggressive guidelines (20), and they frequently test outside the recommended age ranges (21). Older physicians and those paid fee-for-service rather than salaries seem to be more likely to recommend PSA testing (22). Patients who receive more information about the benefits and harms of prostate cancer screening are less interested in screening (23). Men are best served when they are given sufficient information to weigh the risks of detection and treatment against the risks of undiagnosed disease (24).

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12.6
CHRONIC RENAL FAILURE

Joseph Hobbs

Chronic renal failure (CRF) is caused by primary glomerulopathies, such as glomerulonephritis (21%), and secondary glomerulopathies, such as diabetes mellitus (28%), tubulointerstitial diseases, obstructive uropathy, uncontrolled hypertension (25%), and renal vascular diseases. The glomerular injury and permanent glomerular loss is caused by an inflammatory response to both immunologic and nonimmunologic factors that ultimately lead to glomerulosclerosis, proteinuria, and progressive decline in renal function (1). Renal function loss (less than 50%) results in a common adaptive response of the remaining glomeruli, which, depending on the amount of glomerular loss, maintains renal excretory function. If renal functional loss exceeds 50%, CRF is more likely to ensue. CRF is associated with a functional or structural obstruction of postglomerular capillaries, glomerular hypertension, glomerular hypertrophy, epithelial foot process fusion, mesangial expansion, and glomerulosclerosis. Other factors possibly contributing to the predictable decline in renal function in CRF include systemic hypertension, increased renal prostaglandins, dietary protein, phosphate retention, and hyperlipidemia (2).

I. Age-related decline in renal function.

Declining renal function with age affects the management of fluid and electrolyte disturbances and the use of potentially nephrotoxic drugs. This age-related decline in renal function is caused by a slow, progressive sclerosis and fibrosis of functional excretory units of the kidney without evidence of primary renal disease, resulting in a decline in creatinine clearance (C_{Cr}) but with a normal serum creatinine. The normal serum creatinine occurs in part because of the decreased muscle mass of older patients, resulting in decreased creatinine production and subsequent decreased urinary creatinine excretion. This age-related decrease in renal function can be assessed by estimating (C_{Cr}) using the following for men:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{\text{Plasma creatinine} \times 72}$$

Multiply C_{Cr} by 0.85 for women.

Decreased renal sodium conservation and excretion capacities in the elderly decreases the compensatory response to deficits or excess in the effective circulating volume. Decreased renal water conservation in the elderly is caused in part by decreased pituitary responsiveness to rising osmolality and a decreased renal responsiveness to antidiuretic hormone, thus increasing susceptibility to hypernatremia when hypotonic volume losses occur.

II. Assessment of chronic renal failure

A. History.

Symptoms associated with CRF do not occur until the final stages in the disease progression, when renal function deterioration is substantial enough to produce uremia [i.e., glomerular filtration rate (GFR) less than 20% of normal]. These symptoms could include fatigue, findings associated with anemia, volume depletion or volume excess, oliguria, and other findings consistent with uremia, including encephalopathy. Many of the earlier historical findings are related to the initiating events (e.g., frequent urinary tract infections) or the underlying disease (e.g., diabetes mellitus) (see Chapter 12.2 and Chapter 17.2). Early identification of CRF in asymptomatic patients or those at increased risk for CRF permits interventions aimed at enhancing the preservation of renal function. Patients at risk for the development of CRF include those with diabetes mellitus, hypertension, vascular disease, dysproteinemia, vasculitis, chronic urinary tract infection, and immune complex-mediated glomerulonephritis (e.g., poststreptococcal infection and systemic lupus erythematosus).

B. Physical.

Abnormal physical findings associated with CRF also occur late in the process, except those related to underlying disease processes. Late findings include edema, hypertension, pallor, easy bruising, bone pain, cardiac dysrhythmias induced by hyperkalemia, asterixis, and other neurologic manifestations of uremia.

C. Laboratory assessment.

When the discovery of renal dysfunction occurs as a result of routine laboratory assessments, it is necessary to determine whether the renal failure is an acute process, caused by prerenal, renal, or postrenal factors, or a chronic process.

1. **Assessment of acute renal failure.** Prerenal azotemia is usually characterized by a blood urea nitrogen (BUN) and creatinine elevation at ratios greater than 20:1, urinary sodium concentration (U_{Na}) less than 10–20 mEq/L, and urinary osmolalities (Uosm) greater than 450 mOsm/ kg, acellular urinary sediments, and a fractional excretion of sodium (FeNa) of less than 1%. The renal etiologic factors involved in acute renal failure cause BUN and creatinine elevation at ratios of 10:1, U_{Na} exceeding 20–30 mEq/L, Uosm less than 350 mOsm/kg, urinary sediment with renal tubular cells and casts, and FeNa greater than 1%. In postrenal causes of acute renal failure, assuming bilateral obstruction, the initial findings may be similar to those of prerenal disease, but in time U_{Na} will exceed 20–30 mEq/L, FeNa will be greater than 2%, and urine dilution will ensue.

2. **Assessment of chronic renal failure.** In chronic renal disease, when functional decline progresses more rapidly than anticipated by the reciprocal of creatinine over time, a superimposed acute process could be present. Such acute deterioration of renal function in CRF can be caused by congestive heart failure, overdiuresis, excessive insensible volume loss, gastrointestinal (GI) volume loss, hypotension, and other factors, such as uncontrolled hypertension, exposure to nephrotoxic substances, infections, urinary tract obstruction, and renal vein thrombosis. These and other causes of acute renal disease often result in a reversible decline in renal function, which can result in permanent functional decline if the causes are not rapidly corrected.

   Evaluations of CRF should proceed when BUN and serum creatinine are elevated, assuming that causes of acute renal failure have been eliminated in patients at risk for chronic renal damage, even when these initial findings are not present, because only minimal changes in serum creatinine occur before the GFR falls below 50% of normal. An initial estimation of GFR can be obtained by determining the C_{cr} using a 24-hour urine collection. A reduction in C_{cr} would imply intrinsic renal disease, but GFR can also exist when the C_{cr} is normal or supernormal, representing the initial compensatory hyperfiltration response to substantial renal function loss. A urinalysis can detect albumin in amounts that reflect substantial renal dysfunction but must be correlated to an estimate of the concentration of solutes in the urine (e.g., specific gravity). A more precise estimated protein excretion can be obtained from a 24-hour urine sample for protein, which is more reliable when at least 1 g of creatinine is excreted in the same collection. Comparing the urinary concentration of protein and creatinine in a random urine sample (e.g., U_{prot}/U_{Cr} ratio) can approximate total daily protein excretion, with normal values less than 0.2 (200 mg/d). This is a useful tool to follow the progression of proteinuria, detect levels of proteinuria indicative of glomerular disease, and determine nephritic-range proteinuria (e.g., U_{prot}/U_{Cr}ratio greater than 1.0 reflects urinary protein excretion greater than 3.5 g/d). Diminished renal capacity to concentrate urine and maximally acidify urine, as well as conserve sodium in response to decreased effective circulating volume are indicators of advanced chronic renal disease. Detection of microalbuminuria has been shown to identify those at increased risk for both cardiovascular and renal complication of type I diabetes mellitus and has been used as a screening tool to select patients in whom early interventions to slow the progression of chronic renal disease should be employed.

III. Course of chronic renal failure.

As GFR falls below 50% of normal, creatinine and BUN begin to rise proportionately (BUN to creatinine ratio of 10:1). When the GFR falls below one third of normal, metabolic acidosis develops because of the kidney's inability to excrete fixed acids at the rate of acid production. Metabolic acidosis may initially present as a non-anion gap metabolic acidosis caused by decreased renal ammonia production and renal tubular dysfunction. However, the classic large anion gap metabolic acidosis of chronic renal failure is caused by the renal retention of phosphates, sulfates, ammonia, urate, and hippurate. At a GFR less than 10% of normal, the kidney is unable to maintain normal potassium levels in response to large potassium loads, which causes hyperkalemia even though the remaining renal tissue and GI tract have enhanced potassium excretion. Patients with advanced CRF may develop hyperkalemia as a result of excess intake of exogenous sources of potassium, use of drugs that limit potassium excretion [e.g., triamterene, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs], progressive metabolic acidosis, infections, or any process that reduces renal blood flow. Through other adaptive mechanisms, the kidney is capable of maintaining sodium homeostasis in CRF but has diminished capacity to excrete sodium loads, which can lead to edema and hypertension and conserve sodium when there is a loss of effective circulating volume. Chronic and uncontrolled hypertension can accelerate

the loss of functional renal units (3). As the GFR declines to low values (less than 25% of normal), there is renal phosphate retention, causing hyperphosphatemia and a reciprocal fall in serum calcium. This hypocalcemia causes the release of parathyroid hormone (PTH), but the calcemic response of PTH is blunted because of GI and skeletal PTH resistance caused in large part by decreased renal synthesis of 1,25-dihydroxyvitamin D. The resulting secondary hyperparathyroidism can lead to renal osteodystrophy (4). Decreased functional renal mass results in decreased production of erythropoietin and the anemia of CRF, which is characterized as hypoproliferative, normocytic, and normochromic anemia. Bleeding tendencies with normal prothrombin time (PT), partial thromboplastin time (PTT), and prolonged bleeding times can occur late in CRF because of uremia-induced platelet dysfunction. When the decline in renal function reaches a GFR of 10 mL/min, renal replacement therapy is required to sustain life.

IV. Management of chronic renal failure.

Diminishing the impact of several factors known to independently increase the rate of renal function decline has been shown to decrease the progression of chronic CRF. These factors include systemic hypertension, glomerular hypertension, dietary protein intake, hyperglycemia, and possibly hyperlipemia (5).

A. Hypertension.

Aggressive measures must be employed to normalize blood pressure in chronic renal disease (see Chapter 9.1). The ameliorating impact of blood pressure normalization on the progression of CRF occurs independently of agents used to treat hypertension. Agents used in the treatment of hypertension and early renal failure include ACE inhibitors, calcium channel blockers, and diuretics, and their use must be individualized to each clinical setting. However, evidence suggests that greater renoprotective benefits derived from the use of ACE inhibitors independent of their blood pressure lowering effect in diabetic and nondiabetic nephropathies (6). Because of the tendency to sodium retention in CRF, diuretics are frequently used to control hypertension. Thiazide diuretics (e.g., metolazone) can be effective at GFRs greater than 30–40 mL/min. When GFR falls below these levels, more potent medullary loop diuretics (e.g., furosemide) should be used as resistance to thiazide ensues. To avoid the resistance to loop diuretics caused by persistent sodium reabsorption at renal tubular sites other than the site of action of the loop diuretics, the addition of a thiazide is advised to enhance diuresis. The combination of loop and thiazide diuretics also delays the need for larger quantities of loop diuretics, thus decreasing the risk of ototoxicity (7,8).

B. Microalbuminuria and macroalbuminuria.

Microalbuminuria in diabetes mellitus provides a window for detecting diabetic nephropathy at an earlier stage before a decline in GFR or an elevation in BUN and creatinine occurs (9). The use of ACE inhibitors when microalbuminuria or macroalbuminuria is detected has been shown to slow the progression of diabetic renal disease independent of the presence of systemic hypertension. This ameliorating effect may occur because ACE inhibitors decrease intraglomerular pressure by blocking angiotensin II's vasoconstricting effect on the efferent arteriole and an associated decline in urinary protein excretion (10). There is also a renoprotective effect caused by ACE inhibitors in patients with nondiabetic nephropathies with and without proteinuria. Prospective treatment with ACE inhibitors of patients with chronic renal disease prior to the presence of microalbuminuria or proteinuria should be considered.

C. Glycemic control.

Maintaining glycemic control near normal levels has been demonstrated to reduce the incidence of diabetic retinopathy and diabetic nephropathy in patients with type I diabetes mellitus, with similar evidence mounting for type II diabetes mellitus. Early detection and aggressive treatment of hyperglycemia together with hypertension control delays the onset of nephropathy (6,11).

D. Dietary protein restriction.

Levels of dietary protein restriction (300–800 mg/d when GFR is less than one third of normal) necessary to achieve the renoprotective effects in type I diabetes mellitus described in studies may be difficult to achieve. Reasonable protein restriction that avoids protein malnutrition individualized to each patient should be employed (12,13).

E. Renal osteodystrophy.

Monitoring phosphate levels and using non- aluminum-containing phosphate binders (e.g., calcium carbonate) to maintain near-normal (2.5–5.0 mg/dL) phosphorus levels (a calcium phosphorus product of less than 55 mg/dL) will ameliorate some of the negative impact of PTH elevation and calcium lowering and decrease the development of renal osteodystrophy. Calciferol can be used to decrease phosphate retention as well by increasing intestinal absorption of calcium. Aluminum-containing antacids (e.g., Amphojel) should be used to control hyperphosphatemia in the event that phosphate levels cannot be maintained with calcium carbonate or if hypercalcemia ensues. Otherwise, their use should be minimized because aluminum accumulation in CRF can contribute to the development of renal osteodystrophy and altered mental status. These factors, which control hyperphosphatemia, decrease the risk of renal osteodystrophy and avoid visceral and vascular calcification, which may contribute to cardiovascular complications and death (14).

F. Hyperlipidemia.

Although the effect of the control of hypercholesterolemia on the progression of CRF is not known, aggressive management of hypercholesterolemia is warranted because dyslipidemias cause glomerular and interstitial injury of the renal parenchyma in addition to their general adverse impact of vasculature (see Chapter 17.4) (15).

G. Hyperkalemia.

When GFR falls below 20 mL/min, potassium intake should be restricted to less than 40 mEq/d. If hyperkalemia occurs, the source of excess potassium intake, decreased potassium excretion, or cellular extrusion of potassium should be eliminated. Further treatment of persistent and severe hyperkalemia is directed at antagonizing myocardial effects by using calcium gluconate, shifting potassium intracellularly with glucose and insulin or with sodium bicarbonate if metabolic acidosis is severe, removal of potassium-sparing diuretics, use of ion-exchange resins [e.g., sodium polystyrene sulfate (Kayexalate)], and, in emergency settings, dialysis.

H. Metabolic acidosis and sodium and water hemostasis.

The acidosis of renal failure requires the use of sodium bicarbonate when pH is less than 7.3 and serum bicarbonate concentrate (HCO_3^-) is less than 12 mEq/L. Sodium restriction should be implemented based on the clinical setting, but 6–8 g of sodium per day creates a palatable diet. Water restriction may be required in patients who develop hyponatremia when they consume free water at rates greater than the renal water clearance rate.

I. Anemia.

Partial correction of the anemia of CRF, which is caused by insufficient intrinsic erythropoietin production, can be achieved using recombinant human erythropoietin. Partial correction of the anemia of renal failure improves the quality of life and supplementation in predialysis and dialysis patients. However, other causes of anemia must also be considered. Concomitant iron deficiency anemia will impair the treatment of the anemia of CRF. Monitoring markers, such as ferritin, transferrin percent, and total iron binding capacity, are useful in determining the adequacy of iron stores (16).

J. Other measures.

All patients with CRF should receive pneumococcal, hepatitis B, and influenza vaccines.

V. Renal replacement therapy.

Consultation with a renal team should occur early in the predialysis period to promote transition of patients to renal replacement therapy in a nonurgent setting. This early contact with the renal team ensures that patients have an appropriate understanding of the types of renal replacement therapies available to them. The renal team can also affect the quality of life of the predialysis renal patient by providing specific patient education and assessments concerning medical treatment of CRF as well as treatment of associated problems (e.g., anemia). Current renal replacement therapies include hemodialysis, intermittent peritoneal dialysis, continuous ambulatory peritoneal dialysis, and renal transplantation. The choice of renal replacement therapy should be individualized based on the availability of a donor kidney, the patient's desire for independence, previous abdominal surgeries, underlying medical conditions, and patient's age.

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12.7
UROLITHIASIS

Joseph E. Ross

Urolithiasis affects 10% of the U.S. population, and its occurrence is increasing in industrialized countries. Eighty percent of affected individuals are men, and stones occur three to four times more often in whites than in blacks. The peak age of onset in men is 35 and in women is 30. Unless proper prevention is undertaken, the urolithiasis recurrence rate is 15% at 1 year, 50% at 5 years, and 80% at 25 years (1).

The composition of the stones is 80% pure calcium oxalate or a mixture of calcium oxalate and calcium phosphate; struvite stones account for 10%–20%, uric acid 5%–10%, and cystine stones 1%.

I. Clinical presentation.

The presenting symptom is pain, which strikes suddenly and is immediately severe. Patients try multiple positions in an attempt to decrease their discomfort. Pain typically starts in the flank but may localize

at the costovertebral angle. It may radiate to the lower abdomen, groin, or perineum. Pain is often associated with nausea and vomiting. Fever is unlikely unless there is a coexisting urinary tract infection.

II. Diagnosis.

Hematuria, microscopic or gross, is present 80% of the time. A stone may be seen on a plain film of the abdomen as 90% of stones are radiopaque. Identification may be obscured or confused with abdominal or pelvic calcium deposits.

Noncontrast helical computed tomography (CT) is superior to intravenous pyelography (IVP) or ultrasonography in evaluating patients presenting with acute flank pain. Advantages include rapid results, performance without use of iodinated contrast or patient preparation, and high sensitivity and specificity in detecting renal and ureteral stones and ureteral obstruction (2). The level of obstruction and the size of the stone can be accurately measured using helical CT. Unlike IVP, helical CT does not give information about renal function.

Laboratory workup for suspected urolithiasis includes (a) urinalysis, (b) urine for culture and sensitivity if infection is suspected, and (c) a multiphasic screening panel, including blood urea nitrogen, creatinine, calcium, phosphorus, protein, electrolytes, and uric acid. In patients with recurrent stones, a 24-hour urine specimen for total volume, creatinine clearance, calcium, cystine oxalate, phosphorus, magnesium, uric acid, citrate, sodium, and pH are indicated.

III. Medical management.

Most stones (80%–90%) pass spontaneously with supportive therapy. Passage may occur within hours, days, weeks, or even months. Resolution of renal colic may occur with stone passage or with lodging of the stone in the renal pelvis, ureter, or urethra.

Initial treatment includes hydration with oral fluids (3–4 L/d) and pain control. Indications for admission include inability to maintain oral hydration, uncontrolled pain requiring administration of intramuscular or intravenous narcotics, or coexisting pyelonephritis.

Patients must strain their urine to collect any stones for analysis for chemical composition. General recommendations for recurrent stone prevention can be made, but they must be modified pending determination of stone composition.

A. Calcium stones.

Most calcium-containing stones are caused by idiopathic hypercalciuria in normocalcemic patients. If an elevated serum calcium is encountered, consider hyperparathyroidism (5% of calcium stones), renal tubular acidosis, sarcoidosis, malignancy, excessive vitamin D supplementation, and use of lithium.

B. Oxalate stones.

Causes of oxalate-containing stones include excess intake of oxalate-containing foods (spinach, rhubarb, pecans, peanuts, asparagus, cocoa, beets, peppers, okra, chocolate, draft beer, Swiss cheese, lime peels, wheat germ, baked beans, squash, tea, cranberry juice, and orange juice), malabsorptive syndromes, chronic diarrhea, bowel resection or bypass, and excessive vitamin C intake.

C. Uric acid stones.

Uric acid stones are radiolucent and are seen primarily in gout, but they also occur in malignancies and glycogen storage diseases.

D. Struvite stones.

These stones are seen in urinary tract infections with bacteria-containing urease enzymes. Causative organisms include *Proteus*, *Providencia*, *Pseudomonas*, *Klebsiella* (64% of organisms), *Serratia* (29%), and *Enterococcus* (5%) species. Struvite stones are never seen in *Escherichia coli* or *Citrobacter* infections.

Primary treatment consists of antibiotic therapy and stone removal. Recurrences are high due to the inability to completely remove the large, hard, staghorn calculi that are typical of struvite stones.

E. Cystine stones.

Cystine stones are very hard and are caused by a hereditary defect of amino acid transport. These stones often require invasive management.

IV. Invasive management.

Most stones that are 5 mm or less in diameter will pass with supportive therapy and cause minimal obstruction. Active intervention is often needed for stones larger than 5 mm or if persistent obstruction occurs.

Extracorporeal shock wave lithotripsy (ESWL) is best used for upper ureteral stones and renal pelvis stones smaller than 2 cm. ESWL is not recommended for struvite stones because bacteria or endotoxins inside the stone may be dispersed systemically. Percutaneous nephrolithotomy is used when obstruction of the ureteral pelvic junction occurs, if ESWL fails with cystine and staghorn calculi stones, and for stones larger than 2 cm. Lower or midureteral stones may be treated by ureteroendoscopy followed by stone basket retrieval and possible stent placement, or by pushing the stone higher up the ureter and then treating with ESWL. Open surgery is required in 1%–2% of all patients. ESWL and ureteroendoscopy are outpatient procedures. Percutaneous nephrolithotomy requires a 2- to 4-day inpatient hospital stay.

V. Prevention.

Daily fluid intake of 3–4 L/d with avoidance of nonsoftened and mineral water should be instituted for all patients to prevent stone recurrence. Specific measures include (3,4) the following:

A. Calcium stones

1. Reduce protein in the diet as protein enhances calcium, urate, and oxalate excretion.
2. Restrict sodium to 2.5 g/d to decrease excretion of urinary calcium.
3. Limit calcium intake to 800–1,000 mg/d.
4. Increase fiber to decrease calcium absorption.
5. Hydrochlorothiazide, 25–50 mg bid.
6. Potassium phosphate, 1,500 mg/d in 3–4 divided doses (efficacy equivalent to thiazide).
7. Potassium citrate, 20 mEq bid (especially if potassium low due to hydrochlorothiazide).
8. Sodium cellulose phosphate (Calcibind), 2.5–5.0 g tid with meals if restricted calcium diet and thiazide diuretics fail, serum phosphate is normal, and no evidence of bone disease exists.

B. Oxalate stones

1. Restrict consumption of oxalate-containing foods (see above).
2. Avoid vitamin C supplements because these stimulate oxalate excretion.
3. Reduce protein in the diet because protein enhances calcium, urate, and oxylate excretion.
4. Cholestyramine (Questran) 1–4 g qid.
5. Calcium carbonate 1–4 g/d in 3–4 divided doses to precipitate oxalate in the intestinal tract.
6. Potassium citrate 20 mEq bid.
7. Pyridoxine 200–400 mg/d if deficiency found.

C. Uric acid stones

1. Allopurinol (Zyloprim) 100–300 mg/d.
2. Potassium citrate 20 mEq bid to increase urine pH to 6–7.
3. Acetazolamide (Diamox) 250 mg at bedtime in resistant cases.

D. Struvite stones

1. Methenamine (Urised), 1–2 tablets qid, may act as a urine antiseptic.
2. Inhibitors of the urease enzyme have limited effectiveness due to side effects.
3. Prophylactic suppressive antibiotics.

E. Cystine stones

1. Penicillamine 1–2 g/d in divided doses to increase urine pH to greater than 7.

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12.8
URINARY INCONTINENCE

Timothy R. Malloy

Urinary incontinence affects 15%–30% of community-dwelling elders and more than 50% of those who are institutionalized (1). Incontinent individuals are predisposed to perineal rashes and ulcers, urinary tract infections, falls, fractures, embarrassment, social isolation, and depression.

Because of the stigmatization of incontinence, afflicted individuals seldom seek medical attention; if they do, the problem is often inadequately evaluated. This is unfortunate because urinary incontinence is curable in many cases, especially those involving patients who have adequate mobility and mental functioning. Relying on patients to self-report incontinence results in most cases remaining undetected. Family physicians may have greater success by asking patients some probing questions, such as “Do you ever have accidents with your urine”

I. Transient incontinence.

refers to a group of conditions that cause abrupt-onset incontinence but resolve when treated. The causes of transient incontinence can be remembered with the use of the mnemonic DIAPERS (delirium, infection, atrophic urethritis, pharmaceuticals, excessive urinary output, restricted mobility, stool impaction). The source of most of these causes of transient incontinence lies outside the urinary tract, and with appropriate management, the incontinence usually resolves.

II. Established incontinence

can be divided into problems with bladder activity (detrusor hyperactivity or hypoactivity) or with bladder outlet functions (outlet incompetence or obstruction) (Table 12.8-1). Two indispensable tools that can help the clinician determine the type of incontinence are the voiding record and the postvoid residual (PVR) urine volume. The patient's voiding record provides information about the magnitude of the problem and an estimate of functional bladder capacity (the amount of urine voided each time). The PVR volume helps the clinician to assess whether the patient is emptying his or her bladder adequately. PVR volumes of less than 50–100 mL are suggestive of urge or stress incontinence, and PVR volumes greater than 100 mL are consistent with overflow (retention) incontinence.

Type	Predominant symptoms	Postvoid residual	Volume of urine lost
Hyperactive bladder (urge, detrusor instability)	Urge or warning	Low	Large
Hypoactive bladder (neurogenic bladder)	Inability to void voluntarily; often wet without warning	High	Small volumes but nearly continuous
Outlet incompetence (stress incontinence)	Urine loss with coughing, sneezing, changing positions	Low	Small
Outlet obstruction (overflow incontinence)	Hesitancy, often wet without warning, “dribbling”	High	Small volumes but nearly continuous

Table 12.8-1. Types of established incontinence

A. Urge incontinence

(detrusor hyperactivity) is the most common type of established incontinence affecting older adults. This type of incontinence is frequently associated with neurologic disorders, such as cerebrovascular disease or Alzheimer's disease, is characterized by the involuntary loss of urine, and has as its key symptom the abrupt, strong desire to void (urgency) (see Chapter 6.8). Even though frequently seen with neurodegenerative illness, most patients with urge incontinence do not have a neurologic disorder. The first step in management is behavior modification, using routine 2-hour toileting and urge control techniques. Because the duration of a typical bladder contraction is less than 60 seconds, patients can often learn to sit still, to “wait out” a contraction until after the sensation of urgency passes. Then, under less hurried conditions, the patient can proceed to the toilet.

In addition to these behavioral strategies, patients often gain relief with anticholinergic medications, such as oxybutynin (Ditropan), 2.5 mg/d up to 5 mg tid, or imipramine (Tofranil), 10–50 mg at bedtime, each of which decreases the intensity of bladder contractions. Because of undesirable anticholinergic side effects, such as dry mouth, most patients tolerate the selective muscarinic blocker tolterodine (Detrol) 2 mg bid much better than oxybutynin or imipramine.

B. Stress incontinence

can be thought of as bladder outlet incompetence. It is defined as the involuntary loss of urine during coughing, sneezing, laughing, or any other maneuver that increases intra-abdominal pressure. When the patient with a full bladder is in a standing position and is asked to bear

down, the result is likely an immediate loss of urine, which is essentially pathognomonic for stress incontinence. Treatment should be directed to improving bladder outlet strength. Kegel exercises, estrogen preparations, and α-adrenergic medications, such as phenylpropanolamine-chlorpheniramine (Ornade) twice daily, can be useful measures to improve outlet function. Because the internal urethral sphincter muscle is largely responsible for maintaining outlet competence and is under α-adrenergic influence, medications such as phenylpropanolamine are often effective. Mechanical treatments, such as the use of a pessary or surgical correction, also may be appropriate in some cases.

C. Overflow incontinence secondary to obstruction

is the involuntary loss of urine associated with overdistention of the bladder. There may be a variety of presenting symptoms, but usually there is a history of continuous dribbling and a sensation of incomplete voiding and hesitancy. A PVR volume of more than 100 mL provides corroborating evidence of overflow incontinence. This type of incontinence is usually the result of bladder outlet obstruction secondary to prostatic enlargement (see Chapter 12.4). Treatment of overflow incontinence is targeted at relieving the obstruction. α-Adrenergic blocking agents, such as terazosin (Hytrin), 1–10 mg at bedtime, and doxazosin (Cardura), 1–8 mg at bedtime, have been used successfully to decrease the resistance of the internal urethral sphincter and may even reduce the amount of prostate tissue. Postural hypotension associated with the use of these α-blockers can be largely avoided with the use of the more selective tamsulosin (Flomax), 0.4–0.8 mg at bedtime. Transurethral resection of the prostate remains a viable treatment option in selected individuals.

D. Overflow incontinence secondary to bladder hypoactivity

accounts for another form of overflow incontinence. Bladder hypoactivity may also be associated with central nervous system lesions, especially of the spinal cord, and occasionally is seen in patients with neuropathy, as in diabetes or vitamin B deficiency (see Chapter 6.9). The family physician should search for potentially reversible causes of hypoactive bladder, such as use of strongly anticholinergic medicines and stool impaction. When addressing potentially reversible causes of hypoactive bladder, it may be necessary to decompress the bladder with the use of an indwelling catheter for 7–14 days. Once decompressed, the bladder may again resume its contractile function. This form of incontinence is difficult to manage with pharmacologic measures but can be managed successfully with intermittent self-catheterization or, less preferably, long-term indwelling catheterization.

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12.9
NO-SCALPEL VASECTOMY

Ronald D. Reynolds

No-scalpel vasectomy (NSV) is a refined method of delivering a loop of vas deferens through the scrotal skin for occlusion (1). Stretching an opening in the skin rather than cutting through tissue with a scalpel speeds the procedure and minimizes postoperative swelling, bruising, and pain (2). NSV is gaining popularity among vasectomists in this country.

I. Preoperative consultation.

A. Preparation.

Mailing an informational brochure or videotape prior to the preoperative appointment helps to ensure that the patient will be well informed. Husband and wife should attend the preoperative visit together.

B. Counseling

must include clear statements that vasectomy is **permanent** and is done only for contraception. Potential complications, such as bruising, bleeding, hematoma, infection, epididymitis, and orchitis, are discussed in detail. Men who are not comfortable with permanent loss of fertility or who expect the operation to fix sexual or marital problems should not be operated on. Patients who are young, immature, or reacting to a life crisis (e.g., divorce, unplanned child) often later regret their vasectomy decision.

C. Physical examination

includes vital signs, heart and lung auscultation, and a thorough genital examination looking for scrotal skin problems, testicular masses, hernia, and varicocele. The latter can only be found if the patient is examined while standing. Particular attention is given to **simultaneous palpation of both vas deferens,** which are the size of a spaghetti noodle and have a dense consistency unlike that of any other scrotal structure. NSV may be difficult if the scrotal skin is thick and doughy, the scrotum is short, the vas cannot be easily separated from adjacent scrotal structures, or if there has been previous scrotal surgery.

D. Consent for surgery

is signed and witnessed. The consent should include statements of understanding regarding the permanence of the procedure, the fact that fertility remains for a time after the operation, the patient's responsibility for using other contraception until two postoperative sperm counts are zero, and the small chance of a late failure.

II. Operative preparation

A. Relaxation

can be provided with oral diazepam, 10 mg given 30 minutes preoperatively. Often, only “verbal anesthesia” is necessary to put the patient at ease. Some vasectomists provide headphones and a CD or tape player so that the patient can listen to his favorite music. Very apprehensive patients are prone to vasovagal reactions. Atropine, 0.4 mg IM preoperatively, will prevent problems in such patients. A warm room aids scrotal relaxation.

B. Sterile preparation

of the genital area with warmed povidone-iodine or chlorhexidine gluconate solution is done after clipping or shaving the anterior scrotum has been completed. The penis is noosed up out of the operative field with a long rubber band clipped to the patient's shirt with a hemostat. This is more comfortable to remove than tape. Sterile draping is applied from nipples to knees.

C. Instruments

unique to NSV include a ring-tipped forceps with an internal diameter of 3.5 mm, and a sharpened, curved hemostat called a dissecting forceps. (Neither a Wilson nor a Babcock clamp should be substituted for the ring forceps because they do not hold the skin tight to the vas.) The instrument set also includes two delicate straight hemostats, a delicate curved hemostat, needle holder, Steven's tenotomy scissors, and Allis tissue forceps. A sterile battery-operated hot cautery and 5-0 braided polyglycolic acid suture (Vicryl or Dexon) on a small taper-point needle complete the set.

III. Vasal isolation.

Three-finger vasal isolation manipulates the vas to the upper anterior scrotum, just under the median raphe. The shortest side (usually the right) is done first so that the same scrotal opening can be used for the second side.

A.

The long finger of the nondominant hand is placed deep behind the scrotum.

B.

The thumb is placed on the median raphe, immediately above or below the intended scrotal opening.

C.

The thumb moves across the midline toward the opposite side, moving the anterior scrotal skin with it, and then flexes to join the long finger, effectively surrounding the entire hemiscrotum.

D.

As scrotal contents are “milked” out of the grasp, the vas comes into palpation. It is held firmly by pinching the thumb and long finger together.

E.

The index finger is brought in to stretch the anterior scrotal skin taut over the vas (Figure 12.9-1A).

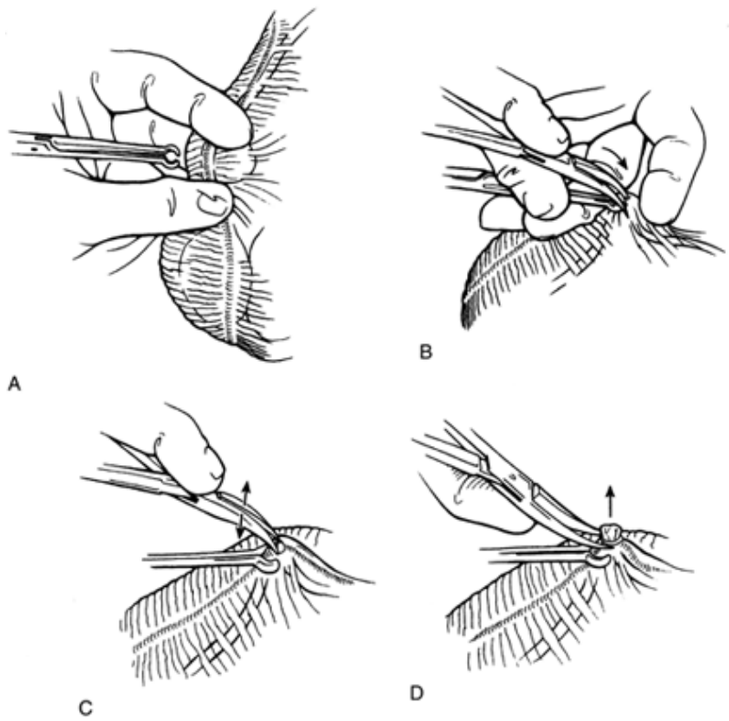

FIG. 12.9-1. A: The vas is held in three-finger isolation and grasped in the ring forceps. **B:** One blade of the dissecting forceps punctures all scrotal layers. **C:** Scrotal layers are opened down to the vas lumen. **D:** The dissecting forceps skewers and lifts the vas free. (Drawing courtesy of Jef Dirig.)

IV. Local anesthesia

A.

A mixture of half 2% lidocaine and half 0.5% bupivacaine gives both quick onset and prolonged duration. Six milliliters is usually sufficient. Epinephrine is not used because the vasectomist needs to see and address all bleeders intraoperatively. Injection pain is minimized with use of a 27-gauge needle.

B. Local anesthetic

is injected subdermally in a quarter-sized area overlying the isolated vas. The needle is then advanced toward the groin along the vas and 2–3 mL is injected perivasally. The first vas is released and the second is grasped with three-finger isolation. Perivasal block is administered on the second side.

V. Vasal delivery

A.

The shortest side is again held in three-finger isolation. The 3.5-mm ring forceps is applied around the vas in the area of anesthetized skin. The forceps must approach directly perpendicular to the vas. As the tips touch the skin, they should be open about 4 mm (Figure 12.9-1A). The pad of the long finger helps push the vas up into the grasp of the ring as the ring is closed and locked around the vas.

B.

A check that the correct side is grasped must be done. Traction on the ring forceps in the testicular direction tenses the vas, which can be palpated coursing to the right or left of the root of the penis. Both sides should be palpated.

A. Rotation of the handle of the ring forceps

toward the patient's feet creates a loop of vas rising up out of the then-horizontal ring. The nondominant hand holds the blades of the ring forceps between thumb and long finger, and the index finger tightly stretches scrotal skin over the loop of vas (Figure 12.9-1B).

B. The dissecting forceps

is held in the dominant hand with tips pointing downward and the index finger on the hinge. The forceps approaches with tips at a 45-degree vertical angle to the most prominent point of the vasal loop. The near blade punctures the scrotal layers down to the vasal lumen in one smooth maneuver, as if starting an intravenous line (Figure 12.9-1B).

C. Scrotal layers are opened

by removing the single blade, closing the dissecting forceps, and placing the closed tips back into the same hole, at the same angle and to the same depth. The tips are opened to create a skin opening about twice the width of the vas (Figure 12.9-1C). Bare vas with its lumen open should be exposed in the bottom of the skin opening. If not, further single-blade puncture through the remaining layers, followed by double-blade stretch, will expose bare vas.

D. Delivery of the vas

is done by skewering it with the downward-facing far blade of the dissecting forceps. Supinating the hand rotates the forceps 180 degrees, so that the tips face upward (Figure 12.9-1D). This hangs a loop of vas on the forceps tip. The forceps are gently closed but not locked, so as not to cut through the vas. As the ring forceps is opened, a loop of vas about 1.5 cm tall lifts out of the skin. The ring forceps is replaced around the apex of the loop, and the dissector is removed. If the vas does not lift free, it is regrasped in the ring, and further dissection is carried out to free it from remaining scrotal layers.

E. Tamponade

of the vasal loop by tight skin or scrotal layers may render the loop bloodless. If the artery of the vas cannot be identified, the delicate curved mosquito hemostat is used to stretch the constricting tissue.

VI. Vasal occlusion.

The lowest failure and complication rate is achieved by dividing the vas, cauterizing the lumen 5 mm in the inguinal direction with a red hot-wire cautery and covering the inguinal end in its sheath (3). Sheath closure is most accurately done with suture, being careful to include a bite of the purse-string in the posterior sheath wall (4). Some vasectomists prefer metal clips for sheath closure. Leaving the testicular end open creates a vent to prevent pressure buildup in the epididymis and testicle, thereby reducing the incidence of late epididymitis and orchitis.

VII. The second side.

The second side is done just like the first. The vas is isolated by the three-finger technique under the same opening and grasped with the ring

forceps. The ring should be placed around the inferior third of the opening, surrounding vas and skin. When the ring forceps is then rotated toward the feet, the opening will be perfectly placed to proceed with vasal delivery.

VIII. Postoperative management

A.

A dab of **antibiotic ointment** is placed on the opening and about ten separated loose pieces of 4 × 4-inch gauze are placed on the scrotum. A supporter is put on. Mild narcotic pain medicine or a nonsteroidal anti-inflammatory, or both, may be prescribed. The opening is kept dry for 24 hours. NSV generally causes little swelling, but occasionally a patient may choose to apply ice for comfort.

B. Activity is restricted

to lying down for the first day and light activity for the second and third days. A 10-pound lifting restriction is given for the first 2–3 days. Thereafter, most men can resume normal activities.

C. Ejaculation is proscribed for 7 days

to allow the vasal seal to strengthen.

D.

At **a 1-week postoperative visit,** collection of sperm counts is discussed, and sample cups and order forms are dispensed.

E. Adequate contraception must be used until azoospermia is documented.

The first sperm count should be obtained after 4 weeks (sperm cannot survive in the ampulla of the vas for more than 3 weeks) and 15 ejaculations (the number needed for most men to clear the ampulla). A repeat count is done 2 weeks later. If both are zero, other contraception can be discontinued. There is still a tiny chance of late failure at this point, but additional sperm counts are not done.

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XIII. PROBLEMS RELATED TO THE FEMALE REPRODUCTIVE SYSTEM

13.1
VAGINITIS AND CERVICITIS

Barbara D. Reed

Vaginitis and cervicitis are common medical problems for women, occurring in most women at least once and in many women numerous times. The severity of these entities ranges from mild symptoms of vaginal discharge, odor, or itching, to severe, debilitating, and unrelenting symptoms. Diagnosis of the specific cause of the symptoms can be straightforward, but misdiagnosis by patients and physicians is very common. Careful attention to presentation, office laboratory data, and the selective use of microbiologic identification techniques are critical for accurate diagnosis and prevention of long-term morbidity.

I. Vaginitis.

Vaginitis consists of infections or irritations that often cause increased vaginal discharge, odor, itching, or irritation, although vaginal infections can also be asymptomatic. Most cases of vaginitis are diagnosed, in order of decreasing prevalence, as bacterial vaginosis (BV), *Candida* vulvovaginitis (CVV), or *Trichomonas* vaginitis (TV).

A. Clinical presentation.

Although the clinical presentations of the prototype of each of the three most common types of vaginitis differ, the overlap in the presentations is considerable, thereby making diagnosis by history alone highly inaccurate.

1. BV, associated with anaerobic overgrowth in the vagina and often a predominance of *Gardnerella vaginalis* or *Mobiluncus* spp., classically presents with an increase in vaginal discharge (described as creamy and often discolored) and a fishy vaginal odor that is often most prominent after intercourse. Itching is not a prominent feature.
2. CVV is typically associated with vaginal or vulvar itching, or both, and a thick, cottage-cheese-like discharge, although there may be no discharge at all. Discharge is not discolored (yellow, green, or dark), and odor is unusual.
3. TV, like BV, is associated with an increased, often discolored, discharge, and a new odor, but it may also include itching as a prominent feature.
4. Vaginitis of unknown etiology. More than 40% of women with vaginal symptoms and findings do not fall into the previous three categories (1). These women may complain of any of the symptoms mentioned in Section I.A.1, Section I.A.2 and Section I.A.3, with increased discharge or itching being the most common presentations. Prominent vulvar discomfort, often described as burning or itching, may suggest vulvodynia, which may be repeatedly misdiagnosed as CVV. Other possible diagnoses include streptococcal vaginitis, desquamative inflammatory vaginitis, lactobacillosis, urinary tract infections, and cervicitis, but in many cases the diagnosis remains unclear. Repeated examination, if symptoms persist, is recommended to avoid missed treatable diagnoses and to offer patient support.

B. Diagnosis.

The accurate diagnosis of the cause of vaginal symptoms is simple in only the minority of cases. Careful attention to the history and physical findings is helpful, but the diagnosis is most accurately confirmed with the laboratory findings (2). Telephone diagnosis is inaccurate and should be reserved for emergency situations in which an examination is not possible. Self-diagnosis by patients is also inaccurate, despite previous history of similar symptoms, and hence repeated treatment for persistent symptoms should prompt a careful evaluation. Diagnosis includes a sexual history, with attention to other possible sexually transmitted infections, and evaluation for cervical infection if indicated by sexual history, demographics, or physical examination. The sensitivity of the vaginitis diagnosis is equivalent whether the specimens are collected by the patient using a cotton swab inserted into the distal vagina or by a medical provider during a pelvic examination.

1. Bacterial vaginosis can be diagnosed accurately using the physical examination and office laboratory data. One method of diagnosis consists of documenting three of four of the following Amsel criteria (3): homogeneous discharge, pH of vaginal discharge greater than 4.5, positive amine test (fishy odor when potassium hydroxide is added to discharge), and clue cells on normal saline preparation (epithelial cell outline completely obscured by bacterial coating on the cells). In addition, vaginal discharge reveals an altered background bacterial flora, with lack of the normal predominance of long rods (*Lactobacillus* sp.) and replacement with short rods (straight or curved) or cocci. The Nugent scoring system, using only data from the Gram-stained vaginal discharge, can be used for diagnosis as well (4). BV is not typically associated with a large number of white blood cells (WBCs). If WBCs are predominant, consider dual infection (possibly with *Candida* or *Trichomonas*) or a coexisting cervicitis.
2. CVV is accurately diagnosed at the office visit only if *Candida* is identified on the potassium hydroxide preparation. This identification can be made based on the presence of budding yeast forms or pseudohyphae. Screening of a thick preparation of vaginal discharge (smeared on a dry slide at the time of the pelvic examination to ensure an undiluted specimen, with potassium hydroxide added to the slide at least 3 minutes prior to microscopic examination), observed at low power with confirmation of the organism at high power, maximizes identification. Budding yeast or pseudohyphae are identified in only 50% of CVV cases, however; hence inaccuracy is common in this diagnosis if additional testing is not done. Culture for *Candida* species should be used in women with suspected CVV but a negative potassium hydroxide preparation and in women with recurrent or persistent symptoms.
3. TV is diagnosed by the observation of motile, heart-shaped, flagellated forms on a microscopic examination of fresh, saline-suspended vaginal discharge. These organisms are slightly smaller than WBCs and resemble WBCs when they dry out on a slide or cytology smear. Hence, vaginal discharge should be suspended in normal saline during the pelvic examination and only applied to the microscopic slide immediately before examination at low and high power. Even under these conditions, only in 50% of cases have motile trichomonads been observed. In cases of a negative normal saline preparation but suspected TV or in patients with persistent vaginal symptoms, repeated examinations and culture for *T. vaginalis* using modified Diamond's media increases diagnostic accuracy.

C. Management.

Treatment for BV, CVV, and TV is effective in more than 80% of cases when an accurate diagnosis is made and appropriate treatment instituted (5). Continuing symptoms or early recurrence (within a month) require reexamination for dual infection and to reconfirm the diagnosis.

1. Bacterial vaginosis
   a. First-line treatments include metronidazole (Flagyl, Protostat), 500 mg PO bid for 7 days (cost is approximately $12); clindamycin vaginal cream 2% (Cleocin), 5 g (1 applicatorful) in vagina at bedtime for 7 days (cost is approximately $50); or metronidazole vaginal gel (MetroGel), 5 g (1 applicatorful) in vagina bid for 5 days (approximately $60). Clindamycin, 300 mg PO bid for 7 days, can also be used, as can metronidazole, 2 g PO once, but the one-time dose is associated with more recurrences. Side effects of the oral metronidazole include nausea and vomiting if alcohol is ingested while the patient is on the medication. All three regimens are associated with the risk of CVV in 5%–10%. Allergy to each of these medications may occur. The value of treatment of sexual partners is controversial. A trial of treatment of sexual partners should therefore be reserved for recurrent or persistent infection.
   b. Recurrent or persistent infections can be managed with clindamycin (Cleocin), 300 mg PO bid for 14 days (cost, approximately $42), or with

povidone-iodine gel or suppositories bid for 14–28 days (if available). Pregnant patients may be treated with metronidazole, 250 mg PO tid for 7 days, the oral clindamycin regimen, or intravaginal metronidazole gel.

2. *Candida* vulvovaginitis
   a. First-line treatments consist of the imidazoles and the triazoles, such as miconazole (Monistat), 200-mg suppository intravaginally, 1 each night for 3 nights; 2% vaginal cream, 1 applicator intravaginally each night for 7 nights, or 100-mg vaginal tablet, intravaginally each night for 7 nights; clotrimazole (Gyne-Lotrimin, Mycelex G), 100-mg vaginal tablet intravaginally each night for 7 nights; 1% vaginal cream, 1 applicator intravaginally each night for 7 nights, or 500-mg vaginal tablet intravaginally, once; butoconazole (Femstat), 2% cream, 1 applicator intravaginally each night for 3 nights; terconazole (Terazol), 80-mg suppository or 0.8% vaginal cream, 1 application each night for 3 nights or 0.4% vaginal cream intravaginally, each night for 7 nights; or tioconazole (Vagistat-1), 6.5% ointment intravaginally once. The only oral agent approved for treatment of CVV is fluconazole (Diflucan), 150 mg PO once, although others have used itraconazole (Sporanox), two 100-mg tablets PO qd for 3 days when approved treatments have failed. Costs range from $10 to $52 per treatment.
   b. Recurrent or persistent infections can be managed with any of the above 7-day dosage regimens for a prolonged course of 14–21 days. In addition, a trial of the fluconazole oral regimen (150 mg PO once; cost approximately $19) or ketoconazole (200 mg PO bid for 5–14 days; cost approximately $39), or itraconazole (Sporanox, 200 mg/d PO for 3 days; cost approximately $52) may be given. Older but potentially effective regimens include gentian violet vaginal staining, once or twice per week, or boric acid suppositories, 600-mg capsule in vagina qd for 14 days (cost approximately $14).
   c. Prophylaxis for CVV may be used monthly, including clotrimazole, one 500-mg vaginal tablet monthly; ketoconazole, 200 mg/d PO for 5 d/mo; fluconazole, 150 mg PO once each month; or miconazole, 100-mg vaginal tablet twice weekly.

Trichomonas vaginitis

   a. First-line treatment consists of metronidazole (Flagyl, Protostat), 2 g PO in a single dose or 500 mg PO bid for 7 days, costing approximately $5. Due to the sexually transmitted nature of this infection, all sexual partners of the patients should be notified and treated.
   b. Patients with recurrent or persistent infection can be treated with longer courses of therapy, including metronidazole, 500 mg PO bid for 14 days or 2 g/d PO for 3 days. Metronidazole gel, 5 g in vagina bid for 5 days, can be used concomitantly with PO metronidazole but is ineffective as solitary treatment for TV. Higher oral doses, such as 2–4 g daily for 14 days, may be used for difficult cases. Case reports suggest that tinidazole 250 mg PO qid with 500 mg intravaginally bid for 14 days, or paromomycin 250 mg intravaginally qd for 14 days may be effective for persistent infections. Povidone-iodine suppositories (in vagina bid for 14–28 days) or clotrimazole (100-mg vaginal tablet at bedtime for 7 nights) may be tried for symptom relief, but organism eradication is less likely. During pregnancy, metronidazole may be used after the first trimester. Lactating patients may take 2 g of metronidazole PO with discontinuation of breast-feeding for 24 hours (see also Chapter 22.2).

D. Prevention.

Multiple preventive measures for CVV, such as dietary modifications, avoidance of tight clothing, use of underwear with a cotton crotch, testing and treatment for diabetes, avoidance of oral contraceptives, and ingestion of *Lactobacillus* sp., have been tried with limited and mixed results (6). Although a trial of these interventions may be useful in women with persistent

and recurrent CVV, each intervention should be carefully evaluated for efficacy and should be discontinued if not helpful to avoid further morbidity and unnecessary lifestyle disruption. TV is a sexually transmitted infection; the consistent use of condoms with sexual partners will prevent the recurrence of this infection in the majority of cases and should be encouraged. No clear preventive measures have been identified in cases of BV.

II. Cervicitis.

Cervicitis is an inflammation of the endocervical tissue caused by bacteria, viruses, and possibly other irritants. The most commonly diagnosed causes include infection by *Neisseria gonorrhoeae, Chlamydia trachomatis,* or herpes simplex virus (HSV) type I or II, although the majority of clinical cases of cervical inflammation (indicated by discolored cervical discharge and inflammation on cytology smear) have negative tests for these three organisms. Other cervical infections exist, such as those caused by human papillomavirus (HPV), cytomegalovirus, *Mycoplasma hominis*, and *Ureaplasma urealyticum,* but the role of these in causing clinical cervicitis is less clear, and the resolution of cervicitis following treatment or eradication of these organisms has not been documented.

A. Clinical presentation.

The majority of cases of cervicitis are asymptomatic, unless they are associated with increased vaginal discharge or pelvic inflammatory disease. Hence, women typically present with abnormal cervical findings on a routine examination or may complain of a discolored vaginal discharge and be found to have copious cervical discharge, or may present due to the diagnosis of a sexually transmitted disease (STD) in her sexual partner. A high level of clinical suspicion and a low threshold for laboratory testing for cervicitis is needed if ongoing unrecognized infection, increased spread in the community, and possible long-term morbidity (infertility, pelvic inflammatory disease, pregnancy complications) and mortality are to be minimized.

The cervix may appear normal or may have increased erythema, increased friability, and increased mucus from the endocervical glands. The presence of “mucopus” (a nonclear cervical mucus) suggests cervical infection and should be further evaluated, as should the other findings listed previously. All women with a partner diagnosed with any STD should also be evaluated for cervical infection with *N. gonorrhoeae* or *C. trachomatis.*

B. Diagnosis.

Diagnosis of *N. gonorrhoeae* and *C. trachomatis* should be pursued in any suspected case of cervicitis (*N. gonorrhoeae* is discussed further in Chapter 19.6). The diagnosis of *C. trachomatis* infection requires laboratory testing for confirmation (see Chapter 19.7). Although the standard for *C. trachomatis* testing has been cell culture, this technique is not commonly used because of the need to maintain organism viability until culture and the laboratory requirements for performing the test. Numerous other tests of relatively high sensitivity and good specificity are now available, including polymerase chain reaction, DNA probes, direct monoclonal antibody testing, and enzyme-linked immunoassays. Familiarity with the test used and with the false-negative and false-positive rates inherent in the test allows accurate interpretation of results and communication with patients. Patients with possible HSV cervicitis, including those with cervical erosions, vulvar lesions, marked cervical erythema, a history of exposure to HSV-I or II, or cervicitis in pregnancy should be cultured for HSV infection (see Chapter 19.8). Cytology testing is not accurate for *C. trachomatis* (or *Trichomonas*) infection and should not replace microbiologic testing, but it should be kept current for the identification of cervical HPV infection with precancerous lesions. The value of testing for *U. urealyticum* or *M. hominis* is not substantiated to date and is not recommended at this time.

C. Management.

Cervicitis caused by *N. gonorrhoeae* and *C. trachomatis* should be managed aggressively and the test of cure documented due to the morbidity associated with these infections. Treatment for *N. gonorrhoeae* is included in Chapter 19.6 . Treatment for *C. trachomatis* cervicitis in non-pregnant women includes doxycycline (Vibramycin), 100 mg PO bid for 7 days, or azithromycin (Zithromax), 1 g PO in a single dose. Alternative regimens

include ofloxacin (Floxin), 300 mg PO bid for 7 days; erythromycin base, 500 mg PO qid for 7 days (recommended treatment during pregnancy); erythromycin ethylsuccinate, 800 mg PO qid for 7 days; or sulfisoxazole, 500 mg PO qid for 10 days (less effective). New data suggest that the cure rate during pregnancy is greater with azithromycin, 1 g PO once, than with erythromycin base. Ofloxacin should be avoided in adolescents (17 years or younger). HSV infection can be treated acutely and during any recurrences with a 7- to 10-day course of acyclovir 200 mg PO 5 times a day or 400 mg PO tid, famciclovir (Famvir) 250 mg PO tid, or valacyclovir (Valtrex) 1 g PO bid. Counseling of the patient (and sexual partners) regarding transmission, recurrences, and pregnancy risks is indicated. Cervical cytology should be performed if it has not been done within the past year to document the need for any cervical surveillance or treatment for HPV-related lesions.

The need for and effectiveness of treatment for cervicitis of unknown origin, associated with inflammation in the cervical discharge or on cytology but without documented infection with *N. gonorrhoeae, C. trachomatis,* or HSV, remains unclear. Because no evidence suggests the necessity of treating asymptomatic cervicitis in this category, patients without symptoms can be observed. Women with marked cervical discharge and those whose cervical inflammation continues to cause confusion with more serious cervical epithelial abnormalities may be treated empirically with medications used for *C. trachomatis, M. hominis,* or *U. urealyticum,* such as the doxycycline, ofloxacin, or azithromycin protocols listed previously.

D. Prevention.

The majority of organisms (bacterial or viral) associated with cervicitis are sexually transmitted. Hence, consistent and correct use of condoms during sexual activity (intercourse or oral sex) is needed to prevent recurrences. All sexual partners of women with cervicitis of known cause should be evaluated, counseled, and treated.

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13.2
DYSMENORRHEA AND PREMENSTRUAL SYNDROME

Pamela D. Parker

Premenstrual syndrome (PMS) is a term used to describe an array of somatic, cognitive, affective, and behavioral disturbances that recur in cyclic fashion during the luteal phase of the menstrual cycle and resolve with the onset of menstruation. More than 150 symptoms have been documented, varying from mild to severe enough to disrupt normal activities and interpersonal relationships. Not all cycles are associated with PMS symptoms, and not all premenstrual changes should be labeled PMS.

I. Diagnosis

A. Clinical presentation.

There is no typical presentation of PMS. Some of the more commonly reported physical symptoms include abdominal bloating and cramping, breast tenderness, fluid retention and weight gain, acne, cold sores, fatigue, and head and muscle aches. Frequently noted emotional changes include anxiety, panic, depression, heightened aggressiveness, hostility, food craving, forgetfulness, insomnia, irritability, mood lability, poor concentration, tearfulness, and reduced coping skills. The American Psychological Association has included severe PMS in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition as an axis I diagnosis entitled late luteal phase dysphoric disorder.

B. Etiology.

PMS represents a biophysiologic, endocrine phenomenon. Altered levels of various hormones have been offered as the cause for premenstrual symptomatology. These include estrogen, progesterone, prolactin, growth hormone, thyroid hormone, follicle-stimulating hormone, luteinizing hormone, antidiuretic hormone, insulin, prostaglandin, and cortisol. Studies have failed to confirm any of these as absolutely causative. Research has centered on the role of neurotransmitters and their effects on the female hormonal milieu (1). Endorphins, monoamines, and serotonin have all been implicated in altered physiologic and behavioral states in humans. Instability of circadian rhythm during the luteal phase with a clinical picture similar to seasonal affective disorder has been identified in symptomatic women (2). Premenstrual symptomatology and behavior may also stem from social, psychological, or cognitive dysfunction (3).

II. Assessment

A. Three key elements.

PMS only occurs in the presence of cyclic hormonal changes.

1. Symptoms occur in the luteal phase resolve within 1–2 days of onset of menses, and there is a symptom-free period during the follicular phase.
2. Symptoms must be documented through several menstrual cycles and are sufficient to disrupt a woman's life to some degree.
3. Other medical and psychological disorders must be ruled out.

B. Physical examination.

A detailed medical, surgical, gynecologic, social, and family history must be obtained. Do not forget to ask about use of alcohol, tobacco, and recreational drugs. A complete physical examination, including pelvic, must be performed. The need for in-depth neurologic or psychological evaluation may become apparent.

C. Laboratory studies.

No specific diagnostic test is currently available for detecting PMS. The laboratory investigation should be tailored to the individual patient. For example, complete blood count and thyroid studies should be considered in patients with menorrhagia or chronic fatigue (see Chapter 2.2 and Chapter 13.3).

D. Cycle charting.

Charting the menstrual cycle and documenting ovulation using basal body temperature measurements are important in the diagnostic process. A symptom log must also be maintained for at least three consecutive cycles. Patients write down the symptoms that trouble them most and rate their severity throughout the entire menstrual cycle (4). Presence of luteal phase symptoms in at least two cycles, lack of follicular phase symptoms, and absence of other specific disease entities strongly suggest the diagnosis of PMS.

III. Management.

The clinician must approach PMS from a biopsychosocial perspective and must individualize the treatment plan to maximize the therapeutic response.

A. Psychosocial.

Patients and significant others must be educated about PMS. Stress management strategies should be taught. Sufficient rest and regular exercise have been demonstrated to alleviate some PMS symptomatology, as have acupuncture, reflexology techniques, and light therapy (5,6).

B. Nutrition.

A well-balanced diet with adequate protein, fiber, and carbohydrates is essential. Caffeine, salt, excess sugar, alcohol, and recreational drugs

may worsen physical symptoms and emotional lability. Multivitamins and calcium and magnesium supplements can be used. Pyridoxine (vitamin B_6) may reduce fatigue, depression, and irritability in selected women. Doses higher than 50 mg/d have been found to cause irreversible neurotoxicity in some cases (7).

C. Pharmacologic.

If premenstrual complaints do not respond to the previously mentioned suggestions, medical therapy can be initiated. Symptom logs assist the clinician in tailoring treatment to the individual needs.

1. **Ovulation suppression.** Without menstrual cyclicity, PMS cannot occur. Oral contraceptives, medroxyprogesterone (Depo-Provera), levonorgestrel (Norplant System), and gonadotropin-releasing hormone agonists have been tried with variable success. Hysterectomy without oophorectomy does not cure PMS.
2. **Suppression of physical symptoms.** Prostaglandin inhibitors, such as naproxen or mefenamic acid, can relieve headache, body aches, and dysmenorrhea. Spironolactone 25–50 mg bid for days 14–28 may reduce fluid retention. Danazol 200 mg/d for days 19–28, bromocriptine 5 mg/d for days 10–26, and tamoxifen 10 mg/d for days 5–24 are effective in reducing mastalgia, although adverse side effects limit duration of therapy.
3. **Suppression of psychologic symptoms.** Alprazolam, often prescribed for its anxiolytic effects, has also been found to increase food cravings, impair task performance, and exacerbate negative mood during the premenstruum (8,9). The addictive potential of benzodiazepines must be weighed against possible benefits. Buspirone, 10 mg bid-tid for days 16–28, may reduce premenstrual anxiety. Selective serotonin reuptake inhibitors (specifically citalopram, sertraline and fluoxetine) have been cited in many well-controlled studies as safe and effective agents for treatment of both PMS and premenstrual dysphoric disorder (10). Episodic treatment during the luteal phase may be more beneficial, with fewer side effects and less economic impact than continuous therapy (11).

   PMS is a complex reproductive disorder. Successful management requires continued communication and collaboration between patient and clinician.

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13.3
ABNORMAL GENITAL BLEEDING IN WOMEN AND GIRLS

Pepi Granat

The patient with abnormal genital bleeding (not typical for that patient) might need immediate intervention or a routine office visit. Age and menstrual history suggest the likely index of suspicion for serious causes and the appropriate clinical approach.

I. Bleeding requiring urgent care.

The most common cause of an unusual bleeding pattern is pregnancy or its complications (1).

A. Assessment.

Think of the worst first (ectopic pregnancy, uncontrolled hemorrhage, trauma, large degenerating fibroids) and train staff to do the same. Is this an emergency? The patient who phones the clinic/office must be queried in sufficient depth to allow proper triage; staff members who answer telephones should be trained to screen such calls.

1. **Severity**
   a. **Rate of flow.** How heavy is the bleeding? Pad counts are unreliable because of differences of absorbency but may give a rough estimate. The patient's own opinion is probably more valid. When did it start? Is the blood bright red or dark, with or without clots? If it is heavier than she has ever seen it, if it is flowing, if brighter red than menstrual blood, and if there are clots or pieces of tissue, there might be significant hemorrhage and the patient should not wait even a short time. If she cannot get to the office immediately she should go to the nearest emergency room, by ambulance or 911. She should be instructed to retrieve any tissue passed for the purpose of analysis.
   b. **Amount of flow.** A rough estimate of blood loss can be made by asking how much more bleeding than a usual period she has had since onset. (Normal menstrual blood loss is 20–80 cc.)
2. **Associated symptoms.** Has there been fever, dizziness, abdominal pain, diarrhea? Any of these could signal associated pelvic infection or abscess, shock, severe loss of blood volume, dehydration, other intra-abdominal pathologic process, or bleeding tendency.
3. **Likely causes.** Has this ever happened before? What have previous pelvic exams revealed, such as known fibroids? Does she have an intrauterine device (IUD)? Ask about abuse and trauma. What was the date of last period, or of any bleeding? Is pregnancy a possibility? Has she performed a proprietary pregnancy test? Such tests are quite reliable and results, with dates, should be noted. Any history of sexual activity presupposes pregnancy; even when the possibility is denied, a pregnancy test should be done. Postmenopausal women must be asked date of last bleeding. Find out present and recent past medication and hormone regimens (including adherence), with names and dosages. Any use of a medication, including drops, creams, and/or "natural" remedies, should be noted. Hormonally active nostrums, such as ginseng, found in drug stores, health food stores, and mail-order or internet pharmacies, can cause bleeding (see Chapter 22.3).
4. **Physical examination.** Check vital signs; do abdominal, perineal, vaginal, pelvic, and rectal exam. The exam must meticulously pinpoint the exact source, which may not be obvious.

B. Management.

Acute, heavy bleeding requires close observation, accurate determination of the source and likely cause, and immediate therapy. Hospitalization, hydration, and transfusion may be required.

1. **Medical.** If the bleeding is uterine, intravenous conjugated estrogen (Premarin) 25 mg can be given acutely every 4 hours for 24 hours, or until bleeding stops (2). Also, one can give Premarin orally, 10–20 mg/d in divided doses (3). Antiemetics should be given for nausea.

2. **Surgical.** After one or two doses, if bleeding has not slowed or if patient is unstable, dilatation and curettage (D&C) should follow (3).
3. **Follow-up.** After bleeding stops, combination oral contraceptive pills (OCs) without placebo break, or a progestin alone, should be given for 3–4 months. Then cyclic OCs can be given. Anemic patients should receive iron (2).

II. Nonurgent genital bleeding

A. Nonuterine bleeding.

Determine the source. This sounds easy but may not be. Patients and even physicians can be unclear as to where the blood is coming from. A laceration of the cervix, or of the vagina, especially if high in a fornix, may appear to be uterine. Urinary or rectal bleeding may be mistaken for vaginal bleeding.

1. **Vulvar or vaginal causes:** infection, laceration, tumor, foreign body.
2. **Extravaginal causes:** perineal, urinary, rectal
3. **Systemic medical causes:** bleeding diathesis, especially thrombocytopenia; von Willebrand's disease; liver, renal, endocrine disease.

B. Uterine bleeding.

Age-grouping is important (3). For ages 13–40 years, anovulatory bleeding (dysfunctional uterine bleeding, DUB) is common and may be treated as such without an exhaustive search for all other causes initially, as long as there is a normal medical history, pregnancy test, complete blood count (CBC), Pap smear, and a normal bimanual pelvic examination. One must consider pregnancy-related causes, especially ectopic pregnancy, even when bleeding is light or moderate, and even in young and perimenopausal women. A common response of patients is, “I couldn't be pregnant; I just had my period.” Once pregnancy is ruled out, the diagnosis of DUB, although one of exclusion, does not require total certainty before reasonable treatment for anovulation is implemented. Although not all uterine bleeding in this group will prove to be DUB, serious pathology in the face of normal findings is unlikely. If hormonal manipulation fails, a more complete workup can follow.

A very different scenario pertains to the peri- and postmenopausal woman, in whom bleeding must be investigated before anovulation can be assumed.

1. **Differential diagnosis** of noncyclic uterine bleeding (non-DUB) (4): uterine leiomyoma, endometrial polyp, endometrial hyperplasia or carcinoma, leiomyosarcoma, cervical or vaginal neoplasia, endometritis, adenomyosis, bleeding associated with pregnancy (threatened or incomplete abortion, trophoblastic disease, ectopic pregnancy), bleeding associated with the puerperium (retained products of conception, placental polyps, subinvolution of the uterus), coagulopathies [von Willebrand's disease (5), platelet abnormalities, thrombocytopenic purpura], iatrogenic causes and medications, systemic diseases (liver, renal, thyroid).
2. **Anovulation** (DUB). Physiologic causes are adolescence [although 4%–20% of adolescents have a coagulopathy underlying their abnormal bleeding (4)], perimenopause (although abnormal bleeding must be considered neoplastic or hyperplastic until proven otherwise), lactation, and pregnancy.

   Pathologic causes are hyperandrogenic anovulation (e.g., polycystic ovary syndrome, congenital adrenal hyperplasia, androgen-producing tumors), hypothalamic dysfunction (e.g., secondary to anorexia nervosa), hyperprolactinemia, hypothyroidism, primary pituitary disease, premature ovarian failure, and iatrogenic factors (e.g., secondary to radiation therapy or chemotherapy)

   Types of DUB (defined as bleeding associated with anovulation, in the absence of other pathology) are estrogen withdrawal, which occurs after removal or irradiation of ovaries, or after giving and then withdrawing estrogen to a person without ovaries (mid-cycle bleeding can be due to preovulation drop in estrogen); and estrogen breakthrough, which is due to stimulation of endometrium from unopposed low- or high-level estrogen. (Low-dose estrogen produces intermittent light spotting; high-dose

estrogen yields amenorrhea followed by profuse bleeding. Cyclic progesterone corrects this); progestin withdrawal, which occurs only if there has been prior estrogen priming; and progestin breakthrough, which can occur when endometrium becomes so atrophic that lack of estrogen effect yields too little and too ragged a lining for synchronous cellular events. (Estrogen replacement therapy can restore responsiveness. This occurs after months on OCs or depoprogesterone. Adding estrogen for a week usually corrects the problem [1]).

C. Assessment

(initial evaluation as with urgent bleeding, see Section I.A)

1. **History and physical examination.** A detailed, sensitive history and physical exam with good exposure for the speculum exam, and optimal palpation of pelvic organs using bimanual and rectovaginal techniques, is crucial to finding serious and treatable pathology. A Pap smear and breast exam should be done. Obesity and hirsutism should be noted (see Chapter 17.1). An estimate of prior hormonal influences should be made in an attempt to classify the type of anovulation..
2. **Basic laboratory tests** should include pregnancy test (ß-human chorionic gonadotropin), CBC with platelets and differential, sedimentation rate or C-reactive protein, prothrombin time, partial thromboplastin generation time, thyroid-stimulating hormone, and, if indicated, ristocetin cofactor for von Willebrand's disease. These will suffice to make the presumptive diagnosis and initiate treatment (1).
3. The **examination findings** may suggest other studies, such as endometrial biopsy (easily performed by many family physicians), hysteroscopy, colposcopy, pelvic and/or endovaginal sonography, hysterosalpingography, and hysterosonography. Most procedures carry known and even unknown risks. For instance, a recent study found that women with endometrial cancer who had a prior hysteroscopy had significantly more peritoneal tumor implantation (6).
4. If **ultrasonography** is performed, an endometrial biopsy is mandatory with an endometrial stripe greater than 8 mm. An endometrial height of less than 4 mm nearly rules out hyperplasia. Between 4 and 8 mm, other features of the clinical presentation (such as persistent bleeding) and the patient's (and physician's) tolerance for uncertainty must guide the decision regarding biopsy.
5. **Management.** Treatment for specific pathology depends on the underlying cause and may be managed by the family doctor or require referral to a gynecologist, endocrinologist, or gynecologic oncologist. Ovulatory, heavy periods (menorrhagia) may be managed with antiprostaglandins. If, by exclusion or judgment, DUB is the working diagnosis, either an OC or cyclic progesterone can be used. Natural micronized progesterone, 200 mg, can be given for 12–14 days, monthly. Medroxyprogesterone or norethindrone in doses of 5 or 10 mg/d (or even higher initially to stop the bleeding) for 12–14 days can also be used. Duration of treatment depends on circumstances of bleeding, fertility or contraceptive needs, and the age of the patient.

D. Special considerations

1. **Structural or anatomical causes concurrent with DUB.** Fibroids, especially when large, can degenerate and be the primary source of bleeding. But fibroids are common and their presence, especially if small, does not mean that they caused the bleeding. DUB may still be the primary diagnosis. DUB or infection can occur with an IUD in place, which may be retained if treatment of the underlying cause is successful.
2. **Post-menopausal bleeding**
   a. For the woman not on hormones the decision is clear. She needs a thorough investigation of the cause of the bleeding, including endometrial sampling to rule out endometrial cancer (see also Chapter 13.6).
   b. For the woman on hormones an individual decision must be made based on her prior problems and her hormone regimen.

1. Patients taking unopposed estrogen should be told that they must have endometrial biopsies yearly.
2. Although continuous or monthly progesterone is protective, endometrial cancer is not entirely ablated by its addition to the estrogen regime; it must be ruled out by endometrial biopsy in the face of persistent bleeding.
3. Patients taking progesterone less than monthly should have endometrial sampling if bleeding is off schedule. It is reasonable to obtain an endometrial sample without prior ultrasono-graphic examination; the procedure is simple and yields definitive tissue.
4. Patients taking tamoxifen are at higher risk for endometrial cancer; those taking raloxifene are at lower risk.

3. **Perimenopause.** As early hormonal treatment is now common, a physician who is making a decision must take into account the special circumstances of the bleeding. In some cases, one can treat the hormonal transition as DUB before doing more testing. In others, endometrial sampling and/or imaging is advised. It is better to err on the side of endometrial sampling.
4. **Cervical stenosis.** If endometrial biopsy is impossible, an ultrasound scan with acceptable endometrial height (less than 4–5 mm) may suggest therapy for DUB. If the endometrial height is greater than 8 mm, referral to a gynecologist (with probability of D&C) is indicated.

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13.4
PAP SMEAR EVALUATION FOR CERVICAL CANCER

Diane M. Harper

The Pap smear, named for Dr. George Papanicolaou, is a screening tool that has helped to decrease the incidence of cervical cancer by 74% in the past 60 years. The American Cancer Society estimates that there will be 12,800 new cases of cervical cancer in 2001, with 4,600 of these women dying from the disease. Risk factors for cervical cancer include multiple sexual partners, early intercourse, human papillomavirus (HPV) infection, smoking, HIV infection, and immunosuppression. The detection, diagnosis, and eradication of cervical cancer precursors help prevent the development of invasive cervical carcinoma. It has been estimated that each year approximately 1.5 million women in the United States have low-grade cervical cytologic abnormalities and 110,000 have high-grade abnormalities. These abnormalities are generally asymptomatic and are detected during the patient's screening Pap smear.

I. Pap smear collection

A. Recommended screening.

Start at age 18 or at the time of first sexual intercourse, then every 1–3 years, depending on risk factors, up to age 65.

B. Optimum sampling

Avoid douche, vaginal intercourse, or lubricant for 24 hours prior to the examination. Use a speculum lubricated only with warm water. Fully visualize the cervix. Sample the transformation zone, which is usually present on the ectocervix. Use an endocervical brush to sample the endocervical canal. Fix the specimen immediately.

C. The pathologist's interpretation

of the Pap smear can be influenced by the patient's past cervical history and any current abnormal physical findings, making it prudent to include this information on the requisition form.

D. Absence of endocervical cells or metaplastic cells

suggests an inadequate smear. The smear should be repeated.

II. Reporting system.

A new classification system, the Bethesda System, was developed in 1988 and revised in 1991 (1) (Table 13.4-1) and revised again in 2001. The Bethesda System format of the Pap smear includes the following:

Specimen adequacy
Satisfactory for evaluation
Satisfactory for evaluation but limited by (reason specified)
Unsatisfactory for evaluation (reason specified)
General categorization
Within normal limits
Benign cellular changes (see descriptive diagnosis)
Epithelial cell abnormality (see descriptive diagnosis)
Descriptive diagnoses
Benign cellular changes
Infection
Trichomonas vaginalis
Fungal organisms morphologically consistent with *Candida*
Predominance of coccobacilli consistent with shift in vaginal flora
Bacteria morphologically consistent with *Actinomyces*
Cellular changes consistent with herpes simplex virus
Other
Reactive changes
Reactive cellular changes associated with:
Inflammation (includes typical repair)
Atrophy with inflammation (atrophic vaginitis)
Radiation
Intrauterine device
Other
Epithelial cell abnormalities
Squamous cell
Atypical squamous cells of undetermined significance
Low-grade squamous intraepithelial lesion encompassing human papillomavirus, mild dysplasia/CIN I
High-grade squamous intraepithelial lesion encompassing moderate and severe dysplasia, carcinoma in situ/CIN II and CIN III
Squamous cell carcinoma
Glandular cell
Endometrial cells, cytologically benign, in a postmenopausal woman
Atypical glandular cells of undetermined significance
Endocervical carcinoma
Endometrial adenocarcinoma
Extrauterine adenocarcinoma
Adenocarcinoma not otherwise specified
Other malignant neoplasms
Hormonal evaluation (vaginal smears only)
Hormonal pattern compatible with age and history
Hormonal pattern incompatible with age and history (reason specified)
Hormonal evaluation not possible (reason specified)

CIN, cervical intraepithelial neoplasia.
From the National Cancer Institute Workshop, Bethesda, MD, 1991.

Table 13.4-1. Revised Bethesda system for cervical and vaginal cytology, 1991

A. Statement of adequacy

B. A general categorization

C. Descriptive diagnoses

include benign cellular changes (infection or reactive changes). Epithelial cell abnormalities are squamous and glandular. The squamous components include atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesion (LSIL), which includes any HPV changes; high-grade squamous intraepithelial lesion (HSIL); and squamous cell cancer (SCC). The glandular components include atypical glandular cells of undetermined significance (AGUS), adenocarcinoma in situ (AIS), and adenocarcinoma.

III. Management of normal and abnormal Pap smears

A. Within normal limits.

Repeat Pap smear annually (or every 3 years if low risk and patient has had three consecutive normal smears 1 year apart).

B. Benign cellular changes

1. Infection may be fungal, trichomonal, bacterial, actinomycetal, or herpetic. Treat if symptomatic. Continue annual Pap smears.
2. Reactive changes include inflammation, atrophy, radiation damage, or be related to use of an intrauterine device. No treatment indicated. Continue annual Pap smears.

C. Epithelial cell abnormalities

1. **Squamous cell abnormalities**
   a. **ASCUS.** The ASCUS/LSIL ratio should be 3:1 or less. A greater frequency may represent overuse of the ASCUS diagnosis. This result can be categorized by the pathologist in terms of whether the changes favor a reactive or a premalignant/malignant process. If the reading favors a reactive process, perform a follow-up Pap smear in 6 months. If patient has repeated readings of ASCUS, regardless of subclassification, then recommend colposcopy (2). A positive HPV test for high-risk types after one ASCUS indicates the need for colposcopy. A negative HPV test is reassuring and the woman can continue with annual screening. If a diagnosis of ASCUS is qualified by a statement favoring a neoplastic process, manage as for a diagnosis of low-grade squamous intraepithelial lesion. If a patient with a diagnosis of ASCUS is at high risk (e.g., previous positive Pap tests, poor compliance for follow-up), consider colposcopy.
   b. **LSIL** If the woman is compliant with follow-up, the Pap smear can be repeated in 6 months. If any abnormal reading occurs at the sixth month repeat, the woman should have colposcopy. Many incident HPV infections represented as LSIL will spontaneously revert to normal within 6 months. Alternatively, a woman with a LSIL Pap result can go directly to colposcopy.
   c. **HSIL.** A woman with a HSIL Pap result must have a colposcopy with directed biopsy.
   d. **Squamous cell cancer** Refer for staging and therapy.

2. **Glandular cell abnormalities**
   a. **AGUS.** Refer for colposcopy immediately.
   b. **AIS or adenocarcinoma.** Refer for staging and therapy (3).

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13.5
PELVIC INFLAMMATORY DISEASE

Martin A. Quan

Acute pelvic inflammatory disease (PID) is an ascending infection of the female genital tract involving the uterus, fallopian tubes, ovaries, and adjacent pelvic structures. More than a million American women are diagnosed and treated for acute PID each year, and one fourth of them develop serious sequelae, including tubal factor infertility, ectopic pregnancy, and chronic pelvic pain. Although it is widely accepted that PID frequently arises from a cervicitis caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis,* a growing body of evidence suggests that bacterial vaginosis may also play a role in initiating the ascending infection (1) (see Chapter 13.1, Chapter 19.6, and Chapter 19.7).

I. Epidemiology.

Epidemiologic risk factors that identify a patient at increased risk for acute PID include age less than 25 years, sexarche prior to age 16 years, multiple sexual partners, history of a sexually transmitted disease (including PID), the postinsertion period in intrauterine device (IUD) users, vaginal douching more than three or four times per month, and the presence of bacterial vaginosis (2).

II. Clinical presentation.

Women with acute PID present with a wide spectrum of nonspecific clinical symptoms and signs, ranging from being relatively asymptomatic to feeling quite ill.

A. History.

Lower abdominal pain usually described as constant and dull and of less than 14 days' duration is the most common complaint reported by patients with acute PID. Other manifestations include abnormal vaginal discharge, abnormal vaginal bleeding, gastrointestinal upset, and dysuria.

B. Physical examination

Cervical motion tenderness and adnexal tenderness (unilateral in up to 20% of cases) are the physical findings most frequently elicited in patients with PID. Rebound tenderness is present in two thirds of patients, and an adnexal mass or fullness in 16%–49% of patients. Fever is a variable finding reported in 24%–60% of patients (2).

C. Laboratory evaluation

1. **Hematologic studies**
   a. **White blood count.** A leukocytosis is present in only 50% of cases.
   b. **Erythrocyte sedimentation rate (ESR).** Although classically elevated in PID, the ESR is normal (less than 15 mm/h) in 25% of patients (3).
   c. **C-reactive protein.** A C-reactive protein exceeding 5 mg/dL is found in 71% of patients with PID (4).
2. **Cervical Gram's stain.** The finding of gram-negative intracellular diplococci in three or more neutrophils per oil immersion field corroborates the diagnosis of gonococcal cervicitis and supports the diagnosis of

PID. Similarly, the finding of 10 or more neutrophils per oil immersion field is pathognomonic for the diagnosis of mucopurulent cervicitis and corroborates the diagnosis of PID.

3. **Examination of the male partner.** Examination of the male partner for the presence of urethritis can be a source of confirmatory evidence for the diagnosis of PID in 50% of cases (5).
4. **Pregnancy testing.** A sensitive pregnancy test should be routinely obtained in all patients with suspected PID because of the great difficulty encountered in clinically differentiating patients with PID from those with ectopic pregnancy. Urine monoclonal antibody pregnancy tests and qualitative serum pregnancy tests become positive at human chorionic gonadotropin (hCG) levels as low as 25 mIU/mL and detect up to 96% of ectopic pregnancies (6,7). Quantitative serum pregnancy tests detect hCG levels as low as 5 mIU/mL, and a negative test result virtually excludes the diagnosis of an ectopic gestation (8).
5. **Cervical cultures and nonculture tests.** Laboratory documentation of a cervical infection with *N. gonorrhoeae* or *C. trachomatis* corroborates the diagnosis of PID. Nonculture tests, which offer a more rapid turnaround time than do cultures, include direct immunofluorescent antibody tests for *Chlamydia* as well as enzyme immunoassay tests, DNA probe tests, and nucleic acid amplification assays for the detection of chlamydia and gonorrhea (9,10 and 11).
6. **Culdocentesis.** Purulent fluid aspirated from the cul-de-sac supports the diagnosis of acute PID but can also be found in other causes of peritonitis, such as acute appendicitis or ruptured diverticular abscess.
7. **Pelvic ultrasonography.** Sonographic findings consistent with acute PID include distention and dilatation of the fallopian tubes, fluid in the cul-de-sac, and the finding of a complex, multiloculated adnexal mass.
8. **Endometrial biopsy.** The histopathologic finding of plasma cell infiltration in the endometrial stroma obtained on biopsy confirms the diagnosis of PID (12).
9. **Diagnostic laparoscopy.** Diagnostic laparoscopy is regarded by many authorities as the standard for the diagnosis of acute PID. Criteria required for the diagnosis include abnormal erythema and edema of the fallopian tubes and spontaneous or expressible tubal inflammatory exudate.

III. Establishing the diagnosis.

Because of the difficulty of diagnosis and the serious consequences of untreated PID, current guidelines for the diagnosis of PID developed by the U.S. Centers for Disease Control and Prevention (CDC) reflect a lowering of the diagnostic threshold. However, it is important to recognize that a clinical diagnosis of PID may be correct only two thirds of the time (2).

A. Minimum diagnostic criteria.

Provided that competing diagnoses can be adequately excluded, the CDC recommends that a provisional diagnosis of PID be made and a therapeutic trial of antibiotics be initiated in patients with simple lower abdominal tenderness coupled with cervical motion and adnexal tenderness on examination (13).

B. Additional diagnostic criteria

For patients with severe presentations, it is prudent to seek additional diagnostic criteria to allow a more reliable diagnosis to be made. Such criteria call for fulfillment of the minimum diagnostic criteria listed in Section III.A plus at least one of the following (14):

1. Temperature exceeding 38.3°C
2. Abnormal cervical discharge
3. Elevated ESR or C-reactive protein
4. Laboratory documentation of a gonococcal or chlamydial cervical infection
5. The finding of a tubo-ovarian abscess on pelvic ultrasonography
6. Histopathologic evidence of endometritis on endometrial biopsy
7. Laparoscopic abnormalities consistent with PID

IV. Management

A. Need for hospitalization.

Current CDC guidelines favor hospitalization under the following circumstances (14):

1. The diagnosis is uncertain, or a surgical emergency, such as ectopic pregnancy or acute appendicitis, cannot be adequately excluded.
2. A tubo-ovarian abscess is present.
3. Pregnancy.
4. Failure to respond clinically to oral antimicrobial therapy.
5. Severe illness, nausea and vomiting, or high fever.
6. Inability to follow or tolerate an outpatient oral regimen.
7. Immunodeficiency (i.e., HIV), infection with low CD4 counts, taking of immunosuppressive therapy (see Chapter 19.4).

B. Antibiotic therapy.

Antibiotic therapy remains the cornerstone of treatment for acute PID. Empirical, broad-spectrum antimicrobial therapy targeting *N. gonorrhoeae, C. trachomatis,* enteric gram-negative facultative bacteria (including *Escherichia coli*), and certain anaerobic bacteria (such as *Bacteroides* sp.) is recommended. Regardless of the antibiotic regimen prescribed, it is incumbent that a follow-up examination be performed in all patients 48–72 hours after the start of therapy to assess whether the anticipated clinical improvement and resolution of fever has been achieved.

1. **Inpatient regimens.** Parenteral therapy can be discontinued as soon as 24 hours after the patient has improved clinically. Regimens suggested by the 1998 CDC guidelines are as follows (15):
   a. Doxycycline, 100 mg IV (or PO) q12h, plus cefoxitin, 2 g IV q6h (or cefotetan, 2 g IV q12h), followed by doxycycline, 100 mg PO bid for a total of 14 days.
   b. Clindamycin, 900 mg IV q8h, plus gentamicin, 2.0 mg/kg IV followed by 1.5 mg/kg IV q8h, followed by either doxycycline, 100 mg PO bid, or clindamycin, 450 mg PO qid, to complete 14 days of total therapy.
2. **Outpatient regimens.** Suggested regimens are as follows:
   a. Cefoxitin, 2 g IM plus probenecid, 1 g PO concurrently, or ceftriaxone, 250 mg IM, or other third-generation cephalosporin, IM once, plus doxycycline, 100 mg PO bid for 14 days.
   b. Ofloxacin, 400 mg PO bid for 14 days, plus metronidazole, 500 mg PO bid for 14 days.

C. Additional measures.

General supportive measures, such as bed rest, sexual abstinence until cure is achieved, hydration, and provision of antipyretics and appropriate analgesia, are recommended in the management of PID. If the patient has an IUD, removal of the device is recommended following the institution of antibiotic therapy. Epidemiologic treatment of gonorrhea and chlamydia is recommended for sexual partners of patients with PID if they had sexual contact with the patient during the 60 days preceding the onset of symptoms in the patient.

D. Surgical treatment

Surgical treatment has a limited role in the management of acute PID. Possible indications for surgical intervention include confirmation of the diagnosis in a patient failing to respond despite optimal antibiotic treatment, excision of chronically infected pelvic organs, and drainage of pelvic abscesses.

V. Prevention.

In addition to ensuring that both the patient and her partner receive effective treatment and follow-up, preventive measures generally revolve around epidemiologic measures designed to prevent the transmission of STDs. Such measures include promotion of safe sexual behavior, the increased use of mechanical and chemical methods of contraception as a means of preventing the transmission of STDs, the early recognition and treatment of cervicitis, and screening of young, sexually active women at increased risk for cervical chlamydial infection (16).

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13.6
MENOPAUSE

Cynda Ann Johnson

Description of the menopause

(1,2 and 3)

I. Definition.

Natural menopause is defined as the failure of ovarian follicular development in the presence of adequate gonadotropin stimulation, resulting in the cessation of spontaneous menstrual periods. Follicle-stimulating hormone and luteinizing hormone levels are continuously elevated after menopause, whereas they may fluctuate in the perimenopausal period. Menopause may also be secondary to surgical intervention or drug effect, particularly that of chemotherapeutic agents. The average age of menopause in the United States is 51.4 years, whereas the average age for a woman to enter the menopause transition or perimenopause is 47. The perimenopause usually lasts from 4 to 5 years, during which the woman begins to notice changes in her menstrual cycle and may experience hot flashes. Age of menopause in women who smoke averages 2 years younger than in those who do not smoke. Evidence of menopause before age 35–40 is designated premature menopause and usually necessitates a workup for causality.

A. Symptoms

Whereas vasomotor symptoms are an early indication of menopause, atrophic symptoms appear somewhat later. Many other consequences are associated with menopause and the concomitant decrease in estrogen production, including increased risk of coronary heart disease (CHD) and osteoporosis, and possibly Alzheimer's disease, colon cancer, and macular degeneration.

B. Treatment/prevention of menopausal symptoms/consequences

1. **Estrogen replacement therapy** (ERT) is the only pharmacologic treatment that directly targets all estrogen deficiency-related consequences of menopause. ERT should be started as soon as possible after menopause to achieve maximum benefit. Whether long-term ERT should be recommended to all women in whom it is not clearly contraindicated is controversial.
2. **Other therapies** may be indicated as adjuncts or alternatives to estrogen for treatment of specific symptoms.
   a. **Vasomotor symptoms.** Clonidine hydrochloride is a mainstay of symptomatic therapy. Other therapies that have been shown to improve symptoms in some studies are methyldopa, high-dose progesterone, vitamin E, phytoestrogen supplementation (soy products), and the herb black cohosh. The latter may have significant side effects and should only be used for a maximum of 6 months. Nonsmoking women still in the perimenopausal period can be prescribed low-dose (20 µg ethinyl estradiol) oral contraceptive pills for both cycle control and treatment of vasomotor symptoms, as well as prevention of unintended pregnancy.
   b. **Headaches** These can be treated by standard treatment regimens or verapamil hydrochloride, starting at 80 mg/d (see Chapter 6.1).
   c. **Urogenital atrophy** Vaginal estrogen cream can be used therapeutically. Replenishment therapy (water, glycerin, mineral oil, palm oils) can be used to provide symptomatic relief only.
   d. **Osteoporosis** General measures for osteoporosis prevention and treatment include an appropriate program of weight-bearing and muscle-strengthening exercise, risk factor reduction (including smoking cessation and moderation of alcohol intake), and fall prevention measures. Adequate nutrition should include calcium 1,200–1,500 mg/d and vitamin D. Several selective estrogen receptor modulators and bisphosphonates are now approved for the prevention and treatment of osteoporosis. Other pharmacologic treatments include progesterone, calcitonin, and fluoride. Phytoestrogens in high doses demonstrate a positive effect on bone density (see also Chapter 17.6).
   e. **Coronary heart disease** Important measures for the prevention and treatment of CHD are regular physical activity; achievement and maintenance of desirable weight, blood pressure, and lipid levels; eating a healthful diet that is low in fat, cholesterol, and salt, and high in dietary fiber; as well as addition of antioxidants such as vitamins C and E (see also Chapter 9.2).

II. Hormone replacement therapy

(4,5)

A. Definition.

Estrogen replacement therapy refers to the administration of estrogen in the menopause. Hormone replacement therapy (HRT) usually refers to the administration of both estrogen and progestin but could also refer to the use of either hormone alone.

B. Rationale.

The four currently accepted reasons for ERT are to prevent or minimize vasomotor symptoms, to reduce the discomfort or potential complications of urogenital atrophy, to retard bone loss so as to prevent the consequences of osteoporosis, and to decrease the risk of coronary artery disease. However, newer studies have called into question the use of estrogen for secondary prevention of coronary artery disease.

C. Other effects of HRT

1. Because estrogen stimulates endometrial cell biosynthesis, women with a uterus who used unopposed estrogen were found to have a sixfold increase in cancer of the uterus as opposed to nonusers. Progestins counteract this negative effect. When given in doses equivalent to medroxyprogesterone acetate (MDA) 10 mg/d for at least 12 days of the month, the endometrium does not develop beyond the stage of normal proliferation.
2. Fear of breast cancer is the most common factor in women considering estrogen replacement. The degree, if any, to which estrogen replacement influences the development and/or spread of breast cancer is controversial. In studies that have shown increased risk, the risk increased with longer duration of use and was reduced after cessation of use. Breast cancers that developed appeared to be more localized and associated with lower mortality than those that developed in women not exposed to ERT. The addition of a progestin to the regimen does not appear to lower the risk and may increase the risk of development of breast cancer (see also Chapter 13.8).
3. Estrogens generally have a positive effect on the lipid profile; progestins may blunt some of these effects.

D. Contraindications to ERT.

Contraindications to the use of menopausal estrogen include known or suspected pregnancy; undiagnosed abnormal genital bleeding; known or suspected breast cancer; estrogen-dependent neoplasia; and active thrombophlebitis or thromboembolic disorders or a history of these disorders associated with estrogen use.

E. Evaluation of the patient before instituting HRT.

The history should focus on menstrual and menopausal history, family history of cancer of the breast and uterus, and risk factors for osteoporosis and coronary artery disease, including family history. The physical examination should emphasize the breast examination and pelvic examination with Pap smear. Mammograms should be carried out yearly in women on HRT. Other tests to be used in selected individuals include a progesterone challenge test, transvaginal ultrasonography, endometrial biopsy, and bone densitometry.

F. Initiation of therapy

1. HRT may be begun during the perimenopausal years if the woman is symptomatic, with the understanding that HRT may not reliably inhibit ovulation. If HRT is being considered to control dysfunctional uterine bleeding, an endometrial biopsy should be undertaken prior to therapy.
2. Postmenopausal patients who will be prescribed approved HRT regimens do not routinely need an endometrial biopsy prior to therapy.

G. Types of hormones and routes of administration

1. **Estrogen.** Standardized ERT regimens are administered by the transdermal or oral route, using conjugated estrogens, estradiols, estrones and, more recently, ethinyl estradiol.
2. **Progestin** A variety of progestins are used in HRT regimens. Most commonly used in the United States is medroxyprogesterone acetate, which is inexpensive and low in androgen side effects. Micronized progesterone, considered to be a natural progesterone, is also available. Studies have shown an improved lipid profile in women using micronized progesterone when compared to other progestins in an HRT regimen. In standard HRT regimens the progestin is administered transdermally, orally, or via an intrauterine contraceptive device (IUD).

H. Sample HRT regimens.

HRT regimens are continuously being refined in the search for a combination that will result in the fewest side effects while achieving total amenorrhea. When that is not possible, sometimes regular withdrawal bleeding is preferred over irregular bleeding. Other estrogens and progestins can be used if selected in dosages equivalent to those described below.

1. **Combined continuous HRT.** Conjugated estrogens, 0.625 mg, and MDA, 2.5 mg, are given daily. Occasional vaginal bleeding is common

during the first 6 months, and endometrial biopsies should be restricted during that time. If spotting continues thereafter, an endometrial biopsy is carried out; if no pathology is found, the MDA may be increased to 5 mg daily.

2. **Combined cyclic HRT.** Conjugated estrogens, 0.625 mg, and MDA, 2.5 mg, are given simultaneously on calendar days 1–25, then stopped for the remainder of the month. A predictable vaginal bleeding pattern usually results during the drug-free interval, but amenorrhea is eventually achieved in a high percentage of women. Some women experience estrogen withdrawal symptoms during the drug-free days.
3. **Cyclic sequential HRT.** Conjugated estrogens, 0.625 mg, are administered on calendar days 1–25 plus MDA, 10 mg, on days 16–25. This regimen has a long history of safety and efficacy, with a predictable bleeding pattern. An endometrial biopsy should be performed if vaginal bleeding begins on a day that either hormone is given. Some women experience estrogen withdrawal symptoms during the drug-free days.
4. **Continuous, sequential HRT.** Conjugated estrogens, 0.625 mg, are administered continuously with MDA, 10 mg, given on calendar days 1–14 (i.e., 2 weeks) for ease of compliance. More than 80% of women have withdrawal bleeding on this cycle, but an endometrial biopsy need not be carried out unless bleeding occurs before the tenth day of the month or there is a change in the usual bleeding pattern.

   As a guide to the clinician, it is recommended that regimens 2–4 be strongly considered during early menopause, to be followed by a switch to a combined continuous regimen several years later because breakthrough bleeding is very common soon after presumed menopause. Frequent breakthrough bleeding upon initiation of therapy causes some women to discontinue and not restart HRT.

III. Follow-up examinations.

The patient should be reevaluated 3–6 months after initiation of HRT to determine the adequacy of the HRT regimen and review side effects. Once an appropriate regimen has been established, the patient should be evaluated yearly.

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13.7
BENIGN BREAST CONDITIONS AND DISEASE

Kathryn M. Andolsek

Benign breast conditions and diseases are common. The health care provider should perform an accurate history and physical examination, utilize appropriate procedures, differentiate benign from significant medical conditions, reassure patients with benign conditions, manage common symptoms and conditions, and seek consultation when

necessary. The provider must recognize the emotional distress common during this process and provide timely and effective communication. The provider should also know how to counsel patients regarding risk factors, recommend preventive strategies for breast cancer, and facilitate breast-feeding.

I. Anatomy and physiology

A. Breast anatomy.

The breast is composed of 6–20 lobes with glandular, ductal, fibrous, and fatty tissue. Because more lobes are present in the outer quadrants, especially the upper outer quadrants, many breast conditions (among them, breast cancer) occur more frequently in these regions. Each lobe contains several lobules, which contain ducts that join to form one of the 6–10 major ducts that emerge at the areola. Six to 10 pinhole openings are present on the areola. One opening drains each single lobe.

B. The normal breast changes in size and texture throughout the menstrual cycle.

During the premenstrual phase, acinar cells increase in number and size, the ductal lumens widen, and breast size and turgor increase. These changes reverse in the postmenstrual phase.

C. Breast findings in newborns.

Newborns commonly have hypertrophied breast tissue caused by stimulation from maternal hormones. In most cases spontaneous regression occurs.

D. Prepubertal children

may develop unilateral or bilateral soft mobile subareolar nodules of uniform consistency that usually resolve spontaneously within a few months. Biopsy should be avoided as it may impair pubertal breast development.

E. Breast findings in girls.

Breast bud development (thelarche) is typically the first sign of puberty in most girls (average age 11 years; range 9–13.4 years). It is considered “premature” if it occurs earlier than age 8. Premature thelarche without other signs of pubertal development or accelerated growth is usually benign and requires no treatment after medical evaluation excludes true precocious puberty, estrogen-producing tumors, ovarian cysts, or exogenous estrogen exposure. Other signs of puberty generally begin within 6 months of breast development and are completed within four years. Full breast development is usually the last sign of puberty. Thelarche is considered “delayed” if stage 1 persists beyond 13.5 years; stage 2 persists more than 1 year; stage 3 greater than 2.2 years; or stage 4 more than 6–8 years (1).

F. Breast findings in boys.

Most boys experience gynecomastia (breast enlargement) in the middle phases of pubertal development. Usually one breast grows first; the process may become bilateral. Although it can be psychologically disturbing, workup is indicated only if there is rapid progression, onset before puberty, or association with true precocious puberty. More than 90% of affected boys experience regression within 3 years.

G. Breast development

may begin on one side and be asymmetrical. If there is a discrepancy in size, the left breast is usually larger.

H. Anomalies of breast development

are common. The most common anomaly (1%–5% of individuals) is polymastia (accessory breast tissue). Polythelia (accessory nipple) is occasionally misdiagnosed as a mole. Accessory breast tissue is usually located along the embryonic breast line.

II. Assessment of an individual with breast complaints

A. History.

History includes the patient and family history of breast, ovarian, endometrial, prostate, and colon cancers. For women, it includes the menstrual and reproductive history (age of menarche and menopause); parity (age of the first term pregnancy); whether currently pregnant; use of hormonal therapy or contraceptives; breast-feeding experience; whether breast self-examination is performed; and breast surgery (previous biopsies, reason, dates, results). Alcohol use may increase a woman's risk of breast cancer but does not appear to increase the risk of proliferate benign breast disease. As genetic information becomes more widely available, carrier status for tumor suppressor genes such as *BRCA1, BRCA2*, or *p53* should be noted. One in 800 women carries the *BRCA1* gene. This prevalence in-

creases to one in 40 women in certain high-risk ethnic groups, such as those of Ashkenazi Jewish ancestry. Only 16% of women with a family history of breast cancer are *BRCA*-positive. Known genetic causes are responsible for only 5%–15% of breast cancers. **Currently, genetic screening is not part of the routine evaluation of individuals with breast-related complaints.**

B. Symptom review.

Describe when and in what setting symptoms first occurred, any change over time, and past history of similar symptoms. Women should be asked about the relation of symptoms to the menstrual cycle.

C. Examination of the breast.

Inspection and palpation should be done in a well-lighted room; privacy is facilitated by draping parts of the body not being examined. Changes in size, shape, symmetry, or texture are noted. Inspection occurs with the patient seated, arms at side; seated with hands on hips; and seated with arms above the head. Nipples should be examined for deviation, retraction, skin changes, or discharge. Palpation is performed with the patient supine, arms flexed at a 90-degree angle at the sides. Palpation includes supraclavicular, infraclavicular, and axillary nodes. Compression may identify a mass and/or elicit a discharge.

D. Pertinent findings

1. **Asymmetry of breast.** Differences in size and symmetry are common; if extreme or symptomatic, plastic surgery may be considered.
2. **Overly large breasts (macromastia).** Only rarely are large breasts caused by endocrinologic or pathologic processes.

E. Diagnostic tests

(1)

1. **Imaging.** Mammography is discussed in Chapter 1.3 . A “diagnostic” rather than a “screening” mammogram is obtained to evaluate women with breast complaints. Important diagnostic information may be obtained regarding a known or undetected mass. **However, a negative mammogram should never preclude biopsy of an appropriate lesion.** Ultrasonography may be preferable in women under 30 years of age to differentiate whether a mass is solid or cystic, and as an adjunct to aspiration or biopsy, since mammography is unable to visualize lesions well in younger women. Magnetic resonance imaging is utilized in some settings.
2. **Aspiration.** Lesion should be grasped between index and second fingers and held tightly, and the region swabbed with alcohol. Anesthesia can be accomplished with local infiltration of 1% lidocaine, especially if the lesion is near the areola. A 20- to 22-gauge 1.5-inch needle on a 10- to 20-mL syringe should be inserted with a single thrust while negative pressure is applied on the syringe. If no fluid is obtained, gentle retraction on the plunger should be continued as the needle is repositioned and moved back and forth through the center of the lesion 6–10 times. The needle should be redirected 5–10 degrees with each attempt. Specimens should be placed on a glass slide, thinned as with a blood smear, and “fixed” with a cytofixative. Characteristics of the fluid are noted (especially if bloody). Cytologic examination is generally not useful. A negative result does not preclude the need for biopsy of a clinically suspicious lesion. If the mass resolves, reexamine the patient in 4–6 weeks. Biopsy is indicated if there is a residual mass, no fluid is obtained, or the mass recurs.
3. **Fine-needle aspiration (FNA).** FNA involves cytologic aspirate of mass usually with ultrasound guidance. Specimen must have adequate number of epithelial cells for interpretation (sensitivity 87%).
4. **Fine-needle aspiration and biopsy (FNAB)** Indications for biopsy include any suspicious lesion; bloody nipple discharge or bloody fluid following cyst aspiration; persistent mass; suspicious skin changes; inflammatory changes unresponsive to antibiotic; suspicious axillary nodes; or suspicious microcalcifications on mammography. The sensitivity of FNAB is 60%–98 and specificity 90%–100%.

5. **Triple Test.** The “triple test” combines physical examination, mammography, and FNAB. If all three are congruent it is highly predictive (sensitivity 97%–100%; specificity 98%–100%).
6. **Open Biopsy.** An open biopsy may be “excisional” (removal of the entire mass) at the same time as it establishes a definitive diagnosis. Frequently the diagnosis can be obtained without this degree of surgical intervention.

F. Emotional well-being of the patient.

The evaluation of a breast complaint is extremely stressful for many women. Most patients assume that their sign or symptom indicates cancer. The provider should anticipate the emotional responses typical in patients and family. Timely assessment, diagnostic evaluation(s), and consultation when necessary should be provided. It may be useful to inquire how to best assist with the period of uncertainty and convey results. Realistic estimates of the likely timeliness involved in diagnosis are beneficial. Adequate time should be made available to address questions and additional methods of contact (office visits, telephone calls, and email) offered.

G. Evaluation and management

is usually linked to the predominant sign or symptom: pain, nipple discharge, or mass. If a patient with pain or nipple discharge also has a mass, excluding breast cancer in the mass is crucial.

III. Fibrocystic breast disease (FBD).

Fibrocystic changes are the most common benign condition of the breast, occurring to some extent in most, if not all, women. Many experts consider such changes to be part of the natural history of the breast and not a disease. Changes are most common in women 35–45 years old and rare in postmenopausal women. A single cyst may enlarge and cause symptoms as a result of its size. No treatment is necessary unless the woman is symptomatic or if physical findings are worrisome in terms of cancer.

A. History.

If she is symptomatic, the most common symptom is cyclical pain (mastalgia). The pain is generally bilateral, located in the upper outer quadrants, begins a few days prior to menstruation, diminishes with the onset of menses, and may be associated with an increase in breast size. Family history is common.

B. Physical examination.

Cysts are smooth, regular, rubbery, easily movable lumps or areas of local tenderness without a discrete mass that range in size from 1 mm to many centimeters. Compression causes tenderness. Larger cysts are more common as women age. It may be helpful to examine the patient at another point in her menstrual cycle.

C. Diagnostic evaluation

1. FBD is usually differentiated from malignancy by the nature of the pain, typical changes in breast and mass size, and the number of lesions.
2. If there is any doubt regarding the diagnosis or if a single mass is present, evaluate as described in Section VI.B .
3. Breast cancer risk. There is no increased risk of cancer in women with FBD unless proliferative or hyperplastic lesions with atypical epithelial cells are present on biopsy.

D. Management.

Most women do not require treatment. Treatment if necessary is focused on the predominant symptom or sign: mass (Section VI) or pain (Section V.C).

1. A well-padded support bra and loose light clothing may relieve discomfort.
2. Weight reduction is recommended in women with a body mass index greater than 30 mm/kg.
3. Many previously recommended therapies (dietary restriction of caffeine and methylxanthines in chocolate, tea, coffee, cola drinks, theophylline; use of vitamins including A, E, and thiamine; use of diuretics) have not been demonstrated efficacious in randomized controlled clinical trials. Calcium may be beneficial.
4. Low estrogen/high progesterone oral contraceptives may be used but the patient may not notice significant change until after 1–2 years of use.
5. Progesterone, such as medroxyprogesterone, 5–10 mg daily for 10 days before menses, may be given for a trial of 4–6 months. Side effects include weight gain, depression, breakthrough bleeding, and lipid alterations.

6. If thyroid-stimulating hormone (TSH) is elevated even when other thyroid hormones are normal, a trial of thyroid replacement may be helpful (see Chapter 17.3).
7. *cis*-Linoleic acid (evening primrose oil) at a dose of 1 g every 8 hours may be beneficial. However, the benefit may not be seen for 3 to 4 months.
8. Danazol is the only pharmacologic agent approved by the U.S. Food and Drug Administration for FBD. Sixty percent to 90% of women benefit, but significant side effects (hirsutism, amenorrhea, weight gain of 4–6 pounds, hot flashes, and acne) are common. It is generally reserved for women with severe symptoms. Dose at 200–600 mg/d PO initially. Once the desired effect is obtained, dose at 50–100 mg/d as maintenance. Some women benefit from 200 mg daily, given on days 14–28 of the menstrual cycle. Duration of treatment is usually limited to 4–6 months. Once danazol is discontinued the treatment response may persist for months to years (2).
9. Surgery (subcutaneous mastectomy; oophorectomy) should only be considered after medical management has failed for women with recalcitrant symptoms. Surgery may be useful for patients with one large dominant cyst.
10. Bromocriptine, tamoxifen, and luteinizing hormone-releasing agents have been used but have significant side effects.

IV. Acute breast pain

A.

Breast pain (mastalgia) is the most common breast symptom/sign for which women seek care. Pain without an associated mass is unlikely to be the presenting symptom of breast cancer although the evaluation may lead to its coincidental diagnosis. Pain should be differentiated as acute or chronic, cyclical or noncyclical.

B.

Acutely painful breast lesions include trauma, fat necrosis, mastitis, and breast abscess.

1. Trauma may produce a hematoma or rupture of a cyst. The patient complains of pain and tenderness. Mild swelling and discoloration may be present. Unless a coagulopathy is suspected no diagnostic tests are indicated.
2. Fat necrosis is suggested by the sudden onset of trauma, especially if there is a history of fibrocystic disease. Physical examination reveals localized pain, swelling, and erythema. Evaluation should be performed to exclude malignancy if symptoms persist for more than a week.
3. Frequently “breast pain” is discovered on examination not to be in the breast at all but rather in the underlying pectoralis muscle or rib.
4. Mastitis and breast abscesses almost always occur in lactating women or in women with a history of a bite or penetrating trauma. These conditions are more common in women pregnant for the first time. Breast engorgement usually occurs on the second or third postpartum day. Mastitis presents one week or more after delivery. Moderate to severe pain, tenderness, erythema, swelling, and warmth is usually localized to one breast (one quadrant or lobule). Axillary adenopathy may be present. There may be purulent drainage. The patient is febrile and appears toxic. History and physical examination are diagnostic. Leukocytosis is common. Breast milk cultures are not useful.
5. *Staphylococcus aureus* is typically causative in breast-feeding women. Treatment for mild infection includes warm compresses and 7–10 days on oral antibiotics deemed safe for a nursing infant (dicloxacillin 500 mg PO every 6 hours; amoxicillin clavulanate 375–500 mg tid; cephalexin 500 mg qid; clindamycin 300 mg qid for penicillin-allergic patients). Patients should be reassessed in 48–72 hours.
6. Breast-feeding can be continued on the affected breast. The infant is not at risk for developing infection.
7. Abscess. Pitting edema over an area of inflammation and fluctuation is suggestive of abscess development. For patients with infections un-responsive to conservative management, severe infection, abscess, or deep

infection, the wound should be drained and cultured. Breast-feeding should be discontinued and parenteral antibiotics (nafcillin or cefazolin) given for 2–3 days; this should be followed by oral antibiotics. Nonpuerperal abscesses are usually caused by anaerobes if subareolar; by staphylococci in other locations. They are treated with clindamycin or metronidazole and either nafcillin or cefazolin.

8. If the clinical setting is atypical (the woman is not breast-feeding or she does not improve with antibiotics), a biopsy of indurated areas to exclude an underlying cancer should be considered.
9. Presence of a periareolar inflammatory mass, breast abscess in a nonlactating woman, or a mammary duct fistula should raise suspicion of periductal mastitis. Tobacco use is associated with an increased prevalence of this condition. Further evaluation is warranted.

V. Chronic breast pain

A.

Chronic breast pain may be cyclical or noncyclical. Consider a visual analogue scale to measure the patient's pain and follow it over time.

B. Noncyclical pain.

Often unilateral and reported by women in their forties and fifties. Physical examination is necessary. Mammography or ultrasonography in women younger than 35 years is usually negative and confirms a benign etiology. Treatment includes use of a support bra, nonsteroidal anti-inflammatory agents (NSAIDs), or acetaminophen. Danazol may be beneficial but its use is limited due to side effects.

C. Cyclical Pain

1. Most cyclical breast pain is associated with the menstrual cycle. Pain is usually worse in the luteal phase and abates following menstruation. Most women report some degree of cyclical breast pain at some point in their lives. Eleven percent to 30% experience severe pain that interferes with function. Cyclical breast pain is not always associated with premenstrual syndrome; 60% of women with premenstrual syndrome (PMS) report breast pain as the predominant symptom (see Chapter 13.2). High likelihood of spontaneous resolution.
2. Breast support and analgesia may be beneficial. As with FBD, there is no evidence of benefit from dietary change.
3. Topical application of NSAID gel has been used in some patients.
4. Evening primrose oil 500 mg, two tablets tid, has been demonstrated efficacious in a randomized controlled clinical trial with no apparent adverse effects.
5. Three to four months of oral contraceptives may be required to determine a therapeutic effect.
6. Use of gonadotropin-releasing hormone agonists may lead to osteoporosis and cardiovascular disease.
7. Danazol has significant adverse effects (voice change, hirsutism, weight gain, acne). 200 mg qd in the luteal phase (day 14–28) may be effective and minimize the total dose (2).
8. Tamoxifen 10 mg qd is efficacious as a continuous dose and only during the luteal phase. Side effects limit its long-term use.
9. Bromocriptine, though effective, is associated with significant side effects that limit its use.
10. The following have not been demonstrated to be efficacious: progesterone, diuretics.

VI. Breast mass

A.

A breast mass is generally cystic or solid. Ultrasonography and/or aspiration may allow differentiation of characteristics. Solid masses have a higher association with malignancy.

B. Breast cysts.

More common in premenopausal women older than 40 years, they require surgical biopsy if the aspirated fluid is bloody, if the mass does not resolve following aspiration, or if the cyst recurs. It is not necessary to send aspirated fluid for cytologic examination. Nonpalpable cysts identified during routine mammography do not require further evaluation or treatment.

C. Fibroadenoma.

Fibroadenoma, the most common solid tumor, contains both fibrous and epithelial elements. These tumors occur in young women, usually within 20 years of puberty. They are more common and occur at earlier ages in black women than in white women. Multiple lesions may develop. Growth may be rapid especially at the end of a menstrual cycle and in pregnancy. Older women characteristically have a single, solitary, more slowly growing lesion. Fibroadenomas frequently calcify and may involute after menopause. Occasionally they may develop in a postmenopausal woman after administration of estrogen.

1. **History.** The painless mass is generally discovered by the patient.
2. **Physical examination.** A well-defined, rubbery, movable, nontender, 1- to 5-cm mass can generally be palpated. The usual location is the upper quadrant.
3. **Diagnostic procedures.** Aspiration of the mass should be attempted. A fine-needle biopsy may be diagnostic. Mammography is not usually helpful, especially in young patients.
4. **Breast cancer risk.** Fibroadenomas are neither cancerous or premalignant but may require excisional biopsy to confirm the diagnosis.
5. **Management.** Excisional biopsy is both diagnostic and curative.
6. **Cystosarcoma phyllodes** is a rapidly growing fibroadenoma that recurs if not completely excised. This tumor is rarely malignant but, because of its extreme size, simple mastectomy may be necessary to achieve complete removal.

D. Solid mass.

Cancer should be excluded in a woman who presents with a solid mass. A woman with a clinically suspicious lesion should undergo mammography and biopsy. If she has a clinically benign lesion and is younger than 40, excision or ultrasonography and FNA is recommended.

VII. Nipple discharge

(3). Normal, healthy women commonly have some degree of clear or milky nipple discharge following pregnancy and lactation that can either spontaneously drain from the breast or be produced by palpation. This discharge may be more frequently noted just before menses or with breast stimulation as part of sexual activity. The amount of fluid is small and the volume does not change over time. Characteristics of pathologic discharge include unilaterality; presence from a single duct; association with a mass; spontaneous, intermittent, persistent occurrence in a postmenopausal woman; and bloody to sero-sanguinous color.

A. History.

History should elicit the nature of discharge, (association with a mass, unilateral or bilateral, single duct or multiple ducts, spontaneous or requires expression, relation to menses, color), the menopausal status of the patient, and association with hormonal therapy. **Nipple discharge in a postmenopausal woman is more ominous** and is more likely to be caused by cancer.

B. Physical examination.

It is important to determine if the fluid comes from the nipple and if it involves more than one duct. A “pseudodischarge” is a stain on clothes from an abrasion, eczema, or viral condition (e.g., herpes). If nipple crusting is present, Paget's disease should be excluded.

C. Characteristics of the fluid.

The characteristics of the fluid may aid in diagnosis. Green, black, creamy, or mucoid discharge is characteristic of FBD. Bloody or serosanguinous discharge is associated with malignancy.

D. Fluid analysis.

The discharge can be tested for the presence of blood (with a Hemoccult slide). Gram's staining can be performed to identify white blood cells if there is a concern about infection. Fat stain can demonstrate fat globules indicative of milk if galactorrhea is suspected. Cytologic examination of the nipple discharge is not generally useful.

E. Diagnostic procedures

1. **Mammography** may reveal abnormalities such as the presence of an associated mass.
2. **Galactography.** The role of galactography and/or ductography in a woman with a nipple discharge is controversial. A negative galactogram does not replace the need for terminal duct excision.

3. **Surgical referral.** Patients should be referred to surgery if their discharge is spontaneous, unilateral, associated with a mass, and/or bloody.

F. Galactorrhea.

Although galactorrhea can have many causes, it is usually benign. It may persist following childbirth. It has been described in women who jog because friction between the nipple and clothing can stimulate prolactin. Athletic activities may also trigger endorphin release from the hypothalamus, which stimulates prolactin secretion. Correlation is poor between lactation and serum prolactin levels.

1. **History** should include recent childbirth (normal if 6 months or less from most recent delivery), excessive breast stimulation, and medication use. Determine if galactorrhea is present from both nipples and from multiple ducts. Galactorrhea from multiple ducts in a nonlactating woman may occur in certain syndromes (Chiari-Frommel, Argonz-Del Castillo), presumably as a result of the increased prolactin secretion from chest wall involvement (thoracotomy, herpes zoster infection, radiation to the chest wall, burn).
2. **Menstrual history.** Any associated change in menstrual pattern, such as amenorrhea or oligomenorrhea, is suggestive of a central nervous system lesion. Brain computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained to rule out a pituitary lesion even if the serum prolactin level is normal.
3. **Central nervous systems symptoms.** Approximately 20% of patients have a prolactin-secreting pituitary tumor. Headache or visual change may indicate the presence of an intracranial process. Conditions that affect the pituitary and/or the hypothalamus (tuberculosis and multiple sclerosis) are rare causes.
4. **Medication history.** Medication may be the cause of galactorrhea in 20% of patients. Drugs associated with galactorrhea include digitalis, marijuana, heroin, dopamine receptor blockers, phenothiazine, haloperidol, methoclopramide, isoniazid, central nervous system dopamine depleters, antidepressants (tricyclic antidepressants such as imipramine and serotonin, selective serotonin reuptake inhibitors such as fluoxetine), reserpine, methyldopa, atenolol, cimetidine, benzodiazepines, amphetamines, verapamil, cocaine, depomedroxyprogesterone, other progesterones, oral contraceptives, and copper-containing intrauterine devices (IUDs). Herbal products that can cause galactorrhea include fenugreek seed, fennel, and red clover (see Chapter 22.3).
5. **Other chronic medical conditions** (chronic renal failure, hypothyroidsm, Cushing's disease) may cause galactorrhea.
6. **Diagnostic evaluation.** Serum prolactin level, TSH (hypothyroidism), and renal function tests can be useful. Further endocrine workup may be indicated.
7. **Serum prolactin.** If serum prolactin is greater than 75–100 mg/mL, brain CT or MRI is necessary to rule out pituitary adenoma. Nonpituitary prolactin-producing malignancies are less common but include bronchogenic carcinomas, renal adenocarcinomas, Hodgkin's disease, and T-cell lymphoma.
8. **CT or MRI** is necessary if serum prolactin is elevated; if serum prolactin is normal but the patient has an aberration in her menstrual pattern; or if any central nervous system symptoms or signs are present.
9. **Galactorrhea** is not associated with an increased risk of cancer.
10. **Management.** Discontinue any potentially causative medication if possible. Treat any diagnosed disorder such as thyroid diseases. If serum prolactin is elevated, the patient may have a pituitary adenoma (generally a chromophobe adenoma). If elevated serum prolactin but no pituitary adenoma is demonstrable, treatment may still be indicated to decrease the risk of hyperprolactin-associated osteoporosis (see Chapter 17.6). If a microadenoma is present but fertility is not desired, and the risk of osteoporosis

does not warrant treatment, patients can be followed without therapy. Microadenomas may regress spontaneously and do not typically transform in to macroadenomas. Serum prolactin levels can be followed every 6 months, with repeat CT or MRI every 2–5 years. If a macroadenoma is present, therapy is indicated to prevent further growth. Medical management consists of bromocriptine, 2.5 mg/d for 1 week, increased to 2.5 mg bid-tid or pergolide and cabergoline. Side effects include nausea, nasal congestion, and postural hypotension. Tumor regrowth may occur following withdrawal of the medication. Bromocriptine can be used to lower prolactin levels to normal to allow fertility and to shrink tumor size preoperatively. Transsphenoidal surgery is an option for large tumors and in patients with macroadenomas who wish to become pregnant. Surgical success is limited as these tumors frequently recur. Radiation may be an option for patients who are not surgical candidates.

11. **Chiari-Frommel syndrome** is the presence of galactorrhea and amenorrhea that persist longer than 6 months post partum in the absence of nursing. Menses return over a period of months to years in about half of patients.
12. **Post-oral contraceptive galactorrhea.** Milk production is triggered by the withdrawal of estrogen and progesterone. This usually resolves spontaneously. Some patients eventually develop radiologically evident pituitary adenomas.

G. Cheesy discharge.

Duct ectasia is a chronic inflammatory reaction resulting in permanent distention of the major ducts. The typical patient is a multiparous woman 40 years or older who notes thick, white, or discolored cheesy material draining from the nipple and noncyclic burning breast pain. Physical examination reveals induration under the areola, repeated infections around the areola, or isolated slit-like nipple retraction with or without crusting of the nipple. Discolored, cheesy, thick fluid can be expressed. Women who smoke cigarettes may increase the risk. Treatment involves excision of the major duct systems under the areola. No further investigation is necessary.

H. Bloody discharge.

Clear, bloody, serosanguineous, or brown-green discharge (suggesting old blood) from a single duct opening on one breast should be investigated. Causes include intraductal papilloma, ductal estasia, or intraductal cancer. An associated mass may or may not be present.

1. **Diagnostic evaluation** Cytology is not useful. A mammogram may or may not demonstrate a small lesion in a major duct.
2. **Management** includes surgical exploration of the duct and removal of the papilloma, if present. A papilloma is histologically benign with only a slight potential for malignant degeneration.

I. Yellow or greenish discharge.

Diagnostic possibilities in premenopausal women include FBD, papillomatosis, duct ectasia, and mastitis. If the clinical picture is uncharacteristic or the patient does not recover rapidly with a course of antibiotics, the cause should not be assumed to be mastitis. In postmenopausal women or women with a discharge and an associated mass, cancer must be excluded.

VIII. Painful nipples

A. Breast-feeding women.

Tenderness of the nipples is a common symptom when breast-feeding is begun (see Chapter 14.11).

1. Proper positioning of the baby at the breast and correct techniques to “break suction” are essential. Nursing position may be changed. Any engorgement should be treated. Alternate which breast is presented first and begin with the less sore one. Warm or cold compresses and crushed ice applied to nipples before nursing may be beneficial. Milk should be expressed until “let-down” occurs.
2. Nipples should be examined for the presence of fissures or local infection. Position the baby so that the most cracked or tender portion of the

breast is at the corner of baby's mouth and not aligned with the roof of the mouth or tongue. Avoid petrolatum and zinc oxide. The area can be washed with warm water and can air dry with colostrum applied.

3. A *Candida* infection may be present, which requires treatment with topical antifungal cream. Thrush, *Candida* diaper rash, or maternal *Candida* vaginitis should be treated concurrently.
4. Nipple shields should be avoided.

B. Non-breast-feeding women.

Nipples can develop painful localized irritation and bleeding in joggers. Small elastic bandages can be applied before running or other athletic activities. Emollients or low-dose hydrocortisone cream may ameliorate symptoms.

C.

A unilateral, weeping, ulcerated, irritated nipple is suggestive of Paget's disease, especially in middle-aged or older women, and may be associated with an underlying ductal carcinoma. Evaluation is necessary.

IX. Gynecomastia

(4)

A.

Gynecomastia has a bimodal distribution. Most boys at puberty develop bilateral gynecomastia, which resolves without treatment within 3 years. It is also common for men in their fifties and sixties to experience breast enlargement. Men with unilateral gynecomastia, especially with rapid onset or progression, pain, asymmetry, and associated erectile dysfunction, and boys with rapid progression, onset before puberty, or association with precocious puberty should be evaluated further.

B.

Drugs and medications that can cause gynecomastia include estrogen (whether he is taking it himself or absorbing it from the genital skin of a partner who uses vaginal cream), anabolic steroids, corticosteroids, clomiphene, marijuana, methadone, testosterone, amphetamines, spironolactone, digoxin, reserpine, methyldopa, hydroxyzine, ketoconazole, cimetidine, tricyclic antidepressants, and phenothiazine.

C.

Medical conditions that cause gynecomastia include cancer [testes, liver, bronchiole, stomach, or pancreas, especially the human chorionic gonadotropin (hCG)–producing neoplasms], hyperthyroidism, hypogonadism, cirrhosis, renal failure, severe pulmonary disease, Klinefelter's syndrome, testicular feminization, and refeeding after starvation.

D.

Laboratory evaluation includes thyroid function tests, renal and liver function studies; if these are normal, gonadotropins, such as luteinizing hormone, hCG, estradiol, and testosterone, should be obtained. If hCG is elevated, testicular ultrasonography and search for other hCG-secreting tumors should be undertaken. If estradiol is elevated, a search for an estrogen-secreting tumor should be undertaken.

E.

Fat deposits may mimic breast mass in men.

F.

Older men develop gynecomastia at an age close to that at which male breast cancer occurs. A combination of physical examination and FNA can establish the correct diagnosis in the majority of patients. Mammography may add little additional information.

X. Lactation issues.

Some breast problems are confined to lactation. Nipple discomfort with nursing is discussed in Section II ; mastitis in Section IV .

A. Plugged milk duct

can present as a white blister on the nipple following breast-feeding and a hardened area in the breast. Soak the nipple in warm water before next nursing. Gently rub a clean wash cloth across the tip of the nipple. As baby nurses, massage behind the hard area to encourage milk expression.

B. Galactocele.

A galactocele is a milk-filled cyst. These sometimes resolve spontaneously.

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13.8
BREAST CANCER

Kathi D. Clement

James Broomfield

Breast cancer accounts for 32% of cancers in women, with an estimated 170,000 new cases diagnosed each year (1). Breast cancer is primarily a disease of older women, with 80% of cases occurring in patients older than 50 years. A woman now has a 1-in-8 risk of developing breast cancer in her lifetime. Breast self-examinations, physical examinations by a physician, and mammography all help with earlier detection, but overall mortality has remained the same.

I. Risk factors.

Age is the most important risk factor for breast cancer. As a woman ages her risk of breast cancer increases. A 30-year-old woman has a 1-in-2,212 risk, whereas the 70-year-old woman has a 1-in-14 risk and an 80-year-old woman a 1-in-10 risk. Hormonal influences (e.g., early age of menarche, menopause after age 55) and nulliparity increase the risk of breast cancer. Prolonged (greater than 10 years) hormone replacement therapy may increase the risk of breast cancer. Family history in a first-degree relative (sister or mother), especially if the cancer occurred premenopausally, increases the risk of developing breast cancer. There also is an increased risk of breast cancer if a woman has two or more close relatives (aunt or cousin) with a history of breast cancer especially if diagnosed premenopausally. Prior breast pathology, such as benign breast disease with a biopsy showing proliferative changes, specifically atypical ductal hyperplasia, is strongly associated with increased risk. Lobular carcinoma in situ (LCIS), although without malignant potential, is thought to be a marker of subsequent development of invasive carcinoma of either breast. LCIS is a rare incidental finding in biopsy specimens because it does not produce a palpable mass or mammogram pattern. Dietary factors, including high fat intake and moderate alcohol consumption, might increase the risk of breast cancer. Genetic alterations in the *BRCA1* and *BRCA2* genes render women more susceptible to breast cancer, but only 5% of breast cancers are felt to be hereditary (2).

II. Detection and diagnostic methods

A. Breast self-examination.

Monthly breast self-examination is important because up to 75% of breast cancers are discovered by patients as a lump.

B. History and breast examination by a physician.

The history should include date the lump was found, prior breast problems, and possible risk factors. The patient should be examined in the upright and supine positions, and the examination should be unhurried. Abnormal findings other than an obvious mass might include skin edema or peau d'orange, slight retraction of the skin, breast swelling, satellite lesions, redness, axillary adenopathy, or overt ulceration. Lesions smaller than 1 cm are detected less than one third of the time by physicians, so the examiner's tactile sensation is important.

C. Mammograms.

Mammography is an integral part of evaluating a breast lump. This procedure, coupled with the physician examination, is superior to

either modality alone. Screening mammography of an asymptomatic woman provides two views of each breast. Diagnostic mammography, because of a palpable abnormality, pain, previous history of breast cancer, augmented breasts, or prior abnormal mammogram, might require additional views or ultrasonographic scanning. The U.S. Food and Drug Administration (FDA) recently approved use of the T-Scan (Siemans AG, Cherry Hill, NJ), which is an adjunct to mammography. The T-Scan uses a hand-held probe that evaluates suspicious areas by measuring the differences in electrical conduction between malignancy and normal tissue. Breast imaging should be performed before palpable masses are biopsied because hemorrhage can distort the tissue structure. Mammography fails to detect at least 10% of breast cancers; many of these are in younger women, where denser breast tissue obscures architectural distortions and microcalcifications. Finally, even if the mammogram is normal, large palpable masses should be biopsied.

D. Biopsy.

Skinny-needle aspiration of cells from a potential tumor site is useful if a larger mass is palpable. Positive cytology permits immediate planning of treatment. Other types of needle biopsies include needle localization aided by ultrasonography and stereotactic biopsy. Open biopsy is required if there is bloody fluid on aspiration, recurrence of the cyst after one or two aspirations, bloody nipple discharge, nipple excoriation, or signs of inflammatory breast carcinoma (peau d'orange changes). The specimen should be sent for pathology as well as estrogen and progesterone receptor analysis.

III. Management.

Breast carcinoma is generally divided into two types according to origin: ductal system (90%) or breast lobules (10%). Distinction should be made between in situ intraductal (noninvasive) carcinoma and infiltrating ductal or lobular (invasive) carcinoma. Once the diagnosis has been made, a metastatic workup is done, including a complete blood count, liver enzymes, chest radiography, and, in some cases, bone scanning. Considerations for surgical therapy include not only size and histology of the tumor but also the patient's wishes. Today modified radical mastectomy has replaced the radical mastectomy as the most common type of surgery. Breast-conserving surgery combined with radiation therapy might be equivalent to a mastectomy in some cases (3). Radiation therapy begins as soon as the surgical scar heals, with the dose to the breast not to exceed 5,000 cGy. Greater doses result in cosmetic skin distortion.

A. Staging.

Staging of a tumor represents the clinical evaluation of the cancer (Table 13.8-1). This process involves evaluation of primary tumor size, axillary node involvement, and whether distant metastasis has occurred. The most important factor in prognosis of patients with breast cancer is the axillary node status. Sentinel node biopsy is a new technique to help determine this, but without the morbidity of an axillary node dissection. Although there is no single optimum treatment for any patient subgroup, adjuvant therapy improves overall survival and prevents recurrence. Current adjuvant therapy for premenopausal women with positive nodes consists of a combination of cyclophosphamide, methotrexate, and 5-fluorouracil; tamoxifen might be added to this regimen. Tamoxifen alone is the treatment of choice for postmenopausal women with positive nodes. However, tamoxifen carries a risk of thromboembolic phenomena and endometrial carcinoma. Therapy is more debatable in node-negative patients.

Stage I	Tumor mass <2 cm, but axillary nodes not clinically involved
Stage II	Tumor mass <2 cm, and axillary nodes clinically involved; or any tumor 2–5 cm, with or without node involvement
Stage III	Any tumor with mass >5 cm, skin involvement or chest wall attachment, clinically fixed axillary nodes, arm edema, supraclavicular nodes, or skin ulceration
Stage IV	Metastatic disease

Table 13.8-1. Breast cancer staging

B. Treatment strategies.

For advanced or recurrent breast cancer, treatment strategies depend on extent and location of disease, menstrual status, whether a disease-free interval occurred, receptor status, general health status, and patient wishes. Palliation may occur with tamoxifen or oophorectomy in premenopausal women. Tamoxifen helps with regression in two thirds of patients with positive estrogen receptors. Tamoxifen has also been studied in women with more than three relatives and felt to have a *BRCA* mutation. Although it seemed to reduce the absolute risk of developing breast cancer, it was studied for a 5-year period only and was not approved for those under the age of 35 (4). More aggressive chemotherapy is needed if recurrent or metastatic disease is present; this might include combinations of doxorubicin, cyclophosphamide, prednisone, methotrexate, 5-fluorouracil, and vincristine.

C. Follow-up examinations.

Clinical follow-up should continue on a regular basis. Evaluation should include tumor marker levels, liver enzymes, chest radiography, and annual physical and pelvic examination. Although 10-year survival for early-stage lesions is 75%–85%, women continue to die of breast cancer 15–20 years later.

IV. Special considerations

A. Pregnancy and breast cancer.

Two percent of all breast cancers are diagnosed in pregnancy, which does not influence prognosis. If cancer is found during the first or second trimester, a mastectomy and axillary dissection should be carried out. Therapeutic abortion does not improve outcome. Third-trimester patients can be observed until delivery and then receive prompt therapy. Chemotherapy administered during the second and third trimesters has no adverse effect on the developing fetus (5).

B. Carcinoma of the male breast.

Male breast carcinoma accounts for 0.5% of all breast cancers. It too is more common in older men and can also be *BRCA1* or *BRCA2* related. Workup and treatment are similar to that for female breast cancer.

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Helpful Websites

1. http://www.familydoctor.org/ (AAFP website for patient information).

2. http://cancernet.nci.nih.gov/ (National Cancer Institute's primary web site for both health professionals and the public).

13.9
COLPOSCOPY

Gary R. Newkirk

I. Introduction.

Diagnosis and management of genital epithelial dysplasia requires mastery of colposcopy, punch biopsy, and endocervical curettage (ECC). The colposcope is essentially a stereoscopic operating microscope combined with a bright-light source. The ultimate challenge for the colposcopist is to distinguish the normal from abnormal and to provide histologic sampling of abnormal areas. Colposcopy helps to identify patients who may have invasive genital malignancy requiring advanced cancer therapies and women who have premalignant changes, which frequently can be managed with outpatient procedures, such as cryotherapy or loop electrosurgical excision procedure (LEEP).

II. Indications for colposcopy

A.

Papanicolaou (Pap) smear indications (see Chapter 13.4)

1. Smear with dysplasia or cancer
2. Persistent unexplained atypia
3. Evidence of human papillomavirus (HPV) infection

B.

Suspicious visible lesion of the cervix, vagina, or vulva

C.

Follow-up of previously treated patients

D.

History of diethylstilbestrol exposure

E.

Colposcopy highly recommended

1. Patients with visible condylomata
2. Sexual partner with condylomata
3. Unexplained vaginal discharge, itching
4. HIV-infected women
5. Intravenous drug abusers

III. Contraindications for colposcopy.

Contraindications usually delay rather than prevent the examination.

A.

Active gonococcal, chlamydial, or trichomonal infections

B.

Uncooperative patient

C.

Heavy, active menses

IV. Basic cervical colposcopic findings

A.

Normal cervical findings

1. Squamous epithelium
2. Columnar epithelium
3. Squamous metaplasia
4. Squamocolumnar junction

B.

Variants of normal

1. Nabothian cysts
2. Atrophy
3. Pregnancy changes
4. Inflammatory or infectious process
5. Traumatic changes, clefts, or prior therapy

C.

Abnormal cervical mucosal patterns, indicating the need for biopsy

1. Leukoplakia [a white area prior to application of acetic acid (vinegar)]
2. Acetowhite change (a whitening following vinegar application)
3. Punctation (a vessel pattern of small red dots)
4. Mosaic (a vessel pattern with the appearance of chicken-wire)
5. Atypical vessel pattern (abnormal branching, hairpins, corkscrew patterns)

V. Basic procedural steps for colposcopy of the cervix

A.

Perform a bimanual examination.

B.

Insert speculum.

C.

Adjust and focus colposcope initially on low power.

D.

Gently blot off excess mucus; apply normal saline to further clean and highlight vessel patterns.

E.

Apply acetic acid to allow for acetowhite changes within areas of dysplasia.

F.

Colposcopically examine the cervix, identifying areas of abnormality that will require biopsy.

G.

Lugol's iodine solution may be applied to further identify abnormal areas. Lack of black staining on squamous epithelium implies dysplasia.

H.

Perform ECC to evaluate for occult cervical canal disease. This procedure is contraindicated in pregnancy.

I.

Perform punch biopsies of abnormal areas.

J.

Apply Monsel's solution for local hemostasis.

K.

Carefully examine the vagina and vulva, and biopsy abnormal areas.

VI. Interpretation and management of biopsy results

A.

Histologic diagnosis of cervical cancer requires definitive staging and advanced therapy, such as radical hysterectomy and radiation therapy.

B.

A positive ECC result or colposcopic evidence of endocervical canal involvement requires further tissue biopsy with either cold cone or LEEP.

C.

A negative ECC result (normal tissue, no dysplasia) and no colposcopic evidence of dysplasia in canal with low-grade squamous dysplasia on ectocervix can be managed with either:

1. Expectant management, which requires repeat colposcopy and biopsy in 4–6 months to rule out progression.
2. Cryotherapy, LEEP, and laser ablation (for large lesions), which can be considered for low-grade lesions.
3. Definitive treatment if dysplasia persists or progresses.

D.

High-grade squamous dysplasia requires definitive therapy, including LEEP, laser excision, or cold cone. Cryotherapy can be performed in selected cases but never with a positive ECC. Only rarely is hysterectomy done for dysplasia with a negative ECC result.

E.

Adenomatous or glandular atypia or dysplasia usually requires cone biopsy to evaluate possible adenocarcinoma of the canal.

VII. Complications and morbidity of colposcopy

A.

Infection or bleeding occurs in less than 1% of women.

B.

The most severely dysplastic tissue is not biopsied, and the degree of dysplasia is underestimated, resulting in delayed or inadequate therapy.

XIV. FAMILY PLANNING AND MATERNITY CARE

14.1
CONTRACEPTION

JoAnn Rosenfeld

I. Definition

A. Contraception, or birth control (BC),

is the use of methods and devices to prevent conception. Pregnancy is not a disease, so women and physicians must work cooperatively to find the best method for the couple. Any form of contraceptive method (except oral contraceptives in smoking women older than 35) has a lower morbidity and mortality than pregnancy (1).

B. The effectiveness of contraceptive method

is expressed as the percentage of sexually active women who do not become pregnant when using a method for a year, or the number per 100 women-years. Methods have an "ideal" effectiveness rate, and an "actual" or typical use effectiveness rate (what happens when women actually use it), usually lower.

II. Methods

A. Abstinence

1. **Effectiveness.** Ideally this method would be 100% effective, but in reality this is not the case.
2. Indications. It works best for settled couples and teenagers.
3. Special groups. The method is good for teenagers and is protective against sexually transmitted diseases (STDs) and AIDS.
4. Side effects. None.

B. Coitus interruptus

1. Effectiveness is variable, from 85% ideally to approximately 50% in reality. It is considered an unreliable method of BC.
2. Indications. Settled couples and those who want to avoid hormonal BC. This may be best in monogamous or mature couples who can discuss their sexual experiences.
3. Contraindications. Teenagers.
4. STD protection. None.
5. Side effects. At times, both women's and men's satisfaction and orgasms may be adversely affected.

C. Rhythm (periodic abstinence)

With the rhythm method, sexual relations are restricted to the "safe" period in the menstrual cycle. The couple abstains from sexual relations for 2–4 days on either side of her day of ovulation, which should be 14 days before her next menstrual period.

1. Effectiveness is variable, from 85% ideally to approximately 50% in reality. It is an unreliable method of BC.
2. Indications. Settled couples and those who want to avoid hormonal BC.
3. Contraindications. Teenagers and women with irregular periods, including the time after menarche or premenopausal years.
4. STD protection. None.

D. Natural family planning (NFP) method.

NFP is a well-established course of using rhythm and measurement of basal body temperatures plus cervical mucus production to pinpoint days before and after ovulation more accurately.

1. Effectiveness is approximately 85%–95%.
2. Indications. Because of the investment in time and commitment to take this course, this method works best with well-established couples and couples desirous of not using hormonal or "active" methods.
3. Special populations. Good for breast-feeding mothers; not good for teenagers.
4. Contraindications. Irregular periods.
5. STD protection. None.

E. Barrier methods.

Although these methods are very effective, they must be used consistently but nevertheless fail on occasion. Of the 10 million women who use barrier contraception, approximately one third report not using their method every time (2).

1. Gels, creams, suppositories. There are a wide variety of gels, creams, and suppositories with a variety of viscosities, ease of cleaning, smells, tastes, and capacity to effervesce.
   a. Effectiveness is approximately 65%–85%.
   b. Indications. Patients who do not wish to use hormonal methods; easy access, an inexpensive method, no visits with a provider.
   c. Contraindications. Vaginal infections, allergy to contents.
   d. STD protection. Some, especially when used with condoms.
   e. Side effects. Messy.
   f. *Notes:* Spermicides must be inserted before sexual intercourse and reapplied before a second or subsequent intercourse. The woman cannot douche for 8 hours after sex. Use of a condom or diaphragm increases the efficacy and decreases the risk of STD or AIDS transmission considerably.
2. Male condom. Use has increased significantly since the AIDS epidemic has necessitated the use of condoms to prevent HIV transmission. The proportion of women using condoms between 1988 and 1995 increased from 15% to 20% of all women. Condom use declines as women grow older and marry (1).
   a. Effectiveness 85%–95%.
   b. Indications. Prevention of STDs and AIDS; male condoms permit spontaneity and have no hormonal effects; good choice for new couples.
   c. Contraindications. Allergy to latex.
   d. Side effects. Many couples dislike the decrease in sensation and pleasure attributed to condoms.
   e. STD protection. Good.
   f. Special groups. Good for lactating women, teenagers.
3. Female condoms
   a. Effectiveness is approximately 75%–85%.
   b. Indications. Women who want to control their method and do not want hormonal effects or a physician's visit may use female condoms. Women whose partners do not want the male condom but who want STD protection may desire this method.
   c. Contraindications. Allergy to latex.
   d. STD protection. Possibly.
4. Diaphragm. Diaphragms must be used with spermicides. They must be left in place for 8 hours after use. Their efficacy increases with use.
   a. Effectiveness 85%–95%.
   b. Indications. Women who do not want hormonal effects or who have intermittent well-planned sexual intercourse.
   c. STD protection. Some.
   d. *Notes:* The diaphragm must be fitted by a physician, and must be refitted after a pregnancy or a weight gain or loss of 20 lb or more. They should be used for a year only and then replaced.
5. Cervical cap. Caps are rubber suction cups, prescribed and sized by a physician, that must be used with a spermicide. Approximately 20% of women cannot be fitted for the cap.
   a. Effectiveness: 85%–95%.
   b. Indication. No hormonal effect, good effectiveness.
   c. Contraindication. Allergy to latex or abnormal gynecologic anatomy would be an absolute contraindication.
   d. STD protection. None.
   e. *Notes:* There is some evidence that these are associated with cervical abnormalities. Women with cervical Pap test abnormalities should use another form of contraception (see Chapter 13.4).

F. Hormonal methods

1. Emergency contraception (Table 14.1-1)

Brand	Pills per dose[a]
Ovral	2 white pills
Alesse	5 pink pills
Levlen	4 light-orange pills
Lo/Ovral	4 white pills
Triphasil	4 yellow pills
Prevens	4 pills and pregnancy test
Plan B	1 pill

[a] The treatment regimen is one dose within 72 h but as soon as possible after unprotected intercourse, and another dose 12 h later. If nausea occurs and the woman regurgitates either dose, she should take it again after an antiemetic.

Table 14.1-1. Emergency contraception

   a. Effectiveness is estimated to be 98% per first use.
   b. Indication. For failure of contraception (condom breakage) or failure to use contraception.
   c. Contraindication. Pregnancy.
   d. *Note:* No STD protection. Works less well after first use.
2. Combination oral contraceptive pills (OCPs). The pill is the most widely used method by women in their twenties. Despite evidence that use of OCPs decreases the risk of ovarian and endometrial and only slightly (relative risk 1.1) increases the risk of breast cancer, many women do not feel comfortable using OCPs (3,4).
   a. Effectiveness is 96%–99.5%.
   b. Indications. Excellent effectiveness. Women who need effective contraception, those who like to separate contraception from coitus, and those who have a regular and organized lifestyle that allows them to take daily medication will do well on OCPs. OCPs have a variety of noncontraceptive benefits, including improvement of acne, 50% decrease in the risk of pelvic inflammatory disease, improvement of fibrocystic breast disease, decreased incidence of and improvement in functional cysts of ovary, and an increase in bone mass density in patients with primary and secondary amenorrhea. OCPs decrease the risk of breast cancer in long-term users, decrease the incidence of epithelial ovarian cancer, and decrease the risk for endometrial cancer (4).
   c. Contraindications. Hepatitis, liver abnormalities, estrogen-dependent cancers, severe hyperlipidemia, migraine headaches, lupus erythematosus, smoking and older than 35 years, unexplained vaginal bleeding, pregnancy, thrombotic disease history, certain medications (chronic antibiotic use, antituberculosis drugs, anticonvulsants, antipsychotics).
   d. Side effects. Side effects such as BTB, breast changes, hair changes, weight gain, and headaches, whether proven or perceived, also decrease the use, acceptability, and satisfaction with OCPs. Newer second- and third-generation OCPs significantly decrease the incidence of BTB and progestin-related side effects.

      Women who have BTB on one pill should change to a pill with higher estrogenic potential. If the BTB is late in the cycle, just before the monthly bleeding, a pill with a higher progestin activity may be tried. If breast tenderness, nausea, or acne is a problem, a pill with a second- or third-generation progestin or one with lower progestin

activity should be used. Women who forget pills should use backup contraceptive methods, such as barrier methods.

e. Pill choice. A triphasic pill is a good beginning pill (Ortho-Tri-Cyclen, Triphasil, Ortho-Novum 7/7/7, Tri-Levlen, Tri-Norinyl, etc.). The pills with norgestimate, norgestrel, desogestrel, and gestodene are associated with less breakthrough bleeding (BTB) (Lo/Ovral, Ovral, Ortho-Cept, Ortho-Cyclen, Ortho-Tri-Cylcen); however, those with norgestrel may have more androgen-like effects, such as acne and hair changes, and their use should be avoided in adolescents. Low-dose estrogen pills (Estro-Cyp, Alesse) may be a good choice for women with estrogen side effects, but these drugs may allow BTB. Women with BTB may need a monophasic pill with 35 µmg ethinyl estradiol or equivalent (Ortho-Novum 1/35, Norinyl 1/35) or the pills with norgestrel (Ovral, Lo/Ovral).

3. Progestin-only oral contraceptives.
   a. Effectiveness 96%–99.5%.
   b. Indications. Women who are older than 35 and smoke. Those with a history of thrombotic or liver disease. Breast-feeding women. Women who are older than 45, who have had problems with estrogen side effects or have had deep venous thrombosis or hyperlipidemia may do well on these pills. These are a good choice for women who are breast-feeding; these pills may have some positive impact on breast milk production. There has been no measurable impact found on the coagulation; nevertheless, the package insert suggests that these be avoided in women with deep veinous thrombosis or other thrombotic conditions.

      Notes: These must be taken at the same hour every day because of the low dose. Women taking these pills often have BTB. Up to 40% of women on progestin-only OCPs have irregular cycles. They may induce ovarian cysts; therefore, women with recurrent cysts may want to use a combination pill. These should be avoided in women on chronic rifampin or anticonvulsants. Because of the low dose, any diminution by liver changes would likely inactivate the pill.

4. Depo-Provera is an injectable progestin that lasts 14 weeks.
   a. Effectiveness is 99.8%.
   b. Indication. Women with erratic lifestyle or those who cannot remember to take pills. It is a good choice for women on medications that affect the liver because the levels of these medications, especially anticonvulsants and antipsychotics, are not affected. It is a good choice for women who need very efficient methods, such as those at risk in occupation or because of health. It can be used by breast-feeding mothers. It is an excellent choice for women for whom estrogen in contraindicated, women with congenital heart disease, women who have experienced thrombotic events, women older than 35 and smoke, or woman with hyperlipidemia.
   c. Contraindication. Absolute contraindications include pregnancy and, because of this, unexplained vaginal bleeding. Liver disease, breast cancer, and cardiovascular disease are relative contraindications. It takes longer to return to fertility after discontinuation of Depo-Provera. Ovulation may not return for 12 months.
   d. *Notes:* Given every 3 months at a dose of 150 mg quarterly IM, it must be injected during the first 5 days of the menstrual cycle.
5. Intrauterine devices (IUDs)
   a. Contraceptive effectiveness is approximately 98%.
   b. Indications. IUDs are indicated for women who want to space their pregnancies, those who avoid taking pills or don't want to have to remember to take pills, and those who wish to avoid hormonal effects but do not want to undergo sterilization.

c. Contraindications. Nulliparous women, women who have had pelvic inflammatory disease or infections, and women with multiple partners or abnormally shaped uteruses should not use an IUD.
d. *Notes:* Although IUDs do not increase the risk of tubal pregnancy, if an IUD user becomes pregnant, the chance of its being an ectopic pregnancy is increased. Ultrasonographic examination to determine placement of pregnancy, if the woman had an IUD, is mandatory. If a woman has an intrauterine pregnancy with an IUD in place, the chance of spontaneous abortion is 60%. If the IUD is removed immediately, the chance of spontaneous abortion drops to 30%. The IUD should be removed if the woman become pregnant.
e. Side effects. Increased menstrual bleeding and dysmenorrhea.

G. Sterilization

1. Female sterilization. Female sterilization is the most common form of sterilization worldwide and is primarily achieved by tubal ligation done immediately post partum (50%) or at any other time. Although tuboplasties with subsequent successful pregnancies are possible, the woman and the physician should consider tubal ligation in any form to be permanent. Thus, it should be only used when the woman has completely finished childbearing.
2. Male sterilization. Approximately 7%–12% of couples use male sterilization, primarily vasectomy (see Chapter 12.9). It is very effective but expensive in comparison with nonsurgical methods.

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14.2
INFERTILITY

Keith A. Frey

The diagnosis of infertility is established after 1 year of unprotected intercourse in which a pregnancy has not been achieved. By this definition, approximately 15%–17% of couples in the United States are affected. There are many causes of infertility, including abnormalities of any portion of the male or female reproductive system. Infertility is due to a single cause in the majority of couples, but more than one factor contributes to infertility in approximately 15% of couples. Therefore, a comprehensive diagnostic evaluation is recommended for all couples.

I. Common diagnoses and pathophysiology

A. Male factors.

A male cause for infertility occurs in 26%–30% of couples. The most common male etiologic factor is a varicocele. Other causative factors include oligospermia or azoospermia, disorders of sperm function or motility (asthenospermia), and abnormalities of sperm morphology (teratospermia). Antisperm antibodies as a cause of male infertility is quite rare.

B. Ovulatory dysfunction.

Disorders of ovulation account for approximately 21% of cases of infertility. The possible causes may be grouped under four major headings:

1. **Hypothalamic anovulation** includes anatomical defects, congenital defects, psychological trauma, anorexia nervosa, pseudocyesis (false pregnancy), and pharmacologic agents.
2. **Ovarian anovulation** includes ovarian tumors, pseudo-ovulation, premature ovarian failure, and ovarian dysgenesis.
3. **Pituitary anovulation** includes pituitary tumors and ischemia.
4. **Integrative anovulation** includes nonpsychogenic weight disturbances and polycystic ovary syndrome.

C. Tubal damage.

Infertility due to tubal damage or adnexal adhesions accounts for approximately 14% of cases of infertility. Tubal obstruction may result from previous episodes of salpingitis, although many cases of tubal occlusion are encountered in which no episodes of salpingitis are recalled by the patient (see Chapter 13.5). Endometriosis may result in the anatomical distortion of adnexal structures.

D. Endometriosis.

The chronic inflammation associated with endometriosis may disrupt normal conception by interfering with ovum capture and gamete and embryo transport, or by causing tubal damage. Endometriosis is the cause of approximately 6%–20% of infertility cases.

E. Cervical mucus abnormalities.

Insufficient quantity or quality of cervical mucus is an uncommon cause of infertility. Factors that contribute to such unreceptive ("hostile") cervical mucus include hormonal disruption, previous surgery or cautery, or cervical infection.

F. "Unexplained" infertility.

No specific etiologic factor is identified in approximately 28% of infertile couples after an initial diagnostic survey.

II. Diagnostic evaluation.

A thorough diagnostic survey of both spouses is necessary to evaluate all areas of the reproductive system. A meeting with the couple early in the evaluation provides an opportunity to review reproductive biology, discuss the rationale for subsequent tests, and assess the couple's coping skills.

A. History.

The initial assessment of the couple consists of a thorough history of each partner, taken individually, to assess current and past contributing symptoms, illness, medication, or surgery. The key elements of such a history are outlined in Table 14.2-1 .

Marriage
Duration of infertility
Fertility in previous relationship
Sexual potency and techniques
Frequency of intercourse
Use of coital lubricants
Adult illness
Acute viral or febrile illness in past 3 mo
Orchitis
Renal disease
Sexually transmitted diseases
Tuberculosis
Occupation and habits
Exposure to radiation, chemicals, excessive heat (e.g., hot tub)
Childhood illness
Cryptorchidism
Age at puberty
Surgery
Herniorrhaphy
Retroperitoneal surgery
Vasectomy
Review of systems
Focus on endocrine conditions
Gynecologic history
Coital frequency
Contraceptive use
Diethylstilbestrol (DES) use by mother
Douches and lubricant use
Menarche
Menses (regularity and flow)
Mittelschmerz
Drug use
Alcohol, tobacco, and other drugs
Anabolic steroids, nitrofurantoin, cimetidine

Table 14.2-1. Key areas of infertility history

B. Physical examination.

As with the history, a thorough physical examination of each partner is essential. Areas of special attention for each physical are listed in Table 14.2-2 .

Male	Female
Hair pattern	Breast formation and galactorrhea
Genitalia	Distribution of body fat
Meatus size and location	Hair pattern (virilization)
Prostate and seminal vesicles	Neurologic
Scrotum	Anosmia
Testicular size (>4 cm in long axis)	Visual fields
Varicocele (standing and with Valsalva's maneuver)	Pelvis
Neurologic	External genitalia
Anosmia	Retrovaginal area (endometriosis)
Visual fields	Uterus and adnexa
	Vagina and cervix

Table 14.2-2. Physical examination in infertility: areas of special attention

C. Laboratory studies.

Each couple is evaluated with a few routine laboratory and appropriately timed studies to assess every major reproductive factor that may contribute to the infertility. This comprehensive diagnostic survey can and should be completed for the majority of couples in 3–6 months. The evaluation should be individualized based on the findings of the history and physical examination, but an initial survey of all major reproductive factors is necessary in all couples and can be coordinated by the family physician (1). The specifically timed diagnostic tests required for an infertility survey are outlined in Table 14.2-3 .

Routine laboratory tests
Male
CBC
Semen analysis (at least 2)
Urinalysis
Female
CBC
Pap smear
Urinalysis
Basal body temperatures
Timed diagnostic tests for the female
Follicular phase
Hysterosalpingography
Preferred test for tubal patency
Performed 2–6 d after cessation of menses
Laparoscopy
Performed if hysterosalpingogram is nondiagnostic
Ovulatory phase
Postcoital (Sims–Huhner) test
Determines number and condition of sperm and their ability to penetrate cervical mucus
Luteal phase
Endometrial biopsy
Determines if luteal phase defect exists
Performed 2–3 d before expected menses
Requires informed consent and histologic dating
Serum progesterone
May be an alternative to endometrial biopsy
Sample drawn 5–7 d after supposed ovulation

CBC, complete blood count.

Table 14.2-3. Laboratory and diagnostic testing in infertility

1. **Male factors.** The male is evaluated with a complete blood count, urinalysis, and at least two semen analyses. Each semen analysis is performed on a fresh (within 2 hours), warm specimen obtained by masturbation after at least 2 days of abstinence. Normal results vary between laboratories but in general include a volume (2–5 mL), complete liquefaction within 30 minutes, sperm count (60–150 million/mL), sperm motility (>60%), and morphology (>60% normal forms). Evidence of oligospermia after two or more semen analyses requires further evaluation, including blood levels for luteinizing hormone, follicle-stimulating hormone, and testosterone.
2. **Ovulatory dysfunction.** Anovulation or inconsistent ovulation may be diagnosed by history (irregular menses), a non-biphasic basal body temperature

pattern, abnormally low serum progesterone levels in the luteal phase, or endometrial biopsy.

3. **Tubal factors.** The female partner must undergo an evaluation for tubal patency. A hysterosalpingogram is obtained if the history and physical examination show no evidence of tubal damage. Otherwise, the patient is referred for laparoscopy.
4. **Cervical mucus factors.** If significant white blood cells (WBCs) are noted on cervical mucus samples at the time of expected ovulation (such as during a postcoital test), then a specific bacteriologic diagnosis should be sought.

III. Management.

Treatment should not be initiated until the diagnostic survey is complete and the infertility cause or causes identified. The diagnosis should be shared with the couple together and the treatment options outlined. The workup, diagnosis, and treatment of infertility can precipitate intense emotional reactions. The sensitive physician discusses such emotions as guilt, anger, self-doubt, depression, and grief (2). Helping the couple understand their motives for parenting can be helpful. These motives may include a desire to parent, to experience a pregnancy, to meet the expectations of others, and to promote genetic continuity. The physician should assist the couple in the development of mutual support and an

adaptive “couple-coping” style. This assistance includes the discussion of sexual issues and the encouragement to nurture their intimacy. Periodic meetings with the couple to review diagnostic or treatment progress provides further opportunity to reinforce coping skills. Referral to self-help groups, such as RESOLVE, Inc. (http://www.resolve.org/), assist the couple in broadening their support systems.

A. Male factors.

Consultation with a urologist is necessary to coordinate treatment for a varicocele or other causes of sperm dysfunction (3).

B. Ovulatory dysfunction.

Treatment with clomiphene should be considered for women diagnosed with anovulation. Amenorrheic and oligomenorrheic women attempting to conceive are among the most suitable patients for clomiphene. Patients with other cause for their anovulation respond best to specific therapy, such as surgery for a pituitary tumor. The starting dose for clomiphene is 50 mg/d PO on menstrual cycle days 3–7. The dosage should only be increased if the patient is not ovulating. If a midluteal progesterone is greater than 10 pg/mL, continue the same clomiphene dose. If the progesterone is less than 10 pg/mL, then increase the dose of clomiphene by 50 mg per cycle until the patient is ovulating. The patient should be aware of the common side effects of clomiphene therapy: ovarian enlargement (13.9% of cases), vasomotor flushes (10.7%), and abdominal or pelvic discomfort (7.4%). Ovulation should be expected 3–8 days after the treatment ends and should be confirmed by a biphasic basal body temperature and an elevated serum progesterone on day 21 (4). If ovulation does not occur despite clomiphene therapy, consultation with an infertility specialist is recommended.

C. Tubal damage.

Tubal deformity or blockage often requires surgical correction via laparoscopy or laparotomy with tubal microsurgery.

D. Endometriosis.

The treatment of infertile women with endometriosis depends on the degree and location of the endometrial deposits. Conservative surgical treatment may enhance fertility by destroying endometrial implants and endometriomas. The laparoscopic cauterization of early-stage endometriosis has been shown in one study to improve pregnancy rates. Ovulation suppression by danazol, progestins, and gonadotropin-releasing hormone analogues has been shown not to be effective in the treatment of endometriosis-associated infertility. Superovulation with clomiphene or human menopausal gonadotropins has been shown to be effective in such patients (5).

E. Cervical mucus abnormalities.

Cervicitis should be treated with antibiotics based on a culture-established etiology (see Chapter 13.1). Low-dose estrogens are often the best treatment for poor cervical mucus that is not due to an infectious cause. Conjugated estrogens may be used in a dose of 0.625 mg daily for the 9 days prior to expected time of ovulation.

IV. Prognosis.

The specific prognosis of infertility is difficult to determine due to the multiple etiologies. For most causes of infertility, conception will not occur without specific treatment. However, favorable pregnancy rates are reported when specific therapy is instituted. If the comprehensive diagnostic workup fails to establish a diagnosis or if appropriate treatment is unsuccessful, the physician should consider referring the couple to an infertility specialist. The options for adoption should also be discussed with the couple at this time (6).

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14.3

GENETIC DISORDERS AND PREGNANCY

2002
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I. Introduction

Genetic information is used to evaluate the risk a patient may have for a genetic disorder or to counsel patients about future risks for childbearing.

A. General risks for pregnancy.

Data that are useful in providing a baseline risk for abnormal outcomes related to pregnancy are shown in Table 14.3-1 (1).

Abnormal outcome	Risk, 1 in
Congenital abnormality detected at birth	30
Severe physical or mental handicap	50
Spontaneous abortion	8
Stillbirth (North America)	125
Perinatal death	150
Death after 1 wk of survival (North America)	200

From Harper, PS. *Practical genetic counseling,* 4th ed. Oxford: Butterworth-Heinemann, 1993, with permission.

Table 14.3-1. Data useful in providing baseline risk for abnormal outcome in pregnancy

B. Types of genetic disorders.

Genetic disorders can be classified into the following five categories. (In counseling pregnant patients, the physician often deals with the first three disorders.)

1. **Chromosome disorders** are caused by the loss, gain, or abnormal arrangement of one or more chromosomes. The incidence of these disorders in the population is about 0.2%.
2. **Mendelian disorders** are single-gene defects caused by a mutant allele at a single genetic locus. The transmission pattern is further divided into autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive. The incidence of these disorders is about 0.35%.
3. **Multifactorial disorders** involve interactions between genes and environmental factors. The nature of these interactions is poorly understood. The risks of transmission can be estimated empirically, and the estimated incidence in the population is about 5%.
4. **Somatic genetic disorders** are mutations in somatic cells. They often give rise to malignant lesions. Although the mutation is not inherited, many of these events require a genetic predisposition.
5. **Mitochondrial disorders** arise from mutations in genetic material found in mitochondria. Mitochondrial DNA is transmitted only through the maternal line.

II. Chromosome disorders

A. Down's syndrome

is the most common chromosome disorder, occurring in 1 in 800 births in the United States. The physical examination of a newborn with the disorder demonstrates hypotonia. In addition to craniofacial features of brachycephaly, oblique palpebral fissures, epicanthal folds, broad nasal bridge, protruding tongue, and low-set ears, affected children may have Brushfield's spots, short broad fingers, a single flexion crease in the hand (30% of affected children and about 5% of normal children have the simian crease), and a wide space between the first two toes. About one third of the children have congenital heart disease, and there is an increased risk of duodenal atresia and tracheoesophageal fistula. The mean IQ is 50. There are increased problems with hearing, vision, hypothyroidism, leukemia, cervical spine instability, and Alzheimer's disease. Persons with Down's syndrome have a 50% chance of surviving until age 50. Risk factors to be considered in predicting Down's syndrome are as follows (2):

1. **Robertsonian translocation.** A mother whose baby has Down's syndrome has a 4% chance of having a translocation of chromosome 21. If she has the defect, the risk of another pregnancy resulting in an infant with Down's syndrome is 1 in 3. The stated risk without translocation for women younger than 30 is about 1%. For patients older than 30, the risk is the same as that for other women their age.
2. **Increasing maternal age.** The incidences of Down's syndrome and other chromosome disorders, by age, are shown in Table 14.3-2 . Prenatal diagnosis should be offered to women older than 35, and this group of patients is the largest referred for prenatal genetic testing. With this criterion, 25% of all Down's syndrome births may be detected.

Maternal age (yr)	Risk for Down's syndrome	Total risk for chromosome abnormalities[b]
20	1/1,667	1/526
21	1/1,667	1/526
22	1/1,429	1/500
23	1/1,429	1/500
24	1/1,250	1/476
25	1/1,250	1/476
26	1/1,176	1/476
27	1/1,110	1/455
28	1/1,053	1/435
29	1/1,000	1/417
30	1/952	1/385
31	1/952	1/385
32	1/769	1/322
33	1/602	1/286
34	1/485	1/238
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
39	1/136	1/83
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

[a] Because sample size for some intervals is relatively small, 95% confidence limits are sometimes relatively large. Nonetheless, these figures are suitable for genetic counseling.
[b] 47,XXX excluded for ages 20 to 32 years (data not available).
From Simpson JL. Screening for fetal and genetic abnormalities. *Baillieres Clin Obstet Gynaecol* 1991;5:675–696, with permission.

Table 14.3-2. Chromosome abnormalities in liveborn infants, by maternal age[a]

3. **Low maternal AFP.** In testing for neural tube defects, one can identify another subset of pregnant patients at risk for Down's syndrome. Because

the liver in a fetus with Down's syndrome is immature, the α-fetoprotein (AFP) level is lower. This test can identify another 20% or so of fetuses with Down's syndrome, with an amniocentesis rate of 5%. The test also can be used to assign patients older than 35 to a lower risk group. It is performed between 14 and 18 weeks of gestation.

4. **The "triple test."** Measuring serum AFP, estrogen, and human chorionic gonadotropin (hCG) levels can further define the risk for Down's syndrome. Levels of hCG are higher and levels of unconjugated estriols are lower in serum from women whose fetus has Down's syndrome. Detection rates of 60% with an amniocentesis rate of 5% have been reported.

   All the biochemical tests for screening can have false-positive results. It is very important to confirm gestational age with ultrasonography before proceeding with amniocentesis for evaluation of an abnormal result of serum testing. The consensus is that routine screening with multiple biochemical markers is not exclusively recommended. All of the screening studies do not guarantee that a newborn will not have Down's syndrome. The definitive studies are amniocentesis and chorionic villus sampling. Chorionic villus sampling has the advantage of disclosing Down's syndrome earlier, which allows for abortion earlier in pregnancy. The disadvantage is that sampling is not useful for detecting neural tube defects. In counseling patients, the physician should discuss the cost of the studies, the risks, and the concerns of the parents. Although it once was thought that only women who would have an abortion should have testing for Down's syndrome, it is acceptable to use the testing to identify a high-risk pregnancy that may require help from a tertiary center.

B. Other chromosome abnormalities.

Trisomy 18 is the next most common trisomy. The incidence is 1 in 8,000 births. Fewer than 10% of affected patients survive until age 1. Trisomy 13, the third most common trisomy, has an incidence of 1 in 20,000. Fifty percent of affected children die in the first month, and fewer than 5% survive beyond age 3 years. Cri du chat syndrome is due to a deletion involving chromosome 5. The incidence is 1 in 20,000, and the clinical features are severe mental retardation, hypotonia, and a kitten-like cry. Life expectancy is the same as that for other patients with similar IQs.

III. Mendelian disorders

A. The genogram.

The first step in detecting a mendelian disorder is completion of a family history. A genogram, used by fewer than 20% of family physicians, is extremely useful for showing patterns of genetic inheritance. A recent study indicated that 75% of patients referred for genetic counseling had another significant family disorder that could affect a pregnancy. Reports demonstrate that 90% of physicians can readily interpret data from a genogram written by other colleagues. To save time, a medical assistant can query patients for the initial information before a physician obtains the history. The information collected includes the following:

1. **Demographics.** Name, date of birth, age, sex, place of residence, and date of death for all relatives.
2. **Medical disorders.** A list of the diseases members of the family have had; a history of spontaneous abortions.
3. **Social factors.** Relationships and their quality.
4. **Reminder area.** A place on which to write previous family crises (e.g., "lost job, May 1996").

   In the construction of a genogram, squares are used to represent male subjects and circles to represent female subjects. Three generations should be represented, with each generation drawn on a horizontal row. Standard symbols for pedigree charts are shown in Figure 14.3-1 .

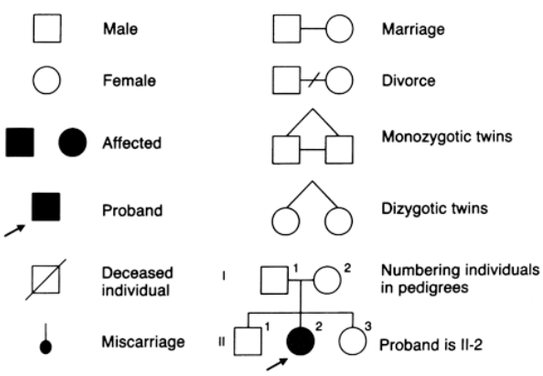

FIG. 14.3-1. Emergency contraception

B. Nationality.

In screening for mendelian disorders, certain questions about nationality should be asked because there some diseases have greater incidence in certain groups. Patients of Caribbean, Latin American, Mediterranean, or African descent should be undergo hemoglobin testing for sickle cell anemia or thalassemia disorders. Patients with Ashkenazi Jewish origins should be screened for Tay-Sachs disease.

C. Inborn errors of metabolism.

Currently, hundreds of molecular tests are available for the prenatal diagnosis of genetic disorders. Indications for these tests include a family history of the disorder, particularly if an older child had the disorder, and the patient having had three spontaneous abortions. Samples can be obtained by chorionic villus sampling or amniocentesis.

D. Other factors.

A mother with a personal history of phenylketonuria should immediately be placed on a rigorous phenylalanine-free diet to ensure that the fetus will not have mental retardation as a result of the mother's condition. Ideally, the diet should be started in the preconception period.

IV. Multifactorial disorders

A. AFP and neural tube defect.

The most common genetic disorder screened for prenatally is neural tube defect.

1. **Physiology.** AFP is manufactured in the yolk sac, gastrointestinal tract, and liver. The protein enters the amniotic fluid through urination, secretions, and transudation from blood vessels. Small amounts leak into the maternal serum. Relative levels are shown in Figure 14.3-2 .

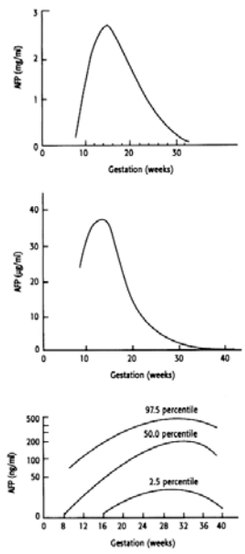

FIG. 14.3-2. Approximate relationship between α-fetoprotein values in fetal serum **(A)**, amniotic fluid **(B)**, and maternal serum **(C)**. Note different laboratory units for each graph. (From Habib ZA. Maternal serum α-fetoprotein: its value in antenatal diagnosis of genetic disease and in obstetrical-gynaecological care. *Acta Obstet Gynecol Scand Suppl* 1977;61:14, with permission.)

2. **Neural tube defect.** The incidence of neural tube defect is 1 or 2 in 1,000 births. Risk factors for the defect in the United States are shown in Table 14.3-3 . Preconception supplementation with folic acid decreases the incidence of neural tube defect. Neural tube defects are associated with high rates of mortality, morbidity, and long-term developmental disability.

Risk factor	Incidence
No family history	1 in 1,000
Family history on maternal side	1 in 100
Family history on paternal side	1 in 500
Parent with the defect	3 in 100
Previous infant with the defect	2 in 100
Maternal diabetes	2 in 100

Table 14.3-3. Laboratory and diagnostic testing in infertility

3. **Screening for neural tube defect.** In the United States, if 1,000 pregnant patients are screened at 16–18 weeks gestation, 25–50 of them have increased levels of AFP in maternal serum (MSAFP) and 40–50 have low results (Figure 14.3-3). Patients with high levels can undergo ultrasonography to assess for gestational age, multiple gestation, or significant abnormality. Another option is to repeat the MSAFP testing in 1–2 weeks in patients with abnormally high or low results. If the studies confirm the previous abnormal results, ultrasonography should be done. After the ultrasonographic screening, about 17 patients with increased MSAFP levels will have no ultrasound findings to explain the increase, and 20–30 patients with decreased MSAFP levels will have no explanation.

These patients may then undergo amniocentesis. One or two of the 17 patients with high levels will have a significant neural tube defect, and 1 in 65 with low MSAFP levels will have a chromosome abnormality (1 in 90 chance of Down's syndrome). A patient with an abnormally high MSAFP level and no neural tube defect has an increased risk of stillbirth, low-birth-weight infant, neonatal death, and congenital anomalies.

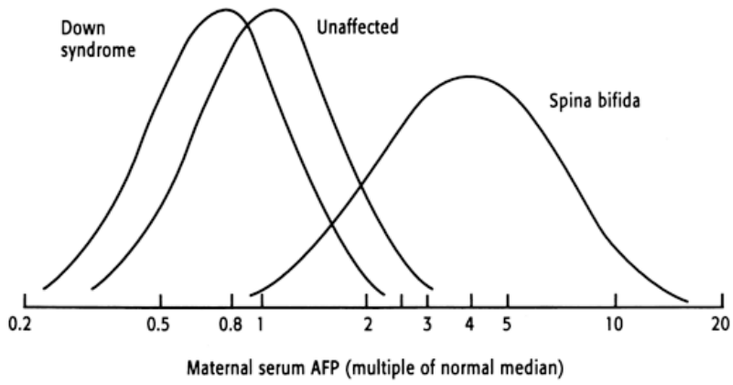

FIG. 14.3-3. Log gaussian distribution of α-fetoprotein levels in maternal serum at 16–18 weeks gestation in singleton pregnancies for open spina bifida, unaffected pregnancies, and Down's syndrome. (From Wald NJ, Cuckle HS. Recent advances in screening for neural tube defects and Down's syndrome. *Baillieres Clin Obstet Gynaecol* 1987; 1:656, with permission.)

B. Cleft lip with or without cleft palate.

The overall risk for recurrent cleft lip is 4% if a sibling or parent has the abnormality. The incidence is 10% with two previous siblings. A newborn who also has lip pits or depressions on the lower lip may be manifesting an autosomal dominant trait, and this has a 50% recurrence rate for a sibling.

C. Other multifactorial disorders.

Generally, the rate of multifactorial disorders is less than 5%. The recurrence rate is 2%–5% for cardiac anomalies, 1%–2% for tracheoesophageal fistula, 1% to 2% for hernia, 6%–10% for hypospadias, and 4%–8% for hip dislocation.

V. General considerations.

In North America, about 8% of pregnancies meet the criteria for prenatal diagnosis by amniocentesis or chorionic villus sampling.

A.

All patients have the right to receive information about their genetic risk for a pregnancy. This allows a parent to make an informed choice about having a child with an abnormality.

B.

All patients have the right to refuse testing. What a patient decides to do about any given risk factor is entirely up to the patient. Genetic testing is

voluntary, with the exception of state testing for disorders, such as neonatal screening for phenylketonuria, hypothyroidism, and other inborn errors of metabolism. Referral to a geneticist is useful in difficult situations or for patients with complex or unusual genetic disorders. Genetic screening is not expected to detect all genetic disorders in a given population.

C.

A summary of specific questions that can be asked of a patient is given in Table 14.3-4 .

Question	Comment
Are you older than age 35?	Fetus is at risk for chromosome abnormalities
What is the ethnic origin of each parent?	Tay-Sachs disease in French–Canadian, Cajun, and Jewish ancestries; sickle cell disease in African, Mediterranean, Middle Eastern, Caribbean, Latin American, and Indian descent
Is there a family history of mental retardation?	Fragile X syndrome, Down's syndrome (Chromosome abnormalities account for about 25% of mental retardation)
Is there a family history of Down's syndrome or other chromosome abnormalities?	Robertsonian dislocation
Is there a family history of diseases that might be tested for? (These are usually diseases found in younger children or infants.)	Tay-Sachs disease, hemophilia, cystic fibrosis, thalassemia
Is there a family history of defects in infants and other children whom we can test for by ultrasonography?	Congenital heart problems, polycystic kidney disease
Has there been a history of multiple spontaneous abortions?	Chromosome abnormalities or Potter's syndrome (missing or underdeveloped kidneys)
Are the parents related to each other?	Any relationship closer than second cousin is associated with increased risk
Does the mother have a history of epilepsy, diabetes, or phenylketonuria?	These conditions may lead to birth defects, and preconception management is essential
Is there a history of blood clotting problems in either parent?	Hereditary hemoglobinopathies
Do you use recreational drugs or alcohol?	Associated syndromes with alcoholism and addiction
Are you taking any medications?	Certain drugs are associated with birth defects

From Dugoff L. Genetic screening of gravidas: what is called for today? *OBG Mgmt* 1998;9:54–64, with permission.

Table 14.3-4. Twelve key questions that can identify genetic risk

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14.4
PRENATAL CARE

Walter L. Larimore

Family-centered prenatal care is the delivery of effective, efficient, accessible, safe, and economical quality care for the psychosocial, spiritual, and physical needs of the mother, child, father, and family unit. This approach emphasizes health instead of disease, patients instead of providers, and serving instead of controlling. Family physicians with this philosophy view childbirth as a vital life event in the family and a foundational event in the formation of community and society. The family physician is ideally suited to provide this care; whether the family physician will deliver the baby or provide "shared prenatal care" with a delivering midwife or physician. An in-depth review of routine prenatal care is beyond the scope of this chapter; however, basic information that is frequently needed during prenatal care is provided, and Figure 14.4-1 illustrates important considerations and decision points in prenatal care.

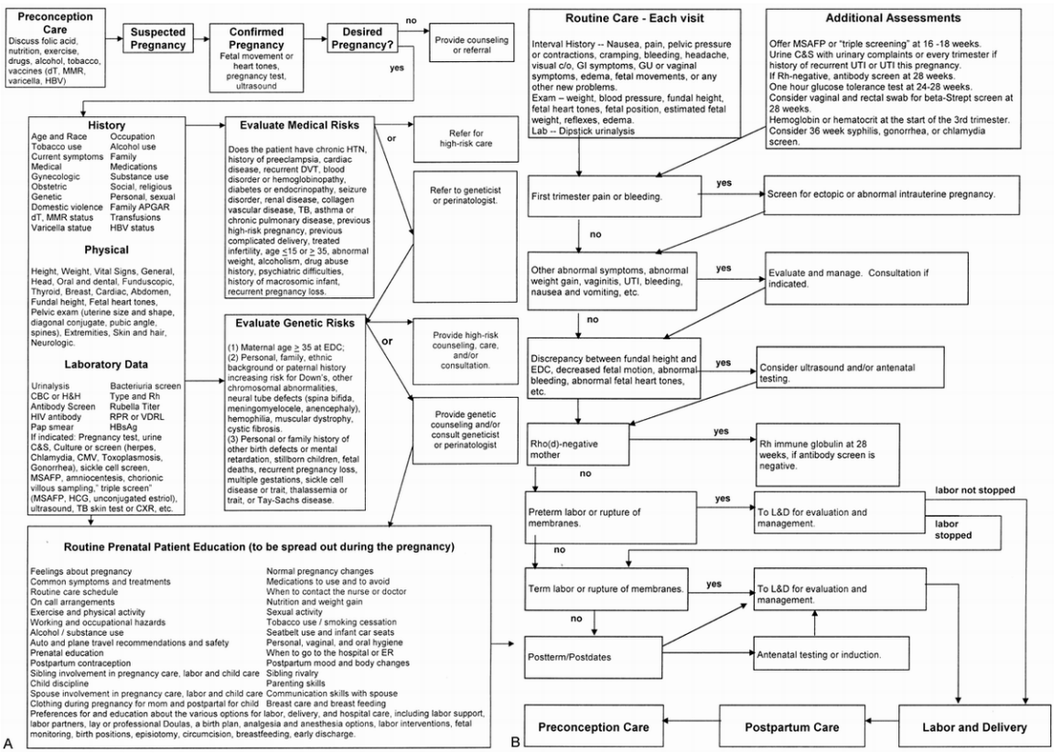

FIG. 14.4-1. Important considerations and decision points in prenatal care.

I. Nutrition

A. Weight gain.

Recommendations for weight gain are based on a prepregnancy ideal body weight (IBW) or body mass index (BMI). The optimum weight gain for best perinatal results is controversial. According to several studies, a total weight gain of 24–35 pounds during pregnancy is associated with the best outcome. A weight gain of at least 20 lb is associated with a successful pregnancy outcome for most women whose prepregnancy weight is 85%–120% of IBW. There is a general consensus that the woman who enters pregnancy substantially below her desired body weight is at greater risk and should gain a greater amount of weight during the pregnancy. Although authorities do not agree about the optimum weight gain for the patient who is overweight, there is strong support for the view that the overweight patient may not need to gain as much as the patient who begins pregnancy at normal weight. Substantial deviations in weight at the start of pregnancy may signal the need for consultation or referral to a registered dietitian. Adolescents should aim for the higher end of the range and women shorter than 62 inches for the lower end of the range (Table 14.4-1). Of course, weight gain with twins would be greater (Table 14.4-2) (1).

Prepregnancy weight	% Ideal body weight	Body mass index	Recommended total weight gain (lb)	First-trimester weight gain (lb)	Second- and third-trimester weight gain (lb/wk)
Underweight	<90	<23	28–40	5	1–1.25
Acceptable	90–120	23–25	25–35	3.5	1
Overweight	121–135	25–27	15–25	2	0.5–0.75
Severely overweight	135–150	27–30	At least 15	2	0.5
Obese	>150	>30	At least 15	2	0.5

Table 14.4-1. Recommended weight gain during singleton pregnancy

Prepregnancy weight	Body mass index	0–20 wk (lb/wk)	20–28 wk (lb/wk)	28–40 wk (lb/wk)	Total gain (lb)
Underweight	<19.8	1.25–1.75	1.50–1.75	1.25	50–62
Acceptable	19.8–26.0	1.00–1.50	1.25–1.75	1.00	40–54
Overweight	26.1–29.0	1.00–1.25	1.00–1.50	1.00	38–47
Obese	>29.0	0.75–1.00	0.75–1.25	0.75	29–38

Table 14.4-2. Recommended weight gain during twin pregnancy, by gestational week

B. Dietary and caloric requirements during pregnancy.

For most patients a well-balanced diet consisting of intake of approximately 2,300 kcal/d will provide adequate nutrition during the pregnancy. For pregnant teenagers, especially those younger than 15 years, a daily intake of 2,400 kcal or more is recommended. The diet should provide for an increased intake of certain nutrients, specifically protein, calcium, iron, and folic acid. Although most patients will be able to obtain adequate protein and calcium from dietary sources, the patient who is unlikely to increase her

dietary intake of milk or soy products will probably require calcium supplementation. In addition, many physicians prefer to prescribe supplemental iron and vitamins, particularly folic acid. For calorie requirements during pregnancy, see Table 14.4-3 .

Stage	Normal activity	High activity
First and early second trimester	25–30	35–40
Late second and third trimester	25–35	35–45

[a] Kcal/kg ideal body weight.

Table 14.4-3. Calorie requirements during pregnancy[a]

C. Vitamin supplementation

1. The iron need in pregnancy is 30–60 mg/d elemental iron (e.g., 100 mg ferrous fumarate, 150 mg ferrous gluconate, or 300 mg ferrous gluconate). The available data from controlled trials provide no compelling evidence for routine as opposed to selective iron supplementation in populations with a low prevalence of iron deficiency. Iron-rich foods include lean beef, pork, poultry, legumes, and whole grains. Vitamin C enhances the absorption of iron.
2. Folate requirements in pregnancy are 0.8 mg/d (the amount in most prenatal vitamins). If there is a history of neural tube defect, malabsorption syndrome, hemoglobinopathy, treatment with phenytoin, and (possibly) adolescence, begin prepregnancy with 4 mg/d. Otherwise all women of reproductive age should be taking 0.4 mg/d of folic acid.

3. Calcium needs are at least 600 mg/d, or 1 quart of milk per day. There are meta-analysis data indicating that calcium supplementation may reduce the risk of developing hypertension and, possibly, proteinuric preeclampsia and preterm delivery.
4. Vegetarians should make sure they get 400 IU/d of vitamin D, 1 mg/d of vitamin B_{12}, and 1,000 mg/d of calcium.
5. Megavitamins and dietary supplements. The physician should be alert to the excess consumption of vitamins or "health food" supplements of any type, as intake of these substances may prove toxic and possibly teratogenic.

II. Risk of genetic abnormality

(see also Chapter 14.3). There is an easy rule-of-thumb for calculating the genetic risk of maternal age (2). Remember that the approximate risk of trisomy 21 in a 35-year-old woman is 1 in 360. Every fifth year after 35, the denominator is divided by about 3. To figure the risk of all chromosomal abnormalities, multiply the trisomy risk by 2 (or divide the denominator by 2) (Table 14.4-4).

Age at delivery	Trisomy 21 calculated risk (actual risk)	All chromosomal abnormalities calculated risk (actual risk)
35	1/360 (1/365)	1/180 (1/178)
40	1/120 (1/109)	1/60 (1/63)
45	1/40 (1/32)	1/20 (1/18)
50	1/13 (1/12)	1/7 (1/7)

Table 14.4-4. Risk of fetal chromosomal abnormalities by maternal age

III. Determination of gestational age.

Pregnancy milestones or maneuvers can help estimate gestational age (Table 14.4-5). However, gestational age is most accurately determined by ultrasonography (see Chapter 14.12).

Milestone or maneuver	Gestational age (wk)
Transvaginal ultrasonography—fetal heart movement	5–6
Transabdominal ultrasonography—fetal heart movement	6–7
Doppler stethoscope—fetal heart tones	10–12
Fundal height to pelvic brim	12
Perception of fetal movement to mother ("quickening")	16–20
Conventional fetoscope—fetal heart tones	18–20
Perception of fetal movement to examiner	20
Fundal height to umbilicus	20

Table 14.4-5. Pregnancy milestones or maneuvers to help estimate gestational age

IV. Common symptoms in pregnancy

(see also Chapter 14.6).

A. Morning sickness

is experienced by most pregnant women. This can be alleviated through appropriate dietary measures, such as keeping a small amount of food in the stomach at all times, as well as avoiding spicy food, fried food, and heavily seasoned food. However, no controlled trials support these recommendations. Milk may cause nausea and vomiting, and as there is no need for the extra calcium until the 20th week, milk can be omitted from the diet during this time. Nonpharmacologic treatments include a band that places pressure on a wrist acupressure point, biofeedback, and self-hypnosis. Oral pharmacologic treatments include pyridoxine (vitamin B_6), 12.5–25 mg q8h used alone, or pyridoxine, 25–50 mg PO tid-qid used in combination with doxylamine, 10–12.5 mg PO qd-bid. Doxylamine is available over the counter

in 12.5-mg (Decapryn) and 25-mg tablets (Unisom Nighttime Sleep-Aid Tablets). The latter combination is contained in the prescription drug Diclectin, which is currently available in Canada. The combination is not teratogenic but is rarely recommended by U.S. physicians. Another option is phosphorated carbohydrate solution (Emetrol); 1–2 tablespoons every 15 minutes to 5 doses may be useful. One physician has reported success with more than 50 years experience using 1 cc of pyridoxine IV qd for 2–3 days (3). Newer data indicate that more than 90% of women with hyperemesis gravidarum are infected with *Helicobacter pylori*, although controversy exists over how to treat *H. pylori* during pregnancy. Amoxicillin and metronidazole after the first trimester are safe in pregnancy. The addition of omeprazole (Prilosec) should probably be coordinated with a perinatologist. A risk-benefit assessment of pharmacologic and nonpharmacologic treatments for nausea and vomiting of pregnancy is available (4).

B. Vaginal bleeding

is common in early pregnancy, occurring in approximately 20% of all pregnant patients. It is generally thought that light bleeding or spotting is due to implantation. However, bleeding that is more than slight or that occurs later in the pregnancy requires immediate investigation, as it may be the first sign of threatened abortion, hydatidiform mole, ectopic pregnancy, or other potentially serious conditions (see Chapter 14.10).

C. Vaginal discharge

is common in pregnancy, with many women noting increased vaginal discharge during pregnancy. If this becomes symptomatic or a problem, further investigation is warranted, using culture and microscopic techniques. Symptomatic monilial and chlamydial infections and bacterial vaginosis should be treated with appropriate medications (see Chapter 14.6). Treatment of symptomatic bacterial vaginosis with oral medications reduces the risk of preterm labor more effectively than topical medications. The current evidence does not support screening and treating all pregnant women for bacterial vaginosis to prevent preterm birth. For women with a history of a previous preterm birth there is some suggestion that detection and treatment of bacterial vaginosis early in pregnancy may prevent a proportion of these women from having another preterm birth (5). Increased vaginal discharge or secretions may signal preterm cervical changes or labor and may warrant vaginal examination.

D. Urinary complaints,

especially urinary frequency, are common in early pregnancy, stemming both from increased pressure on the bladder caused by an enlarging uterus and from an increased glomerular filtration rate.

Urinary complaints are also common during the final trimester as the fetus begins the descent into the pelvis. Urinary complaints in the second trimester, or at any time in the pregnancy, may indicate urinary tract infection (UTI) and should be investigated by urine culture. UTI has been associated with a significant increase in preterm contractions, preterm labor, prematurity, fetal loss, and chronic pyelonephritis following pregnancy, and should be treated with antibiotic therapy for 7–10 days followed by a post-treatment culture. Antibiotic selection should be based on the results of a culture and sensitivity testing, the patient's previous history of drug reaction, and/or the date of the pregnancy. Upper tract infection accompanied by fever, malaise, and flank pain may warrant 10–14 days of antibiotic therapy and/or hospitalization (see Chapter 14.6 and Chapter 22.2).

E. Back pain

in pregnancy is common. It occurs in up to 56% of all pregnancies, with one third of these being reported as severe and aggravated by mechanical and hormonal factors. Usual recommendations include stretching and strengthening exercise, oral or topical analgesics, massage, heat therapy, or cryotherapy. Acupuncture has been demonstrated to be more effective than physiotherapy (6). Specially shaped pillows help reduce back pain in late pregnancy and improve sleep (7). However, up to 50% of back pain in pregnancy is caused by sacroiliac subluxation, which can be treated quickly, safely, and simply with manipulation; this results in more than 90% of treated patients reporting relief of pain and resolution of signs of sacroiliac subluxation. Readers who wish to learn the technique are referred to a review on the topic (8).

F. Leg cramps

occur in 5%–30% of all pregnancies. Some evidence exists for therapies such as oral calcium, sodium chloride, or vitamin C (9). One trial demonstrated significant benefit to using oral magnesium supplements (122 mg once in the morning and twice in the evening) in decreasing the frequency and intensity of leg cramps (10).

V. Diagnostic criteria for gestational diabetes mellitus (GDM) screening

(also see Chapter 14.6)

A. Risk factors

include obesity, history of miscarriage or fetal death, age 40 or older, history of premature infant, family history of diabetes, polyhydramnios, history of infant with macrosomia (>4,000 g) or congenital malformation, preeclampsia, excessive weight gain, and glycosuria.

B. Universal screening

is no longer recommended. The American Diabetes Association recommends that women at risk for GDM be screened with a 50-g glucose load given at 24–28 weeks without regard to the time of day or the last meal. Women with a plasma glucose exceeding 140 mg/dL during a 1-hour glucose tolerance test (GTT), a fasting plasma glucose exceeding 140 mg/dL, or a random plasma glucose greater than 200 mg/dL need a 3-hour GTT.

C. Diagnosis.

Administer a 3-hour fasting GTT with a 100-g glucose load. Two or more of these plasma values (*not* fingerstick values) must be met or exceeded for diagnosis of GDM: Fasting, 105 mg/dL; 1 hour, 190 mg/dL; 2 hours, 165 mg/dL, and 3 hours, 145 mg/dL.

VI. Indications for Rh_o(D) immune globulin in Rh-negative women.

Administer Rh_o(D) immune globulin ante partum at 28–32 weeks and post partum (if the baby is Rh-positive) to prevent hemolytic disease of the newborn in subsequent pregnancies. Rh_o(D) immune globulin is also indicated for spontaneous or induced abortion, ectopic pregnancy, chorionic villus sampling, amniocentesis, vaginal bleeding, significant abdominal trauma, external cephalic version, and transfusion of unmatched Rh-positive blood or any platelet transfusion. For a more detailed discussion, see Chapter 14.8 .

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Recommended Office Resources

1. Ratcliffe S, Sakornbut E, Byrd J, eds. *Handbook of pregnancy and perinatal care in family practice: science and practice*. London: Hanley & Belfus, 1995, 2000.

2. Larimore WL, Byrd JA, Reed M. *Normal pregnancy. ABFP reference guide*, 7th ed. American Board of Family Practice, 1999, Louisville, KY. (Updated every 2 years and available on the Internet at http://www.familypractice.com/references/referencesframe.htm [go to “ABFP guides” and then “pregnancy.”])

3. Larimore WL, ed. Updates in maternity care. *Prim Care Clin N Am* March 2000;27(1). (Includes chapters Periconception Care; Maternal Infections; Drug Use in Pregnancy; Prenatal Screening; Risk Assessment; Nutrition, Exercise, Work and Sex in Pregnancy; Alternative Medicine in Pregnancy; call 1-800-654-2452 for information.)

4. Enkin M, Nelison J, Keirse MJ, eds. *Guide to effective care in pregnancy and childbirth*, 3rd ed. Oxford: Oxford University Press, 2000. (The classic evidence-based guide to pregnancy care)

14.5
ECTOPIC PREGNANCY

Michael A. J. Purdon

Robert H. Scott

Ectopic pregnancy occurs when a fertilized ovum implants anywhere but the uterine cavity. One in every 66 pregnancies is ectopic; 96.5% of these are in the uterine tubes (1). This can become a surgical emergency when there is tubal rupture with internal bleeding. Common risk factors include a history of pelvic inflammatory disease, previous tubal

surgery, history of infertility or previous ectopic pregnancy, in-utero diethylstilbestrol exposure, smoking, and use of assisted reproductive technologies (2). Contraception failures, particularly with progestin-only contraception or intrauterine device (IUD), are at higher risk for ectopic implantation.

I. Diagnosis

A high index of suspicion is key.

A. Symptoms.

Pelvic, abdominal, or referred pain is almost always present before rupture but is highly variable in location, character, and severity. The onset of pain is usually at 6–8 weeks gestational age. Often there is amenorrhea followed by irregular vaginal bleeding. However, 40%–50% of patients will experience vaginal bleeding that may be mistaken for a normal period (2).

B. Signs

may include localized lower quadrant tenderness with or without a palpable mass, peritoneal irritation with guarding and rebound tenderness (suggesting tubal rupture with hemoperitoneum), or cervical motion tenderness. The uterus may be of normal size or 6–8 weeks gestational size. Signs of shock—pallor, diaphoresis, dizziness, weakness, orthostatic pulse and blood pressure changes—may be present. Syncope occurs in up to 37%; fever is present in less than 2%.

C. Laboratory tests

include complete blood count (CBC), quantitative ß-human chorionic gonadotropin (ß-hCG) and serum progesterone. The ß-hCG will double in about 2 days if there is a viable intrauterine pregnancy (IUP). The doubling time for ectopic pregnancy is 3 or more days. A falling value signals nonviability. A single value is not interpretable (one third of women who rupture have serum ß-hCG level below 100), and serial testing should only be used if the patient remains hemodynamically stable.

The positive predictive value for IUP with single progesterone level of 25 ng/mL or greater is 99.6%. No viable pregnancy is seen when the progesterone level is less than 5 ng/mL. Intermediate values are harder to interpret.

D. Special examinations

1. Transabdominal ultrasonography can detect IUP at 42 days' gestational age, which corresponds to a ß-hCG of 6,000 IU/L. Thus, absence of IUP with ß-hCG is ectopic pregnancy until proved otherwise.
2. Transvaginal ultrasonography can detect IUP at ß-hCG levels of 1,000–2,000 IU/L, or about 32 days' gestation (1). Ectopics may not be seen directly until after they are large enough to cause tubal rupture. Thus, absence of IUP and a ß-hCG level exceeding 1,000 IU/L is ectopic pregnancy until proved otherwise when the transvaginal probe is used. This technique can also be useful in identifying small amounts of blood in the cul-de-sac.
3. Laparoscopy is as effective as laparotomy in patients who are hemodynamically stable. It can show early, unruptured ectopic pregnancy and can be used for management.
4. Laparotomy is indicated if required urgently to control bleeding or when definitive treatment is not possible by laparoscopy or medication.
5. Dilatation and curettage may be used if the ß-hCG level is not rising normally, or if a single progesterone level is less than 5 ng/mL and ultrasonography is negative for IUP (3). If there are no chorionic villi and the ß- hCG is rising, ectopic pregnancy is assumed to be present.
6. Culdocentesis can identify hemoperitoneum. It may help to make an emergency decision to operate, but it provides less information and more uncomfortable than transvaginal ultrasonography.

E. Differential diagnosis

includes appendicitis, salpingitis or pelvic inflammatory disease, ruptured corpus luteum cyst, twisted ovarian cyst, urinary tract disease, and threatened or incomplete uterine abortion. Consider concurrent problems, such as IUP and appendicitis, or IUP and ectopic pregnancy (rare, except in patients who have undergone in vitro fertilization).

Also consider rare types of ectopic pregnancy: interstitial, abdominal, cervical, ovarian, or multiple.

II. Management

A. Emergent presentation.

Emergency laparotomy is indicated if signs of intraperitoneal bleeding or shock are present. Fluids and blood transfusions are given as required. Ultrasonographic examination may waste critical time.

B. Nonemergent presentation

1. Surgical. Perform laparoscopy or laparotomy to remove the ectopic pregnancy, and consider tubal repair. Surgical management is favored if pain is prolonged for more than 24 hours, quantitative ß-hCG is more than 10,000 mIU/mL, or in ectopics larger than 3.5 cm on ultrasound.
2. Methotrexate, 50 mg/m^2 given as a single IM injection, is approximately 90% effective [4]. Eligible patients have a gestational sac diameter less than 3.5 cm on ultrasound, with no fetal cardiac activity present and no evidence of rupture. Absolute contraindications include breast-feeding, immunodeficiency, liver disease, blood dyscrasia, pulmonary disease, peptic ulcer disease, or renal dysfunction. Pelvic pain due to tubal abortion typically occurs 3–7 days later and lasts 4–12 hours. This can be confused with tubal rupture, and patients should be followed closely for signs of hemodynamic instability. The ß-hCG level may rise for 3–4 days but should then fall 15% between days 4 and 7 (3). If not, reevaluate, and consider a second dose or laparoscopy. Surgical backup should be available at all times.
3. Expectant management. The natural history of ectopic pregnancy is variable, and many such pregnancies resolve without significant symptoms. Success varies between 47% and 100% and depends on low initial (<1,000 mIU) and subsequently falling ß-hCG levels (3).

C. Rho(D) immune globulin

(RhoGAM 300 µmg) should be given to Rh-negative women as indicated, regardless of the method of management. The microdose (MICRhoGAM 50 µmg) is used prior to 12 weeks gestation.

D. ß-hCG levels

should be followed weekly until undetectable, regardless of the method of treatment.

III. Prognosis and counseling.

Maternal morbidity is about 1% in the United States. Another ectopic pregnancy occurs in 6%–12% of patients. Fertility is compromised and only one third of patients will subsequently deliver a live infant. The chance for future fertility is increased if the contralateral tube is normal. Patients should be encouraged to discuss their feelings about the loss of the pregnancy and the possibility of compromised fertility in the future.

IV. Prevention

A. Counsel patients

about practicing “safe sex” to avoid pelvic infections.

B. Treat salpingitis

early and vigorously (see Chapter 13.5).

C. Avoid using an IUD

in women with a high risk of exposure to sexually transmitted diseases (see Chapter 14.1). Hormonal contraceptive methods are preferable in this population.

D. Early diagnosis of ectopic pregnancy

allows conservative, tube-sparing surgery or the use of methotrexate.

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14.6
MEDICAL PROBLEMS DURING PREGNANCY

Michael J. Stephenson

This chapter addresses both specific medical problems that are major potential contributors to the mortality and morbidity associated with pregnancy and conditions that have features unique to pregnancy.

I. Gastrointestinal problems

A. Nausea of pregnancy.

Between 50% and 90% of pregnancies are affected by nausea and vomiting, typically starting around 4–6 weeks, peaking at around 8–12 weeks, and disappearing by 20 weeks. The cause is still unclear but female sex hormones, especially progesterone, may be responsible. The spectrum ranges from mild nausea to the severe form, known as hyperemesis gravidarum, which occurs in approximately 1%–2% of pregnancies. In hyperemesis gravidarum, the existence of multiple pregnancies and hydatiform moles should be excluded. If vomiting occurs beyond 20 weeks of pregnancy, then other diagnoses should be considered. The condition is associated with slow recovery and frequent relapses.

1. **Clinical presentation** ranges from mild nausea in the morning to a total inability to keep any food or liquids down. Progression to hyperemesis gravidarum can lead to starvation, dehydration, electrolyte abnormality, and, in extreme cases, death.
2. **Diagnosis** is based on history of nausea and vomiting. Severity is determined by the frequency of emesis, fluid intake, and loss of weight. Weight loss greater than 5% of prepregnant weight increases risk of poor fetal growth and outcome. If severe, check for dehydration (e.g., of mucous membranes), skin turgor, postural drop in blood pressure, or compensatory tachycardia.
3. **Laboratory investigations** should include electrolytes (sodium plasma levels less than 120 mEq/L are associated with irreversible brain damage and death if untreated), urea, creatinine; consider calcium and parathyroid hormone levels (to rule out transient hyperparathyroidism) and urine analysis for ketones. Obstetric ultrasound (if symptoms are severe) should be done to rule out twins and hydatidiform mole. If underlying diabetes is present, consider gastroparesis.
4. **Management** consists of reassurance that symptoms are transient for most people. Dietary changes, such as a bland diet taken in small amounts frequently, increased carbohydrate intake, decreased fat intake, and minimizing exposure to food odors, may be helpful in mild cases. Drug therapy is controversial because of the potential risk of teratogenicity (see Chapter 22.2). Current options for oral medications include pyridoxine, 25 mg tid; dimenhydrinate (Gravol), 25–50 mg prn q6h; or phosphorated carbohydrate solution (Emetrol, Naus-A-Way), 10–15 mL every 15 minutes for a maximum of five doses (1). If oral measures fail or severe dehydration is present, consider referral or hospitalization. Then take the following measures:
    a. Start intravenous rehydration. Initial correction should be slow (maximum dose of 12 mEq of sodium per 24 hours) to bring sodium levels up to 120–130 mEq/L.
    b. Administer intravenous dimenhydrinate (Gravol), 100 mg/L at 125 mL/h.
    c. Gradually reintroduce oral fluids and feeding.
    d. Consider a trial of enteral feeding (2).

B. Abdominal pain in pregnancy.

Most pregnant women experience some abdominal pain, often diagnosed as round ligament strain or abdominal wall pain; however, approximately 1 in 500 have a surgical problem.

1. **Appendicitis** occurs in approximately 1 in 1,500 pregnancies. Fetal loss ranges from 1% to 5% in uncomplicated appendicitis to as high as 20% in perforated appendicitis, with a maternal mortality of 4% in perforated appendicitis. Clinical presentation of appendicitis is commonly nausea, vomiting, and abdominal pain. In one series, 30% of cases occurred in the first trimester, 48% in the second trimester, and 25% in the third trimester (3). Diagnosis is based on abdominal tenderness in the right lower quadrant (85%) or right upper quadrant (20%) (at 20 weeks, the appendix may be at the level of the umbilicus), rebound tenderness (60%), a white blood cell (WBC) count greater than 16,000/mm^3 in 50% (in pregnancy, normal levels can be up to 15,000 WBCs/mm^3), and ultrasound is of limited usefulness (4). Management is surgery.
2. **Pancreatitis** occurs in 1 in 1,000–5,000 pregnancies (see Chapter 11.6). Ninety percent of cases involve cholelithiasis as well. Diagnosis is based on serum amylase, lipase concentrations, and ultrasound. Management is the same as for nonpregnant individuals. Maternal mortality ranges from 5% to 15%, with perinatal mortality as high as 38%.
3. **Gastrointestinal reflux.** This occurs in 30%–50% of all pregnancies. Dietary management is the first stage of therapy, as for nonpregnant individuals, followed by antacids. For second-line therapy, sucralfate (Carafate, Sulcrate) and ranitidine have been used in the second and third trimesters.
4. **Intestinal obstruction** occurs in 1 in 3,000–17,000 pregnancies. It generally occurs in the fourth or fifth month due to the uterus becoming an abdominal organ and again in the eighth or ninth month as the fetal head enters the pelvis. Ninety percent of patients present with abdominal pain, 82% with vomiting, and 71% with abdominal tenderness. The cause is adhesions in 90% and volvulus in 25%. Diagnosis is by supine and upright x-rays, and treatment consists of bowel decompression with IV/suction with surgery as an option.
5. **Inflammatory bowel disease.** One in 1,000 women of childbearing age may be affected.
6. **Acute cholecystitis/cholelithiasis.** Acute cholecystitis occurs in 1–8 in 10,000 pregnancies. The differential is the same as in the nonpregnant women except that one needs to consider preeclampsia, acute fatty liver, and the HELPP syndrome (hemolysis, elevated liver enzymes, and low platelet count). There is an increased risk of miscarriage in the first trimester and premature labor in the third trimester. Treatment is similar to that for nonpregnant individuals except that elective surgery is best done in the second trimester. Cholelithiasis occurs in 3%–12% and causes 7% of all cases of jaundice in pregnancy (see also Chapter 11.4).
7. **Other diagnoses** to remember are ectopic pregnancy, occurring in 16.8 in 1,000 pregnancies, resulting in 6% of maternal deaths and severe preeclampsia where 5% of patients will have right upper quadrant pain.

C. Liver disease in pregnancy.

Four conditions are relevant. The best understood, the HELLP syndrome, is discussed in Chapter 14.8 . The other three conditions are hepatitis A, B and C, intrahepatic cholestasis of pregnancy (ICP), and acute fatty liver of pregnancy (AFLP), which is very rare.

1. **Hepatitis A, B, and C** (see also Chapter 11.5). Acute hepatitis A and C occur in approximately 1 in 1,000 pregnancies, with hepatitis B occurring in 1–2 in 1,000 pregnancies. If hepatitis is suspected, screen for A, B, and C; if the patient is a B carrier, check for D; and if there is a history of travel, consider E.

   A neonate of a hepatitis A-infected women can be treated with immune globulin in a dose of 0.02 mL/kg IM. For hepatitis B, chronic carriers account for 5–15 in 1,000 pregnancies. Perinatal transmission occurs in 10%–20% of pregnancies and can be averted by active and passive immunization in the neonate. Hepatitis E mortality can be as high as 20%. The only treatment option is prevention through strict food and water precautions.

2. **ICP of pregnancy** is of unknown etiology, occurring in 1–2 in 10,000 pregnancies and in 60%–70% of subsequent pregnancies. There is an increased risk of maternal coagulopathy and an increase in fetal morbidity and mortality (5).
   a. Clinical presentation typically occurs after week 30, with mild to moderate abdominal pain and marked pruritus, initially of the soles and palms and then becoming more generalized. Approximately 20% of patients develop mild jaundice occurring 2–4 weeks after the onset of pruritus.
   b. Diagnosis is based on abnormal liver function tests: transaminases elevated 2–10 times normal, total bilirubin elevated by 2.1–5.0 mg/dL (reaching 10 mg/dL rarely), and serum bile salt is elevated up to 100 times normal. Perform hepatitis A and B screening to rule out hepatitis. The diagnosis is confirmed retrospectively because all symptoms and laboratory abnormalities are normal by 4–6 weeks postpartum.
   c. Patients are treated symptomatically with reduction in stress and a low-fat diet. Drugs such as antihistamines can be used with caution, and delivery is determined by obstetric considerations.
   d. Drug therapy with cholestyramine (maximum dose 12–24 g/d) gives variable results. Early trials of ursodeoxycholic acid with or without *S*-adenosylmethionine are promising.
3. **AFLP** is very rare, and 40%–50% of cases are associated with toxemia. Fifty percent of cases occur in primigravidas, and if the condition is not treated, maternal mortality is 85%–90%. Clinical presentation is very abrupt, with severe vomiting, abdominal pain, and jaundice. There are variable increases in bilirubin and alanine aminotransferase (ALT). Prothrombin time, creatinine, and uric acid are increased. The only management option is prompt delivery of the fetus.

II. Hypertension in pregnancy.

Hypertensive disorders occur in 5%–7% of pregnancies (see also Chapter 9.1).

A. Chronic hypertension.

In pregnancy, the diastolic pressure drops approximately 10 mm Hg by 20 weeks, which can result in underdiagnosis of chronic hypertension predating the pregnancy. If the pregnant hypertensive patient does not develop preeclampsia, the outcome is excellent.

1. Diagnosis is based on a blood pressure (BP) of at least 140/90 recorded before week 20 using the disappearance of the Korotkoff sounds for the diastolic pressure. It is suggested that a woman with a diastolic BP greater than 75 mm Hg in the second trimester or greater than 85 mm Hg in the third trimester should be monitored more closely (6). Diagnosis is more secure if documented prior to the pregnancy and if preeclampsia, which can occur prior to 20 weeks, has been ruled out.
2. Management of mild hypertension (systolic 140–159 mm Hg or diastolic 90–109 mm Hg, or both) consists of antihypertensive therapy if the diastolic pressure is greater than 100 mm Hg (or between 90 and 100 mm Hg if end-organ damage is present).
3. Management of severe hypertension (systolic greater than 160 mm Hg or diastolic greater than 110 mm Hg). Severe hypertension requires immediate treatment.
4. Drug therapy. Discontinue angiotensin-converting enzyme inhibitors, propranolol, and possibly diuretics. First-line treatment is methyldopa (maximum dose 4 g/d in divided doses). This drug is considered safe in pregnancy. Second-line treatment is atenolol, 25–50 mg PO bid-tid, or labetalol, 100 mg PO q6–8h. Third-line treatment is hydralazine, 10–20 mg PO qid.

B. Chronic hypertension with superimposed preeclampsia.

This condition is more likely to occur in a nullipara, and the following factors are shown to be predictive of future preeclampsia (7).

1. Maternal history of preeclampsia (fourfold increase in risk).
2. Sister with proven preeclampsia (sixfold increase in risk).

3. Mean arterial pressure during second trimester (if £90 mm Hg, preeclampsia is unlikely to develop)
4. Pressor tests. The best validated test is the rollover test, which is done between 28 and 32 weeks. The subject lies in the left lateral position until the diastolic pressure stabilizes. She then lies supine, and her blood pressure is taken after 5 minutes. A positive test result is a 20 mm Hg increase in diastolic blood pressure.
5. Laboratory tests. Correlation between uric acid concentration and disease severity exists with more severe preeclampsia associated with an increased range (as a percentage of control) from approximately 150% to 200%. The 24-hour urine calcium excretion is also abnormal. Development of spot urine tests or ratios, such as calcium to creatinine, may be clinically useful in the future.

III. Thrombocytopenia in pregnancy

A. Idiopathic thrombocytopenia (ITP)

(see also Chapter 18.3). ITP occurs in 1–2 of 10,000 pregnancies, but the real incidence may be higher because in 1.2% of pregnancies the platelet count is less than 100,000. Pregnancy does not affect the natural history of ITP, but the fetus can also develop thrombocytopenia (in 15%–65%).

1. Diagnosis is based on history of unusual bleeding or bruising. There is a low platelet count and prolonged bleeding time. Platelet-associated immunoglobulin G (IgG) is present in 90%, and circulating antiplatelet antibodies are present in 50%.
2. Management. Maintain the maternal platelet count over 20 × l0^9/L and up to 50–100 × 10^9/L for delivery. Use corticosteroids, initially 1 mg/kg per day with a rapid reduction to a maintenance dose. Intravenous IgG (0.4 g/kg per day for 5 days) results in an increase in platelet counts lasting 2–4 weeks. Use platelet transfusions in severe cases. There is no reliable method of predicting fetal platelet counts, but fetal scalp blood sampling early in labor or percutaneous umbilical blood sampling can be done. The latter procedure appears to be safe at term.

B. Pregnancy-associated thrombocytopenia (PAT).

PAT occurs in up to 8.3% of pregnancies; the fetus is not at risk and the dilemma is how to distinguish PAT from ITP. The platelet count is generally 100–150 × 10^9/L and falls slowly.

1. Management. If there is a past history of ITP and the platelet count is less than 75 × 10^9/L, then treat as ITP (8).

C. Alloimmune thrombocytopenia (AIT).

Possibly 1:1,000 babies are affected, although 1:5,000 have clinical disease resulting from transplacental passage of maternal antiplatelet antibodies against fetal platelet antigen inherited from the father.

Different incompatibilities of antigens result in disease of variable severity. Platelet counts are often less than 20,000 with a risk of neonatal intracranial hemorrhage (ICH) of 10%–20%. The first affected child is always a “surprise” and 50% of cases involve the first born.

Consider AIT if the neonate has a platelet count of less than 50,000 or had an ICH.

Treatment options include platelet transfusions and/or IV γ-globulin. Consider a cranial ultrasound to rule out a silent ICH.

Management of subsequent pregnancies is problematic because nearly 100% of subsequent pregnancies are affected.

IV. Renal disease in pregnancy.

In pregnancy, the urinary tract is affected by physiologic changes, such as the expansion in blood volume, increase in glomerular filtration, and dilatation of the ureters secondary to hormonal production. The end result is urinary stasis, which is aggravated by the obstructive effect of the gravid uterus. In this situation, the presence of asymptomatic bacteriuria becomes very significant.

A. Asymptomatic bacteriuria

(see also Chapter 12.1). The incidence is 4%–8% of pregnancies and is of concern because about 30% of women with

asymptomatic bacteriuria go on to develop pyelonephritis. Eradication of the bacteriuria reduces the risk of pyelonephritis to about 5% and has been shown to reduce the incidence of preterm labor, which is four times higher if untreated, and low birth weight. Asymptomatic bacteriuria is generally defined as 100,000 colonies/mL or more; however, pyelonephritis can occur even with colony counts of 20,000–50,000/mL.

1. Diagnosis is positive if the colony count is 100,000/mL or greater on at least two successive urine samples done early in pregnancy. Perform a urine nitrite dipstick test at each visit if risk factors for bacteriuria, such as low socioeconomic status, sickle cell trait, urinary tract abnormalities, and diabetes, are present.
2. Management. Antibiotic choice is based on culture results (80% *Escherichia coli*; others include *Klebsiella*, *Proteus*, and *Streptococcus* group B). The role of single-dose therapy is unclear. Options include nitrofurantoin 100 mg PO at bedtime for 10 days; ampicillin or amoxicillin 500 mg PO qid for 7–10 days; and co-trimoxazole DS 1 tablet PO bid for 7–10 days. After the first trimester, cephalexin 250–500 mg PO qid for 7–10 days can be given. Repeat urine culture after treatment; if culture result is still positive, treat for 2–3 weeks. If condition recurs, treat for 2–3 weeks. If the patient continues to have recurrences, give prophylactic treatment for the remainder of pregnancy using nitrofurantoin 50 mg PO at bedtime, or amoxicillin 250 mg PO at bedtime. Regular repeat urine cultures should be done throughout the pregnancy. Screening with dipstick and culture or dipstick and subsequent culture if dipstick-positive are cost effective in preventing pyelonephritis when compared to no screening.

B. Cystitis

occurs in 1%–2% of pregnancies, arising de novo (see also Chapter 12.1).

1. Diagnosis is based on a history of dysuria, frequency, urgency, and suprapubic discomfort. There is no fever, possibly bladder tenderness, and no flank tenderness. Urinalysis, culture, and sensitivity confirm diagnosis.
2. Management is as above, except that a 3-day regimen of antibiotics is usually sufficient, provided a follow-up urine culture is done.

C. Acute pyelonephritis

(see also Chapter 12.2). Acute pyelonephritis occurs in 1% of pregnancies, including 30% of those involving untreated asymptomatic bacteriuria. Not eradicating asymptomatic bacteriuria results in an incidence of 3%. Common pathogens are *E. coli* (77%), *Klebsiella* (11%), *Proteus*, and *Enterobacter* (4%). *Streptococcus* group B is more likely in pregnancy. Preterm labor may complicate up to 10% of cases of pyelonephritis (9).

1. Diagnosis is based on a history of fever, chills, back pain (82%), lower tract symptoms (40%), nausea, and vomiting. There may be signs of dehydration and costovertebral tenderness. Laboratory testing includes complete blood count (CBC) with differential, electrolytes, blood urea nitrogen (BUN), creatinine, urine analysis, and urine and blood cultures.
2. Management
   a. Hospitalize the patient if toxic.
   b. Rehydrate the patient sufficient to maintain a minimum urine output of 30 mL/h.
   c. Treat with antibiotics for 14 days, *orally* if not toxic. Options include co-trimoxazole DS, 1 tablet PO bid, or cephalexin, 500 mg PO q6h, or amoxicillin, 500 mg PO q6h. Intravenous options include gentamicin or tobramycin IV/IM 3–5 mg/kg per day divided q8h, or amikacin IV 15 mg/kg per day plus ampicillin IV 1–2 g q4h.
   d. Switch to oral antibiotics after 3–4 days if patient is afebrile.
   e. If recovery is not prompt, consider the following:
      1. Urinary obstruction. Consider obtaining an ultrasound scan (dilatation, perinephric abscess), plain film abdominal radiograph (renal calculi), or “one-shot” pyelogram (calculi or structural abnormalities).

2. Pulmonary injury. Respiratory insufficiency occurs in 1 in 50 women with severe pyelonephritis. Generally, it is mild and the only treatment is oxygen therapy.
3. Septic shock syndrome. This is uncommon despite the observation that 15%–20% of women with pyelonephritis have bacteremia.

D. Chronic renal failure.

If mild there are relatively few complications. If moderate to severe there is increased risk of hypertension, proteinuria, preterm labor, and intrauterine growth retardation (IUGR).

E. Urolithiasis.

Incidence 1 in 90–3,800. Urolithiasis is more common in multiparous patients, generally occurring in the second or third trimester. Flank pain is the most common symptom, with 90% of patients also having hematuria. About 20%–40% of patients also have a urinary tract infection (UTI). There is an increased risk of pyelonephritis and preterm labor. Approximately 75% of stones pass with conservative management. If the stone persists, then modified excretory urography and surgical removal should be considered.

V. Diabetes in pregnancy

(see also Chapter 17.2)

A. Gestational diabetes (GDM).

GDM is defined as “carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy” (10). It occurs in 1%–3% of pregnancies due to the development later in pregnancy of a state of relative insulin resistance. There is debate about whether GDM should be universally screened for and about the type and extent of morbidity associated with GDM. There is an increase in maternal hypertensive disorders and fetal macrosomia in 20%–30% (11).

1. Diagnosis. Screen all women at 24–28 weeks, or screen only those with the following risk factors: marked obesity, family history of diabetes, past history of glucose intolerance, macrosomic infants, and current glycosuria. Use a 50-g glucose challenge test. Positive test consists of a 1-hour blood sugar of 7.78 mmol/L (140 mg/dL) or greater. The oral glucose tolerance test is done with a l00-g glucose load. Diagnostic criteria from the Fourth International Workshop-Conference on Gestational Diabetes (11) in milligrams per deciliter are fasting blood sugar, 95; 1-hour blood sugar, 180; 2-hour blood sugar, 155; and 3-hour blood sugar, 140. The test result is positive if two or more values are exceeded. In comparison with former diagnostic criteria, these increase the false positive rate.
2. Management
   a. Blood sugar management. The aim of treatment is to maintain the preprandial blood sugar at 80 mg/dL (4.4 mmol/L) and/or the postprandial blood sugar at 140 mg/dL (6.7 mmol/L). Monitor blood sugar, either by capillary blood sugar or by laboratory measurement of fasting blood sugars, approximately every 1–2 weeks. Diet should consist of 40% carbohydrates based on 30–32 kcal/kg of body weight. For overweight patients, reduce to 25 kcal/kg. Insulin starting dose (after 28 weeks) is NPH insulin 20 units every morning and 10 units of regular insulin. Modify the dose based on capillary blood sugar, fasting and 2 hours after meals. Add an evening dose of NPH if the fasting blood sugar is still elevated (12).
   b. Pregnancy management. There is debate as to how much monitoring should be done during pregnancy (13). Some authors propose that nonstress testing should start at 36 weeks and that ultrasound should be done close to term to determine fetal weight in an attempt to identify macrosomic fetuses. Indications for cesarean section are identical to those used in other situations. It is unclear if macrosomia alone is an indicator for cesarean section. Induction of labor before term is not indicated unless usual obstetric indications are present.

B. Antepartum diabetes.

Antepartum diabetes occurs in approximately 1% of pregnancies and is associated with an increase in congenital malformations (three to four times the normal rate) and a perinatal mortality of 1%–5% (which is now close to the nondiabetic rate). Nephropathy and hypertension

or renal disease lead to poorer outcomes; retinopathy worsens but visual acuity can be maintained with laser therapy.

1. Diagnosis is generally established before pregnancy but should be considered if polyhydramnios or macrosomia is present. Laboratory testing should include routine antenatal screen, 24-hour urine for protein and creatinine, fasting and 2-hours-after-meals blood sugar and hemoglobin, regular urine cultures, especially if nephropathy is present, ultrasound at 18 weeks, and screening for neural tube defects.
2. Management
   a. Preconception counseling. Research shows a reduction in congenital malformations if blood control is tight and hemoglobin is not greatly elevated before and after conception.
      1. First trimester. The main concerns are tight glucose control and avoidance of hypoglycemia, which is more common in this trimester. The following steps should be taken: refer immediately to a high-risk obstetrics program, refer to ophthalmologist to assess retinopathy, refer to dietitian, institute a diabetic diet at 30–35 kcal/kg of ideal body weight daily split into three meals and three snacks. Educate on “sick day” management. Other steps include development of a protocol for hypoglycemic reactions consisting of a 10-g carbohydrate snack (2 sugar cubes, 4 oz juice, etc.), and glucagon, 1 mg SC, if the above fails. Home capillary blood sugar monitoring should be done four times per day, and the dose and type of insulin should be adjusted to achieve tight control between 5.6 and 6.7 mmol/L. No clinical trials have shown insulin pumps to be superior in terms of outcome.
      2. Second trimester. Regular prenatal visits should be scheduled, e.g., every 2 weeks, during which fetal growth is monitored using fundal height and ultrasound if needed. Insulin doses will need adjusting as these will increase up to twice prepregnant doses. Blood pressure should be monitored and attempts made to predict the occurrence of preeclampsia.
      3. Third trimester. There should be ongoing maternal and fetal monitoring with the nonstress test as indicated. Obstetric considerations should determine delivery type and timing as there is no evidence that early delivery improves outcome in otherwise uncomplicated diabetic pregnancies. Amniocentesis for lung maturity should be considered if the diabetes is poorly controlled or if early delivery is necessary. During delivery an infusion of normal saline with 25 units of regular insulin per 250 mL of normal saline is used to maintain maternal blood sugar between 3 and 6 mmol/L. In the postpartum period, adjust the insulin requirement using regular insulin and a sliding scale. (For management of diabetic ketoacidosis in pregnancy, see ref. 14 .)

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14.7
POSTDATE PREGNANCY

Sandra M. Sulik

Postdate pregnancy (PDP) is pregnancy lasting beyond 42 weeks, or 294 days from the first day of the last menstrual period. The incidence of PDP is approximately 10% (1).

The advent of early prenatal care and accurate estimate of gestational age based on known last menstrual period, known date of conception, and early ultrasound have decreased the overestimation of postdates and therefore the need for intervention.

The most common cause of PDP is inaccurate dating of the pregnancy. Other causes include previous PDP (50% recurrence rate), history of high parity, first pregnancy, excessive maternal weight gain, and lower socioeconomic status. In rare cases, postdate pregnancy is associated with anencephaly and placental sulfatase deficiency.

I. Assessment of fetal well-being,

necessary during the postdate period (after 42 weeks) to maintain a low risk of mortality and morbidity to the infant, includes the following:

A. Amniotic fluid volume.

Oligohydramnios is readily measured and correlates highly with perinatal morbidity and mortality in the postdate period (2). After 41 weeks gestation, the amniotic fluid volume declines approximately 25% per week. Changes in fluid volume can occur quickly and often dramatically in the postdate period. An amniotic fluid index (AFI) less than 3.0 is an indication for delivery (3).

B. The nonstress test (NST)

measures fetal heart rate accelerations after spontaneous movement. A reactive NST (at least two accelerations at least 15 beats per minute above the baseline that last 15 seconds within a 10-minute window) is reassuring of fetal well-being during the postdate period, and the test should be performed biweekly after 41 weeks gestation (4).

C. Acoustic stimulation testing,

which uses the application of low-frequency mixed vibroacoustic sound generated by an electronic larynx, can be used to test fetal well-being. A nonreactive acoustic stimulation test indicates the need for further assessment of the fetus and consideration for delivery (5).

D. The biophysical profile

can be used to assess placental insufficiency, but data show that the biophysical profile adds little useful information to a normal AFI and a reactive NST (6).

E.

There is no evidence that NST and OB ultrasound to assess AFI between 40 and 42 weeks improves fetal outcomes (1).

II. Management

of postdate pregnancy remains controversial. Expectant as opposed to active management yields no difference in perinatal mortality and neonatal morbidity.

A. Expectant management

1. After 36 weeks, weekly office visits are essential for evaluation of weight, fundal height, blood pressure, fetal movements, and cervical examination.
2. Daily fetal monitoring should begin after 40 weeks. Any decrease in movement perceived by the mother should be further evaluated with an NST.
3. After 41 weeks, biweekly NSTs and weekly ultrasound for AFI assessment is indicated. A nonreactive NST indicates a need for further evaluation with an oxytocin challenge test. If the oxytocin challenge test is nonreactive, delivery should be considered.
4. If clinical evaluation remains normal and the NSTs are reactive, then continued expectant management is appropriate. Once the cervix ripens (Bishop score >5–6), induction of labor should be considered.
5. At 43 weeks gestation, all patients should be delivered because fetal morbidity and mortality are significantly increased.

B. Active management

of the PDP advocates the induction of all women who reach 42 weeks gestation without signs of ensuing labor. Women should be informed that 500 inductions are necessary to prevent one perinatal death and that there is no evidence that induction changes the risk for caesarean delivery (7).

1. Cervical ripening agents. Dinoprostone, a prostaglandin E_2 (PGE_2) analogue, has been shown to improve induction outcome as well as decrease the length of induction time in patients with an unfavorable cervix. Prepidil (gel) in a standard dose of 0.5 mg administered intracervically can be used every 6 hours as needed to a maximum dose of 1.5 mg PGE_2 or 7.5 mL PGE_2 gel (8). Cervidil (10 mg vaginal insert) is introduced into the posterior fornix of the vagina for 12 hours. Continuous fetal monitoring is recommended during use of either agent. Both agents require refrigeration and are extremely expensive. Misoprostol, a PGE_1 analog, is also used for cervical ripening and labor induction (not FDA approved). Cytotec 25–50 μmg inserted intravaginally into the posterior fornix used every 3–4 hours up to a total dose of 100 μmg significantly reduces labor time. Uterine hyperstimulation and tachysystole can occur; therefore, continuous fetal monitoring is recommended. Misoprostol is temperature stable and inexpensive (9).
2. Membrane stripping or sweeping has also been used as a method for inducing labor. Sweeping membranes weekly from 39 weeks can reduce the number of women who reach 41 weeks gestation. Risks of the procedure include membrane rupture, infection, and bleeding (10).
3. Amniotomy, with or without oxytocin, is widely used to induce labor. Early amniotomy shortens the duration of labor and reduces the incidence of dystocia but does not reduce the need for anesthesia or cesarean section. Timing of the amniotomy is important because once it is done, the patient is committed to delivery. Amniotomy is best performed in conjunction with the administration of oxytocin when there are regular uterine contractions and the head is well applied to the cervix (11).
4. Oxytocin administration remains the most common form of labor induction. Various protocols exist. The use of the low-dose infusion (starting at 1.0–2.0 mU/min and increasing the dose every 15–30 minutes with a maximum of 20 mU/min) is associated with less uterine hyperstimulation, water intoxication, and antidiuretic effect than high-dose protocols. Fetal monitoring should be continuous during the oxytocin infusion to ensure fetal well-being (12).

III. Complications

of postdate pregnancy include postmaturity of the infant, birth asphyxia, meconium aspiration, and macrosomia leading to shoulder dystocia.

A. Complications during induction of labor

(see Chapter 14.10)

B. Neonatal complications

include birth asphyxia, postmaturity of the infant, and meconium aspiration. Macrosomia occurs more often (3%–7% in PDP)

and is associated with an increased risk for shoulder dystocia, neurologic injuries to the shoulder girdle, and cephalohematoma. Hypoglycemia is often seen during the neonatal period in the macrosomic infant.

C. Maternal complications

include an increased incidence of postpartum hemorrhage, vaginal and rectal lacerations, endometritis, and cesarean section.

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14.8
OBSTETRIC PROBLEMS DURING PREGNANCY

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Preeclampsia and Eclampsia

Preeclampsia is a clinical syndrome predominantly occurring in the primipara that is manifested by reduced placental perfusion and abnormal function of the vascular endothelial cell. Vasospasm and vascular permeability lead to the hallmark signs and symptoms of hypertension, proteinuria, generalized edema, weight gain, reduced renal function, and gastrointestinal (GI) distress. In severe cases, patients may manifest central nervous system (CNS) and hepatic abnormalities with thrombocytopenia. Eclampsia differs only by the addition of one or more seizures to the preeclamptic syndrome.

I. Diagnosis

A. Clinical presentation.

Preeclampsia occurs rarely before 20 weeks gestation unless associated with molar pregnancy, multiple gestation, or the lupus anticoagulant. A precise clinical definition of preeclampsia is still not available.

1. Hypertension usually occurs, defined as an absolute blood pressure greater than 140/90 or a systolic blood pressure (SBP) greater than 30 mm Hg above baseline and a diastolic blood pressure (DBP) greater than 15 mm Hg above baseline.
2. Generalized edema is defined as edema involving hands, face, and all extremities and persisting after bed rest.

3. GI disturbances are usually abdominal pain, nausea, and vomiting.
4. CNS disturbances are headache, visual changes, confusion, coma, seizures (eclampsia only), and hyperreflexia.
5. Weight gain greater than 5 pounds in 1 week occurs.
6. Coma, cardiovascular accident, hepatic and renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) (see Section I.B.2 below), accelerated hypertension, and proteinuria greater than 5 g/24 hours are associated with severe disease and increased mortality.
7. Rollover test may be positive.
8. Distinguishing between essential hypertension, pregnancy-induced hypertension, and preeclampsia may sometimes prove difficult.

B. Laboratory studies

are essential in assessing severity.

1. Proteinuria of 1 g/L or more on urine dipstick or 300 mg/24-hour urine or more is cause for concern. More than 5 g/24 hours is severe.
2. Hemolysis, elevated liver enzymes, and low platelets (<100,000 platelets per microliter), called the HELLP syndrome, is a marker of severe disease and impending disseminated intravascular coagulation (DIC). The presence of the HELLP syndrome increases the risk of developing eclampsia.
3. Hemoconcentration with hemoglobin greater than 15 mg/dL may be present.
4. Elevation of uric acid, blood urea nitrogen (BUN), creatinine, and bilirubin may be indicative of increasing severity.
5. Elevation of prothrombin time, partial thromboplastin time, d-dimer, and fibronectin, and decrease in fibrinogen, antithrombin III, and platelets are suggestive of DIC.

II. Treatment

centers on preserving fetal and maternal health.

A. Fetal surveillance

should be done, once the diagnosis is established, on the following schedule:

1. Nonstress test twice per week
2. Biophysical profile once per week
3. Fetal movement counts daily (>10 daily is considered normal)

B. Maternal surveillance

(Figure 14.8-1)

1. During the biweekly visit, check BP, weight, proteinuria, reflexes, retinoscopy, and edema.
2. Consider ordering a 24-hour urine for protein excretion and creatinine clearance, and blood for platelets, electrolytes, uric acid, and clotting parameters every 2–4 weeks.
3. Doppler flow velocimetry may help if absent end-diastolic frequencies or reverse diastolic flow patterns are present.

C. Delivery of the placenta

is the ultimate treatment.

1. If BP is less than 140/90, proteinuria is mild, and the patient is asymptomatic, consider ambulatory treatment, especially if the cervix is unfavorable and remote from term (1).
2. Obstetric interventions will depend on very careful perinatal management, obstetric consultation, and balancing issues such as maternal preference, gestational age, disease severity, presence of labor, cervical status, and fetal lung maturity.
3. Delivery should always be considered if seizures, fetal compromise, or increasing maternal disease are present. There is no reason to continue the pregnancy past 40 weeks because placental blood flow may continue to fall.
4. If the patient is still smoking, that may prove disastrous for the pregnancy.
5. **Pharmacotherapy**
   a. Methyldopa (Aldomet), 250 mg tid, is standard for BP greater than 160/100.
   b. Nifedipine 10–30 mg PO tid may be superior to methyldopa (2).
   c. Labetolol 100–400 mg bid is an acceptable alternative.

d. Intravenous hydralazine (Apresoline), labetalol, or nitroprusside have been used emergently.

e. Angiotensin-converting enzyme inhibitors, diuretics, and central α-agonists are not indicated.

f. Glucocorticoids, such as betamethasone 12 mg IM q24 hours × 2 doses, can enhance fetal lung maturity between 28 and 34 weeks gestation.

g. Magnesium sulfate is the anticonvulsant of choice. If SBP exceeds 160 or DBP exceeds 100, or both, start with a 4- to 6-g IV bolus followed by 1–3 g per hour. Check the magnesium level 4 hours later. The desired level is 4–8 mg/dL. Follow reflexes, respirations, mental status, and urine output (3).

h. Aspirin at 60–325 mg/d in high-risk patients and on diagnosis may reduce morbidity; however, its use is still questionable and may be associated with an increased risk of abruption.

i. Calcium in amounts of 1,500–2,000 mg/d may be of benefit.

j. Remember, eclampsia may occur up to 23 days post partum.

k. Bed rest and dietary manipulations have shown no benefit and may exacerbate the preeclampsia.

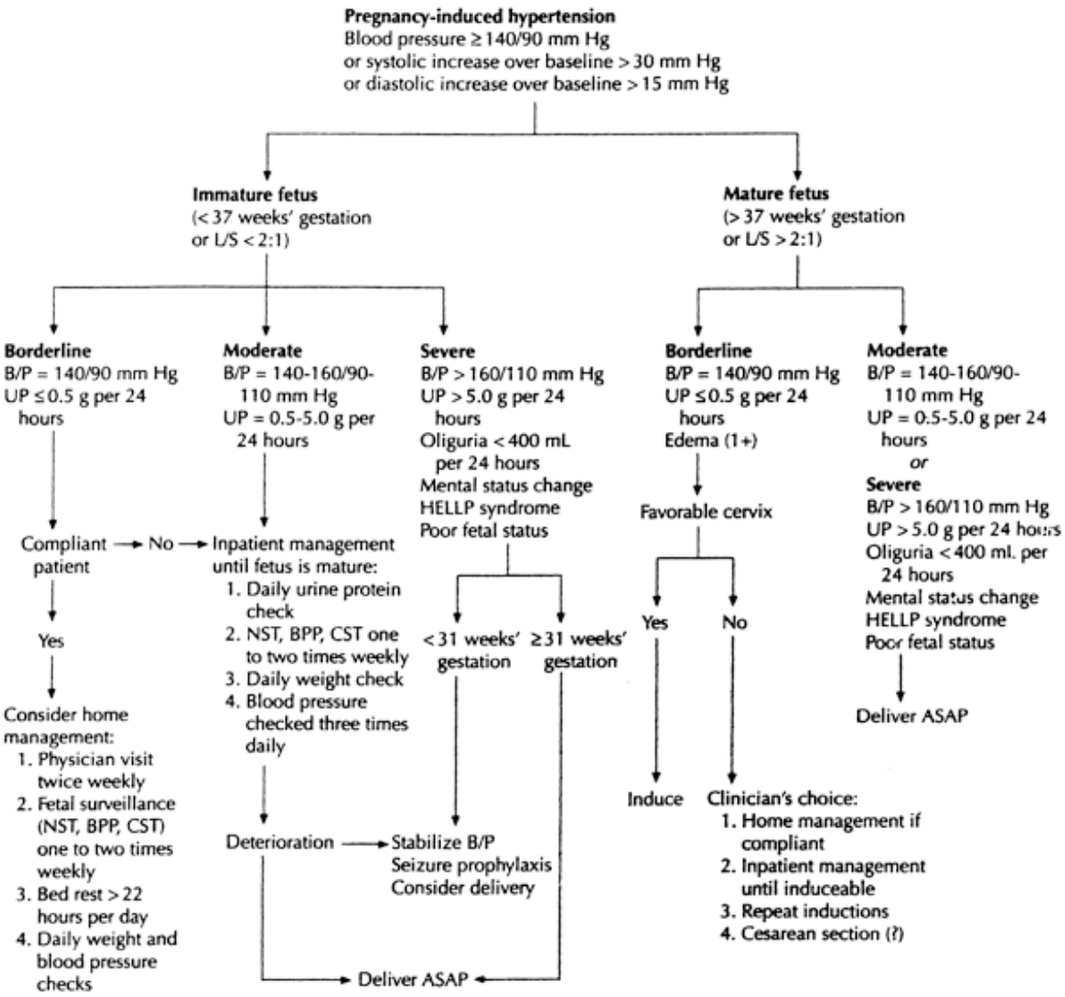

FIG. 14.8-1. Algorithm for the management of pregnancy-induced hypertension. (L/S, lecithin/sphingomyelin; UP, total protein excretion in a 24-hour urine collection; B/P, blood pressure; NST, nonstress test; CST, contraction stress test; BPP, biophysiologic profile; ASAP, as soon as possible.) (From Fadigan AB, Sealy DP, Schneider EF. Pre-eclampsia: progress and puzzle. *Am Fam Physician* 1994;49:849, with permission.)

Isoimmunization of Erythrocytes in Pregnancy

Erythrocyte (red blood cell, RBC) isoimmunization in pregnancy has drastically diminished since 1968 but has not disappeared. The decreased incidence is due in part to smaller family sizes, but mostly due to the introduction of anti-D immune globulin [formerly referred to as Rh_o(D) immune globulin]. Careful attention to maternal blood typing, prior obstetric history of RBC immunization, and careful prophylaxis of the nonimmune gravida for all potential risks of fetomaternal transfusion are critical elements of managing this potentially lethal complication of pregnancy (4).

I. Diagnosis

is made by identifying antibodies against fetal erythrocytes in the maternal circulation. Once the antibody is specifically identified, the hemolytic potential of these erythrocytes is determined.

A. Maternal antibody profile

identifies virtually all abnormal antibodies.

B. An indirect Coombs' test

is usually done automatically if the antibody screen result is positive.

C. Major Antigens

1. D or Rhesus D (formerly Rh) is the most clinically significant.
2. Other Rhesus (C, c, E, e)
3. ABO (usually not hemolytic, but 98% of all hemolytic disease is Rhesus or ABO).
4. Kell, Duffy, Kidd, Diego are other rare hemolytic antigens.

D. Population distribution.

Fifteen percent of whites are D-negative, and 8% of blacks are D-negative. One percent of Asians and Native Americans are D-negative.

II. Fetal and perinatal complications

A.

Immune hydrops fetalis (severe)

B.

Anemia (mild to severe)

C.

Heart failure

D.

Hyperbilirubinemia leading to kernicterus

E.

Extramedullary hematopoiesis

F.

Fetal demise

III. Causes of isoimmunization

A.

Incompatible blood transfusion is mostly seen with non-Rh and non-ABO sensitization. Major antigens D or Rhesus D (formerly Rh) are the most clinically significant.

B.

Possible clinical settings of incompatible transplacental hemorrhage are:

1. Procedures: amniocentesis, cesarean section, and, to a lesser extent, external version
2. Any antepartum bleeding
3. Abortion, spontaneous and elective
4. Molar pregnancies

C.

Fetal-maternal hemorrhage. In 75% of pregnancies there is some evidence of fetal blood in the maternal circulation, most frequently less than 0.1 mL.

IV. Management.

Prevention is the key.

A.

Rh/ABO typing. Every pregnant patient should have Rh/ABO typing at the first prenatal visit.

B.

Antibody screening. Every patient must have an antibody screening; if positive, identification and titration of the antibody is essential. The majority of maternal antibodies identified are nonhemolytic. Screening should be at first visit and considered prior to administration of anti-D immune globulin at 28–32 weeks.

C.

D-positive (Rh-positive), O-type blood requires no therapy.

D.

D-negative gravidas should:

1. Receive anti-D immune globulin (Rh Ig, RhoGAM) 300 μmg as a single dose at 28–32 weeks gestation. Consider repeat antibody screening at 28–32 weeks gestation to identify isoimmunization earlier in pregnancy (4).
2. Receive anti-D immune globulin (Rh Ig, RhoGAM) 300 μmg as a single dose within 72 hours of delivery when susceptible to isoimmunization (delivery of D-positive or Rh-unknown infant) (4).
3. Receive 300 μmg anti-D (Rh Ig) within 72 hours of a potential transfusion (see Section III.B). Some physicians still use minidose (50 μmg) anti-D (4).

E.

Postpartum. Any deliveries at risk for increased fetal-maternal transfusion (cesarean section, increased blood loss, pregnancy-induced hypertension, manual removal of the placenta) should consider quantification of the fetal- maternal transfusion if the baby's blood type is D-positive. The Betke- Kleihauer test assesses the amount of fetal blood in the maternal circulation. If less than 15 mL of blood is transfused, give the routine 300 µmg of anti-D Rh Ig; if more than 15 mL of blood is transfused, 300 µmg per 15-mL transfusion should be given.

F.

The patient with a positive antibody screen and an identified antigen (D, C, c, E, or e) should be treated as follows:

1. If the antibody titer is 1:6 or higher or is elevated four times baseline in monthly measurement, amniocentesis for optical density should be considered.
2. If the titer is 1:6 or higher or an elevation of four times baseline is present and a perinatal center is available, cordocentesis for fetal hemoglobin concentration is a good alternative (4).

V. Treatment,

usually carried out at a perinatal center, is based on the following:

A.

Intraperitoneal fetal transfusions are effective.

B.

Intravascular fetal transfusion into the umbilical vein or intrahepatic vein is also effective.

C.

Plasmapheresis, corticosteroids, and promethazine have no proven benefit.

D.

Delivery decisions are based on the fetal risk of immaturity versus rising hemolysis risks with continued pregnancy.

E.

Fetal distress may be present, with the characteristic sinusoidal heart rate indicating repetitive decelerations. The severely distressed fetus should be delivered.

F.

Delivery where a level II or III neonatal intensive care unit is available is essential in the sensitized mother. Fetal exchange transfusion should be readily available (4,5).

Preterm Labor

Preterm labor (PTL) is a leading cause of perinatal morbidity and mortality in the United States. Ten percent of all births are complicated by PTL. Large societal costs result from neonatal intensive care and long-term treatment for complications. When developmental defects are excluded, 70-80% of neonatal mortality is attributable to low birth weight. Early, accurate diagnosis of PTL provides for secondary prevention of premature births. Primary prevention attempts to reduce risk factors for prematurity. Once the patient is in PTL, a comprehensive management plan is essential.

I. Diagnosis of preterm labor

A. Clinical presentation.

Detecting preterm labor early enough for effective intervention has proven to be a challenge in practice. The patient presents between 20 and 37 weeks gestation with uterine contractions or irritability producing cervical dilatation and/or effacement.

B. Risk evaluation.

Risk factors for preterm labor include low socioeconomic status, nonwhite race, age less than 18 or more than 40, low prepregnancy weight, prior preterm births, at least one spontaneous second-trimester abortion, absence of prenatal care, and maternal substance abuse (tobacco, cocaine). Risk-scoring systems (Papiernik, Creasy) have sensitivity less than 50% and a positive predictive value of less than 20% for detecting patients who will undergo preterm labor, but they can be used to increase your level of suspicion and for primary intervention (6).

C. Evaluation of contractions.

Self-palpation has poor sensitivity in detecting preterm labor (15%). The U.S. Food and Drug Administration has approved home uterine monitoring in women with a history of preterm labor. The cost is high and the benefit is equivocal.

D. Routine cervical examinations.

There is no predictive advantage to routine cervical examinations in pregnant women with average risk (6). However, these may prove useful in women with a history suggestive of incompetent

cervix and should be performed in women with a complaint of preterm contractions to evaluate for cervical change.

E. Fetal fibronectin.

Fetal fibronectin is an extracellular protein that is believed to act as an adhesive between the developing embryo and the uterine surface. It is present in vaginal secretions at implantation but disappears by 20 weeks estimated gestational age (EGA). In a patient with suspected preterm labor, the posterior vaginal fornix and cervix are swabbed, and the sample is sent to the lab for a fetal fibronectin monoclonal antibody assay. The negative predictive value of a negative test is greater than 90%, and a positive test is correlated with imminent delivery (7).

F. Transvaginal ultrasonography of the cervix.

Wedging of the internal cervical os on transvaginal ultrasonography has been associated with preterm delivery, and may prove more sensitive than the digital vaginal exam (7).

II. Management

A. Conservative

1. Treat underlying causes (urinary tract infection, cervicitis, dehydration, substance use).
2. Hydration decreases contractions, but no causal relationship has been identified. Use 500–1,000 mL lactated Ringer's solution, followed by 125 mL/h (if not contraindicated).
3. Bed rest does not prolong pregnancy and may have adverse maternal effects.

B. Tocolytic therapy

1. Tocolytics have successfully lengthened pregnancy by an average of 48 hours, which may provide enough time to administer corticosteroids or to transfer to a tertiary care center. The decision to use tocolytics should be influenced by maternal condition, fetal size and maturity, and fetal condition.
2. Contraindications include advanced labor, preeclampsia or eclampsia, abruptio placentae, chorioamnionitis, dead or distressed fetus, anomalies incompatible with life, fetal maturity, and maternal hemodynamic instability (7).
3. Direct comparison of tocolytics has shown them to have similar efficacy, and choice usually depends on side effects. For all tocolytics, use the minimum necessary to stop contractions, monitor for side effects, and discontinue or switch to an oral agent as soon as labor ceases. See Table 14.8-1 for a list of tocolytics, dosages, and potential complications.

Medication	Dosage	Precautions/complications	Contraindications
Magnesium sulfate	4–6 g IV load, then 2–4 g/h drip, continue 12 h after contractions stop. Therapeutic level 5–8 mg/dL	Pulmonary edema. Toxic levels may cause profound hypotension, paralysis, tetany, cardiac arrest, respiratory depression, and renal failure. Areflexia at 8–10 mg/dL, respiratory suppression at >10 mg/dL	Hypocalcemia, myasthenia gravis, renal failure
Terbutaline (β_2-agonist)	0.25–0.5 mg SC q3–4 h or 10 mg PO q2h × 24 hr, then 10–20 mg q4–6h	Hypokalemia, hyperglycemia, hypotension, pulmonary edema, tachycardia and arrhythmias, cardiac insufficiency, myocardial infarction, and maternal death	Maternal arrhythmias, uncontrolled diabetes mellitus, hypertension or thyrotoxicosis
Ritodrine (β_2-agonist)	Start 0.05 mg/min IV and increase by 0.05 mg/min q10–20 min (max, 0.35 mg/min)	Same as terbutaline	Same as terbutaline
Nifedipine (calcium channel blocker)	10–20 mg PO q4–6h	Transient hypotension	Maternal liver disease
Indomethacin (NSAID)	50–100 mg PR; and/or 25 to 50 mg PO q6h	Renal failure, GI bleed, hepatitis, oligohydrammios, constriction of ductus arteriosis. Possible risk of necrotizing enterocolitis and intraventricular hemorrhage in neonates	Aspirin sensitive asthma, coronary artery disease, GI bleed, renal failure, oligohydramnios, fetal cardiac or renal anomalies
Sulindac (NSAID)	200 mg PO q12 (up to 6 doses)	Same as indomethacin	Same as indomethacin

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Table 14.8-1. Tocolytics for management of preterm labor

4. Adverse effects
   a. Pulmonary edema has been associated with the concomitant use of tocolytics (primarily β_2-agonists and magnesium sulfate) and corticosteroids. The risk can be decreased by limiting fluid intake to less than 2,000 mL/d, restricting sodium intake to 4–6 g/d, monitoring serum potassium and glucose, and avoiding steroids with high mineralocorticoid potency. Do not withhold corticosteroids from preterm labor. For magnesium sulfate, the target serum level is 5–8 mg/dL. Higher levels (10–12 mg/dL) result in respiratory suppression. Monitor deep tendon reflexes, which disappear at levels of 8–10 mg/dL. The nonsteroidal anti-inflammatory drugs can cause constriction of the ductus arteriosus in the fetus and a decreased amniotic fluid index. These effects are reversible if use is restricted to a short period (24–48 hours). Nifedipine has few adverse effects (6,7). See Table 14.8-1 for additional complications and precautions.

C. Corticosteroids

1. **Fetal risk reduction.** Antenatal steroids given between 24 and 34 weeks EGA have been proven to reduce the incidence and severity of respiratory distress syndrome and intraventricular hemorrhage. There is some evidence that steroids may decrease the risk of patent ductus arteriosus and necrotizing enterocolitis in the neonate (7).

2. **Complications.** There have been no significant maternal or fetal complications associated with antenatal steroids. Pulmonary edema in the mother has occurred with the use of tocolytics and steroids together, but not with corticosteroid use alone, and may be due in part to increased fluid volume, multiple gestations, and/or infection. As expected, closer monitoring of gestational diabetes may be necessary after steroid administration, and steroids may mask maternal fever (6,7).
3. **Dosage.** Corticosteroids result in significant benefits, starting within 24 hours and persisting for a week. Corticosteroids are indicated in preterm labor between 24 and 34 weeks EGA unless delivery is imminent. There are two accepted steroid courses, chosen for their ability to cross the placenta, their longer duration of action, and their proven efficacy in clinical trials. Higher or more frequent doses than those listed below do *not* provide any additional benefit.
   a. Betamethasone: two 12-mg doses given IM 24 hours apart.
   b. Dexamethasone: four 6-mg doses given IM 12 hours apart.

D. Antibiotics.

In premature rupture of membranes, antibiotics have been shown to prolong latency and improve neonatal outcome (6,7 and 8). Treatment of group B *Streptococcus*-positive mothers prior to delivery has been proven to decrease the incidence of neonatal sepsis (7). Some preliminary studies have indicated that antibiotics can prolong the pregnancy in preterm labor, but definitive evidence is lacking.

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14.9
INTRAPARTUM CARE

Susan E. MacDonald

Intrapartum care of the healthy term pregnant woman is the subject of this chapter, beginning with her arrival at the labor ward in active labor.

I. Admission

A. History.

The woman in active labor gives a history of regularly occurring contractions, of increasing frequency, length, and intensity and associated with pain in the abdomen and/or back. Establish whether she has had, and the time of, obvious or suspected rupture of the membranes. Ask whether it was clear, green (meconium), or bloody. Determine whether there has been abnormal bleeding or pain. Review her antenatal history, confirming her due

date and whether there were any significant problems in this pregnancy. Review her past obstetric history, medical history, and psychosocial history, identifying problems therein that are active or relevant to her current labor (e.g., previous shoulder dystocia or cesarean section) (see Chapter 14.10).

B. Physical examination.

Perform a complete physical examination at the time of admission, focusing attention on the areas identified in the history as being of concern. Confirm the uterine size and the fetal lie, presentation, and position. Inspect the vulva for herpes. Confirm a history of rupture of the membranes by sterile speculum examination, pH test, and microscopic evidence of "ferning" when the fluid is air dried on a slide. Digitally examine the cervix for softness, effacement, dilatation (in centimeters), and location. Confirm a vertex presentation and ascertain its station relative to the ischial spines.

C. Investigations.

The antenatal investigations do not need to be repeated. Draw blood for a complete blood count and typing. Do a urinalysis.

D. Problem formulation and plan.

Assess the risk level of the pregnancy and the current labor. Make the appropriate plan for management and maternal-fetal surveillance. Assess the plan on an ongoing basis and adjust management appropriately.

II. Labor management.

The monitoring of fetal and maternal well-being of the low-risk woman in labor does not require highly technical equipment or much intervention, but it does require close observation.

A. Stage I

, from onset of labor to full dilatation at 10 cm, is divided into latent and active phases. The latent phase, which may be more sensitive to anesthetics and sedatives, has slow dilation until 3–4 cm. The active phase is characterized by more rapid dilation.

1. **Monitoring and care**
   a. **Maternal nutrition and position.** Allow a low-residue, low-fat diet in labor with frequent small meals (e.g., tea, fruit juice, broth, toast). Encourage upright posture, which might result in a shorter first stage and lower requirements for analgesics.
   b. **Fetal surveillance.** The fetus is monitored to detect and prevent problems that could lead to fetal morbidity and mortality.
      1. **Amniotic fluid** When the membranes are (naturally or artificially) ruptured, assess the fluid for the presence of meconium and blood. Meconium has been associated with increased perinatal morbidity. Blood may signify abruption. In both situations, closer surveillance may be in order.
      2. **Fetal heart rate (FHR) monitoring.** The FHR should be monitored every 15–30 minutes, and this should be done immediately following a contraction. This can be by simple auscultation or by Doppler ultrasonography. Continuous electronic fetal monitoring (EFM) in labor results in the reduction of the rate of neonatal seizures, the long-term impact of which is unclear. EFM also leads to a significant increased rate of cesarean and operative deliveries (1).
         a. **Baseline fetal heart rate pattern.** Assess the FHR pattern for baseline rate and variability. The baseline FHR (i.e., the rate between contractions at term) is usually 120–160 beats/min. FHR may be lower in the postterm infant and higher in the premature infant. Variability (the beat-to-beat variation in the FHR) may be diminished or absent in the premature or "sleeping" fetus. Otherwise, absence of variability may indicate fetal compromise. Causes include hypoxia, drug use in labor, or congenital anomalies. Tachycardia (>160 beats/min) can be caused by fetal hypoxia or maternal fever. Bradycardia (<120 beats/min) can be normal in the postterm infant or indicative of severe hypoxia, maternal systemic lupus erythematosus, or fetal heart block.

b. **Periodic heart rate changes.** Document accelerations and decelerations. Accelerations of 15–25 beats/min above baseline are often associated with fetal movement or contractions and are reassuring. Decelerations are of three patterns: early, late, and variable. In early decelerations, the heart rate decreases with the start of the contraction and recovers as the contraction diminishes. This type of deceleration is usually secondary to fetal head compression or umbilical cord compression. Late decelerations begin as the contraction peaks. The lowest FHR is reached well after the peak of the contraction and recoverery does not take place until after the end of the contraction. These are associated with uteroplacental insufficiency and resultant hypoxia. Variable decelerations begin at no fixed time in relation to the contraction and may be the result of cord compression.

   Management of worrisome FHR patterns includes fetal scalp acid-base sampling, if available. Appropriate management is based on the fetal scalp pH. In the case of a prolonged deceleration, change maternal position, give oxygen, and check for cord prolapse. A nonreassuring FHR pattern, poor pH, or a prolonged deceleration may indicate the need for immediate delivery, consultation with an obstetrician, or both.

c. **Progress.** Periodically assess the cervix for further dilation, effacement, and descent of the head. These examinations should not be done more often than necessary to minimize discomfort and, when the membranes have already ruptured, the risk of infection. An acceptable rate of dilatation in the active phase may be 0.5–1.5 cm/h, with primiparas generally progressing more slowly than multiparas. Slow progress may be but is not necessarily a sign of abnormal labor. Interpret the rate of progress in the context of both fetal and maternal well-being.

d. **Pain control can be nonpharmacologic or pharmacologic.** Anything that relaxes and distracts the woman from her pain is beneficial. Maternal movement and position changes help with pain tolerance. Encourage the use of hot and cold compresses, baths, showers, or reassuring touch from her partner and labor coach.

   1. **Systemic drugs** include narcotics, tranquilizers, and inhalation gases. Narcotics provide reasonable analgesia but are also associated with dose-related maternal sedation, hypotension, nausea and vomiting, and neonatal respiratory depression. Dosage: Meperidine (Demerol), 50–100 mg IM, q4–6h. If narcotics are used, always have the antagonist naloxone (Narcan) available for the infant at delivery. Dosage: Naloxone, at 0.01 mg/kg SC, IV, or endotracheally (2). Phenothiazine tranquilizers are often given with the narcotic for their antiemetic properties. Dosage: Promazine (Sparine), 25 mg IM, q4–6h, given with meperidine. Inhalation options are not universally available because of concerns about ventilation and long-term exposure of personnel. Nitrous oxide (50% concentration in 50% oxygen) should be administered under maternal control, with personnel in attendance. This does not interfere with uterine activity or pushing ability.
   2. **Regional anesthesia** options include the epidural, spinal, and pudendal anesthetics. Epidurals generally provide more effective pain relief than narcotics or pudendal block. However, epidurals may lengthen labor and result in increased incidence of fetal malposition, increased need for oxytocics, and increased rate of operative vaginal delivery (but not of cesarean section) (3).

B. Second stage

comprises 10 cm dilatation to delivery of the infant. Confirm full dilatation. Allow the unanesthetized woman to push in the position of her choice and according to her own urges. For women with epidural, delayed pushing up to 2 hours, unless there is an irresistible urge, visibility of head, or medical indication to shorten the second stage, may reduce the need for obstetric interventions (4). Give her guidance and feedback on her propulsive efforts. Sustained and early bearing down may result in a slightly shorter second stage but may be associated with compromise of maternal-fetal gas exchange (5). Auscultate every 5 minutes, following every contraction-pushing series. As long as there is progress, intervention is generally only required if there is a concern about maternal or fetal well-being.

1. **Care of the perineum.** Episiotomy should not be done unless indicated, as it does not reduce the risk of severe perineal trauma or urinary incontinence, nor does it improve perineal healing or prevent fetal trauma. Indications include relief of maternal or fetal distress or for prevention of progress by a nonyielding perineum. Time it at the last possible moment to avoid blood loss. Local anesthetic is injected into the unanesthetized perineum along the anticipated line of the incision, be it *midline* or *mediolateral*.
2. **Spontaneous delivery of the occiput anterior infant**
   a. **Delivery of the head.** Minimize perineal trauma by conducting a *controlled* delivery of the head. At crowning, guide the woman to give small, short pushes of submaximal power, and to pant between the pushes. Assist her to nudge the head out. Suctioning should be done in the presence of meconium. Allow the head to restitute.
   b. **Shoulders.** Check for the presence of a nuchal cord. Slip it over the head or shoulders, or double clamp and cut between the clamps. Deliver the anterior shoulder first by gentle downward traction on the head, then the posterior shoulder by upward traction. Watch (often by squatting yourself) the posterior perineum to control for lacerations and extensions. The rest of the infant easily follows. The cord is clamped and cut, often by the woman's partner. The vigorous infant can be placed directly on the maternal abdomen.

C. Third stage

1. **Delivery of the placenta.** Spontaneous delivery of the placenta almost always occurs. The signs of delivery include (a) the uterus becoming firmer, (b) a gush of blood, (c) the uterus rising in the abdomen, and (d) the umbilical cord lengthening. Maintain firm gentle traction on the cord while the abdominal hand pushes upward on the anterior wall of the uterus to prevent uterine inversion (2). Routine administration of oxytocics may shorten the third stage and reduce the risk of postpartum hemorrhage. Dosage: Oxytocic (Oxytocin Injection, USP) 10 units IM is usually given with delivery of the anterior shoulder, although some wait until delivery of the placenta is complete. There is a small risk of hypertension. Manual removal of the placenta is considered if the placenta is not delivered within 30 minutes.
2. **Vaginal repair.** Inspect the vagina, periurethral tissues, and cervix (if anesthesia allows) for tears. Confirm the presence or absence of a third- or fourth-degree tear, and repair these first. Repair an episiotomy or tear with 2-0 absorbable suture, in the standard fashion, ensuring hemostasis and anatomical restoration, with the minimal suturing required.

D. The first hour post partum.

Follow the woman closely for any evidence of bleeding. Check her fundus frequently, and massage if not firm. If her flow seems too fast or heavy, then manage according to postpartum hemorrhage instructions. Encourage and assist with early breast-feeding.

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14.10
COMPLICATIONS DURING LABOR AND DELIVERY

James L. Greenwald

Bleeding occurs in the third trimester in 4% of pregnancies. Half of the cases of bleeding are attributable to placental abruption (2%) or placenta previa (2%). Premature rupture of the membranes (PROM) and dystocia are more common than the hemorrhagic complications of labor and delivery, but they rarely result in significant maternal or neonatal morbidity or mortality.

I. Placental abruption,

or abruptio placentae, is defined as premature separation of a normally inserted placenta from the endometrium. Hemorrhage occurs into the decidua basalis and usually, but not always, dissects through to the cervix. It can occur in any trimester. Early in pregnancy, abruption can manifest clinically as threatened or spontaneous abortion, and on ultrasound as a subchorionic hemorrhage. Before onset of labor in the second or third trimester, abruption can be associated with bleeding, pain, and fetal demise. Abruption complicating labor can result in hemorrhage, severe pain, fetal distress, and fetal demise.

A. Diagnosis

1. **History.** Risk factors include chronic hypertension, preterm PROM, external trauma, cigarette smoking, uterine leiomas, and cocaine abuse (1) (see also Chapter 5.7). Abruption increases somewhat with increasing maternal age. Cocaine abuse is particularly important, causing at least a threefold increase in the rate of abruption. The increase in the use of this drug may in part be responsible for the increased national incidence of abruption (1).
2. **Physical examination.** Uterine tenderness, back pain, vaginal bleeding, and fetal distress may each be seen in more than half of cases. Less common but still occurring in more than 10% are hypertonic contractions, rapid progress of labor, preterm labor, and fetal demise. Abruption may rarely present as shock.
3. **Imaging**
   a. **Ultrasound.** An ultrasound examination should be performed as soon as possible when abruption is suspected. Although a clot may not be seen in as many as 50% of cases, the study is still useful in excluding placenta previa. A hemorrhage greater than 60 cc or 50% of the surface that attaches to the uterus is associated with a 50% mortality (2).
   b. **Magnetic resonance imaging (MRI)** may detect a higher percentage of suspected cases of abruption where the diagnosis is not

obvious clinically. However, lack of portability renders MRI less useful in an emergency situation.

4. **Laboratory.** Blood tests occasionally demonstrate renal failure and coagulation defects associated with increased maternal and fetal complications. Hypofibrinogenemia is found in 30% of patients with abruption and associated fetal demise (3). Proteinuria is also a common accompaniment.

B. Complications

1. **Maternal.** Maternal mortality is rare and may be due to shock, renal failure, or disseminated intravascular coagulation (DIC). Most of the blood loss is maternal, but some fetal-maternal transfusions may occur. Any significant bleeding in pregnancies where the mother is at risk for anti-D isoimmunization should prompt treatment with Rh immune globulin.
2. **Fetal.** Abruption is associated with a 25%–30% perinatal mortality. Although the majority of perinatal deaths are related to extreme prematurity, intrauterine fetal demise is possible even at term related to disruption of placental function. Abruption is associated with poorer neurodevelopmental outcome in low-birth-weight infants but not in normal-weight infants.

C. Management.

Continuous monitoring must be done when the diagnosis is made, and an immediate cesarean section should be performed if severe signs of fetal distress are present. Labor often progresses rapidly with abruption and may be allowed to progress if no fetal distress is noted, although rapid deterioration may be seen. In spite of the high incidence of recurrence (12%), preventive measures are not available to lower the increased incidence of fetal demise (7%) in pregnancies with a history of abruption.

II. Placenta previa

occurs when the site of placental implantation impinges on the internal cervical os. Bleeding from separation of the placenta in the presence of previa is a common cause of bleeding in the second and third trimesters. Depending on the precise location of the placenta, the previa may be qualified as being total (completely covering the internal os), partial (partially covering), or marginal (edge of placenta touching the os).

A. Diagnosis

1. **History.** Classically, placenta previa is diagnosed after painless bleeding in the second or third trimester. A higher than normal rate of placenta previa is associated with previous cesarean section, previous induced or spontaneous abortion, advanced maternal age, and smoking (1). Accordingly, placenta previa is associated with placenta accreta, an abnormally adherent placenta that commonly causes excessive bleeding in the third stage of labor due to incomplete separation. This is especially noted in patients with repeated cesarean sections, indicating that both conditions may be related to endometrial defects. The rate of accreta may be as high as 65% after multiple cesarean sections (2).
2. **Examination.** In modern obstetrics, there is no reason to perform a cervical examination in suspected previa before performing an ultrasound examination, due to the risk of perforating the portion of placenta that is palpable through the os. Prior to the widespread availability of ultrasound on obstetric units, cervical examination at term was often performed after the patient was prepared for possible cesarean delivery (“double setup”). Nowadays a double-setup examination is done only when the localization of a low-lying placenta is not clear from the ultrasound.
3. **Blood tests** are generally normal in the absence of anemia due to massive hemorrhage.
4. **Imaging**
    a. **Ultrasound.** An ultrasound should be performed with the onset of painless bleeding in pregnancy. False-positive and false-negative rates may each approach 5%. Bladder overdistention is associated with false positives, and consideration should be made to catheterizing the bladder before performing an ultrasound. Clinical judgment

is important. Heavy bleeding, especially when coexisting with signs of fetal distress, should lead to an immediate delivery.

b. **Incidentally discovered placenta previa.** In this age of "routine" obstetric ultrasound, previa is frequently diagnosed prior to any bleeding and commonly overdiagnosed. One study of 267 patients having placenta previa diagnosed on ultrasound performed between 14 and 20 weeks gestation showed that the previa persisted to the time of delivery in only 2.5% of patients with partial or marginal previa, although it persisted in 26% of patients with total previa (2).
c. **MRI** can clearly outline the location of a placenta previa, but it is much more expensive and less readily available.

B. Complications

1. **Maternal.** Women with placenta previa have a mortality of 0.03%, or about three times the overall U.S. rate of mortality in childbirth. Other complications include an increase in cesarean birth, fetal malpresentation, premature labor, and postpartum hemorrhage.
2. **Fetal.** Perinatal fetal mortality is less than 5%, primarily due to increased premature births by cesarean section (2). In addition to the common forms of morbidity associated with prematurity, neonatal anemia is common and related to the degree of maternal hemorrhage. Respiratory distress syndrome occurs more commonly than would be predicted by the rate of prematurity. Other effects, such as an increased incidence of congenital anomalies, may be associated with the causes of abnormal implantation. It is likely that a number of spontaneous abortions occur due to a low insertion of the placenta.

C. Management

1. In preterm placenta previa prior to 36 weeks gestation without evident fetal jeopardy, authorities recommend attempting delay in delivery by avoiding vaginal examination and tocolysis. The efficacy of these procedures in reducing infant mortality or morbidity in previa or other causes of prematurity has yet to be proved by a large, prospective study. Reliable patients with minor degrees of bleeding who have been adequately observed for premature delivery and fetal distress may be managed at home without increased maternal or infant morbidity or mortality. In practice, few patients with placenta previa meet these criteria (3).
2. Prompt delivery should be the goal in term placenta previa. Hemorrhage and shock must be ma naged aggressively, and the delivering physician should be prepared to perform an emergency cesarean section or hysterectomy if bleeding from placenta accreta cannot be controlled.

III. Premature rupture of membranes

is defined as rupture of the fetal membranes more than 1 hour before the onset of active labor. The duration between membrane rupture and the onset of active labor contractions is defined as the latent period.

A. Diagnosis

1. **History.** The patient may report a gush of fluid from the vagina. If the flow does not persist, the physician should ask the patient to examine the clothing for an odor of urine. On past history, risk factors include vaginal group B streptococcal colonization, cigarette smoking, prior preterm delivery or PROM, hypertension, diabetes, amniocentesis, and cervical surgery during the pregnancy.
2. **Examination**
   a. On examination of the vagina with a sterile speculum, a flow of fluid, sometimes containing vernix caseosa or meconium, is diagnostic, as is seeing or palpating the fetal scalp.
   b. Preterm PROM. Digital examination shortened the latent period from 11 to 2 days in one study (2). This may be avoided by assessing cervical dilatation and effacement by sterile speculum exam, vaginal or transperineal ultrasound (3).
   c. Signs of acute chorioamnionitis, or acute infection complicating premature rupture, include fever and foul or cloudy amniotic fluid.

d. Readiness of the cervix for labor is determined by direct observation and digital examination. Engagement of the presenting part, cervical softness, forward position of the os, dilatation, and effacement all indicate impending labor and are associated with successful oxytocin induction of labor.

3. **Laboratory**
   a. **Fern**ing**.** Amniotic fluid dries with a characteristic arborization pattern, called *fern*ing, seen on microscopic examination. False-positive fern test results may rarely be seen in the presence of scant fluid due to the presence of cervical mucus.
   b. **Nitrazine test.** This test checks for elevation of the normally acidic vaginal pH due to the presence of amniotic fluid. False-positive results are more common than with the fern test and may be caused by bacterial vaginosis or by contamination of the vaginal sample with blood, lubricant jelly, or povidone-iodine.
   c. **Chorioamnionitis** may be associated with DIC. When this condition is suspected, clotting studies and measurement of renal and hepatic function should be done.

B. Complications

1. **Maternal.** Most maternal complications are due to infection. Chorioamnionitis occurs in 3%–25% of PROM cases. This or subclinical amnionitis may precede postpartum infectious complications of endometritis and pelvic cellulitis. Maternal mortality due to DIC or septic shock is rare (<0.1%).
2. **Neonatal.** Although preterm PROM (prior to 37 weeks gestation) poses a significant risk of morbidity and mortality to the neonate, 75% of incidents occur at term and generally run a benign course. PROM increases the frequency of neonatal sepsis from 0.1% to 1.4%. Fatalities are common in neonatal sepsis, especially in low-birth-weight infants (20% in very low-birth-weight infants versus 12% in normal-weight infants) and those with group B streptococcal sepsis. Although an increase in the latency period in term pregnancy increases the incidence of sepsis, the neonatal mortality is unaffected. Even the presence of acute chorioamnionitis for up to 24 hours does not increase neonatal mortality in term births (4).

C. Management of PROM

1. **Preterm PROM** after 35 weeks may be managed as in term PROM. In preterm PROM before 35 weeks, tocolysis, corticosteroid administration to induce the production of mature lung surfactant, and antibiotic prophylaxis have been used extensively. Antibiotic prophylaxis is designed to lengthen latency through a reduction of amnionitis, but it also reduces the risk of endometritis in the event that a cesarean section is required. Amniocentesis to evaluate pulmonary maturity may be performed in preterm PROM before 35 weeks. A decreased level of amniotic fluid glucose provides rapid confirmation of chorioamnionitis. Other tests of amniotic fluid lack sensitivity in detecting this condition. Intervention in early (prior to 32 weeks gestation) preterm PROM may decrease morbidity from infections, respiratory distress syndrome, and intracranial hemorrhage. Consultation with a perinatologist should be done.
2. **Term PROM**
   a. **Fetal assessment.** Fetal monitoring with external electronic monitor is recommended. Fetal distress can be a sign of chorioamnionitis.
   b. **Ripening the cervix.** Digital exam is performed. If the cervix is not dilated more than 2 cm, vaginal application of a prostaglandin can cut the latency period by at least half, as was shown in several studies. Cervidil, an insert impregnated with 10 mg dinoprostone (prostaglandin E), may be the preferred preparation because it can be removed in the case of hyperstimulation. Administration of misoprostol (25–50 μmg vaginally every 3–6 hours to a maximum of 100 μmg) is a

much less expensive alternative. Prostaglandins are also safe and effective in the induction of labor if the cervix is ripened and not dilated beyond 5 cm (1).

c. **Hyperstimulation.** The use of prostaglandin analogues may cause hyperstimulation of the uterus. This is defined as the presence of prolonged (³2 minutes) contractions, excessively frequent contractions, or *tachysystole* (³6 in 10 minutes) and fetal distress (late decelerations or fetal bradycardia).

d. **Induction of labor with an intravenous infusion of oxytocin** decreases latency significantly but seems not to affect the low rate of maternal or neonatal mortality in term pregnancy. Recent Cochrane Collaboration reviews indicate that induction does offer certain benefits and risks in comparison with expectant management. The benefits—a lower risk of maternal and neonatal infection and increased maternal satisfaction—and risks—increased epidural anesthesia and internal monitoring—must be presented to the patient when oxytocin or prostaglandin is offered (5).

IV. Dystocia

is defined as a delay of labor due to cephalopelvic disproportion, inadequate uterine expulsive forces, or unfavorable presentation. Labor that is delayed after delivery of the head is referred to as shoulder dystocia.

A. Diagnosis

1. Conditions associated with a prolonged first stage of labor. Delayed active phase of labor is associated with overdistention of the uterus (multiple gestation, polyhydramnios), abnormal lie, macrosomia (fetal weight more than 4,500 g), hydrocephaly, obstruction of the maternal reproductive tract (pelvic contraction, tumors, developmental anomalies), and with the onset of chorioamnionitis late in labor. One retrospective study showed a higher incidence of diagnosis of cephalopelvic disproportion and subsequent cesarean section in patients receiving care from obstetrician-gynecologists than in patients of family physicians (6). Friedman's work has been used to subdivide abnormalities in the first stage of labor:
   a. Prolongation of the latent phase of the first stage of labor is defined as more than 20 hours in nulliparas and more than 14 hours in multiparas.
   b. Prolongation of dilatation and descent. In the active phase of the first stage of labor, prolonged dilatation is defined as dilatation less than 1.2 cm/h in nulliparas and less than 1.5 cm/h in multiparas. This is usually accompanied by prolongation of descent, defined as descent less than 1 cm/h in nulliparas and less than 2 cm/h in multiparas. It is important to document carefully that the patient is actually in active labor before making this diagnosis because the management of prolonged latent phase and prolonged active phase are different. It may be easy to confuse these two conditions, such as in a multipara with an elastic cervix and low pain tolerance.
   c. Arrest of dilatation is said to occur if the patient is in the active phase of labor and no cervical change has been noted in more than 2 hours.
2. A prolonged second stage occurs if the patient has been fully dilated for more than 2 hours for nulliparas and more than 1 hour for multiparas. The time allowed is increased by 1 hour if conduction anesthesia is used. Prolonged second stage of labor is associated with obstructions of the reproductive tract (sacral tumors, condyloma, pelvic contraction, distended bladder), conduction anesthesia, and macrosomia or hydrocephaly.
3. Shoulder dystocia should be promptly diagnosed when the anterior shoulder is locked behind the symphysis pubis, preventing delivery beyond the neck.

B. Complications

1. **Maternal.** The major maternal complications associated with dystocia are those related to the increased rate of operative delivery, including

hemorrhage, infections, and prolongation of hospital stay. Dystocia is a contributing factor in 47% of primary cesarean sections.

2. **Neonatal**
   a. **Prolonged latent phase.** Prolonged latent phase is associated with an increased risk of depressed 5-minute APGAR scores and a need for neonatal resuscitation but without long-term sequelae.
   b. **Prolonged first stage.** Most of the morbidity and mortality in infants with prolonged labors is related to events occurring in the second stage. Selection of a cesarean section or use of oxytocin induction prior to the second stage does not affect the infant. Even the increase in amnionitis, which might be caused by prolonged first-stage labor in the presence of a ruptured membrane, is not likely to cause morbidity in a term infant.
   c. **Prolonged second stage.** Prolongation of the second stage of labor up to 6 hours did not increase morbidity in the newborn term infant. Prolonged second-stage labor is associated with an increased incidence of shoulder dystocia and should prompt alertness for the condition.
   d. **Shoulder dystocia** is associated with macrosomia, brachial plexus palsy, and upper extremity fractures.

C. Management

(Table 14.10-1)

Labor pattern	Nulligravida	Multipara	Treatment
Prolonged latent phase	>20 h	>14 h	Rest oxytocin if cervix dilated, if not consider prostaglandins.
Protraction disorders			
Dilatation	<1.2 cm/h	<1.5 cm/h	Oxytocin, if contractions are inadequate. If under 5 cm dilatation, consider prostaglandin.
Descent	<1.0 cm/h	<2.0 cm/h	Oxytocin, if contractions are inadequate. If under 5 cm dilatation, consider prostaglandin.
Arrest disorders			
Dilatation	>2 h	>2 h	Oxytocin, if contractions are inadequate. If under 5 cm dilatation, consider prostaglandin.
Descent	>1 h	>1 h	Oxytocin augmentation, forceps, vacuum, or cesarean delivery.

From American College of Obstetricians and Gynecologists. Tech. Bull. No. 137. *Dystocia* 1989, with permission.

Table 14.10-1. Abnormal labor patterns, diagnostic criteria, and treatment

1. **Prevention**
   a. **Routine amniotomy.** According to a meta-analysis by the Cochrane Collaboration, routine amniotomy in active labor shortens the active phase by a little more than 1–2 hours but may result in an increased incidence of cesarean section. The reviewers recommend limiting its use to women with abnormal labor progress (5).
   b. **Active management involves comprehensive protocols for labor management including the routine use of oxytocin.** The

goal of active management is to lower the incidence of cesarean sections performed for prolonged labor. Studies show that these protocols only reduce the cesarean section rate in institutions where the incidence exceeds 15%. The most important component of active management appears to be one-on-one nursing, which helps to alleviate the patient's anxiety and facilitates prompt diagnosis of dysfunctional labor patterns.

c. **Prolonged latent phase.** Treatment generally involves rest or expectant waiting. Intervention should be undertaken with caution: there is a high rate of mistaking false labor for this condition, and amniotomy before the onset of active labor or introduction of oxytocin before full cervical ripening could lead to amnionitis or unnecessary cesarean section. Sedation with hydroxyzine or use of hypnotic doses of secobarbital (100 mg PO) and morphine (10 mg IM) often allows differentiation from false labor. Oxytocin infusion would be appropriate when other signs, such as macrosomia, oligohydramnios, or maternal exhaustion, indicate a pressing need for prompt delivery.

d. **Prolonged active phase and arrest of labor**

   a. **Therapeutic sleep.** Failed dilatation and descent can be managed with analgesics and hypnotics (see Section IV.D.2), especially in an exhausted patient who has not progressed beyond 6 cm dilatation.

   b. **Oxytocin augmentation of labor** can be used. Newer protocols using a higher starting dose (4–6 mU/min) than the usual (0.5–1.0 mU/min) and a shorter dosage interval (15–20 minutes versus 30–60 minutes) have been proved safe and may shorten the duration of labor by 3 hours. Hyperstimulation is more common with these protocols and must be managed by discontinuation of oxytocin followed by reinstitution at a lower rate.

   c. **Analgesia with narcotics or epidural anesthesia** may help increase a mother's tolerance for prolonged labor. Epidural anesthesia is safer and more effective than narcotic analgesia, but it should be delayed until after the patient has dilated to 5 cm to reduce the associated increased risk of cesarean birth.

   d. **Cesarean section.** Consideration for a cesarean section should be made if more serious signs of fetal distress, such as late decelerations or thick meconium, are present.

e. **Prolonged second-stage labor.** Oxytocin augmentation is often helpful. Catheterize the bladder if distention is suspected. Discontinue or delay the use of conduction anesthesia. If fetal distress ensues and if the delivering physician has adequate training, mid-forceps delivery with rotation using a vacuum device or forceps may be considered when the vertex is arrested in the mid-pelvis in a transverse lie. If a prompt cesarean section can be performed, this is usually preferred, as vacuum or forceps deliveries with more than 45 degrees rotation or anything less than complete descent (outlet forceps) is associated with increased maternal morbidity from bleeding and damage to the pelvic sphincters.

f. **Shoulder dystocia** should be promptly diagnosed and managed.

   a. The assistance of a physician trained in obstetrics, an anesthesiologist, and a pediatric support person should be obtained.

   b. Avoid excessive downward traction on the head or fundal pressure because these maneuvers are associated with injury to the neonate.

   c. General measures. Catheterization of a distended bladder and a generous mediolateral episiotomy will relieve any soft-tissue impediments to rotation and descent. Elevation of the hips may help to relieve any obstruction to the outlet from bedding or pelvic rotation.

   d. The McRoberts maneuver consists of removing the mother's legs from any stirrups and actively flexing them against her abdomen. This is supposed to straighten the sacrum and decrease the angle of pelvic inclination.

   e. Suprapubic pressure may help dislodge the anterior shoulder.

f. The Woods corkscrew maneuver consists of gently rotating the occiput 180 degrees. The anterior shoulder becomes dislodged from the symphysis while the posterior shoulder generally delivers anteriorly in the process. This maneuver can be assisted by sweeping the posterior arm across the fetus's chest and delivering the posterior shoulder.

g. Rarely used maneuvers include replacement of the fetal head (Zavanelli's maneuver) by reversing the stages of head delivery, followed by cesarean section. Clavicle fracture and symphysiotomy are rarely used.

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14.11
POSTPARTUM CARE

Dwenda K. Gjerdingen

I. Early postpartum (0–2 weeks) problems and management

During the first few hours after delivery, the postpartum patient should be monitored carefully for hemorrhage, blood pressure changes, and infection. During this period, and for weeks or months after delivery, patients often experience several problems as outlined below.

A. Pain

1. **General.** Prescribe analgesics. For severe pain (e.g., after a cesarean section), give meperidine, 50–100 mg with or without hydroxyzine hydrochloride (Vistaril) 25–50 mg IM q3–4h. For less intense pain, give ibuprofen 400–800 mg PO q6h or naproxen sodium 500 mg PO bid (for non-breast-feeding women only), or acetaminophen 1,000 mg PO q6h, or acetaminophen, 300 mg with codeine 30 mg (Tylenol No. 3) PO q3–4h.
2. **Specific measures**
   a. **Perineal.** Use ice packs, witch hazel, and tub baths.
   b. **Breast.** Advise the use of supportive undergarments. For breast pain and engorgement in nonnursing mothers, apply cold packs. Some women also find it helpful to manually express milk (without nipple stimulation). For engorgement in breast-feeding mothers, apply warm packs for about 20 minutes before breast-feeding, and feed frequently. For sore nipples, cleanse and dry after breast-feeding, apply moisturizing creams or ointments, and keep feedings brief.

B. Uterine cramps, cesarean wound.

Give analgesics as for general pain.

C. Hemorrhage.

Postpartum hemorrhage is defined as a blood loss of more than 500 mL after delivery. Causes include uterine atony, drugs (e.g., general anesthesia, oxytocin, magnesium sulfate, aspirin, anticoagulants), ruptured or inverted uterus, cervical lacerations, retained or abnormal placenta, coagulation disorders, and intrauterine infection.

Treatment includes the following:

1. Eliminate the cause: Massage atonic uterus, remove retained placenta, replace inverted uterus, repair lacerations.
2. IV fluid (normal saline or lactated Ringer's solution), or blood product replacement.
3. For uterine atony, give drugs that promote uterine contraction:
   a. Oxytocin (Pitocin) 10 units IM, or 10–40 units in 1,000 mL lactated Ringer's solution IV, at optional rate.
   b. Methylergonovine maleate (Methergine) 0.2 mg IM q2–4h
   c. Prostaglandin F as carboprost tromethamine (Hemabate) 0.25 mg IM every 15–60 minutes.
4. If these measures fail, consider transcatheter embolization of the uterine artery. Advantages of this procedure, in comparison with hypogastric artery ligation or abdominal hysterectomy (last resorts), include low complication rate, avoidance of surgical risks, fertility preservation, and shorter hospitalizations (1).

D. Anemia.

Give oral iron (ferrous sulfate) 325 mg PO daily or bid. If symptoms of postural hypotension are present, consider transfusion.

E. Endometritis.

Symptoms include fever, malaise, abdominal pain and tenderness, and purulent or foul lochia; these usually begin days after delivery. Treatment choices include ampicillin sulbactam (Unasyn) 1.5–3 g IV q6h, or ticarcillin/clavulanate (Timentin) 3.1 g IV q6–6h, or cefoxitin (Mefoxin) 1–2 g IV q6–8h, or clindamycin 600–900 mg IV q8h plus gentamicin 1/kg IV q8h, with kinetic adjustments.

F. Transient mood disturbance ("blues").

A majority of women experience brief periods (several hours to 1–2 days) of mood disturbance after giving birth. Management consists of support and reassurance.

G. Hemorrhoids.

Mild to moderate symptoms may be relieved by tub baths; local hemorrhoidal preparations, such as hydrocortisone glyceride suppositories (Anusol-HC) bid for 1–2 weeks; and treatment of constipation with stool softeners, such as docusate (Colace) 100 mg PO daily prn. Use medications with caution in nursing mothers. More severe cases may require surgical excision.

II. Delayed postpartum problems

A. Fatigue.

Seen in a majority of women, fatigue is often related to physical recovery, increased work demands, and reduced sleep. If fatigue is moderate to severe, rule out anemia (with a hemoglobin test), thyroid dysfunction (check the level of thyroid-stimulating hormone), and depression (see also Chapter 2.2).

B. Mastitis.

Symptoms include breast inflammation, fever, and chills. Management includes frequent nursing, warm compresses, and antibiotics to cover *Staphylococcus* or *Streptococcus*, such as methicillin 1 g IV q4–6h, cefazolin 1 g IV q6–8h, or dicloxacillin 500 mg PO q6h.

C. Thyroiditis.

Painless thyroiditis begins 1–3 months after delivery with a period of thyrotoxicosis, often followed by a hypothyroid phase at 3–6 months postpartum. In a minority of cases, the hypothyroidism continues indefinitely. Symptoms of hyperthyroidism (fatigue, palpitations) can be treated with ß-blockers (e.g., propranolol, begin with 10 mg qid, maintain with 20–80 mg PO qid). Symptomatic hypothyroidism (fatigue, dry hair and skin, impaired concentration, depression) can be treated with levothyroxine (Synthroid), initial dose 0.05 mg, increase by 0.025 mg every 2–3 weeks, up to a maximum of 0.2 mg/d; attempt to withdraw after 6 months (see also Chapter 17.3).

D. Carpal tunnel syndrome.

Symptoms include hand pain, numbness, and weakness; examination may show positive Tinel's and Phalen's signs, weakness, and abnormal nerve conduction. Treatment options include night splints, diuretics, nonsteroidal anti-inflammatory drugs (naproxen, 250–500 mg PO bid), steroid injections, avoidance of provocative activities, and surgical decompression (see Chapter 15.5).

E. Depression.

Symptoms consist of persistent mood disturbance (for 2 weeks or more), diminished pleasure, change in appetite or weight, change in sleep

patterns, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished concentration, and recurrent thoughts about death. Because postpartum depression may be secondary to thyroid disorders or anemia, evaluation should include thyroid-stimulating hormone and hemoglobin levels. Treatment includes social support and psychotherapy (often including couple therapy) and/or antidepressant medications. The drugs of choice are selective serotonin reuptake inhibitors, such as paroxetine (Paxil) 20–50 mg/d, sertraline (Zoloft) 50–200 mg/d, and fluoxetine (Prozac) 20–80 mg/d. Side effects include headache, sexual dysfunction, anxiety, nervousness, insomnia, anorexia, nausea, and diarrhea. For nursing mothers, antidepressants should be used with caution. Amitriptyline (Elavil) 75–300 mg/d, desipramine (Norpramin) 25–300 mg/d, nortriptyline (Pamelor) 25–150 mg/d, and Sertraline (Zoloft) 50–200 mg/d have not been found in quantifiable amounts in nurslings' sera, nor have adverse events been reported; however, potential delayed effects have not been well studied (2,3) (see also Chapter 5.2).

F. Respiratory infections.

Infections of the respiratory tract are more common in the postpartum period, especially for women who return to work (4). Treatment is the same as for non-postpartum adults, except that women who are breast-feeding should avoid tetracyclines, sulfonamides, and antihistamines.

G. Sexual changes.

Many women note discomfort with intercourse and a loss of sexual desire for weeks or months after delivery. These problems are associated with both cesarean and vaginal deliveries, and occur more commonly in women who breast-feed (5).

III. General management.

Encourage the following:

A.

Use of available social supports.

B.

Adequate maternity leave (3–6 months or more, if possible).

C.

Negotiation of flexible benefits, such as part-time or flexible hours and use of personal days to care for a sick child.

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14.12
DIAGNOSTIC ULTRASOUND IN OBSTETRICS

Michael D. Prislin

I. Overview

Obstetrical ultrasound examinations have become an increasingly common part of antepartum care during the past 30 years. Indeed, more than 80% of all pregnant women in the United States undergo at least one ultrasound examination. Yet evidence supporting the use of obstetric ultrasound as a routine component of prenatal care is lacking (1). Therefore, clinical guidelines continue

to recommend that obstetric ultrasound examinations be performed only for specific indications (2).

An analysis of 850 consecutive obstetric ultrasounds performed in our family health center revealed that a relatively small number of indications accounted for more than 90% of the studies performed. These indications include confirmation of a viable intrauterine pregnancy; estimation of gestational age; evaluation of size-date discrepancies; evaluation of vaginal bleeding during pregnancy; determination of fetal presentation; screening for fetal anomalies; and assessment of fetal status. A discussion pertinent to each of these indications follows.

II. Confirmation of a viable intrauterine pregnancy.

Advances in transvaginal sonography have markedly improved the ability to detect an early intrauterine pregnancy. The gestational sac can be found as early as 4 weeks; however, caution must be exercised as a pseudosac commonly arises during ectopic pregnancy. The presence of a yolk sac confirms the existence of an intrauterine pregnancy and can be seen as early as 5 weeks. An embryo within the gestational sac and fetal cardiac activity can generally be detected during week 6 (3).

III. Estimation of gestational age.

Estimation of gestational age is predicated on knowledge of a last normal menstrual period (LMP) prior to conception. In up to 40% of pregnancies an accurate LMP cannot be determined. Obstetric ultrasound scanning provides estimation of gestational age through the measurement of various fetal landmarks for which gestational age-size correlations have been established. Ultrasound determination of a gestational age is most accurate early in pregnancy. As the pregnancy progresses individual variations in fetal growth occur and measurements of some fetal landmarks become technically more difficult to perform.

Crown-rump length is the landmark measurement of choice for first-trimester and early second-trimester pregnancies. Biparietal diameter, head circumference, abdominal circumference, and femur length are used for second-trimester and third-trimester pregnancies. Estimations of gestational age performed during the second and third trimester represent averages of at least three landmark measurements and are expressed as ranges, allowing for individual variation in fetal growth. Variability in estimation of gestational age ranges from ±4 days in first-trimester examinations to ±7–10 days in early to middle second-trimester examinations, ±14 days in late second-trimester examinations, and ±21 days in third-trimester examinations (4).

IV. Size-date discrepancies.

A significant difference between the measured value of fundal height and the estimated gestational age as determined by LMP constitutes a size-date discrepancy.

A. Dating-related discrepancies.

Size-less-than-dates and size-greater-than-dates discrepancies most commonly arise from inaccurate calculation of the LMP, inaccurate determination of fetal size, or individual variation in fetal growth. Ultrasound evaluation provides a valuable third point of reference in the determination of an accurate gestational age. In our experience, ultrasound examinations result in the confirmation of LMP-based estimated gestational ages in approximately 70% of size-date discrepancies and result in ultrasound-based redating of estimated gestational age in approximately 22% of cases.

B. Non-dating-related discrepancies.

In approximately 8% of cases, size- date discrepancies cannot be accounted for by factors related to estimating gestational age. Conditions contributing to size-date discrepancies commonly detected by obstetric ultrasound include (for size less than dates) fetal demise, oligohydramnios, major fetal anomaly, abnormal presentation, and intrauterine growth retardation (IUGR). Conditions contributing to size-date discrepancies commonly detected by obstetric ultrasound (for size greater than dates) include major fetal anomaly, abnormal presentation, molar pregnancy, multiple gestation, macrosomia, polyhydramnios, and uterine anomalies.

Ultrasound evaluation of IUGR is a particularly crucial task that deserves further comment. A single ultrasound examination in a pregnancy with a clearly established estimated gestational age can be highly suggestive of

IUGR if the abdominal circumference is lower than the 10th percentile for that gestational age. The concomitant presence of oligohydramnios significantly increases the likelihood of IUGR. A lag of interval growth documented by serial ultrasound examinations over a 2- to 3-week period establishes the diagnosis of IUGR. Whether the IUGR is symmetrical or asymmetrical and thus related to ureteroplacental insufficiency can be ascertained by examining the ratio of head circumference to abdominal circumference. An increasing head-to-abdominal circumference ratio connotes asymmetrical IUGR.

V. Evaluation of vaginal bleeding during pregnancy

A. First-trimester bleeding.

Ultrasound evaluation of first-trimester bleeding is usually concerned with confirming the presence of a viable intrauterine pregnancy. The absence of a yolk sac by 7 weeks gestation is a poor prognostic indicator, as is a fetal heart rate less than 85 beats per minute (3). While ectopic pregnancies can, in some instances, be visualized using transvaginal ultrasound, the greatest utility remains in confirming the presence of an intrauterine pregnancy. Serial ultrasound examinations in combination with serial quantitative ß-human chorionic gonadotropin evaluations can also be used to discriminate between early intrauterine pregnancies, inevitable or missed abortions, and ectopic pregnancies (see Chapter 14.4 and Chapter 14.5).

B. Second- and third-trimester bleeding.

Ultrasound evaluation of late second- and third-trimester bleeding is concerned with the detection of placenta previa and abruptio placentae. Ultrasound is the diagnostic study of choice for placenta previa. An apparent previa or a low-lying placenta is a common ultrasound finding during early and middle second-trimester studies. In most of these cases, repeat studies late in the second trimester or early third trimester demonstrate placental “migration.” This is really a misnomer because the placenta does not migrate; rather, increasing uterine size causes elongation of the lower uterine segment, which in turn increases the distance between the placenta and the internal cervical os.

Ultrasound diagnosis of abruptio placentae is less clear-cut. Often ultrasound imaging can demonstrate placental separation from the uterine wall or the presence of a sonolucent area between the placenta and the uterine wall, representing formation of a hematoma. However, a negative ultrasound study result does not exclude the presence of a placental abruption.

VI. Determination of fetal presentation.

Although ultrasound evaluation reliably defines fetal presentation, an abnormal fetal presentation detected prior to 35 weeks gestation has little prognostic significance. If detected after 34 weeks of gestation, an abnormal presentation is more likely to persist until term. Such a finding may be addressed through an ultrasound-assisted external version, optimally performed at 37–38 weeks gestation.

VII. Screening for fetal anomalies.

Because ultrasound imaging provides direct visualization of fetal anatomical structures, it can be a valuable tool in detecting fetal anomalies. Easily visualized structures include fetal cranial structures; fetal heart and aorta; fetal spine; fetal abdominal wall; fetal liver, stomach, bowel, and peritoneal cavity; fetal kidneys, bladder, and genitalia; and fetal limbs. However, the expertise of the ultrasonographer also has an important role in the successful detection of fetal anomalies. Hence, the concomitant presence of other risk factors, including advanced maternal age, pregestational diabetes, abnormal maternal serum α-fetoprotein (increased or decreased), or the sonographic detection of IUGR or amniotic fluid volume abnormalities (either increased or decreased), is of crucial importance. Such patients may benefit from a targeted fetal anatomical ultrasound evaluation performed by an ultrasonographer experienced in detecting fetal anomalies (5).

VIII. Assessment of fetal status.

Real-time ultrasound assessment of fetal respiratory activity, fetal movement, and fetal neuromuscular tone and the ultrasound measurement assessment of amniotic fluid volume, when added to a nonstress fetal heart rate study, constitutes a fetal biophysical profile. Although a full biophysical profile adds specificity to the highly sensitive but nonspecific nonstress test, it is generally too time consuming and expensive to use in routine antepartum fetal surveillance. However, assessment of amniotic fluid volume has proven

to be of value in predicting the occurrence of fetal distress during labor in postdate pregnancies. Fetal distress in this context is frequently associated with umbilical cord compression, which in turn is highly correlated with the presence of oligohydramnios. Thus, in most centers, amniotic fluid volume determination is now combined with nonstress testing in the antepartum screening of postdate pregnancies.

IX. Ultrasound evaluation of the cervix in the assessment of preterm labor.

Although not among the commonly encountered indications for obstetric ultrasound enumerated earlier in this chapter, recent experience gained using transvaginal ultrasound measurements of cervical length to assess preterm labor merits comment. Substantial shortening of cervical length as measured by transvaginal ultrasound is associated with increased risk for preterm labor, and visualization of dynamic shortening of the cervix is highly suggestive of active preterm labor (6).

X. Summary.

A systematic obstetric ultrasound examination should include the following components: documentation of fetal number, position, and viability; estimation of amniotic fluid volume; fetal biometric measurements to estimate gestational age; a fetal anatomical survey; evaluation of the placenta; and assessment of uterine and adnexal structures. Although the use of this technology on a routine basis remains controversial, obstetric ultrasound, when performed for specified indications such as those described in this chapter, has proven to be an extremely valuable addition to antepartum care.

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XV. MUSCULOSKELETAL PROBLEMS AND ARTHRITIS

15.1
OSTEOARTHRITIS

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I. Epidemiology and pathophysiology.

Osteoarthritis (OA) is a degenerative disease of the cartilage of joints and is the most common form of joint disease (1). Risk factors associated with OA include advancing age, major trauma, and chronic excess body weight. There is also growing evidence that certain occupational groups are at increased risk for OA. The disease is marked by an irregularly distributed loss of cartilage thought to be mediated by complex remodeling interactions between chondrocytes, the matrix, cytokines, growth factors, the synovium, and mechanical factors. As the cartilage degenerates, joint stresses are increasingly transmitted to the underlying bone, which leads to the formation of subchondral sclerosis, subchondral cysts, and marginal osteophytes. Although OA is much more common with advancing age, the changes seen in osteoarthritic cartilage are clearly distinct from those seen with normal aging (2).

II. Diagnosis

B. Clinical presentation.

OA is generally a monoarticular or oligoarticular disease. Commonly affected joints include distal interphalangeal (DIP), proximal interphalangeal (PIP), first carpometacarpal, knee, hip, and lumbosacral or cervical spine. Initially, the disease is characterized by joint pain occurring with motion and relieved by rest. As the disease progresses, pain can occur with minimal motion and even at rest. Although joint stiffness can occur, it is usually of short duration (less than 30 minutes). OA does not cause systemic symptoms, such as fatigue, weight loss, and fever. Paresthesias and weakness (secondary to nerve root impingement in OA of the spine) may also occur.

C. Physical examination.

Joints affected by OA may show decreased range of motion, joint deformity, bony hypertrophy, and, occasionally, intra-articular effusions. Crepitance, pain on passive and active movement, and mild tenderness may be found. Evidence of inflammatory changes is usually absent. During late stages of OA there may be demonstrable joint instability. Other signs include Heberden's nodes (DIP joints), Bouchard's nodes (PIP joints), gelatinous cysts, and muscle atrophy.

D. Laboratory findings.

There are no specific laboratory tests for OA. OA does not cause elevation in the erythrocyte sedimentation rate, abnormalities in the hemogram, or presence of autoantibodies. If there is a joint effusion, the synovial fluid is noninflammatory (with fewer than 2,000 white blood cells) and contains a predominance of mononuclear white blood cells and a good mucin clot. The diagnosis of OA is usually based on clinical and radiologic features.

E. Radiographic features.

Early in the course of the disease, radiographs may be normal. As the disease progresses, radiographic signs include asymmetrical joint space narrowing and subchondral sclerosis. Osteophytes, subchondral cysts with sclerotic margins, and intra-articular osseous bodies may become evident. Finally, subchondral bony collapse may result from the compression of weakened and deformed trabeculae.

III. Treatment.

Management of OA should focus on pain relief, prevention of progressive joint damage, and maintaining function. Treatment should be customized to the individual patient.

B. Nonpharmacologic management.

Emphasis should be placed on exercises directed toward muscle strengthening and improvement or maintenance of range of motion. Other physical modalities include heat (hydrotherapy, paraffin baths, short-wave or microwave diathermy) and ultrasound. Cold applications (ice) after exercise are also beneficial. Joint immobilization should be avoided because it can lead to rapid progression

of OA (3). Reducing body weight to ideal weight is important in improving functional capacity and slowing the processes that lead to further disability (4). The use of adaptive mobility aids (e.g., canes and walkers) and assistive devices at home (e.g., elevated toilet seats) is also an important aid in joint protection and safety (5). If a cane is used for hip or knee OA it should be carried in the contralateral hand and advanced with the affected (ipsilateral) leg. Appropriate cane length equals the height of the greater trochanter.

C. Pharmacologic management.

Approaches include acetaminophen, salicylates, traditional nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (Cox-2)–selective NSAIDs (e.g., celecoxib and rofecoxib), and intra-articular steroids. Acetaminophen is advocated for use as the first-line therapy by some authors (6), but salicylates and NSAIDs are still the most commonly used first-line medication for the relief of pain related to OA. Frequently prescribed NSAIDs used for OA include ibuprofen, naproxen, diclofenac, piroxicam, and sulindac. Intra-articular steroids are generally reserved for the instance of a single painful joint unresponsive to other modalities. Adverse effects of salicylates and NSAIDs include dyspepsia, gastrointestinal (GI) bleeding, interference with platelet function, and hepatic and renal dysfunction. Because of the potential adverse effects of chronic use, especially in the elderly, it is better to prescribe shorter courses at the lowest effective dose. In patients at high risk for GI bleeding (older than 75 years, renal dysfunction, history of GI bleeding, and concomitant use of anticoagulant medicines), use of a Cox-2 inhibitor may be as effective, more expensive, but a safer substitution for a traditional NSAID (7).

D. Surgical intervention.

Arthroscopic lavage and osteotomy are surgical approaches used to decrease the pain of OA of the knee, but total joint replacement is the primary surgical intervention for OA of the knee and hip. Indications for joint replacement are intractable pain and decline in function.

E. Psychosocial issues.

Depression, anxiety, and poor coping skills related to the patient's disability can contribute to impairment and should be addressed. Involvement in community support groups (e.g., Arthritis Foundation) may be beneficial.

F. Topicals.

There is preliminary evidence that topical 0.025% capsaicin cream applied qid to all four sides of the knee can reduce pain over a 4-week period.

G. Alternative medicines

(see Chapter 22.3). It is important to ask patients about the use of alternative medicines as there is an increasing frequency of their use. There is some preliminary evidence that glucosamine and chondroitin sulfate may have a mild short-term effect in terms of decreasing symptoms of OA (8). There are no data on the long-term safety of continued usage, but in the short term these drugs appear safe. In the United States both are marketed as unregulated nutritional supplements. There is even less evidence to support the use of other alternative medicines, including copper bracelets, magnets, and collagen hydrolysates.

IV. Prevention

B. Primary prevention.

Primary prevention aims at weight reduction, avoidance of traumatic injury, prompt treatment of injury, and work site programs designed to minimize work-related mechanical joint stress.

C. Secondary prevention.

This includes screening for decrements in physical functional status (i.e., activities of daily living, instrumental activities of daily living, and mobility).

D. Tertiary prevention.

Tertiary prevention includes the prescription of appropriate adaptive equipment and mobility aids to reduce disability in the patient with known osteoarthritis.

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15.2
RHEUMATOID ARTHRITIS AND RELATED DISORDERS

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The rheumatic diseases include more than 100 diagnoses. We focus in this chapter on four commonly seen diffuse connective tissue diseases: rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), and systemic sclerosis.

I. Rheumatoid arthritis

A. Definition.

RA is a chronic, systemic, inflammatory synovitis affecting many joints. Diagnostic criteria have 90% sensitivity and specificity if more than four of the following seven criteria are present:

1. Early morning stiffness for more than 6 weeks
2. Arthritis involving more than three joints for more than 6 weeks
3. Wrist, metacarpophalangeal, or proximal interphalangeal (PIP) joint involvement
4. Symmetrical arthritis
5. Rheumatoid nodule or nodules
6. Positive rheumatoid factor titer
7. Bony radiographic changes

B. Clinical presentation

1. History. Onset is usually indolent, with early malaise and fatigue (indicating the systemic nature of the disease). Morning stiffness (usually lasting more than 60 minutes) and joint symptoms in areas described above under diagnostic criteria.
2. Physical examination (see diagnostic criteria above). Inability to make a complete fist suggests arthritis of the joints of the hand. Proliferative synovitis with effusions and limited articular motion are important but easily overlooked clues to the diagnosis. Rheumatoid nodules, found in 20%–25% of patients, are located periarticularly in areas subject to pressure.
3. Laboratory findings. Laboratory findings are often not very useful for diagnosis; they are more useful in defining other causes of arthritis. Up to 30% of patients with RA have a negative test result for rheumatoid factor (and false-positive results occur in infections, primary lung and liver disease, and other rheumatic diseases).
4. Radiography. Single posteroanterior views of involved joints, often the hands and wrists, are useful for diagnosis. Radiographic findings are

uniform joint space narrowing, periarticular osteoporosis, marginal “rat-bite” erosions at the junction of articular cartilage, and inflamed synovium.

C. Treatment.

New evidence suggests that joint damage begins early in the disease and that long-term outcomes have been poor with conventional therapy (1). Therefore, early aggressive therapy is advocated to prevent or delay joint destruction. Although nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin therapy may control symptoms, the opportunity to control the disease may be lost if more potent therapies are not initiated early.

1. NSAIDs. No NSAID is more effective than aspirin, and all are associated with gastrointestinal (GI) side effects. Dosing is often more convenient than that for aspirin. New NSAIDs, selective for cyclooxygenase-2 (COX-2) inhibition, produce equivalent pain relief with reduced gastrointestinal (GI) complications when compared with nonselective NSAIDs. Celecoxib (Celebrex) is indicated for pain of rheumatoid arthritis at a dosage of 100–200 mg bid (2).
2. Second-line agents are frequently used in combination.
   a. Injectable gold salts. Gold sodium thiomalate (Myochrysine) and aurothioglucose (Solganal) are more effective than oral formulations (3). Give 10 mg IM as a first dose, 25 mg for second and third doses, then subsequent doses of 50 mg/wk to a total of 0.8–1.0 g. If improved, give 50 mg every 2–4 weeks indefinitely. Complete blood count (CBC), platelets, and urinalysis should be performed prior to each injection. Four to six months may pass before any effect is seen.
   b. Antimalarials. Hydroxychloroquine (Plaquenil) can be given at 200 mg PO bid, reduced to 200 mg/d after 3–6 months if improved, for maintenance. This regimen requires a baseline retinal examination, to be repeated every 6 months.
   c. Steroids. These are usually given at low doses (up to 7.5 mg prednisone daily). Ensure adequate bone protection.
   d. Methotrexate (Rheumatrex). Initiate therapy at three 2.5-mg tablets weekly. Discontinue with development of any pulmonary symptoms until they resolve. Eliminate or significantly restrict alcohol. Ensure nonpregnant state and adequate birth control. Monitor CBC and liver function tests every 4–8 weeks. Supplement with folic acid, 1 mg/d (4).
   e. Biological therapies. Tumor necrosis factor (TNF) inhibitors (injectable preparations that block TNF-α) may dramatically suppress disease activity. Etanercept (Enbrel) and infliximab (Remicade) have been effective in reducing signs and symptoms of RA in patients whose disease is refractory to methotrexate.
3. Consult with a rheumatologist for initial therapy and the development of a plan for follow-up by the primary care physician. Uncontrolled swelling should suggest additional consultation at any time during the course.

D. Prevention.

There are no preventive measures for RA. Early aggressive therapy appears to be the best option for prevention of disease progression and disability.

II. Juvenile rheumatoid arthritis.

Characterized by chronic synovial inflammation of unknown cause, JRA may develop at any age. However, onset is usually before age 16 years, with girls affected more often than boys.

A. Clinical presentation.

There are three onset subtypes:

1. Systemic onset (Still's disease). The patient has a toxic appearance with spiking fevers, evanescent centripetal salmon-pink rash, generalized lymphadenopathy, hepatosplenomegaly, and pericardial or pleural effusions. Tests for rheumatoid factor (RF) and antinuclear antibody (ANA) are rarely positive. Polyarthritis usually develops within weeks

to months of disease onset. About 20% of children with JRA have a systemic onset.

2. Polyarticular onset. Multiple joint involvement without dramatic systemic symptoms occurs in 40% of children with JRA. Malaise, growth retardation or weight loss, low-grade fever, mild adenopathy, and anemia are sometimes present. RF-positive children with polyarticular-onset JRA have a worse prognosis, more rheumatoid nodules, and more vasculitis than those who are RF-negative.
3. Pauciarticular onset. This type of occurs in 40% or more of children with JRA. Four or fewer joints are involved in the first 6 months of the disease.
   a. Early-onset subgroup. Age of onset is under 6 years, and most of those affected are female; patients are usually positive for ANA and negative for RF. Knees, ankles, wrists, or elbows are usually involved. Hips are spared, and sacroiliitis is absent. This form of the disease has no systemic features, except iridocyclitis, which develops in 10%–60% of patients (see Section C, Prevention).
   b. Spondyloarthropathy subgroup. This type predominantly affects boys with asymmetrical arthritis, mostly in lower extremity joints; 50% are HLA-B27 positive.

B. Treatment.

Early diagnosis and appropriate therapy are important to minimize disability and deformity. Seventy-five percent of patients have long remissions. Many patients complain little of joint pain but limit or modify motion due to pain. Decreased activity, morning stiffness, and “gelling” are common.

1. Aspirin may be used, although most experts advocate the use of NSAIDs due to fear of Reye's syndrome.
   a. Dosage is 80 mg/kg per day, up to 120 mg/kg per day if symptoms are not controlled on lower doses (serum level should be 18–25 mg/dL).
   b. Reye's syndrome occurs more frequently in children treated with aspirin for chickenpox and influenza. Aspirin should be discontinued briefly during infections with varicella, influenza, or unknown suspected viral illness.
2. The NSAIDs tolmetin and naproxen are approved in patients as young as 2 years. Ibuprofen and naproxen are available as elixirs.
3. If NSAIDs are incompletely effective, intramuscular gold may be considered. The recommended dosage is 1 mg/kg per week (up to 50 mg/dose). Monitor CBC and urinalysis. Methotrexate and etanercept (2) are being used with increasing frequency.
4. Systemic corticosteroids are avoided except for severe polyarthritis or severe systemic disease unresponsive to more conservative treatment. Disabling pain or flexion contracture may occasionally be treated by intra-articular steroid injection (see Chapter 15.6).
5. Exercise to maintain or regain muscle and joint strength, range of motion, and function.

C. Prevention.

There are no known preventive interventions for JRA. Careful attention to joint function is important. Iridocyclitis is often asymptomatic; early involvement of an ophthalmologist to identify and treat iridocyclitis is mandatory to prevent disability.

III. Systemic lupus erythematosus

A. Definition.

The presence of four or more of the American Rheumatism Association Preliminary Criteria for SLE is a reliable indicator for the diagnosis.

1. Malar rash, tending to spare the nasolabial folds
2. Discoid rash: follicular plugging with alopecia and atrophic scarring in older lesions
3. Photosensitivity

4. Oral ulcers, classically painless
5. Nonerosive arthritis involving two or more peripheral joints
6. Serositis
7. Renal disorder manifested by persistent proteinuria greater than 0.5 g/d or cellular casts
8. Neurologic disorder manifested by seizures or psychosis
9. Hematologic disorder, either hemolytic anemic with reticulocytosis, leukopenia (less than 4,000 cells/μL on two or more occasions) or lymphopenia (less than 1,500/μL on two or more occasions) or thrombocytopenia (<100,000/μL)
10. Immunologic disorder: antibody to double-stranded DNA or Smith antigen
11. Antinuclear antibody

B. Clinical manifestations

1. History. Arthritis or arthralgia is usually the earliest symptom. Skin, hair, and mucous membranes are involved in 85% of cases, ranging from mild malar rash to ulcerations, patchy to diffuse alopecia, and mucosal ulceration. Pleuritis, pericarditis, or a combination of both produces chest pain. Central nervous system (CNS) involvement may result in subtle changes in cognitive function, depression, or a seizure disorder. Almost all patients are fatigued and feel general malaise.
2. Physical examination
   a. Joints. Symmetrical arthritis most commonly involves the PIP joints (80%), followed by wrists, knees, ankles, elbows, and shoulders. Although complaints of joint pain are prominent, usually there is not much objective joint inflammation; therefore, joint destruction is rare.
   b. Other physical findings are as listed in the diagnostic criteria (Section III. A).
3. Laboratory findings
   a. Anemia, elevated sedimentation rate (ESR) or C-reactive protein, and polyclonal gammopathy reflect systemic inflammation.
   b. ANA is present in nearly 100%, but this is a less specific finding, especially at low titer.
   c. Antibodies to native, or double-stranded, DNA are very specific to SLE and fluctuate with disease activity. Increased titers may herald the onset of glomerulonephritis.
   d. For monitoring disease activity, routinely measure CBC, renal function, urinalysis, ESR, and complement (C3 or C4).

C. Treatment

1. For mild, newly diagnosed disease, give maximal doses of salicylates or NSAIDs and hydroxychloroquine, 200 mg once or twice a day. Low-dose corticosteroids can be added.
2. For acute illness with renal or CNS dysfunction, give high-dose corticosteroids, such as prednisone, l mg/kg per day divided q12h, tapered slowly when evidence of active disease subsides. NSAIDs should be used adjunctively. Addition of antimalarials should be considered as tapering of steroids continues. Pulsed high-dose steroid therapy and immunosuppressive agents are used in poorly responsive patients or those with glomerulonephritis, in consultation with a rheumatologist.

D. Prevention.

Currently there are no proven methods for prevention of SLE.

IV. Scleroderma (systemic sclerosis)

A. Definition.

Systemic sclerosis (SSc), or scleroderma, is a generalized disorder of connective tissue characterized by fibrosis of skin and visceral organs.

1. Limited SSc (lSSc), or CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia). Skin involvement is limited to distal extremities (beyond knees

and elbows) or above clavicles. Almost all have Raynaud's and esophageal involvement. Calcification and telangiectasias may be seen. Lung involvement is common and manifests as pulmonary hypertension.

2. Diffuse (dSSc). This type of SSc has more widespread skin involvement and more common visceral involvement. Almost all have Raynaud's phenomenon and esophageal disease. Monitor for pulmonary involvement (fibrosis with restrictive lung disease and secondary pulmonary hypertension), GI involvement (primarily esophageal dysfunction), and renal crisis (hypertension, microangiopathic hemolysis, thrombocytopenia, and renal failure).

B. Clinical manifestations

1. History. Most patients present with Raynaud's phenomenon and edematous swelling of fingers; arthralgias may be present. Rarely, esophageal symptoms present first.
2. Physical findings include edema of hands or feet, followed by thickening of skin of fingers (sclerodactyly). The patient may have digital pits secondary to Raynaud's phenomenon. Other CREST features or visceral involvement may be seen, as described in Section IV.A.1 and Section IV.A.2 .
3. Laboratory findings. Most patients are positive for ANA; a nucleolar pattern is associated with dSSc and a centromere pattern with lSSc. ESR is often normal. Screen for visceral involvement with chest radiograph, CBC, urinalysis, creatinine, and pulmonary function tests with diffusion capacity of carbon monoxide (D_LCO).

C. Treatment.

Evaluation of treatment of SSc is difficult because of the disease's slow progression, the tendency for spontaneous improvement, and limited objective criteria for determining improvement or deterioration. The main goal is prevention of complications (5).

1. Raynaud's disease, or digital gangrene, should be managed with nifedipine (or other calcium channel antagonists), 10 mg tid titrated to effective doses; the extended-release form may be tried. Antiplatelet therapy (aspirin, 81–325 mg/d) may be tried. Protect extremities in particular as well as the entire body from cold.
2. Avoid corticosteroids.
3. Monitor blood pressure intensively and make early use of angiotensin-converting enzyme inhibitors to prevent renal crisis.
4. Consider penicillamine for skin disease (start with 250 mg/d and titrate upward to 750–1,000 mg/d). Monitor for adverse effects.
5. Perform routine pulmonary function testing with D_LCO to screen for pulmonary fibrosis and pulmonary hypertension.
6. Take standard antireflux measures. Promotility agents may be helpful. Rotate antibiotics for malabsorption syndromes.

D. Prevention.

No preventive interventions are available for scleroderma. Interventions to prevent complications are as noted above (Section IV.C).

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15.3
FIBROMYALGIA

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Fibromyalgia is a nonarticular rheumatologic syndrome characterized by widespread musculoskeletal pain and tenderness on palpation at characteristic sites, called tender points. Nonmusculoskeletal symptoms often accompany the nonarticular musculoskeletal pain. Fatigue, sleep disturbance, anxiety or depression, headache, irritable bowel syndrome, dysmenorrhea, and paresthesias are among the more common nonmusculoskeletal features.

I. Diagnosis

B. History.

Fibromyalgia occurs predominantly in women; only 5%–20% of fibromyalgia patients are men. The most common age of presentation is 40–50 years; whites predominate in most series. The prevalence in the general population is 4%–10%. Pain is the cardinal symptom and is widespread. According to the American College of Rheumatology, the pain must be above and below the waist, on both sides of the body, and along the axial skeleton (1). Associated nonmusculoskeletal symptoms are commonly seen; these include fatigue, sleep disturbance (with a characteristic alpha wave intrusion on delta rhythm sleep on the polysomnogram), headache, irritable bowel syndrome, dysmenorrhea, and paresthesias. Anxiety and depression are common. There is also frequently an overlap with chronic fatigue syndrome (2).

C. Physical examination.

There must be tenderness on digital palpation (using 4 kg of force, or enough to blanch the nail bed of the thumb) in at least 11 of the following 18 (9 pairs of) tender point sites:

1. Occiput: bilaterally at the suboccipital muscle insertions a few centimeters below the nuchal ridge
2. Low cervical: bilaterally at the anterior aspects of the intertransverse spaces at C5–C7, corresponding to the upper trapezius trigger point of Travell (3)
3. Trapezius: bilaterally at the midpoint of the upper border of the trapezium, corresponding to the supraspinatus tendon area
4. Supraspinatus: bilaterally above the medial border of the scapular spine, corresponding to the middle trapezius myofascial trigger point of Travell
5. Second rib: bilaterally at the second costochondral junctions, probably representing costochondritis
6. Lateral epicondyle: bilaterally 2 cm distal to the epicondyles, probably representing lateral epicondylitis or extensor-supinator enthesitis
7. Gluteal: bilaterally in the upper outer quadrants of the buttocks in the anterior fold of muscle and corresponding to the multifidus myofascial trigger point of Travell
8. Greater trochanter: bilaterally just posterior to the trochanteric prominence and probably representing a trochanteric bursitis
9. Knee: bilaterally at the medial fat pad proximal to the joint line and corresponding to anserine bursitis

D. Laboratory studies.

There are no routine laboratory markers for fibromyalgia. Specifically, the complete blood count and erythrocyte sedimentation rate are normal. Rheumatologic serologies are not diagnostic. Although abnormalities in T-cell subsets have been described, these tests are not recommended for routine use at this time.

II. Treatment of fibromyalgia

B. Injection.

The tendonitis, bursitis, and costochondritis tender points (lateral epicondyle, trapezius, greater trochanter, knee, and second rib) may be injected with lidocaine (Xylocaine) and corticosteroid (see Chapter 15.6).

C. Stretch and spray.

The myofascial trigger points of Travell (occiput, low cervical, supraspinatus, and gluteal tender points) may be stretched and fluormethane vapocoolant applied; alternatively, these may be injected with 0.5% procaine (3).

D. Pharmacotherapy.

Low-dose selective serotonin reuptake inhibitors, such as fluoxetine (Prozac), 10–20 mg/d, or paroxetine (Paxil), 5–l0 mg/d, or low-dose heterocyclics, such as amitriptyline (Elavil), 10–50 mg/d, or cyclobenzaprine (Flexeril), 10–30 mg/d, are recommended (see Chapter 5.2). Nonsteroidal drugs may also be tried. Tramadol (Ultram) may also prove useful for the treatment of fibromyalgia pain (4).

E. Exercise.

Low-impact aerobic fitness training has proved to be of benefit in fibromyalgia (5). Gentle stretching is probably also beneficial.

F. Behavioral therapy.

Electromyographic biofeedback training and cognitive-behavioral therapy have proven benefit in patients with chronic fibromyalgia symptomatology (5).

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15.4
GOUT

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Gout is an inflammatory disease caused by the deposition of uric acid crystals in and around joints, subcutaneous tissues (tophi), and kidneys. Uric acid is a product of purine oxidation. Gout typically presents as an acutely painful monoarticular arthritis that may progress to chronic arthritis after years of progressively more severe and frequent episodes interspersed with variable symptom-free periods. Hyperuricemia is a marker for gout, but they are not one and the same; each can exist without the other. Approximately 40% of patients have normal uric acid levels during an acute episode of gout (1). However, the risk of gout is proportional to the degree and duration of hyperuricemia. Primary hyperuricemia results from inborn errors of metabolism, either reduced excretion (90% of patients) or increased production (10%) of uric acid. Secondary hyperuricemia associated with gout is the result of other diseases or drug therapies that raise uric acid levels. The family physician must be adept at diagnosing and treating acute flares of gout as well as minimizing recurrences and progression to chronic gouty arthritis.

I. Diagnosis.

A. Clinical presentation.

Gout primarily affects middle-aged men (ages 40–60) and postmenopausal women. The first metatarsophalangeal (MTP) joint is involved in 50% of initial acute gouty attacks (podagra), and 75%–90% of gout patients have first MTP involvement eventually. This is probably due to the first MTP's propensity to microtrauma and its relative coolness

compared with the rest of the body. Pain, swelling, redness, and exquisite tenderness develop suddenly in the joint and often the surrounding area. The heel, ankle, knee, midtarsal joints, and olecranon bursa can all be initially involved but less frequently than the first MTP. Gout severity ranges from vague aches and pains of low-grade polyarticular gout to dramatic attacks of extreme monoarticular pain to chronic polyarticular joint swelling, deformity, and disability. Even in untreated gout, acute attacks resolve within several days to weeks. Acute attacks of gout are less common in elderly people, in whom it may present insidiously with a chronic polyarticular arthritis associated with subcutaneous tophaceous deposits on the fingers, toes, and elbows, which may be misdiagnosed as rheumatoid arthritis (2).

B. Synovial fluid examination.

Presumptive diagnosis of acute gout can be made based on clinical signs and symptoms, a negative joint culture, hyperuricemia, and a significant response to colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs). However, definitive diagnosis requires examination of synovial fluid or tophi, looking for needle-shaped urate crystals. These are found inside synovial fluid phagocytes or free within tophaceous deposits and are strongly negatively birefringent under a polarized microscope lens. The calcium pyrophosphate crystals of pseudogout are, on the other hand, weakly positively birefringent and rhomboid.

II. Clinical stages of primary gout

A. Asymptomatic hyperuricemia.

Defined as uric acid levels greater than 8 mg/dL in men and more than 7 mg/dL in women, hyperuricemia is present in about 5% of the U.S. male population, of whom 5% will develop acute gout. Levels normally rise during puberty in men and in women after menopause. It normally takes 20–30 years of hyperuricemia before a patient has his first episode of gouty arthritis. Treatment of asymptomatic hyperuricemia is not routinely recommended because of expense, potential drug toxicity, and the low risk of renal complications. Lowering the serum urate level does not protect the patient from “gouty nephropathy.” Chronic renal disease is almost always due to concurrent diseases, such as hypertension and diabetes, rather than gout itself (see Chapter 9.1 and Chapter 17.2).

B. Acute gouty arthritis

1. Associated factors. Gout is historically associated with overeating and alcoholic binges. Approximately half of gouty individuals weigh 15% or more than ideal body weight, and three fourths or more exhibit hypertriglyceridemia, which correlates with obesity (3). Dietary excesses of purine-rich food (e.g., sweetbreads, sardines, anchovies, kidney, liver, bacon, veal, turkey, scallops, and mussels) can also contribute. Ethanol metabolism increases serum lactate, which blocks renal uric acid excretion, leading to gouty attacks. Other factors provoking gouty attacks include rapid changes (either up or down) in serum uric acid levels, infection, surgery, and emotional stress.
2. Timing of gouty attacks is quite variable and unpredictable. After an initial gouty arthritis attack, it may be weeks or decades before the next one. However, gout recurs within 1 year in more than half of patients. As time passes, gouty attacks tend to occur more frequently, with less time between attacks, greater severity, and polyarticular involvement; in addition, the attacks take longer to respond to therapy. For unknown reasons, gouty attacks may be slightly more common in spring.
3. Differential diagnosis. Gout in the elderly is often polyarticular and involves upper extremity joints (especially proximal interphalangeal joints and distal interphalangeal joints). Women present 70% of the time with polyarticular disease rather than the classic monoarticular arthritis seen in men (4). Gout can be misdiagnosed as inflammatory osteoarthritis, particularly given that erosions on radiographs are seen in both conditions (see Chapter 15.1). Gout may be mistaken for

rheumatoid arthritis because tophi may resemble rheumatoid nodules and rheumatoid factors often become weakly positive as people age (see Chapter 15.2). It may be difficult to differentiate cellulitis or septic arthritis from gout, particularly when a low-grade fever, leukocytosis, redness, or desquamation is present. The term pseudogout, for calcium pyrophosphate deposition disease, belies the difficulty in clinically differentiating it from gout. For definitive diagnosis, joint fluid must be aspirated for culture and a search for urate crystals.

C. Intercritical or interval gout.

During the intervals between acute gouty attacks, patients with early gout are virtually asymptomatic. Intercritical gout describes these symptom-free periods. Urate crystals can be aspirated from quiescent joints during these interval periods; therefore, the finding of urate crystals during an acute episode provides little reassurance of a nonseptic cause, and antibiotic therapy should be based on clinical presentation, Gram's stain, and culture (5). Crystals remain present in joints as long as hyperuricemia persists; when serum uric acid levels are reduced to normal, urate crystals slowly dissolve and finally disappear from the joint.

D. Chronic tophaceous gout.

has become increasingly rare due to more widespread drug treatment for hyperuricemia and gout. Tophi without prior episodes of gouty arthritis are unusual because they normally occur after gout has been present for more than 10 years. Tophi can occur anywhere but tend to occur in the helix of the ear, proximal ulnar surface of the forearm, olecranon, Achilles tendon, prepatellar bursa, or near active joints. Tophi are not seen on radiographs unless they are calcified. The classic radiographic finding of chronic gout is sharply marginated erosions proximal to the joint space with an overlying rim of cortical bone. Uric acid calculi can be seen as filling defects on intravenous pyelograms.

III. Secondary gout

is caused by overproduction or underexcretion of uric acid due to drugs or other disease processes. Overproduction of uric acid occurs in myeloproliferative and lymphoproliferative disorders, polycythemia, hemolytic anemia, multiple myeloma, and other malignancies. Renal disease, diuretics, low doses of salicylates, chronic lead intoxication (“saturnine gout”), nicotinic acid, alcohol, ethambutol, and pyrazinamide all cause underexcretion of uric acid. Acute uric acid nephropathy occurs primarily in patients undergoing chemotherapy for hematologic or myeloproliferative disorders and can be prevented by several days of allopurinol administration and adequate hydration before initiation of chemotherapy (see Chapter 18.4).

IV. Therapy of acute gouty attacks.

A. NSAIDs

are considered by most to be the drugs of choice for acute gouty attacks due to their efficacy and the fact that they have relatively few side effects. They are effective, particularly if used at initial high (maximal) doses with rapid tapering over 2–8 days. They may require However, 12–24 hours may be needed before clinical improvement is seen. How soon NSAID therapy is instituted after onset of symptoms is more important than which NSAID is chosen. NSAIDs can cause gastrointestinal (GI) toxicity (nausea, abdominal discomfort, GI bleeding, peptic ulcer disease), nephrotoxicity, and central nervous system side effects (headache, dizziness, confusion), and therefore must be used with caution, especially in the elderly or in patients with underlying disease. Indomethacin has been used for years and is effective at a dose of 50 mg PO q6h for 2 days followed by a tapering dose during the next week. All NSAIDs are about equally effective, although long-acting NSAIDs may be less so.

B. Colchicine

terminates most acute gout attacks within 6–12 hours; however, it is limited by its GI side effects and is often poorly tolerated by elderly people. Colchicine is much more effective if given within the first 12–24 hours of an acute attack. Its mechanism of action is not entirely known but apparently reduces the inflammatory response to urate crystals and diminishes phagocytosis. It is normally given 0.5 mg PO every 1–2 hours until

symptoms abate, GI symptoms (cramps, diarrhea, vomiting) preclude further use, or the maximum total daily dose is reached. Possible bone marrow toxicity limits the total dose for a single day to 5 mg (less if the patient has hepatic or renal disease). Because of oral colchicine's GI side effects, IV colchicine is sometimes used; the clinical response is faster with fewer GI complaints, but the IV form can cause neuropathy, myopathy, bone marrow suppression, and, in rare cases, death. The dose is 2 mg diluted in 20 mL saline and injected slowly over 5 minutes into a freely flowing IV line; extravasation or infiltration can result in painful tissue necrosis. A dose of 0.5–1 mg IV may be repeated every 6 hours up to 4 mg total for a single attack. No additional colchicine should be given for the following week to patients given the full 4-mg IV dose.

C. Corticosteroids.

are normally used in cases when NSAIDs or colchicine cannot be tolerated or are ineffective. Prednisone, 40–60 mg/d PO, can be given for 3–5 days and then tapered over 10 days, but many patients rebound when it is discontinued. Rebound can be avoided by using colchicine prophylactically, 0.5–0.6 mg PO bid, which should then be discontinued 6–8 weeks later. In patients with gout involving only one or two joints or who are unable to tolerate oral therapy, intra-articular corticosteroid injections are useful. These usually result in resolution of an acute gouty episode within 12–24 hours.

D. Adrenocorticotropic hormone.

has been used with success at doses of 40–80 units IV or IM q12h for 2–3 days when other measures fail, including combination therapy with NSAIDs, colchicine, and/or corticosteroids.

V. Therapy of chronic tophaceous gout.

Fortunately, chronic tophaceous gout is becoming less common as prophylaxis and aggressive treatment regimens become more widespread. Colchicine may be used to help prevent acute attacks, and NSAIDs decrease inflammation. Tophi may be mobilized by uric acid-lowering agents. Patients with severe disease may need physical therapy, occupational therapy, and surgery for amelioration of deformities.

VI. Prophylaxis of recurrent gout.

Unless urate levels are very high (>12 mg/ dL), asymptomatic hyperuricemia need not be treated. Urate-lowering drug therapy is generally lifelong with associated potential side effects, particularly in comparison with lifestyle modification including weight reduction, alcohol restriction, and avoidance of loop diuretics or low-dose aspirin therapy. However, two episodes of gouty arthritis or uric acid stone is enough justification for initiating drug therapy to normalize uric acid. Some patients with infrequent attacks or uric acid stones choose not to take a daily uric acid-lowering agent but simply seek treatment when acute attacks arise. For patients with recurrent gouty attacks, renal stones, renal damage, or asymptomatic uric acid levels greater than 12 mg/dL or those who are undergoing cancer chemotherapy or taking cyclosporine after transplantation, uric acid-lowering therapy should be initiated. Although NSAIDs and colchicine do not lower uric acid levels, one of these should be used prophylactically when initiating uric acid-lowering therapy to prevent precipitating an acute gouty attack. The optimal duration of prophylaxis is unknown, but it can usually be stopped after the uric acid level is brought down to a normal range for 2 months. Colchicine, 0.5 mg bid, is less expensive and produces fewer side effects than does long-term NSAID use; it is usually started several days before the urate-lowering agent is started. Patients should also be educated to avoid aspirin, diuretics, alcohol, purine-rich foods, and prolonged fasting because these all raise serum uric acid levels.

A. Allopurinol (Zyloprim)

is a xanthine oxidase inhibitor that decreases production of uric acid. It is effective in most patients regardless of the source of hyperuricemia (overproduction or underexcretion) because it produces a more soluble metabolite. A 24-hour urinary uric acid determination to differentiate urate overproduction from underexcretion is therefore unnecessary in most patients. Allopurinol is also better tolerated than uricosuric agents, has fewer drug-drug interactions, is effective in patients with renal failure or nephrolithiasis, and is used in a single daily dose. In patients

receiving chemotherapy, allopurinol should be used when daily uric acid excretion exceeds 800 mg per 24 hours in male patients and 750 mg per 24 hours in female patients.

1. Dosage and administration. Allopurinol may be started at 100 mg daily with food and increased at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dL or less is attained. The average effective dose for mild gout is 200–300 mg/d, although some patients need 400–600 mg/d, particularly those with tophaceous gout or those on cancer chemotherapy. Enough fluids should be taken to keep daily urine output greater than 2 L. If an acute attack occurs while taking allopurinol, the dose should be maintained as is and the attack treated as usual (e.g., NSAIDs, colchicine). In elderly patients, a starting dose of 50–100 mg on alternate days, to a maximum daily dose of 100–300 mg based on the patient's creatinine clearance and serum urate level, decreases the risk of hypersensitivity reactions (6).
2. Adverse reactions. Life-threatening hypersensitivity reactions involving skin, kidney, and liver occur rarely but are being recognized with increasing frequency. The most frequent adverse reactions to allopurinol are skin rash, GI reactions (diarrhea, nausea, and alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase elevations), and acute attacks of gout, which can be minimized by proper use. Renal function must be monitored in patients taking thiazide diuretics. Allopurinol may also cause a rash in patients taking ampicillin or amoxicillin, and it may potentiate anticoagulants.

B. Uricosuric drugs.

block renal tubular reabsorption of uric acid. As with allopurinol, they should never be started during an acute attack but should be maintained if an acute attack occurs when the patient is already on them. Before using these agents, a 24-hour urine for creatinine clearance and urine uric acid should be performed, as uricosuric drugs are ineffective for a glomerular filtration rate less than 50 mL/min and can increase the risk of urate stones if the urinary uric acid is already elevated (800 mg per 24 hours). Urate stone formation can be minimized if patients maintain a high fluid intake and alkalinize the urine.

1. Probenecid (Benemid) is started at 250 mg bid for 1 week and then 500 mg bid. The dose is increased by 500 mg every 1–2 weeks until the serum urate level is normal or the 24-hour uric acid excretion is not above 800 mg. The usual effective dose is 1.0–1.5 g/d. Probenecid is well tolerated. It should not be used with salicylates that antagonize its action. It can raise plasma levels of penicillin, sulfonylureas, and NSAIDs. In patients with glucose-6-phosphate dehydrogenase deficiency, it can cause hemolytic anemia.
2. Sulfinpyrazone (Anturane) is started at 100 mg bid with meals and advanced to full maintenance dosage (200 mg bid) within 1 week. Maximum dosage is 400 mg bid. Upper GI disturbance is the most common side effect. It has similar efficacy and toxicity to probenecid.

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15.5
OVERUSE INJURIES

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Overuse injuries are common musculoskeletal disorders that present to a primary care office. Although these injuries have traditionally plagued the serious athlete or active adult, the incidence of overuse syndromes in children is increasing due to their increasing participation in organized sports. Repetitive motion in the workplace is also a large source of overuse injuries, accounting for more than 50% of all occupational illnesses reported in the United States. Successful management includes establishment of a precise diagnosis, identification of etiologic factors, initiation of effective treatment, and prevention of recurrent injury.

I. Etiology.

The etiology of overuse injuries is multifactorial and involves a complex interaction of predisposing factors that lead to a final common pathway of repetitive microtrauma and local tissue injury. The muscle-tendon unit is the most common site of structural injury, but other structures, such as bone, cartilage, ligament, bursa, and fascia, are also susceptible. The growth plate in the skeletally immature athlete is particularly vulnerable to injury from repetitive stresses. When assessing the etiologic factors for a particular injury, it is useful to classify them into intrinsic and extrinsic factors.

A. Intrinsic factors

are characteristics inherent to an individual's body. Those that commonly predispose to overuse injury include muscle inflexibility, muscle weakness, joint laxity, previous injury, anatomical malalignments, and asymmetries of the lower extremity. Frequently a deficit in one area of the body affects the function of a distal or adjacent region.

B. Extrinsic factors

include equipment, training errors, environmental conditions, and biomechanical or ergonomic errors. Both intrinsic and extrinsic factors are often modifiable, and such modification is an important step toward injury treatment and prevention.

II. Treatment approach.

A. Initial treatment.

is aimed at reducing the inflammatory process and should include relative rest and the use of ice. Ice should be applied to the affected area for 15–30 minutes every 2–6 hours as necessary. Prolonged administration of ice is discouraged to avoid cryo-induced nerve injury to the region. Heat should be avoided as long as pain and edema are present. Pharmacologic intervention, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injection, may also be helpful but should be viewed as a method to reduce symptoms rather than provide definitive treatment.

1. NSAIDs may reduce the initial inflammatory process and provide analgesia. The efficacy of one particular agent has not been proven to exceed that of another. Their potential gastrointestinal (GI) and renal side effects warrant cautious and limited use. Cox-2 inhibitors may lessen potential side effects but have no proven additional efficacy. For chronic overuse injuries, NSAIDs have no proven benefit (1).
2. Modalities such as iontophoresis many also aid in initial inflammation reduction.
3. Corticosteroid injection is another method of controlling symptoms by reducing the inflammatory process. Diagnostic information is also obtained if symptoms abate when a local anesthetic (1% lidocaine or 0.5% bupivacaine) is combined with a corticosteroid. The side effects of corticosteroids include subcutaneous fat atrophy or necrosis, depigmentation or hyperpigmentation, tendon rupture, accelerated joint destruction, and infection. Depending on initial response, if partial relief is obtained with a first injection, a second injection may be considered while an injury is healing.

B. Definitive treatment

includes the identification and modification of intrinsic and extrinsic factors that predispose the individual to an overload injury. Specific exercises that address deficits in strength, flexibility, and proprioception of the affected and adjacent structures should be initiated as early as possible. Eccentric muscle-strengthening exercises are especially useful. Correction of biomechanical abnormalities, such as an incorrect throwing motion or poor ergonomics in the workplace, is also an important part of the treatment program. Abnormal contact forces during gait can be improved with shoe orthoses. Finally, incomplete rehabilitation of a previous injury should be addressed.

III. Overuse injuries of the upper extremity

A. Rotator cuff tendonopathy

is the most common cause of nontraumatic shoulder pain in both children and adults. Subacromial (subdeltoid) bursitis often accompanies a rotator cuff injury, but this is usually a secondary process.

1. Etiology of rotator cuff tendonosis is multifactorial and is often different for children and adults. In children, repetitive eccentric overload, as in the throwing athlete, and underlying glenohumeral instability are common precursors to rotator cuff pathology. Frequent predisposing factors include poor strength of the scapulothoracic and rotator cuff musculature, biomechanical abnormalities, and training errors. In adults, impingement of the supraspinatus tendon as it passes beneath the subacromial arch is the most common cause of rotator cuff tendonosis. Narrowing of the subacromial space, leading to impingement, can result from functional deficits of the surrounding soft tissues or anatomical factors, such as bony encroachment of the anterior acromion or hypertrophy of the acromioclavicular joint. Radiographs are helpful in excluding other causes of persistent shoulder pain, including calcific tendonitis, glenohumeral arthrosis, and bone tumors. A supraspinatus outlet view is helpful to evaluate the bony morphology of the anterior acromion. For diagnostic uncertainties or treatment nonresponders, magnetic resonance imaging (MRI) is useful to help guide treatment.
2. Treatment initially includes ice and a limited course of NSAIDs as well as avoidance of aggravating factors. A subacromial corticosteroid injection combined with a local anesthetic may also be helpful to both confirm the source of symptoms and reduce pain. More definitive treatment involves maximizing glenohumeral range of motion, stabilizing the scapulothoracic articulation, strengthening the rotator cuff, and addressing biomechanical or ergonomic errors. For adults with persistent outlet impingement unresponsive to rehabilitation, referral for surgery may be necessary.

B. Epicondylitis.

is the most common overuse problem of the elbow. Both lateral and medial epicondylitis occur in the workplace as well as in an athletic context.

1. Lateral epicondylitis, often referred to as tennis elbow, is characterized by tenderness over the insertion of the extensor forearm tendons onto the lateral epicondyle of the humerus. Pain often radiates distally along the extensor muscle group of the forearm. Symptoms are reproduced with resistance to wrist extension while the forearm is pronated. Resistance to forearm supination frequently reproduces pain as well.
2. Medial epicondylitis is characterized by pain over the medial humeral epicondyle. Patients often complain of decreased grip strength. Pain is commonly elicited with resistance to wrist flexion and forearm pronation. Management for both lateral and medial epicondylitis is similar.
3. Treatment with ice, relative rest, and a limited course of NSAIDs often provides initial relief. Avoiding pronation activities (“palms up”) and counterforce bracing distal to the epicondyle may also be useful in lateral epicondylitis. When pain persists, a cortisone injection at the site of maximal tenderness may be helpful in controlling symptoms.

Rehabilitation should include stretching and strengthening, especially eccentric strengthening, of the forearm musculature, posterior shoulder strengthening, and biomechanical or ergonomic modifications.

C. Carpal tunnel syndrome (CTS).

is an entrapment peripheral neuropathy that is the result of compression of the median nerve between the transverse carpal ligament and the flexor tendons of the wrist.

1. Symptoms of pain, numbness, or paresthesias occur in the sensory distribution of the median nerve, most commonly in the index finger. The problem may be bilateral in up to 50% of cases. Although CTS has classically been identified in middle-aged women who present with nocturnal pain, this problem is also common in workers involved in repetitive manual labor. Perpetual tasks that require a strong grip with flexion and extension of the wrist or that have vibration exposure are at greatest risk. Increased public awareness of the problem, along with litigation and worker's compensation issues, have resulted in a dramatic increase in the incidence of CTS.
2. Diagnosis is based on a careful medical history and physical examination. The majority of patients experience nocturnal pain that is usually severe enough to wake them from sleep. Important physical findings include a percussion test of the median nerve (Tinel's test) and hyperflexion of the wrist (Phalen's test) to reproduce symptoms. For equivocal symptoms or diagnostic confirmation, electrophysiologic testing can be performed. Other conditions associated with CTS include rheumatoid arthritis, diabetes mellitus, hypothyroidism, amyloidosis, pregnancy, and prior wrist trauma (2).
3. Initial treatment involves identification of specific causes, which are often multifactorial. When potential occupational or recreational causes can be identified, work or activity modification may be all that is required. Other early interventions include nocturnal or job-specific splinting and a trial of NSAIDs. Anecdotally, vitamin B_6 100 mg daily may also be of use. Direct injection of corticosteroid into the carpal tunnel often alleviates symptoms but is usually of transitory value (see Chapter 15.6). For refractory cases, median nerve decompression by incision of the transverse carpal ligament resolves symptoms in well-selected cases.

D. Stenosing tenosynovitis

can be caused by repetitive trauma or activity involving the hands.

1. de Quervain's disease is inflammation of the first dorsal compartment of the wrist (the extensor pollicis brevis and abductor pollicis longus) as it courses over the radial styloid. Pain is reproduced by a sharp ulnar deviation of the hand while the thumb is flexed in the palm (a positive Finkelstein's test). Initial treatment includes relative rest, NSAIDs, and a thumb spica splint. Iontophoresis is a useful modality for early treatment of symptoms. If symptoms persist, local corticosteroid injection into the tendon sheath can be beneficial. When nonoperative measures fail to alleviate the symptoms, surgical release of the compartment may be necessary.
2. Trigger finger involves stenosing tenosynovitis of the flexor tendons of the hand. Although the patient may complain of pain at the proximal interphalangeal joint, the problem is located at the palmar surface of the metacarpophalangeal joint. Most commonly there is inflammation at the A_1 pulley, the first of five pulleys that guide the flexor tendon into the finger. A locking or triggering may occur as the stenosed tendon becomes trapped in the pulley. Treatment is directed at tendon sheath injection with corticosteroid. For persistent or recurrent symptoms, a second injection with subsequent application of a trigger-finger splint is helpful. For those patient who do not respond to injection, surgical correction is required.

IV. Overuse injuries of the lower extremity.

A. Knee

1. Patellofemoral pain syndrome or patellofemoral dysfunction refers to anterior knee pain arising from the patellofemoral joint. Symptoms can range from mild activity-related knee pain to severe pain limiting ordinary daily routine. In general, there is a dull, aching, anterior knee pain exacerbated by activities that require repetitive knee flexion or prolonged sitting. The “theater sign” is anterior knee pain produced by prolonged sitting with the knees flexed. The pain etiology is multifactorial and includes a complex interaction of predisposing factors, such as muscular weakness and inflexibility of the lower extremity, malalignments, and biomechanical abnormalities of gait. Radiographs are most helpful in excluding other diagnoses, such as osteochondritis dissecans. Treatment should be aimed at reducing pain and eliminating predisposing risk factors. After a brief period of relative rest, ice, and NSAIDs, a rehabilitation program should aim at correcting deficits in lower extremity flexibility, strength, and proprioception. Patellar taping techniques to correct malalignments may reduce symptoms. Abnormal foot biomechanics, such as excessive pronation, should also be addressed.
2. Patellar tendonitis, also known as jumper's knee, occurs most commonly in athletes involved in jumping or running. Patients report pain at the inferior pole of the patella. Treatment is similar to that for the patellofemoral pain syndrome.
3. Anserine bursitis involves the anserine bursa, located on the medial aspect of the proximal tibia, deep to the insertions of the semitendinosus, gracilis, and sartorius tendons. Inflammation is most common among elderly women who are overweight. A corticosteroid injection into the bursa usually resolves the symptoms and differentiates anserine bursitis from degenerative joint disease symptoms.
4. Prepatellar bursitis, also known as housemaid's knee, results from recurrent trauma to the prepatellar bursa, which causes chronic inflammation. Acute trauma may also lead to immediate swelling of the prepatellar bursa, as can underlying infection. If infection is suspected, aspiration for Gram's stain and culture and appropriate antibiotics are indicated. Protective padding is an essential part of treatment in recurrent cases. Chronic inflammation may respond to a corticosteroid injection, but there is a substantial risk of infection. For refractory cases, surgical excision of the bursa may be required.

B. Leg

1. Shin splints. Both the name and exact cause of this entity, which is common among runners, dancers, and other athletes, continue to generate controversy. The diagnosis is based on diffuse pain and tenderness at the posteromedial aspect of the tibia (the medial tibial stress syndrome) or, less commonly, the anterior lateral aspect of the tibia (anterior tibialis stress syndrome). Other entities, such as a tibial stress fracture or chronic compartment syndrome, should be included in the differential diagnosis. Contributing intrinsic factors include biomechanical abnormalities and deficits in flexibility and strength of the lower extremity. Extrinsic factors include inadequate or excessively worn footwear, insufficient warm-up, uneven or hard running surfaces, and rapid advancement of a training regimen. Initial treatment includes relative rest, ice massages, and NSAIDs. Occasionally, symptoms persist for weeks, especially if the athlete continues at a high level of activity. At times total rest, including cessation of all athletic activities, is necessary to resolve symptoms. Definitive treatment also includes identification and correction of both intrinsic and extrinsic risk factors as well as a gradual increase to premorbid activity levels.
2. Chronic compartment syndrome occurs in association with athletic activities that involve repetitive weight bearing, such as running or

walking. The key to diagnosis is a history of pain with activity that intensifies with increased activity and is relieved by rest. In contrast, the pain of shin splints is often relieved with continued activity and returns with rest. If activity with a chronic compartment syndrome is not curtailed (“pushing through the pain”), there may be prolonged muscle weakness and persistent pain for several days. The most common locations are the anterior compartment, with pain on the anterolateral leg and the dorsum of the foot, and the deep posterior compartment, with posteromedial and instep pain (3). Treatment includes rest and analgesic relief. With persistence of activity-related symptoms, measurement of compartment pressures before and after activity may be required. For refractory cases with elevated compartment pressure or for the rare cases of an acute compartment syndrome, a surgical fasciotomy may be necessary.

C. Foot

1. Plantar fasciitis involves inflammation of the thick aponeurosis that arises from the os calcis and inserts distally onto the proximal phalanges. This structure is vital to maintain the integrity of foot function and serves as a major shock absorber. In addition to obesity, other contributing factors include excessive foot pronation, poor lower extremity flexibility (especially the gastrocnemius-soleus complex), and decreased calf strength. Planus or cavus feet also predispose to abnormal stresses on the plantar fascia. Clinically, plantar fasciitis is often bilateral and is usually insidious in onset. Typically, the pain is most intense when the patient is arising in the morning, with symptomatic improvement on continued activity. On physical examination, there is frequently a single area of severe pain slightly anterior to the medial calcaneal tubercle. Radiographs may show a spur on the inferior distal os calcis, but this is found in many asymptomatic patients and is not pathognomonic. The exact origin of pain from plantar fasciitis remains controversial, but most likely the pain emanates from an enthesopathy or nerve entrapment rather than from the actual bone spur. Initial treatment involves relative rest, appropriate shoe support, and frequent calf stretching. As a second step, night splints with the foot and great toe in slight dorsiflexion may be helpful, as may physical therapy and orthotics. Corticosteroid injections may be helpful in refractory cases, especially in nonathletic individuals. Rarely, surgical intervention is necessary to relieve the symptoms.
2. Achilles tendonitis is another overuse injury caused by repetitive weight-bearing activities. Pain and swelling occur in the tendon, usually 4–7 cm proximal to the calcaneal insertion in a watershed area of relatively poor vascular supply. Dorsiflexion of the foot or local palpation reproduces the symptoms, and the patient may walk with a limp. Initial treatment consists of relative rest, NSAIDs, and ice, along with gentle stretching exercises. Due to the risk of chronicity, early referral for a physical therapy program should be added to address flexibility, resolve strength deficits, and correct foot biomechanical problems.

D. Stress fractures

are created when the repetitive weight-bearing activity of the legs causes the bony architecture to exceed a given threshold (see Chapter 3.6). Although stress fractures commonly occur in athletes who have suddenly increased their training regimen, they may also occur in any patient with a recent increase in activity level or even without activity change when there are other predisposing factors, such as poor biomechanics or osteopenia. In general, women are more susceptible to stress fractures than men.

1. Diagnosis of a stress fracture is based on the history of a gradual increase in pain that resolves with rest, along with point tenderness over the bone. Although radiographs are often normal until 2–4 weeks from the onset of symptoms when reactive sclerosis is evident, some stress

fractures have continued normal radiographs (4). A bone scan can provide diagnostic confirmation as early as 3 days after injury. The most common sites for stress fractures are the metatarsals (especially the second and third), the tibia (common among runners), and the fibula (5).

2. Classification of stress fractures into “at risk” and “not at risk,” based on their potential for long-term morbidity, is a useful approach to management. At-risk stress fractures have a greater potential to result in delayed union or nonunion, bone displacement, or completion of the fracture. These stress fractures often require individualized and prolonged management (Table 15.5-1). Orthopedic consultation is advisable for at-risk fractures.

Location	Frequency	At risk for long-term morbidity	Physical finding	Immediate treatment
Second and third metatarsals	Common	No	Localized tenderness	Rest; symptomatic
Proximal fifth metatarsal	Occasional	Yes	Localized tenderness	Non–weight bearing, casting vs. surgery
Tarsal navicular	Occasional in track and field	Yes	Midfoot pain	Non–weight bearing, casting
Proximal tibia	Common	No	Localized tenderness	Rest; symptomatic
Distal tibia	Common	No	Localized tenderness	Rest; symptomatic
Midtibial anterior cortex	Rare	Yes	Anterior shin pain	Prolonged rest; occasionally surgery
Fibula	Common	No	Localized tenderness	Rest; symptomatic
Femoral shaft	Occasional	No	Thigh pain	Rest; symptomatic
Femoral neck	Rare	Yes	Groin pain	Non–weight bearing, orthopedic referral

Table 15.5-1. Stress fracture identification

3. Immediate treatment for stress fractures that are not at risk includes relative rest, periodic ice, and analgesics (Table 15.5-1). Pain relief should be obtained within 1–2 weeks. Non-weight-bearing activities, such as stationary bicycling or swimming, as well as muscle stretching, should be encouraged until pain subsidence indicates healing. Once complete pain relief is achieved, a gradual resumption of activities can be permitted, with appropriate counseling of injury prevention. In female athletes, a menstrual history should be obtained, looking for a primary or secondary amenorrhea, which is associated with osteopenia and thus a higher incidence of stress fractures.

V. Overuse syndromes in the skeletally immature athlete

(also see Chapter 4.7)

A. Osgood-Schlatter condition

, a traction apophysitis that occurs as the patella tendon inserts on the tibial tuberosity, is a common complaint among peripubertal adolescents. Caused in part by the longitudinal forces created by rapidly growing bones, Osgood-Schlatter disease is associated with an increase in physical activity. There is localized edema and tenderness over the tibial tuberosity. Several days or weeks of relative rest, along with appropriate analgesics, reduces the symptoms to a manageable level, although some pain may persist. A bony prominence may remain due to residual fragmentation of the upper tibial epiphysis. Improvement in lower extremity flexibility, especially in males, may help reduce symptoms. For refractory cases, emphasis on prolonged rest of several weeks may be necessary to alleviate symptoms.

B. Sever's condition.

is a calcaneal apophysitis, similar in etiology to Osgood- Schlatter disease, which occurs in adolescent males. This entity is seen most commonly in soccer players. Inflammation at the insertion of the calcaneal apophysis leads to localized pain, tenderness, and swelling, which may be aggravated by activity. Treatment includes ice, relative rest, judicious calf stretching, and possibly a temporary heel lift.

C. Little leaguer's

elbow is a term used to denote a group of overload injuries of the elbow that result from repetitive stresses in the skeletally immature thrower. The most common of these include (a) fragmentation or avulsion of the medial epicondyle, (b) stress reaction to the apophysis of the medial epicondyle, (c) osteochondrosis of the capitellum, and (d) olecranon apophysitis. Pitchers are most susceptible to this entity, which is aggravated by an excessive number of innings pitched per week. Other predisposing factors include improper warm-up, poor throwing mechanics, and throwing of curve balls. There is pain with the throwing motion and usually localized tenderness over the medial epicondyle. Radiographs are important to exclude bony abnormalities associated with little league elbow. Initial treatment includes rest, ice, and occasionally a short course of NSAIDs. The patient may play a less demanding position (i.e., first base) when symptoms subside as long as he or she remains pain free while throwing. Stretching and strengthening of forearm, shoulder, and scapulothoracic musculature constitutes the mainstay of rehabilitation. A biomechanical analysis of the throwing motion is also advised before return to play. Osteochondrosis of the capitellum often requires further diagnostic workup and may necessitate surgical intervention.

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15.6
ARTHROCENTESIS AND JOINT AND SOFT-TISSUE INJECTIONS

Michael James Henehan

The removal of joint fluid (arthrocentesis) and intra-articular or soft-tissue injection of medication are common primary care procedures. The indications and techniques for these procedures are outlined in this chapter.

I. Indications.

A. Arthrocentesis.

(Fig. 15.6-1)

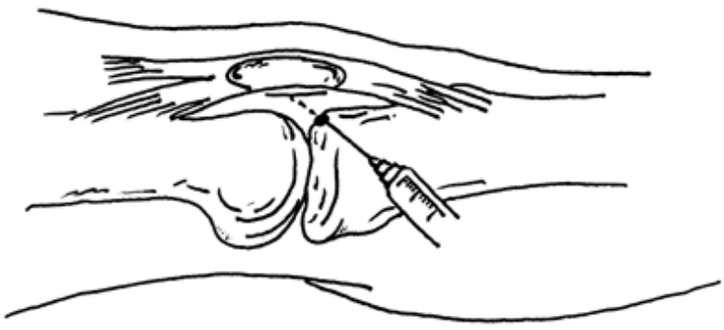

FIG. 15.6-1. Arthrocentesis of the knee.

1. Arthrocentesis can be helpful in evaluating a joint effusion of uncertain etiology. The differential diagnosis includes septic arthritis, aseptic inflammation (rheumatologic process), degenerative changes, and traumatic effusion (hemarthrosis).
2. In rare instances, repetitive joint aspiration is indicated to relieve pain and restore joint range of motion. In general, treatment of the underlying problem is preferred because otherwise the joint fluid will reaccumulate rapidly, and repeated arthrocentesis risks a joint infection.

B. Intra-articular and soft-tissue injection.

(Fig. 15.6-2)

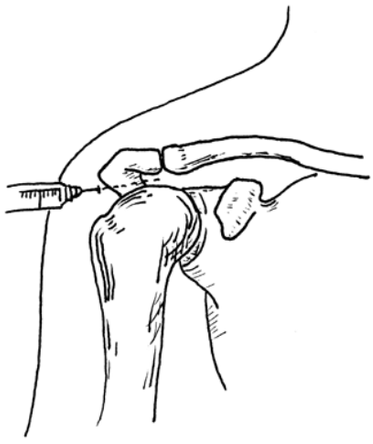

FIG. 15.6-2. Injecting the subacromial space: lateral approach.

1. **Diagnostic.** Intra-articular and soft-tissue injection can be helpful in differentiating the source of pain.
2. **Therapeutic**
   a. Therapeutic injections relieve inflammation in tendon sheaths, bursae, muscles, and joints in inflammatory, noninfectious arthropathies.
   b. Therapeutic injections provide adjunctive therapy for joints and soft-tissue inflammation not responsive to systemic therapy.

II. Risks and risk management.

A. Intravascular injection.

Always aspirate back before injecting. If blood is aspirated, redirect the needle and proceed again.

B. Tendon rupture.

Avoid injecting directly into a tendon. Ideally, the medication should be injected into the surrounding bursa or tendon sheath. Allow 2 weeks before reinjecting or permitting significant load bearing when injecting around large tendons.

C. Hypersensitivity.

Ask about allergies before injecting.

D. Infection.

Use sterile technique, and avoid multiple injections.

E. Anatomical hazards.

Review the anatomy to avoid accidentally hitting nerves, large blood vessels, or organs.

F. Hematoma.

Apply a pressure dressing.

G. Postinjection pain.

Pain occurs in about 5% of patients. It is thought to be a local inflammatory response. The pain usually lasts 24–36 hours and occurs within hours of the injection.

H. Tissue atrophy.

Fat degeneration can occur due to the catabolic properties of corticosteroids. The more superficial the injection, the more likely atrophy is to occur.

I. Skin discoloration.

This is usually a lightening of pigmentation due to the corticosteroid. The change is most pronounced in dark-skinned individuals. It is most likely to occur with superficial injections.

III. Contraindications to joint injection.

A.

Suspicion of septic arthritis or bacteremia

B.

oagulopathy

C.

Cellulitis overlying the site of the injection

D.

More than three steroid injections in a weight-bearing joint during a 12-month period (relative contraindication)

IV. Supplies.

A.

Antiseptic solution (e.g., povidone-iodine)

B.

yringes. A 10- to 30-mL syringe is used for arthrocentesis, and a 3- to 10-mL syringe for joint or soft-tissue injection.

C.

eedles. A 16- to 18-gauge 1.5-in. needle is used for arthrocentesis, and a 25-gauge 1.5-in. needle for joint or soft-tissue injection.

D.

edication. Local anesthetic may be used prior to arthrocentesis. Steroid and anesthetic are used for intra-articular or soft-tissue injection.

E.

ther supplies. Specimen containers, gauze pads, sterile gloves, sterile drapes, and plastic strips bandages are needed. A sterile hemostat is helpful to grasp the needle hub if the syringe must be removed to empty the aspirate or switch to another syringe.

V. Selecting medications.

One percent lidocaine (Xylocaine) alone is injected for diagnostic trials; O.5% bupivacaine (Marcaine) can be used if a longer anesthetic effect is desired. If inflammation is suspected, a steroid may be added. Typically, either a long-acting steroid is injected, such as betamethasone (Celestone Soluspan), or an intermediate-acting steroid, such as methylprednisolone acetate (Depo-Medrol). Lidocaine, bupivacaine, and the steroid can be mixed in the same syringe.

VI. Technique.

A. Arthrocentesis.

1. Obtain informed consent.
2. Use sterile technique, including sterile skin preparation.
3. Decide what equipment and medication you will need and have it available before you start the procedure.
4. Synovial fluid can be very viscous, and a large-bore needle (i.e., 18-gauge) is needed to aspirate the fluid.
5. When using a large-bore needle, local anesthetics are helpful. One percent lidocaine superficially injected using a 27- or 30-gauge needle (i.e., a tuberculin needle and syringe) provides adequate anesthesia. Ethyl chloride sprayed on the skin immediately before inserting the needle can also be helpful.
6. During aspiration of a joint, the fluid generally flows easily. If fluid is not immediately aspirated on entering the joint, the needle can be gently repositioned while suction is maintained on the syringe.
7. If the joint is to be injected after aspiration, leave the needle in place and change the syringe to inject the medication. This ensures that you are injecting into the joint. A sterile hemostat is helpful in removing the needle from the syringe while keeping the needle positioned in the joint.
8. The total volume of fluid (anesthetic and steroid) as well as the steroid dose depends on the joint size. In general, smaller joints require less steroid and a smaller injection volume (Table 15.6-1).

Structure to be injected	Total volume of injection (lidocaine + steroid)	Dose of steroid
Small joints (e.g., digits, acromioclavicular joint) Soft-tissue structures (e.g., tendom sheaths, carpal tunnel)	0.5–1.0 mL	Betamethasone (or equivalent), 0.5–2 mg; methylprednisolone (or equivalent), 4–10 mg
Medium joints (e.g., ankle, elbow) Soft-tissue structures (e.g., subacromial space, trigger points, bursae, epicondylitis)	1–5 mL	Betamethasone (or equivalent), 2–4 mg; methylprednisolone (or equivalent), 20–40 mg
Large joints (e.g., knee)	3–10 mL	Betamethasone (or equivalent), 4–6 mg; methylprednisolone (or equivalent), 30–80 mg

Table 15.6-1. Volume of injections and steroid dosages

B. Soft-tissue injection.

1. Follow steps 1–3 in Section VI.A .
2. Local anesthetic is generally not needed to inject a joint or soft-tissue structure.
3. During injection of a soft-tissue structure or joint, the fluid should flow easily. If it does not, you may be injecting into the tendon or may not

be in the joint. Gently reposition the needle and attempt to inject again. Always aspirate before injecting to avoid undesired intravascular injection of medication.

4. Soft-tissue injections work best when the fluid is infiltrated into several parts of the inflamed area. This can be done by fanning out the injection (Fig. 15.6-3). With this technique, the needle is repositioned by bringing the needle tip back to just below the skin surface and then passing it back into a different location within the inflamed tissue. Part of the steroid preparation is injected with each repositioning.

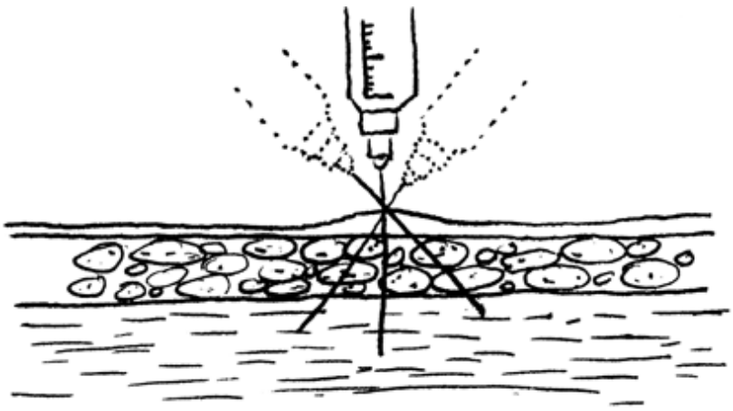

FIG. 15.6-3. Repositioning the needle when injecting soft-tissue structures.

VII. Synovial fluid analysis.

(Table 15.6-2) typically includes appearance, characteristic of mucin clot, cell count, glucose, Gram's stain, culture, and crystal studies. Additional studies that may be helpful in some situations include fungal

studies as well as measurement of lactate dehydrogenase, complement, rheumatoid factor, and antinuclear antibodies.

Characteristic	Normal	Inflammatory	Septic
Color	Clear	Yellow	Cloudy
Viscosity	High	Low	Low
White blood cell count (mm^3)	0–200	2,000–50,000	>50,000
Neutrophils (%)	<25	Variable	>65

Table 15.6-2. Synovial fluid analysis

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XVI. DERMATOLOGIC PROBLEMS

16.1

PYODERMA AND CELLULITIS

Michael L. O'Dell

Pustular skin infections are common complaints in family physicians' offices. Such illnesses are often related to a break in the skin and may have minor or life-threatening implications.

I. Impetigo

A.

Clinical presentation of small-vesicle impetigo begins with small, reddened macules progressing to water-filled vesicles surrounded by a band of erythema. A honey-colored crust follows rupture of the vesicle. *Streptococcus* infection is often the cause of small-vesicle impetigo and, sporadically, impetigo predates poststreptococcal nephritis. *Staphylococcus aureus* infection may cause small-vesicle impetigo as well.

B.

Clinical presentation of bullous impetigo begins as a large flaccid blister or blisters. The blister quickly becomes filled with cloudy, purulent-appearing fluid. Occasionally, staphylococcal scalded skin syndrome accompanies bullous impetigo.

C.

Treatment. Good hygiene speeds healing and helps prevent spread of the illness to others. Systemic therapy is needed in immunosuppressed patients, those with extensive disease, patients with eczema, or those who live in communities that are experiencing an outbreak of poststreptococcal nephritis. Impetigo may be topical with mupirocin (Bactroban) tid for 5 days. If warranted, antistaphylococcal agents, such as erythromycin, a penicillinase-resistant synthetic penicillin (PRSP) [e.g., dicloxacillin (Dynapen), 12.5–50.0 mg/kg per day or 250 mg qid], or cephalosporin may be used.

II. Ecthyma

A.

Clinical presentation. Ecthyma occurs on the legs of the debilitated as small bullae, followed by an adherent crust and then by a slowly healing, ulcerated lesion.

B.

Treat with erythromycin, PRSP, or cephalosporin and attention to nutrition.

III. Folliculitis, furuncles (boils), carbuncles, and hidradenitis suppurativa.

A. Folliculitis

1. Clinical presentation. Lesions appear as yellowish pustules, with an encircling thin band of erythema around hair follicles, generally in the intertriginous areas. Often, patients have diabetes. Hot-tub folliculitis occurs in users of poorly maintained hot tubs.
2. Treatment includes improved hygiene and application of topical agents, such as mupirocin or bacitracin. Presence of extensive lesions warrants erythromycin, PRSP, or cephalosporin. Hot-tub cellulitis is a self-limited illness, but immunocompromised patients should receive antipseudomonal medication.

B. Furuncle

1. Clinical presentation. A tender, fluctuant lesion, with surrounding erythema extending into the subcuticular space, is present. Furuncles more commonly occur in adolescents and in those with poor hygiene, seborrhea, diabetes, or immunodeficiency. Facial furuncles may result in cavernous sinus thrombosis.
2. Treatment for furuncles is drainage. Following drainage, antibiotics are generally not needed. Facial furuncles may require systemic erythromycin, PRSP, or cephalosporin therapy.

C. Carbuncle

1. Clinical presentation. Carbuncles appear as a collection of furuncles, generally on the back of the neck in men older than 40 years.

2. Treatment. Drainage or debridement (or both) is required, and erythromycin, PRSP, or cephalosporin is often needed. Surgical consultation is useful.

D. Hidradenitis suppurativa

1. Clinical presentation. Furunculoid lesions are present in the axillae, inguinal area, scrotum, labia, or mons pubis. They usually occur in males or individuals with acne conglobata.
2. Treatment. Drainage is necessary, and erythromycin, PRSP, or cephalosporin is useful. Retinoic acid is useful where acne conglobata is present. Surgical excision is often necessary.

IV. Erysipelas

A.

Clinical presentation. Erysipelas is an acute illness marked by redness, pain, and swelling in the area of rash, which has a spreading, irregular, but sharply defined border. Lymphatic involvement is prominent. Erysipelas affects all age groups. Patients are often febrile and have an elevated white cell count. Sepsis may occur in the elderly, young children, persons with diabetes, or immunosuppressed individuals.

B.

Treat with oral penicillin or erythromycin. Facial involvement should be managed with intravenous PRSP to prevent cavernous sinus thrombosis.

V. Cellulitis

A.

Clinical presentation. Cellulitis is a spreading infection of the epidermis and subcutaneous tissue that generally begins following a break in the skin. The affected skin is warm, reddened, and painful without a sharply demarcated border. Source, location, immunocompetence, and rapidity of spread dictate treatment.

1. Patients with uncomplicated cellulitis generally have a *Streptococcus* infection, although *Staphylococcus aureus* infection is common as well.
2. Injury in brackish water may result in halophilic *Vibrio* infection.
3. Cellulitis near the eye may involve the orbit or be superficial to the septum of the orbit. It is often difficult to distinguish between the two infections. Infections of the orbital space (orbital cellulitis) often present with proptosis, chemosis, and pain with motion of the eye. Sinusitis is often present and is the source of the infection. Orbital cellulitis threatens life and vision and may quickly spread to the central nervous system (CNS) or cause cavernous sinus thrombosis. Infections of the preseptal space (periorbital cellulitis) often result from superficial trauma; they lack signs of proptosis, chemosis, or pain with eye movement and are generally not life threatening.
4. Infections of the face or neck may result from trauma but are often the result of poor dental hygiene. Odontogenic infections may quickly spread to the submental and retropharyngeal spaces, resulting in airway compromise and collapse.
5. Diabetics and immunocompromised patients may harbor unusual organisms (see Chapter 17.2 and Chapter 19.4).

B.

Treatment. The affected body part should be elevated.

1. Patients with uncomplicated disease. Oral erythromycin, PRSP, or cephalosporin should be started, with IV desirable if the patient has systemic signs or symptoms. In patients with lower extremity cellulitis, good household support is necessary to ensure elevation of the extremity, and hospital admission should be considered if home support is lacking.
2. Brackish water injury. Antibiotic should cover halophilic *Vibrio,* such as doxycycline (200 mg immediately, 100 mg bid for 10 days); and an antipseudomonal aminoglycoside should also be given.
3. Infection involving the orbit requires inpatient treatment with ophthalmologic or ear-nose-throat consultation for potential drainage. In children, IV antibiotic therapy with a PRSP and cefuroxime (75 mg/kg per day divided q6h) is needed. For adults, IV PRSP is used. For infection outside the orbit, not crossing the septum, PRSP alone is generally used in adults and children.

4. Infections of face or neck associated with trauma-induced infections require PRSP. Infections of the face or neck resulting from poor dentition are managed with penicillin or clindamycin and drainage.
5. Management of cellulitis in immunocompromised patients and those with diabetes is best dictated by culture from the leading edge of infection. Empirical therapy should consist of cefoxitin, or, if the patient appears significantly ill, imipenem-cilastatin (Primaxin).

16.2

FUNGAL INFECTIONS OF THE SKIN

Lars C. Larsen

Valerie B. Laing

I. Tinea infections.

Tinea infections are caused by the dermatophytes: *Trichophyton*, *Microsporum*, and *Epidermophyton*. Infections may be subacute or chronic and are usually not invasive. These fungi selectively inhabit the keratin in the skin, hair, and nails. Tinea infections are not highly contagious.

A. Clinical presentation.

Infections commonly involve the scalp (*T. capitis*), body (*T. corporis*), groin (*T. cruris*), feet (*T. pedis*), hands (*T. manuum*), face (*T. faciei*), and nails (*T. unguium;* onychomycosis). Annular erythema with scaling is characteristic. Edema, plaques, pustules, and vesicles may be present in varying degrees. Onychomycosis is characterized by elevation of the distal nail, with subungual thickening and crumbling.

B. Diagnosis.

Diagnosis is based on the clinical presentation of lesions and confirmed by examination of a potassium hydroxide preparation of skin scrapings, nail debris, or broken hair. Scrapings from a leading edge of inflammation yield the highest results. Scalp infections caused by *Microsporum* species (less than 25% of cases in the United States) may fluoresce blue-green with Wood's light examination. Fungal cultures are reserved for cases in which the diagnosis is in doubt. Documentation of cure in scalp infections and justification for prolonged systemic therapy in onychomycosis are additional indications for cultures.

C. Management.

Oral antifungal medications are necessary for the management of tinea capitis and onychomycosis. Topical agents are usually adequate for most other tinea infections, with oral medications occasionally required for extensive involvement. Ancillary measures to avoid heat and moisture and increase exposure to air are beneficial.

1. **Tinea capitis.** Oral treatment with griseofulvin for 4–6 weeks in adults (or until culture is negative; ultramicrosize tablets, 375 mg/d); children older than 2 years: microsize suspension for 6–8 weeks, 15–20 mg/kg per day. Other effective treatments include terbinafine for 4 weeks (children: less than 20 kg, 62.5 mg/d; 20–40 kg, 125 mg/d; more than 40 kg, 250 mg/d; adults: 250 mg/d); itraconazole (Sporanox) for 2–4 weeks (children: 5 mg/kg per day; adults: 100 mg/d); or fluconazole (Diflucan) for 2–4 weeks (children: 6 mg/kg per day). Concurrent twice-weekly shampooing (Head & Shoulders, Selsun Blue, or Nizoral) may reduce spore shedding.
2. **Tinea corporis, tinea cruris, tinea pedis, tinea manuum, tinea faciei.** Topical medication until 2 weeks after the rash clears is curative for most infections. Oral therapy may be necessary for extensive, refractory, or recurrent disease. Effective topical medications include those in Section II.C.2 . Additional medications effective against tinea include the following over-the-counter (OTC) medications: those containing undecylenic acid (Desenex, Cruex) and tolnaftate (Dr. Scholl's, Aftate, Tinactin). Effective prescription medications are those containing

haloprogin (Halotex 1% cream, solution, bid), oxiconazole (Oxistat cream, bid), sulconazole (Exelderm cream, solution, daily; bid for tinea pedis), naftifine (Naftin cream, daily; use gel bid), terbinafine (Lamisil 1% cream, solution, bid), ciclopirox (Loprox cream, bid), and butenafine (Mentax cream, daily). Oral medication regimens for adults: tinea corporis/cruris—terbinafine (Lamisil)(250 mg/d × 1–2 weeks), itraconazole (100 mg/d × 2 weeks or 200 mg/d × 1 week), fluconazole (150 mg once weekly × 2–3 weeks), or ultramicrosize griseofulvin (375 mg/d × 2–4 weeks); tinea pedis/manuum/faciei—terbinafine (250 mg/d × 2 weeks), itraconazole (100 mg/d × 4 weeks or 400 mg/d × 1 week), fluconazole (150 mg once weekly × 4 weeks), or ultramicrosize griseofulvin (750 mg/d × 4–8 weeks) (1).

3. **Onychomycosis.** Treatment regimens include oral terbinafine (adults, single daily dose, 250 mg/d for 6 weeks for fingernails, 12 weeks for toenail infections), itraconazole (Sporanox) therapy (adults, 200 mg daily for 3 months or 200 mg bid for 1 week each month × 3–4 months) (2), or fluconazole (adults, 150 mg once weekly for 6–12 months). Topical medications for control of infection contain ciclopirox (Penlac nail lacquer, Loprox 1% cream, bid) and terbinafine (Lamisil 1% cream, bid).

D. Prevention.

Preventive measures include wearing of loose undergarments, wearing of cotton socks or sandals, avoidance of other occlusive clothes, and tight control of blood sugar in persons with diabetes. Sharing of contaminated combs and hairbrushes should be discouraged.

II. Candidal infections.

Superficial candidal infections of the skin and mucous membranes may be acute or chronic and are most often caused by the fungus *Candida albicans*. Infection often indicates abnormalities of the epithelium or host immunologic system that are associated with moist, warm, and macerated skin; antibiotic therapy; or systemic conditions, such as diabetes mellitus and HIV infection. Candidiasis is not highly contagious.

A. Clinical presentation.

Common sites for infection include the mouth (thrush), angles of the mouth (angular cheilitis, perlèche), between moist skin folds (intertrigo), in diaper areas of infants (diaper dermatitis), on the glans and prepuce of the penis (balanitis), and in periungual skin and nails (paronychia). Skin infections typically present as erythematous plaques with “satellite” papules or pustules, or both; maceration, fissures, and exudate may be present. Lesions involving the mucous membranes include erythematous plaques and superficial erosions covered with creamy white exudate.

B. Diagnosis.

Diagnosis is based on the typical clinical presentation of lesions and is confirmed by microscopic examination of a potassium hydroxide preparation of exudate, skin, or mucosal scrapings. Fungal pseudohyphae and spores are readily identified. Culture for the presence of candidal species is rarely needed.

C. Management.

Topical antifungal agents are the mainstay of treatment for candidal infections of the skin and mucous membranes. It is also important to avoid heat and moisture, unnecessary antibiotic or corticosteroid therapy, and use of cornstarch. Blood sugar in persons with diabetes should be tightly controlled. Systemic antifungal therapy is generally reserved for chronic and resistant infections, systemic infections, and for prophylaxis in immunocompromised hosts.

1. **Thrush.** Most patients can be treated with nystatin oral suspension. Treat for 10–14 days or until 2 days after lesions clear; dosage for infants is 1 mL in each side of mouth qid; adult dosage is 2–3 mL in each side of mouth qid held as long as possible or clotrimazole oral troches (10 mg 5 times per day for 14 days). Treatment with fluconazole (100 mg PO single dose) or itraconazole (200 mg PO single dose) provides an alternative.
2. **Intertrigo, perlèche, diaper dermatitis, balanitis, paronychia.** OTC topical medications include creams, ointments, solutions, or sprays containing miconazole (Micatin) or clotrimazole (Lotrimin AF; Mycelex OTC 1%). Prescription medications include those containing clotrimazole

(Lotrimin 1% cream, lotion, solution; apply bid), ciclopirox olamine (Loprox 1% cream, lotion; apply bid), miconazole (Monistat-Derm 2% cream; apply bid), ketoconazole (Nizoral 2% cream, apply daily), and econazole (Spectazole 1% cream; apply daily). If maceration is present, soaks with Burow's solution for 15–20 minutes tid can be helpful.

D. Prevention.

Preventive measures include wearing loose cotton undergarments, frequent diaper changes, conservative use of antibiotics and corticosteroids, tight control of diabetes, exposure of moist areas to air (also, blow drying with cool air after bathing), and well-fitted dentures to prevent drooling. Aggressive treatment of oral, penile, vaginal, and perirectal infections may prevent transmission to sexual partners.

III. Tinea versicolor (pityriasis versicolor).

Tinea versicolor results from infection of sebum-producing skin follicles by the yeast-like organism *Malassezia furfur.* Infection is common and is often chronic and recurrent. It is exacerbated by warm humid weather and use of oils on the skin. Tinea versicolor is not highly contagious.

A. Clinical presentation.

A fine scale covering lighter colored skin is characteristic, with small circular lesions coalescing to involve large areas. It often becomes noticeable in the summers when the surrounding skin tans. Macules, plaques, and erythema may be present. Although the upper thorax and back are commonly affected, lesions may also be found on the arms, face, and intertriginous areas.

B. Diagnosis.

Diagnosis is based on the clinical presentation of skin lesions and is confirmed by microscopic examination of a potassium hydroxide preparation of skin scrapings, which yields characteristic “spaghetti and meatballs” hyphae and spores. Culture for *M. furfur* is rarely needed.

C. Management.

Selenium sulfide suspension (e.g., Selsun Blue) may be used for acute or prophylactic therapy. Acute therapy includes application of a 2.5% suspension (prescription) for 10–20 min/d for 7 days or a single overnight application, repeated in 1 week. Prophylaxis with daily 5-minute applications of 1% (OTC) or 2.5% suspensions is useful, particularly in warm weather. Although more expensive, acute therapy for 2–4 weeks with topical agents (see Section II.C.2) is effective. Oral ketoconazole, 400 mg taken once and repeated in 1 week, is an alternative for extensive or bothersome infections. Patients should work up a sweat 1 hour after the dose and not bathe immediately afterward. Itraconazole (200 mg daily for 7 days) and fluconazole (300 mg taken twice one week apart or 400 mg taken as a single dose) are also effective (1).

D. Prevention.

Skin oils should be avoided. Prophylactic therapy with selenium sulfide suspension usually prevents clinically significant recurrences in susceptible individuals.

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16.3

PEDICULOSIS AND SCABIES

Aubrey L. Knight

Pediculosis is an infestation with the lice *Pediculus humanus* var. *capitis* (head louse), *P. humanus* var. *corporis* (body louse), or *Phthirus pubis* (crab louse). Scabies is an infestation with the mite *Sarcoptes scabiei* var. *hominis.*

I. Clinical manifestations.

A. Pediculosis

1. **Pediculosis capitis.** Lice infestation of the scalp is most common in children. The infestation is transmissible by close contact, and there are commonly small epidemics in schools. There is frequently a secondary inflammation leading to pustules, crusting, and cervical adenopathy. The infestation is found most commonly on the back of the head, the neck, and behind the ears.
2. **Pediculosis corporis.** Body lice infestation is uncommon and most often affects adults. It is associated with poor hygiene. Patients complain of itching and often have red pustules, 2–4 mm in diameter on an erythematous base. Chronic infestation leads to skin thickening and diffuse pigmentation.
3. **Pediculosis pubis.** Crab lice is a sexually transmitted infestation, with at least 30% of affected persons having at least one other sexually transmitted disease (1). The majority of patients complain of pruritus. The infestation may spread to all hairy areas. Delay in treatment may lead to inflammation and regional adenopathy.

B. Scabies.

Mite infestation results from direct skin contact with an infected person and leads to pruritus, especially at night. Eventually the infestation becomes widespread. On examination, burrows in the web spaces between the fingers, wrists, hands, feet, genitals, and waistline area are seen. The mite almost never affects the head and neck region in adults. Discrete vesicles and papules are frequently seen in similar locations. If left untreated, secondary inflammation with pustules, nodules, and regional adenopathy will develop. Additionally, there may be a cellular or humoral hypersensitivity with local inflammatory changes for up to 30 days after the infestation (postscabetic syndrome).

II. Diagnosis

A. Pediculosis

1. Scalp and pubic lice can be seen on the individual hairs by careful visual examination or under the microscope.
2. On Wood's light examination, live nits fluoresce white and empty nits fluoresce gray.
3. Examination of seams of clothing may reveal body lice and their eggs.

B. Scabies

The diagnosis is suspected when burrows are found or when dermatologic features in the characteristic locations are present. The definitive diagnosis is made with identification of the mite, egg, egg casing, or feces. The diagnosis can be aided by the following techniques.

1. With a magnifying lens, the burrows can be seen in the typical locations. The dark spot at the end of the burrow is the mite. It can be removed with a needle and examined under the microscope.
2. By adding a drop of potassium hydroxide to a slide with a skin scraping, better visualization of the mite, egg, egg casing, and feces is often possible.
3. Apply mineral oil to a suspicious lesion to improve the yield. After the application of the mineral oil, scrape the lesion and look for mites, eggs, egg casings, or feces with and without potassium hydroxide.
4. Use Burrow's ink test. If burrows are not obvious, apply ink to a suspicious area of rash. After washing off the ink with alcohol, any area that remains stained represents a burrow. This area can be scraped and examined.

III. Treatment

A. Pediculosis.

1. Lindane (Kwell, Scabene) cream, lotion, and shampoo are effective in treating head, body, and pubic lice. The shampoo should be left on the hair for 5–10 minutes prior to rinsing. After treatment, nits will remain and should be removed with a fine comb (nit comb). When the eyelashes

are involved, careful manual removal is necessary. The lotion and cream should be applied over the entire affected area, washed off after 10 minutes, and repeated in 7–10 days. Lindane should be avoided in infants and pregnant women.

2. Pyrethrum (Rid, A-200) is available as shampoos, sprays, and gels and should be used as described with lindane.
3. Permethrin (Nix creme rinse, Elimite) is useful in the management of head and pubic lice. As in management with lindane, the nits must be removed with a nit comb.
4. Malathion 0.5% (Ovide) lotion is an alternative for refractory pediculosis. It has ovicidal activity, and is applied to the affected area and washed out 8–12 hours later.

B. Scabies.

1. Lindane (Kwell, Scabene) 1% lotion or creme should be applied over the affected area and left on for 8–12 hours. Repeat application 7–10 days after the initial application is often necessary. Use of lindane should be avoided in infants and pregnant women.
2. Permethrin (Elimite) 5% cream is considered the drug of choice by many experts and, as with lindane, should be applied to the affected area and left on for 8–12 hours (1).
3. Crotamiton (Eurax) 10% cream should be applied daily, left on for 8–14 hours, and reapplied once a day for 5 days. This may be less effective than lindane or permethrin.
4. Low- to mid-potency topical corticosteroids (1% hydrocortisone or 0.1% triamcinolone) may be beneficial in the treatment of postscabetic syndrome.

IV. Prevention

(2)

A.

All close contacts of individuals infected with pediculosis or scabies should be treated concomitantly.

B.

All clothing, bed linens, and towels should be washed in a normal cycle.

C.

Education regarding institution of adequate hygiene is important.

D.

Gaining control of a school-based head lice infestation requires discussion with school administrators.

E.

Safe sex (pubic lice)

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16.4

ACNE VULGARIS

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Acne vulgaris is one of the most common skin conditions encountered by the family physician. It can range from a minor annoyance to a potentially disfiguring disease, and its psychological burden (particularly for an afflicted teenager) can often take on much more importance than the physical appearance. Acne is extremely common, particularly in the teen years, with 80% of young adults having some degree of problem. Acne vulgaris starts with abnormal keratinization of the skin (cohesive hyperkeratosis), which

blocks the pilosebaceous unit and leads to the development of microcomedones. These may grow to larger comedones or may become the site of bacterial overgrowth (especially with *Propionibacterium acnes*) and inflammation, with increased white blood cells (WBCs) and subsequent papular or pustular acne. Finally, the pilosebaceous unit may undergo hypertrophic changes (especially from the effect of androgens) and develop nodules and cysts (1).

I. Diagnosis

The diagnosis of acne is fairly straightforward. Lesions may consist of open or closed comedones (“blackheads” and “whiteheads,” respectively), papules, pustules, nodules, or cysts. The face is most often affected, with the shoulders, back, and chest following in decreasing order. True acne vulgaris always has some comedones; if they are absent, consider other acneiform dermatoses (such as rosacea or steroid acne).

A. Description and classification.

An appropriate description of the patient's acne is crucial to guide therapeutic choices and allow the physician to judge whether the condition has improved with therapy. Both the type of predominant lesion (comedonal, papular, pustular, nodular, or cystic) and the quantity (mild, moderate, severe, or very severe) should be noted (2). Thus, one patient may have very severe comedonal acne (hundreds of lesions), and another may have mild nodulocystic acne (few nodules and cysts).

II. Treatment.

Options for treatment are based on several factors: (a) the predominant lesion and skin type, (b) the distribution of lesions, (c) the patient's preferences that will affect compliance, and (d) some degree of trial and error.

A. General issues.

Patients should avoid the use of makeup or, when “necessary,” use a noncomedogenic preparation. Dietary restrictions are not needed as chocolates and other foods have not been proven as causative agents. Gentle washing twice a day with a mild soap (or benzoyl peroxide wash) is sufficient for cleaning, and overscrubbing of the face should be avoided. Finally, the agents are usually used cumulatively. Thus, antibiotic therapy for papular and pustular acne is added to topical retinoids, which were added to benzoyl peroxide therapy. As the condition of the skin improves, the antibiotics may be decreased or stopped, then the retinoids decreased, and so on.

B. Oral contraceptives (OCs).

Female patients may benefit from the use of OCs with nonandrogenic progestins, such as norgestimate or desogestrel. Therapy must be continued for 2–4 months for an effect to be noted (3).

C. Benzoyl peroxide preparations.

(soaps, lotions, gels) used once or twice a day are an excellent starting point for all types of acne. There are many preparations available over the counter (e.g., Panoxy bar) or as a prescription (e.g., Benzac 5% wash). The strengths range from 2.5% to 10%, with increased drying of the skin associated with higher concentrations (there is no increase in antibacterial activity). The water-based preparations are also less drying, and these can be used instead of other bath soaps on the affected areas.

D. Comedonal acne is best treated with a topical retinoid.

, such as tretinoin (Retin-A, Avita), adapalene (Differin), or tazarotene (Tazorac) applied thinly at bedtime. Always start with the lowest dose and increase strength over several weeks or months as needed and as tolerated. Erythema and irritation is common at first and can be minimized by decreasing frequency to every other day or every third day as needed. The gel and alcohol forms are more drying, and stronger. They are best used in patients with relatively oily skin or when creams fail. The patient should not apply the tretinoin until at least 1–2 hours after any benzoyl peroxide product. Used in close proximity, these agents can cause irritation and will effectively inactivate each other.

E. Papular and pustular acne calls for the addition of antibiotics.

Oral and topical agents can be used, depending on how widespread the lesions are and whether the patient prefers oral or topical therapy.

1. **Topical antibiotics** are applied thinly bid after washing (with benzoyl peroxide agent) and drying the skin. Common preparations are available as solutions, gels, lotions, ointments, and creams, including erythromycin (A/T/S 2%, Erycette), clindamycin (Cleocin T), tetracycline (Topicycline), and sodium sulfacetamide (Novacet). Azelaic acid (Azelex) has both antibacterial and keratolytic activity, but warnings are needed for patients with dark complexions due to possible hypopigmentation (4).
2. **Oral antibiotics** are indicated when lesions are extremely widespread or severe. First-line agents include tetracycline or erythromycin at 1 g/d in divided doses. Tetracycline may cause photosensitivity, and qid dosing on an empty stomach makes compliance difficult. Gastrointestinal (GI) upset can be common with erythromycin. If these agents fail, minocycline (Minocin) 50–100 mg bid, or doxycycline (Vibramycin) 50 mg (occasionally 100 mg) bid, and less commonly trimethoprim- sulfamethoxazole (Septra) 160–180 mg bid can be helpful. Oral agents are generally stronger than topical agents and can be used when topicals fail.

F. Nodulocystic acne,

the most severe form of acne vulgaris, can cause emotional and physical scarring. Treatment starts with judicious use of the agents above, but the condition can often be resistant to these therapies. When this happens, **isotretinoin**(Accutane) can be tremendously successful. Isotretinoin is indicated only for severe, recalcitrant, nodulocystic acne. This agent is highly teratogenic, and its use in women of childbearing potential requires written informed consent, negative pregnancy testing before starting, and highly effective contraception throughout the course of therapy. Isotretinoin is dosed at 0.5–2.0 mg/kg per day divided bid for 16–20 weeks. It has numerous side effects, including cheilitis, myalgias, arthralgias, epistaxis, xerosis, liver function elevation, hyperlipidemia, and leukopenia. Frequent (every 2–4 weeks) monitoring of liver function tests, triglycerides, and complete blood count (CBC) is advised (5). Properly used, isotretinoin can be very successful in inducing a state of remission for the acne and even a cure. If the acne recurs, it is usually much more responsive to the less toxic agents described previously.

III. Patient education

is crucial in the management of this chronic condition. Initially, patients must understand that it commonly takes 4–8 weeks of treatment for significant improvement and that the acne may get worse before it gets better. It also must be continually reinforced that acne is controlled and not “cured” (with rare exceptions). Patients often stop the medicine when they see improvement, only to be frustrated when it flares up a few weeks later. Decreasing or eliminating medications should be done under supervision with follow-up. A good rule of thumb is to see patients about every 6 weeks, until satisfactory improvement is noted. Then medications may be titrated downward as tolerated, rechecking every 2–4 months. Finally, this condition is often the teenager's first opportunity to take responsibility for their own health needs and this can be very empowering for them. The follow-up visits also provide an opportunity to address other health care issues, such as sex, smoking, and drug and alcohol use.

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16.5

COMMON DERMATOSES

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Thomas A. Bzoskie

Primary care has been called the medical discipline that specializes in the diagnosis and management of diseases of the skin and its contents. Here we review the diagnosis and management of several of the more common dermatoses encountered by primary care physicians.

Acne Rosacea

I. Clinical presentation.

Rosacea was initially termed acne rosacea due to its apparent similarity to teenage acne. It is a vascular disorder consisting of an erythematous, papulopustular eruption that most commonly affects the cheeks, nose, chin, and forehead. Telangiectatic vessels account for the erythematous flush that characteristically involves the cheeks and nose. Rosacea may also be present on the earlobes, neck, and chest. Rhinophyma is present when rosacea of the nose is associated with telangiectasia, sebaceous gland hyperplasia, and advanced erythema and pustular activity. This condition is disfiguring for many, yet it may be a patient's only manifestation of rosacea. Ocular rosacea is a major cause of red eye and dry eye. It may also present with blepharitis, conjunctivitis, chalazia, keratitis, or iritis.

II. Etiology.

The etiology of acne rosacea is unknown.

III. Incidence.

Rosacea affects approximately 13 million people in the United States. It is most common in fair-skinned, middle-aged individuals of northern or eastern European descent. Rosacea is more common in women, but it is often more severe in men.

IV. Differential diagnosis.

The differential diagnosis of rosacea includes acne vulgaris, perioral dermatitis, seborrheic dermatitis, steroid-induced acne, and lupus erythematosus.

V. Testing.

There are no tests specific for, or indicated in, the diagnosis of acne rosacea.

VI. Treatment.

As with other dermatoses, therapy for rosacea should be prescribed in relation to the magnitude of the disease and can be escalated as indicated.

A. Topical antibiotics.

Antibiotic therapy for rosacea is most effective against papules and pustules, and it usually produces only mild improvement of erythema and telangiectasia. Appropriate initial management of rosacea often involves the use of topical antibiotic preparations of metronidazole, clindamycin, erythromycin, or sulfur-containing compounds. Topical metronidazole is most commonly used, but it may produce irritation of the skin. This may be limited by use of a new 1% topical solution that is thought to cause less irritation. In addition, sparing use of 0.5%–1% hydrocortisone may minimize this adverse reaction.

B. Oral antibiotics.

The efficacy of oral antibiotics may have much to do with their anti-inflammatory effects. Tetracycline (250–1,000 mg/d), minocycline (100–200 mg/d), doxycycline, clindamycin, erythromycin, clarithromycin, ampicillin, and metronidazole all have been shown effective. Oral tetracyclines are often used with topical therapy for facial rosacea and in conjunction with artificial tears for ocular rosacea (1).

C. Avoidance.

Time-honored proscriptions in the management of acne rosacea have included avoidance of spicy foods, hot foods, hot beverages, and alcohol. Although ingestion of these may in fact produce flushing, the vasodilatation they produce is short lived; consequently, their preclusion has not proved to be necessary or helpful.

D. Topical corticosteroids.

Whereas short-term use of low-potency topical corticosteroids, such as hydrocortisone 0.5%–1%, may decrease erythema and inflammation, longer term use of these agents may increase the

formation of telangiectasia. Individual telangiectasia, if present, may be electively electrodesiccated with a fine epilating needle that is inserted directly into the telangiectatic vessels.

E. Retinoids.

Isotretinoin reduces the size of sebaceous glands and alters keratinization. It may be helpful in management more advanced cases of rosacea, particularly those involving rhinophyma. Retinoids may be used either topically, in the form of retinoic acid lotions, gels, or solutions, or systematically, as isotretinoin (2). Careful monitoring of liver function tests is indicated when prescribing isotretinoin. In addition, women of childbearing age should be on two reliable forms of contraception while taking isotretinoin because of the medication's well-established teratogenic potential. *Note: The FDA has not approved the use of retinoids for management of rosacea.*

Atopic Dermatitis

I. Clinical presentation.

Atopic dermatitis usually first presents in infants and young children. In infants an eczematous dermatitis characterized by crusted, erythematous lesions on the cheeks may be the first evidence of atopy. Older children typically present with a flexor surface eczema, usually appearing in the antecubital area, wrists, popliteal area, and ankles. The hallmark of atopic patients is severe pruritus, which is the primary symptom and precedes the rash. Pruritus leads to scratching, which produces an inflammatory response that leads to still more itching and scratching. The repeated inflammation and trauma secondary to scratching may eventually cause the affected skin to become excoriated and thickened (lichenified). As the process of atopy progresses to the chronic state, other regions of the skin may be involved. A generalized atopic reaction may be present in the most severe cases.

II. Etiology.

Predisposition to atopy is probably hereditary, possibly combined with environmental and infectious factors. Patients with atopic dermatitis are very frequently the offspring of parents or families with histories of atopy, allergic rhinitis, hay fever, and asthma (see also Chapter 8.6). In addition, in many instances atopy is found in patients who have elevated immunoglobulin E (IgE) levels. In these individuals, IgE-mediated cellular immunity is affected in an abnormal manner when stimulated by commonly occurring, otherwise harmless skin substances producing pruritic symptoms (3).

III. Incidence.

Atopic dermatitis affects more than 15 million adults and children in the United States. Sixty percent of patients present in the first 12 months of life. The next 30% are seen before age 5 years (4). In half of childhood cases, the condition spontaneously remits during adolescence. Approximately 8% of children and 1%–2% of adults have atopic dermatitis.

IV. Differential diagnosis.

The differential diagnosis of atopic dermatitis should include allergic contact dermatitis, drug eruptions, ichthyosis, lichen simplex chronicus, psoriasis, scabies, seborrheic dermatitis, and acrodermatitis.

V. Testing.

There are no tests specific for, or indicated in, the diagnosis of atopic dermatitis.

VI. Treatment.

Patients with a history of atopic dermatitis may have an increased propensity to develop contact dermatitis when exposed to usually innocuous skin irritants. These may be found in cosmetics, hair preparations, common household and industrial cleaning products, rubber gloves, and other substances found in the workplace (5,6). A careful history with particular attention to household and occupational exposures usually proves beneficial.

A. Topical steroids

often provide relief for the inflammatory reaction. “Start low and go slow” is a good general rule to follow when using steroids. For infants and small children, 0.25%–1% hydrocortisone ointment is usually sufficient to achieve good results. Ointments retard loss of moisture through the epidermis and may discourage scratching in older patients. In older children and adults, 1% hydrocortisone ointment is adequate in many instances. Triamcinolone acetonide ointment 0.025%–0.1% bid after bathing or fluorinated corticosteroid ointments may be transiently required in severe or refractory cases.

B. Systemic steroids

may be indicated in the management of severe exacerbations and generalized atopic dermatitis. When needed, systemic steroids should be tapered as quickly as possible and replaced with topical treatment.

C. Systemic antipruritics

, such as the antihistamines diphenhydramine, hydroxyzine, and cyproheptadine, may provide symptomatic relief.

D. Topical antihistamines

and local anesthetic creams should be avoided due to their propensity to become an allergen when applied to inflamed skin.

E. Emollient lotions

or bath oils added to the bath water often provide relief by promoting moisture retention within the epidermis. Their use is particularly helpful in cold weather, when humidity is low and heavier clothing may rub, irritate, and defat the skin.

F. Products

that come into contact with the skin or clothes should be hypoallergenic, when possible. Wool, synthetic fibers, and other cutaneous irritants often exacerbate the itching.

G. Overzealous personal washing

and bathing should be discouraged, particularly in the winter months, to avoid excessive drying and defatting of the skin. Personal washing should be done in cool water using soap substitutes. Colloidal oatmeal or cornstarch added to the bath water may provide an added measure of comfort to the patient with atopic dermatitis.

H. Secondary skin infections.

should be considered when oral antihistamines and topical corticosteroids are not sufficient to keep the patient comfortable. *Staphylococcus aureus* colonization occurs in more than 90% of atopic dermatitis lesions (4).

I. Topical antibiotic ointments.

, such as mupirocin, polymyxin B, or bacitracin, may be indicated to address secondarily infected atopic areas. When applied three times daily, these ointments are effective in many cases. Topical antibiotics should be used with a modicum of caution because they may produce allergic skin reactions.

J. Systemic antibiotic therapy

should consist of dicloxacillin, amoxicillin plus clavulanic acid, first-generation cephalosporins, clindamycin, or a macrolide. Avoid the latter if the patient is concomitantly taking medications that may produce adverse drug interactions (e.g., terfenadine or theophylline).

K. Stress.

Several investigators have commented on the relationship between atopic dermatitis and stress as well as the relationship between atopy and physical irritants and foods (7). Encourage adequate rest and facilitate control of stress.

L. Dietary management.

, independent of other interventions, is not usually effective in the management of atopic dermatitis. However, avoidance of certain foods, especially eggs, peanuts, wheat, cow's milk, soy, and shellfish, may decrease the incidence of atopic reactions in some patients (8).

Lichen Simplex Chronicus (LSC)

I. Clinical presentation.

The patient presents with one or several areas of lichenified skin associated with severe pruritus. The lesions may occur at any location, but the medial ankle and posterior neck are the most common locations, especially in women. LSC may also present equally in both sexes as an anogenital process. Hypertrophic vulvar dystrophy (as LSC is called in gynecologic literature) is a vulvar presentation of the disease (also see Chapter 13.1).

II. Etiology.

Chronic rubbing or scratching in response to pruritogenic stimuli produces the characteristic circumscribed area of thickened skin that is pathognomonic of LSC. Because this lichenified dermatitis may be a variant of neurodermatitis, underlying anxiety often plays a significant etiologic role.

III. Incidence.

A familial or personal history of hay fever, asthma, or atopic dermatitis is noted frequently in patients with LSC.

IV. Differential diagnosis.

The differential diagnosis of LSC includes atopic dermatitis, contact dermatitis, and lichen sclerosis.

V. Testing.

There are no tests specific for, or indicated in, the diagnosis of LSC.

VI. Treatment.

Counseling and behavior modification are crucial in the long-term treatment of LSC.

A. Topical corticosteroid ointment.

(1% hydrocortisone or the equivalent) used bid-qid during the acute presentation decreases the acute inflammatory and pruritic process. Small lesions may be treated with Cordran tape, which uses the topical steroid flurandrenolide impregnated under an adhesive dressing.

B. Steroids.

may be injected into the lesion. This provides more effective amelioration of the pruritus.

C. Emollient lotion

or bath oils added to the bath water often provide relief by adding to the moisture content of the epidermis.

D. Systemic antipruritics

, including the antihistamines diphenhydramine, hydroxyzine, or cyproheptadine, may provide symptomatic relief to many. In addition to their primary role, the fat-soluble antihistamines may reduce itching through mild sedation.

E. Topical antihistamines

and local anesthetic creams should be avoided due to their propensity to be allergenic when used on inflamed skin.

F. Unna boot.

Localized extremity LSC may be treated with occlusion under a medicated gauze bandage.

G. Anxiolytics

also may prove helpful in decreasing the behaviors secondary to an underlying anxiety.

Allergic Contact Dermatitis

I. Clinical presentation.

Allergic contact dermatitis (ACD) eruptions are characterized by macular erythema and papules, vesicles, or bullae. Chronic ACD usually presents as a lichenified, scaling dermatitis that may include fissures, papules, and vesicles. The shape and location of the rash of ACD is varied and may provide clues about the inciting agent. Plant allergens typically produce a linear rash involving the extremities. Textile-related ACD involves the clothed areas, particularly the posterior neck, upper back, lateral thorax, waist, and flexor surfaces, with a relative sparing of the axillary and undergarment areas. This pattern underscores the contribution of factors such as pressure, friction, heat, and perspiration to the clinical presentation. When ACD presents on the hand, it typically is located in the finger webs and on the dorsa of the hands. In all patients in whom ACD is suspected, a detailed history of household and occupational contacts is of paramount importance.

II. Etiology.

Contact dermatitis is produced by contact of the skin with a sensitizing external agent. The dermatologic reaction transpires through the interaction of an allergen (sensitizing external agent) with a specific T-cell antibody. This reaction is characteristic of the dermatitis that occurs when skin is exposed to poison oak, poison ivy, some metals (particularly nickel), and some metallic salts. The resultant immunologic cascade after such a sensitizing contact may cause a delayed type hypersensitivity that is most noticeable after 24–72 hours.

III. Incidence.

ACD accounts for approximately 7% of all occupation-related illness in the United States and fully 30% of dermatitis on the hand (9).

IV. Differential diagnosis.

The differential diagnosis of ACD includes the following dermatitides: irritant contact, atopic, nummular, seborrheic, dyshidrotic, and autosensitization.

V. Testing.

The only test to be considered in the diagnosis of ACD is the patch test. However, because patch tests have both high false-negative and false-positive rates, their utility in the diagnosis of ACD is questionable. Patch testing may prove helpful in circumstances where the specific diagnosis proves elusive. Of the more than 2,800 known potential allergens, only 23 are currently available for clinical use in the United States (9).

VI. Treatment

A. Avoidance.

The optimal treatment of ACD requires identification of the responsible allergen and instruction to the patient on avoidance of the offending substance. Allergens may be present in otherwise innocuous materials

(e.g., rubber, textiles, metals), and thus the specific offender may prove difficult to isolate. When counseling patients with ACD reactions to such complex materials, the physician should try to provide information about other products likely to contain the allergen and should try to suggest alternatives.

B. Symptom control.

In addition to avoidance, treatment of ACD should be directed to the relief of symptoms.

1. **Drying agents.** Acute vesicular eruptions may be helped by drying agents, such as aluminum acetate solution (Burow's solution), diluted to 1:40 and applied as either compresses or soaks.
2. **Emollients.** Chronic, lichenified lesions respond best to emollient creams, lotions, or bath oils added to the bath water.
3. **Antihistamines.** Pruritus may be lessened by oral antihistamines, such as diphenhydramine, hydroxyzine, or cyproheptadine. Topical antihistamines and anesthetics should be avoided due to the risk of inducing a secondary allergy.
4. **Topical corticosteroid creams or ointments** (hydrocortisone 0.5%–2.0%) are helpful in the management of the acute, inflamed dermis where their use decreases itching and skin reactivity.
5. **Oral corticosteroids.** Some ACD reactions, especially those secondary to *Toxicodendron* oleoresin (poison oak and poison ivy) and gold or other heavy metals, may persist in the skin for weeks to months after exposure. Management of these recalcitrant reactions may require oral corticosteroid medication, whose dosage should be tapered slowly over 3–4 weeks to minimize the risk of rebound inflammation.

C. Desensitization.

Unfortunately, hyposensitization through oral or intramuscular administration of an identified allergen has not been demonstrated to be effective.

Irritant Contact Dermatitis

I. Clinical presentation.

The appearance of irritant contact dermatitis (ICD) may vary from mild redness and roughening (chapping) to severe blistering and ulceration. Multiple factors determine the severity of the ICD reaction, including the specific properties of the irritant, its physical state and concentration, and the length of time it remains in contact with the skin. Patient factors include the skin area affected, perspiration, pigmentation, dryness, and the concomitant presence of other skin disease. Environmental factors, including temperature, relative humidity, friction, pressure, and occlusion, may also contribute to the presentation.

II. Etiology.

ICD is caused by local inflammation following contact of the skin with a noxious substance. It does not involve the immunologic recognition of specific antigens and may occur on initial exposure to an irritant. These reactions may be considered the equivalent of acute and/or chronic chemical burns.

III. Incidence.

ICD is much more common than ACD. It is one of the most common causes of both industrial and household contact dermatitis.

IV. Differential diagnosis.

The differential diagnosis of ICD includes the following dermatitides: atopic, nummular, seborrheic, dyshidrotic, and autosensitization.

V. Testing.

Because ICD is a diagnosis of exclusion, a negative patch test may be helpful in establishing the specific offending agent.

VI. Treatment.

A. Identification and avoidance of offending materials

is the mainstay of treatment.

B. Topical corticosteroids.

A brief course of a low- to moderate-potency topical corticosteroid cream or ointment may be indicated to decrease the acute inflammatory reaction.

C. Patient and environmental factors.

may be modified with the goal of rendering the patient less susceptible to the irritant when continued exposure is anticipated. Protective coverings, screens, gloves, and clothing may be helpful.

Seborrheic Dermatitis

I. Presentation.

Seborrhea usually presents as a papulosquamous disorder centered around a chronic overproduction of sebum accompanied by erythema and scale formation. It is commonly seen as dandruff in adults and cradle cap in infants. Predominantly, seborrheic dermatitis is limited to the scalp but may also involve the face (eyebrows, paranasal area, nasolabial folds, external auditory canals, and area behind ears), chest, groin, and other hairy or intertriginous areas. Seborrhea may present as mild or severe and may coexist with other diseases, including psoriasis, acne rosacea, and acne vulgaris.

II. Etiology.

The cause of seborrheic dermatitis is unknown. The role of bacteria (*Corynebacterium acnes*) or fungi (*Candida* in infants and *Pityrosporum* in adults) is controversial. *Pityrosporum ovale* probably is a causative factor, but both genetic and environmental factors seem to influence the onset and course of the disease. Although stress may aggravate seborrhea, neurologic abnormalities as a cause are unlikely.

III. Incidence.

Seborrheic dermatitis affects all age groups. It is present in 2%–5% of the population. Seborrhea has a bimodal age distribution, appearing in infancy (birth to 3 months) and later adult life (fourth to seventh decades) and is slightly more common in male than female subjects.

IV. Differential diagnosis.

When seborrhea is very extensive or treatment resistant, the diagnosis of immunodeficiency should be entertained.

A. In adults

, consider psoriasis, tinea capitis, tinea cruris, candidiasis, impetigo, and rosacea (see Chapter 16.1 and Chapter 16.2).

B. In infants

, atopic dermatitis, eczema, scabies, histiocytosis X, and multiple carboxylase or complement deficiencies should also be considered.

C. Testing.

No specific tests are indicated in the diagnosis of seborrhea. Clinical diagnosis is based on the appearance of the characteristic chronic, erythematous, greasy, scaling plaques.

V. Treatment.

The management of seborrhea of the face, chest, and groin is often aided by the local application of medicated shampoos to the affected areas. The brief use of topical steroid creams, ointments, or lotions is indicated to decrease inflammation and itching. The goal is to quickly decrease the strength of the steroid used to the lowest level that controls symptoms. Most patients can be weaned from steroids after a brief interval.

A. Medicated shampoo.

Seborrhea of the adult scalp may be managed with medicated shampoos that contain coal tars, zinc pyrithione, or selenium sulfide, as single or combination ingredients, as first-line therapy. These agents are most effective when left on the scalp for 5–10 minutes before rinsing. Hair should be shampooed daily for the first 2–3 weeks, after which shampoos can usually be tapered to 3–4 times weekly as individually indicated. Hair conditioners may be used following use of these shampoos if the hair becomes excessively dry.

B. Topical corticosteroids.

Inflammation and pruritus may require the use of topical steroids. Lotions or solutions are usually easier to apply to the scalp than ointments and creams. Start with medium-potency agents, such as triamcinolone acetonide 0.1% at bedtime for 2 weeks, and then decrease to the lowest potency steroid at bedtime for 2 weeks that will control scaling and pruritus. Reduction to triamcinolone acetonide 0.025% lotion or hydrocortisone 1% or 2.5% lotion usually proves effective. Topical steroid efficacy may be enhanced if the patient wears a plastic shower cap overnight after the application. The goal is to reduce reliance on steroids and achieve maintenance therapy with medicated shampoos. In most instances, patients can be weaned from topical steroids within 2–4 weeks. However, some patients require more prolonged or intermittent use of steroids to achieve control of symptoms and manage exacerbations.

C. Infants and children.

The treatment of infants and children should be much less aggressive.

1. **Mineral or olive oil** applied to the scalp lesions can be used to soften and help in the removal of plaques associated with infantile seborrhea or cradle cap.

D. Shampoo.

Mild baby shampoos are first line when managing cradle cap. They should be left on the scalp for 5 minutes before rinsing in order to be effective in removing the seborrheal debris.

E. Treatment-resistant cases.

Seborrhea that is not responsive to the above protocols may be helped by the use of sodium sulfacetamide 10% and sulfur 5% applied as a thin layer bid with or without topical corticosteroid or ketoconazole 2% cream applied at bedtime for 3 weeks in conjunction with other ongoing therapy. Ketoconazole 2% shampoo used 3 times per week for a month, or systemic use of ketoconazole 200 mg, one tablet daily may prove effective (10).

Keratosis pilaris

I. Presentation.

Because inflammation surrounding inspissated follicular keratin plugs causes the affected skin surface to feel rough and dry, the most common presenting complaint of patients with keratosis pilaris is that their skin is bumpy, itchy, and cosmetically unacceptable. Keratosis pilaris is generally found on the lateral and extensor aspects of the proximal upper and lower extremities and buttocks. When present on the thighs and buttocks, folliculitis may be the most noticeable or first reported pathology. Occasionally, the trunk and the cheeks of the face may also present with the typical sterile pinpoint follicular papule and or pustules of keratosis pilaris. This dermatitis is frequently more severe in cold, dry climates.

II. Etiology.

The cause of keratosis pilaris is unknown.

III. Incidence.

Keratosis pilaris is an extremely common chronic disease characterized by follicular plugging with keratin debris.

IV. Differential diagnosis.

The differential diagnosis of keratosis pilaris should include acne vulgaris, molluscum contagiosum, miliaria pustulosa, psoriasis, dry skin, ichthyosis, atopic dermatitis, or drug-related eruption.

V. Testing.

No specific tests are indicated in the diagnosis of keratosis pilaris.

VI. Treatment.

Keratosis pilaris is very resistant to all forms of treatment. The goal of treatment is to achieve symptomatic control. It may take 6–8 weeks from initial treatment before significant improvement is appreciated.

A. Mild soap.

Wash the affected areas with mild soaps on a mild abrasive scrub pad several times daily. Irritation of the skin by excessive abrasion with the scrub pad must be avoided.

B. Emollient lotions or bath oils.

added to the bath water may provide some help. Their use is especially helpful in cold weather when heavier clothing may tend to rub, irritate, and defat the skin.

C. Keratolytic agents.

Use either as single agents or apply alternately.

1. Urea 10% lotion (apply locally bid).
2. Lactic acid-containing lotions or creams (apply locally bid). Preparations at the 5% concentration are available without prescription. Patients who show resistance to these may respond to a 12% concentration, which requires a prescription.

D. Benzoyl peroxide.

The comedolytic and antibiotic properties of benzoyl peroxide, as 5% or 10% lotion, cream, or gel, can be helpful in the management of the keratin plugs.

E. Retinoids.

Patients whose condition is more severe respond well to topical retinoids in the form of tretinoin 0.05% or 0.1% cream applied nightly.

F. Inflammatory lesions.

The inflammatory component of keratosis pilaris is managed as an acneiform eruption and/or folliculitis.

1. **Topical antibiotics.** Treat with preparations of clindamycin or erythromycin.
2. **Oral antibiotics.** Systemic antibiotics with activity against *Staphylococcus aureus*. Occasionally, vigorous antibiotic therapy may be required for several months to quiet the inflammatory reaction.

Pityriasis rosea

I. Presentation.

Pityriasis rosea (PR) is a common, acute, benign, distinctive, eruptive dermatitis with a self-limiting course. Patients with

PR present with the distinctive rash and many complain of a mild transient itching. Pruritis may be pronounced, with extensive eruptions. The initial lesion (herald patch) is a 2- to 10-cm, round to oval, salmon pink, erythematous plaque that may precede the generalized eruption of PR by 1–3 weeks. The rash of PR is characterized as a few to hundreds of 1- to 2-cm oval plaques that are typically limited to the trunk and proximal extremities. This macular rash is erythematous with a finely scaly periphery. The lesions' long axis follows the dermatomes. The exanthem follows a classic “Christmas tree” pattern. The outbreak of PR usually lasts 2–10 weeks; if it persists longer than 12 weeks, the diagnosis should be reconsidered.

II. Etiology.

Evidence is accumulating that the cause is human herpes virus type 7.

III. Incidence.

PR occurs most frequently in patients between 10 and 35 years old, although it may occur at any age. There is a seasonal predilection for PR, with most new cases noted during the colder months.

IV. Differential diagnosis.

The herald patch may resemble tinea corporis. The subsequent diffuse rash can mimic secondary syphilis, pityriasis versicolor, drug eruptions, nummular eczema, and guttate psoriasis. Hypopigmentation is rarely seen in PR, but hyperpigmentation may be seen in dark-skinned patients.

V. Testing.

No specific tests are indicated for PR, but secondary syphilis should be ruled out when the diagnosis of PR is entertained. Clinical diagnosis of PR may be based on the presence of a herald patch, if present.

VI. Treatment.

No specific therapy is available, and treatment is symptomatic.

A. Antipruritic lotions.

Calamine lotion may be effective for mild itching and help prevent scratching. Topical antihistamines should be avoided.

B. Topical steroids.

Triamcinolone 0.1% or hydrocortisone 1% applied bid may be indicated in selected instances to ameliorate itching.

C. Systemic antihistamines

, such as diphenhydramine or hydroxyzine, or antihistamines with antiserotonin activity, such as cyproheptadine, may help to relieve moderate to severe pruritus.

D. Oral steroids.

These are reserved for the rare extensive case with intensive itching.

E. Ultraviolet light.

The severe pruritus that may be produced by PR may prove responsive to ultraviolet B therapy in doses that produce a mild erythema (11). Direct sun exposure hastens the resolution of exposed lesions.

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16.6
PSORIASIS

Stephen D. Saglio

I. Diagnosis.

Psoriasis appears as nonscarring, occasionally pruritic, salmon pink, thickened papules and plaques, with sharp margins and silver-white scale. Lesions are typically seen on extensor surfaces, the sacral area, buttocks, and scalp but rarely on the face. Often worse in winter (low humidity) and milder in summer (higher ultraviolet light exposure) (1).

A. Scalp.

Hair loss is uncommon.

B. Nail changes.

Seen in about 10% of patients. Pitting and “oil spots” (yellow-brown spots) under the nail are pathognomonic.

C. Koebner's phenomenon.

Lesions occur at sites of minor trauma (scratch marks) in otherwise normal skin.

D. Auspitz phenomenon.

Minuscule blood droplets are seen after removing scale.

E. Differential diagnosis

(see Chapter 16.5)

1. Seborrheic dermatitis has similar sites and morphology.
2. Candidiasis is potassium hydroxide-positive (see Chapter 16.2).
3. Drug eruptions may cause a psoriasiform eruption or a true psoriasis episode. ß -Blockers, gold, methyldopa, lithium, nonsteroidal anti-inflammatory drugs, antimalarials, angiotensin-converting enzyme inhibitors, and alcohol have been implicated. Psoriasis may occur after months of use.
4. Secondary syphilis resembles guttate psoriasis (see Chapter 19.5).
5. Pityriasis rosea has a characteristic truncal distribution and “herald patch.”

F. Variants

1. Guttate psoriasis. Scattered, small (1–2 cm), disseminated lesions, sparing palms and soles, appear, commonly after a streptococcal infection and may disappear in a few weeks. Guttate psoriasis is more common in children and young adults.
2. In 3%–20% of cases, psoriatic arthritis may precede or follow appearance of skin lesions and is usually seronegative.
3. Severe, unstable variants are generalized pustular psoriasis (von Zumbusch), erythrodermic psoriasis, palmar and pustular pustulosis.

II. Management.

No cure is available. The treatment plan must be tailored to the patient's perception of the condition and commitment to its management.

A. Mild to moderate plaque psoriasis.

Topical therapy is the mainstay if less than 20% of the body surface area is involved (2).

1. Emollients soften and disguise scaling. Apply immediately after bathing and as needed, up to twice daily. Ointments (petrolatum, Aquaphor) are more effective than creams or lotions.
2. Exposure to sunlight is helpful. Sunburn can exacerbate psoriasis. Commercial sun beds are not effective (3).
3. Topical fluorinated corticosteroid ointments are usually the first-line prescription agents. Grade III [betamethasone valerate 0.1% (Valisone)] to grade I [(clobetasol propionate 0.05% (Temovate)] strengths are usually required. Apply after removing scales by soaking in water then gently rubbing with a soft brush; avoid harsh scrubbing. Overnight occlusion with plastic film increases potency. Use for 2 weeks as pulse therapy. Ointments are better for skin, lotions for scalp. Use lower potencies for face and genitals, and on children. Limit use of superpotent preparations (grade I) to 2 weeks and less than 50 g/wk to avoid side effects (4).

   Side effects include skin atrophy, hypopigmentation, striae, and telangiectasia. Use occlusion cautiously with superpotent preparations. Avoid systemic corticosteroids entirely.

4. Keratolytics (salicylic acid, urea, α -hydroxy acids) applied on the plaques twice a day can help thin and remove scales so that other agents may penetrate better.
5. Anthralin (Drithocreme, Anthra-Derm) must be applied for several weeks. Creams are preferable to pastes and ointments. Apply daily after bathing to the affected skin. Start with low concentration (0.1%) and brief (5 minute) contact time, washing off afterward. Increase gradually each week to 2% and 10–30 minutes until clearing or skin irritation occurs. Micanol is a new formulation that is less staining.

   Side effects include staining of adjacent skin and clothes (brown, purple). Do not use for face or skin folds.

6. Coal tar preparations are quite effective and extremely safe. They are less irritating than anthralin, but longer contact time (several hours) is required. Odor is unpleasant. A common regimen is 0.5%–1.0% crude coal tar in petroleum jelly, with the concentration increased every few days to a maximum of 10%.
7. Calcipotriene ointment 0.005% (Dovonex), a vitamin D_3 analogue, is more effective than fluocinonide. It is colorless and nonstaining. Apply twice daily. Irritation, usually not severe, is a common side effect (up to 20%) (4). Safety in children, pregnancy, and breast-feeding is not established. Hypercalcemia has not been reported with recommended doses (less than 100 g/wk) (5).
8. Tazarotene a topical vitamin A analogue that is applied once daily to affected skin. Has a slower onset of action than topical steroids (up to 2 weeks), but longer remissions. Side effect is local skin irritation. Avoid pregnancy.

B. Scalp involvement

1. **Mild.** Treat with tar shampoos (Zetar, Pentrax), then betamethasone valerate 0.1% lotion 2 times per week. Massage shampoo into scalp and leave for 1–2 hours.
2. **Severe or thick adherent plaques.** Remove plaques with 10% liquor carbonis detergens (LCD) in Nivea oil and occlude with a plastic cap overnight. Alternatively, use anthralin (see Section II.A.5). After removal of plaques (may take three treatments), use steroid cream or lotion (see Section II.A.2) and overnight occlusion.

C. Severe or widespread cases.

Consider referral for phototherapy or systemic medications. Patients with more than 20% body surface area involvement or with severe variants (see Section I.F.3) are often candidates.

III. Prevention and patient education

A. Avoid exacerbating stimuli.

Patients should never scratch or rub lesions (Koebner's phenomenon). Keep skin well hydrated; avoid harsh soaps, sunburn, and other forms of skin injury. Avoid suspect medications (see Section I.E.3).

B. Stress reduction and aerobic fitness.

may be helpful for one third of patients.

C. Patient education.

Psychosocial effects can be devastating. Schedule frequent follow-up visits. Address the chronic, relapsing nature of the disease so that expectations are realistic. Patient understanding of the condition and treatment increases effectiveness. Many self-help groups are available.

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16.7

URTICARIA

William A. Alto

I. Overview.

Urticaria manifests as a common and reversible skin eruption. The lesions are usually multiple, palpable, circumscribed, erythematous, blanchable, pruritic papules (wheals) and plaques ranging in size from 2 mm to 30 cm. They result from vasodilatation and increased vascular permeability in the superficial dermis caused by release of mast cell mediators of inflammation, such as histamine and other vasoactive substances. Angioedema is the result of a similar process involving the deep dermis and subcutaneous tissue. Urticaria and angioedema are classified by their time course as acute or chronic (lasting more than 6 weeks) and by the presumed inciting agent or mechanism.

II. Classification and diagnosis

A. Acute urticaria.

The wheals of acute urticaria develop rapidly over 15 minutes and dissipate within 90 minutes to 24 hours. Rarely they can last 48 hours. As lesions resolve new crops appear, and the patient may mistakenly report that the individual “hives” have been present for days or weeks.

1. **Allergic urticaria** is IgE mediated (type 1 hypersensitivity). It is caused by direct contact with or inhalation of an allergen, such as grasses, pollens, insect toxins, drugs or foods, or simultaneous infections.

   Medications commonly associated with urticaria include penicillin, cephalosporins, sulfonamides, aspirin, and nonsteroidal anti-inflammatory drugs. Latex can be a contact or an inhalation antigen. Foods frequently linked with transient urticaria are eggs, nuts, shellfish, strawberries, chocolate, and tomatoes. Infection-associated urticaria is more common in children. Offending agents include *Streptococcus*, Epstein-Barr virus, hepatitis virus A-C, and *Ascaris lumbricoides.* Blood transfusion reactions and urticaria following the administration of blood products have an immune etiology.

   A careful patient history often identifies the cause. Radioallergosorbent testing or treatment of the underlying infection is occasionally helpful. Direct challenge tests may be life threatening. Elimination diets are unwieldy.

2. **Physical urticarias** are provoked by skin stimulation, resulting in mast cell degranulation. Duration is brief, lasting only 30–60 minutes. Dermatographism is the most common physical urticaria. Cholinergic urticaria is characterized by small (1–3 mm) pruritic papules with blanched centers. Physical exercise, hot showers, fever, and anxiety are antecedent stimuli. Other uncommon (cold) and rare (solar, localized heat, delayed pressure, vibratory, and aquagenic) causes of urticaria can be identified by application of the offending agent or force (1). Delayed-pressure urticaria has a 4- to 6-hour lag time between the stimulus and the appearance of a wheal, which may last several hours.
3. **Chemical or contact urticarias** do not involve IgE release. A number of drugs can cause the direct release of histamine in susceptible individuals: aspirin, amphotericin B (Fungizone), dextromethorphan, narcotics, polymyxin B (Aerosporin), quinine, reserpine, scopolomine (Transderm Scop), and radiographic contrast-containing iodine. Nonimmunologic urticaria does not require prior exposure to the offending agent. Certain foods, including spoiled mackerel and tuna, may cause urticaria because of their high histamine content (scombroid poisoning).

B. Chronic urticaria.

occurs in about 25% of patients who develop urticaria (2). By definition, the wheals have been present for at least 6 weeks and do not represent recurrences of acute urticaria.

1. Most patients with chronic urticaria have an autoimmune mast cell disease with an autoantibody to the α subunit of the high-affinity IgE receptor on mast cells and basophils, which results in histamine release when activated. An associated thyroiditis is frequently identified. An autologous serum inoculation test may help in diagnosis (3).

   Other less common causes of chronic urticaria include food or food additive allergies (less than 1%), psychological stress, and, rarely, parasitic infections. Focal infections, candidiasis, and undiagnosed malignancy are rarely, if ever, the cause of chronic urticaria.

2. Urticarial vasculitis is an indicator of underlying disease and must be differentiated from the acute and chronic urticarial wheals. Urticarial vasculitis is suggested by the presence of painful wheals lasting more than 24 hours, wheals with underlying purpura, or those with residual hyperpigmentation. Biopsy is indicated. Systemic signs and symptoms of an underlying disease that are frequently present include arthralgias, malaise, fever, nephritis, and laboratory abnormalities, including an elevated erythrocyte sedimentation rate and acute phase reactants. Systemic lupus erythematosus and other connective tissue diseases may occur concomitantly with urticarial vasculitis (see Chapter 15.2).

C. Angioedema

frequently accompanies the urticarial wheals of chronic, cold, or solar urticaria. It has indistinct borders; typically involves the mouth, lips, larynx, tongue, and mucosa of the gastrointestinal tract; and lasts 2–3 days.

Adverse reaction to drug therapy is the most common cause of severe angioedema. Hereditary autosomal dominant angioedema is rare (less than 0.4%). Penetrance is variable and acquired cases occur, so that a family history may not be helpful. If the fourth component of complement (C4) is low, then the diagnosis should be confirmed with an assay of C1 esterase inhibitor, which is also low.

III. Differential diagnosis.

Large urticarial wheals may be confused with erythema multiforme (EM). EM has an acute onset and the typically evolving target lesions that last at least 7 days and fade by 4 weeks.

Insect bites may occasionally resemble urticaria. The patient's history and location of the lesions will help clarify the etiology.

Mastocytosis (urticaria pigmentosa, solitary mastocytoma, systemic disease, and mastocytosis with associated hematologic disorders) is characterized by histamine and other vasoactive substances released from overabundant mast cells. Urticaria and flushing are common symptoms (4). Triggers for histamine release are listed in Sections 1–3 above.

Dermatitis hepatiformis and bullous pemphigoid can occasionally resemble urticaria. They are longer lasting. Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a fixed rash.

IV. Treatment.

Avoidance of factors that trigger acute urticaria is the most important treatment. A careful history coupled with knowledge of frequently implicated triggers can help prevent further attacks.

Local therapies that provide symptomatic relief include cool compresses, topical antipruritics such as doxepin cream (Zonalon), and 1% menthol in aqueous cream.

Antihistamine therapy with H_1 receptor blockers is more effective for acute urticarias. Regular dosing around the clock offers better control. Older antihistamines [hydroxyzine HCl (Atarax) 25 mg qid, diphenhydramine (Benadryl) 25–50 mg qid, and chlorpheniramine (Chlor-trimeton) 4 mg] are as effective as the newer nonsedating variety. Doxepin (Sinequan) 10–25 mg bid can also be used orally. The dose is titrated upward as necessary. Histamine H_2 blockers are sometimes helpful when treatment with H_1 blockers is inadequate, but they are seldom effective alone.

Management of chronic urticaria is less satisfactory because the autoimmune etiology may ultimately necessitate immunosuppressive therapy. Androgens, corticosteroids, cyclosporine, intravenous immunoglobulins, and

plasmapheresis have been used with success. Evaluation and treatment is usually coordinated by dermatologists. Patients should be advised to avoid aspirin and other nonsteroidal anti-inflammatory agents and opioid narcotics.

Life-threatening episodes of angioedema (e.g., laryngeal edema) can be managed by epinephrine IV, SQ, or 2% topical spray along with systemic antihistamines and corticosteroids. Danazol is used in hereditary angioedema. Angiotensin-converting enzyme inhibitors should be avoided.

The best approach to urticarial vasculitis is identification and treatment of the underlying disease.

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16.8

STASIS DERMATITIS, STASIS ULCERS, AND DECUBITUS ULCERS

Carol E. Blenning

I. Stasis dermatitis.

Stasis dermatitis (SD) arises as a complication of incompetent venous valves in the legs that no longer control venous return from superficial to deep veins and from distal to proximal veins. The leaky valves cause increased venous pressure due to back flow as leg muscles relax. This venous hypertension causes chronic venous insufficiency and the resultant skin changes known as SD (1).

A. Clinical presentation.

SD is found in the lower extremities because of their dependent location, and in the setting of varicose veins and chronic edema from venous incompetence. Early stages are associated with mild erythema, scaling, and pruritis, usually at the medial ankle extending proximally and often over a distended vein. In the later stages, chronic extravasation of erythrocytes leads to hemosiderin deposition in the dermis and hyperpigmentation. SD can present acutely with inflammation, crusting, exudates, and excoriation. But the more chronic version typically involves brawny (tan or reddish brown) edema of the skin (dermal fibrosis). Contact dermatitis and secondary infection can complicate SD, and severe unchecked SD often leads to stasis ulcer, especially in the more fibrotic, central area (1,2).

B. Differential diagnosis.

Distinguishing SD from cellulitis can be difficult, so establishing its chronicity is helpful. The clinician should also consider contact dermatitis, burn, superficial thrombophlebitis, and lichen simplex chronicus. History and physical examination are generally sufficient to establish the diagnosis.

C. Management.

Control of chronic edema is paramount in successful management of SD: elevation of the legs when seated, avoidance of prolonged standing, and use of compression stockings with a gradient of at least 30–40 mm Hg (greater than antiembolic hose) are all effective methods. Skin care should include avoidance of irritants and liberal use of emollients. Sometimes intermediate-potency topical steroids are also beneficial (2).

D. Prevention.

Prevention of chronic edema prevents SD. Therefore, the control of hypertension and congestive heart failure is important (see Chapter 9.1 and Chapter 9.4).

The general population should exercise regularly, interrupt prolonged periods of sitting or standing with walking, and elevate the legs whenever possible.

II. Stasis ulcer.

A stasis ulcer (SU) is a “hole in the skin” occurring in the fibrotic areas of SD (1) that appears as a depressed lesion with destruction of the epidermis and at least the upper dermis, and heals with scarring.

A. Clinical presentation.

The increased venous pressure in the lower extremities associated with SD can cause ulcerations (3) that are well demarcated and have irregular, shaggy borders, surrounding dermatitis with hyperpigmentation and edema, and, occasionally, cellulitis. They are usually located over the medial ankle and leg, an area drained by perforating veins that have become incompetent. SU usually occurs in older women. It is chronic and recurs frequently (1).

B. Differential diagnosis.

Several other ulcerative skin lesions can resemble an SU.

1. Hypertensive or ischemic ulcers tend to be painful, deep, and punched out in appearance. They are associated with decreased pulse, pale and atrophic skin, and loss of hair, and occur most often in those with risk factors: tobacco use, diabetes, hypertension, and hyperlipidemia (3).
2. Factitious ulcers are unusual, come in “artificial” shapes, and have straight and angular borders.
3. Ulcers resulting from excoriation can resemble SUs, but evidence of the underlying dermatosis should be apparent (e.g., eczematous dermatitis in the setting of chronic venous insufficiency).
4. Pyoderma gangrenosum occurs most often on the anterior shin. It is purplish and raised, with undermined, ragged borders. It can occur in the setting of internal disorders such as ulcerative colitis.
5. Decubitus ulcers occur over pressure points and are outlined below.
6. Vasculitic disorders can lead to ulcerations. Both arteritis (associated with lupus erythematosus, periarteritis nodosa, and dermatomyositis) and blood dyscrasias (e.g., sickle cell anemia and thalassemia) cause ulceration due to inadequate tissue oxygenation locally (3).
7. Diabetics with severe neuropathy experience ulcerations over pressure-bearing areas, such as the plantar aspect of the heels, metatarsal heads, and great toe. These ulcers tend to be well demarcated and surrounded by thick callus. Because the etiologic factor is neuropathy and not vascular insufficiency, the extremity should be warm, dry, and numb and have normal pulses.

   Deep venous thrombosis can occur in the setting of chronic leg edema, pigmentation, and ulcer, and this pattern is referred to as post-phlebitic syndrome (1).

C. Management.

Treatment of SU can take months and can even require skin grafting. The leg must be elevated for at least 30 minutes 3–4 times per day above the level of the heart. Gentle debridement clears necrotic material; then the ulcer is covered with a semipermeable dressing under pressure (more convenient) or with a wet or dry nonadherent dressing or bandage. Topical steroids delay healing and should not be used; also contraindicated is the use of topical antiseptics (e.g., Betadine) because of cellular toxicity, or topical antibiotics. Enzymatic debriding agents have not been proven effective, and silver sulfadiazine has given inconsistent results. All of these ulcers are colonized, so that antibiotics are only indicated for secondary infections and the goal cannot realistically include the clearance of bacteria but rather resolution of the secondary infection (1,2). For more severe edema, short-term diuretics can be helpful, as can intermittent pneumatic compression pumps, except with uncompensated congestive heart failure. However, for most patients compression stockings are recommended. These should be placed upon awakening, delivering a gradually decreasing amount of pressure from ankle to knee. Zippered backs or Velcro closure simplifies the application (1).

D. Prevention.

Preventive measures for SU are based in the control of SD and chronic edema (see above) (2). Compression stockings are shown to prevent recurrence, once the ulcer is healed.

III. Decubitus ulcer.

Decubitus ulcers (DUs) are areas of skin breakdown resulting from the high pressures generated by a prolonged or repeated point of skin contact overlying a bony prominence. They are staged as follows:

- Stage 1: nonblanchable erythema seen over intact skin
- Stage 2: ulceration of epidermis, dermis, or both
- Stage 3: ulceration extending to the subcutaneous layer
- Stage 4: ulceration extending to muscle, bone, and/or supporting tissues (4)

A. Clinical presentation.

Mechanical pressure, moisture, friction, and shearing forces all contribute to the formation of DUs, which often arise when an elderly person experiences a fall and/or immobilization (4). Pressure-induced vascular insufficiency leads to tissue hypoxia, which leads to skin breakdown. Secondary infection with skin and gastrointestinal flora, including anaerobes, is a potential complication. Risk factors for DU include age (70% of patients with DU are older than 70 years), neurologic deficit, malnutrition, immobility, and debilitating medical disease. Sedentary habits, loss of ambulatory capacity, and muscular atrophy all lead to prolonged periods of time spent in one position. Caution in assisting or attempting mobility is advised as this can generate the shearing forces that exacerbate tissue ischemia in the presence of increased pressure. In fact, pressure as low as 45 mm Hg can, when combined with friction, lead to DU formation. The presence of a single DU can lead to multiple DUs when pressure avoidance at the first lesion causes increased pressure elsewhere. The ulceration itself is like the tip of an iceberg. The deeper ischemic tissues widen to the bony pressure point in a cone shape, especially when there is minimal adipose cushion. The overall mortality rate from DU is 8% (5).

B. Differential diagnosis

Same as for SU (see above).

C. Management.

Addressing immobility is key in the management of DU. Such measures include physical therapy and use of durable medical equipment that advances mobility and improves home safety. Debilitated patients benefit from multivitamins, vitamin C (500 mg PO bid), and either pressure-reducing devices (air and foam pads or mattresses) or pressure-relieving mattresses (dynamic devices that inflate and deflate). Stage-specific management is recommended as follows:

- Stage 1: Eliminate excess pressure and maximize nutrition and hygiene.
- Stages 2–4: Keep wound clean and moist, changing saline dressings while they are still damp. Synthetic dressings are more effective but also more expensive than saline dressings. Efficacy likely relates to fewer dressing changes, which means fewer disruptions of the reepithelialization process, and to the greater protection synthetic dressings offer against contamination. Because bacterial colonization is universal, swab cultures of the ulcer have no value in defining the source of infectious processes such as cellulitis, osteomyelitis, and sepsis. Instead, use cultures of blood and wound border, sampled by needle aspirate or biopsy technique. In these situations, systemic antibiotics are indicated. Otherwise, topical antibiotics can be of use if a non-infected ulcer is not healed within 2 weeks
- Stages 3 and 4: Late-stage DU often requires surgical or enzyme debridement. Consultation with a wound specialist (often a plastic surgeon) is indicated (4).

D. Prevention.

For high-risk populations, such as the elderly and debilitated, home visits for safety evaluation and physical therapy are of benefit. Also, frequent repositioning relieves pressure (5), and careful skin inspection can identify early “hot spots.” Donuts (annular cushions) are not preventive for those in wheelchairs (they reduce venous drainage, increasing local edema and risk of skin breakdown) (4).

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16.9

COMMON SKIN CANCERS

Robert A. Baldor

I. Skin cancers.

A. Incidence.

Skin cancers are the most commonly diagnosed cancers in this country, accounting for one third of all cancers. The majority are preventable and curable. Basal cell carcinoma (BCC) is the most common (600,000 cases per year), followed by squamous cell carcinoma (SCC) (200,000 cases per year) and malignant melanoma (MM) (48,000 cases per year). MM accounts for the majority of skin cancer deaths (8,000 deaths per year), and its incidence has doubled in the last decade.

B. Risk factors.

Predisposing factors for all types of skin cancer include fair skin (blonde hair, blue eyes), poor tanning ability, and a predilection to burn. However, all individuals are at risk with excessive exposure to ultraviolet (UV) light from solar radiation. UV light damages epidermal DNA. Twenty to thirty years of exposure is required to induce tumor development. Tanning booths use UVA light, a longer wavelength than UVB, but there is no evidence to support the use of tanning booths to acquire a protective tan, and tanning booth exposure adds to the lifetime dose of UV radiation.

C. Prevention.

Skin cancers are preventable. Patients should be counseled to avoid sun exposure and use broad-spectrum sunscreens (those that screen UVB and UVA rays) with a minimal sun protection factor (SPF) of 15. Sunscreens have been shown to prevent BCC and SCC in animal models, but they appear to be ineffective in preventing MM. In addition, these cancers are curable if detected early and treated promptly. Patients' skin should be examined periodically, and high-risk individuals should be instructed in regular self-examinations.

II. Nonpigmented cancers.

A. Basal cell carcinoma.

BCCs are found in areas of sun exposure, with 90% occurring on the head or neck. These are raised nodular lesions with central ulceration surrounded by a pearly or thready border with telangiectasias. The surrounding skin is often wrinkled or sagging, secondary to loss of normal thickness and elasticity from chronic sun damage. There are three main clinical types. Most common is the nodular type, also known as ulcerative or rodent tumor. This begins as a nodule that ulcerates as the tumor progresses. Superficial BCCs tend to occur on the trunk and can be multiple. They are flat and reddish pink but typically have a thready border consistent with BCC. The morphea-like or sclerosing BCCs are less common.

These plaque-like lesions are somewhat indurated, ivory colored, and telangiectatic, but they do not always have a thready border.

If BCCs are excised when smaller than 2 cm, there is a less than 5% likelihood of recurrence; if they are larger than 2 cm when excised, 20% will recur within the first year. Less than 0.1% of BCC will metastasize, but they cause local destruction.

B. Squamous cell carcinoma.

SCC can be thought of as a continuum of disease, including actinic keratosis (AK) and carcinoma in situ (Bowen's disease; BD), both of which involve atypia of the epithelial keratinocytes. AK is characterized by localized nests of atypia and dysplasia within the keratinocytes. With BD, this atypia encompasses the full thickness of the epidermis. With SCC, there is invasion into the dermis.

AK (also known as solar keratosis) is common in the elderly and seen in most areas of chronic sun exposure (face, back of hands, forearms). AKs are circumscribed, rough lesions with indistinct margins. Size ranges from pinpoint to plaque-like nodules of varying colors, and occasionally the nodules are scaly, with skin horns. Clinically, it can be difficult to tell whether a lesion is an AK or an SCC, but because SCC represents an invasion into the dermis, these lesions are firmer, indurated, and adherent to the underlying dermis. Approximately 20% of AKs slowly transform into SCC; therefore, they should be removed or, at the very least, followed closely.

Bowen's disease is characterized by an erythematous, hyperkeratotic, scaly plaque with sharp irregular borders and erosions or ulcerations on the surface. The condition is often seen on areas of skin that are not exposed to sun. BD can be mistaken for a patch of psoriasis or eczema. Like AK, these lesions can transform into SCC, so they must be managed or followed closely.

SCC is a disease of the elderly (mean age 70 years), although they can be seen in younger individuals. In addition to the usual risk factors, SCCs are also associated with environmental exposures (arsenic, petroleum, and smoking) and inflammatory dermatoses (discoid lupus, chronic osteomyelitis, hidradenitis suppurativa, chronically draining pilonidal sinus, severe burns, leg ulcers, and psoriasis managed with methotrexate). In addition, renal transplant patients who are on chronic suppression are at higher risk. The link between chronic inflammation and immune suppression is unclear. A viral etiology is postulated, possibly human papillomavirus (HPV 5).

SCCs are nodular to plaque-like with a variety of colors. Frequently, there is ulceration and scaling. Occasionally, SCC can be verruciform. Two to three percent of lesions metastasize to the local or regional lymph nodes. The main morbidity is from local destruction.

C. Management.

1. Management of AK and BD consists of removal. Destructive means include electrodesiccation and curettage, cryosurgery (topical liquid nitrogen is acceptable), acetic acid applications, and fluorouracil (Efudex). Recently, tretinoin (Retin-A) has shown promise in the management of small AKs.
2. There are three underlying principles for managing BCC and SCC: (a) remove the cancerous tissue; (b) preserve normal tissue and function; and (c) achieve an optimal cosmetic result. Simple destruction is appropriate for lesions that are smaller than 2 cm and are not in areas that would present problems should there be a recurrence or growth (around eyes, nose, and mouth). Destruction can be achieved with electrodesiccation and curettage or with cryotherapy. However, unlike the case of precancerous lesions, liquid nitrogen treatment is not sufficient, and a cryoprobe must be used to achieve sufficient depth of freeze to destroy the tumor. BCCs respond better to freezing than do SCCs. Fluorouracil can also be used, although it is not the optimal therapy, and should be reserved for patients, such as nursing home residents, who would find it difficult to come to the office for a procedure.

Surgical excision with a 2- to 3-mm margin is an excellent way to manage BCC and SCC. Not only is the lesion removed, but the specimen can confirm the diagnosis and determine whether the skin margins are clear of tumor. Occasionally, BCC occurs in areas that are difficult to excise, in which case referral may be necessary to achieve complete excision. A shave or punch biopsy would be appropriate to confirm the diagnosis prior to referral.

For larger lesions, those located in high-risk areas, or recurrent lesions, it would be appropriate to refer for Moh's surgery. This is a specialized technique whereby the lesion is removed in a slowly enlarging, concentric pattern. The margins are examined under frozen section, and tissue is removed until there is microscopic confirmation that the margins are clear.

III. Pigmented cancers.

A. Benign lesions.

1. **Acquired nevus.** Common nevi, or moles, change predictably over time, beginning as a simple lentigo, transforming into junctional nevi, compound nevi, and, finally, intradermal nevi. Frequently, moles involute and disappear.

   Simple lentigos are not related to solar exposure and can be seen anywhere on the body. They arise in early childhood and are less than 5 mm round, macular, brown or black, with smooth or slightly jagged edges. Simple lentigo should be distinguished from ephelides (freckles). Ephelides are the result of increased production of melanin by melanocytes in response to sunlight, whereas lentigo consists of a number of melanocytes clumping together. Junctional nevi remain small and are similar in appearance to simple lentigo but may contain hair. They arise in childhood or early adolescence in sun-exposed areas of skin.

   During later adolescence or early adulthood, melanocytes migrate through the epidermal-dermal junction, creating a compound nevus. As these cells cross the junction, nevi rise above the surface of the skin. These well-circumscribed papules remain smaller than 6 mm in circumference, are tan to brown, and have a smooth or rough surface. Occasionally, there is hair growth. The final stage is that of the intradermal nevi. As the melanocytes migrate to the dermis, the nevi lose pigmentation to become flesh-colored papule and may disappear. Progression other than these normal stages should be considered suspicious. Indeed, any new mole that develops after age 40 should be evaluated closely.

2. **Congenital nevus.** This lesion is present at 1% of all births, although some authorities manage any pigmented lesion seen within the first year of life as a congenital nevus. Small congenital nevi (< 3 cm) have a 1%–2% chance of malignant transformation during the individual's lifetime, doubling the underlying risk of MM. Giant congenital nevi (> 20 cm) have a 4%–8% risk of malignant transformation. Treatment is controversial, and options include careful observation with removal for suspicious changes or removal when the child is old enough to undergo a procedure under local anesthesia.
3. **Dysplastic nevus.** This lesion has variations of color (tan, brown, pink, red, blue) and size; many dysplastic nevi are larger than 7 mm with irregular, distinct borders. Dysplastic nevi are markers for MM-prone individuals, who have a lifetime risk of developing melanoma of 6%. This risk increases substantially if two family members have MM (up to 100% in some studies). Dysplastic nevus syndrome refers to the development of multiple lesions (100 or more). Normal individuals have 25–40 acquired nevi. Dysplastic nevus syndrome is probably an inherited familial disorder.

   These patients need to be followed periodically (every 3–12 months), with biopsy of the worst-looking lesions. Total-body photographs or

spot photographs can be used to follow particular lesions. Twenty percent of melanomas arise from dysplastic nevi. Patients must be counseled to avoid the sun and to use SPF-15 sunscreen.

A shave biopsy is not appropriate for pigmented lesions. The depth of the lesion is an important prognostic indicator and is essential to future management of the disease. A punch biopsy is fine if it can encompass the whole lesion. However, if one merely punches the worst-looking area of the pigmented lesion, it is possible to miss malignant cells elsewhere in the lesion. Therefore, these lesions should be managed with excisional biopsy techniques.

4. **Solar lentigo.** Solar lentigo (liver or age spots) is a benign indicator of sun-related damage to skin. Classically, uniform tan or brown macules are seen on the back of the hand and forearms of older individuals. Treatment is not necessary, although patients frequently request therapy because of cosmetic concerns. Tretinoin and “bleaching” creams, such as hydroquinone (Melanex), can be used. The benefits of cryotherapy must be weighed against the potential for scarring.
5. **Seborrheic keratosis.** Commonly seen in older individuals, this is a sharply demarcated, verrucal, warty, raised lesion with brown, black, and tan coloring and a waxy appearance. It appears to be stuck onto the skin and varies in size from a few millimeters to several centimeters. Lesions are typically seen on the face, neck, and trunk. Seborrheic keratosis is an autosomal dominant trait. Onset occurs in the 40s and progresses slowly progresses. Lesions are occasionally seen as firm, dark black nodules, which should raise suspicion of nodular melanoma.

B. Malignant melanoma

1. **Description.** Risk factors for MM include a genetic predisposition, excessive UV light exposure (including severe childhood sunburns), and having multiple nevi (as few as 20 nevi increases the risk; individuals with more than 200 nevi are at highest risk). If there is a family member with MM, other members have a 2%–8% increased risk. This is primarily a disease of whites. The majority of MMs arise de novo.

   Remember the ABCD evaluation for MM. Lesions that possess these characteristics (listed below) should be watched closely or biopsied. A lesion need not possess all four characteristics to be an MM.

   A = Asymmetry A line drawn through the middle does not create matching halves.

   B = Border Uneven scalloped or notched edges.

   C = Color Variable shades of brown or black and hues of blue, gray, white, pink, or red.

   D = Diameter Size greater than 6 mm (the diameter of a pencil).

   MMs are classified as four types. The majority (70%) are **superficial spreading** MMs. **Lentigo maligna** melanomas account for 5% of MMs; they arise from a precursor lesion known as a lentigo maligna or Hutchinson's freckle, which is a large pigmented macule seen in sun-exposed areas. These have a good prognosis because they tend to spread superficially before invading. Unfortunately, **nodular** MM (5%) does not follow the ABCD criteria. These present as black nodules, which may or may not have variations of color and tend to invade early. **Acral-lentiginous** MMs (5%) arise on the hands or feet and are the most common type seen in Asians and blacks. Often they are not observed until late in progress because they are hidden on the soles of the feet, between the toes, or underneath a nail.

2. **Treatment.** Treatment of persons with MM consists of surgical excision. For lesions that are thinner than 0.5 mm, a 1-cm margin is sufficient. Lesions that are thicker than 1 mm require a 3-cm margin with a deep incision into the underlying fat and fascia. When removing a lesion that is suspicious for MM, use an elliptic incision with 1-cm margins. Should the biopsy reveal a lesion thicker than 0.5 mm, wider

reexcision of the area is necessary. Lesions thinner than 0.75 mm are associated with a 99.5% 10-year survival rate. Lesions thicker than 3 mm have only a 48% 10-year survival rate.

Lymph node exploration is not indicated for lesions thinner than 1 mm. Patients with greater than 3 mm invasion should be treated as if MM had spread to the nodes, but without doing a nodal dissection. Controversy arises for patients with lesions between 1 and 3 mm invasion. Obviously, any suspicious nodes, even with a thicker lesion, should be explored.

3. **Staging.** Stage 1 disease is localized to the skin (80% 5-year survival); stage 2 disease indicates that the lymph nodes are involved (30% 5-year survival); stage 3 involves metastases, typically to the central nervous system (50% 1-year mortality).

XVII. ENDOCRINE AND METABOLIC PROBLEMS

17.1
OBESITY

Meg Hayes

I. Overview.

Obesity is increasing in prevalence in both sexes, in all age groups and races, and at all educational levels. Obesity has increased from 12% of the population in 1991 to 17.9% in 1998 (1). The incidence is highest for adults, with an estimated 97 million, or 54.9%, meeting criteria for overweight status (2). Obesity is associated with increased risk of death in all adult age groups for all categories of death (3). Obesity substantially raises the risk of morbidity from type 2 diabetes mellitus, coronary artery disease, hypertension (HTN), dyslipidemia, osteoarthritis, obstructive sleep apnea, gallbladder disease, osteoarthritis, and cancers of the breast, prostate, endometrium, and colon.

II. Clinical assessment.

Assessment of body fat, risk factors, and patient motivation provide the basis for development of an appropriate treatment plan.

A. Body mass index (BMI).

Relative weight for height correlated with body fat content for adults. An indirect measure of body fat, this measurement should not be used to evaluate growing children, frail elderly, pregnant or lactating women, individuals with high muscle mass, or patients with disorders that preclude obtaining an accurate measurement of height.

BMI = [*weight* (*pounds*)/*height* (*inches*)^2] × 704.5 or

weight (kilograms)/height (meters)^2

Table. No caption available.

Underweight: BMI < 18.5	Obesity Class I: BMI 30.0–34.9
Normal: BMI 18.5–24.9	Obesity Class II: BMI 35.0–39.9
Overweight: BMI 25.0–29.9	Obesity Class III: BMI ≥ 40

B. Waist circumference (WC) and waist-to-hip ratio (WHR).

Excess abdominal fat is a risk factor for development of obesity-related health problems, including Type 2 diabetes, hypertension, and cardiovascular disease (4). For adults, a BMI of 25–34.9, with a WHR >1.0 or WC >102 cm (40 in.) in men or WHR > 0.8 or >88 cm (35 in.) in women, identifies patients at **high risk** for the development of obesity-associated comorbidity.

C. Risk status.

Comorbidities compound the health risks associated with obesity. Comorbidities are usually exacerbated by excessive weight and improved with weight reduction.

1. Patients with coronary or peripheral atherosclerotic disease, type 2 diabetes mellitus, and obstructive sleep apnea are at **very high risk** for disease complications and mortality.
2. Other obesity-related diseases include osteoarthritis (especially knee, hip, and back), gastroesophageal reflux disease, infertility, urinary stress incontinence, cholelithiasis, idiopathic intracranial hypertension, and lower extremity venous stasis.
3. Patients with three or more of the following are classified at **high risk**: tobacco abuse, hypertension, hypercholesterolemia, impaired fasting glucose, family history of premature coronary heart disease.
4. Conditions that promote weight gain include such preexisting illnesses as Cushing's disease and hypothyroidism; medications such as steroids and tricyclic antidepressants; psychological factors such as depression; and menopausal period associated with an average 5-lb weight gain.

D. Patient motivation.

Factors that allow the patient to successfully enter into a weight reduction program include motivation, previous history of weight loss, social support, capacity and willingness to engage in physical activity.

III. Treatment.

Goals of a weight loss program are to prevent additional weight gain, reduce body weight, and maintain lower weight over time. Initially set a 4- to 6-month goal for weight reduction of 10% or a reduction of BMI by two units. As targets are met the patient may maintain the reduced weight or set a new goal of weight reduction. Either strategy should include permanent lifestyle modification of healthy eating habits, increased physical activity, and behavior modification including stress reduction and self-monitoring. Treatment options are employed based on the BMI and adjusted risk:

Table. No caption available.

BMI 18–<25, no adjusted risk:	healthy diet and physical exercise
BMI 25–<27, moderate risk:	as above plus low calorie diet
BMI 27–<30, high risk:	as above
BMI 30–<35, very high risk:	as above plus medication and very low calorie diet
BMI 35–<40, extremely high risk:	as above
BMI 40+, extremely high risk:	as above plus surgical intervention

A. Calorie reduction.

A decrease of 300–500 kcal/d provides a weight loss of 0.5–1 lb/wk with a 6-month 10% weight reduction for BMI 25–30. A decrease of 500–1,000 kcal/d provides weight loss of 1–2 lb/wk with a 6-month 10% weight reduction for BMI 30–35.

1. To calculate a 500 kcal/d deficit:

   Calculate the **resting energy expenditure (REE):**

   (10 × *weight* [*kg*]) + (6.25 × *height* [cm]) - (5 × age [years])* = *REE*

2. Estimate **total caloric need** to maintain weight:

   total caloric need = REE × activity factor

   (activity factor = 1.6 for men, 1.5 for women)

3. Calculate **adjusted caloric intake:**

   total caloric need - 500 kcal = caloric energy deficit[5]

B. Pharmacotherapy.

In selected patients, medication is an appropriate adjunct to low-calorie diet, physical activity, and behavior modification. Weight loss medications create an energy deficit through reduced food consumption or reduced absorption.

1. Centrally acting anorectic mechanism
   a. Phentermine, 8 mg tid with meals or 15–37.5 mg in the morning
   b. Sibutramine: 5–15 mg/d, adrenergic-serotonergic
   c. Reduced absorption in gastrointestinal (GI) tract
      a. Orlistat: 120 mg tid

C. Surgical intervention.

For patients with extremely high risk and BMI greater than 40 who have failed medical management, surgical consultation may be an appropriate option. The Roux-en-Y gastric bypass and vertical-banded gastroplasty are the two most common procedures used for weight management. The family physician should ensure that dietary changes, physical activity, and behavior modification are part of the overall strategy for weight reduction.

D. Patent education.

Follow-up, in the form of office visits, telephone contact, and written communication, is an important component of a successful weight loss program. Encourage social support through family and friends, newsletters, the internet, weight loss groups, and exercise partnerships.

E. Contraindications to weight loss.

Absolute contraindications to weight loss are terminal illness and anorexia nervosa. Temporary contraindications include pregnancy and lactation; unstable psychiatric, medical, or surgical status; and bulimia nervosa. Patients with osteopenia or osteoporosis should

undergo discussion of risk and undertake medical management to maintain bone mineral density.

IV. Obesity management across the life span.

BMI is not an accurate measure of body fat in children who have not achieved full height. Increasing numbers of children are overweight and will continue this trend into their adult years, placing them at higher risk to develop comorbid conditions early in life. Emphasis on healthy eating habits and physical activity can help children maintain normal weight while supplying adequate nutrition for growth and development.

Elderly persons are at increased risk of becoming overweight with loss of physical activity and decreased energy expenditure. Regular, moderate exercise and a diet low in fat and high in fiber can control weight while providing for nutritional needs. Issues of polypharmacy, drug interactions, and age-related physiologic factors should be considered before medication is prescribed for obese elderly patients.

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* = +5 for men and -161 for women.

17.2

DIABETES MELLITUS

Charles Kent Smith

John P. Sheehan

Margaret M. Ulchaker

I. Classification

A. Type 1 (insulin-dependent) diabetes mellitus

(DM) is characterized by insulin deficiency due to autoimmune pancreatic ß-cell destruction.

B. Type 2 (non-insulin-dependent) DM

is characterized by insulin resistance and variable insulin secretory defects. Obesity (specifically abdominal), hypertension, and dyslipidemia often coexist (cardiodysmetabolic syndrome, previously known as Reaven's syndrome X).

C. Gestational DM

(see Chapter 14.6)

D. Secondary DM

(not covered in this chapter)

II. Initial approach to the patient

A. Clinical history

yields important clues to the presence and correct classification of DM.

1. Type 1 DM.
   a. Recent onset of polydipsia, polyuria, significant weight loss, fatigue, and ketonuria occurs in a patient generally younger than 30 years.
   b. Clinical duration of symptoms is relatively short despite a long prodrome of autoimmune pancreatic islet destruction.
2. Type 2 DM
   a. Patient may present with polydipsia, polyuria, history of weight gain or loss, fatigue, glycosuria, obesity (especially abdominal),

hypertension, dyslipidemia, positive family history of DM, or previous gestational DM in a patient generally older than 40.

b. Clinical duration of mild hyperglycemia with minimal symptoms may be prolonged in such a way that patients may present with DM complications (peripheral neuropathy, retinopathy, nephropathy).

3. Gestational DM (see Chapter 14.6)
4. Secondary DM. Consider DM in the context of the primary condition.

B. Physical examination.

The presence of DM complications noted on a careful initial physical examination at time of diagnosis strongly favors a diagnosis of type 2 DM. Unfortunately, DM complications at diagnosis remain common, confirming longstanding undiagnosed DM.

C. Laboratory diagnosis

1. Fasting serum glucose ≥ 126 mg/dL on two occasions in ambulatory setting.
2. Random serum glucose ≥ 200 mg/dL on two occasions in ambulatory setting.
3. A 2-h postload plasma glucose (glucose tolerance test no longer routinely needed to diagnose DM).
   a. Indications
      1. Equivocal serum glucose levels, especially in the presence of other stigmata of cardiodysmetabolic syndrome.
      2. Presence of complications suggestive of DM when random serum glucose and fasting serum glucose are nondiagnostic.
   b. Diagnostic when 2-h postload glucose ≥ 200 mg/dL
   c. Patient status and preparation
      1. Usual state of health (no exogenous glucocorticoid therapy or total parenteral nutrition)
      2. Dietary carbohydrate intake of 300 g daily for the 3 days prior
      3. Overnight fast of 8 hours
      4. Ingestion of 75 g of anhydrous glucose with 300 mL water to prevent nausea or emesis. Phlebotomy for serum glucose in sodium fluoride tube 2 hours after glucose ingestion.
4. The hemoglobin A_{1c} is not a diagnostic criterion for DM. Therefore, a normal hemoglobin A_{1c} does not rule out a diagnosis of DM.
5. Other abnormalities of glucose tolerance
   a. Impaired glucose tolerance
      1. Fasting plasma glucose < 126 mg/dL
      2. 2-h post-load (75 g anhydrous glucose) plasma glucose of ≥ 140 mg/dL and £ 199 mg/dL
   b. Impaired fasting glucose
      1. Fasting plasma glucose ≥ 110 mg/dL and < 126 mg/dL

D. Laboratory classification.

Clinical history, physical examination, ambient glucose levels, and degree of ketosis usually suffice for appropriate diagnostic classification. In equivocal settings, C-peptide or insulin levels (low in type 1 patients) coupled with pancreatic islet cell antibodies (positive in 90% of new-onset type 1 DM patients) allows correct classification.

E. Treatment goals.

Since publication of the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetic Complications Trial (EDIC) (the extension of the DCCT), and numerous position statements from the American Diabetes Association, the ultimate goal for all patients, with few exceptions, is normalization or near-normalization of blood glucose levels within the constraints of hypoglycemia. Exceptions may include extremes of age, limited life expectancy, and advanced diabetic complications, including cardiac and cerebrovascular disease. Intensive patient training by a skilled team is vital to the safety and efficacy of the treatment plan.

1. Short-term goals are (a) correction of hyperglycemia and ketosis, (b) elimination of hypoglycemia, and (c) reintegration of patient into society.

2. Long-term goals
   a. Preservation of residual insulin production in type 1 patients through early physiologic insulin replacement, facilitating long-term optimal glycemic control and forestalling “brittleness.”
   b. Attainment and maintenance of normal or near-normal body weight to optimize insulin sensitivity, minimize insulin requirements, and minimize cardiovascular risk.
   c. Optimization of physical fitness through individualized realistic exercise schedules for optimal weight maintenance, insulin sensitivity, and cardiovascular risk.
   d. Prevention of microvascular complications through optimal glycemic control, normotension, and avoidance of excess sodium and protein intake.
   e. Prevention of macrovascular disease via aggressive conventional risk factor reduction.

F. Patient training, education, and motivation.

Patient training programs in the following areas are vital for short- and long-term goal achievement: pathophysiology of DM and the prevention of complications; therapeutic options for optimal control and lifestyle flexibility; dietary instruction/training; exercise integration; foot care; and sick-day and minor-illness management. Patients must be well versed in integration of these principles into their daily lives.

III. Management of type 1 diabetes mellitus: insulin considerations.

A. Indications for outpatient initiation of insulin

include the following: patient is not vomiting, has no evidence of clinical dehydration, has no evidence of diabetic ketoacidosis (DKA), and the necessary support staff are readily available.

1. It is impossible to accurately predict insulin sensitivity based on weight alone.
2. Conservative initial starting doses in an otherwise well patient are in the range of 0.25–0.5 unit per kilogram of body weight.

B. Choice of insulin

1. Human insulin should be used for all patients.
   a. Animal source insulin (beef and pork), which is antigenic, is gradually being withdrawn from the market.
   b. Some patients report being less aware of their hypoglycemia with human (as opposed to animal) insulin, although the issue remains controversial.
   c. See Table 17.2-1 for insulin types and kinetics. The table reflects the kinetics seen in actual clinical practice rather than those reported by the manufacturers in nondiabetic individuals

Activity	Classification	Name	Onset (h)	Peak (h)	Duration (h)
Rapid-acting	Insulin	Regular	0.5–1	2.5–3.5	6
	Insulin analogue	Lispro	0–0.25	1	3
Intermediate-acting	Insulin	NPH	1–3	6–8[a]	10–19
	Insulin	Lente	1–3	6–8[a]	10–19
Long-acting	Insulin	Ultralente	2–4	10–16	18–24
	Insulin analogue	Glargine	2–4	None	24–36

[a] Considerable fluctuations in day-to-day kinetics depending on absorption.

Table 17.2-1. Insulin kinetics as seen in clinical practice

C. Injection site

principles are important for insulin absorption rate.

1. Site selection
   a. Buttocks are the preferred site for bedtime injections of intermediate-acting insulin to minimize the risk of nocturnal hypoglycemia via (i) slow absorption, (ii) avoidance of the 2 a.m. counterregulatory nadir, and (iii) optimization of control of dawn surge in hepatic glucose output (dawn phenomenon).
   b. Upper abdomen is preferred for the other injections because of (i) its more rapid insulin absorption and (ii) better control of the early postprandial glucose level. Upper arms can be used as an alternative.
   c. Avoid injecting into legs and buttocks before meals due to slower absorption from these sites.
   d. Site consistency. Patients must be instructed regarding the consistent use of anatomical regions for premeal and bedtime injections with adequate site rotation within these regions to prevent lipohypertrophy.

D. Insulin injection timing issues

1. Use of the subcutaneous site versus physiologic portal insulin results in delay in insulin absorption and an unavoidable mismatch between onset and peak of the insulin action and the onset and peak of blood glucose rise after carbohydrate ingestion.
2. Injection interval
   a. Lispro insulin 0–10 minutes premeal, due to its rapid onset of action.
   b. Regular insulin 30–40 minutes premeal helps to improve postprandial glycemic control.
   c. A small snack (15 g carbohydrate) at the peak of the insulin action (3 hours for regular insulin and 6–8 hours for Neutral Protamine Hagedorn [NPH] or lente insulin) prevents hypoglycemia at this high-risk time.

E. Intensive insulin therapy programs

1. Multiple daily insulin injections
   a. Principles
      1. The use of multiple injections results in (a) smaller individual insulin doses, (b) more physiologic matching of carbohydrate and insulin, and (c) reduced risk of hypoglycemia.
      2. Evidence continues to accrue suggesting that early physiologic insulin replacement “rests” the pancreas, decreases insulitis, and preserves any residual ß-cell function.
   b. Program options
      1. The tid program with NPH/Lente
         a. Two thirds of total daily dose is given in the morning. One third of dose is Lispro/Regular insulin. Two thirds of dose is NPH insulin (isophane insulin suspension) or Lente insulin.
         b. One third of total daily dose is given in the evening with half of the dose as Lispro/regular insulin before supper and half of the dose as NPH/lente given between 10 p.m. and 1 a.m.
         c. Ratios must be modified pending patient's preferred mealtime carbohydrate distribution.
         d. The tid program with ultralente: (a) ultralente as basal (40%–60% of total daily dose given in two divided doses) and (b) premeal Lispro/regular insulin titrated to carbohydrate intake.
      2. The qid program: (a) Premeal dose (tid) of Lispro insulin titrated to carbohydrate intake, (b) a small prebreakfast dose of ultralente insulin to cover hepatic glucose (5% of total daily dose), and (c) bedtime NPH or lente (15% of total daily dose).
      3. The qid program: (a) Premeal dose (tid) of regular insulin titrated to carbohydrate intake and (b) bedtime NPH or lente (20% of total daily dose)

4. The qid program: (a) Premeal dose (tid) of Lispro insulin titrated to carbohydrate intake and (b) bedtime insulin glargine (40% total daily dose)

2. Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy
   a. Indications
      1. Failure of multiple insulin injection regimens
      2. Exuberant dawn phenomenon
      3. Need for convenience and flexibility
      4. Pregnancy
      5. Preconception
   b. Setup
      1. Lispro insulin is programmed at set hourly basal rates to control hepatic glucose output in the fasting state and attain “the happy liver” (approximately 40%–60% total daily dose).
      2. Remainder of dose is premeal/snack Lispro insulin titrated to carbohydrate intake.
      3. Lispro insulin used nearly exclusively due to superior kinetics

F. Insulin adjustment

1. Baseline dose
   a. Doses of Lispro, regular, NPH, lente, ultralente, or glargine insulin can be readily adjusted based on premeal, postprandial, and bedtime home blood glucose test results.
   b. Assuming a total daily dose of 0.5 unit per kilogram of body weight, supplementing the baseline dose by 1 unit of insulin will drop an elevated blood glucose by approximately 50 mg/dL.
2. Algorithm
   a. Home adjustment algorithm for the patient using supplemental Lispro/regular insulin:
      1. Use before meals and at bedtime.
      2. Example: In a patient taking 0.5 unit insulin per kilogram body weight, the following calculations apply:
         a. Premeal dosing. Add 1 unit of Lispro/regular insulin for every 50 mg/dL elevation in blood glucose above 120 mg/dL; that is, at 170 mg/dL, add 1 unit Lispro/regular; at 220 mg/dL, add 2 units Lispro/regular.
         b. At bedtime. Add 1 unit of Lispro/regular insulin for every 50 mg/dL elevation in blood glucose above 150 mg/ dL; that is, at 200 mg/dL, add 1 unit Lispro/regular; at 250 mg/dL, add 2 units Lispro/regular.
3. In the context of frequent follow-up, optimal control can be achieved with gradual insulin titration. Once achieved in the newly diagnosed patient, insulin requirements may gradually decline (“honeymoon phase”). Although insulin therapy can be discontinued for weeks to (occasionally) months, it may not be prudent to do so entirely. Maintaining a dose as low as 0.2 unit per kilogram of body weight in divided doses may prevent progressive insulitis and delay complete loss of ß-cell function.

IV. Management of type 1 diabetes mellitus: dietary considerations

A. Basic principles.

Dietary recommendations continue to change somewhat, with the current emphasis on individualization and carbohydrate counting while maintaining low fat (<30% of total daily calories), high fiber, and moderate protein intake. Better matching of insulin to intake of total carbohydrate through gram counting of carbohydrate allows the incorporation of modest amounts of sucrose in the diet.

B. Ideal body weight (IBW).

Several formulas exist for estimation of IBW. A simple nomogram is as follows:

1. Female IBW
   a. Assume 100 lb for first 5 feet of height.
   b. Add 5 lb for every inch in height above 5 feet.
   c. A 5 feet 5 in. tall woman should weigh 125 lb.
2. Male IBW
   a. Assume 106 lb for first 5 feet of height.
   b. Add 6 lb for every inch in height above 5 feet.
   c. A 5 feet 8 in. tall man should weigh 154 lb.
3. Add 10% for a large-framed individual; subtract 10% for a small-framed individual.

C. Caloric requirements

1. Caloric requirements vary with age, sex, IBW, level of physical activity, and concurrent illness.
2. Formulas for calculation. The Harris-Benedict equation approximates well, but a simpler formula follows:
   a. IBW (lb) × 10 = resting energy expenditure (REE) calories.
   b. Activity factor: Add 10% for inactivity, 30% for moderate activity, and 50% for significant activity (e.g., manual labor, intense exercise).
   c. Total caloric requirements = REE + activity factor × weight loss factor

D. Nutrient distribution.

Carbohydrate should be 50%–60% of total daily calories, whereas fat should account for less than 30% and protein for 20% of total daily calories.

E. Priorities of patient training

1. Emphasize carbohydrate counting and consistency with three meals. Add 15-g carbohydrate snacks to cover insulin peaks (regular/NPH/ Lente), in the context of an appropriate total caloric intake.
2. Other priorities include fat gram counting and maintenance of low fat intake (goal is less than 30% of total intake). Sodium intake goal is less than 2,000 mg/d. Optimizing fiber intake and limiting protein intake are also important.

V. Management of type 1 diabetes mellitus.

Home blood glucose monitoring (HBGM) considerations

A. Basic principles

1. Accuracy in HBGM is critical to safety and success of intensive therapy.
2. Frequency
   a. Minimum of 4 tests per day should be done before meals and at bedtime.
   b. Testing 1 hour after a meal is necessary to accurately determine the adequacy of the premeal Lispro insulin doses.
   c. Additional testing is done when hypoglycemia or hyperglycemia is suspected.
   d. Periodic 2 a.m. and 4 a.m. tests
   e. Prior to driving
3. Meters are easy to use and have “no blot” technology, thus eliminating timing by the patient. The blood volume required has progressively decreased, with some meters requiring as little as 0.3 μL. Many meters have memories that can store a large volume of results and can download data to personal computers. Patients must follow manufacturer's instructions carefully to achieve accurate results.
4. Sources of error in HBGM: improper cleansing of finger; failure to wipe away first drop of blood when alcohol is used to cleanse finger; volume of blood applied to strip is too much or too little; meter is not calibrated to strip lot number; damaged strips resulting from exposure to heat, light, humidity, or cold; out-of-date strips; meter not properly cleaned; and failure to use glucose control solutions to verify strip accuracy.
5. Patient precision is vital to successful use of the insulin algorithm and sick-day management.

VI. Management of type 1 diabetes mellitus: exercise considerations

A. Physical fitness

is a goal for all individuals with DM. Benefits of exercise include improvement of insulin sensitivity, aid in weight control, and reduction of cardiovascular risk and stress. Safe exercise plans must be individualized based on age, cardiovascular status, foot problems, neuropathy, and retinopathy. Even increased activity, such as grocery shopping, results in a lowering of blood glucose levels. Uncompensated physical activity is a very common cause of hypoglycemia.

B. Insulin adjustment for exercise or activity.

Use for planned physical activity.

1. Reduce insulin dose that is active during the exercise by 1–2 units for every 20–30 minutes of exercise.
2. Occasionally, individuals have a delayed or sustained response to physical activity such that their bedtime insulin dose may need to be reduced by 1–2 units following, for example, evening physical activity.
3. Insulin pump patients have the option to program a temporary reduction in their basal insulin infusion rates.

C. Carbohydrate adjustment for exercise or activity

1. Use for either planned or spontaneous activity.
2. Augment carbohydrate intake as follows: Add another 15-g carbohydrate snack (over and above the planned snacks) for every 20–30 minutes of physical activity, depending on the intensity of activity.

VII. Standard of care for follow-up.

Once glycemic control has been established, maintenance of glycemic control depends on the frequency of follow-up.

A.

Minimum visit frequency is once every 3 months.

B.

Review history; perform an interim physical examination; identify patient errors and omissions; adjust the patient's insulin dosage, diet, and exercise program; and do ongoing patient training. Laboratory evaluations should include hemoglobin A_{1c} every 3 months and annual assessments of urine microalbumin/creatinine ratio, thyroid-stimulating hormone, blood chemistries and lipids (full panel). In addition, an electrocardiogram (ECG) and ankle-brachial indices (see following section) should be obtained annually.

VIII. Dawn phenomenon

A. The dawn phenomenon

is a markedly elevated fasting blood glucose secondary to an exuberant rise in hepatic glucose output. This hyperglycemia results from a surge in counterregulatory hormone concentrations (catecholamines, growth hormone, and cortisol) in the absence of nocturnal hypoglycemia.

B. Treatment

1. Delaying the timing of bedtime insulin until closer to midnight and titrating up the bedtime NPH, lente, or glargine insulin usually suffices.
2. In some instances, however, the dose increase results in hypoglycemia prior to the dawn surge. Continuous subcutaneous insulin infusion is ideal, so that basal rates can be preprogrammed to coincide with the patient's individual dawn surge.

IX. Somogyi's phenomenon

A. The Somogyi phenomenon

is posthypoglycemia hyperglycemia due to a surge in counterregulatory hormones, rather than insulin “run-out” or overtreatment with excess carbohydrate.

B. Strategy.

Perform HBGM at 2 a.m. and 4 a.m. in addition to premeal and bedtime HBGM. If the Somogyi phenomenon is identified, a dose reduction of the bedtime injection is indicated, coupled perhaps with a shift in the timing of the injection as late as possible (midnight or thereafter), with emphasis on the lower buttocks as the injection site of choice.

X. Hypoglycemia.

Recurrent. In a well-designed, physiologic, individualized treatment program, most episodes are related to patient error.

A. Patient-related errors

include insulin-carbohydrate mismatch, delayed or missed meals, missed snacks, uncompensated exercise, erratic insulin

injection site rotation, and lack of adequate HBGM (inaccurate tests or low frequency of HBGM).

B. Non-patient-related problems

include unpredictable absorption or kinetics of NPH or lente insulin or possibly insulin autoantibodies. This is best treated by minimizing use of longer acting insulins by either the qid programs (III.E.1.b[1][a]) or CSII (III.E.2).

XI. Hypoglycemia unawareness

A.

Hypoglycemia can be a major problem in intensive therapy. In most cases, it is reversible to varying degrees through program revisions designed to eliminate hypoglycemia.

B.

Once hypoglycemia has been eliminated for a reasonable period, the patient's subjective awareness and counterregulatory response improve, with the exception of the glucagon response. Improvement in hypoglycemia awareness facilitates safe lowering of ambient glucose levels and hemoglobin A_{1c}.

XII. Diabetic ketoacidosis (DKA).

Prevention and management. DKA is a syndrome of hyperglycemia, ketonemia, and ketonuria of varying intensity that results in death in 10% of cases.

A.

Causes. Minor illnesses are the most common cause, such as upper respiratory and urinary tract infections. Major illnesses (e.g., myocardial infarction) are a less common cause.

B.

Most cases of severe DKA can be averted through aggressive attention to the sick day management guidelines (see Section XXI.B).

C.

If intractable emesis occurs, take the following measures:

1. Administer early intravenous hydration with 1–2 L of fluid (in emergency room or office).
2. Administer SC insulin, not IV insulin, as the half-life of a bolus of regular insulin is 5 minutes.
3. Administer parenteral antiemetics.
4. Do not delay. Delay in seeking therapy is the major factor in severe DKA episodes, which result in costly hospitalizations in intensive care units and even death.

D.

Management. Identify and address the underlying illness. Rule out silent myocardial infarction as cause of DKA.

1. Correct the volume depletion.
   a. Give 1–2 L of normal saline in the first 1–2 hours to correct hypotension and establish good urine output. In children and adolescents, give 500 mL of normal saline per hour for the first 1–2 hours.
   b. Total volume deficit is frequently 5–6 L. In most individuals, volume can be replaced over 12–24 hours, depending on the underlying cardiac and renal status.
2. Insulin treatment. Start a low-dose IV infusion at the rate of 0.1 unit/kg per hour to result in a 100 mg/dL per hour fall in blood glucose. Adequately dilute the insulin to allow fine titration (50 units regular human insulin in 500 mL normal saline). This dosage overcomes the common clinical problem of having 1 unit/h be the lowest infusion rate possible. To maintain a sufficiently high insulin dose to correct ketosis without hypoglycemia, the intravenous fluids must be changed to dextrose 5% or 10% when blood glucose level falls below 250 mg/dL.
3. Electrolyte replacement
   a. Potassium replacement may be initiated once urine output is documented. Use 20–40 mEq/L IV fluids and monitor serum values q2h.
   b. Bicarbonate therapy is indicated only for severe acidosis (pH < 7.2) or a bicarbonate concentration of less than 5 mEq/L. The goal is to raise pH above 7.2, not to achieve total correction. Forty to 80 mEq/m^2 of bicarbonate may be infused over 2 hours and the levels reassessed. Bicarbonate should not be given by IV push because that could result in cerebral edema, which is often fatal.

c. Phosphate repletion has more theoretical than proven practical benefits unless severe depletion is present (serum phosphorus <0.5 mg/dL).
d. Magnesium repletion. If deficiency is severe (serum magnesium level <1.0 mEq/L) or the patient is symptomatic (seizures, tetany, cardiac arrhythmias), then replace with magnesium chloride at a dose of 1 mEq/kg per 24 hours, assuming normal renal function.

4. Monitor DKA progress. Clinical and laboratory monitoring of the patient should be documented on a flowsheet. Laboratory parameters should be followed at least every 2 hours until stability emerges.

XIII. Hyperglycemic hyperosmolar nonketotic coma

A. Characteristics.

This development occurs in type 2 DM patients, most commonly with underlying renal insufficiency or cerebrovascular disease (cerebrovascular accident or subdural hematoma). The degree of dehydration is more severe than that of DKA. Blood glucose levels range from 600 to 2,000 mg/dL, and ketosis is absent.

B. Therapy

is similar to that for DKA in terms of IV fluids, insulin, and electrolytes, but hydration rates must be lower.

1. The initial infusion rate of normal saline should not exceed 1 L/h to expand the extracellular space, with the IV fluid being switched to half normal saline once blood pressure is stable and good urine output is established. Fluid should be replaced over a 24-hour period.
2. Often insulin therapy is not needed on an ongoing basis once the acute metabolic derangement has been corrected and any underlying precipitating illness treated or resolved.

XIV. Recurrent diabetic ketoacidosis or brittle diabetes mellitus.

Nonadherence to a well-designed treatment program or lack of same is the cause. If, after comprehensive patient retraining, the problem persists, then occult psychological issues, such as marital disharmony or dysfunctional family, should be explored. The assistance of a psychologist or psychiatrist experienced in diabetes management is essential.

XV. Initial management of type 2 diabetes mellitus

A. Minimally decompensated presentation

1. Clinical picture includes obesity and mild to moderate hyperglycemia with or without symptoms.
2. Treatment strategies include patient education, training, and motivation; an individualized hypocaloric diet with diet training; and an exercise plan tailored to the individual.
3. Emphasize permanent lifestyle modification.

B. Moderately decompensated presentation

1. Clinical picture. Obesity, severe symptomatic hyperglycemia (fasting blood glucose >300 mg/dL), and mild dehydration or decompensation calls for more urgent lowering of blood glucose levels, largely for symptomatic relief and reversal of the glucotoxic effect of the prior sustained hyperglycemia on pancreatic islet insulin secretion and action.
2. Treatment strategies
   a. Temporary insulin therapy with pre-breakfast and bedtime dosing of NPH or lente insulin at a starting daily dose of 0.5 unit per kilogram of weight and an algorithm for hyperglycemia similar to that for type 1 DM patients will rapidly yield symptomatic relief and reversal of islet and peripheral/target organ glucotoxicity.
   b. Prescribe an individualized hypocaloric diet with diet training and an exercise plan.
   c. The long-term goal is tapering and withdrawal of insulin, assuming that glycemic control can be maintained with diet and oral agent therapy.

C. Severely decompensated presentation

1. Clinical picture shows a severely symptomatic patient with blood glucose levels exceeding 500 mg/dL, marked dyslipidemia (serum triglycerides >1,000 mg/dL), and hyperosmolality with absence of ketosis.

2. Treatment strategies
   a. Intravenous fluids and insulin (similar to DKA) in the hospital setting are necessary for acute reversal of the metabolic derangement, followed later by a switch to pre-breakfast and bedtime dosing of NPH or lente insulin.
   b. Start patient training and education with an individualized hypocaloric diet and exercise plan.
   c. The long-term goal is tapering and withdrawal of insulin, assuming that glycemic control can be maintained with diet and oral agent therapy.

D. Consider pharmacotherapy for obesity

(sibutramine or orlistat) in patients who are not losing weight.

XVI. Special situation: the nonobese type 2 diabetic patient.

Patients who are at less than 120% IBW may benefit from modest weight loss toward IBW, with a hypocaloric diet and exercise training program. Exercise may be especially beneficial to these patients, many of whom are relatively insulinopenic and poor responders to oral agents.

XVII. Dietary management of type 2 diabetes mellitus

A. The IBW and caloric requirements

are the same as those for type 1 DM patients. Reduction in daily caloric intake by 500 calories will facilitate a 1 lb/wk weight loss.

B. Goals in obese patients

1. Reduction in body weight
   a. Strategies. Reduce fat intake through fat gram counting, high fiber intake, reduced sodium intake, and the use of artificial sweeteners and low-fat products.
   b. A reduction of even 10% in weight can have a major impact on the clinical course of a type 2 patient. Patients need not reduce to IBW to achieve euglycemia, but the closer they are, the better all the other markers of the cardiodysmetabolic syndrome will be (e.g., dyslipidemia, hypertension).
2. Manage concurrent dyslipidemia and hypertension.

XVIII. Very low-calorie diets.

are occasionally used in specialty centers for the more difficult or noncompliant patients. Recidivism remains common.

XIX. Exercise therapy for type 2 diabetes mellitus.

All of the benefits of exercise for the type 1 patient apply even more to the type 2 patient, with the added benefit of raising the frequently depressed high-density lipoprotein (HDL) cholesterol. Adherence to an ongoing exercise routine is one of the most powerful predictors of maintenance of weight loss.

XX. Pharmacotherapy of type 2 diabetes mellitus

(see Table 17.2-2)

Medication	Usual recommended starting dose	Usual maintenance dose	Maximum daily dose	Dose frequency
Biguanide				
Metformin	500 mg bid	1,000 mg bid	2,550 mg	bid or tid
Metformin xr	500 mg qd	1,000–2,000 mg qd	2,000 mg qd	qd
Thiazolidinediones (glitazones)				
Rosiglitazone	2 mg bid	2–4 mg bid	8 mg	bid preferred; can be qd
Pioglitazone	15 mg qd	30–45 mg qd	45 mg	qd
α-Glucosidase inhibitors				
Acarbose	25 mg tid	50–100 mg tid	300 mg	tid
Miglitol	25 mg tid	50–100 mg tid	300 mg	tid
Repaglinide	0.5mg tid 0–15 min premeal	2–4 mg tid 0–15 min premeal	16 mg	bid-qid pending meal/ snack frequency
Nateglinide	120 mg tid premeal	120 mg tid premeal	360 mg	tid with meals
Sulfonylureas				
Glimepiride	1 mg qd	4–8 mg qd	8 mg	qd or bid
Glipizide GITS	2.5 mg qd	10–20 mg qd	20 mg	qd or bid
Glipizide	5 mg bid	10–20 mg bid	40 mg	bid
Micronized glyburide	1.5 mg bid	3–6 mg bid	12 mg	bid
Glyburide	2.5 mg qd	5–10 mg bid	20 mg	bid
Tolbutamide	500–1,000 mg	500–3,000 mg	3,000 mg	bid or tid
Tolazamide	100–250 mg	100–1,000 mg	1,000 mg	qd or bid
Acetohexamide	250–500 mg	250–1,500 mg	1,500	qd or bid
Chlorpropamide	100–250 mg	100–500 mg	750 mg	qd

Table 17.2-2. Oral agents used to treat diabetes mellitus

A. Insulin sensitizers

1. Metformin
   a. Indication. Metformin therapy is indicated for obese (>120% IBW), diet-failure patients with type 2 DM who are free from liver disease, have good renal function (normal serum creatinine), and have no underlying chronic hypoxic condition (e.g., chronic obstructive pulmonary disease, asthma, or advanced congestive heart failure). Lactic acidosis is a risk if any of these underlying conditions exist; hence, the contraindication. Metformin should be discontinued on the day of any iodinated dye-load procedure or surgery and should be withheld for 48 hours after the procedure. Metformin should not be restarted until a normal post-test/surgery serum creatinine is confirmed. Metformin should also be withheld during treatment for pneumonia or acute myocardial infarction. Metformin is contraindicated in individuals with known hypersensitivity to the drug or any of its components.
   b. Mode of action. Metformin is an insulin sensitizer with a primary mode of action of controlling hepatic glucose output. It is an antihyperglycemic agent. It is not a hypoglycemic agent; therefore, it cannot cause hypoglycemia when used as monotherapy.

c. Dosing
   1. Use as monotherapy or in combination with sulfonylureas or insulin. Combination therapy results, on average, in an additional 50 mg/dL lowering of blood glucose.
   2. Initial dose (500 mg bid with food) can be titrated to a maximum of 2,550 mg in an 850 mg tid dosing schedule. Maximum effective dose is seen at 1,000 mg bid.
   3. An extended release preparation is now available to facilitate dosing convenience and reduce frequency of diarrhea.

d. Other effects. Metformin facilitates weight loss and an improvement in the lipid profile.

e. Adverse effects. Gastrointestinal (GI) side effects of nausea, flatus, and diarrhea can occur but are usually self-limited (1–2 weeks). Side effects can be minimized by taking the agent with food. Long-term discontinuation rate due to GI side effects is only 3%–4%.

2. Thiazolidinediones (glitazones)

a. Indications. Therapy with rosiglitazone or pioglitazone therapy is indicated for obese (>120% IBW) diet-failure patients with type 2 DM who are free of liver disease, hepatic transaminases £1.5 times the upper limit of normal, and who have good left ventricular function. Therapy is contraindicated in patients who have New York Heart Association class III or IV congestive heart failure. Glitazones are contraindicated in individuals with known hypersensitivity to the drug(s) or any of their components. They can be used safely in patients with end-stage renal disease.

b. Mode of action. Glitazones are insulin sensitizers that activate peroxisome proliferator-activated receptors (PPARs). Clinical effect from this activation is delayed, and the maximal effect of a given dose level may not be seen for 8–12 weeks. The primary mode of action of glitazones is to enhance skeletal muscle glucose uptake both directly and also indirectly via reduction in free fatty acids. At higher doses they also reduce hepatic glucose output. They are antihyperglycemic and as such when used as monotherapy or in combination with metformin (only pioglitazone is FDA-approved for combination therapy with metformin) cannot cause hypoglycemia.

3. Dosing

1. Rosiglitazone
   a. Initial dose of 2 mg bid can be titrated to 4 mg bid. Can be given qd but better glucose lowering effect noted with bid dosing in clinical trials.
   b. Dosing independent of food intake.
   c. Can be used as monotherapy or in combination with metformin.
2. Pioglitazone
   a. Initial dose of 15 mg qd can be titrated to 45 mg qd.
   b. Dosing independent of food intake.
   c. Can be used as monotherapy or in combination with metformin, sulfonylureas, or insulin
3. Adverse effects
   1. Idiosyncratic hepatic dysfunction. The flagship glitazone troglitazone was voluntarily removed from the U.S. market by its manufacturer from in March 2000, secondary to the occurrence, among a small number of treated patients, of fulminant hepatic failure resulting in transplantation and/or death. The incidence of elevations in hepatic transaminases in treated patients was 2%. Rosiglitazone and pioglitazone have a lower risk of elevations in hepatic transaminases (0.35% and 0.26%). Current recommendations are for monitoring of hepatic transaminases

at baseline, then every 2 months thereafter for the first year and periodically thereafter.

2. Pedal edema. Edema, varying from trace to 4+, can develop as a consequence of glitazone therapy. No predisposing factors appear to exist. Patients who experience edema with one glitazone may occasionally tolerate another. Frequently, starting at a low dose with slow titration can help. This edema can potentially precipitate congestive heart failure (CHF) in susceptible patients.
3. Dilutional anemia
4. Weight gain. The weight gain seen with glitazone therapy in some patients appears to be in excess of that expected from reduction/elimination in glycosuria.

B. α-Glucosidase inhibitors

1. Indications. Acarbose and miglitol are generally indicated as second-line pharmacologic treatment for individuals with type 2 DM who have previously failed diet therapy. Contraindications include cirrhosis, inflammatory bowel disease, other bowel disease, and malabsorption and known hypersensitivity to the drugs or any of their components.
2. Mode of action. α-Glucosidase inhibitors interfere with digestion and absorption of dietary carbohydrate. Therefore, their primary effect is on postprandial blood glucose levels. They are antihyperglycemic agents and as such when used as monotherapy or in combination with metformin (acarbose only) cannot cause hypoglycemia. However, hypoglycemia can occur when they are used in combination with a sulfonylurea or insulin. When hypoglycemia occurs, it must be managed with pure glucose because the digestion and absorption of alternative carbohydrates will be blocked.
3. Dosing
   a. Starting dose of 25 mg tid to be taken with the first bite of each meal.
   b. Titration to 50 mg tid, up to a maximum dose of 100 mg tid
   c. May be used as monotherapy or in combination with sulfonylureas. Acarbose may also be used in combination with metformin or insulin.
   d. Adverse effects include flatus and nausea, which lessen over time. Small numbers of patients experience an elevation in transaminases (usually in individuals with a body weight of less than 60 kg).

C. Secretagogues

1. Sulfonylureas
   a. Indications. Although in the past sulfonylureas were considered to be first-line pharmacotherapeutic agents for type 2 DM, new treatment patterns generally utilize these drugs as second-line agents in the setting of mild to moderate hyperglycemia. Their use is contraindicated in patients with elevations in hepatic transaminases. A relative contraindication is sulfa allergy. Caution must be used in the setting of end-stage renal disease. Sulfonylureas are contraindicated in individuals with known hypersensitivity to these medications.
   b. Mode of action is augmentation of pancreatic insulin secretion.
   c. Dosing. See Table 17.2-2 .
   d. Adverse effects are weight gain and hypoglycemia. Hypoglycemia frequency is reduced with glimepiride. The first-generation agents (chlorpropamide, tolazamide, tolbutamide, and acetohexamide) are now rarely used because they carry a poor side effect profile, including protein binding, syndrome of inappropriate secretion of antidiuretic hormone, and the chlorpropamide flush.
2. Glucovance-fixed-combination glyburide/metaformin
   a. Doses available
      1. 1.25 mg/250 mg
      2. 2.5 mg/500 mg
      3. 5 mg/500 mg

b. Benefits
   1. Dosing convenience
   2. Superior glycemic control with side effect reduction as compared to forced titration monotherapy

3. Repaglinide
   a. Indications. Patients with type 2 DM who have failed dietary therapy. Contraindicated in individuals with known hypersensitivity to the drug or any of its components. No sulfa moiety. Can be used in patients with sulfa allergy/sulfonylurea allergy.
   b. Mode of action. Binding to a specific islet cell receptor results in more rapid secretion of insulin in response to food eaten as compared with sulfonylureas. Effect is seen especially on postprandial and to a lesser extent on fasting glucose levels
   c. Dosing
      1. Initial dose of 0.5 mg taken 0–15 minutes before a meal can be titrated to a maximum dose of 4 mg taken 1–15 minutes before a meal or snack for a maximal daily dose of 16 mg.
      2. Must be dosed in conjunction with food to have optimum glucose lowering effect.
      3. Can be used as monotherapy or in combination with metformin.
      4. Adverse effects. Hypoglycemia can occur, but does so less frequently than with sulfonylureas due to the rapid onset and shorter duration of action. This is especially pertinent when patients delay or miss meals. In addition, the lack of an increase in basal insulin secretion lowers the risk of hypoglycemia.

4. Nateglinide
   a. Indications. Type 2 DM inadequately controlled by diet. Contraindication is hypersensitivity to nateglinide or any of its components. No sulfa moiety. Can be used in patients with sulfa allergy/ sulfonylurea allergy. Can be used as monotherapy or in combination with metformin.
   b. Mode of action. The phenylalanine derivative nateglinide binds to the potassium channel in the islet, resulting in more rapid insulin secretion from the pancreatic islets. It uniquely restores early insulin secretion, which is lost early in the course of type 2 DM. Early insulin secretion is very important in the regulation of hepatic glucose production postprandially.
   c. Dosing
      1. 120 mg tid prior to meals
   d. Adverse effects
      1. Hypoglycemia is the most common side effect and is seen at a much lower rate than that with any other secretagogue.

D. Insulin

1. Insulin source. All insulin should be human insulin.
2. Long-term insulin therapy indications.
   a. Insulinopenic nonobese type 2 DM patients who have failed optimum diet, exercise, and oral agent therapy are best managed on insulin programs described for type 1 DM patients.
   b. Insulin is indicated in secretagogue-failure patients in whom metformin and/or glitazones are contraindicated, are not tolerated, or have failed.
3. Dosing schedules. Several dosing schedules have been advocated, and all have a tendency to progressive weight gain and attendant increasing insulin requirements to try to maintain glycemic control. Administration of NPH, lente, or glargine insulin at bedtime facilitates the best control of dawn hepatic glucose output, thereby minimizing islet glucotoxicity and maximizing islet insulin secretory response to daytime sulfonylureas. Should this regimen fail to give adequate control,

any of the regimens outlined for type 1 DM patients may be used, with the exception of CSII (see Section III). A rare indication for the use of CSII in type 2 DM is the lean insulinopenic patient.

XX. Special testing in diabetes mellitus

A. Ankle-brachial indices

are part of the standard of care because of. their predictive value, not only for peripheral vascular disease (PVD) but also for coronary artery disease and cardiovascular death risk. Blood pressures are measured with a mercury sphygmomanometer and hand-held Doppler at both the dorsalis pedis and posterior tibial arteries and compared with that obtained at the brachial artery. Any reduction in the ankle-brachial index (ankle pressure divided by brachial pressure) below 0.9 is significant and warrants intensive risk factor modification.

B. Stress testing

1. Stress testing will only detect severe flow-limiting disease, which is responsible for less than 30% of all acute infarcts. The majority of acute myocardial infarctions result from plaque rupture in individuals with nonhemodynamically significant degrees of stenosis.
2. Despite the above limitations, stress testing is warranted under certain circumstances as per the American Diabetes Association Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes.
   a. Routine stress testing is not indicated in the asymptomatic diabetic patient with one or no risk factors (as listed below) and a normal resting ECG and 0–1 risk factors (as listed below in b5).
   b. Stress testing is warranted under the following situations:
      1. Typical or atypical (dyspnea or exertional fatigue) symptoms.
      2. Resting ECG suggestive of ischemia or prior infarction.
      3. Peripheral or carotid occlusive disease.
      4. Sedentary lifestyle, age ≥ 35, and planning to begin a vigorous exercise program.
      5. Two or more of the following risk factors:
         a. Total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/ dL, or HDL cholesterol < 35 mg/dL
         b. Blood pressure > 140/90 or treatment for hypertension
         c. Smoking
         d. Family history of premature coronary artery disease
         e. Microalbuminuria or macroalbuminuria

XXI. Special issues

A. Foot care

1. The critical interplay of three pathophysiologic processes—neuropathy, ischemia, and sepsis—results in injury predisposition and potential amputation.
2. Patient should be instructed to inspect and wash feet daily; to use lotion on plantar and dorsal surfaces but not on intertriginous areas; to keep nails trimmed; and to seek podiatric care if needed.
3. Patient should be instructed not to soak feet, walk barefoot, or do “bathroom surgery.”

B. Sick-day guidelines

1. Perform HBGM at a minimum qid; ideally q4h.
2. Monitor urine ketones with voiding or monitor serum ketones with the new Precision Extra meter
3. Maintain aggressive oral fluid intake to prevent onset of hyperglycemia or ketosis: 1 cup salted broth every hour to replace fluids and electrolytes; 2 cups hourly is needed if urine ketones are moderate or higher.
4. Always take full baseline insulin dose.
5. Add more insulin per algorithm; increase algorithm (i.e., take 2 units of Lispro/regular insulin per 50 mg/dL elevation in blood glucose) if making no or slow progress.

6. Replace solid carbohydrates with clear liquid carbohydrates (such as regular ginger ale, regular soda pop, regular Jello) if necessary.
7. Obtain early medical evaluation for underlying illness.
8. Obtain early emergency intervention with intravenous fluids if emesis reoccurs (more than three episodes) or diarrhea is intractable.
9. The goal is prevention of DKA, which has up to a 10% mortality per episode.

XXII. Complications of diabetes mellitus

A. Hypertension in DM

(see Chapter 9.1)

1. In type 1 DM patients, hypertension implies the presence of microalbuminuria or nephropathy until proven otherwise.
2. Treatment
   a. Angiotensin-converting enzyme (ACE) inhibitors have a special role in preserving renal function in type 1 DM patients based on an excellent study with captopril.
   b. Calcium channel blockers are warranted in cases of intolerance of or contraindications to ACE inhibitors or inadequate blood pressure control with these agents. They may have renal protective effects.
   c. Angiotensin II receptor blockers are useful when ACE inhibitors are not tolerated, the most common reason being cough.
   d. ß-Blockers have generally been avoided by endocrinologists unless there are specific indications (e.g., following myocardial infarction) because of symptom masking and delay in recovery of hypoglycemia in type 1 DM patients and worsening dyslipidemia and PVD in type 2 DM patients. However, the combination blocker carvedilol has unique properties that almost negate the potential negatives.
   e. Diuretics should be avoided unless indicated for edematous states because of disturbing data suggesting a 3.8-fold increased cardiovascular death rate.
   f. α-Blockers may be useful add-on therapy (not monotherapy) for patients not achieving goal with first-line agents.

B. Dyslipidemia

(see Chapter 17.4)

1. In type 1 DM, in the absence of nephropathy, dyslipidemia is generally only associated with poor glycemic control. If dyslipidemia is present, it usually indicates a concurrent familial dyslipidemia, which must be aggressively treated along conventional lines.
2. Type 2 DM. Most common is a type IV picture with high triglycerides, low HDL cholesterol, and variable elevations in total and low-density lipoprotein (LDL) cholesterol.
   a. Besides optimizing glycemic control, the addition of fenofibrate 200 mg qd or gemfibrozil 600 mg bid is frequently necessary to lower the triglycerides to an acceptable range (<200 mg/dL).
   b. In the absence of a satisfactory response, the addition of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (pravastatin is the only one approved for combination therapy) with careful follow-up for potential complications is warranted.
   c. Elevated LDL cholesterol must be managed as in a nondiabetic person, with the exception of the avoidance of resins, which may exacerbate any preexisting hypertriglyceridemia.
   d. In the past, niacin has been contraindicated in diabetes due to its adverse effect on glucose control. However, the long-acting formulation of niacin extended-release tablets appears to have good clinical effect in terms of lowering triglycerides and raising HDL cholesterol with minimal adverse effects on glucose control.

C. Proteinuria

1. Type 1 DM
   a. The presence of proteinuria greater than 500 mg per 24 hours, regardless of presence of hypertension, is an FDA-approved indication for the use of captopril 25 mg tid. Other ACE inhibitors may have similar benefits, although definitive long-term data are lacking.

b. Reduction of dietary protein intake toward 0.8 g per kilogram of body weight is prudent

2. Type 2 DM. Management strategies are similar to those of type 1, although definitive studies are still pending.

D. Microalbuminuria

1. As an elevated urine microalbumin/creatinine ratio is a strong predictor of the progression to clinical proteinuria, its presence is an indication for ACE inhibitor treatment. Although currently not FDA-approved, clinical trial data support their use in patients with type 1 or type 2 diabetes.

E. Retinopathy.

An annual dilated ophthalmologic examination is indicated for all, with laser therapy being well established in the preservation of vision. Although not FDA-approved, the benefits of ACE inhibitor treatment in slowing the progression of retinopathy was noted in the EUCLID Trial.

F. Neuropathy

(see Chapter 6.9). Symptomatic pain may be controlled with:

1. Venlafaxine XR starting at a dose of 37.5 mg qd and titrating to an effective dose of 150-225 mg daily.
2. Gabapentin starting at a dose of 100–300 mg hs and titrating to a maximum dose of 800 mg tid. Doses must be significantly reduced in the setting of reduced creatinine clearance.
3. Tricyclic antidepressants (e.g., amitriptyline), starting at low doses of 10–25 mg at bedtime and titrating up, pending patient tolerance.
4. Additional daytime pain relief can be obtained with topical capsaicin cream or dextropropoxyphene-acetaminophen (Darvocet N-100), or both.

XXIII. Pregnancy planning

(see Chapter 14.6). The congenital abnormality rate and risks of macrosomia can be reduced almost to nondiabetic levels through euglycemia at the time of conception and throughout pregnancy. This is best achieved through an intensive program of (a) prebreakfast ultralente, premeal Lispro insulin, and bedtime NPH or lente insulin, or (b) CSII. Individuals with type 2 DM should discontinue all oral agents and initiate intensive insulin therapy prior to conception.

XXIV. Indications for specialty referral

include inadequate support staff (diabetes team) to provide comprehensive diabetes care, failure to achieve glycemic control goals, recurrent hypoglycemia or DKA, DKA or hyperglycemic hyperosmolar nonketotic coma, and diabetic complications (e.g., nephropathy, retinopathy, refractory dyslipidemia, refractory hypertension, unusual neuropathies, peripheral vascular disease, coronary artery disease).

XXV. Networking to optimize diabetes care.

Physicians alone cannot provide all the care and training needed by patients with DM. Physicians need to identify community resources to assist in the modern multidisciplinary team-care approach: nurse educators (certified diabetes educators) who are hospital based or private practice based, dietitians (certified diabetes educators), psychologists, social workers, podiatrists, and endocrinologists.

17.3

THYROID DISORDERS

Roland Sakiyama

Thyroid disorders affect multiple organ systems, resulting in a variety of clinical manifestations. Thyroid disease may present emergently (thyroid storm or myxedema coma), insidiously (hyperthyroidism, hypothyroidism), or asymptomatically (thyroid nodule). Knowledge of the clinical presentation, laboratory evaluation, and appropriate therapy is essential for the practicing family physician.

Hyperthyroidism

I. Diagnosis

A. Clinical presentation

1. Symptoms include nervousness, diaphoresis, heat intolerance, palpitations, fatigue, weakness, weight loss (despite an increased caloric intake), eye complaints, decreased menstrual flow, more frequent bowel movements, irritability, and emotional lability.
2. An abrupt onset of symptoms is common with subacute thyroiditis or silent thyroiditis, whereas an insidious onset is more typical of Graves' disease (diffuse toxic goiter) or toxic multinodular goiter.
3. Apathetic thyrotoxicosis is an atypical presentation of hyperthyroidism, usually seen in the elderly. Patients exhibit apathy, muscle rigidity, depression, dementia, anorexia, marked weight loss, and constipation.
4. General examination may reveal tachycardia, systolic hypertension, hand tremor, onycholysis, warm and moist skin, pretibial myxedema, lid or globe lag, proptosis, chemosis (conjunctival edema), goiter, cervical lymphadenopathy, hyperdynamic precordium, shortened relaxation of deep tendon reflexes, and, occasionally, splenomegaly or gynecomastia. The eyes should be examined carefully for proptosis and limitation of extraocular movements (i.e., Graves' orbitopathy), which is specific for Graves' disease.
5. Thyroid examination may reveal a goiter, bruit (indicating hypervascularity most common in Graves' disease), or tenderness (subacute thyroiditis). Document size, texture, and presence of nodules (a single nodule suggests toxic adenoma, whereas multiple nodules are found in toxic multinodular goiter).

B. The laboratory evaluation

has two goals: first, to document the presence of hyperthyroidism and second, to determine its cause (1).

1. The diagnosis of hyperthyroidism is confirmed by documenting the following.
   a. Suppressed or undetectable thyroid-stimulating hormone (TSH, thyrotropin). Do not rely solely on a suppressed TSH to establish the diagnosis of hyperthyroidism because suppression of TSH can be seen in other disorders.
   b. Increased free T_4 index (or serum thyroxine, T_4).
   c. Increased free T_3 index (or serum triiodothyronine, T_3). Occasionally, a patient may have hyperthyroid symptomatology, a suppressed TSH, normal free T_4 index, but elevated T_3—so-called T_3 toxicosis.
2. Tests used to establish the cause of hyperthyroidism
   a. TSH receptor autoantibody tests [TSI (thyroid-stimulating immunoglobulin) or TRab (thyroid receptor antibody)] are positive in 80% of patients with Graves' disease and are diagnostic of this disorder.
   b. Ancillary tests include erythrocyte sedimentation rate, elevated in subacute thyroiditis, and thyroglobulin (Tg) suppressed (less than 10 ng/mL) in thyrotoxicosis factitia (excessive ingestion of thyroid hormone). Increased Tg is a nonspecific indicator of thyroid inflammation and is seen in most hyperthyroid disorders.
   c. Radiologic evaluation
      1. The radioactive iodine uptake (RAIU) is elevated in Graves' disease, toxic multinodular goiter, toxic adenoma, TSH-secreting tumors, and trophoblastic tumors. A low RAIU (less than 5%) is seen in subacute (painful) thyroiditis, silent (painless) thyroiditis, thyrotoxicosis factitia, or iodine-induced thyrotoxicosis.
      2. The radioiodine thyroid scan shows a diffuse, homogeneous distribution in Graves' disease (diffuse toxic goiter), multiple areas of increased uptake in toxic multinodular goiter, and a single area of increased uptake in toxic adenoma.

II. Therapy

A. ß-Adrenergic antagonists,

or ß-blockers, provide rapid control of sympathetic-mediated hyperthyroid symptoms. Propranolol given in doses of 20–40 mg PO q6h is very effective. Longer acting preparations may also be used.

B. Antithyroid drugs (ATDs).

Propylthiouracil (PTU) and methimazole (Tapazole) are concentrated in thyroid tissue and inhibit thyroid T_4 and T_3 synthesis. Methimazole is often preferred because of its longer half-life (can often be given bid or qd) and at doses of less than 30 mg/d may have a lower risk of agranulocytosis. ATDs are used to lower thyroid hormone levels in anticipation of radioactive iodine therapy or surgery or as long-term therapy in Graves' disease with the goal of inducing a remission of the hyperthyroid condition.

1. Dosage. PTU is started at 100–200 mg q8h for mild to moderate hyperthyroidism to maximal doses of 400 mg q8h for severe hyperthyroidism. Methimazole is started at 10 mg q8h up to 40 mg q8h according to the severity of the disease. For either ATD, the decline in T_4 is delayed for 2–6 weeks while intrathyroidal hormone stores are depleted. As T_4 levels fall, doses of PTU or methimazole are decreased until T_4 is normalized. As the maintenance dose is established, ATDs can often be given qd or bid. Effective ATD dosage is determined by T_4 levels rather than TSH or T_3 levels.
2. Adverse effects of PTU or methimazole include rash, urticaria, nausea, transient leukopenia (not a harbinger of agranulocytosis), and, less commonly, arthralgias, hepatic necrosis, or cholestatic jaundice.
3. Agranulocytosis is idiosyncratic, occurs in 0.4% of patients, and is usually seen within the first 3 months of therapy. Routine monitoring of white blood cells during the initial 3 months is recommended. If agranulocytosis is detected, it is usually reversible upon discontinuation of the drug but may recur with use of the alternative ATD.
4. Long-term remittive therapy for Graves' disease is performed with PTU or methimazole given over a 12- to 24-month period. The dose of ATD is first adjusted until normalization of T_4 occurs. As higher remission rates are seen in patients who normalize their TSH on ATDs, the dosage is then adjusted in an effort to normalize TSH. ATD therapy is continued for 12–24 months and then stopped and T_4 levels monitored. Overall, 40%–70% of patients so treated obtain a remission.
    a. Highest remission rates are seen in patients with T_3 toxicosis, small goiter, decrease in goiter size during therapy, normalization of T_4 and TSH, or disappearance of TSI or TRab antibodies.
    b. Concurrent use of levothyroxine. Higher remission rates were initially reported in patients treated with methimazole combined with levothyroxine. Subsequent studies have failed to support these findings; therefore, combination ATD and levothyroxine therapy is not routinely recommended. However, levothyroxine is often utilized to maintain a normal free T_4 index while escalating ATD doses are given in efforts to normalize TSH.
    c. Monitor patients for relapse every 4–6 weeks for the first 3–6 months, and then every 3 months for the first year following cessation of the ATD. If the patient remains euthyroid, annual monitoring is continued indefinitely. If relapse of hyperthyroidism occurs, alternative therapy is recommended.

C. Inorganic iodine

inhibits thyroid hormone release, resulting in rapid lowering of T_4 and T_3 levels. Five to 10 drops of a saturated solution of potassium iodide (SSKI) or 1 drop of Lugol's solution is given q8h. Inorganic iodine should only be administered after PTU or methimazole has been started to avoid inadvertent stimulation of hormone synthesis. The use of inorganic iodine should be reserved for severe hyperthyroidism or thyroid storm as its use precludes the administration of radioactive iodine for diagnostic or therapeutic purposes.

D. Sodium ipodate

has the dual effects of blocking the peripheral conversion of T_4 to T_3, thus rapidly lowering T_3 and releasing inorganic iodine. Sodium ipodate, 1–3 g/d, is useful in the treatment of severe hyperthyroidism or thyroid storm.

E. Radioactive iodine (I 131)

is commonly used as initial therapy for Graves' disease, toxic adenoma, or toxic multinodular goiter, or as an alternative therapy for the patient with Graves' disease who fails to obtain or maintain a remission with ATDs (1).

1. I 131 is used for permanent ablation of thyroid tissue. Normally, a single I 131 dose is sufficient for treatment of Graves' disease or a toxic adenoma, whereas a toxic multinodular goiter may require a larger dose or repeated treatments. Concurrent or recent use of inorganic iodine precludes the use of I 131.
2. I 131 is contraindicated in patients who are pregnant, and women are advised not to become pregnant for 6 months after I 131 therapy.
3. Fifteen percent of patients with Graves' disease may develop or have worsening of their Graves' orbitopathy following I 131 therapy (2). These effects are often transient and can be prevented by administration of prednisone.
4. Iatrogenic hypothyroidism following I 131 ablative therapy for Graves' disease is seen in 50%–90% of patients during the ensuing 10 years. Following I 131 therapy, the patient is monitored for resolution of their hyperthyroid condition by measuring the free T_4 index every 4–6 weeks until normal. Once the patient is euthyroid a TSH is performed every 6–12 months to monitor for hypothyroidism.

F. Surgery

is infrequently recommended, except for patients with a very large goiter (especially if adjacent structures are compromised), pregnant women intolerant of ATDs, or nonpregnant patients who desire ablative therapy but refuse radioiodine.

III. Thyroid storm

is severe hyperthyroidism with the presence of fever and CNS abnormalities (confusion, agitation, restlessness, apathy, or coma).

A. Laboratory findings

include a high free T_4 and T_3 index, suppressed TSH, leukocytosis, hyperglycemia, and hypercalcemia.

B. Treatment

includes cooling measures, correction of dehydration and electrolyte imbalances, and nutritional support. PTU (orally or via nasogastric tube) is given first to inhibit synthesis of T_4 and T_3, and then sodium ipodate (3 g/d) or sodium iodine (0.5–1.0 g IV q12h) is given to inhibit release of T_4 and T_3 and block peripheral deiodination of T_4 to T_3.

Hypothyroidism

I. Diagnosis

A. Clinical presentation

1. Symptoms include weakness, fatigue, lethargy, cold intolerance, weight gain, dry, coarse skin and hair, decreased sweating, easy bruising, exertional dyspnea, constipation, menorrhagia, arthralgias, and impaired cognition (memory, speech, attention).
2. Examine the patient for bradycardia; cool, dry skin; brittle nails; periorbital or hand edema; goiter; or delayed relaxation of deep tendon reflexes.

B. Laboratory evaluation

1. TSH is elevated in patients with primary hypothyroidism.
2. The free T_4 index is decreased.
3. The free T_3 index may be decreased, but typically its decline occurs later in the course of the disease. Therefore, this is not a useful test.
4. Anti-thyroid peroxidase (anti-TPO) antibodies are present, usually to a high level, in Hashimoto's thyroiditis (chronic lymphocytic thyroiditis).
5. In subclinical hypothyroidism, the T_4 index is normal but TSH is elevated. If the TSH is greater than 10 mU/L, the risk of subsequent overt

hypothyroidism is significant, and treatment is begun. For the borderline TSH (4–9 mU/L), there are no firm guidelines, but therapy is considered for the patient with positive anti-TPO antibodies, abnormal serum lipid levels, a history of smoking, or symptoms compatible with hypothyroidism (3).

II. Replacement therapy

is best accomplished with levothyroxine, a synthetic isomer of T_4 The use of levothyroxine precludes the need for T_3 because T_3 is produced via peripheral deiodination of T_4.

A. Dosage requirements

for levothyroxine vary according to the patient's age and weight. The average replacement dose for adults is 112 µg/d, or 1.6 µg/kg per day. The elderly usually require lower doses and on average require 100 µg/d.

B. Initiation of therapy

in a healthy adult younger than 50 years, with no known cardiovascular disease, is begun at near the full anticipated replacement dose (usually 100 µg/d). In older individuals and patients with known cardiovascular disease, or if the risk of cardiovascular disease is unknown, levothyroxine is initiated with 25–50 µg/d and increased by 12.5–25.0 µg every 6–8 weeks until TSH is normalized.

C. Adequate replacement therapy

is assured by remeasuring TSH 6–8 weeks after a dosage change. If TSH remains elevated, the dose is increased by 12.5 µg/d, and if TSH is suppressed, the dose is decreased by 12.5 µg/d. The goal of levothyroxine replacement therapy is normalization of TSH. Suppression of TSH is avoided due to the increased risk of accelerated osteoporosis, induction of cardiac arrhythmias, and increase in left ventricular mass.

D.

Patients should avoid taking levothyroxine at the same time as calcium carbonate because the latter reduces T_4 absorption.

E.

T_3 (liothyronine, Cytomel) as monotherapy is not recommended due to its short half-life and wide fluctuations in plasma T_3 levels. Thyroid hormone replacement therapies with combinations of T_4 and T_3 are being studied. Preliminary reports suggest improvement in some cognitive performance, mood, and physical status, but with the potential for increased pulse rate and liver effects (4).

III. Myxedema coma

is severe hypothyroidism complicated by marked hypothermia, hypotension, bradycardia, hypoventilation, and unresponsiveness. If myxedema coma is suspected, a TSH and free T_4 index are obtained and presumptive therapy begun.

A. Supportive measures

include assisted ventilation, warming devices, volume repletion for hypotension, and glucocorticoids if adrenal insufficiency is suspected.

B. Therapy with levothyroxine

is given intravenously as a loading dose of 200–300 µg in the first 24 hours, followed by 100 µg in the next 24-hour period, followed by 50–100 µg/d until oral therapy can be instituted.

Thyroiditis

I. Acute suppurative thyroiditis

can be caused by bacteria, fungi, mycobacteria, or parasites. Patients present with a warm, erythematous, tender thyroid as well as systemic signs of infection. Therapy includes fluid support, appropriate antimicrobial therapy, and surgical drainage of fluctuant areas.

II. Subacute (painful) thyroiditis

is caused by a viral infection of the thyroid (5).

A. Clinical presentation

includes the prodromal symptoms of myalgias, low-grade fever, lassitude, sore throat, and dysphagia. Following this viral prodrome is the abrupt onset of anterior neck pain, which may be unilateral or bilateral and may radiate to the mandible or ear.

1. Physical findings include low-grade fever and a tender, enlarged thyroid with firm to hard consistency.
2. Laboratory abnormalities include a mildly elevated white blood cell count, mild anemia, and invariably an erythrocyte sedimentation rate greater than 50 mm/h.

B. Thyrotoxicosis

occurs in 50% of patients due to the release of intrathyroidal T_4 and T_3 into the systemic circulation. In addition, the RAIU is suppressed to less than 5% due to follicular cell damage. ß-Adrenergic antagonists are used for symptomatic treatment, whereas nonsteroidal anti-inflammatory agents are useful for thyroid pain. Thyrotoxicosis is transient (2–16 weeks) and resolves when stores of thyroid hormone are depleted. ATDs are ineffective, and radioactive iodine ablative therapy is contraindicated.

C. Transient hypothyroidism

(2–9 months) may follow the thyrotoxicosis. Full recovery is the rule, although permanent hypothyroidism may develop in 5% of patients; therefore, periodic monitoring of TSH is recommended.

III. Silent (painless) thyroiditis and postpartum thyroiditis

have an autoimmune etiology.

A. Clinical presentation.

Patients lack anterior neck pain and therefore present in either the thyrotoxic phase or later, in the hypothyroid phase of their disease. Women with postpartum thyroiditis generally develop thyrotoxic symptoms 6 weeks to 3 months after delivery, and hypothyroid symptoms 3–6 months post partum. Examination reveals a small, firm, nontender goiter in 50% of patients.

B. Silent thyroiditis versus Graves' disease.

Patients who present with hyperthyroid symptoms, a small to modest nontender goiter, and who lack Graves' orbitopathy may have either silent thyroiditis or Graves' disease. The presence of TSI antibodies and an elevated RAIU is consistent with Graves' disease, whereas their absence suggests silent thyroiditis.

C. Therapy and long-term monitoring

is similar to that for patients with subacute thyroiditis. Full recovery is the rule, although permanent hypothyroidism may be found in up to 6% of individuals.

IV. Hashimoto's thyroiditis

(chronic lymphocytic thyroiditis) typically presents with an asymptomatic goiter, although 20% of patients present with hypothyroidism. Patients with a family history of hypothyroidism or personal history of autoimmune disorders should be screened. Examination reveals a mild to moderately enlarged thyroid that is firm and has a bosselated (pebbly) surface.

A. Laboratory evaluation.

Positive anti-TPO antibodies are found in 90% of patients. An elevated TSH and decreased free T_4 index indicates hypothyroidism, whereas an elevated TSH and normal free T_4 index is consistent with subclinical hypothyroidism.

B. Treatment with levothyroxine

is indicated for the patient with hypothyroidism, subclinical hypothyroidism with a TSH greater than 10 mU/L, or positive anti-TPO antibodies, as well as for the euthyroid patient with progressive goiter enlargement.

Thyroid Nodule

Clinically evident thyroid nodules can be found in 5% of the population. A solitary thyroid nodule is malignant 5%–15% of the time.

I. Clinical presentation

A. Historic findings

that are suggestive but not diagnostic of malignancy include family history of thyroid cancer, history of irradiation of the head and neck region, patient younger than 20 years or older than 60 years, rapid nodule growth, or presence of distant metastases.

B. Physical findings

suspicious for malignancy include a very firm nodule, fixation to adjacent structures, vocal cord paralysis, enlarged regional lymph nodes, or a nodule larger than 4 cm in diameter.

II. Diagnostic studies

A. Laboratory evaluation

1. TSH should be measured in all patients and a calcitonin level obtained if there is a family history of medullary carcinoma.
    a. The combination of elevated TSH and a confirmatory low free T_4 index is diagnostic of hypothyroidism, and levothyroxine therapy

is begun. If the nodule resolves, the patient is observed; if there is no change in nodule size, then further evaluation is indicated.

b. Suppressed TSH suggests the presence of an autonomous or toxic adenoma. An RAIU and thyroid scan are obtained to confirm the diagnosis. Malignancy is highly unlikely in a toxic (autonomously functioning) adenoma.

2. Fine-needle aspiration (FNA) has an 83%–99% sensitivity and 70%–90% specificity.
   a. If FNA confirms or raises suspicions of malignancy, then the patient is referred for surgical excision.
   b. If the FNA indicates that the nodule is benign, the patient can be observed or placed on levothyroxine suppressive therapy. A repeat FNA in 6 months to confirm the benign findings is recommended.
   c. A nondiagnostic FNA, or an FNA-benign nodule that progressively enlarges, should be viewed as suspicious and surgery considered.
3. Radionuclide thyroid scanning and ultrasonography do not have sufficient specificity to recommend their routine use. Ultrasonography is helpful in documenting the size of a nodule that is being managed expectantly and in delineating a pure simple cyst (rarely malignant).

III. Therapy

A.

For thyroid malignancy, total thyroidectomy is recommended. Postoperative I 131 is used to ablate any remaining thyroid tissue. Life-long levothyroxine is begun to reduce the TSH to the lower limits of normal. Serial monitoring of the surgical site, monitoring for the presence of regional lymph nodes, serum Tg testing, and chest radiography are performed. Often a rise in Tg is the first indication of a recurrence of thyroid tissue (normal or malignant). If recurrence is suspected, levothyroxine is discontinued for 6 weeks and an I 131 total-body scan is performed. Alternatively, synthetic TSH may be administered intramuscularly and an I 131 total-body scan performed while continuing levothyroxine (6).

B

For the benign nodule removed surgically, patients may be observed expectantly or be placed on levothyroxine therapy with the hope of preventing enlargement of remaining thyroid tissue or development of new nodules.

C

For the benign nodule that is being clinically observed, the benefit of levothyroxine therapy is unclear. A 6-month trial of levothyroxine can be initiated and therapy continued if there is complete regression of the nodule.

Nonthyroidal Illness and Thyroid Function

Abnormalities in thyroid test results can be found in patients who have a number of non-thyroidal illnesses (NTIs) or conditions, including caloric restriction, recent surgery, chronic liver disease, chronic renal disease, diabetes mellitus, infections, malignancy, psychiatric disorders, and with certain drugs (ß-adrenergic blockers, amiodarone, phenytoin, glucocorticoids, dopamine, cholecystographic dyes, heroin, and methadone).

I. The low T_3

syndrome is the most common abnormality found in NTIs and is characterized by low free T_3 index, elevated reverse T_3, normal free T_4 index, and normal TSH.

II. In the low T_4

syndrome, the free T_4 index as well as free T_3 index are decreased, reverse T_3 is increased, and TSH is normal to minimally elevated.

III. Euthyroid hyperthyroxinemia

is less commonly found in NTIs. Increased T_4, normal to low T_3, normal to suppressed TSH, and normal free thyroxine are found.

IV.

Free thyroxine (the non-protein-bound fraction of T_4 as measured by equilibrium dialysis or ultracentrifugation) and TSH are the most valuable measures of a patient's true thyroid state in the presence of NTI.

V.

Patients are considered euthyroid and are not treated with liothyronine or levothyroxine. The thyroid laboratory abnormalities typically resolve with improvement in the NTI.

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17.4

DYSLIPIDEMIAS

Marvin Moe Bell

Hypercholesterolemia is a major risk factor for coronary heart disease (CHD). High levels of low-density lipoprotein (LDL) cholesterol are the main target for cholesterol-lowering therapy. Low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides (TGs) are additional risk factors for CHD. The benefit of treating people with dyslipidemias has been demonstrated in both primary prevention (people without CHD) and secondary prevention (people with known CHD) trials. Guidelines for detection, evaluation, and management of high blood cholesterol have been published by the National Cholesterol Education Program and are generally followed in this chapter (1).

I. Screening

A.

Recommended for all adults older than 20 years, every 5 years.

B.

Measure total cholesterol and HDL (nonfasting testing is okay).

C.

Total cholesterol levels are defined as follows:

1. Desirable: less than 200 mg/dL (5.2 mmol/L)
2. Borderline: 200–239 mg/dL (5.2–6.2 mmol/L)
3. High: greater than 240 mg/dL (6.2 mmol/L)

D.

HDL: desirable is greater than 40 mg/dL (1.0 mmol/L)

II. Diagnosis

A.

If total cholesterol is borderline or high or to monitor treatment, obtain a lipid profile after a 12-hour fast.

B.

LDL is calculated as follows (valid if TGs less than 400 mg/dL): LDL = total cholesterol - HDL - (TGs/5)

C.

Document other CHD risk factors:

1. Nonmodifiable risks: age (men older than 45, women older than 55), family history of premature CHD.
2. Modifiable risks: cigarette smoking, hypertension, diabetes, low HDL (less than 40 mg/dL).
3. Protective factor: HDL more than 60 mg/dL.

D.

Categorize for treatment based on LDL and risk factors:

1. LDL less than 100 mg/dL is the goal for people with established CHD or diabetes.
2. LDL less than 130 mg/dL is the goal for people without CHD but with two or more risk factors.

3. LDL less than 160 mg/dL is the goal for people without CHD and with fewer than two risk factors.

III. Management principles

A.

Rule out and treat secondary causes of hyperlipidemia (especially with marked hypertriglyceridemia):

1. Endocrine: type II diabetes, hypothyroidism (see Chapter 17.2 and Chapter 17.3).
2. Renal: nephrotic syndrome, chronic renal failure (see Chapter 12.6)
3. Lifestyle: alcoholism, anabolic steroids (see Chapter 5.3 and Chapter 5.7)

B.

Statin drugs are first-line therapy for virtually all people with established CHD to rapidly reduce LDL levels toward the goal of 100 mg/dL.

C.

Diet modification is important and should be tried for several months before considering drug therapy for primary prevention. Weight loss and increased exercise are key components of diet therapy.

D.

Delay drug therapy in premenopausal women and young adult men with high LDL who are otherwise at low risk for CHD.

E.

Consider drug therapy in high-risk postmenopausal women and elderly people with high LDL who are otherwise in good health.

IV. Dietary therapy

A.

Healthy diet recommendations for the general public are the same as those of a step I diet, which includes the following:

1. Reduce total fats to less than 30% of calories and saturated fats to less than 10% of calories (limit meat to 6 oz/d, use lean cuts of beef and pork with fat trimmed, remove skin from poultry, avoid fried foods and highly saturated oils such as palm or coconut, and use low-fat dairy products).
2. Reduce cholesterol to less than 300 mg/d (limit egg yolks to 4 per week, and avoid organ meats).
3. Substitute monounsaturated fats in the diet (olive and canola oils are good sources).
4. Increase complex carbohydrates to 55%–60% of calories (fresh fruit, vegetables, and whole-grain products).

B.

Water-soluble fiber in the diet or as a supplement can help to lower LDL. Sources include oat bran, beans, fruit, and psyllium (Metamucil).

C.

A more restricted step II diet may be tried with the assistance of a dietitian if cholesterol control is inadequate and the patient is willing. Saturated fats are limited to 7% of calories and cholesterol to 200 mg/d.

V. Drug therapy for elevated low-density lipoprotein level

A.

Effective drug classes include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), bile acid sequestrants (resins), and nicotinic acid.

B.

For primary prevention, consider addition of a drug if diet and exercise fail to lower LDL to goal levels within 3–6 months. Encourage their use when LDL remains greater than 190 mg/dL (4.9 mmol/L) or greater than 160 mg/ dL in people with two other CHD risk factors.

C.

If response to the first drug is inadequate, a drug from another class or a combination of drugs from different classes may be tried. Resins used with nicotinic acid or statins have been very safe and effective. Combination of statins with nicotinic acid or fibrates increases the risk of myopathy.

VI. Hypertriglyceridemia

A.

TG levels are defined as follows:

1. Normal: less than 150 mg/dL (1.7 mmol/L)
2. Borderline high: 150–199 mg/dL (1.7–2.2 mmol/L)
3. High: 200–499 mg/dL (1.7–5.6 mmol/L)
4. Very high: greater than 500 mg/dL (5.6 mmol/L)

B.

Very high TGs warrants therapy to reduce the risk of pancreatitis. Treatment of borderline or high TGs to reduce CHD risk remains controversial but is often recommended.

C.

Therapy includes exercise, weight reduction, alcohol restriction, and treatment of contributing causes. Niacin or fibrates may be useful in resistant cases.

VII. Isolated low high-density lipoprotein (<40 mg/dL)

A.

Recommend smoking cessation, exercise, weight loss if obese, and avoidance of androgens and progestins.

B.

Medications are generally not helpful; fibrates are not effective at increasing HDL when the TG level is normal.

VII. Formulary of lipid-lowering drugs

A. HMG-CoA reductase inhibitors (statins)

1. Advantages. These agents are extremely effective in lowering LDL, and they may prevent atherosclerotic plaque rupture. They are the most convenient and best tolerated of lipid-lowering drugs.
2. Problems. First, they are expensive. Second, elevation of liver function tests (LFTs) to three times normal occurs in 1%–2% of patients (monitor LFTs and use caution with liver disease). Third, myositis or myopathy with high serum creatinine phosphokinase (CPK) develops in 0.5% of patients, more often when statins are used with niacin or fibrates. Warn patients and check CPK if muscle soreness occurs.
3. Dosing (Table 17.4-1)

	Usual starting dose	Dosing range
Lovastatin (Mevacor)	20 with dinner	10–80
Pravastatin (Pravachol)	10 or 20 at bedtime	10–40
Simvastatin (Zocor)	20 in evening	5–80
Fluvastatin (Lescol)	20 or 40 at bedtime	20–80
Atorvastatin (Lipitor)	10 daily	10–80
Cerivastatin (Baycol)	0.4 in evening	0.2–0.4

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

Table 17.4-1. HMG-CoA reductase inhibitors (statins) dosing (mg)

B. Bile acid sequestrants (resins)

1. Advantages. Bile acid sequestrants lower LDL, are very safe, and can be used in combination with any other class of lipid-lowering drug.
2. Problems. These agents may raise TGs; often cause constipation, bloating, nausea, or heartburn; may reduce absorption of other medications (thiazides, digoxin, thyroxine, and warfarin should be taken 1 hour before or 4 hours after a resin).
3. Dosages. Take cholestyramine 4 g or colestipol (Colestid) 5 g (one scoop or packet) orally bid with liquids and a meal to start; gradually increase to a maximum of 8–16 g bid for cholestyramine or 15 g bid for colestipol. Colestipol also comes as 1-g tablets dosed 2–16 g/d.

C. Nicotinic acid (niacin)

1. Advantages. Niacin does it all: lowers LDL, lowers TGs, raises HDL, is inexpensive, and is available over the counter.
2. Problems include flushing (often resolves over time, aspirin 325 mg 30 minutes before dose may prevent flush), dyspepsia (avoid in patients with peptic ulcer disease), hyperglycemia (use caution in diabetics), hyperuricemia (use caution with gout), and liver function abnormalities (may be worse with sustained-release niacin, monitor LFTs).
3. Dose. Take 100 mg orally tid with meals to start, gradually increase to 500–1,000 mg orally tid. Extended-release niacin (Slo-Niacin, Niaspan) taken at bedtime may reduce flushing but is more costly.
4. Niacinamide is ineffective for cholesterol reduction.

D. Fibric acid derivatives (fibrates)

1. Advantage. Fibrates effectively lower TGs, fenofibrate lowers LDL.
2. Problems. Gemfibrozil may raise LDL. Mortality in long-term studies may be higher with gemfibrozil than with placebo (this is definitely

true for the related drug, clofibrate). Use with caution in liver or renal disease; may cause cholelithiasis.

3. Indications are severe hypertriglyceridemia unresponsive to diet, exercise, and treatment of contributing causes.
4. Dosage of fenofibrate (Tricor) is 67–200 mg once daily with a meal, and gemfibrozil (Lopid) is 600 mg bid 30 minutes before a meal.

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17.5
HYPERCALCEMIA

Richard D. Blondell

Hypercalcemia (considered by most laboratories to be a calcium concentration greater than 10.5 mg/dL) occurs when bone resorption exceeds the kidneys' ability to excrete the excessive calcium load (e.g., malignancy, hyperparathyroidism, immobilization), with decreased renal excretion of calcium (e.g., diuretics) or with increased absorption of calcium from the gut (e.g., sarcoidosis, milk-alkali syndrome). A rapid presumptive diagnosis can often be made with a careful history, a directed physical examination, routine laboratory testing, and chest radiography. More than 90% of cases are due to primary hyperparathyroidism or malignancy.

I. Clinical presentation.

Symptoms and signs often reflect the underlying disease but vary with the serum level of ionized calcium (the physiologically active form) and with the rate of development of hypercalcemia. Hypercalcemia may present as an acute or chronic illness with lethargy, nausea, vomiting, polydipsia, polyuria, impaired renal function, nephrocalcinosis, muscle atrophy, bradycardia, electrocardiographic changes (e.g., short QT), or subtle psychological symptoms (e.g., anxiety, indecisiveness, loss of energy, excessive worry, irritability). Other symptoms (e.g., anorexia, weight loss, bone pain) may be due to hypercalcemia but often are directly due to the underlying disease (see Chapter 2.1).

II. Diagnosis.

The clinician should search for the underlying cause of hypercalcemia. Most asymptomatic patients identified with “routine chemistry” have primary hyperparathyroidism, but most of those who appear ill have a malignancy.

A. Testing errors.

Prolonged tourniquet use can cause hemoconcentration and a spurious hypercalcemia. Because almost half of the total serum calcium is protein bound, an adjustment may be indicated for serum protein variations. An increase of protein by 1 g/dL raises the measured total serum calcium level by about 0.8 mg/dL. Ionized calcium levels must lie within a narrow range (4.6–5.1 mg/dL). Because serum calcium levels may fluctuate, values that are minimally elevated (10.5–11.5 mg/dL) should be repeated several times. The average value, not the lowest, is then used for decision making.

B. Medications.

Some patients taking thiazides may develop hypercalcemia, which may take 2 or more weeks to resolve once the medication is stopped. Lithium salts can also cause hypercalcemia. Hypervitaminosis D may be seen in patients who consume excessive amounts (more than 50,000 U/d) of

vitamin D. The milk-alkali syndrome is now an uncommon cause of hypercalcemia given the current therapy for ulcer disease.

C. Hyperparathyroidism

is due to an autonomously functioning benign parathyroid adenoma about 80% of the time. Idiopathic or familial parathyroid hyperplasia accounts for most of the rest, but rarely there may be multiple adenomas, carcinoma of the parathyroid, or ectopic parathyroid hormone (PTH) production. The diagnosis can be made with PTH radioimmunoassays.

D. Malignancy.

Although hypercalcemia is sometimes due to the ectopic secretion of a PTH-like peptide or PTH, it is usually due to bone resorption from metastatic disease. It typically occurs late in the course of the malignant disease and is a poor prognostic sign. About one third of the cases are due to lung cancer (see Chapter 10.5), one third to breast cancer (see Chapter 13.8), and the rest to renal cell cancer, squamous cell cancer of the head or neck, lymphoma, leukemia, and myeloma (1). Even with widespread skeletal metastases, hypercalcemia is usually not associated with prostate cancer.

E. Sarcoidosis.

About 10%–20% of patients with sarcoidosis have hypercalcemia due to abnormal vitamin D metabolism. A radiograph of the chest usually suggests this disease. Other chronic granulomatosis diseases (e.g., tuberculosis, fungal infections, leprosy) may also produce hypercalcemia.

F. Immobilization

may produce hypercalcemia in some patients (e.g., an adolescent in a body cast, quadriplegics). Hypercalcemia is usually not seen in patients with Paget's disease of the bone unless they are immobilized.

G. Other causes.

Hypercalcemia can also be associated with clinically apparent adrenal insufficiency and thyrotoxicosis. Idiopathic hypercalcemia is sometimes seen in postmenopausal women; this can be corrected with estrogen replacement. The diagnosis of other causes of hypercalcemia may require a systematic diagnostic strategy and a detailed understanding of the pathophysiology (2).

II. Treatment.

The cornerstone of treatment is management of the underlying cause. If the patient has limited symptoms and signs, management of the underlying disease is often all that is required. Hospitalization is indicated if the patient has serious signs (e.g., confusion, psychosis, dehydration, azotemia) (3). Patients with hyperparathyroidism should be treated by physicians who are experienced in the medical and surgical treatment of that disorder.

A. Acute therapy

is used to bring the serum calcium level to a normal level by limiting bone resorption, promoting renal excretion, and limiting gut absorption of calcium.

1. Intravenous fluids. Rehydration with normal saline (NS) at 300–500 mL/h is an appropriate initial therapy. If the patient's cardiac status permits, this can be followed by a saline diuresis with NS or half NS (as indicated by serum electrolytes) and furosemide (20–40 mg q2–4h). Fluid intake and output must be carefully monitored.
2. Calcitonin has an onset of action within hours, but tachyphylaxis and expense limit long-term use.
3. Pamidronate, a bisphosphonate, inhibits bone resorption. Effects are seen within 2 days, peak in 7 days, and last 2 weeks. For hypercalcemia due to malignancy, a single dose of 60 mg in 1,000 mL of intravenous fluids is infused over at least 4 hours. For severe hypercalcemia (greater than 13.5 mg/dL), 90 mg is infused over 24 hours.
4. Corticosteroids can be effective for hypercalcemia associated with malignancies and sarcoidosis, but the onset of action may be delayed for several days. They are ineffective for primary hyperparathyroidism.
5. Other therapies. Oral phosphate, plicamycin, etidronate, and dialysis are additional acute therapeutic options.

B. Long-term therapy.

Maintenance of hydration, dietary restrictions of calcium intake, oral corticosteroids in the lowest effective dose (for patients with malignancies and sarcoidosis), and oral phosphates are all appropriate

for long-term therapy (3). Patients with primary hyperparathyroidism are treated surgically (4).

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17.6
OSTEOPOROSIS

Fred E. Heidrich

Susan M. Ott

Osteoporosis (OP) is a syndrome in which bone density is decreased and fractures may occur after minimal trauma (1). Hip fracture is the most serious consequence of OP. Other common sequelae include distal forearm and vertebral compression fractures. The fractures usually occur in the latter half of life, but bone loss begins in the third decade. Maximizing bone gained in childhood and adolescence and minimizing losses in the middle years of life are key to bone health in old age.

I. Diagnosis.

Osteopenia is decreased bone density more than one standard deviation below the mean for young women. *Osteoporosis* is bone density more than 2.5 standard deviations below that mean. A person with *established OP* has a fracture in addition to low bone density. OP is usually detected after a person has had a typical fracture with minimal trauma or during bone density screening. However, efforts to intervene early depend on recognition of risks for bone loss before fractures occur. Although bone density is currently the standard way to quantify OP, other bone properties, such as microstructural integrity, also play a role in OP.

A. Risk factors.

Potentially modifiable factors are gonadal hormone deficiency states, such as gonadal failure, surgical or natural menopause, oligomenorrhea (fewer than four periods per year, including extreme athleticism, anorexia, or use of depot-medroxyprogesterone); low calcium intake; inactive lifestyle; tobacco use; alcoholism; use of bone-thinning drugs (such as steroids, anticonvulsants, heparin); and low weight. Other risk factors include age, heredity (parent with hip fracture), race (blacks have the lowest incidence), and female sex. OP may be secondary to disease states (see Section I.C). A woman with a vertebral compression fracture is four times more likely to have a new vertebral fracture as a woman of the same age and bone density with no preexisting fracture. Such compression fractures are often asymptomatic; two thirds of such patients do not note any increase in pain associated with the fracture, but it is nonetheless an important indicator of risk.

B. Bone density

is best assessed by dual-energy x-ray absorptiometry (DEXA) at the hip. Other techniques include peripheral DEXA and quantitative ultrasonography. Results are commonly reported as *T* scores (number of standard deviations from a young woman's mean value) and *Z* scores (sd from an age-matched mean). At age 50 years, one third of women have osteopenia; and by age 65 years, 40% are normal, 40% have osteopenia, and 20% have osteoporosis. Only 10% of 80-year-old women have a “normal'” bone

density. There is still debate about recommendations for general screening, but these tests are useful in selected cases. Most fractures occur in high-risk patients, such as the frail elderly. Identification of those with low bone density indicates those most likely to benefit from aggressive pharmacologic intervention.

C. Differential diagnosis.

Consider metastatic lesions, multiple myeloma, immobilization, weight loss, renal or hepatic failure, intestinal malabsorption, renal calcium loss, gonadal deficiency, and excesses of cortisol, parathormone, or thyroxine. Alcoholism should always be considered, particularly when OP occurs in young people or middle-aged men (see Chapter 5.3). Many of these conditions can be excluded by history and physical examination. In OP, the complete blood count (CBC), electrolytes, thyroid-stimulating hormone, phosphate, and calcium are normal, but alkaline phosphatase may be temporarily elevated following a fracture. Specific tests occasionally useful in OP evaluation are urinary calcium (normally 50–250 mg/d), serum 25-hydroxyvitamin D, parathyroid hormone (PTH), and serum and urinary protein electrophoresis. Tests for bone resorption rate (e.g., pyridinolines or collagen telopeptides) and formation rate (e.g., osteocalcin or bone-specific alkaline phosphatase) may occasionally guide therapy but cannot be used for screening of individual patients.

II. Prevention.

Although OP is clinically manifest in the elderly, prevention efforts should include all age groups.

A. Calcium

alone is not sufficient to prevent OP, but it is an important adjuvant. Recommended daily intake (2) is 500 mg for children aged 1–3; 800–1,300 mg for children aged 4–18; 1,000 mg for persons aged 19–50; and 1,200 mg thereafter. A quick assessment of dietary calcium intake is 300 mg for each serving of dairy product and 200 mg for the rest of the diet. Calcium carbonate is the most cost-effective supplement and is best absorbed when taken with food. Persons lacking sun exposure and those older than 75 years should also take 400–800 IU vitamin D daily, administered as part of most multiple-vitamin preparations (3).

B. Lifestyle.

Weight-bearing exercise (walking, running, dancing, aerobic exercise, sports, weight-lifting, tai chi) as appropriate has skeletal as well as cardiovascular, muscular, and emotional benefits in all age groups. Participation in a program for 30–60 minutes 3–5 times per week is a reasonable goal. Smoking and overconsumption of alcohol should be discouraged for many reasons, including bone health. Unnecessary weight loss should be discouraged despite cultural fashions because women who lose weight also lose bone density. The kyphosis of established osteoporosis results in a protruding abdomen, which patients may misinterpret as excess fat.

C. Fall prevention.

People at risk for falls should be counseled regarding footwear (laced, low heel, traction sole), vision aids, and environmental hazards (poor lighting, floor-level obstructions, slippery surfaces, lack of handrails, cool temperature). Use of medicines that affect alertness or cause postural syncope must be minimized in the elderly. Elderly people are more prone to postural hypotension after a large meal.

D. Pharmacologic approaches.

Hormone replacement therapy (HRT) results in about a 50% reduction in fractures, based mainly on observational studies. Randomized trials show that estrogen increases bone density as well as or better than alendronate. Consider HRT for all women with premature decrease of ovarian function (see Section I.A) as well as that at natural menopause. Estrogen may not be effective for bone protection in inadequately nourished women. Conjugated estrogens, 0.625 mg daily or the equivalent, is helpful in maintaining bone health. In older women, 0.3 mg stabilizes bone density. Bone loss similar to that at natural menopause occurs on cessation of HRT, so it should be continued indefinitely for maximal protection against hip fracture.

Raloxifene, 60 mg daily, is also effective at decreasing fracture rates. The bisphosphonates alendronate and risedronate are also FDA approved for

prevention of OP and may be useful as described in Section III in high-risk patients with low bone density. Estrogen should be given with caution in women with established coronary artery disease or a history of thrombosis.

III. Therapy.

Calcium and vitamin D supplementation, appropriate lifestyle, and fall prevention efforts remain important in therapy of established osteoporosis. It is also necessary to consider and address causes of secondary OP Section I.C). Additional therapy as given below may be used for patients with low bone density (*T* score £2.5), particularly when other risk factors (family or personal history of OP fractures, current smoking, unstable gait) are present.

A. Bisphosphonates.

These agents decrease both bone formation and resorption, with a very long half-life (more than 10 years) in bone. A halving of fracture rates is seen in women with osteoporosis (4). They remain effective for at least 5 years of use, but longer term effects are uncertain. Alendronate (10 mg daily) and risedronate (5 mg daily) are the two agents currently approved for management of OP and are quite similar. Either should be taken with a full glass of water on an empty stomach, following which no oral intake should occur for 30 minutes. The patient should avoid reclining for at least 30 minutes after dosing to prevent esophagitis. Avoid using during pregnancy, renal failure, or hypocalcemic states. Once-weekly doses of alendronate, 20–70 mg, have also been shown to increase bone density.

B. Gonadal hormone therapy.

HRT increases bone density in women with established OP, but large randomized fracture end-point studies are lacking. For women with longstanding deficiency, start with a decreased dose of estrogen for several months before advancing to the therapeutic dose (0.625 mg conjugated or esterified estrogen or equivalent). Gonadal hormone replacement in men can result in increased bone density but may have adverse effects on serum lipids and hematocrit, and should be avoided in men with a history of prostate cancer. Men with demonstrated low testosterone may be treated with intramuscular testosterone enanthate or cyprionate, 150–200 mg every 2 weeks. HRT should be continued indefinitely in the absence of contraindications as the benefits decrease within a year or two of stopping therapy. Raloxifene (60 mg/d) is effective in preventing fractures in women with osteoporosis (5). It appears to decrease the risk of breast cancer (see Chapter 13.8). It improves lipid status, but a beneficial effect on heart disease has not been established. It increases the risk of venous thrombosis and often accentuates hot flushes.

C. Calcitonin.

Bone density gains with calcitonin are less than with the above agents, and data on fracture prevention are controversial, but the drug has a long-term excellent safety record. It has a modest analgesic effect in acute fractures. It is usually administered intranasally as one spray (200 units) daily on alternating sides.

D. Stimulators of bone formation.

A variety of regimens centered on sodium fluoride, intermittent PTH, or growth hormone have been tried as a means of promoting bone formation, but no regimen has yet been devised that can be recommended.

E. Thiazides.

Thiazide diuretics may promote increased bone density by decreasing renal calcium excretion. Effects on bone density are beneficial but modest. If an antihypertensive is indicated, possible bone benefits may enter into the choice of agents (see Chapter 9.1). These drugs can improve bone density in patients with high urine calcium.

F. Physical therapy.

Gait and balance training may prevent falls and thus fractures. Spinal extension exercises and instruction in lifting technique may prevent vertebral crush fractures. Brief bed rest and local heat complement the use of analgesics in the management of compression fractures. Protective padding prevents hip fractures in elderly people who fall (6), as long as they are wearing the padding.

IV. Chronic steroid users.

About half of the patients receiving long-term corticosteroid therapy have substantial bone loss, particularly during the first 6 months of therapy. Doses of prednisone of 7.5 mg/d or greater are often implicated, although the elderly may experience loss with lower doses. Management

includes minimizing the dose of steroid given, maintaining physical activity, and aggressively implementing the preventive and therapeutic strategies given above. Hypercalciuria, if present, may be aggravated by high-dose vitamin D and helped by thiazides. In worrisome cases, measurements of vertebral or hip bone density may guide use of bisphosphonate or hormonal therapy.

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XVIII. DISORDERS OF THE BLOOD

18.1
IRON DEFICIENCY ANEMIA

S. Shekar Chakravarthi

I. Introduction

(1,2). Worldwide, iron deficiency is the most common cause of anemia. In the United States, at sea level, the cutoff low value of hemoglobin in the adult male is 14 g/dL, adult female 12 g/dL, and pregnant women 11 g/dL. With advancing years a slight decline in the hemoglobin in the male is to be expected; 10.5 g/dL in infants 6 months to 2 years and 11.5 g/dL in children 2 to 12 years is accepted. Iron deficiency results in a defective synthesis of hemoglobin and smaller red cells (microcytic) with less hemoglobin within the cell (hypochromic). Increased requirements, inadequate dietary iron, malnutrition, low iron stores, eating disorders, pica, and lead poisoning are likely causes in infants and children. In adults, common causes of gastrointestinal (GI) blood loss are the use of nonsteroidal anti-inflammatory drugs, peptic ulcer disease, angiodysplasia, diverticulosis, malignancy, and, rarely, parasites such as hookworms. Frequent blood donations and phlebotomies, surgical procedures, and, in females, menstrual disorders, pregnancy, and lactation can lead to iron deficiency. The daily loss of iron in an adult is about 1 mg, and menstrual loss can be an additional 20 mg per month. Normally less than 10% of the daily dietary intake of iron is absorbed.

II. Clinical presentation.

With an insidious onset and gradual progression of symptoms the body can compensate and tolerate low hemoglobin (less than 7 g/dL). In the elderly, some of these signs and symptoms may be subtle or dismissed as age related.

A. Symptoms.

Weakness, malaise, fatigue, dyspnea on exertion, palpitations, dizziness, chest pain, headaches, and pica may be present.

B. Signs.

Tachycardia, systolic murmur, and even high-output failure may be the cardiac signs. Epithelial changes include pallor of the conjunctiva, lips, nail beds, and palmar skin creases, dry skin, and nail changes such as brittle and spoon-shaped nails (koilonychia). Angular stomatitis, glossitis, and, rarely, dysphagia from pharyngeal and esophageal webs may also be present.

III. Diagnosis

A. Detailed history and physical examination

are essential. Differential diagnosis of microcytic hypochromic anemia includes thalassemia, anemia of chronic disease, and sideroblastic anemia.

B. Laboratory.

The test result would depend on the stage of development of iron deficiency. The classic hypochromic microcytic picture develops when iron stores are exhausted. Anisocytosis, poikilocytosis, and target cells may be present on the peripheral smear. Increased red cell distribution width with a low mean corpuscular volume is suggestive of iron deficiency anemia.

1. Serum ferritin level is decreased to less than 12 µg/L (normal: 18–300 µg/L). A low serum ferritin indicates iron deficiency; however, ferritin, which is an acute phase reactant, may be elevated in the presence of infection, inflammation, and malignancy.
2. Iron binding capacity (IBC) is increased, usually to more than 375 µg/dL (normal: up to 300 µg/dL).
3. Serum iron is decreased, often to less than 60 µg/dL (normal: 100 µg/dL).
4. Transferrin saturation is decreased to less than 16%.
5. Reticulocyte count, which is indicative of red blood cell replacement and bone marrow function, is decreased when iron stores are exhausted.
6. Erythropoietin level is normal or high.
7. Transferrin receptor level is increased.
8. Erythrocyte protoporphyrin is increased.

Local laboratory values for normal range may differ.

Bone marrow biopsy is not usually necessary but would demonstrate absence of iron stores. In anemia of chronic disease, serum iron may be low but the IBC is not elevated. **Hemoglobin electrophoresis** will detect thalassemias, and lead testing will help rule out lead poisoning.

IV. Management

(3). In the nonmenstruating adult, iron deficiency could represent GI blood loss; therefore, appropriate workup should be initiated and the cause addressed. With the initiation of iron replacement therapy, reticulocyte count should rise within a week and a 2 g/dL hemoglobin increase should be seen in 3 weeks. To replenish the stores, continue replacement for 6 months. Treatment failures are due to noncompliance, malabsorption, inadequate dosing, ongoing blood loss, or incorrect diagnosis.

A. Iron replacement

1. **Oral.** This is the preferred method of replacing the iron stores gradually. Ferrous sulfate, which is inexpensive and commonly used, is better tolerated when given with meals. GI side effects are dose related and include nausea and constipation. Ferrous sulfate 325 mg (65 mg of elemental iron) started once daily may be titrated up weekly up to 3 times a day. Target dose is 150–200 mg of elemental iron per day. Foods, milk, coffee, and tea reduce absorption and vitamin C enhances absorption. Ferrous fumarate 300 mg (100 mg of elemental iron) or ferrous gluconate 300 mg (37 mg of elemental iron) may be tolerated better than ferrous sulfate. Drugs such as histamine-2 blockers, proton pump inhibitors, antacids, and methyldopa reduce absorption.

   For children, iron supplements in the form of drops, elixir, and syrup are available. The regimen for management of iron deficiency in children is 3–6 mg/kg per day of elemental iron in divided doses. Liquid preparations are given by dropper or straw to prevent staining of teeth.

2. **Parenteral** (4). In the presence of severe side effects, GI intolerance, or poor absorption due to inflammatory bowel disease, iron may be given parenterally. Intravenous route is recommended and iron dextran (Imferon 50 mg/mL) is preferred. The formula for the total dose of iron required is as follows:

   Dose (mg) =[15 - patient's Hgb (g/dL)] × body wt (kg) × 3

   A test dose of less than 0.5 mL of the undiluted solution is given. If no allergic reaction is noted, a 2-mL dose may be given daily. If given intramuscularly the Z-track technique should be utilized to prevent staining of skin. An alternative regimen consists of the total calculated dose, diluted in saline solution, and infused over a few hours. Though most reactions are mild, life-threatening anaphylactic reactions may occur. Arthralgias, myalgias, and phlebitis may occur as a delayed reaction. Severe reactions have been noted in patients with collagen vascular disease.

V. Prevention

Breast milk or formula should be encouraged during the first year of life, as cow's milk is a poor source of iron. Along with a diet rich in iron, supplemental iron should be provided when the requirement is high, such as during infancy and growth spurts, in people who donate blood on a frequent basis, in menstruating girls and women, and in pregnant and lactating women.

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18.2

PERNICIOUS ANEMIA AND OTHER MACROCYTIC ANEMIAS

Paul M. Paulman

Pernicious anemia (PA) is caused by a deficiency of cobalamin (vitamin B_{12}) and presents as a macrocytic anemia. PA is the most common cause of macrocytic anemia. Macrocytosis is defined as an average red cell volume (mean corpuscular volume, or MCV) of greater than 95 fl.

I. Vitamin B_{12} deficiency

A. Daily requirement.

The daily requirement of B_{12} is 1 µg. The average Western diet provides 5–15 µg/d. Animal products are the sole source of B_{12}. Normal body stores of B_{12} approach 4–5 mg (more than a 5-year supply).

B. Causes of B_{12} deficiency

1. PA is an autoimmune disease associated with antibodies to gastric parietal cells or their product intrinsic factor, which is necessary for absorption of B_{12}.
2. Ileal disease (Crohn's disease, Whipple's disease, sprue, and others) impairs B_{12} absorption (see Chapter 11.9).
3. Ileal resection or gastrectomy.
4. Small bowel bacterial overgrowth.
5. Fish tapeworm (*Diphyllobothrium latum*) infestation.
6. Food-bound malabsorption occurs with achlorhydria, which prevents cleavage of B_{12} from food. Elderly patients taking stomach acid suppression medications, histamine-2 blockers, and proton pump inhibitors may be at risk for B_{12} deficiency.
7. Inadequate B_{12} oral intake occurs rarely, primarily in vegans, who consume no animal protein.
8. Certain drugs, including *p*-aminosalicylic acid, colchicine, and neomycin, can cause B_{12} deficiency.

C. Clinical manifestations of B_{12} deficiency

1. Incidence. Up to 5% of the general population have B_{12} deficiency, with patients older than 60 years at greatest risk (1). B_{12} deficiency may take years to manifest because of the large body stores.
2. Symptoms include paresthesias, generalized weakness, fatigue, anorexia, indigestion, diarrhea, and depression. Patients may be asymptomatic. Symptoms of B_{12} deficiency may be subtle and are often attributed to other disease processes.
3. Physical signs include weakness of the extremities, ataxia, pallor, loss of vibratory and position sense, memory loss, changes in mood, and hallucinations. Congestive heart failure can be present in very severe cases of anemia (see Chapter 9.4).

D. Laboratory findings

1. Macrocytosis (MCV >95 fl) is the earliest hematologic finding in B_{12} deficiency. Macrocytosis may not occur if iron deficiency or thalassemia is present along with B_{12} deficiency.
2. Low B_{12} level (<110 pg/mL) is the earliest laboratory finding in B_{12} deficiency. Normal values may vary with age.
3. Anemia (hemoglobin <12 g/dL for women or <14 g/dL for men) may be present. Anemia occurs after B_{12} stores are depleted.
4. Hypersegmented neutrophils (>5 lobes in the cell nucleus) are present.
5. Serum gastrin level may be elevated.
6. The Schilling test measures the oral absorption of B_{12}.
7. Suggested laboratory evaluation for suspected B_{12} deficiency:

a. Serum B_{12} level
b. Complete blood count (CBC)

c. Peripheral blood smear examination for hypersegmented neutrophils
d. Schilling test to document oral B_{12} absorption

E. Treatment

1. Address causes of decreased intake or malabsorption if possible.
2. If B_{12} cannot be replaced via the oral route, give 500–1,000 μg of B_{12} IM every day for 1 week, then 500–1,000 μg of B_{12} weekly for 1 month, then monthly for life or until the malabsorption is corrected. Serum potassium may decrease during B_{12} replacement and should be monitored.

F. Follow-up.

Evaluate CBC and serum B_{12} level annually.

II. Folate deficiency

A. Daily requirement.

The daily requirement of folate is 100 μg, increased in pregnancy and other physiologic states. The average Western diet supplies 400–600 μg of folate daily. Body stores can reach 5 mg (3- to 4-month supply). Folate sources include green vegetables, yeast, and liver (2).

B. Causes of folate deficiency

1. Inadequate oral intake
   a. Alcoholics
   b. Teenagers
   c. Infants
2. Malabsorption
   a. Gastrectomy
   b. Small bowel disease, Crohn's disease, sprue
   c. Anticonvulsants and other drugs
   d. Alcohol
3. Increased folate demand
   a. Pregnancy
   b. Hemolysis with reticulocytosis
   c. Exfoliative skin disease
   d. Malignancies, including lymphoma and leukemia
   e. Infancy
   f. Hemodialysis
4. Folate antagonists. Methotrexate and other antineoplastic agents, trimethoprim, triamterene, and pentamidine are folate antagonists.
5. Impaired folate metabolism
   a. Alcohol
   b. Enzyme deficiencies (rare)

C. Clinical features

1. Symptoms may be identical to B_{12} deficiency, including anorexia and fatigue. Folate deficiency causes no neurologic symptoms.
2. Physical signs include weakness, pallor, and glossitis. Congestive heart failure can occur if the anemia is severe.

D. Laboratory features

1. Serum folate is the most useful test in folate deficiency. Normal folate values range from 5 to 15 ng/mL.
2. Anemia (hemoglobin <12 g/dL for women or <14 g/dL for men).
3. MCV is greater than 95 fl.
4. Suggested laboratory evaluation of folate deficiency includes a serum folate and CBC with red blood cell (RBC) indices.

E. Treatment

1. Adequate therapy is 1 mg/d of folate orally (or IM if malabsorption is present). In a patient with macrocytic anemia, B_{12} should be given with oral folate until the diagnosis is established because some B_{12}-deficient patients may show a hematologic response to oral folate.
2. Treat and eliminate cause of folate deficiency if possible.

F. Annual follow-up

1. Diet history
2. CBC with RBC indices
3. Serum folate level

G. Prevention.

Oral folate supplements, 1 mg/d of folate orally, should be given to high-risk patients. Oral folate supplements taken by women prior to conception and through pregnancy have been shown to decrease the incidence of neural tube defects in the fetus.

III. Other causes of macrocytosis not responsive to B_{12} or folate

A. Cancer chemotherapy agents

(see Chapter 10.5, Chapter 11.11, and Chapter 13.8)

B. Inborn errors of metabolism

(see Chapter 14.3)

C. Myelodysplastic syndrome

(see Chapter 18.4)

D. Liver disease

(see Chapter 11.5)

E. Hypothyroidism

(see Chapter 17.3)

F. Reticulocytosis

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18.3
BLEEDING DISORDERS

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Angela W. Tang

Bleeding disorders are caused by abnormalities in coagulation factors, platelets, or blood vessels and result in bleeding anywhere in the body. Such disorders may be inherited or acquired. Occasionally, an asymptomatic patient is found to have an abnormal platelet or coagulation study that generates concern.

I. Diagnosis

The cause of abnormal bleeding is usually suggested by a thorough history and physical examination.

A. History.

Bleeding episodes should be characterized. It is important to note that not all easy bruising is abnormal; spontaneous bruising on the trunk or bruising of areas greater than 3 cm in diameter on the extremities is more likely pathologic. Childhood onset of symptoms and a family history of bleeding problems suggest an inherited disorder. When an inherited disorder is mild, it may not be evident until adulthood or until significant trauma or surgery occurs. Other important aspects of history are bleeding responses to surgery, dental procedures, childbirth, and menstruation and prior requirements for transfusion. Underlying diseases, such as liver dysfunction and infection, can lead to acquired bleeding problems. A thorough review of medications, including aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulant drugs, is essential. Finally, symptoms of large volume loss, such as light-headedness, dyspnea, and chest pain, may trigger more urgent inpatient evaluation or consultation with a hematologist.

B. Physical examination.

The central nervous system (CNS), gastrointestinal (GI) tract, joints, deep tissue, skin, and mucous membranes should be evaluated for bleeding. Petechiae, mucocutaneous bleeding, or slow oozing after trauma suggests deficient platelet number or function, whereas deep or visceral bleeding (hemarthroses, deep hematomas) is indicative of a problem with coagulation factors. There may be evidence of accompanying medical problems, such as infections, malignancy, and liver and renal disease.

C. Laboratory.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) evaluate coagulation factors. A complete blood count (CBC) assesses platelet number. Bleeding time will be prolonged (more than 7 seconds) in both qualitative platelet dysfunction and thrombocytopenia. The peripheral smear confirms abnormalities seen on CBC and may provide additional clues to causes of bleeding (schistocytes in disseminated intravascular coagulation, large platelets in idiopathic thrombocytopenic purpura).

D. Management.

The choice of outpatient versus inpatient management depends on the severity of the hemostatic abnormality. Supportive therapy for hemodynamic compromise should be considered for severe bleeding. Management of underlying etiologies or concurrent medical problems is often imperative in improving the bleeding disorder. Aspirin-containing products and NSAIDs should be avoided in bleeding disorders unless otherwise indicated. Contact sports should be avoided in significant bleeding disorders.

II. Hemophilia

A. Hemophilia A

is an X-linked recessive disease that is attributable to deficiency of coagulation factor VIII. As a rule, only men and boys are affected, but occasionally female carriers are clinically affected. The bleeding tendency varies with factor VIII levels. Patients with mild hemophilia (5%–50% of normal concentrations) bleed only in response to major trauma or surgery. Patients with moderate hemophilia (1%–5%) bleed in response to mild trauma or surgery, and those with severe hemophilia (less than 1%) bleed spontaneously.

1. Laboratory findings are prolonged aPTT and decreased factor VIII assay.
2. Treatment
   a. Cryoprecipitate 1–2 bags/10 kg q8–12h for 1–3 days or longer can raise factor VIII levels.
   b. Heat-pasteurized factor VIII concentrates 8–15 U/kg IV q8–12h. Higher dosages (to keep factor VIII levels as high as 50% of normal or more) are required in preparation for surgery or in severe hemorrhage.
   c. Recombinant DNA-derived clotting factors are now available for hemophilia A, eliminating the risks of viral transmission.
   d. Desmopressin acetate (DDAVP) 0.3 μg/kg IV may be used to raise factor VIII levels in preparation for minor surgery in mild hemophiliacs. It may be readministered in 8 hours.
   e. ε-Aminocaproic acid 4–6 g q6h is an inhibitor of fibrinolysis that can be used as an adjunct to factor VIII concentrate or DDAVP.

B. Hemophilia B

is a sex-linked recessive bleeding disorder due to deficiency of coagulation factor IX. Hemophilia B is clinically identical to hemophilia A but is less common. Acquired factor IX deficiency may occur concomitantly with deficiencies of factors II, VII, and X and in patients with vitamin K deficiency.

1. Laboratory findings are prolonged aPTT and decreased factor IX assay.
2. Treatment
   a. Treat with infusion of factor IX concentrates. Recombinant preparations are available to eliminate the risk of viral transmission. The dosing consideration is the same as that for factor VIII, except that the initial dose must be at least doubled because of the significant extravascular distribution of factor IX.
   b. Fresh frozen plasma (FFP) contains low levels of factor IX activity and may be used in patients with mild disease.
   c. DDAVP is ineffective in management of hemophilia

C. Factor XI deficiency

is inherited as an autosomal recessive trait and is common in Ashkenazi Jews. The correlation between bleeding propensity and factor levels is less consistent than that for factor VIII and IX deficiencies. Spontaneous hemorrhage and hemarthrosis are rare.

1. Laboratory finding is prolonged aPTT. Factor XI assay is usually decreased to less than 10% in homozygotes and to 20%–60% in heterozygotes.

2. Treatment. Give FFP 10–20 mL per kilogram body weight initially, and 5–10 mL/kg per day maintenance. Factor XI activity level of 30% is usually sufficient for hemostasis.

D. Prothrombin (factor II) and factors V, VII, X, and XIII and fibrinogen deficiencies are exceedingly rare

Spontaneous hemorrhages may occur with some of these deficiencies. The treatment mainstay is FFP, although factor concentrates are available for deficiencies of factors II, VII, and X.

E. Circulating anticoagulants

are antibodies that inhibit specific coagulation factors, prolonging the aPTT or PT. Factor VIII inhibitor is the most common inhibitor that causes bleeding. Lupus anticoagulant prolongs aPTT but causes excessive thrombosis rather than bleeding. Inhibitors may be detected by the failure of normal plasma to correct bleeding times. Management of bleeding may involve massive plasma or concentrate infusion, use of activated prothrombin complex concentrates, plasmapheresis, and immunosuppression.

III. Vitamin K deficiency.

Vitamin K has an important role in hemostasis as a cofactor in the γ-carboxylation of glutamic acid residues for coagulation factors II, VII, IX, X, protein C, and protein S. Vitamin K deficiency may develop within a week if both intake and endogenous production of vitamin K is eliminated. Vitamin K deficiencies may occur with warfarin use, postsurgical states, antibiotic therapy, biliary obstruction, liver disease, nutritional deficiencies, and malabsorption syndromes, such as inflammatory bowel diseases and ingestion of nonabsorbed fat substitutes in diet foods.

A. The laboratory finding

is prolonged PT. The aPTT may be prolonged if the deficiency is severe. Assays for factors II, VII, IX, and X are typically low if measured.

B. Treatment

1. Mild deficiencies may be corrected with vitamin K, 10–20 mg SC.
2. Severe bleeding should be managed by transfusion of FFP, 15 mL/kg IV initially, followed by 5–8 mL/kg q8–12h as needed, along with vitamin K administration. Vitamin K may be given IM or IV for quicker results. If given IV, administer slowly, 1 mg every 2–5 minutes, to decrease the risk of anaphylaxis.
3. Hospitalized patients at risk for vitamin K deficiency should receive prophylactic vitamin K 10 mg PO or SC weekly.

IV. Liver disease

(see Chapter 11.5). Many patients with acute or chronic liver disease develop hemostatic abnormalities. The bleeding disorder may range from asymptomatic to significant hemorrhage.

A. Laboratory findings

show prolonged PT and aPTT from decreased clotting factor synthesis. Thrombocytopenia, decreased fibrinogen concentration, and prolonged bleeding time may be seen. Platelet dysfunction may also occur.

B. Treatment

1. Give vitamin K, 10–20 mg SC, although it may be ineffective.
2. FFP may transiently improve hemostatic function.
3. Platelet transfusions may be required if the patient is thrombocytopenic, actively bleeding, or in preparation for surgery.
4. The value of DDAVP, fibrinolytic inhibitors, and conjugated estrogens remains uncertain.

V. Disseminated intravascular coagulation

is the consequence of activation of both the coagulation and fibrinolytic systems and may be a life-threatening condition. Usually a predominance of bleeding or thrombosis exists. DIC occurs secondarily to an initiating event, such as malignant neoplasm, infection, leukemia, obstetric complications, liver disease, shock, connective tissue diseases, massive trauma, snake bite, or extensive tissue damage, such as burns or frostbite.

A. Laboratory findings

include decreased fibrinogen (often the cardinal manifestation of DIC that correlates closely with bleeding), elevated fibrin

degradation products (FDPs) including D-dimer, thrombocytopenia, prolonged PT and aPTT, and schistocytes (fragmented red blood cells).

B. Treatment

Treatment of the underlying condition is paramount. Use of cryoprecipitate, FFP, and platelet transfusions is considered in the event of major bleeding. Heparin is indicated if there are thrombotic complications.

VI. von Willebrand's disease

(vWD) is an autosomal dominant disorder characterized by deficient or defective von Willebrand factor (vWF). vWF facilitates platelet adhesion by linking platelet membrane receptors to vascular subendothelium, and it serves as the plasma carrier for factor VIII. The severity of bleeding is highly variable even within an individual patient over time.

A. Laboratory.

Bleeding time may be prolonged but correlates poorly with bleeding risk. Prolonged aPTT occurs if factor VIII activity is decreased. vWF concentration is low. Reduced ristocetin cofactor activity is the most sensitive and specific test. Measurements of vWF antigen, vWF multimers, and ristocetin-induced platelet agglutination are useful for the subclassification of vWD.

B. Treatment

1. Oral contraceptives may be given to women because they mimic the hormonal changes of pregnancy, thus increasing vWF and factor VIII levels.
2. Give DDAVP, 0.3 μg/kg IV. A nasal spray has recently become available, making administration easier. DDAVP is contraindicated in patients with type IIB vWD because of the potential for exacerbating thrombocytopenia.
3. Factor VIII concentrate has been used successfully.
4. Give cryoprecipitate, 1–3 bags per 10 kg/d. Treatment with cryoprecipitate or factor VIII concentrate may need to be continued for 5–10 days following major surgery or trauma.

VII. Thrombocytopenia

is defined as a platelet count less than 150,000/μL. In general, platelet counts greater than 50,000/μL are not associated with significant bleeding. Severe spontaneous bleeding usually does not occur with platelet counts exceeding 20,000/μL in the absence of other hemostatic abnormalities.

A. Drug-induced thrombocytopenia

has been associated with the use of quinidine, heparin, thiazide diuretics, alcohol, H_2 antagonists, estrogens, trimethoprim-sulfamethoxazole, quinine, gold salts, phenytoin, rifampin, ticlopidine, sulfonamides, and chemotherapeutic agents. Many other drugs have been implicated on rare occasion (1). Thrombocytopenia usually resolves within days of discontinuation of drug unless there is slow excretion of the drug. Prednisone, 1 mg/kg PO qd, may decrease the duration of thrombocytopenia in some cases. Plasma exchange or platelet transfusions may be considered if hemorrhage is severe.

B. Autoimmune (“idiopathic”) thrombocytopenia

(ITP) is a disorder of antibody-mediated platelet destruction. This syndrome may occur in association with other diseases, including sepsis, thyroid diseases, pregnancy, HIV infection, malignancies, granulomatous disorders, systemic lupus erythematosus, and other rheumatologic disorders.

1. Acute ITP usually occurs in children and often follows a viral infection of the preceding 3 weeks. Most cases resolve spontaneously within 6 months.
   a. Laboratory. Platelet count is often less than 20,000/μL. Peripheral smear shows large platelets.
   b. Treatment. Give prednisone 1–3 mg/kg per day and γ-globulin 0.4–1.0 g/kg per day IV. Platelet transfusions are usually reserved for severe hemorrhage.
2. Chronic ITP is usually seen in adults, and spontaneous remissions are rare.
   a. Laboratory. Platelet count usually is greater than 20,000/μL but may drop lower.
   b. Treatment. Prednisone 1–2 mg/kg per day PO, immunoglobulin, splenectomy, danazol 200 mg PO tid, immunosuppressive therapy,

and anti-Rh(D) antibodies may be considered, depending on the severity of the disease.

c. Thrombotic thrombocytopenic purpura is characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever, and renal dysfunction. Initial therapy must include plasmapheresis coupled with infusion of FFP.

C. Hemolytic uremic syndrome

is closely related to thrombotic thrombocytopenic purpura, but renal failure is the predominant manifestation and there are no neurologic disturbances. Dialysis for renal failure may be required (see Chapter 12.6).

D. Other causes

of thrombocytopenia include hypersplenism, transfusions, DIC, nutritional deficiencies of folic acid or vitamin B_{12}, bone marrow infiltration due to myelophthisic disease (e.g., tuberculosis, metastatic carcinoma, myelofibrosis), primary hematopoietic disorders (e.g., leukemia, aplastic anemia, myelodysplasia, multiple myeloma), and various viral, bacterial, and rickettsial infections. Therapy is directed at the underlying disorder.

VIII. Qualitative platelet disorders

may occur with uremia, liver disease, cardiopulmonary bypass surgery, paraproteinemia, and myeloproliferative disorders. It may also occur with the use of drugs such as NSAIDs, aspirin, ticlopidine, clopidogrel, ß-lactam antibiotics, alcohol, antihistamines, calcium channel blockers, dipyridamole, and quinidine. Therapy is directed at the underlying disease or at removing the offending agent. Treatments that have been of use in some of the above conditions include DDAVP, corticosteroids, conjugated estrogen, cryoprecipitate, and platelet transfusions, if indicated.

IX. Abnormalities of vascular strength or structure

may lead to bleeding in the absence of a hematologic defect. For example, senile purpura presents with dark purple, irregularly shaped areas of skin bleeding on sun-exposed areas in the elderly. Purpura simplex presents with ecchymoses of the legs in healthy females, especially during menses. Management of these conditions consists of reassurance and possibly avoidance of antiplatelet medications. Cushing's syndrome and scurvy also may present with abnormal skin bleeding, and treatment is directed at the underlying condition. Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia) is an autosomal dominant disorder associated with bleeding from abnormal capillaries in the GI tract and nasal mucosa. Patients with Marfan's and Ehlers-Danlos syndromes have fragile skin vessels, easy bruisability, and a tendency to form aneurysms of large arteries with potential rupture.

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18.4

THE LEUKEMIAS

Carmen Rebecca Rexrode

The leukemias are a group of illnesses characterized by the malignant infiltration of bone marrow by abnormal cell lines that produce high numbers of leukocytes, which are often nonfunctional. These disorders are categorized according to the type of cells produced, and the chronic or acute clinical course of the disease. Any cell line can be affected. The following is an overview of the most common leukemias found in children and adults.

I. Acute leukemias in childhood

A. Acute lymphoblastic leukemia (ALL).

This most common of all childhood cancers has a peak incidence at age 2–3 years. Up to 80% of children achieve 5-year event-free survival, with poor prognosis for relapse.

1. Presentation includes pallor, fatigue, bleeding, fever, bone pain, adenopathy, arthralgias, and hepatosplenomegaly.
2. Diagnosis is based on characteristic appearance of the bone marrow aspirate.
3. Management is based on risk-based stratification and usually includes high-dose induction chemotherapy with vincristine, prednisone or dexamethasone, and l-asparaginase, with intrathecal therapy (methotrexate or radiation).
4. Prognostic indicators include age at diagnosis (children aged 1–9 years fare better than infants or children older than 10 years), sex (girls do better than boys), race (white better than black), and white blood cell (WBC) count at the time of diagnosis (under 50,000 is better). A good indicator of lasting remission is rapid response of cell counts to chemotherapy.
5. Watch for opportunistic infections, cytomegalovirus, dehydration, and thrombocytopenia during treatment. Long-term survivors may show cognitive impairment from intrathecal irradiation.

B. Acute myelogenous leukemia (AML).

Fifteen to twenty percent of childhood leukemias are classified as AML.

1. Presentation is similar to that of ALL.
2. Diagnosis is based on bone marrow aspirate containing more than 30% blasts of characteristic appearance.
3. Management includes high-dose induction chemotherapy, often with cytarabine and anthracycline, with central nervous system (CNS) prophylaxis (chemotherapy or radiation).
4. Watch for myelosuppression, leukostasis with initially high WBC counts, and infection. Long-term monitoring of cardiac, renal, and auditory function may be required.

II. Chronic leukemias in adults

A. Chronic myelogenous leukemia (CML).

CML may be an indolent disease that progresses to an acute phase over a period of weeks to years. Ninety to ninety-five percent of patients test positive for Philadelphia chromosome, a reciprocal translocation between the long arms of chromosomes 9 and 22.

1. Presentation. Clinical symptoms may be absent; increased WBC count may be found incidentally. Some patients present with splenomegaly. Median age at diagnosis is 67 years.
2. Diagnosis is made from the characteristic appearance of the bone marrow aspirate, including Philadelphia chromosome.
3. Indicators of poorer prognosis include larger spleen, older age, male gender, elevated lactate dehydrogenase (LDH), abnormal chromosomes, and higher number of blasts in bone marrow.
4. Treatment is based on the age of the patient and stage of disease.
   a. If patient is asymptomatic, no treatment may be given.
   b. Bone marrow transplantation (BMT) is considered in patients younger than 60 years.
   c. For chronic phase, α-interferon is often used.
   d. For accelerated phase, combination chemotherapy including α-interferon, cytarabine, hydroxyurea, and/or busulfan is often used.
   e. For blast crisis, intensive combination chemotherapy is indicated, with consideration of BMT if remission is achieved.
5. Watch for transformation to blast crisis, splenomegaly, anemia, thrombocytopenia, infection, pulmonary fibrosis, and hyperuricemia. Splenectomy may be indicated.

B. Chronic lymphocytic leukemia (CLL).

About 95% of cases of CLL arise in B cells, with the remainder being T-cell or promyelocytic in origin. Cells may be morphologically mature but are usually immunologically immature.

1. Presentation. Clinical symptoms may be absent, with an increased WBC count found incidentally. If the disease progresses, uncontrolled lymphocytosis will progress to generalized large lymph nodes, then often pancytopenia, hemorrhage, and infection.
2. Diagnosis is based on characteristic appearance of the bone marrow aspirate.
3. Treatment decisions are based on the patient's age and symptoms.
   a. No treatment may be given if the patient is asymptomatic.
   b. In symptomatic patients, chemotherapy is considered, using steroids, monoclonal antibodies, involved-field radiation, or BMT.
4. Watch for infectious complications, including herpes zoster virus infection, *Pneumocystis* infection (consider prophylaxis), *Candida* infections, and secondary malignancies, including treatment-induced leukemias (rare).

C. Hairy cell leukemia.

This chronic disease originates in B cells. Prognosis is generally good, with about 85% 5-year survival.

1. Presentation may include fatigue, anemia, bleeding splenomegaly, pancytopenia, or, occasionally, leukocytosis.
2. Diagnosis is based on bone marrow aspirate with cells demonstrating prominent cytoplasmic projections (hairy cells).
3. Treatment is not required in many cases. If treatment is indicated, the usual agents are α-interferon, 2-chlorodeoxyadenosine, and pentostatin. Indications for treatment include anemia, thrombocytopenia, neutropenia, infection, tissue infiltration, massive splenomegaly, and symptoms of autoimmune disease.
4. Watch for infection, including fungal and opportunistic infections, especially during and immediately following treatment.

III. Acute leukemias in adults

A. Acute lymphoblastic leukemia (ALL).

Peak incidence of ALL is in children age 2–3 years. Clinically, ALL in children older than 10 and in adults is a very different disease than ALL in children, with older children and adults having a poorer prognosis. Any patient older than 10 is considered high risk. Definitive diagnosis is crucial, as this disease is often confused with AML, hairy cell leukemia, and lymphoma, all of which have very different treatments and prognoses.

1. Presentation may include fatigue, poor wound healing, anemia, neutropenia, and thrombocytopenia.
2. Diagnosis is based on characteristic appearance of the bone marrow aspirate. Recurrences can be outside the bone marrow.
3. Treatment is with induction chemotherapy that may include vincristine, prednisone, anthracycline, and/or L-asparaginase. CNS prophylaxis is usually performed. If remission is achieved, then an allogenic BMT is considered. For recurrence, induction is repeated.
4. Watch for anemia, thrombocytopenia, disseminated intravascular coagulation, infection (pay careful attention to dental hygiene), and neutropenic fever (use broad-spectrum antibiotics). Electrolyte imbalances and abnormalities of calcium and phosphate can also occur. BMT recipients may be susceptible to graft-versus-host disease.
5. Complications in long-term survivors can include relapse, secondary malignancy, infertility, psychological and intellectual problems, and neuropathy and cardiomyopathy due to chemotherapy.

B. Acute myelogenous leukemia (AML).

Median age at diagnosis of AML is about 60 years. Sixty to seventy percent of patients achieve remission with treatment, with 15% 5-year survival. Many patients have identifiable etiologic agents (previous cytotoxic drugs, radiation exposure, benzene exposure, previous myeloproliferative disorder), but lack of these factors does

not rule out the disease. Subtypes include myeloblastic, promyelocytic, monocytic, myelomonocytic, megakaryoblastic, and erythroleukemia.

1. Presentation may include weakness, bleeding, or infection, with elevated WBC count.
2. Diagnosis is based on characteristic appearance of bone marrow aspirate.
3. Management is similar for the various subtypes and usually includes chemotherapy with agents such as daunorubicin or cytarabine.
4. Watch for hemorrhagic complications with induction, including disseminated intravascular coagulation, as well as for thrombocytopenia. Careful attention to hygiene and dental care is needed, with prophylactic antibiotics for dental work. Patients with prolonged decreased WBC count may need granulocyte colony-stimulating factor.

IV. Additional resources

The National Cancer Institute web site at http://cancernet.nci.nih.gov/ is an excellent source of treatment information for leukemias and is updated monthly. The PDQ Cancer Treatment Statements are especially helpful in providing useful information in an office setting.

XIX. INFECTIOUS DISEASES

19.1
VIRAL UPPER RESPIRATORY INFECTIONS AND INFLUENZA

George L. Kirkpatrick

I. Influenza virus

A. Clinical presentation

1. The “flu.” Influenza has one of the more characteristic sets of clinical findings. Onset is usually sudden, with shivering, sweating, headache, aching in the orbits, and general malaise and misery. Fever in adults ranges up to 102°F and even higher in children. The most consistent signs are polymyalgias, weakness, and malaise. Cough is frequently quite severe.
2. **Bronchiolitis** is generally found in children younger than 2 years. It typically begins with mild cough and congestion that progresses to a more severe cough and tachypnea. Respirations become rapid and shallow with a prolonged expiratory phase. Because the infants are not able to breathe well, they are also unable to suck or drink and so can become dehydrated. The findings include intercostal retractions, nasal flaring, and rales on auscultation, which also may suggest pneumonia. A chest radiograph shows only hyperinflation with no infiltrates (see Chapter 4.3).
3. **Pneumonia.** Although cases of influenza pneumonia can be numerous and severe, more people die from ischemic heart disease during an influenza epidemic (see Chapter 10.2).

B. Diagnosis

1. Influenza is an RNA virus of predominantly two subtypes, A and B, although a type C has been described. *Morbidity and Mortality Weekly Report* reports the pattern as influenza spreads around the world, giving physicians advance warning that influenza is in the community.
2. Pattern of infection. Influenza in the United States usually occurs during December, January, and February. The effect on a community is an overwhelming number of new similar cases with typical symptoms in a short period of time.
3. Tests available. Influenza type A can be detected in less than an hour by rapid enzyme immunoassay tests on throat swab specimens. Both types A and B can be isolated from viral cultures in 4–10 days. Newer assays detecting viral neuraminidase or using reverse-transcriptase polymerase chain reaction (RT-PCR) are now available to identify both types from respiratory secretions.

C. Management

1. General. Management of influenza is generally symptomatic, involving the use of decongestants, analgesics, and antitussives. Because of the severity of myalgias, headache, and cough associated with influenza, a narcotic-containing product is frequently indicated. Cardiovascular status should be evaluated. Cases of bronchiolitis and pneumonia may require respiratory support.
2. Antiviral agents. If *Morbidity and Mortality Weekly Report* surveillance reports or rapid enzyme immunoassay testing are suggestive of the presence of influenza type A virus, empirical use of amantadine (Symmetrel) or rimantadine (Flumadine) may benefit patients of all ages. These agents are most effective early in the disease process, although they reduce symptoms and shorten the course of disease even when begun midway into the illness. The dosage of either amantadine or rimantadine is 100 mg twice a day, except for elderly or renal-compromised patients for whom the dosage is 100 mg once a day. The dose for children up to age 10 years is 3 mg/lb per day as a single

dose. Recently, a new class of antiviral drugs, the neuraminidase inhibitors, has been shown to be effective in the management of both types of influenza. Zanamivir (Relenza) is applied intranasally as 2 inhalations q12h. Oseltamivir (Tamiflu) is taken orally as 75 mg bid, except in renal impairment where the dose is 75 mg qd. Neither is approved for use in children, and both should be started early in the disease process.

D. Prevention

1. Transmission occurs mainly by way of hand contact. The virus may survive on countertops and other objects for several hours. Hand washing reduces viral spread. Masks are of very little practical use.
2. Immunization. A specific influenza vaccine is produced each year based on currently active influenza subtypes. Immunize high-risk groups, such as the elderly and children with underlying heart, lung, or metabolic diseases, or control influenza by immunizing all school children, military personnel, and employees of large companies. Immunologic senescence in the institutionally confined, frail elderly frequently prevents development of immunity after vaccination. Prophylaxis during the influenza season may be more effective for this group.
3. Prophylaxis. Amantadine or rimantadine can be used prophylactically in a dose of 100 mg twice a day for adults and 3 mg/lb per day for children up to age 10 when the predominant virus being seen epidemically is influenza type A.

II. Respiratory syncytial virus

A. Clinical presentation

1. **Bronchiolitis.** Respiratory syncytial virus (RSV) is responsible for the great majority of cases of acute bronchiolitis. Rhinorrhea and nasal congestion generally follow an incubation period of 4–5 days. After 2 or 3 days of mild symptoms, the infant develops lethargy and a moist irritating cough associated with tachypnea and hyperinflation of the lungs.
2. **Bronchitis.** After age 2 years, bronchitis becomes the most common clinical presentation, and RSV is second only to influenza as the most common cause.
3. **Fever and respiratory distress.** In elderly patients, the symptoms become quite severe, with higher fever, respiratory distress, more severe cough, and occasionally respiratory failure requiring intubation and respiratory support. Death from either cardiovascular collapse or overwhelming pneumonia is seen in the elderly, particularly those with heart or lung diseases.

B. Diagnosis

1. RSV is a single-stranded RNA paramyxovirus, with two antigenically distinct groups (types A and B.) In infants, the group A viruses are associated with more severe infections.
2. The pattern tends to follow a winter and spring incidence, with the peak mainly in January in most years. The pattern of outbreaks of RSV tends to be a steady trickle of cases over several weeks to several months.
3. Tests. The diagnosis can be made in a few hours with a rapid diagnostic test using the enzyme-linked immunoassay procedures (Abbott test pack RSV; Directigen RSV by Becton-Dickinson). A nasal swab or nasopharyngeal washing is sent to the laboratory. Nasopharyngeal washings may be cultured for respiratory viruses, with RSV being detected in 7–10 days as a general rule.

C. Management

1. Supportive. Patients with a mild case of bronchiolitis should be treated with outpatient hydration and rest, with hospitalization considered if respiratory distress develops or if the patient becomes dehydrated. Oxygen is the cornerstone of therapy for hospitalized patients.
2. Ribavirin (Virazole) as a continuous aerosol using 6 g in 300 mL of water in a croup tent 6–20 h/d for up to 6 days is an antiviral treatment for severe cases of bronchiolitis. Intubated patients should receive ribavirin

from the ventilator. There is little evidence that ribavirin use in nonintubated patients is necessary. It is not cost effective.

D. Prevention.

Transmission occurs by large-droplet inoculation of the nose or eyes or contact with contaminated surfaces or fomites. The virus is recoverable from countertops for up to 6 hours. Good hand washing prevents transmission. Viral shedding occurs for an average of 7 days from the time of symptom onset.

III. Parainfluenza virus

A. Clinical presentation.

Croup (laryngotracheobronchitis) in young children, especially in fall and spring, is the most common presentation of parainfluenza viruses. Children between the ages of 6 months and 3 years are affected primarily. Infected children present with a 1- to 3-day history of rhinorrhea and congestion, associated with barking cough and hoarseness. Fever is usually low grade, and there may be an increased respiratory rate. Severe stridor suggests bronchiolitis. Sore throat, bronchitis, and laryngitis are also commonly seen.

B. Diagnosis.

Viral cultures of nose and throat washings may be found positive in 4–14 days after plating the cultures. The diagnosis of croup can be confirmed with lateral neck radiographs demonstrating hypopharyngeal overdistention and variable subglottic narrowing. The frontal view demonstrates the classic “pencil-tip” sign of the subglottic region.

C. Management.

Croup is a frightening family experience, especially for new parents of very young children. It is a self-limited illness. Patients usually respond to breathing cool air (or in some cases warm mist in a steamed bathroom) and require little additional therapy (see also Chapter 4.3). Physicians should look for the coexistence of underlying illnesses and reassure the family.

1. Racemic epinephrine, 0.25–0.50 mL of a 2.25% solution in 2–3 mL of normal saline administered as an aerosol, gives rapid relief in resistant cases. Rebound airway tightness frequently develops.
2. Dexamethasone, 0.6 mg/kg IM one time, although controversial, is frequently administered. Follow-up doses are usually not needed.

D. Prevention.

Parainfluenza viruses are stable in small-particle aerosols that can contaminate humidifiers. Careful cleaning of respiratory therapy equipment is vital to prevent spread of this virus.

IV. Rhinoviruses and coronaviruses

A. Clinical presentation

1. **The common cold.** This includes the symptoms of sneezing, tearing, nasal stuffiness, postnasal drainage, sore throat, hoarseness, and cough.
2. **Laryngitis** may be the isolated single clinical finding of a rhinovirus infection.
3. **Malaise, headache, sore throat, and low-grade fever** suggest infection by coronaviruses.

B. Diagnosis

1. Rhinoviruses are nonenveloped RNA viruses of the Picornaviridae family. They replicate only in primates and include more than 100 antigenic subtypes, which makes culturing and identification difficult.
2. Coronaviruses are single-stranded RNA viruses that rarely produce a positive culture.

C. Management

of infections by both virus types generally requires only symptomatic treatment. Because viral replication is reduced at elevated body temperatures, fever reduction may be counterproductive. Recent evidence suggests that dexamethasone may inhibit some rhinovirus subtypes and modulate airway inflammation caused by the rhinovirus (1).

D. Prevention.

Hand-to-hand transfer or contact with contaminated surfaces results in easy transmission of these viruses. Disinfection of environmental surfaces and good hand washing remain the most useful means of prevention.

V. Adenoviruses

A. Clinical presentation

1. **Epidemic keratoconjunctivitis.** Adenoviruses are the most common cause of typical “pink-eye,” a very contagious infection mainly found in day care centers and schools (see Chapter 7.1).
2. **Pharyngoconjunctival fever.** Adenovirus types 3 and 7 are known to cause a syndrome of pharyngitis, cough, fever, headache, myalgias, malaise, and conjunctivitis. Conjunctivitis is always present, whereas the other symptoms vary in their expression and intensity. These virus types are frequently found in lakes and inadequately chlorinated swimming pools. The illness lasts approximately 7–10 days.
3. **Bronchiolitis.** Adenovirus types 7 and 21 can cause a severe bronchiolitis that may lead to permanent bronchiolar damage.
4. **Croup, laryngitis, and mild upper respiratory infections** are commonly seen.

B. Diagnosis.

Adenoviruses are double-stranded DNA viruses with 41 recognized serotypes and more than 100 subtypes. Cultures take up to 21 days to become positive. Using monoclonal antibodies, the Bartels Viral Respiratory Screening and Identification Kit detects RSV, influenza A and B, parainfluenza 1–3, and adenoviruses in a few hours from a throat swab. A similar rapid direct immunofluorescence assay is available from Diagnostic Products Corporation (Patho DX RVP).

C. Management

is entirely symptomatic. Antibiotics are of no benefit.

D. Prevention.

Besides the usual aerosolized droplets and surface contact, fecal-oral transmission is common in children. The virus can be isolated for several weeks from respiratory secretions, tears, and stool.

Chapter Reference

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19.2
GASTROENTERITIS

Charles E. Henley

Diarrhea due to gastroenteritis is one of the leading causes of infant mortality worldwide and results in the hospitalization of more than 200,000 children each year in the United States (1).

I. Causative agents

of gastroenteritis include rotavirus, which causes sporadic viral gastroenteritis; Norwalk virus, which causes epidemic viral gastroenteritis; and enteric adenovirus, the second most common cause of viral gastroenteritis in young children. Rotavirus is the most common cause of gastroenteritis and affects mainly infants and young children. It can be severe enough to require hospitalization, whereas Norwalk virus causes a self-limiting, mild illness that can affect both adults and children and tends to occur in family, school, or community outbreaks.

II. Clinical presentation.

Viral gastroenteritis usually presents with symptoms of nausea, vomiting, and crampy abdominal pain of varying intensity due to excessive fluid in the upper gastrointestinal tract and increased peristalsis. Blood and fecal leukocytes are usually not present in the stool (2). In this way it can be differentiated from most of the bacterial pathogens that are inflammatory

and invade the mucosa of the colon, producing a bloody diarrhea. Other physical signs besides the voluminous, nonbloody stools are those associated with dehydration, such as decreased urination, mental status changes, dry mucosal membranes, and lethargy. A history of day care exposure, foods eaten, and recent exposure to antibiotic use are also important. Patients with bloody diarrhea, abdominal tenderness, and fever or severe dehydration should be hospitalized.

III. Diagnostic testing

should be focused rather than all-inclusive. If the history and examination of the stool for blood and leukocytes lead to the conclusion that the diarrhea is noninflammatory, then routine stool cultures may be an expensive waste of time.

A. Laboratory tests

are not helpful in differentiating between inflammatory and noninflammatory diarrhea, but the plasma glucose, creatinine, and electrolytes of sodium, potassium, and HCO_3 are useful in assessing volume and acid-base status.

B. Viral detection

is expensive and may be unnecessary, but the best test for rotavirus is the enzyme-linked immunosorbent assay, which detects viral antigens.

IV. Management.

Because the course of viral gastroenteritis is self-limiting, the goals of therapy are to replace fluids and electrolytes lost secondary to the diarrhea. Most patients can be treated at home with oral rehydration therapy (ORT).

A. Mild to moderate dehydration

can be managed with ORT, even in the face of continued vomiting. It is rapid, safe, and inexpensive and can be used no matter what the patient's serum sodium is at the onset of therapy. Several ORT solutions, such as Pedialyte and Rice-Lyte, are commercially available, with 45 and 50 mEq/L of sodium, respectively. ORT has also been used successfully in more severe dehydration, but if there are signs of shock, uremia, ileus, or fluid loss greater than 10 mL/kg per hour, then treatment with intravenous fluids (normal saline or half normal with dextrose) is indicated.

1. The World Health Organization (WHO) has recommended a recipe for ORT using easily obtained materials: ¾ teaspoon salt, 4 tablespoons sugar, 1 teaspoon baking powder, 1 cup orange juice, 1 L clean water. This solution is relatively high in sodium (90 mmol/L) and should be reduced in salt if there is concern about retention of sodium and water.

B. Refeeding.

The question of when and how to initiate feedings again can be simplified by following certain guidelines.

1. ORT can be continued during the diarrhea, even if there is nausea and vomiting.
2. Breast-feeding should continue uninterrupted, in addition to ORT.
3. Formula-fed infants should have a lactose-free, full-strength formula reintroduced after 6–24 hours of ORT. The American Academy of Pediatrics recommends starting with a 1:1 dilution and gradually progressing to full strength. If the diarrhea worsens, return to ORT and gradually refeed with dilute formula, up to full strength over 6–72 hours.
4. In weaned children, foods such as rice, wheat noodles, and bananas are good initially, but lactose-containing foods, caffeine, and raw fruits should be avoided for 24–48 hours (3).

C. Antidiarrheal agents

should be used with caution.

1. Anticholinergic agents are generally ineffective and are contraindicated in children.
2. Absorbents, such as kaolin and pectin (Kaopectate), may create more formed stools but may not actually cause a reduction in fluid loss or duration of the diarrhea.
3. Antisecretory agents, such as bismuth subsalicylate (Pepto-Bismol), can increase intestinal sodium and water reabsorption and block the effects of enterotoxins.

4. Antimotility agents, such as loperamide (Imodium) and diphenoxylate plus atropine (Lomotil), work by decreasing intestinal motility and reducing the distention that causes cramping and pain associated with gastroenteritis. Side effects include drowsiness, tachycardia, and paralytic ileus. Antimotility agents should be avoided in infants and used cautiously, if at all, in older children or adults because they can increase the morbidity associated with certain bacterial diseases, such as shigellosis.

D. Vaccines.

In 1998, the U.S. Food and Drug Administration approved a live virus vaccine for rotavirus. However, the Advisory Committee on Immunization Practices (ACIP) has recommended that the vaccine no longer be used due to an association with intussusception in some infants following vaccination (4).

V. Food-borne gastroenteritis

occurs in approximately 6.5 million patients each year in the United States, resulting in about 7,000 deaths (2). The etiology of food-borne gastroenteritis includes such viruses and bacteria as *Staphylococcus aureus, Salmonella typhi, Clostridium difficile,* and their enterotoxins, as well as some parasites, such as *Giardia lamblia.* These illnesses are usually associated with ingestion of undercooked meats, contaminated seafood or water, or foods left unrefrigerated. Because most cases of food-borne gastroenteritis resolve with supportive care alone, an extensive workup may be unnecessary except for public health concerns; or if one suspects botulism, which requires therapy with a specific antibody to the neurotoxin; or for patients who exhibit signs of extreme toxicity.

VI. AIDS

patients commonly have gastrointestinal symptoms, which may be caused by an array of agents such as *Mycobacterium avium,* adenovirus, cytomegalovirus, *Cryptosporidium, Isospora belli,* and *Campylobacter jejuni.* These patients are prone to *Salmonella* infection and are at risk for *Clostridium* infection as a result of frequent antibiotic use. Therapy should be focused on the treatable causes of the diarrhea and the therapeutic measures that alleviate morbidity, such as the previously discussed antidiarrheal agents. Attention should also be paid to prevention of the spread of gastrointestinal infection, especially in hospitalized patients where there is potential for fecal-oral transmission of enteric pathogens (5).

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19.3

INFECTIOUS MONONUCLEOSIS

R. Eugene Bailey

I. Definition.

Infectious mononucleosis is caused by the Epstein-Barr virus (EBV) and most commonly affects young adults aged 15–35 years. During primary infection, EBV antibodies emerge after 14–21 days of incubation, peak

during the acute phase, and then decline to lower levels, where they persist indefinitely and serve as markers of immunity to the disease.

II. Diagnosis.

The diagnosis of infectious mononucleosis is made by the accurate assessment of clinical, hematologic, and serologic manifestations of the illness (1).

A. Clinical manifestations

1. Classic triad is fever, sore throat or pharyngitis, and lymphadenopathy.
2. Manifestations, according to age group and frequency, are as follows (2):
   a. Younger than 35 years: lymphadenopathy (94%), fever (89%), sore throat or pharyngitis (78%), splenomegaly (49%), rash (7%), hepatomegaly (6%), and jaundice (4%).
   b. Older than 40 years: fever (95%), lymphadenopathy (47%), sore throat or pharyngitis (43%), hepatomegaly (45%), splenomegaly (33%), jaundice (27%), and rash (12%).

B. Hematologic manifestations

1. White blood cell (WBC) count is usually elevated 2–3 weeks after infection and is often 10,000–15,000 cells/μL (10.0–15.0 × 10^9/L).
2. Atypical lymphocytosis occurs in approximately 70% of diagnosed cases. Both B and T cells contribute to the characteristic atypical lymphocytes (approximately 30%) but may also be associated with cytomegalovirus infections, viral hepatitis, measles, rubella, and serum sickness.
3. Mild thrombocytopenia is seen in about 50% of patients; severe thrombocytopenia may occur infrequently.

C. Serologic manifestations

(3)

1. **Monospot test.** The Monospot test is a latex agglutination test that measures production of heterophile antibodies during acute and recent EBV infection. The use of this test is limited because of false-negative readings in 10%–20% of adult cases (due to lack of production of heterophile antibody) and a false-positive rate of 5%–15% (due to cross-reactivity with other illnesses, such as cytomegalovirus infection, adenovirus infection, and toxoplasmosis).
2. **EBV-specific antigens.** Other techniques have been developed to detect EBV because of the limitations of the Monospot test. These are generally more expensive and require referral to laboratories.
   a. Viral capsid antigens (VCA). Antibodies to viral capsid antigens (VCA-IgM and VCA-IgG) are elevated during acute infection with EBV. IgM is undetectable after 3 months and peaks generally in 3–4 weeks. Although suggestive of disease, the VCA-IgG titer often has peaked by the time the patient seeks medical care, so that acute-phase or convalescent-phase sera yield false-negative rates of 80%–90%. Therefore, VCA-IgM titer is the most predictive tool for early diagnosis of acute primary infection (4).
   b. Early antigens (diffuse and restricted). Early antigens occur in 70%–90% of patients, are detectable after 2–3 months, and are present in 20% of remote infections.
   c. Nuclear antigen (NA or EBNA). The antigen is undetectable during acute illness. Nuclear antigen develops after 2 months and persists indefinitely; the absence of this antigen may suggest immunodeficiency.

III. Treatment

A. Therapy

for infectious mononucleosis is largely supportive because the disease is usually self-limited. Bed rest is recommended during the febrile stage, and strenuous exercise should be avoided for at least 3 weeks, especially if splenomegaly is present.

B. Medications,

in general, are of little benefit, with the exception of acetaminophen or ibuprofen to control pain symptoms and fever. Aspirin should be avoided to avert the rare and potentially fatal Reye's syndrome.

C. Antibiotics

are of no value in mononucleosis, except in patients with secondary bacterial infection. Use of amoxicillin is strongly associated with a rash, which does not appear to represent an allergic reaction.

D. Corticosteroids,

though advocated by some physicians, should be avoided unless severe complications develop, such as airway obstruction, neurologic involvement, hemolytic anemia, thrombocytopenic purpura, myocarditis, or pericarditis.

E. Intravenous γ-globulin

for immune thrombocytopenia refractory to corticosteroids is effective (5).

IV. Complications.

Although infectious mononucleosis is almost always self-limited, several complications may develop during the course of the illness.

A. Upper airway obstruction

from tonsillar enlargement and generalized inflammation, severe thrombocytopenia, and severe hemolytic anemia can be life-threatening complications. Prednisone is generally given in these situations at dosages of 60–80 mg/d for 5–7 days, then tapering over 14 days. Any potential benefit derived from the use of corticosteroids in the management of these complications should be balanced against any side effects (6).

B. Insertion of an artificial airway

appears to be replacing emergency tonsillectomy as a first-line treatment in patients with complete airway obstruction.

C. Spontaneous rupture of the spleen

is rare, occurring in 0.1%–0.5% of patients with confirmed infectious mononucleosis. Because of the risk of hemorrhage, splenectomy is the treatment of choice for rupture (7).

D. Hepatitis

resulting from EBV infection can be severe, but transaminase levels are generally not high (see Chapter 11.5). Supportive measures should be taken and other possible causes ruled out in patients who present with jaundice or abnormal liver function tests.

E. Sports

during convalescence should be avoided due to the potential for spontaneous splenic rupture. Strenuous activity should be avoided for at least 3–4 weeks after the onset of clinical disease. Contact sports should be avoided for an additional period as long as splenomegaly is present. The physical examination is unreliable for determining the presence of an enlarged spleen. A flat plate of the abdomen and an ultrasound or computed tomography scan should be obtained before an athlete is allowed to return to contact sports (8).

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19.4

HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME

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Human immunodeficiency virus (HIV) is a retrovirus that infects human lymphocytes and other cells, causing progressive immune dysfunction resulting in acquired immuno-deficiency syndrome (AIDS). AIDS is characterized by opportunistic infections, malignancies, and other clinical manifestations. Without treatment, the average latency period from initial HIV infection to the development of AIDS is about 10 years.

I. HIV prevention.

All patients should be assessed for risk factors for HIV. Physician-initiated discussion of safe sex and drug use are appropriate at well-adolescent and health care maintenance visits, and may influence patient behavior.

II. HIV testing.

HIV testing should be offered to all patients, especially those with a history of injection drug use or at-risk sexual activity. A positive screening test result (enzyme-linked immunosorbent assay) is confirmed by Western blot or other specific test. Patients almost always test positive within 6–12 weeks of exposure, although there are reports of delayed seroconversion. HIV infection is generally considered to have been ruled out with a final negative test at 6 months.

III. Management of HIV-infected patients.

With the advent of potent combination antiretroviral therapy, HIV is becoming a chronic disease necessitating long-term care for many patients. Expert consultation is encouraged for clinicians with little experience in managing HIV disease. Advice regarding the treatment of HIV-infected patients is also available from the National HIV Telephone Consultation Service (“Warmline”) at (800) 933-3413.

A. Initial history

should be comprehensive, highlighting concomitant infections (sexually transmitted diseases, tuberculosis [TB], hepatitis, and opportunistic infections), travel, drug allergies, illicit drug use, and psychiatric illness, and, for women, Pap smears and past pregnancies. Social history should assess impact of infection on support systems, work history, etc. Review of systems for fever, night sweats, recurrent oral or vaginal candidiasis, diarrhea, lymphadenopathy, and dermatitis may help in disease staging, as may physical examination of the mouth, skin, lymph nodes, and abdomen.

B. Laboratory screening.

Confirmatory HIV serology should be considered. A complete blood cell count and platelet count, renal and liver chemistries, fasting glucose and lipid panel, albumin, as well as syphilis and hepatitis B and C serologies should be obtained. Baseline CD4 lymphocyte count and viral load (VL) should be determined with two measurements. Skin testing for TB should be performed annually. Cervical Pap smears should be performed every 6 months for the first year, then annually if normal.

C. Antiretroviral therapy.

Antiretroviral agents comprising three distinct drug classes that interfere with viral replication and slow HIV disease are available. Potent regimens have been shown to suppress viral replication, elevate CD4 cells, and reconstitute the immune system. Current guidelines suggest considering combination antiretroviral therapy for symptomatic patients, and for asymptomatic patients with CD4 <500 or VL <20,000 by reverse-transcriptase polymerase chain reaction (more than 10,000 if measured by branched-chain DNA assay) (1). Therapy can be considered for patients with acute or early (<1 year) infection as well. Thus, if and when to initiate antiretroviral therapy is a complex decision that should be individualized. Combination therapy with three agents from two classes of

drugs is the standard of care for initial therapy. Second- and third-line regimens, chosen when viral resistance develops, are increasingly difficult to tolerate. The optimal regimen balances potency with tolerability to promote maximum adherence. Complex drug interactions with and among antiretroviral agents must also be addressed. Genotypic and phenotypic resistance testing may also be helpful in designing an optimal antiretroviral regimen (2). Rapid development of new agents requires frequent revision of treatment guidelines, available on standard web sites (Table 19.4-1).

www.cdc.gov
www.hivatis.org
www.hivinsite.ucsf.edu
www.hopkins-aids.edu
www.medscape.com
www.ucsf.edu/hivcntr

Table 19.4-1. Useful internet resources

1. **Nucleoside reverse transcriptase inhibitors (NRTIs).** These drugs inhibit reverse transcriptase by competing with host nucleotides. The agents in this class are zidovudine (azidothymidine, AZT; 300 mg bid), lamivudine (3TC; 150 mg bid), stavudine (d4T; 20–40 mg bid), didanosine (ddI; 400 mg qd), and abacavir (ABC; 300 mg bid). Zalcitabine (ddC) is infrequently used due to its relative inefficacy. Lactic acidosis has been identified as a rare but potentially fatal side effect of all drugs in this class. Common side effects include gastrointestinal (GI) intolerance with AZT and ddI; peripheral neuropathy with ddI, ddC, and d4T; pancreatitis with ddI; and bone marrow suppression with AZT. ABC can cause a potentially fatal hypersensitivity reaction characterized by fever, rash, nausea, and malaise. Patients who have discontinued ABC should not be rechallenged with this agent.
2. **Nonnucleoside reverse transcriptase inhibitors (NNRTIs).** These drugs inhibit reverse transcriptase by binding to it and changing its shape. The agents in this class are nevirapine (Viramune, NVP; 200 mg bid), efavirenz (Sustiva, EFV; 600 mg qd), and delavirdine (Rescriptor, DLV; 400 mg tid). DLV is rarely used because of relative inefficacy and frequent dosing. Rash (including occasional Stevens- Johnson syndrome) and increased transaminase levels are common class side effects. EFV can cause central nervous system (CNS) side effects. These drugs all affect the P450 system, so drug interactions must be considered.
3. **Protease inhibitors (PIs).** These drugs inhibit protease, thereby preventing formation of new virus. The agents in this class are saquinavir (Fortovase or Invirase, not recommended as a single protease inhiitor), indinavir (Crixivan 800 mg q8h), ritonavir (Norvir, 600 mg bid), nelfinavir (1,250 mg bid), and amprenavir (Agenerase; 1,600 mg bid). Lopinavir is a new second-generation protease inhibitor. It is formulated as Kaletra in combination with ritonavir and dosed at 400/100 mg bid. Class side effects include GI intolerance, hyperglycemia/diabetes mellitus, fat redistribution, hyperlipidemia, and liver function test (LFT) abnormalities. Drug-specific side effects include diarrhea with nelfinavir and lopinavir, paresthesias with ritonavir and amprenavir, rash with amprenavir, and nephrolithiasis with indinavir. These drugs, especially ritonavir, can inhibit enzymes in the P450 system, so drug interactions need to be carefully considered. Such drug interactions can be employed to therapeutic advantage when a combination of protease inhibitors is used.

D. Immunizations.

Influenza and pneumococcal vaccines are recommended. Hepatitis B vaccine is indicated for hepatitis B seronegative patients. Live

virus vaccines are generally contraindicated in patients with AIDS but should not be withheld when indicated in less immunocompromised patients. Measles-mumps-rubella (MMR) vaccine use is not contraindicated.

E. Prophylaxis against opportunistic infections.

Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is indicated when the CD4 count falls to less than 200 cells/μL, or following an episode of PCP (3). Trimethoprim- sulfamethoxazole (TMP-SMX), 1 double-strength (DS) tablet daily, is the drug of choice; alternatives include single-strength (SS) TMP-SMX, TMP-SMX DS three times weekly, dapsone [check for glucose-6-phosphate dehydrogenase (G6PD) deficiency before administering] with or without pyrimethamine, or inhaled pentamidine if no other options are available. Toxoplasmosis prophylaxis is indicated for patients with positive *Toxo-plasma* titers who have a CD4 count less than 100. TMP-SMX is an effective prophylactic agent against *Toxoplasma gondii*; alternative prophylaxis is usually with dapsone plus pyrimethamine and folinic acid. Prophylaxis against *Mycobacterium avium complex* (MAC) disease is indicated for a CD4 count less than 50; clarithromycin and azithromycin are the preferred agents. Increasing evidence suggests that prophylaxis against these illnesses can be safely discontinued in individuals who respond to combination antiretroviral therapy with a sustained rise in their CD4 count greater than the CD4 thresholds noted above.

IV. Complications of HIV disease

A. Systemic

1. **Fungal infections** with *Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis*, and *Coccidioides immitis,* often with disseminated disease in blood, bone marrow, liver, spleen, and CNS, require management with amphotericin B and/or oral azole drugs (itraconazole, fluconazole).
2. **MAC disseminated infection** typically presents with progressively worsening constitutional symptoms such as fevers, night sweats, and weight loss in patients with a CD4 count less than 50. Bone marrow involvement is common. MAC is generally managed with ethambutol plus either clarithromycin or azithromycin; rifabutin, ciprofloxacin, or amikacin can be added for severe infections.
3. ***Mycobacterium tuberculosis* infection** (**TB**) can occur early or late in the course of HIV disease. With advanced HIV disease, disseminated TB is more common than the localized pulmonary form. TB involving the bone marrow, GI tract, pericardium, CNS, or lungs is most common. Initial treatment with a four-drug regimen, including isoniazid, pyrazi namide, ethambutol, and rifampin or rifabutin for the first 2 months, is generally recommended, followed by an additional 7 months of therapy based on sensitivity results (4). Directly observed therapy should be considered if compliance is a concern. Potentially dangerous drug interactions between rifampin and some antiretroviral agents often require substitution of rifabutin for rifampin. Guidelines regarding the treatment of tuberculosis, especially HIV-related tuberculosis, change frequently; updated CDC guidelines on the management of comorbid tuberculosis and HIV disease can be found at http://www.cdc.gov/ (also see Chapter 10.4).
4. **Weight loss and wasting** are almost universal in AIDS. Opportunistic infections and malignancies, inadequate oral intake, chronic diarrhea, and depression can accelerate the wasting process. Consultation with a nutritionist can be helpful. Megestrol and tetrahydrocannabinol can promote increase in weight by improving appetite; resistance exercise training has shown more benefit in increasing lean body mass. Growth hormone can also increase lean body mass, but it is expensive and the safety of its long-term use unclear (5).
5. **Kaposi's sarcoma (KS)**, while typically confined to the dermis, can involve the viscera as well (see below).

B. Hematologic

complications of HIV infection commonly include leukopenia, anemia, and, less commonly, thrombocytopenia. Destruction of CD4 cells, HIV-mediated disruption of the hematopoietic system, low erythropoietin levels, anemia of chronic disease, and bone marrow suppression by HIV-related medications, opportunistic infections (such as MAC or B19 parvovirus), or malignancies should all be considered in the differential diagnosis of hematologic abnormalities. Treatment is generally directed at the underlying cause; granulocyte colony-stimulating factor can be used for significant neutropenia (absolute neutrophil count less than 500).

C. Skin disease.

KS typically presents as raised or flat violaceous lesions on the skin and/or hard palate (see Section IV.J below). Sometimes a biopsy is needed to distinguish KS from bacillary angiomatosis, which results from *Bartonella henselae* infection. Perioral and anogenital recurrent herpes simplex virus (HSV) infections are treated with oral acyclovir; intravenous acyclovir or foscarnet can be used for refractory or resistant infections. Herpes zoster infection confined to one or two dermatomes is treated with oral acyclovir, but disseminated infections or those involving the eye should be treated with IV acyclovir. Staphylococcal folliculitis and seborrheic derma titis are more common in HIV infection. Cutaneous reactions to medications are common, including maculopapular or urticarial rashes, erythema multi forme, fixed drug eruptions, or more severe reactions such as the Stevens- Johnson syndrome or toxic epidermal necrolysis.

D. Oral cavity diseases

include candidiasis (thrush), KS, hairy leukoplakia, aphthous ulcers, and periodontal disease. Thrush can appear as erythematous patches or white plaques. Treatment with topical clotrimazole is usually effective, but systemic treatment with ketoconazole or fluconazole is sometimes required. Oral and esophageal aphthous ulcers often respond to prednisone; thalidomide has shown benefit for these conditions as well.

E. Eye disease.

Cytomegalovirus (CMV) retinitis occurs in persons with advanced HIV disease (CD4 <50). Patients may note floaters, visual defects, or frank peripheral or central vision loss. Induction therapy with IV ganciclovir or foscarnet, followed by maintenance therapy with IV or oral ganciclovir or IV foscarnet can be effective in halting or slowing disease progression. Ganciclovir intraocular implants are convenient and similarly effective, and early data suggest that valganciclovir is an effective oral alternative to IV ganciclovir for induction therapy. *Treponema pallidum, Toxoplasma gondii*, and fungi are also associated with symptomatic disease and ophthalmologic findings.

F. Pulmonary disease

1. ***Pneumocystis carinii* pneumonia (PCP)** most commonly occurs in patients with a CD4 count less than 200. Patients usually present with nonproductive cough, fever, and progressive dyspnea. Chest radiograph shows infiltrates or diffuse interstitial involvement but can be normal. Diagnosis is confirmed with induced sputum, bronchoalveolar lavage, or biopsy specimens. The treatment of choice is TMP-SMX; adjuvant prednisone therapy improves survival in patients with PaO_2 less than 70 mm Hg. Second-line therapies for PCP include intravenous pentamidine, dapsone and trimethoprim, dapsone and trimetrexate, or clindamycin and primaquine.
2. **Bacterial pneumonia.** Mycobacterium tuberculosis (TB) can occur early or late in the course of HIV disease. Pulmonary infiltrates should be carefully evaluated for TB because of the severity of its course in HIV-infected persons, as well as the public health implications. Typical bacterial pneumonias, especially those caused by *Streptococcus pneumoniae, Haemophilus influenzae*, and *Staphylococcus aureus*, are common in HIV disease. Standard antibiotic therapy is usually effective.
3. **Fungal infections.** Pulmonary involvement with *Cryptococcus, Histo plasmosis, Aspergillus, Blastomyces*, or *Coccidioides*, while not as common as PCP or bacterial pneumonias, should be considered in patients with low CD4 counts.

4. **KS** can cause pulmonary disease, occasionally without dermal lesions. Radiographs characteristically show reticulonodular interstitial disease with pleural effusions.

G. GI disease

1. **Candidal esophagitis** causes dysphagia, odynophagia, and retro sternal pain. Response to empirical therapy with fluconazole or ketoconazole establishes the diagnosis and avoids endoscopic evaluation. Treatable HSV and CMV infections, which can cause painful ulcerations, are identified by endoscopic biopsy. Aphthous ulcers have a similar presentation and can be treated with prednisone and/or thalidomide.
2. **Diarrhea,** often with severe weight loss, occurs in more than half of AIDS patients. Bacterial stool cultures can identify *Salmonella, Cam pylo bacter,* and *Shigella* species. In patients with fever, blood cultures should also be obtained. *Clostridium difficile* enteritis, identified by *C. difficile* antigen in stool, is managed with oral metronidazole. Stool tests for ova and parasites can reveal *Entamoeba histolytica, Giardia lamblia,* and other infectious agents that respond to usual therapies. *Cryptosporidium* infection produces watery diarrhea, abdominal pain, nausea, and vomiting; treatment with paromomycin or azithromycin might help, but the most effective intervention appears to be potent antiretroviral therapy. Symptomatic control of diarrhea with diphen oxylate hydrochloride with atropine, loperamide, tincture of opium, or octreotide can be helpful. Sigmoidoscopy with biopsy and culture is indicated when results of initial stool studies are negative. CMV enterocolitis is often accompanied by diarrhea, weight loss, abdominal pain, fever, and anorexia, and can lead to severe complications such as perforation. Ganciclovir and foscarnet provide limited benefit.

H. Neurologic disease

1. ***Cryptococcus neoformans*** causes meningoencephalitis in 6%–10% of AIDS patients, usually in patients with a CD4 count less than 100. The most common symptoms are fever, headache, and altered mental status. Meningeal signs and symptoms are uncommon. Serum and cerebrospinal fluid cryptococcal antigen is positive in 95% and 90% of patients, respectively. Acute treatment with amphotericin B for 2 weeks (minimum), usually with flucytosine, followed by fluconazole for 8–10 weeks is recommended. Patients with mild disease, low cerebrospinal fluid titers, and normal mental status can be treated initially with fluconazole alone. Lifetime maintenance therapy with fluconazole is currently recommended to prevent reoccurrence of disease; the safety of discontinuing lifelong suppressive therapy against cryptococcosis in patients who enjoy a sustained immunologic response to combination antiretroviral therapy is under investigation.
2. ***Toxoplasma gondii*** encephalitis usually presents in patients with a CD4 count less than 100. Symptoms and signs include altered sensorium, seizures, focal motor or sensory abnormalities, cerebellar dysfunction, or neuropsychiatric manifestations. Empirical therapy is recommended for patients with multiple ring-enhancing lesions on computed tomography (CT) scans or magnetic resonance images; CNS lymphoma presents similarly and should be considered if empirical antitoxoplasmosis therapy is not effective. Treatment with pyrimeth amine and folinic acid plus either clindamycin or sulfadiazine is continued for 6–8 weeks. Clinical or radiographic improvement can be expected within 2–3 weeks. Failure to respond usually generates an evaluation for lymphoma. Maintenance therapy with pyrimethamine and clindamycin or sulfadiazine is required to prevent relapse.
3. **AIDS dementia complex (ADC)** is a common condition in advanced AIDS. It is characterized by cognitive, motor, and behavioral dysfunction. Early manifestations include difficulties with concentration and

memory. Eventually, performance of complex tasks becomes more difficult; slowing of thought processes and verbal response is typical. As the disease progresses, motor impairment and behavioral disturbances can become severe. The condition may respond to potent combination antiretroviral therapy, ideally including at least two antiretroviral agents that cross the blood-brain barrier.

4. **Distal symmetric polyneuropathy (DSPN)** presents as painful or burning paresthesias in a stocking-glove distribution on the extremities. It usually begins in the lower extremities but can include the upper extremities as well. DSPN is a common adverse effect of combination antiretroviral therapy, especially to regimens including d4T and ddI, but can also be caused by HIV itself. The most effective therapeutic options include tricyclic antidepressants and gabapentin.
5. **Progressive multifocal leukoencephalopathy (PML),** caused by infection by JC virus, occurs late in the course of HIV disease. PML usually develops insidiously with a single focus (e.g., limb weakness, ataxia, visual defects) but can progress to multiple foci, delirium, sei zures, and death. Prolonged survival and remission has been reported with effective combination antiretroviral therapy

I. Gynecologic disease.

Chronic vaginal candidiasis, recurrent HSV infection, and condyloma acuminatum are common. Cervical dysplasia can progress rapidly in HIV-infected women, resulting in cervical neoplasia. Pelvic inflammatory disease can be difficult to diagnose because leukocytosis is uncommon (see also Chapter 13.1 and Chapter 13.5).

J. Malignancies.

KS is the most common AIDS-associated malignancy. Treatment modalities include radiation therapy, cryotherapy, intralesional chemotherapeutic drug injections, systemic chemotherapy, and α-interferon therapy. Non-Hodgkin's lymphoma often presents at an advanced stage, behaves aggressively, and responds poorly to treatment. Primary CNS lymphoma is usually managed with radiation but can be difficult to distinguish from *T. gondii* encephalitis.

V. Pregnancy and HIV.

Women with advanced HIV disease are at risk for having low-birth-weight infants, prematurity, chorioamnionitis, and fetal demise. Perinatal transmission occurs in about 25% of births unless antiretroviral therapy is given. Zidovudine therapy during pregnancy, labor, and delivery and for the newborn during the first 6 weeks of life can decrease the risk of perinatal transmission to approximately 8%. Combination antiretroviral therapy may further decrease transmission and may be indicated to promote maternal health (6). An appropriate regimen can be chosen with the help of an expert consultant. Invasive procedures that might promote transmission, such as fetal scalp monitoring, scalp sampling, and episiotomy, should be utilized only when clearly indicated. Caesarean section should be offered to all HIV-infected women with a viral load greater than 1,000 but has increased morbidity in HIV-positive women. Breast-feeding is contraindicated because it promotes transmission of HIV.

VI. HIV in children.

Polymerase chain reaction, repeated at designated intervals, can be used to diagnose HIV in most infants by 4 months of age (7). Common early manifestations of HIV infection in children include oral candidiasis, lymphadenopathy, hepatosplenomegaly, fever, diarrhea, recurrent bacterial infections, failure to thrive, and developmental delay.

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19.5
SYPHILIS

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Syphilis, “the great imitator,” was a significant cause of cardiovascular disease and the major cause of insanity and blindness in the United States during the first half of the 20th century (1). In 1998, primary and secondary cases of syphilis represented an incidence of 2.6 cases per 100,000, an 86% decrease from the 1990 figure of 20.3 per 100,000 (the peak of the most recent U.S. epidemic). Specific geographic foci and populations account for the majority of cases (2,3). Patients present with signs and symptoms of primary, secondary, or tertiary infection, which may be detected by serologic testing in the latent stage (4). Consider syphilis in patients with skin problems as well as those with sexually transmitted disease. *Treponema pallidum* is the responsible spirochete.

I. Presentation

A. Primary syphilis

typically presents as one or more characteristic chancres (papules that ulcerate) about 3 weeks after infection, but may last for 3 to 90 days at the site of the inoculation. It is a classically painless, indurated, clean-based ulcer. Painless regional lymphadenopathy is common. The chancre is several millimeters to 2 cm in diameter; it is usually found on the genitals (including the cervix) but may be perianal, rectal, or oral. It usually resolves without treatment in 3–6 weeks. The disease is contagious during this period. Transmission occurs in about one third of those exposed (4,5,6,7 and 8).

B. Secondary syphilis

develops 2 weeks to 2 months after the appearance of the chancre. Its manifestations include adenopathy, mucocutaneous lesions (ulcers and flattened eroded lesions known as mucous patches), and, most commonly, a maculopapular rash on the palms and soles, although the rash can be of any kind except vesicular. It may start on the trunk and spread to the extremities in a pityriasis rosea-like pattern. Accompanied by condylomata latum [soft, flat-topped, red-to-pale, coalesced papular lesions occurring in moist areas] (4,5,6,8), diffuse or patchy, “moth-eaten” alopecia may occur in the scalp and beard areas, with loss of eyelashes and the lateral third of eyebrows. Systemic symptoms may include malaise, low-grade fever, sore throat, headache, and arthralgia. Hepatosplenomegaly, cardiac arrhythmia, nephritis, cystitis, iritis, prostatitis, and gastritis may occur secondarily to spirochetemia.

C. Early latent (<1 year after exposure) or late latent syphilis (of unknown duration or >1 year after exposure)

has no clinical manifestations. It is diagnosed when a positive nontreponemal screening test -result is confirmed by a positive treponemal antibody test. Relapse of mucocutaneous lesions may occur creating an infectious state. If untreated, 35% of patients will develop tertiary syphilis (8).

D. Tertiary syphilis

refers to gumma and cardiovascular syphilis, but not to neurosyphilis (4). Cardiac manifestations include aortitis, aortic dilatation and regurgitation, and nonatherosclerotic coronary ostial stenosis (5,8). -Gummas are granulomatous lesions of the skin, skeletal, and respiratory systems that represent a delayed sensitivity reaction with local destruction responding to antibiotics. Symptoms may occur 10–40 years after the primary infection. Aortitis does not respond to antibiotics (4,5,8).

E. Neurosyphilis

can occur during any stage of syphilis (4). The patient may present with clinical evidence of neurologic involvement, such as cranial nerve palsies (Argyll Robertson pupils), auditory symptoms, signs or symptoms of meningitis; ataxia (tabes dorsalis with its wide-based “steppage” gait); bladder or bowel incontinence; optic abnormalities, such as neuroretinitis, optic neuritis, or uveitis; peripheral neuropathy; shooting pains; personality change; speech disturbances; facial tremor; and hyperactive reflexes may also occur. It can lead to meningovascular stroke syndromes and seizures. The cerebrospinal fluid (CSF) leukocyte count is elevated at greater than five white blood cells per cubic millimeter. The Venereal -Disease Research Laboratory (VDRL) CSF test is the standard serologic test for CSF; when reactive in the absence of a bloody tap it is considered diagnostic of neurosyphilis, although it may be nonreactive in the presence of neurosyphilis. A negative CSF fluorescent treponemal antibody absorption (FTA-ABS) test excludes neurosyphilis due to its high sensitivity. Neurosyphilis is diagnosed based on combinations of reactive serologic test results, abnormal CSF cell count, or protein in a patient with a reactive VDRL-CSF test with or without clinical manifestations (4,8).

F. Congenital syphilis

affects infants born of syphilis-infected mothers. Pregnant women should be screened for syphilis at their first prenatal visit. In communities and populations at high risk for congenital infection, serologic testing and sexual history should be taken at 28 weeks gestation and at delivery. Sequelae include hydrops fetalis (diagnosed by ultrasound), stillbirth, prematurity, anemia, thrombocytopenia, deafness, mental retardation, seizures, and bony deformities such as frontal bossing, depending on the stage of maternal disease. Symptoms of infected infants may include serosanguinous nasal discharge, anemia, periostitis, maculopapular rashes, hepatosplenomegaly, and lymphadenopathy within 3 months of birth. Later signs include Hutchinson's teeth, saddle nose, saber shin, and interstitial keratitis (3,4 and 5,7).

G. HIV and syphilis

(also see Chapter 19.4). Although the clinical and laboratory presentations of syphilis in HIV-positive patients are similar, false-negative treponemal and nontreponemal tests occur more frequently in this population. In the event of negative serology and strong clinical suspicion, skin lesion biopsied material should be examined for the presence of spiro chetes or for direct fluorescent antibody staining (4,7). These patients may have higher initial rapid plasma regain (RPR) titers, multiple chancres, and more a higher incidence of Jarisch-Herxheimer reactions. They may more often have slower resolution of the chancres and more treatment failures (4,9,10). Some experts recommend CSF examination before therapy and appropriate modification of treatment, as well as CSF examination after therapy. HIV-infected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months post therapy. All persons with HIV should be evaluated for syphilis (4).

II. Diagnosis

A. Early syphilis.

Darkfield examination and direct fluorescent antibody tests of biopsied lesions are the gold standard of diagnosis.

B. Serologic tests.

Presumptive diagnosis is possible with following two types of serologic tests.

1. VDRL and RPR tests are nontreponemal tests (i.e., the interaction of the spirochete with host tissue yields an antibody against a lipoidal antigen). VDRL and RPR tests have sensitivities of 78% and 86%, respec tively, and are used for screening. They become positive 4–6 weeks after -infection and 1–3 weeks after the appearance of the primary lesion. It is expected that they will become nonreactive following treatment; however, some patients demonstrate a serofast reaction, maintaining persistently low titers for life. The titers correlate well with disease activity but can be falsely negative at the very early or late stage, initially due to developing antibody response and later due to waning antibody response. The titers are both qualitative and quantitative and can be used to monitor response to treatment (4,5). The tests are not interchangeable. If titers to VDRL are followed, subsequent testing must be VDRL, and if RPR is used first, then it must be used subsequently. A fourfold -change in titer, equivalent to a change of two dilutions (from 1:16 to 1:4), is considered to be clinical response to treatment. Use of consistent laboratory testing sites is recommended. Common causes of false positivity are viral infections, pregnancy, malignancy, immunizations, connective tissue disorders, and intravenous drug use (4,5).
2. FTA-ABS and microhemagglutination–*Treponema pallidum* (MHA-TP) -tests are used to confirm a positive VDRL or RPR. These tests do not correlate well with disease activity and should not be used to monitor treatment response. The FTA-ABS remains positive for life in most people despite treatment (9). Consider other sexually transmitted diseases, including HIV infection, in all patients diagnosed with syphilis.

III. Treatment.

Parenteral penicillin G (Bicillin L-A) is the drug of choice for management of all stages of syphilis. Monitor for the occurrence of the Jarisch- Herxheimer reaction (fever, hypotension, headache, and myalgias) in the first 24 hours after any treatment for syphilis. Antipyretics are helpful.

A.

For primary, secondary, and early latent syphilis, the treatment regimen is as follows:

1. Adults are given benzathine penicillin G, 2.4 million units IM in a single dose.
2. Children are given benzathine penicillin G, 50,000 units per kilogram IM in a single dose (up to the adult dose of 2.4 million units). Children should have a CSF examination to exclude neurosyphilis, with a review of birth and maternal medical records to assess whether this the syphilis is congenital or acquired. Children with acquired syphilis should be evaluated for sexual assault or abuse (4).
3. Alternatively for nonpregnant adults, doxycycline 100 mg bid PO for 2 weeks or tetra cycline 500 mg qid PO for 2 weeks may be given to-penicillin-allergic patients.

B.

Therapy for late latent syphilis or latent syphilis of unknown duration is as follows:

1. Adults: Benzathine penicillin G, 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals.
2. Children: Benzathine penicillin G, 50,000 units per kilogram IM, up to the adult dose of 2.4 million units, administered as three doses at-1-week intervals (total 150,000 units per kilogram up to the adult dose of 7.2 million units).
3. Alternatively for nonpregnant adults, doxycycline 100 mg bid or tetracycline 500 mg qid PO. Both drugs should be administered for 2 weeks if the duration of infection is known to have been less than 1 year, otherwise they should be administered for 4 weeks.
4. All patients with latent disease should be evaluated for tertiary disease.

C.

Therapy for neurosyphilis is as follows:

1. Give aqueous crystalline penicillin G, 18–24 million units/d, administered as 3–4 million units IV every 4 hours for 10–14 days (4).

2. Alternatively, give procaine penicillin 2.4 million units IM a day, *plus* probenecid 500 mg orally 4 times a day, both for 10–14 days (4). Desensitize for penicillin allergy.

D.

Therapy for tertiary syphilis

1. Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM at 1-week intervals (4).

E.

Therapy for congenital syphilis is as follows:

1. Aqueous crystalline penicillin G, 100,000–150,000 units/kg per day, administered as 50,000 units/kg per dose IV every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days; *or* procaine penicillin G 50,000 units/kg per dose IM per day in a single -dose for 10 days (4).

F.

Pregnant patients who are allergic to penicillin should be desensitized, if necessary, and treated with penicillin. The procedure should be treated as a medical emergency with skin testing of both major and minor determinants and if positive, desensitized either orally or intravenously in a hospital setting (4).

G.

Treat infants if the mother has untreated syphilis at delivery, has a fourfold or greater increase in nontreponemal titer, was treated with erythromycin or other non-penicillin regimen during pregnancy or was treated for syphilis 1 month or less before delivery, did not have a well-documented history of treatment, had insufficient serologic follow-up of treatment, or had nontreponemal titers that did not decrease at least fourfold. Also treat if the infant has clinical syphilis, a serum (not umbilical cord blood) quantitative nontreponemal serologic titer that is four times greater than the mother's titer, or a positive darkfield or fluorescent antibody test of body fluids (4). The infant workup should include CSF analysis for VDRL, cell count, and protein; a complete CBC with differential; and other tests as indicated, such as long-bone radiography, chest radiography, liver function testing, cranial ultrasonography, ophthalmologic examination, and auditory brain stem response.

H.

Infants and children who require treatment for syphilis but are penicillin allergic should be desensitized.

I.

HIV-positive penicillin-allergic patients with primary or secondary syphilis should be allergy tested and desensitized if the test result is positive.

J.

Patients with reported penicillin allergy should receive skin testing with both major and minor determinants; if results are positive, patients should be desensitized orally or intravenously in a hospital setting (4).

IV. Follow-up.

Following treatment, it is important to monitor titers for evidence of response or treatment failure. A fourfold decrease in antibody titers should be seen. The decline is slower in cases of late latent syphilis, neurosyphilis, and HIV infection. Patients with primary and secondary syphilis should be evaluated serologically and clinically 6 and 12 months after treatment. If there is not a fourfold decline, evaluate for HIV. If reinfection is uncertain, perform CSF evaluation before treating with 7.2 million units administered at three doses of 2.4 million units each at 1-week intervals.

A.

Patients with latent syphilis should be retested serologically and clinically 6, 12, and 24 months after treatment. If titers rise fourfold, high titers (1:32) fail to drop at least fourfold within 12–24 months, or syphilitic signs and symptoms develop, the patient should be evaluated for neurosyphilis and treated if appropriate.

B.

Patients with neurosyphilis should be monitored with CSF examination every 6 months for decreasing cell count if CSF pleocytosis was initially present. If there is no decrease in 6 months or failure to return to normal in 2 years, retreatment should be considered.

C.

HIV-infected patients should be evaluated clinically and serologically for treatment failure 3, 6, 9, 12, and 24 months after treatment.

V. Special considerations.

CSF examination (a) is not recommended for primary, secondary, late latent, or syphilis of unknown duration unless neurologic, ophthalmologic symptoms are present (4); and (b) is recommended for neurosyphilis,

congenital syphilis, children after the newborn period, and some experts recommend CSF examination for HIV patients (4).

VI. Prevention

A.

Sexual transmission happens only when mucocutaneous lesions are present.

1. Treat patients presumptively within 90 days of exposure to primary, secondary, or early latent syphilis.
2. Treat patients presumptively if exposure was more than 90 days prior when the serologic results are not immediately available or follow-up is uncertain.
3. For purposes of partner notification and treatment, consider patients with syphilis of unknown duration whose nontreponemal serologic test titers are greater than 1:32 as having early syphilis.
4. Long-term sex partners of late-syphilis patients should be evaluated clinically and serologically and treated on the basis of the findings

B.

Screen all patients with other sexually transmitted diseases for syphilis.

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19.6
GONORRHEA

Raymond R. Walker

I. Overview.

Gonorrhea continues to be a very prevalent sexually transmitted disease in the United States and the rest of the world. Despite efforts to control this disease, the trend toward lower incidence reversed itself in 1998. The rate had been decreasing for the previous 13 years. In the United States, for the year 1998, the incidence of gonorrhea increased by 9% as reported by the Centers for Disease Control (CDC) in June 2000 (1). The incidence rate was not consistent across states but was up overall. There is approximately a 29% resistance to penicillin or tetracycline. There is a high association with coinfection with *Chlamydia,* which should also be treated.

II. Etiology.

Gonorrhea is caused by *Neisseria gonorrhoeae.* This is a gram-negative coccus (gonococcus), which usually occurs in pairs. There is an association with polymorphonuclear cells (PMNs). The culture is performed on enriched media, such as Mueller-Hinton or Modified Thayer-Martin. The organism is strictly aerobic. Unlike the meningococcus, there is no polysaccharide capsule. It may be cultured from many areas, including urethra, cervix,

throat, rectum, and conjunctiva. In addition to culture diagnosis, there is also a rapid antigen test available. Serologic testing is available, but it takes longer than other tests to return a result and may delay treatment.

III. Presentation.

This is usually associated with a mucopurulent discharge, but such discharge may not always be present. Some individuals may not have any symptoms. Symptoms may be related to location of infection.

A.

Urethritis often presents with a purulent or mucopurulent discharge; however, some patients, especially males patients, may be asymptomatic.

B.

Cervicitis usually is associated with a purulent or mucopurulent discharge, but patients may be asymptomatic. This is often associated with symptoms of urethritis as well. May also be associated with pelvic inflammatory disease (PID) (see Chapter 13.5).

C.

Pharyngitis presents with enlarged tonsils, pain, and purulent exudates, usually associated with oral-genital contact. Frequently involves enlarged cervical lymph nodes.

D.

Conjunctivitis is often the result of transmission from mother to infant at the time of delivery. There is significant swelling and erythema of the conjunctiva and lids, with copious purulent discharge. If not managed, may lead to corneal ulceration.

E.

Monoarthropathy results from hematogenous spread of the disease. This occurs in approximately 1%–2% of infections. These patients appear septic and often have positive blood cultures. The arthropathy is frequently wandering but tends to remain with a single joint. There may also be associated systemic involvement. Rarely, it progresses to endocarditis or meningitis.

IV. Diagnosis.

This usually begins with confirmation of the presence of urethritis (1).

A.

Presence of purulent or mucopurulent discharge.

B.

Gram's stain of urethral secretions demonstrating five or more white blood cells (WBCs) per oil immersion field. Document the presence of WBCs containing intracellular gram-negative diplococci.

C.

Positive leukocyte esterase on voided urine or microscopic exam with at least ten WBCs per high-power field.

D.

If these criteria are absent, diagnosis can be deferred pending culture or rapid antigen testing. Treatment is based on results.

E.

Treatment for patients whose diagnosis does not include urethritis should be recommended only for high-risk individuals with poor likelihood of follow-up. These individuals should be treated for both gonorrhea and chlamydial infection. Partners should also be empirically treated.

V. Treatment.

CDC recommends that all patients being treated for gonorrhea should also be treated for chlamydial infection because of the high incidence of coinfection. This can be done without testing for *Chlamydia.* Chlamydial coinfection is associated with 20%–40% of gonococcal infections. Consideration should be given to looking for other sexually transmitted diseases, such as syphilis and HIV infection, as well as hepatitis B.

A.

Uncomplicated infections are usually managed with ceftriaxone (Rocephin) 125 mg IM as a single dose and doxycycline 100 mg orally twice a day for 7 days. A single dose of azithromycin (Zithromax) 1.0 g orally may be substituted for the doxycycline for improved compliance. Options for the ceftriaxone include cefixime 400 mg orally as one dose, ciprofloxacin (Cipro) 500 mg orally as one dose, or ofloxacin (Floxin) 400 mg orally as a single dose. Test of cure is not required. Patients with persistent symptoms should be evaluated for resistant organisms. Treatment failure is often a result of reinfection or coinfection with other organisms, such as *Chlamydia.* Sexual partners will require treatment, and intercourse should be avoided until completion of therapy.

B.

Pregnant patients should not be treated with quinolones or tetracyclines. Ceftriaxone is safe in pregnancy, as are erythromycin and azithromycin (see also Chapter 22.2).

C.

Patients who are HIV-positive should receive the same treatment as HIV-negative individuals.

D.

Conjunctivitis in adults may be managed with ceftriaxone 1 g IM as a single dose. The eyes should then be irrigated with saline solution once.

E.

Patients with disseminated gonococcal infection (DCI) should be hospitalized and treated for presumptive chlamydial infection as well. Treatment should be ceftriaxone 1 g IM or IV daily until 12–24 hours after the patient improves, at which time oral therapy may be begun. Alternatives include cefotaxime 1g IV q8h, ciprofloxacin 500 mg IV q12h, or ofloxacin 400 mg IV q12h. Oral therapy may be cefixime 400 mg twice a day, ciprofloxacin 500 mg twice a day, or ofloxacin 400 mg twice a day.

F.

Ophthalmia neonatorum is frequently caused by chlamydial infection, but gonorrhea should be considered. Topical therapy alone is not adequate. Recommended treatment is ceftriaxone 25–50 mg/kg IV or IM as a single dose (maximum dose 125 mg). Prophylaxis may be silver nitrate 1%, erythromycin 0.05%, or tetracycline 1% as a single treatment.

G.

Children may be treated with ceftriaxone 125 mg IM as a single dose.

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19.7

CHLAMYDIA INFECTION

Donald R. Koester

Chlamydia species are obligate intracellular bacteria that cause several diseases. *Chlamydia trachomatis, C. pneumoniae,* and *C. psittaci* are species that cause infections in humans. Many persons with chlamydial infections are asymptomatic or experience mild symptoms but can still suffer significant sequelae, such as pelvic inflammatory disease (PID), chronic pelvic pain, infertility, or ectopic pregnancy in women and epididymitis or Reiter's syndrome (reactive arthritis, conjunctivitis, and urethritis) in men.

I. Clinical presentation

A.

Chlamydia trachomatis genital infection is the most frequently reported infectious disease in the United States.

1. Women are exposed to *Chlamydia* through sexual intercourse. The cervix, urethra, and rectum are initial sites of infection. Women are asymptomatic or can have dysuria, vaginal discharge, abdominal pain, or vaginal bleeding after intercourse. Up to 40% of untreated women develop an ascending infection, resulting in endometritis, salpingitis, pelvic peritonitis, or perihepatitis (Fitz-Hugh-Curtis syndrome; see also Chapter 13.5). Physical examination is normal or can show cervical friability, green or yellow endocervical mucopus (from mucopurulent cervicitis), abdominal tenderness, or cervical motion and adnexal tenderness consistent with pelvic inflammatory disease.
2. Men most commonly have urethral infections. Men are asymptomatic or can have mild to severe symptoms of dysuria and penile discharge. Testicular and/or epididymal pain, which is typically unilateral, is present with epididymitis. Physical examination is normal or can show white, gray, or clear urethral discharge. Tenderness and swelling of the epididymis are present with epididymitis.
3. Women and men can develop acute or chronic conjunctivitis when exposed to infectious genital secretions during oral-genital sexual contact,

autoinoculation, or occasionally contact with water in swimming pools (see also Chapter 7.1). Physical examination shows unilateral or bilateral conjunctival erythema, mucopurulent discharge, and preauricular adenopathy.

4. Women and men who practice receptive anal intercourse can develop proctitis or proctocolitis. Symptoms include rectal pain, discharge, and tenesmus. Tenderness on rectal examination is often present.
5. ***Chlamydia*** serovars L1, L2, and L3 cause lymphogranuloma venereum (LGV), which is rare in the United States. LGV causes a self-limited genital ulcer followed by tender inguinal adenopathy located above and below the inguinal ligament. The adenopathy frequently becomes suppurative. Proctocolitis and perirectal or perianal lymphatic tissue inflammation is present with rectal infection in women and men practicing receptive anal intercourse.
6. Infants born vaginally to infected mothers become infected during delivery (1). Ocular prophylaxis does not prevent transmission of Chlamydia from the infected mother to infant. Infected infants can develop conjunctivitis and/or pneumonia (2). Infants develop conjunctivitis 5–12 days after exposure. Physical examination reveals tearing, erythematous conjunctiva, purulent discharge, and eyelid swelling. Infants with chlamydial pneumonia present as early as 2 weeks or as late as 4 months after delivery with paroxysmal cough and tachypnea without fever. Physical findings include rales and sometimes wheezing. Approximately 50% of infants with chlamydial pneumonia also have conjunctivitis.

B.

pneumoniae causes infection more commonly in school-age children and adults. Symptoms include pharyngitis, hoarseness, and headache. Cough is prominent and can persist for weeks to months if the infection is not managed effectively. Pneumonia and bronchitis can also be present (3).

C.

Psittacosis, caused by *C. psittaci,* is a zoonotic infection acquired from infected birds. Symptoms include fever, chills, headache, nonproductive cough, malaise, and myalgias. Complications include confusion, abdominal pain, hepatitis, endocarditis, and Stevens-Johnson syndrome (4).

II. Diagnosis

A.

C. trachomatis is diagnosed by enzyme immunoassay (EIA), direct fluorescent antibody (DFA) tests, nucleic acid hybridization tests (DNA probe), polymerase chain reaction (PCR), ligase chain reaction (LCR), transcription-mediated assay (TMA), and cell culture. The endocervix is the preferred site of specimen collection in women, and the urethra the preferred site in men. PCR and LCR tests detect *C. trachomatis* in first-catch urine (the first 10–30 mL of the urine stream) with a sensitivity comparable to that for a specimen obtained by urogenital swab. Specimen collection technique is important for both culture and nonculture tests. During the physical examination, collect specimens for Pap smear, Gram's stain, or *Neisseria gonorrhoeae* first. Clean the cervix with a sponge or large swab. Insert the appropriate swab 1–2 cm into the endocervical canal and rotate against the canal wall for 10–30 seconds. Do not touch vaginal surfaces while withdrawing the swab. Collect specimens from the urethra by gently inserting the appropriate swab 1–2 cm into the female urethra or 2–4 cm into the male urethra and rotate the swab in one direction for 5 seconds. Collect specimens for the diagnosis of chlamydial conjunctivitis from the everted eyelid. Do not collect exudate alone. Giemsa-stained scraping from the conjunctiva assists with the diagnosis of chlamydial conjunctivitis but is less sensitive than culture, DFA, or EIA.

B.

C. pneumoniae infection is diagnosed by cell culture preferably from the nasopharynx. Microimmunofluorescence IgM antibody serology specific to *Chlamydia* is also available, with a titer of 1 : 32 or greater suggestive of infection. A fourfold rise of acute and convalescent antibody titer is diagnostic (3).

C.

C. psittaci infection is diagnosed by serology or cell culture.

D.

LGV is diagnosed by isolating the LGV strain from the urethra, cervix, ulcer, or node and by serology.

E.

Cell culture is recommended for diagnosis of infections of the rectum and in cases of sexual assault or abuse (2).

III. Treatment

A.

C. trachomatis urethral, endocervical, or rectal infections are managed with azithromycin (Zithromax), 1 g PO single dose, or doxycycline (Vibramycin), 100 mg PO bid for 7 days. Alternative regimens include ofloxacin (Floxin) 300 mg PO bid for 7 days, or erythromycin base (E-Mycin, Eryc) 500 mg PO qid for 7 days, or erythromycin ethylsuccinate (EES) 800 mg PO qid for 7 days. Note that ofloxacin is not recommended for adolescents 18 years or younger or in pregnant or lactating women (1) (see Chapter 22.2). Consider retesting 3 weeks after completion of treatment with erythromycin because side effects can lead to decreased patient compliance.

Pregnant women are treated with erythromycin base 500 mg PO qid for 7 days, or amoxicillin (Amoxil) 500 mg PO tid for 7–10 days. Alternative regimens include erythromycin base 250 mg PO qid for 14 days, or erythromycin ethylsuccinate 800 mg PO qid for 7 days, or erythromycin ethylsuccinate 400 mg PO qid for 14 days, or azithromycin 1 g PO single dose. The U.S. Centers for Disease Control and Prevention (CDC) recommends repeat testing 3 weeks after completion of treatment (1).

LGV is managed with doxycycline 100 mg PO bid for 21 days. An alternative regimen is erythromycin base 500 mg PO qid for 21 days (1).

Conjunctivitis in adults is managed with PO erythromycin or doxycycline as above for 21 days. Conjunctivitis and pneumonia in children are managed with erythromycin suspension (EES, EryPed) 50 mg/kg per day PO in 4 divided doses for 10–14 days (1).

B.

C. pneumoniae is managed with doxycycline or erythromycin as listed in Section III.A for 21 days. The fluoroquinolones taken for 7–14 days have also been shown to be effective (3,5).

C.

C. psittaci infection is managed with doxycycline as in Section III.A . Erythromycin as listed in Section III.A is the best alternative for patients in whom tetracyclines are contraindicated, although its in vivo efficacy has not been determined. Continue treatment for 10–14 days after defervescence (4).

IV. Prevention

A.

Primary prevention includes patient education addressing behavioral changes that may reduce the risk of acquiring infection. Such behavioral changes include delaying the age of first intercourse, decreasing the number of sexual partners, selecting partners carefully, being knowledgeable about HIV infection and other sexually transmitted diseases, and using condoms.

B.

Because chlamydial infections may be asymptomatic and sequelae significant, identification and treatment of infected individuals before they infect their sexual partners or before pregnant women infect their babies is important. The CDC recommends screening sexually active young women with mucopurulent cervicitis, sexually active women younger than 20, women aged 20–24 who either use a condom inconsistently or have had a new or more than one sexual partner during the last 3 months, and women older than 24 who use condoms inconsistently and have had a new or more than one sexual partner during the last 3 months. Screening is done at the time of a pelvic examination in women younger than 20 unless sexual activity has been limited to a single monogamous partner. Perform annual screening on all other women who meet the screening criteria (2). Screen pregnant women for chlamydial infection at the time of the first prenatal visit and again during the third trimester when they are young, have multiple or new sexual partners, do not use barrier contraception, or have a history of previous sexually transmitted diseases (1). Sexually active adolescent men can

be screened with the leukocyte esterase test on urine. A positive test result necessitates further testing for chlamydial and gonorrheal infection to determine the cause of the infection (2). The leukocyte esterase test is not indicated as a screening test for women and older men.

C.

Instruct patients treated for chlamydial infection to abstain from intercourse for 7 days after single-dose treatment or until completion of their treatment with other regimens and until all of their sex partners have been treated. Treat all sexual partners of the previous 60 days preceding onset of symptoms in the infected patient or treat the latest sexual partner even if last sexual contact occurred more than 60 days previously (1).

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19.8

HERPESVIRUS INFECTIONS

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Ann K. Skelton

Herpes simplex virus (HSV) affects more than one third of the world population and is responsible for a wide array of disease, with effects ranging from discomfort to death (1). The three most common types are HSV-1 (affinity for oral sites) and HSV-2 (affinity for genital sites) and varicella zoster virus (VZV). Primary infection causes local viral replication with painful itchy vesicles, seeding of regional neural ganglia, and possible viremia. A unique property of all HSV is the ability to establish lifelong latency in neural ganglia and periodically reactivate. Below we discuss the three most common clinical manifestations of HSV.

I. Herpes simplex

A. Epidemiology.

HSV infects through direct contact of mucous membranes and secretions and has an incubation period of 2–14 days. It can be excreted asymptomatically at the time of primary or recurrent infection.

B. Clinical syndromes

1. **Gingivostomatitis** is usually caused by HSV-1. Primary infection is manifested by fever, cervical adenopathy, and oral, facial, labial, and buccal vesicular lesions, which heal by crusting in 1–2 weeks. Intraoral lesions are ulcerative. Most cases occur at age 1–5 years, but HSV-1 should be considered in a young adult with ulcerative pharyngitis.
2. **Herpes labialis** (cold sores, fever blisters) is usually due to recurrent HSV-1. A prodrome of tingling and itching precedes the appearance of

vesicles on the lip. Lesions may be brought on by stress, fever, ultraviolet light, trauma, and immunosuppression.

3. **Genital infection** is typically caused by HSV-2 and is sexually transmitted. If seen in a preadolescent, one must think of possible sexual abuse. Primary infection causes systemic symptoms of fever, malaise, and lymphadenopathy. Lesions develop on male and female genitalia. Primary perianal HSV-2 infections and proctitis are more common in male homosexuals. Primary infection lasts 2–3 weeks. Recurrent infection is less intense, has rare systemic manifestations, and lasts 1–2 weeks.
4. **Herpetic whitlow,** a viral paronychia characterized by vesicles, occurs by autoinoculation or by direct contact with infected persons.
5. **Herpes gladiatorum** is transmitted by close physical contact in sports such as wrestling and may be seen in almost any skin site, but particularly head, neck, thorax, and upper extremities.
6. **Ocular HSV** presents as a unilateral keratoconjunctivitis with pain, photophobia, chemosis, blurred vision, and tearing (see also Chapter 7.1).
7. **HSV encephalitis,** the most serious and feared type of HSV infection, starts with a nonspecific febrile illness and headache that progresses to seizures and focal neurologic signs.
8. **Neonatal herpes infections** are the result of intrapartum contact with genital HSV or postpartum contact with hospital staff or others shedding HSV. With a primary genital infection, 30%–60% of neonates are infected, compared with only 1%–3% if the infection is recurrent. Consider HSV in an infant showing signs of sepsis; only one third of neonates with HSV have typical skin lesions.
9. **In the immunocompromised host,** prolonged and destructive lesions are found in typical locations and contiguous structures (e.g., esophagus and lungs).

C. Diagnostic testing

1. **Tzanck smear** is obtained by scraping cells from the base of a vesicle. Look for viral inclusions or multinucleated giant cells. Results are rapid but the test is only 60% sensitive.
2. **Viral culture** of lesions and other areas of the body, such as mouth, eyes, urine, cerebrospinal fluid (CSF), and cervix, is the gold standard for diagnosis, though sensitivity is only 70%–80%.
3. **The enzyme-linked immunosorbent assay (ELISA)** shows a rise from acute to convalescent titers. Limitations include inability to detect early infection and to distinguish HSV-1 from HSV-2.
4. **Polymerase chain reaction of CSF** is the diagnostic method of choice for central nervous system (CNS) infections, with a specificity of 100% and a sensitivity greater than 95% at the time of clinical presentation (2).

D. Prevention

1. Infection control measures include careful hand washing to prevent transmission, contact isolation for neonates who have been exposed or who are infected, and use of condoms to prevent spread of HSV-2.
2. Cesarean section prevents vertical transmission for women with an active herpetic lesion during labor.
3. Vaccine development is underway.

E. Treatment

(Table 19.8-1)

Viral infection	Drug of choice	Dosage	Duration (d)
Herpes simplex virus (HSV)			
Orolabial herpes in immunocompetent recurrence	Penciclovir (Denavir)	1% cream applied q2h w/a	4
Genital			
First episode	Acyclovir (Zovirax)	400 mg PO tid or 200 mg PO 5×/d[a]	7–10
	or Famciclovir[b] (Famvir)	250 mg PO tid	5–10
	or Valacyclovir (Valtrex)	1 g PO bid	7–10
Recurrence	Acyclovir	400 mg PO tid	5
	or Famciclovir	125 mg PO tid[c]	5
	or Valacyclovir	500 mg PO bid	5
Chronic suppression	Acyclovir	400 mg PO bid	—
	or Famciclovir	250 mg PO bid	—
	or Valacyclovir	500 mg PO bid	—
Mucocutaneous disease in immuno-compromised	Acyclovir	5 mg/kg IV q8h[d] or 400 mg PO 5×/d	7–14 7–14
Encephalitis	Acyclovir	10–15 mg/kg IV q8h[e]	14–21
Neonatal	Acyclovir[b]	10 mg/kg IV q8h	10–21
Acyclovir resistant	Foscarnet (Foscavir)	40 mg/kg IV q8h	14–21
Keratoconjunctivitis	Trifluridine[f] (Viroptic)	1 drop of 1% solution topically q2h, up to 9 drops/d	10
Varicella-zoster virus (VSV)			
Varicella	Acyclovir	20 mg/kg (800 mg max. qid)	5
Herpes zoster	Valacyclovir	1 g PO tid	7
	or Famciclovir	500 mg PO tid	7
	or Acyclovir	800 mg PO 5×/d	7–10
Varicella or zoster in immunocompromised	Acyclovir	10 g/kg IV q8h[g]	7
Acyclovir resistant	Foscarnet	40 mg/kg IV q8h	10

[a] For severe initial genital herpes, intravenous acyclovir (5 mg/kg q8h for 5–7 d) can be used. Dosage reduction is recommended for creatinine clearance less than 50 mL/min.
[b] Not approved by the Food and Drug Administration for this indication.
[c] For treatment of recurrent HSV in HIV-positive patients, the manufacturer recommends 500 mg PO bid.
[d] Pediatric dosage is 250 mg/m^2 IV q8h for 7–4 d.
[e] Pediatric dosage is 500 mg/m^2 q8h for 10–21 d.
[f] An ophthalmic preparation of acyclovir is available in some countries. Management of HSV ocular infections should be supervised by an ophthalmologist; duration of therapy and dosage depend on response.
[g] Pediatric dosage is 500 mg/m^2 q8h for 7–10 d.
From *Med Lett* 1999;41:114–115, with permission.

Table 19.8-1. Treatment for herpesvirus infections

II. Varicella (chickenpox)

A. Epidemiology.

Transmission occurs by inhalation of infected respiratory secretions or direct contact with lesions of varicella or zoster. Incubation occurs over an average of 14–16 days, ending with development of rash. Patients are infectious from 5 days before onset of rash until lesions have crusted. Varicella affects 90% of household contacts. Generally, immunity is lifelong after infection.

B. Clinical syndromes

1. **Chickenpox** presents with a prodrome of low-grade fever, malaise, and headache that may precede rash by a few days. Skin lesions develop first on the face and trunk. Skin complications include scarring and bacterial superinfection. CNS complications, including Reye's syndrome, occur in 1 in 1,000 cases. Pneumonia occurs in 1 in 400 adults. The mortality rate is 10% and in immunocompromised patients 30%.
2. **Congenital varicella syndrome** occurs in 2% of affected pregnancies, with limb hypoplasia, ocular atrophy, and psychomotor retardation.
3. **Neonatal varicella** occurs when the mother develops varicella around the time of delivery; it has a mortality up to 30%.

C. Diagnostic tests

(Section I.C.3)

D. Prevention

1. Avoidance of VZV during the host's contagious period reduces infection.
2. Active immunization with a live virus vaccine (Varivax 0.5 mL SC for children 12 months to 12 years of age; 0.5 mL, twice, 4–8 weeks apart for those older) results in 94% immunity; duration of immunity is not known.
3. Passive immunization with varicella-zoster immune globulin (VZIG, 1 vial = 125 units = 1.25 mL, 125 units/10 kg up to 625 units, with minimum of 1 vial, IM), administered within 96 hours of a significant exposure, is indicated for neonates, pregnant women, and immunocompromised patients.

E. Treatment

(Table 19.8-1)

III. Herpes zoster (shingles)

A. Epidemiology.

Reactivation of VZV resulting in zoster is associated inversely with immunocompetence and proportionately with age. Factors that decrease immune function are chemotherapy, chronic steroid use, HIV infection, and malignancies. Recurrent shingles occurs in 5% of immunocompetent patients.

B. Clinical manifestations.

Severe pain precedes the development of clustered vesicles on an erythematous base in one to three adjacent dermatomes. Lesions evolve and crust over 10–14 days.

1. Zoster *sine herpete*, or characteristic pain without rash, occurs infrequently. Infection can be confirmed by serologic testing.
2. Disseminated zoster, with more than 20 lesions in dermatomes removed from the primary dermatome, occurs in up to 40% of immunocompromised hosts.
3. Cranial nerve involvement produces symptoms referable to the nerve involved.
   a. Involvement of the ophthalmic branch of cranial nerve V may cause visual impairment or blindness. The presence of Hutchinson's sign (vesicles on the side and tip of the nose) is an indication that ocular involvement is likely, and slit-lamp examination is mandatory.
   b. Ramsay Hunt syndrome, involvement of cranial nerves VII and VIII, produces vesicles on the pinna, ear canal, and tongue. This can result in facial palsy, tinnitus, vertigo, and impairment of taste and hearing.
4. Postherpetic neuralgia (PHN) is characterized by pain persisting 4–6 weeks beyond crusting of lesions. It is more common in older patients, occurring in more than 50% of persons older than 60 years.
5. Unusual complications include CNS and visceral involvement. Pregnancy-related shingles usually has a benign course, with low risk of VZV infection in the fetus.

C. Diagnostic tests

(Section I.C.3)

D. Prevention

is achieved by primary prevention of varicella infections. In the elderly with a history of varicella, reactivation as zoster may be reduced by boosting immunity with varicella vaccine.

E. Treatment

(Table 19.8-1 and Table 19.8-2). Symptomatic treatment is essential during acute illness and may be necessary for PHN. Analgesics help reduce acute pain. Avoid aspirin in children because of risk of Reye's syndrome. Local treatment with wet compresses of water or 5% Burlow's solution is helpful. Prednisone may help reduce the incidence of PHN in persons older than 60 years.

Medication	Dosage
Topical agents	
Capsaicin cream (Zostrix)	Apply to affected area 3–5×/d.
Lidocaine (Xylocaine) patch	Apply to affected area q4–12h as needed.
Tricyclic antidepressants	
Amitriptyline (Elavil)	10–25 mg orally at bedtime; increase dosage by 25 mg q2–4 wk until response is adequate, or to maximum dosage of 150 mg/d.
Nortriptyline (Pamelor)	10–25 mg orally at bedtime; increase dosage by 25 mg q2–4 wk until response is adequate or to maximum dosage of 125 mg/d.
Imipramine (Tofranil) *or* Desipramine (Norpramin)	25 mg orally at bedtime; increase dosage by 25 mg q2–4 wk until response is adequate, or to maximum dosage of 150 mg/d.
Anticonvulsants	
Phenytoin (Dilantin)	100–300 mg orally at bedtime; increase dosage until response is adequate or blood drug level is 10–20 μg/mL (40–80 μmol/L).
Carbamazepine (Tegretol)	100 mg orally at bedtime; increase dosage by 100 mg q3d until dosage is 200 mg 3×/d, response is adequate or blood drug level is 6–12 μg/mL (25.4–50.8 μmol/L).
Gabapentin (Neurontin)	100–300 mg orally at bedtime; increase dosage by 100–300 mg q3d until dosage is 300–900 mg 3×/d or response is adequate. (Drug levels for clinical use are not available)

[a]Additional modalities include transcutaneous electric nerve stimulation (TENS), biofeedback, and nerve blocks.
From Stankus SJ, Dlugoolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. *Am Fam Physician* 2000;61:2442, with permission.

Table 19.8-2. Treatment options for postherpetic neuralgia[a]

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19.9
LYME DISEASE

Robert D. Sheeler

Lyme disease is a multisystem spirochetal illness caused by the organism *Borrelia burgdorferi.* Primary manifestations are systemic and cutaneous. Delayed rheumatologic, neurologic, cardiac, and other complications may follow, especially if the primary illness is unrecognized or untreated. Lyme disease is a tick-borne illness with *Ixodes* genus ticks believed to be the primary or sole agents of transmission.

I. Early presentations

A. Systemic.

Initial presentations may range from asymptomatic seroconversion to a toxic systemic illness with fever, headache, and arthralgias being prominent.

B. Cutaneous.

The classic erythema chronicum migrans skin lesion occurs in 70% of cases and is pathognomonic. It often precedes seroconversion. Erythema chronicum migrans rash typically occurs 3–30 days after exposure. It is an expanding annular lesion 3–68 cm (typically 10–20 cm) in diameter, often lasting several weeks. Lesions are multiple in 10%–50% of cases. A variety of other rashes, some evanescent, may appear.

II. Late presentations

A. Rheumatologic.

Joint involvement occurs in up to 70% of untreated patients, usually 2–24 months from exposure. The arthritis is oligoarticular and migratory, with symptoms in an involved joint lasting days to months. Large joints, especially knees, are most frequently involved. About 10% of patients with Lyme arthritis progress to a more chronic erosive rheumatoid picture (see Chapter 15.2). Involved joints may be swollen, warm, and red.

B. Neurologic.

Acute and chronic neurologic involvement may occur, usually 4 weeks or more after exposure. Lyme neuroborreliosis most commonly manifests as cranial or peripheral neuropathy (see Chapter 6.9). Bell's palsy is the most frequently observed sequela and may be bilateral. Lyme meningitis, encephalitis, vasculitis, chronic encephalopathy, and other sequelae have also been reported. Acute psychosis and other psychiatric presentations are possible.

C. Cardiac.

The vast majority of Lyme cardiac involvement presents with various degrees of heart block from first degree to third degree. Typical onset is 4 weeks after exposure. The heart block is usually self-limited. Some patients require temporary pacemaker support. Myocarditis develops in a minority of patients.

D. Other manifestations

1. **Optic.** A variety of ophthalmic syndromes, from keratoconjunctivitis to more complex processes, have been reported (see Chapter 7.1).
2. **Chronic cutaneous.** The most common chronic cutaneous Lyme lesion is acrodermatitis chronicum atrophicum.

III. Differential diagnosis

A. Infectious diseases.

In systemically ill patients, the differential diagnosis includes Rocky Mountain spotted fever, syphilis, babesiosis, tularemia, relapsing fever, Colorado tick fever, and ehrlichiosis. Ehrlichiosis has been known to occur concomitantly with Lyme disease (which favors the use of the tetracycline class antibiotics in regions where the two coexist) (1,2).

B. Rheumatologic disorders.

More chronic presentations, when joint involvement is predominant, should raise the possibility of rheumatologic diseases, especially rheumatoid arthritis and systemic lupus erythematosus.

IV. Diagnosis and laboratory testing

A. Diagnosis.

The diagnosis of Lyme disease remains contingent on potential exposure to an endemic area and appropriately timed clinical manifestations.

B. Laboratory studies.

Seropositivity alone is not diagnostic of Lyme disease. Combined IgM and IgG enzyme-linked immunosorbent assays and immunofluorescent antibody tests are frequently used. Most patients will test positive by 6 weeks after exposure. Antibiotic treatment may blunt or eliminate observed serologic response. Western blot assays may be helpful in confirmation and in vaccinated patients.

V. Treatment

(3,4)

A. Adults and children older than 9 years

1. **Early disease.** Give doxycycline 100 mg bid for 21–30 days, or amoxicillin 500 mg tid for 21–30 days, or cefuroxime axetil 500 mg bid for 21–30 days.
2. **Mild advanced disease** [mild carditis (first-degree block with PR less than seconds), isolated Bell's palsy, mild arthritis]. Try the above oral regimens, and, if they fail, consider parenteral treatment.
   a. Tetracyclines, including doxycycline, should not be given to pregnant or lactating women. For children 9 years or older, use l–2 mg/ kg divided bid (not to exceed adult dosage).
   b. For smaller children older than 9 years, use pediatric dosing below for amoxicillin, cefuroxime, IV penicillin, and ceftriaxone (not to exceed adult dosages).
3. **More serious, advanced, or persistent disease.** Give ceftriaxone 2 g/d for 14–28 days. Alternately, penicillin G 20–24 million units/d for 14–28 days may be used. In some settings, studies show better responses with ceftriaxone. Response to treatment of more complex disease may not occur for several weeks after treatment.

B. Children 8 years or younger

1. **Early or mild advanced disease** (same criteria as adults for mild advanced disease). Give amoxicillin 50 mg/kg per day divided tid for 21–30 days (not to exceed l.5 g/d) or cefuroxime axetil 30 mg/kg per day divided bid for 21–30 days (not to exceed l g/d).
2. **Advanced and persistent disease.** Give ceftriaxone 75–100 mg/kg per day for 14–28 days (maximum 2 g/d) or penicillin G 300,000 units/kg per day not to exceed 24 million units/d.

VI. Prevention

A.

Protective long sleeves and long-legged trousers can be helpful.

B.

Repellents of various types applied to skin and clothing can decrease exposure.

C.

Frequent “tick checks” (i.e., every 6–12 hours) can decrease exposures and help to prevent infection. Saving of ticks for identification is also important.

D.

Vaccination (5). A series of three shots with LYMErix, which is a recombinant vaccine using the OpsA antigen of *B. burgdorferi,* can offer protection though not complete. Second-generation vaccines are under development. Because of possible immunopathogenicity, some sources recommend that the current vaccine not be given to people with a history of treatment-resistant Lyme arthritis.

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19.10
ROCKY MOUNTAIN SPOTTED FEVER

Frank S. Celestino

I. Overview

A. Etiology.

Rocky Mountain spotted fever (RMSF) is a potentially fatal, tick-borne illness caused by the gram-negative obligate intracellular coccobacilli *Rickettsia rickettsii.*

B. Epidemiology

(1,2). The organism is endemic in parts of North and South America. Despite its name, in the United States RMSF is most prevalent in the south central states, especially Oklahoma, and the mid-Atlantic states, particularly North Carolina. Ticks serve as both the vector and main reservoir of *R. rickettsii.* In the eastern two thirds of the United States and on the West Coast, the dog tick *Dermacentor variabilis predominates,* whereas the wood tick *Dermacentor andersoni* is responsible for transmission in the Rocky Mountains region. Fortunately, less than 10% of ticks from these areas harbor *R. rickettsii.* Ticks need at least 12 hours of attachment and feeding to transmit the bacterium. There are 600–800 new cases of RMSF per year in the United States, with 90% occurring between April and September. The peak age of affected individuals is 5–10 years, with two thirds of victims younger than 16 years. Males are affected twice as often as females due to more frequent exposure.

C. Mortality data.

RMSF is fatal nearly a third of the time if untreated. If recognized early and treated appropriately, less than 5% of affected individuals die. The elderly and African-American males with glucose-6-phosphate dehydrogenase deficiency have especially high mortality rates (1).

II. Clinical presentation

A. Initial presentation.

After an incubation period of 4–12 days (mean 7 days), symptoms begin to develop as a result of the bacterium's ability to invade vascular endothelium and vascular smooth muscle cells, causing widespread vascular injury (2). Patients initially (days 1–2) experience various combinations of nonspecific symptoms including fever, chills, malaise, headache, myalgias, nausea with or without vomiting, anorexia, vague abdominal pain, and photophobia (3). Typically a rash begins by day 3–4 characterized by small (2–5 mm), pink, blanchable macules on the wrists, ankles, and distal extremities, often including the palms and soles. Over the next few days the rash spreads centripetally to the proximal extremities, buttocks, trunk, and (rarely) face, becoming more maculopapular and ultimately petechial if not ecchymotic. Some patients (10%–15% of adults, 5% of children) never develop a rash, so-called Rocky Mountain spotless fever (1). The initial rash can easily be missed on darker complexions.

B. Complications.

Although infection can sometimes be subclinical or mild, most patients experience moderately severe illness, which can be complicated by multisystem illness. This includes pneumonitis, respiratory failure, adult respiratory distress syndrome, myocarditis with arrhythmias, renal failure, hepatitis, lymphadenopathy, diarrhea, gastrointestinal bleeding, anasarca, skin necrosis, coagulopathy, severe hemolysis, encephalitis, stupor, coma, and seizures (1,4).

III. Diagnosis

A. Clinical history and examination.

The classic triad of fever, headache, and rash is present less than 50% of the time at the initial physician visit. Also, less than 50% of patients can recall a tick bite or exposure. Consequently, clinicians must retain a high index of suspicion for RMSF in a patient from an endemic area with an acute febrile illness associated with nonspecific symptoms but no rash, especially if any of the nondiagnostic laboratory abnormalities noted in Section III.C below are present (3). Patients from endemic areas presenting in summer with a seemingly typical viral

syndrome or flu-like illness should be followed closely and counseled about the need to be reexamined at the first sign of any rash.

B. Differential diagnosis.

Depending on the predominant symptoms, the differential diagnosis would include enteroviral infection, measles, atypical measles, infectious mononucleosis, ehrlichiosis, scarlet fever, leptospirosis, meningococcemia, typhus, toxic shock syndrome, bacterial sepsis, immune complex vasculitis, idiopathic thrombocytopenic purpura, and Kawasaki's disease (1,2 and 3).

C. Laboratory findings.

Associated laboratory abnormalities may include a low or normal white blood cell (WBC) count with a left shift, thrombocytopenia, hyponatremia, elevated liver function tests, azotemia, and anemia—all of which are usually mild (1,3). At the time of initial physician contact, these routine tests are often normal, thus making diagnosis difficult. Rarely there are elevations in creatine kinase concentration or fibrin degradation product concentration, or abnormal coagulation studies.

D. Specific rickettsial tests.

A definitive diagnosis of RMSF often cannot be made until the second week of illness when disease-specific serum tests become positive. The diagnosis can then be confirmed by measuring specific antibodies to *R. rickettsii* by latex agglutination, indirect hemagglutination, microimmunofluorescence, or enzyme-linked immunosorbent assay, all of which exhibit greater than 90% sensitivity (1,3). Recently, fluorescent- or peroxidase-tagged antibody testing of a skin biopsy from the rash has demonstrated the capacity to confirm the disease in its earlier stages (3). The test is 100% specific and 70% sensitive, but is unavailable at most hospitals.

IV. Management

A. Antibiotic considerations.

Empirical antibiotic treatment is often needed prior to definitive diagnosis for the patient from an endemic area with fever, nonspecific symptoms, and rash, especially during the summer months (1,3). Tetracycline and chloramphenicol have proven efficacy, whereas the fluoroquinolones manifest efficacy in animal studies and in vitro but have not been formally tested in humans (5). Tetracycline (specifically doxycycline) is preferred because it has the lowest minimal inhibitory concentration values and is now considered safe in short courses for children younger than 9 years (1,3,5). Unlike chloramphenicol, it is also effective for ehrlichiosis, an illness that is often difficult to distinguish from RMSF. Fluoroquinolones will likely supplant chloramphenicol in the future given the latter's proclivity to rarely cause bone marrow suppression.

B. Antibiotic dosages.

All drugs are generally given for 7–10 days or for at least for 2 days beyond the time the patient became afebrile (1,5). Some experts suggest switching to oral formulations once fever is gone.

1. Adults:

   Doxycycline 100 mg IV q12h

   Tetracycline 500 mg PO q6h

   Chloramphenicol 500 mg IV q6h

   Ciprofloxacin 400 mg IV q12h

   Levofloxacin 500 mg IV q24h

2. Children:

   Doxycycline 2.2 mg/kg IV q12h

   Tetracycline 10 mg/kg PO q6h

C. Supportive care.

Provide appropriate treatment and supportive care for the other organ systems that are dysfunctional. Treatment in an intensive care unit setting may be indicated depending on the level of multisystem involvement. Avoid overzealous rehydration to prevent symptomatic edema because vascular permeability is greatly enhanced.

V. Prevention.

Limit tick exposure through the use of protective clothing, sleeping nets, insect repellent, and frequent inspections for and removal of ticks. Ticks are best removed by steady rotational traction using tweezers after covering the tick with oil, gasoline, alcohol, or kerosene. Prophylactic antibiotics are not recommended for asymptomatic patients after a known tick bite as this practice

is costly, provides unnecessary antibiotic exposure to large numbers of people, and can prolong the incubation period (1). No rickettsial vaccine is available, though research continues.

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19.11
PARASITIC DISEASES

Joseph G.M. Lurio

Matthew R. Anderson

A parasite is an organism that lives on or in another living organism (the host) while doing that host some harm. Medically important human parasites include the single-celled protozoans, arthropods (see Chapter 16.3), and helminths (round or flat worms). Although commonly thought of as intestinal pathogens, parasites produce clinical syndromes as diverse as seizures and heart failure.

I. Determining risk.

Before undertaking an extensive workup for parasites, it is prudent to first assess the patient's risk of being infected. The most important step in assessing risk is to obtain a careful history about the patient's social and physical environment, travel history, and personal habits. If this history suggests a risk for parasitic disease, the clinician must then determine which of those parasites are potential pathogens. For travelers, the web page maintained by the U.S. Centers for Disease Control and Prevention (CDC) contains up-to-date lists of infectious diseases by world region. It is unnecessary to rule out parasitic infection for symptomatic individuals who were never in environments where they might have been infected.

A. Populations at risk

1. **International travelers** (especially those traveling outside of industrialized countries and major cities; see Chapter 1.5). Missionaries and immigrants are at particular risk. For information about specific risks in various geographic regions, consult the CDC Web page (1).
2. **Backpackers.** People drinking untreated groundwater are at risk for acquiring *Giardia* and *Cryptosporidium* as well as bacterial pathogens. Processing water with a micropore filter or boiling is preferable to treating with chorine or iodine.
3. **Residents of institutions,** including day care centers, group homes, and nursing homes, are at risk for acquiring *Giardia* as well as bacterial pathogens spread by fecal contamination.
4. **People who engage in oral-anal sex** are at risk for acquiring *Entamoeba. histolytica* and *Giardia lamblia.*
5. **Immunosuppressed patients** show increased susceptibility to some parasites. This group includes malnourished individuals, cancer patients, patients on steroids, and AIDS patients (see Section I.C and Chapter 19.4).

II. Clinical presentations.

Although commonly thought of as intestinal pathogens, parasites can infect all organ systems and produce a diverse set of clinical syndromes.

A. Parasitic infection and symptomatology by organ system

1. **Skin.** Dermatitis (*Ascaris*, *Capillaria hepatica*, hookworms, *Strongyloides*, chigoe flea, cutaneous larva migrans, *Dracunculus*, lice, *Mansonella*, scabies), migratory pruritic swellings (*Loa loa*), subcutaneous nodules (cutaneous leishmaniasis, *Echinococcus*, *Dracunculus*, *Dirofilaria*, *Onchocerca*, sparganum, *Taenia*, *Trypanosoma brucei gambiense*), swimmer's itch (schistosomiasis), temporal and periorbital swelling with conjunctivitis (acute *Trypanosoma cruzi* infection), and ulcers (cutaneous and mucocutaneous leishmaniasis, *T. gambiense, Dracunculus*).
2. **Central nervous system.** Meningoencephalitis (African trypanosomiasis, *Acanthamoeba*, *Angiostrongylus*, *Naegleria*), new-onset seizures or focal neurologic signs consistent with a space-occupying lesion (cysticercosis, malaria, *T. cruzi infection*, schistosomes, toxoplasmosis, trichinosis, hydatid and coenurus cysts).
3. **Eyes.** Vitreous infestation (onchocercosis, ascariasis, ocular toxocariasis), keratoconjunctivitis and corneal ulcers (caused by free-living amebas), uveitis, choroiditis and choroidoretinitis (toxoplasmosis), periorbital swelling and conjunctivitis (*T. cruzi*).
4. **Hematologic.** Microcytic anemia (malaria, babesiosis, hookworm, *Trichuris*, trypanosomes), macrocytic anemia (fish tapeworms), leukopenia (visceral leishmaniasis), eosinophilia (invasive helminths, *Dientamoeba fragilis*, and *Isospora belli*).
5. **Lymphatic.** Elephantiasis (*Filaria*), hepatosplenomegaly (babesiosis, leishmaniasis, visceral larva migrans), lymphadenopathy (African trypanosomiasis, *Mansonella ozzardi*, toxoplasmosis).
6. **Respiratory.** Loeffler's syndrome (*Ascaris lumbricoides*, *Strongyloides*), pneumonitis (hookworms, *Pneumocystis*, *Strongyloides*), chest pain and hemoptysis (paragonimiasis), cough (schistosomiasis), pleural effusion (*Entamoeba histolytica*), pulmonary mass lesion (*Dirofilaria*, echinococcosis), tropical pulmonary eosinophilia (filariasis).
7. **Cardiovascular.** Heart block, congestive heart failure (*Trypanosoma cruzi*), myositis (African trypanosomiasis, trichinosis, toxoplasmosis).
8. **Intestinal.** Appendicitis (*Ascaris*, *Trichuris*); colic, diarrhea, and vomiting (*Capillaria philippinensis*, *Cryptosporidium*, intestinal flukes, *Isospora belli*, *Strongyloides*); obstruction (*Ascaris*, *Hymenolepis nana*, *Taenia saginata*); colitis (*Trichuris*); pruritus ani (*Enterobius*).
9. **Hepatobiliary.** Abscess (*Entamoeba histolytica*, cysticercosis, hydatid disease), biliary obstruction (*Ascaris lumbricoides*), portal hypertension (schistosomes), hepatosplenomegaly (malaria, babesiosis, *Capillaria hepatica*, leishmania, visceral larva migrans).
10. **Genitourinary.** Chyluria (filariasis), hematuria (schistosomes), prostatitis, urethritis, and vaginitis (trichomonads).
11. **Musculoskeletal.** Myositis (trichinosis, toxoplasmosis), cysts (*Echinococcus*, cysticercosis).

B. Parasites in AIDS.

(see also Chapter 19.4).

1. **Definitely exacerbated by HIV infection:** *Toxoplasma gondii, Cryptosporidium species, Cyclospora species, Isospora belli, Leishmania species, Trypanosoma species, Microsporum species, Strongyloides stercoralis*.
2. Possibly exacerbated by HIV: *Blastocystis hominis*.
3. Not exacerbated by HIV: *Giardia lamblia, Entamoeba histolytica, Plasmodium species, Schistosoma species, Ascaris species, Trichuris trichiura, Enterobius species, Plasmodium species*, Babesia species.
4. People with clinical AIDS may have an enteropathy that results in an environment unfavorable to extracellular parasites (***Trichuris*, *Ascaris*,**

Giardia*, *Enterobius), making them *less* likely to harbor these organisms than nonimmunosuppressed individuals living in the same environment.

C. Parasites observed in stool,

Occasionally, roundworms or flatworm segments are passed in the stool. Specimens should be preserved in 70% alcohol and sent to a diagnostic laboratory for identification. Objects such as earthworms or mucus plugs can be mistaken for parasites. Examination for ova is described below.

D. Laboratory abnormalities

1. **Eosinophilia.** Those helminths that invade tissue can produce eosinophilia. Only about 4% of patients presenting with eosinophilia are found to have parasites. *Dientamoeba fragilis* and *Isospora* are the only protozoans that typically cause eosinophilia.
2. **Anemias** are associated with several parasites (see Section I.B.5).
3. **Leukopenia** is associated with malaria and visceral leishmaniasis.

III. Diagnosis of symptomatic infection.

The CDC maintains an excellent web site on the diagnostic evaluation of parasites, which can be accessed via its Division of Parasitic Diseases web site (2).

A. When to perform.

In U.S. laboratories, very few ova and parasite tests (about 1%) indicate the presence of some form of parasite, and most of these are nonpathogenic protozoans. Clinically useful diagnoses come almost exclusively from outpatients or hospitalized patients within 3 days of their admission. As previously stated, careful assessment of exposure risk prior to testing can preclude unnecessary examinations.

B. Office examination

1. **Stool examination (ova and parasites).** Examination of a fresh stool specimen permits visualization of short-lived motile forms that cannot be found in preserved or refrigerated specimens. It should be used in conjunction with a reference laboratory examination of preserved specimens. Use of a purgative (magnesium citrate, 8 oz taken by mouth 1 hour before the examination) may improve yield. A thin film of feces mixed with normal saline is examined initially for trophozoites and amebas. Then a drop of Gram's iodine or Lugol's solution is added to provide better visualization of cysts. Part of the sample should be placed in separate preservative containing vials according to supplied directions and sent to a reference laboratory. Care should be taken to avoid contamination with urine or water. The examination of stool is described comprehensively in *Markell and Voge's Medical Parasitology* (3).
2. **The cellophane tape test** is used to detect *Enterobius* (pinworm) and *Taenia saginata eggs.* Clear cellophane (Scotch) tape is placed with the sticky side down on the unwashed perianal area, preferably in the early morning before bathing or after defecation. The tape is placed (again sticky side down) on a microscope slide, which is then examined for eggs. Adult pinworms can be seen with this technique. Sensitivity is improved by repeating the examination on subsequent days.

C. Clinical laboratory examination

1. **Stool examination (ova and parasites).** Various techniques exist for concentrating and staining stool specimens. Purged stools that are examined immediately are far superior to preserved specimens, especially when one is looking for amebae. When looking for helminth eggs, one or two concentrated preserved specimens is usually sufficient. Table 19.11-1 provides a guide to the interpretation of findings in the ova and parasites examination.

Definite pathogens	Pathogens primarily in immunocompromised hosts	Pathogenicity disputed	Nonpathogens
Cryptosporidium parvum *Cyclospora* spp. *Dientamoeba fragilis* *Entamoeba histolytica* *Giardia lamblia* *Isospora belli*	*Balantidium coli* *Microsporidia* spp.	*Blastocystis hominis*	*Endolimax nana* *Entamoeba coli* *Entamoeba hartmanni* *Iodamoeba butschlii* *Entamoeba polecki* *Entamoeba gingivalis* *Entamoeba dispar*

Note: The presence of "nonpathogenic" organisms implies fecal contamination of the food or water supply and therefore may be clinically relevant.

Table 19.11-1. Interpreting stool ova and parasite results

2. **Stool tests for *Giardia* antigen** are now available in many clinical laboratories.
3. **Serologic testing** can be useful when extraintestinal infection is suspected, as with amebiasis, Chagas' disease, cysticercosis, echinococcosis, filariasis (*Wuchereria bancrofti*), leishmaniasis, schistosomiasis, toxoplasmosis, toxocariasis, and trichinosis.

4. **Directed biopsy** is often necessary for diagnosis of parasites that do not colonize the intestinal tract.
5. **Blood smear.** Blood smear is indicated for malaria (thick and thin film done at time of fever), filariasis (blood drawn during hours of periodic release, usually midnight), and babesiosis. For periodic fevers, blood drawing must be timed appropriately for the clinical syndrome.

IV. Treatment

of parasitic infections is reviewed periodically by the *Medical Letter on Drugs and Therapeutics.* Their recommendations are available free on-line at http://www.medletter.com/ in the "Public Reading Room."

V. Common parasitoses

A. Giardia lamblia.

In about 60% of patients *Giardia* produces no symptoms (asymptomatic cyst passer) and infection resolves spontaneously. Acute giardiasis (1–3 weeks after infection) presents with watery diarrhea and other abdominal symptoms. These symptoms may last for months. Chronic giardiasis presents with symptoms of malabsorption and lactose intolerance.

1. **Diagnosis.** Fecal examination may reveal trophozoites or cysts and should be done in all patients. Unfortunately, examination of three stool samples is only 85% sensitive in chronic giardiasis. Enzyme immunoassay tests for *Giardia* antigen in stool are both sensitive and specific, and an excellent adjunct to microscopy. If stool tests are negative but clinical suspicion is high, more invasive testing may be necessary and referral to a gastroenterologist should be considered.
2. **Treatment.** Metronidazole (Flagyl), 250 mg tid for 5 days (pediatric dose is 15 mg/kg per day in 3 doses for 5 days), or quinacrine (Atabrine) HCl, 100 mg tid PO after meals for 5 days (pediatric dose is 6 mg/kg per day in 3 doses PO for 5 days, maximum 300 mg/d).

B. Enterobius vermicularis.

Pinworms cause intense anal pruritus, usually at night. They can occasionally be seen as threadlike worms that migrate outside the anus at night.

1. **Diagnosis** is generally via visualization of pinworm eggs using the cellophane tape test (see Section II.A.2).
2. **Treatment.** Treat adults and children with mebendazole (Vermox), 100 mg PO, repeated in 2 weeks. Other options include pyrantel pamoate, 11 mg/kg once (maximum 1 g), repeated in 2 weeks, or albendazole, 400 mg once, repeated in 2 weeks.

C. Ascaris lumbricoides.

Ascaris is the world's most common intestinal worm. Hosts are usually asymptomatic, but large infestations can cause intestinal obstruction. Worms occasionally migrate into the biliary tree, causing cholangitis.

1. **Diagnosis** is by stool ova and parasite examination.
2. **Treatment** Treat with albendazole 400 mg once or mebendazole (Vermox), 100 mg PO bid for 3 days.

D. Entamoeba histolytica.

Amebiasis usually produces asymptomatic colonic infection. *E. histolytica* can invade the intestinal wall, producing a colitis with clinical presentations ranging from dysentery to perforation. Amebas can spread hematogenously to any organ in the body; liver abscess is the most common extraintestinal manifestation. Sympathetic pleural effusions may occur when hepatic abscesses are situated near the diaphragm.

1. **Diagnosis** is by ova and parasite examination of stool or of aspirates obtained during colonoscopy. The mucous portion is more likely to contain amebas than the other parts of the stool. For abscesses, ultrasound-directed needle aspiration or serology, or both, may be necessary. *Entamoeba dispar*, which is morphologically indistinguishable from *E. histolytica*, is nonpathogenic. Practically speaking, the two can be differentiated only by symptomatology or the lack thereof, supporting our recommendation *against* the screening of asymptomatic individuals.
2. **Treatment.** Symptomatic disease, both intestinal and extraintestinal, is managed with metronidazole (Flagyl), 750 mg tid for 7–10 days (pediatric dose 35–50 mg/kg per day in 3 doses for 10 days). Alternative management for severe intestinal disease or hepatic abscess consists of administering tinidazole, 600 mg bid or 800 mg tid for 5 days [pediatric dose, 50–60 mg/kg (maximum, 2 g) daily for 3 days]. These treatments should be followed by iodoquinol (Yodoxin) to eliminate asymptomatic intraluminal infection.

E. Isospora belli and Balantidium coli

are protozoa that can cause diarrhea and intestinal cramping.

1. **Diagnosis** is made by ova and parasite stool examination.
2. **Treatment.** *Isospora* infection is managed with co-trimoxazole (Bactrim, Septra), 160/800 mg PO qid for 10 days, then bid for 3 weeks. *B. coli* infection is managed with tetracycline, 500 mg qid for 10 days.

VI. Prevention

A. International travelers

(see Chapter 1.5).

B. Screening

1. Routine testing for asymptomatic parasite carriage in travelers is not recommended.
2. Screening of asymptomatic food workers for parasites is also not recommended.
3. Individuals with a high level of exposure to harmful parasites (missionaries, refugees, and immigrants arriving from endemic regions) should be treated empirically. Testing is both costly and likely to result in false-negative results. Although not FDA-approved for this indication, giving a single dose of albendazole (400 mg taken orally) is superior to treating only those with positive ova and parasite examinations, which is more expensive and results in fewer carriers receiving treatment (4).

References

1. http://www.cdc.gov/travel/destinat.htm (U.S. Centers for Disease Control and Prevention Travel Page).

2. http://www.cdc.gov/ncidod/dpd (U.S. Centers for Disease Control and Prevention Division of Parasitic Diseases).

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Web Resources

http://www.york.biosis.org/zrdocs/zoolinfo/parasit.htm (BIOSIS and the Zoological Society of London.

http://dspace.dial.pipex.com/town/plaza/aan18/general.htm (David Gibson, DSc).

XX. INJURIES AND VIOLENCE

20.1
BITES OF HUMANS AND ANIMALS

Thomas Paul Forks

There are approximately 3 million animal bites per year in the United States, and approximately half of all Americans will be bitten by an animal at some time during their lives. The vast majority of these bites are from dogs, usually the family pet or an animal known to the victim (1). Dog and cat bites are responsible for 1% of all emergency room visits, and approximately 1% of dog bites and 6% of cat bites will require hospitalization. The remainder of animal bites suffered by human beings are inflicted by various wild and domestic animals, including farm animals, foxes, coyotes, skunks, rodents, and reptiles. Snakes account for approximately 45,000 bites annually in the United States, but less than 20% of these bites are inflicted by poisonous snakes.

The most common complication resulting from human and animal bites is infection (2). Infections are usually polymicrobial, involving several genera of bacteria, fungi, viruses, spirochetes, and rickettsia. Other potential complications include tenosynovitis, cellulitis, sepsis, arthritis, osteomyelitis, and fractures of underlying bony structures. Peritonitis and meningitis have also occurred in patients as a result of bites that have penetrated the abdominal cavity or the thin cranial bone of children.

I. Human bites

A. Epidemiology.

The vast majority (80%) of human bites result from closed-fist injuries sustained during fist fights. The resulting lacerations are typically 3–8 mm in length, overlie the third metacarpophalangeal joint of the dominant hand, and are frequently infected by the time the patient seeks medical care. Bacteria are often introduced into the joint when the joint capsule is broken and may spread into the deeper spaces of the hand when the digits are extended. Swelling and edema may decrease mobility of the involved digit. These injuries often have a poor prognosis as patients typically present for medical care after infection has occurred. The majority of the remaining bites (15%) are “love nips.” These accidental, occlusional bites are commonly seen on the genitalia, breasts, shoulders, arms, and hands.

B. Treatment.

After cleansing with povidone-iodine and thorough irrigation with sterile saline, human bites may be left open to close by secondary intention. Although this method has the least incidence of infection, it is accompanied by the greatest scar formation and longest healing time (i.e., several weeks for complete healing) (3). Delayed primary closure has a slightly higher risk of infection. Primary closure has a significant risk of infection and is not advised in the treatment of hand bites, although it may be used in areas with excellent blood supply, such as the face. After dressing the wound, the hand should be splinted in a position of function to maximize the length of the involved tendon and muscle. It is advisable to elevate all hand bites, especially when swelling is present. The lack of elevation when the bitten area is swollen frequently leads to treatment failures. Patients should be reevaluated within 24 hours. Radiographs of the bite site should be obtained to rule out underlying fractures and the presence of foreign bodies, joint space air, and osteomyelitis. In contrast to hand injuries, studies have indicated that human bites to the face can be closed immediately after appropriate irrigation and cleansing, even when presenting late (4).

α-Hemolytic streptococci are the most common organisms cultured from infected hand injuries. Other bacteria commonly cultured from these injuries include *Staphylococcus aureus, Eikenella corrodens, Haemophilus influenzae, and* ß-lactamase-producing oral, anaerobic bacteria.

1. **Outpatient antibiotic therapy.** All patients with closed-fist injuries and occlusional bites to the hand or fingers, even when presenting

within 8 hours of the injury and before overt signs of infection occur, should be considered for antibiotic prophylaxis. This is best accomplished with amoxicillin-clavulanate potassium (Augmentin) 250–500 mg every 8 hours. The dosage in children is 20 mg/kg per day in divided doses every 8 hours. Alternatively, a second-generation cephalosporin, such as cefuroxime axetil (Ceftin), may be used at a dosage of 250–500 mg every 12 hours in adults and 20–30 mg/kg per day in divided doses in children.

2. **Hospitalization.** Intravenous antibiotics are necessary for all patients with clinically infected hand wounds. A surgeon experienced in the treatment of infected hand bites should be consulted. Aerobic and anaerobic cultures must be obtained before starting antibiotics. Intravenous antibiotic options include ampicillin sodium/sulbactam sodium (Unasyn) 1.5–3.0 g every 6 hours, cefoxitin (Mefoxin) 1–2 g every 4–8 hours, cefotetan disodium (Cefotan) 1–2 g every 6–12 hours, and imipenem-cilastatin (Primaxin) 500 mg every 6 hours (5). Diabetic patients that do not respond to initial treatment with oral antibiotics should be considered for coverage with gentamicin (Garamycin) 2 gm/kg load, then 1.7 mg/kg every 8 hours, or similar aminoglycoside antibiotic, because these patients frequently have gram-negative infections.

II. Dog bites

A. Epidemiology.

Dogs are responsible for 80%–90% of animal bites to humans. Annually, 10–20 deaths from dog bites occur (6,7). The majority of these deaths result from the exsanguination associated with head and neck bites in children younger than 4 years. Elderly patients are also at increased risk. One report documents the comminuted fracture of an elderly patient's mandible and the severing of the patient's arm from a dog attack (8). Tears, avulsions, punctures, scratches, and crush injuries may also be present. There is a greater risk of infection in patients older than 50 years who delay seeking treatment for bites on the upper extremity (9) and in patients whose wounds require surgical repair (10).

B. Treatment.

All wounds should be thoroughly cleaned and irrigated in a manner similar to that described for human bites. Dog bites to the hand, wrist, and foot should be left open to close by secondary intention. Bites to the face and other areas with excellent blood supply that appear clinically uninfected may undergo primary closure. Children with severe facial or neck injuries from dog bites should be considered for primary closure under general anesthesia. Positive cultures have been obtained in 90% of clinically infected wounds and in approximately 80% of wounds evaluated less than 8 hours after injury (5). One study found that *Pasteurella multocida* was isolated in 53% of cases, whereas *Streptococcus* was cultured in 29%, and *Staphylococcus* in about 24% (11). Another study (12) found that α-hemolytic streptococci were the most frequently isolated organisms. Patients with poorly functioning immune systems are at risk for the development of *Capnocytophagia canimorsus* sepsis (examine peripheral smear for bacilli) and disseminated intravascular coagulation and should be immediately hospitalized at their initial presentation for treatment of the bite. Anaerobic bacteria, including *Bacteroides, Fusobacterium, Peptostreptococcus,* and *Eubacterium* have also been cultured from infected dog bite wounds.

1. **Outpatient antibiotic therapy.** Antibiotic therapy should be administered to patients with moderate to severe bites; bites on the hands, neck, or face; bites that appear clinically infected; and immunocompromised patients. Wounds should be cultured before antibiotic therapy is begun. Facial bites have a relatively low risk of infection (7%); consequently, some authors feel that these wounds should be managed with reconstructive surgery without prophylactic antibiotics (13). Amoxicillin-clavulanate potassium (Augmentin), 250–500 mg every 8 hours, is the drug of choice for outpatient therapy. Children are

dosed at 20 mg/kg per day in divided doses. Penicillin V potassium (Pen-Vee K), 250–500 mg for every 6 hours, and ampicillin (Omnipen), 250–500 mg every 8 hours (in children, 50–100 mg/kg per day), are other possible choices. In the absence of overt infection, a 3- to 5-day prophylaxis regime is prudent for crush injuries or injuries that involve the hand or a joint.

2. **Hospitalization.** Hospitalization is indicated for patients with systemic manifestations of infection, such as fever and chills, and in patients with severe cellulitis or in whom the infection has spread rapidly and has not responded to outpatient therapy. Intravenous antibiotic therapy can be accomplished with ampicillin sodium/sulbactam sodium, 1.5–3.0 g every 6 hours. Alternative intravenous antibiotics include ceftriaxone sodium (Rocephin), given 1–2 g once daily or administered in divided doses. Children may be administered 50–75 mg/kg once daily or in divided doses.

III. Cat bites

A. Epidemiology.

Cats are involved in approximately 400,000 bites to humans annually. The majority of cat bites occur on the arms, forearms, and hands. Feline canine teeth are sharp and pointed, which facilitates the penetration of bones and joints. The resulting puncture wounds are difficult to clean and irrigate adequately, and 50% of these bites become infected. Patients may develop septic arthritis and osteomyelitis following a cat bite (14). Other patients have developed *Pasteurella* meningitis, pneumonia, and prosthetic joint infections after a cat bite.

B. Treatment.

Puncture wounds can be carefully irrigated. Care must be taken to prevent the extravasation of fluid and bacteria into the surrounding tissues. Puncture wounds should be left open to heal by secondary intention. *Pasteurella multocida* is the most common bacterium isolated from the oral cavity and teeth of cats (15). This organism can cause an intense inflammation with a rapidly expanding cellulitis. A purulent drainage is noted in approximately 40% of patients. Cultures frequently show growth of *Pasteurella* within 24 hours of the bite (2). Wounds that become infected 24 hours post bite usually culture *Staphylococcus* or *Streptococcus* (16). Other isolates cultured from cat bite wounds include *Eikenella* and various gram-negative enteric bacteria and anaerobic bacteria, including *Bacteroides* and *Actinomyces*. *Bartonella henselae*, the etiologic agent of cat-scratch disease, may be inoculated in both cat scratches and bites (17). Infection with this agent may also result in a reactive arthritis with polyarthralgia of the knees and elbows (18).

1. **Outpatient antibiotic therapy.** The drug of choice for the outpatient treatment of cat bites is amoxicillin-clavulanate potassium, 250–500 mg every 8 hours. Children are dosed at 20 mg/kg per day in divided doses based on the amoxicillin component.
2. **Hospitalization.** Severely infected bites requiring hospitalization may be treated with ceftriaxone sodium (Rocephin), 1–2 g in adults and 50–75 mg/kg per day in children. Tularemia has also been shown to be transmitted by cat bites and scratches (19) and should be considered where bites have failed to improve with appropriate treatment. This kind of infection is most appropriately managed with streptomycin, 7.5–10 mg/kg every 12 hours IM or IV for 7–14 days. Children should be dosed at 30–40 mg/kg per day IM in two divided doses for 7 days. In adults, *Bartonella henselae* infections should be managed with erythromycin 500 mg qid or doxycycline 100 mg bid. Children may be treated with erythromycin 30–50 mg/kg per day in divided doses.

IV. Wild animals

A. Epidemiology.

Although wild animals are the most important source of rabies, the bite of any animal, and most specifically that of bats, skunks, foxes, raccoons, and coyotes, must be considered as a potential source of rabies. Postexposure prophylaxis is accomplished using both the rabies immune

globulin and the human diploid cell rabies vaccine. Although rat bites are not a significant risk factor for the development of rabies, they are common in impoverished areas. The majority of these patients are younger than 5 years. These patients are usually bitten on the hands and face while sleeping at night.

B. Treatment.

Antibiotic prophylaxis is indicated as in any other potentially infected bite wound. After local cleansing and irrigation, tetanus must be administered when indicated. Antibiotic prophylaxis may be accomplished using ampicillin, 250–500 mg every 6 hours in adults and 50–100 mg/kg/day in 3 divided doses in children. Penicillin-sensitive adults may be treated with doxycycline hyclate (Doryx) 50–100 mg every 12 hours.

V. Snake bites

A. Epidemiology.

In the United States, approximately 7,000–8,000 poisonous snake bites yearly result in 9–15 deaths. Approximately 20%–30% of poisonous snake bites do not result in envenomation. Snake venoms are complex mixtures of enzymes that result in the disruption of cell membranes, precipitation of free hemoglobin, muscle and local tissue necrosis, thrombocytopenia, abnormal clotting times, and, in severe cases, death. Patients may experience breathing difficulties, perioral tingling, weakness, diplopia, nausea, vomiting, and muscle fasciculations of the tongue, face, and upper chest and arms after pit viper envenomation. Patients may also experience a metallic taste in the mouth. Patients will also commonly experience severe pain and marked swelling at the bite site.

B. Treatment.

Poisonous snake bite is a medical emergency. Field treatment includes calm reassurance of the patient, splinting of the bitten extremity below heart level, and transport to the nearest emergency facility. Cryotherapy and incision and suction are contraindicated.

Emergency treatment includes an assessment of envenomation, cleansing of the wound, administration of tetanus toxoid when needed, and administration of antivenom where indicated. Pit viper bites are primarily hemotoxic in nature. Hallmark findings of pit viper envenomation are pain and swelling. If pain and swelling are not present within 30 minutes of a pit viper bite, the patient was probably not envenomated. Patients thought to have received a dry bite can be observed for an additional 2–4 hours and can be treated as outpatients if no signs of envenomation occur with 8 hours of the bite (20). Patients remaining asymptomatic may be safely discharged home after routine wound care has been accomplished. However, coral snake bites are primarily neurotoxic. Patients envenomated by coral snakes may show minimal signs and symptoms for several hours. Hospitalization (24-hour observation) is indicated for patients of coral snake bites even when it is suspected that the patient received a dry bite. Serial measurements of the bitten extremity should be made and recorded at 15- to 30-minute intervals. Envenomation may be graded as follows: grade 1, no envenomation; grade 2, mild envenomation with pain and edema extending up to 6 inches from the bite site during the first 12 hours; grade 3, moderate envenomation with edema extending up to 12 inches from the bite site accompanied by nausea, vomiting, prolonged bleeding times, and decreases in platelet counts and hematocrit; and grade 4, severe envenomation with marked swelling and extensive systemic involvement.

1. **Antivenom administration.** A new Fab (CroTab), affinity-purified, mixed crotalid antivenom has recently become available and has shown promise in the management of moderate crotalid envenomation (21). This antivenom has been shown to quickly reverse the local effects of the venom and has the unique capacity to completely reverse the neurotoxicity associated with bites of the Mojave rattlesnake. In the event CroTab is not available, polyvalent Crotalidae antivenom (Wyeth) may be administered. When a decision to administer polyvalent Crotalidae antivenom has been made, the patient must first be given a skin test with 0.1 mL of a 1;10 saline solution of horse serum intradermally. It is

preferable to perform skin testing in the emergency room or intensive care unit because of the risk of anaphylaxis. A syringe of 0.3–0.5 mL of a 1;1,000 solution of epinephrine must be available for management of anaphylaxis. Prior to starting the antivenom, a complete blood count, prothrombin time, partial thromboplastin time, electrolytes, blood urea nitrogen, urinalysis, and arterial blood gases should be done. Blood should also be typed and cross-matched. Two large-bore intravenous lines of normal saline or lactated Ringer's solution are typically started, and a Foley catheter should be inserted for accurate urine measurements. Grade 2 envenomations may require up to 6 vials of antivenom, whereas grade 3 and 4 envenomations may require up to 15 and 30 vials, respectively. Antivenom is only effective when administered intravenously and should not be injected intramuscularly, subcutaneously, or directly into the bite site. There is no maximal dose of antivenom. The patient's condition must be continuously reevaluated after each antivenom dosing. A small vial of venous blood (5–10 mL) may be collected after each dose of antivenom dosing. If this blood clots after 20 minutes, no additional antivenom is needed (22). In cases where the patient develops an allergy to the antivenom and has sustained a severe poisoning, the antivenom can be temporarily stopped while the patient is treated with intravenous diphenhydramine (Benadryl), 10–50 mg in adults and 5 mg/kg per day in children. The antivenom may then be restarted at a lower rate.

2. **Antibiotic prophylaxis.** Antibiotic prophylaxis may be accomplished with intramuscular ceftriaxone sodium, 1–2 g per day in adults and 50–75 mg/kg per day in children.

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20.2

BURNS

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Eric D. Morgan

Each year in the United States 2.5 million people seek medical care for burns (1). Although 95% of burn victims do not require hospitalization, burns can be devastating. They are the third leading cause of accidental death and can cause life-long scarring and disfigurement.

I. Initial assessment.

Look for evidence of respiratory distress or smoke inhalation injury, evaluate the cardiovascular status, assess for other injuries, and determine the depth and extent of the burns.

A. Classification of burns

1. **Burn depth**
   a. Superficial burns are painful, dry, red, and blanch with pressure. They usually take 3–6 days to heal without scarring.
   b. **Superficial partial-thickness** burns are painful to temperature and air. They usually blister and are moist, red, weeping, and blanch with pressure. They heal in 7–21 days; scarring is unusual although pigment changes may occur.
   c. **Deep partial-thickness** burns are painful to pressure only. They almost always blister (easily unroofed), are wet or waxy dry, and have variable color from patchy cheesy white to red. They do not blanch with pressure. They take more than 21 days to heal, and scarring may be severe. Distinction from full-thickness burns is often difficult.
   d. **Full-thickness** burns are usually painless. The skin is waxy white to leathery gray to charred and black, is dry and inelastic, and does not blanch with pressure. Healing is very slow, if at all, and may require skin grafting if more than 2% of the total body surface is involved. Scarring is very severe with contractures.
2. **Burn extent** is expressed as a percentage of total body surface area (TBSA). The **rule of nines** method is an appropriate way to estimate TBSA in adults; each leg represents 18% TBSA, each arm 9%, the anterior and posterior trunk each 18%, and the head 9%. For small burns, the surface area of the patient's palm represents 0.4% of the TBSA.

B. Who requires hospitalization?

1. Admit patients with moderate to severe burns (Table 20.2-1).

Type of burn	Criteria	Patient disposition
Minor burn	<10% TBSA partial-thickness burn in a child <15% TBSA partial-thickness burn in an adult <2% full-thickness burn in a child or adult not involving eyes, ears, face, or genitalia	Treat as outpatient care
Moderate burn	10–20% TBSA partial-thickness burn in a child 15–25% TBSA partial-thickness burn in an adult 2–10% TBSA full-thickness burn in a child or adult not involving eyes, ears, face, or genitalia Suspected inhalation injury High-voltage electrical injury Circumferential partial or full-thickness burn Medical problem predisposing to infection (e.g., diabetes, sickle cell disease)	Admit to hospital
Major burn	>20% TBSA partial-thickness burn in a child >25% TBSA partial-thickness burn in an adult >10% full-thickness burn in a child or adult Full-thickness burn involving eyes, ears, face, or genitalia Known inhalation injury High-voltage electrical burns Significant associated injuries (fracture or other major trauma)	Refer to burn center

TBSA, total body surface area.

Table 20.2-1. American Burn Association Burn Injury Severity Grading System

2. Pulmonary dysfunction causes the majority of fire-related deaths. Patients suspected of inhalation injury (coughing, wheezing, dyspnea,

facial burns, sooty mucus, and laryngeal edema) should be observed for at least 12–24 hours (2).

3. Other types of burns that warrant hospitalization include circumferential partial- or full-thickness burns and those resulting from high-voltage electrical injuries.
4. Hospitalize children with burns suspected to be due to abuse and burn victims with underlying conditions that predispose them to infection (e.g., diabetes).

II. Treatment

A. Immediate care.

Remove any hot or burned clothing. Immediately begin cooling but avoid ice and freezing.

B. Airway management.

Maintain the airway and start supplemental oxygen. Intubate if respiratory distress or inhalation injury is present.

C. Fluid resuscitation

1. Prevention of shock from intravascular fluid loss is crucial in those with moderate to major burns.

2. In the first 24 hours, give IV crystalloid solution (e.g., Ringer's lactate). An estimate of the amount of fluid required is 4 mL/kg of body weight for each percentage point of TBSA burned (3). Give half of the total calculated fluid in the first 8 hours. Maintain hourly urine output at 0.5 mL/kg in adults and 1.0 mL/kg in children who weigh less than 25 kg; those with electrical injuries should have an hourly urine output of 1.0–1.5 mL/kg.
3. In the second 24 hours, give IV fluids to maintain baseline fluid needs and urinary output. The crystalloid solution can be changed to 5% dextrose in water 0.45% normal saline with 20 mEq of potassium chloride per liter.
4. The use of colloids (e.g., albumin) appears to offer no advantage over the use of crystalloids (2).

D. Wound management

1. Wash the wound with mild soap and tap water. If a skin disinfectant is preferred, use a very dilute solution (10%–20%) of Hibiclens followed by copious saline irrigation. To prevent excruciating pain, use local or regional anesthesia.
2. Remove necrotic tissue from partial- and full-thickness burns either manually or with whirlpool debridement.
3. Remove ruptured blisters. Blisters may be left intact if there are no signs of infection. Avoid needle aspiration of blisters.
4. Chemoprophylaxis
   a. Superficial burns do not require infection prophylaxis. All other burns should receive topical prophylaxis.
   b. 1% silver sulfadiazine (SSD) is a good first-line agent, but avoid using near eyes or mouth; in persons with sulfonamide hypersensitivity; and in pregnant women, newborns, and nursing mothers. Bacitracin is an effective alternative topical antibiotic in these individuals.
   c. Mafenide acetate cream is useful in burn eschars.
   d. Administer a tetanus booster to all burn victims who are not current with tetanus immunization.
5. Wound dressings
   a. Superficial burns do not require wound dressings. A simple skin lubricant (e.g., aloe vera cream) is sufficient.
   b. All partial- and full-thickness burns should have dressings. Apply a fine-mesh gauze (e.g., Telfa) after the burn has been cleansed and a thin layer of topical antibiotic applied. Hold the dressing in place using either a tubular net bandage or gauze wraps lightly applied.
   c. Change dressings whenever they become soaked with excessive exudates or other fluids.
   d. Deep wounds may require biological dressings or skin grafting.
   e. After epithelialization occurs, use a nonperfumed moisturizing cream until natural lubricating mechanisms return. Avoid the use of preparations high in lanolin.
6. Pain relief. Acetaminophen and nonsteroidal anti-inflammatory drugs (alone or in combination with opioids) are often appropriate for small burn injuries.
7. Decompressive escharotomy may be required for circumferential full-thickness burns if edema causes constriction and ischemia.

E. Follow-up care

1. Monitor for signs of infection, scarring, and contracture, and ensure adequate pain control.
2. Refer the patient to a plastic surgeon if wound epithelialization has not begun after 2 weeks, if subsequent evaluations reveal a full-thickness burn greater than 2 cm, or if development of scar contractures appears likely.

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20.3

SMOKE INHALATION AND CARBON MONOXIDE POISONING

Jeffrey D. Harrison

Smoke Inhalation

The inhalation of heated gas and the products of combustion can cause serious respiratory injury. Approximately one third of patients admitted to burn units have smoke inhalation as a compounding complication. The major limiting factor in burn mortality is smoke inhalation. Any patient suspected of having significant smoke inhalation should be admitted to the hospital for observation and treatment.

I. Injury types

A. Impaired tissue oxygenation

results from carbon monoxide or cyanide exposure and is immediately life threatening.

1. Carbon monoxide (CO) accounts for over half of the fatalities in smoke inhalation (see section “Carbon Monoxide Poisoning ”).
2. Cyanide impairs cellular oxidative metabolism. Suspect cyanide injury when plastics or organic chemicals are fuels (1), especially with high-temperature and low-oxygen-level settings.

B. Thermal injury

results from the inhalation of heated gases.

1. The supraglottic mucosa has little protection from heated gases; this results in edema and airway obstruction 18–24 hours after exposure.
2. The subglottic tissues are generally protected from thermal injury, although steam inhalation can result in tracheobronchial burns.

C. Chemical injury

primarily is caused by insoluble irritant gases that affect the lower airways.

1. Insoluble irritant gases include aldehydes, amines, chlorine, hydrochloric acid, and sulfur dioxide.
2. There may be a delay between exposure and clinical manifestation.

II. Diagnosis of smoke inhalation

A. History.

Postive predictive factors for significant smoke inhalation include unconsciousness, entrapment or being in an enclosed space, and exposure to known toxins (2).

B. Physical findings

1. Facial burns, singeing of eyebrows and nasal vibrissae, carbonaceous sputum, and oropharyngeal carbon deposits are suggestive of inhalation injury.
2. Cyanosis, tachypnea, stridor, wheezing, and crackles are suggestive of the need for aggressive treatment; however, these signs are infrequently found despite the presence of significant injury.

C. Laboratory and radiographic findings

1. Carboxyhemoglobin testing should be carried out on all patients; elevated levels should raise suspicion regarding the presence of other toxins (e.g., cyanide).
2. Arterial blood gases. Hypoxemia and elevated alveolar-arterial (P_AO_2-P_aO_2 > 15 mm) gradient are frequently seen in inhalation injury,

though they are insensitive indicators of injury and do not predict clinical outcome. Pulse oximetry can also be used as a noninvasive measure of oxygenation (1) but may be inaccurate in the presence of carboxyhemoglobin.

3. Chest radiography. Generally, this is an insensitive initial test and should be reserved for hospitalized patients and those with suspected thoracic injury.

D. Bronchoscopy.

Direct fiberoptic visualization of the upper and lower airway provides the most accurate assessment of the injury extent.

III. Treatment

A. Immediate.

Early mortality occurs from asphyxiation due to CO and cyanide.

1. Remove patient from offending environment.
2. Provide 100% oxygen until carboxyhemoglobin level is in the normal range. Maintain a partial pressure of oxygen (Po_2) greater than 75.
3. If cyanide poisoning is present, induce methemoglobinemia. This can be expedited by contacting the local poison control center.

B. Early.

Upper airway obstruction causing fatal injury occurs in the first 8–48 hours after exposure.

1. Direct laryngoscopy provides the most accurate assessment of upper airway injury.
2. Endotracheal intubation should be performed if laryngoscopy reveals even minimal early swelling or obstruction because swelling will continue for the first 24 hours. If direct laryngoscopy is unavailable, endotracheal intubation should be strongly considered if findings are suggestive of inhalation injury (2).
3. Humidified oxygen or air should be given to thin the viscous bronchorrhea that is produced by injured airways.
4. Bronchodilators (albuterol 5% solution, 0.5 mL) may have variable effects, depending on whether obstruction is due to edema or bronchospasm. There is no contraindication to its use in smoke inhalation.
5. Steroids and prophylactic antibiotics are contraindicated. Antibiotics are indicated for proven infection, which tend to occur 2–3 days after the injury.

C. Late.

Adult respiratory distress syndrome is a late complication.

Carbon Monoxide Poisoning

CO is a colorless, odorless gas produced by incomplete combustion of carbonaceous materials. It is responsible for about 3,500 accidental and suicidal deaths in the United States every year. The CO molecule has about 200–250 times the affinity of oxygen for hemoglobin. Toxic effects are due to tissue hypoxia. Carboxyhemoglobin is incapable of carrying oxygen and interferes with oxygen release.

I. Diagnosis

A. History.

History may include suicidal or accidental exposure to auto exhaust, smoke inhalation, or exposure to a poorly vented heater or appliance.

B. Laboratory findings

1. Increase carboxyhemoglobin level. Normal levels are 1%–3%; levels in smokers are 5%–6%.
2. Patients may have a normal arterial partial pressure of oxygen (Pao_2).
3. Pulse oximetry should be considered unreliable; it cannot differentiate oxyhemoglobin from carboxyhemoglobin.

C. Clinical presentation.

Exposure levels correlate with symptoms and prognosis.

1. Mild exposure (1%–15% carboxyhemoglobin) causes headache, dizziness, and nausea.
2. Moderate exposure (16%–40% carboxyhemoglobin) causes severe headache, nausea, vomiting, loss of coordination, and unconsciousness.
3. Severe exposure (40%–60% or greater carboxyhemoglobin) causes seizures, coma, and death (3).

II. Management

A.

Remove the patient from exposure, maintain vital functions, and support ventilation artificially if necessary. Patient should remain quiet so as to decrease oxygen consumption.

B.

Administer 100% oxygen until carboxyhemoglobin is less than 5%; 40%–50% of the body's CO can be eliminated in 1 hour with high-dose oxygen.

C.

Consider hyperbaric oxygen if carboxyhemoglobin level exceeds 25% or if the patient is unconscious (4). Hyperbaric oxygen can reduce the half-life to 22 minutes (4).

D.

Consider transfusion of blood or packed cells.

E.

Cerebral edema should be managed with diuretics and steroids.

F.

In pregnancy, there is increased binding of CO for fetal hemoglobin; therefore, consider use of hyperbaric oxygen or 100% oxygen at lower carboxyhemoglobin levels (15%).

III. Follow-up.

Monitor the patient after severe exposure for the following neurologic symptoms: tremors, mental deterioration, and psychotic behavior.

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20.4

DOMESTIC VIOLENCE

Nancy J. Baker

Domestic violence is defined as interpersonal violence between intimate partners. It is the most common cause of nonfatal injury to women in the United States. A woman's lifetime risk for abuse is 22% (1). One third of homicides in women in the United States are committed by a spouse or intimate partner (1). During 1998 women were victims of intimate partner violence about five times more often than men (2). Between 17% and 31% of women and up to 30% of men experience violence in same-sex partnerships (3).

Domestic violence results from unequal power and control that is carried to the point of abuse. Abusers threaten, intimidate, isolate, kick, hit, stab, shoot, rape, and kill their partners. Conflict escalates over time before it results in explosive violence against a partner. Almost immediately, anger subsides and a “honeymoon” phase begins. The abuser apologizes and usually promises to never again abuse his or her partner. However, as tension returns, violence recurs and the severity of abuse intensifies. Shame and despair increase for the victim, accompanied by a sense of increased isolation from family, friends, and social support systems.

I. Diagnosis

A. Acute injuries.

Studies suggest that intimate partner abuse is common among women who seek treatment in the emergency department. The prevalence of reported abuse by an intimate partner is 2.2% for acute trauma from abuse, 14.4% for past-year physical or sexual abuse, and 36.9% for lifetime emotional or physical abuse (4). Acute injuries include bruises, cuts, firearm wounds, knife wounds, and fractures. Injuries to the head, face, neck, breast, abdomen, and pelvis are common. Multiple anatomical sites of

injury often indicates abuse, as contrasted with single-limb injuries from true accidents.

B. Abuse in pregnancy.

The prevalence of domestic abuse during pregnancy has been estimated to be between 2% and 17% (5). Pregnant women who present with injuries to the breast, abdomen, and genitalia have most likely been beaten. These women face the risk of severe adverse outcomes, including sexually transmitted infections, miscarriage, placental abruption, antepartum hemorrhage, fetal death in utero, uterine rupture, preterm labor, and liver or spleen trauma.

C. Psychological trauma.

Women who have experienced domestic violence may present to the physician with symptoms of psychological distress, including acute or chronic anxiety, depression, posttraumatic stress disorder, suicidal ideation, sleep disturbance, eating disorder, multiple personality disorder, substance abuse, and/or medication noncompliance.

D. Nonspecific symptoms.

Abused persons may also present with nonspecific somatic complaints. Abdominal pain, chest pain, headaches, insomnia, pelvic pain, fatigue, back pain, and a choking sensation are symptoms commonly reported in an emergency setting or during routine health maintenance visits. It is important to avoid prescribing sedatives or narcotics to an abused person so as not to impair that person's judgment or capacity for self-defense.

E. Permanent disabilities.

Joint damage, visual loss, damaged hearing or scars from burns, bites, knife and gunshot wounds may be consequences of physical abuse.

II. Screening for domestic violence

A. Screen all patients for family violence in the medical interview.

After establishing rapport and confidentiality, ask about a past or current experience of domestic abuse. A simple question such as, “Are you in a relationship in which you have been physically hurt or threatened by your partner” is appropriate. Another approach is to say, “Tension and conflict are a part of all relationships. What happens when you and your partner disagree” Even when such questions are asked directly, a victim may deny abuse because of fear for personal safety, financial dependence, embarrassment, or a desire to protect the abuser. Eventually, abused persons are likely to report interpersonal violence to sympathetic personnel who provide support and access to help.

B. Ask follow-up questions.

In the case of injury, ask directly, “Did someone hurt you? Were you hit” This inquiry should be neutral and asked when the suspected abuser is not present. If the patient discloses that she, or he, feels unsafe, it is appropriate to ask additional questions, such as, “Has your partner ever hit, pushed, shoved, grabbed, or slapped you” “Are you afraid of your partner” “Are you 'walking on eggshells' around your partner” “Has your partner forced you to have sex” “Does your partner destroy things you care about” “Has your partner ever threatened or abused your children” “Is there a gun in the home” “Has your partner ever threatened to use a gun when angry” (6).

C. Look for domestic abuse “red flags.”

Suspect domestic abuse if unexplained injuries are present or if the patient's explanation seems implausible. Abused persons may avoid eye contact or seem overly agitated or wary in their encounters with physicians. They may also not show up for appointments or have an appointment canceled by a partner. An abuser may attempt to stay close at hand or be overly vigilant during an examination to monitor what is said to the physician.

III. Domestic abuse intervention

A. Provide unconditional positive regard.

The most important thing a physician can do to help end domestic violence and protect a victim is to recognize and name abuse. When a patient acknowledges that she or he has experienced interpersonal violence with an intimate partner, be explicit that in all cases physical or sexual assault is unacceptable.

B. Diagnose and treat physical injuries.

In a case of suspected or confirmed domestic abuse, perform the appropriate laboratory and radiologic tests to determine the nature and extent of personal injury. Next, suture, cast, or dress wounds, as indicated. In pregnancy, perform additional tests to ensure both fetal and maternal well-being.

C. Assess psychological and child care needs.

Determine whether an abused person is using drugs or alcohol or is suicidal. Each requires urgent and appropriate intervention. Ask whether or not children are safe in the home. If the children have been mistreated or are at risk for abuse, refer them to an emergency shelter or child protection services.

D. Facilitate a safety plan.

The physician and patient need to assess the level of immediate danger, maximize safety at home, and identify personal needs if a quick escape is necessary. A history of escalating violence, recent job loss, marital separation, or financial strain increases a victim's risk. An individualized safety plan must include means to pack and conceal a suitcase, provision for transportation, a “safe” place to go to, and resources necessary for independent living. Provide an abused person with important phone numbers, including the local domestic abuse shelter, the police, an abuse advocate, or an abuse support group. These individuals or agencies can provide wise counsel and legal advice, as well as information on obtaining a restraining order and protective services for dependents.

E. Complete documentation.

A physician's notation in the medical record should include an objective report of the abuse history as reported by the patient, detailed drawings of physical findings, laboratory and radiologic findings, and any photographs of abuse injuries. Document in the chart that the symptoms or injuries treated are abuse related and request a follow-up appointment.

F. Know state's legal requirements.

Every state has legislation designed to protect victims of domestic violence. Although spouse and partner abuse has been defined as a criminal act, few states have mandatory reporting laws for domestic abuse. Controversy exists as to whether such laws ensure safety for competent adult victims. Physicians must be aware of the specific laws and support services for abused persons available in their practice community. Remember to obtain informed consent from an abused person before disclosing the abuse diagnosis to a third party or the police.

G. Resist the need to “fix” the problem of domestic abuse.

In caring for an abused patient, the physician's primary role is to provide a victim with good medical care and safe, reliable information about support services. Respect an abused person's ability to make appropriate choices. It is up to a victim to decide if and when she or he will leave a violent partner. The time frame for change may be long.

H. Recognize that self-care is important.

Working with abused persons in a medical setting can be discouraging. The physician cannot end interpersonal violence. It becomes difficult to provide care to patients who continue to experience abuse and are unable to find resolution to their difficult life circumstances. Remember that abused persons demonstrate courage and resiliency to survive. One must be realistic in one's expectations for patients. It may also be beneficial to schedule time to debrief about this work with trusted colleagues, while maintaining patient confidentiality. If a physician is not confident about dealing with this issue or feels that his or her judgment about abuse is affected by personal bias or the existence of a dual relationship caring for the patient's partner, refer the patient to a skilled professional colleague.

IV. Work to make the office a safe place to discuss domestic abuse.

Posters with messages such as “Hands are not for hitting” or “It's okay to talk about family violence here” help convey a message of caring. Provide patients with educational materials about family violence and community resources. These can be useful tools for working with women and men who experience interpersonal violence in their intimate relationships.

Domestic violence is a common problem and a complex public health issue that must be recognized and treated with sensitivity. In addition to recognizing abuse-related injuries and symptoms, family physicians can provide patients with life-saving information on community resources available to address domestic violence. They can also help teach women and men that optimal interpersonal relationships are based on respect, negotiation, fairness, trust, and non-threatening behavior.

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20.5
CHILD ABUSE AND NEGLECT

Mary Jo Welker

Pamela Dull

I. Introduction.

Child abuse is a common problem encountered in the family physician's office. Because it cuts across all racial, economic, educational, and religious backgrounds and because the presentation of abuse varies widely, providers should include child abuse in the differential diagnosis of presenting problems.

A. Incidence.

In 1998, there were an estimated 903,000 victims of maltreatment nationwide, or 12.9 per 1,000 children (1). The highest victimization rates were for the 0–3 age group, and rates declined as age increased. It was also determined that 53.5% of maltreated children suffered neglect, 22.7% physical abuse, 11.5% sexual abuse, and 6% psychological abuse or medical neglect (1). More alarming than these numbers is that an estimated 1,100 children died as a result of abuse. Children not yet a year old accounted for 37.9% of the fatalities, and 77.5% were younger than 5 years. The true incidence of fatal child abuse in the United States is unknown because of the difficulty in ascertainment, resulting in significant underestimation.

B. Definitions.

The U.S. Child Abuse and Prevention and Treatment Act defines child abuse as any recent act or failure to act resulting in imminent risk of serious harm, death, serious physical or emotional harm, sexual abuse, or exploitation of a child (a person under the age of 18, unless the child protection law of the state in which the child resides specifies a younger age for cases not involving sexual abuse) by a parent or caretaker (including an employee of a residential facility or any staff person providing out-of-home care) who is responsible for the child's welfare.

Types of abuse are defined as follows:

- **Physical abuse** is the infliction of physical injury by punching, beating, kicking, biting, burning, shaking, or otherwise physically harming a child (intentionally).

- **Child neglect** is the failure to provide for a child's basic needs, physically (nutrition, clothing, safety, etc.), emotionally, medically, and educationally.
- **Sexual abuse** includes fondling a child's genitals, intercourse, incest, rape, sodomy, exhibitionism, and commercial exploitation through prostitution or the production of pornographic materials (see Chapter 20.6).
- **Emotional abuse** includes acts or omissions by the parents or other caregivers that have caused, or could cause, serious behavioral, cognitive, emotional, or mental disorder (2).

II. History.

The history may be very direct, as in the direct report of assault, or indirect, as in acting out, preoccupation, nightmares, chronic physical complaints, poor school performance, running away, depression, suicidal thoughts, or social withdrawal. The family physician will need to be alert to clues that indicate abuse or to factors that might place a child at risk for abuse. Child abuse should especially be considered if there is an inconsistent explanation for an injury or if the explanation does not match the injury. The physician should carry out the interview in an open-ended and nonjudgmental manner. If possible, the physician should interview the child and adult(s) separately to enhance reporting of sensitive information.

III. Risk factors.

The National Research Council's Panel on Research and Child Abuse and Neglect has indicated that multiple factors interact in the development of child abuse. First, societal factors, such as high crime rates, high unemployment rates, high poverty rates, and lack of social services, impact the incidence of child abuse. Second, low-birth-weight infants, premature infants, and handicapped children are at risk for abuse. Third, parental factors influence the occurrence of child abuse. These include a personal history of physical or sexual abuse in childhood, teenage parenthood, single parenthood, emotional immaturity, poor coping skills, low self-esteem, previous incidents involving abuse of a child, or a personal history of substance abuse, depression, or other mental illness. Finally, family issues can have a role in child abuse. Lack of social support, domestic violence, lack of parenting skills, multiple young children, unwanted pregnancy, or lack or preparation for having children can impact the incidence of child abuse in a family (3).

IV. Examination and tests.

The most obvious findings of physical abuse are those visible on the surface of the skin. A thorough examination of the skin should document in writing and on diagrams or photos any bruises, scars, tourniquet or bite marks, and burns. Bruises and scars appearing at sites that are unusual for accidental injury (buttocks, back, hands, and feet) are usually the result of abuse. If bruises do not follow the pattern of injury, then one should consider getting a complete blood count with platelets, prothrombin time, and partial thromboplastin time. Tourniquet or restraint marks occur during attempts to hang, choke, or tie a child to a crib, bed, or chair. The size of a bite mark can help distinguish the bite of a child from that of an adult. Burns may be accidental or abusive, but the pattern, inconsistencies in the history, or delay in seeking care can provide clues to the abuse. “Stocking-glove” distribution is a classic sign of abuse.

The oral examination should focus on obvious lacerations, ecchymosis, fractured or loose teeth, and less obvious signs, such as discolored teeth and palate petechiae or erythema. Most oral abuse is the result of blunt trauma or injuries caused by scalding or caustic substances. As there may be age-appropriate nonabusive injuries, consultation or referral to a pediatric dentist may be needed when the history, circumstances, or behaviors do not match.

In cases of sexual abuse, vaginal examination in the lithotomy position may be accomplished on postpubescent girls, but in younger girls or those with extreme physical or emotional pain examination under anesthesia may be necessary. The knee-chest position or supine frog-leg position may be used in young girls. Hymenal and rectal areas should be examined. Many patients may not have obvious trauma, such as lacerations or contusions. Less obvious findings may include abrasions, ecchymosis, labial adhesions, neovascularization, or

friability. Sexually transmitted disease (STD) testing and sperm analysis samples should be obtained if the history is suspicious. If less than 72 hours has passed since the alleged abuse occurred, then use of a rape kit is optimal. Otherwise, if there is a discharge, wet prep and cultures (not DNA probes for children) for gonorrheal and chlamydial infection are indicated (4) (see Chapter 19.6 and Chapter 19.7). If there is evidence of a STD, then institute serologic testing (RPR/VDRL) for syphilis (see Chapter 19.5). If there is a history of multiple or high-risk perpetrators, stranger rape, or anal penetration, then HIV testing is necessary (5) (see Chapter 19.4). Often, even in confessed sexual abuse cases, the physical exam is normal, either because the abuse produced no injuries or the injury healed before the examination was performed.

The rectal examination should focus on sphincter tone. If gluteal stoking causes paradoxical anal sphincter relaxation or if placement in the knee-chest position causes immediate sphincter dilatation to greater than 2 cm, then abuse is strongly suggested. Tears beyond the hair follicle-bearing areas are more likely to represent abuse.

Most skeletal abuse occurs in children younger than 18 months. Frequently, the mechanism of injury and the resulting fracture are inconsistent. The other aids are fracture patterns are as follows: (a) unexplained and often symmetrical fractures of varying ages involving the long bones or ribs; (b) metaphyseal chip or corner “bucket-handle” fracture (rapid acceleration and deceleration forces that can be caused by violent shaking or yanking); (c) long-bone fracture, particularly if it is transverse and oblique and there is no clear history of a consistent major mechanism of injury; (d) any rib fracture in an infant or toddler; (e) hand or foot fracture in an infant or toddler (5).

Head injuries are a major source of morbidity and mortality in child abuse victims. Intracranial injuries are the most devastating consequences of child abuse. Most victims are younger than 1 year and have no external signs of injury. These infants should be meticulously inspected for fingerprint marks (as a physical sign of shaking). Physical examination may show lethargy, increased or decreased tone, rhythmic eye opening, bicycling movements of the extremities, and sometimes posturing. Other important findings are a decreased ability to follow the examiner's face, decreased responsiveness to pain, or poor suck and grasp. The fontanelle is usually full, but it may or may not be tense. Dilated ophthalmoscopy must be performed because 75%–90% of shaken babies have retinal hemorrhages. Those with retinal hemorrhages suffer serious sequelae or death nearly 100% of the time.

V. Management.

All states have laws mandating that professionals who suspect child abuse report it to the local Child Protective Services agency. Caregivers should be informed of this requirement. It is the role of the Child Protective Services agency to determine whether abuse has occurred.

The physician's role is to report suspected abuse, collect medical evidence, and be prepared to testify in court. In the medical chart, accurately document the specifics of the case, using names and including the interviewees' exact words; normal and abnormal findings; and whether Child Protective Services was contacted (if not contacted, explain why). Describe injuries via drawings and text, including the size, location, color, shape, and distribution of injuries. Take color photographs using good equipment, adequate light (flash), and planned composition (two views, close-up and anatomical context, scale of measurement). Label with the patient's name, date of birth, date of incident, and date of visit.

VI. Specific treatment.

With STDs, await test results for children, and treat per protocol for the specific organism. Adolescents may be treated for gonorrheal and chlamydial infection prophylactically. Counsel and offer postcoital contraception to prevent pregnancy in girls presenting less than 72 hours after assault. Some larger cities have sexual assault treatment centers for referral or consultation.

Therapy should be instituted based on the injury sustained. Above all, the child needs to hear that the abuse or injuries are not his or her fault.

VII. Prevention.

The primary care physician has the opportunity to play an important role in preventing child maltreatment. Primary prevention is defined as both the prevention of disease before it occurs and the reduction of its incidence. Primary care physicians should assess stressors on caretakers, such as lack of support, existence of other children, substance abuse, violence, inadequate education, and mental health problems. Physicians may need to refer parents to available resources and educate them on anticipatory guidance, nutrition, safety, and discipline (3).

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20.6

APPROACH TO THE VICTIM OF SEXUAL ASSAULT

Linda M. Petter

The definition of sexual assault varies from state to state. However, in general, the term applies to any form of nonconsenting sexual activity, encompassing all unwanted sexual acts ranging from fondling to penetration. Sexual assault is a crime even if the victim knew the attacker, had intercourse with the attacker before the assault, did not attempt to fight back, or was intoxicated, drugged, or unconscious (1,2,3,4,5,6).

I. Incidence/Prevalance.

In 1994, sexual assault represented 5.5% of all violent crimes reported in the United States. This crime crossed all social statuses, includes all races and spans all ages. One in every six women will be raped during her lifetime. Approximately half of all victims are adolescents. One in 500 women has been assaulted during a pregnancy. Every year more than 60,000 rapes are committed against women older than 50 years.

It is difficult to profile a rapist because so few rapists are apprehended and convicted that a true character profile is not available. However, perpetrators are generally not mentally delayed, lustful, or psychotic. More accurately, they usually are individuals who have experienced failed social relationships, harbor significant insecurities, and/or who have low self-esteem.

II. Obtaining the history of the sexual assault.

When obtaining a history from a patient who has undergone sexual assault, preparation if the key. Provide a quiet, secure, and private environment (a room, not a cubicle with a drape). Excuse any law enforcement officer who is present. It is imperative to obtain the patient's consent during each step of the medical investigation (history, physical examination, collection of evidence, and photography). In some states, this consent is required by law; however, it also serves to help the victim reestablish trust and regain control. Document using the phrase “alleged sexual assault” or “sexual assault by history”; avoid writing, for example, “she was raped.” The word *rape* is not a medical term but rather a legal term. Be specific and state the facts as reported by the victim. Restrict your questioning and documentation to

the medically relevant history—details that are investigatory in nature may lead to discrepancies with police reports. Allow 30–60 minutes for the history and the physical examination. Most importantly, be patient, do not hurry, listen carefully, and do not place blame—the patient is not on trial.

A.

The following key information should be included in the history when possible:

1. Age and any identifying information for both the victim and the assailant.
2. Date, time, and location of the assault.
3. Other circumstances surrounding the assault.
4. Details of all sexual contact, such as penile, digital, or object penetration. Document route of intercourse, such as vaginal, oral, or anal. Also, note any ejaculation or urination by the assailant.
5. If physical restraints were used, and type.
6. Did the victim change clothes, bathe, douche, brush her teeth, urinate, or defecate?
7. Gynecologic history of the victim: last menstrual period, pregnancy, contraceptive use, last voluntary sexual encounter, any recent episode of gynecologic infection or surgery.

III. Physical examination of the assault victim.

The purpose of the physical examination is twofold: (a) to assess the patient for physical injuries and (b) to collect evidence for forensic evaluation and possible legal proceedings. Physical examination and evidence collecting (use of a rape kit) are done congruently. Attempting to collect evidence beyond 48–72 hours after an assault often is difficult to recover and/or may be invalid. Therefore, it is imperative to document the time frame (from time of assault to medical examination) and to encourage victims to proceed with evidence collection as soon as possible. Should the victim wish to pursue prosecution at a later date, evidence collected with a rape kit may be a vital factor in the success or failure of a case going to trial.

Throughout the United States, the use and contents of a rape kit are fairly standard. Rape kit instructions help guide the clinician through the collection and preservation of evidence for forensic evaluation. Health care professionals who have not used a rape kit should familiarize themselves with its contents prior to collecting evidence. Table 20.6-1 lists the contents of a rape kit. It is imperative that the step-by-step rape kit instructions for evidence collection be followed. Once the kit is opened, the “chain of evidence” must be maintained and not breached; evidence cannot be left unattended (7,8,9,10,11,12,13,14,15,16,17,18,19,20).

Instructions and check-off sheet
Large paper sheet
Small paper bags
Large paper bag
Cotton-tipped swabs
Small cardboard boxes
Comb
Paper napkins
Filter paper
Sterile saline
Envelopes
Speculum
Red-topped and purple-topped tubes for blood sample collection
History and physical documentation forms
Patient discharge information form

Table 20.6-1. Recommended contents of a rape kit

Table 20.6-2 is a list of items to be collected. Only the victim should handle her clothes. Clothing can be collected up to one month after the assault, provided

the items have not been laundered. Clothing items should be placed in paper bags, as plastic may promote bacterial growth on blood or semen stains.

Items/specimens	Container
Patient's clothing	Paper bag
Fingernail scrapings, broken fingernail pieces	Separate envelope
Hair strands	Separate envelope
Oropharyngeal swabbing	Air-dried swabs, separate envelope
Pubic hair	Separate envelope (include comb)
Vaginal swabbing	Air-dried swabs
Vaginal washings	Wet mount, air-dried smear
Pap smear	Per routine
Rectal swabbing	Air-dried swabs
Blood samples	Red-topped and purple-topped tubes

Table 20.6-2. Items and specimens to be collected after a sexual assault

Always begin the physical examination in a non-threatening location, such as the ears, eyes, nose, then throat; this helps to regain the victim's trust. Using the rape kit contents, swab the oral cavity. If oral penetration took place, swab the oropharynx for semen retrieval and gonorrhea testing (8). Even if the teeth were brushed or mouthwash used, sperm may be recovered from the oral cavity up to 6 hours later (9).

Observe the patient for signs of extragenital trauma (mouth, throat, arms, wrist, thighs, breasts, etc.), which occurs in 20%–50% of sexual assault cases (7,8,9,10). Document the presence, size, and location of lacerations, bite marks, scratches, and bruises. Only with the patient's consent may you photograph the area(s) of trauma. If consent is refused, use diagrams to document injuries.

The genital examination should be delayed until the end of the examination. Note the condition of the hymen; document any perineal trauma (i.e., abrasions, tears, and bruises). Engorgement of the clitoris and/or labia may last for 1–2 hours after injury (7). If available, use a Wood's lamp to examine the patient's thighs for fluorescing semen stains (urine may also fluoresce). Swab any highlighted areas.

With a comb provided in the rape kit, the patient should comb her pubic area to collect any foreign hair that may be present. In addition, the patient should pluck approximately 15–20 pubic hairs to serve as samples for reference. The speculum should be lubricated only with saline. K-Y jelly may be spermicidal and interfere with wet mount procedures and forensic evaluation. Next, examine the vaginal walls and cervix for ecchymosis, abrasions, and/or lacerations. The cervix should be swabbed and cultures obtained for *Chlamydia* and *Neisseria gonorrhoeae*. If a colposcope with photographic capabilities is available, document the presence of any cervical and/or vaginal microtrauma.

A wet mount should be done to check for the presence of sperm. Motile sperm may be seen up to 8 hours post coitus (11), and nonmotile sperm can be detected beyond 72 hours (4). Document the number of sperm seen under the high-power field. The absence of sperm does not exclude the possibility of sexual assault. The assailant may have undergone a vasectomy. Lastly, the slide should also be examined for the presence of bacterial vaginosis, trichomonads, and yeast (12).

A bimanual and rectal examination should be performed to assess uterine size, pelvic tenderness, and adnexal masses/tenderness. If supported by the history, swab the rectum for sperm, *Chlamydia*, and *N. gonorrhoeae*, and perform a rectal digital examination to assess for sphincter laxity or spasm. The presence of bleeding, mucosal tears, and/or hematomas should be noted (1).

IV. Laboratory examination of assault victims.

A pregnancy test is recommended for all women of childbearing age. The purpose for ordering a ß-human

chorionic gonadotropin level at the time of initial examination is to rule out an established pregnancy. Between 1% and 5% of sexual assaults result in pregnancy (7,8). For a victim of sexual assault, the risk of acquiring syphilis from a one-time sexual exposure is estimated to be less than 1% (6). A VDRL (Venereal Disease Research Laboratory) or RPR (rapid plasma reagin) test should be obtained at the time of the initial visit and repeated 3 months later. Hepatitis serology should be drawn (hepatitis B surface antigen, antibody to hepatitis B core antigen, hepatitis B early antigen, antibody to hepatitis B surface antigen), as well as testing for hepatitis C. The risk of acquiring HIV or hepatitis B from a one-time sexual encounter is less than 1% (6,7,8,9,10,11,12,13). Serology for HIV should be obtained at the initial visit, repeated at 3, 6, and 12 months from the date of exposure. Antibodies may develop within 6 months in 95% of persons who eventually become infected after HIV exposure (4).

V. Treatment.

Treatment for the prevention of pregnancy should be offered and discussed with all victims. Again, timing is important because most postcoital pregnancy interventions are ineffective after 72 hours. Several treatment options exist, such as repeating a pregnancy test 6 weeks after the last menstrual period. However, many victims of sexual assault experience late menses secondary to stress and anxiety, thereby only compounding the emotional climate. As a result, pregnancy interruption is a commonly used alternative. One recommended treatment is to administer high-dose oral contraceptive pills, such as 50 µg of ethinyl estradiol (e.g., Ovral), two tablets now, and repeated in 12 hours (4). This immediate therapy reduces the risk of pregnancy by 60%–90% (8).

The risk of acquiring any sexually transmitted disease (STD) from a single sexual encounter is 5%–10% (4). The U.S. Centers for Disease Control and Prevention treatment guidelines for postcoital prevention of STD are as follows: prophylaxis should be offered if there is evidence that the assailant was infected or if symptoms of infection are present on examination, if poor follow-up is anticipated, or if the patient requests prophylaxis. Treatment should include prophylaxis for gonorrhea, syphilis, and chlamydial infection. Trichomoniasis therapy should be instituted only if organisms are seen on the wet mount examination. If no prophylaxis is given, cultures for gonorrhea and chlamydial infection should be repeated in 2 weeks and nontreponemal tests at 12 weeks. If prophylaxis was given and initial cultures are negative, no additional cultures are needed (7). If the patient was previously unimmunized, hepatitis B virus vaccine should be given at the acute care visit, then repeated at 1 and 6 months. Use of hepatitis B immune globulin should be reserved for patients who have been exposed within 14 days and who present with a high-risk exposure history, such as having an assailant who is a known intravenous drug user or having more than one assailant.

Pre- and posttest HIV counseling must be performed. The theory behind offering treatment is to help prevent cellular infection by treating patients during a “window of opportunity.” The probability of HIV transmission increases depending on several factors, such as local prevalence rates, assailant's serologic status, number of assailants, route of exposure (vaginal, anal, oral), vaginal pH, method of virus entry (blood versus mucous membranes), and presence of other STDs (15,16,17). As in most cases, if the perpetrator is not apprehended, the victim's infection status may not be known for 6–12 months. This time delay further feeds already existing anxiety and fear. In the meanwhile, lifestyle changes are necessary for most victims (i.e., condom use, abstaining from intercourse, discontinuing breast-feeding, postponing planned pregnancies, and so forth). Therefore, treatment decisions must be made on a case-by-case basis; risks and benefits must be discussed and weighed against cost, potential side effects, and lifestyle changes.

Prophylactic HIV treatment may consist of two nucleoside analogues: zidovudine (Retrovir) and lamivudine (Epivir). Each medication should be given simultaneously for 4 weeks or according to future treatment recommendations (13,14,15). Treatment should not commence beyond 72 hours from the time of exposure (13). Table 20.6-3 lists current medications for the prophylaxis of STDs.

Sexually transmitted diseases	Medication	Dosage
Gonorrhea	Cefixime (Suprax)	400 mg orally in a single dose
	Alternatives:	
	Ceftriaxone (Rocephin)[a]	125–250 mg intramuscularly in a single dose
	Ciprofloxacin (Cipro)	500 mg orally in a single dose
	Ofloxacin (Floxin)	400 mg orally in a single dose
Chlamydia	Doxycycline (Vibramycin)[b]	100 mg twice daily for 7 d
	or	
	Azithromycin (Zithromax)	1 g orally in a single dose
	Alternatives:	
	Erythromycin base	500 mg orally four times daily for 7 d
	Amoxicillin	500 mg orally twice daily for 7 d
	Ofloxacin	300 mg orally twice daily for 7 d
Hepatitis	Hepatitis B virus vaccine	1 mL intramuscularly (deltoid) at 0, 1, and 6 m
	and/or	
	Hepatitis B immune globulin	0.06 mL per kg intramuscularly in a single dose; within 14 d of exposure
Human immunodeficiency virus	Zidovudine (Retrovir)	200 mg orally three times daily for 4 wk
	plus	
	Lamivudine	150 mg orally twice daily for 4 wk

[a] Oral medications may be preferred in the future.
[b] Should be avoided in pregnant and lactating women.
From Beebe DK. Emergency management of the adult female rape victim. *Am Fam Physician* 1991;43:2041–2046; Dwyer B. Rape: psychological, medical, and forensic aspects of emergency management. *Emerg Med Rep* 1995;16:105–116; Hampton HL. Care of the woman who has been raped. *N Engl J Med* 1995;332:234–237; Katz MH, Gerberding JL. Postexposure treatment of people exposed to the human immunodeficiency virus through sexual contact or injection-drug use. *N Engl J Med* 1997;336:1097–1100; and *Med Lett Drugs Ther* 1994;36:1–6, with permission.

Table 20.6-3. Medications for prophylactic treatment of sexually transmitted disease

IV. Psychological sequelae of sexual assault

A.

The psychological impact of sexual assault can be profound and long term. Rape trauma syndrome is similar to posttraumatic stress disorder. Phase I (initial, acute reaction) comprises a period of emotional lability, disbelief, fear, anxiety, and/or guilt. Phase II (reorganization phase) encompasses a period of adjustment, integration, and inevitably recovery. Patients with a history of sexual assaulted do not necessarily present to the office with pelvic pain. Symptoms may be gastrointestinal, respiratory, cardiac, musculoskeletal, or neurologic. Victims may manifest drug abuse, phobias, panic disorder, obsessive-compulsive disorder, codependencies, and the like.

B.

Approximately 50% of victims experience depression during the first year following the incident (18). Sexual dysfunction has been reported as high as 24%–40% of victims up to 6 years after the assault (18). These women are significantly more likely than those without a sexual assault history to report somatic symptoms and complain of chronic diseases (19). Visits to doctor's offices increase by 18% during the first year after a sexual assault, 56%

by the second year, and then decline to 31% by the third year (5). It is imperative that proper support services be implemented at the time of initial evaluation and close follow-up scheduled because the initial care a victim receives influences her recovery. Support services may include hospital social workers, local departments of public health, local rape crisis service, district attorney's office, the Rape Abuse and Incest National Network (RAINN; telephone 800-656-HOPE), and the National Coalition Against Sexual Assault (NCASA; telephone 717-728-9764).

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XXI. OCCUPATIONAL AND ENVIRONMENTAL PROBLEMS

21.1
PESTICIDE AND RELATED POISONING

James E. Lessenger

Tons of pesticides are used throughout the world in home, office, industrial, and agricultural applications. New techniques in integrated pest management may reduce the dependence on chemicals in the future. Growth regulators, nutrients, and buffers are sometimes considered in this class of chemicals because they are often used together.

Pesticides using engineered viruses and bacteria have entered the market and it remains to be seen if field use produces injuries.

I. Basics

A.

Pesticides represent hundreds of chemicals mixed into thousands of formulations targeted at a specific pest, crop, or structure. These chemicals are used in gaseous forms as fumigants; in liquid form as mists and sprays applied by aircraft, spraying rigs, hand-held sprayers, and injection into irrigation water; and in solid form as powders, granules, and pellets for broadcast by hand, aircraft, and ground machines. The range of chemicals includes organophosphates, elements, organochlorides, carbamates, dipyridyls, chlorophenoxy compounds, anticoagulants, hydrocarbons, and more.

B.

A person's presence in an area where pesticides are used does not necessarily mean that there will be exposure. Exposure does not necessarily mean there will be adequate contact to produce the physiologic changes of poisoning. Poisoning may not automatically lead to impairment or disability.

II. Outpatient care

A. Remove from exposure.

Persons who are exposed must leave immediately and stay away until the area is safe.

B. Decontamination.

Each exposed person should bathe thoroughly, with careful attention to the hair. Clothing should be removed and be treated as hazardous waste. If exposed, the eyes need to be aggressively irrigated.

C. Emergency care

should be instituted as soon as practicable. Responders must be careful not to expose themselves (1,2).

III. Diagnosis

A. History

may be the only positive data.

1. Contact the employer or applicator for the name of the formulation and the material safety data sheet (MSDS).
2. Question how the exposure occurred, with emphasis on the exact mechanism of exposure, cause and effect relationship of exposure and symptoms, previous exposures and poisoning, and drug- or alcohol-related problems.
3. Symptoms (and signs) may vary by the type of formulation to which the person was exposed, the length and concentration of exposure, and decontamination. Nausea, vomiting, fatigue, and vertigo are common to most poisonings but may also represent other diseases as well as psychogenic illness. The classic symptoms of salivation, lacrimation, urination, and diarrhea—the SLUD syndrome seen in organophosphate poisoning—may not be seen in low-concentration poisoning of short duration, although the person may have fatigue and vertigo (3).

B. Physical examination

1. **Skin.** Rashes should be carefully described and secondary changes caused by scratching and treatment documented. Halogenated hydrocarbons can produce chloracne, often confused with acne vulgaris (4).
2. **Respiratory.** Inhalation of dusts, mists, and gases may cause instantaneous or delayed bronchospasm.
3. **Gastrointestinal (GI).** Nausea, vomiting, diarrhea, and abdominal pain occur as a result of eating contaminated food or by direct ingestion of poison in attempted suicides and homicides.

4. **Neurologic.** Acute or delayed polyneuropathy and chronic lapses in concentration and memory can result from exposure to organophosphates and halogenated hydrocarbons.
5. **Ocular.** Sprays or mists to the eyes can cause problems ranging from simple conjunctivitis to corneal opacities (5,6).

C. Laboratory tests are of limited usefulness.

1. Urine and blood pesticide levels are costly, must be collected as soon after exposure as possible, may take weeks to produce results, and may be negative even in well-documented exposures (5).
2. Blood, liver, and kidney test results may be clouded by the presence of other diseases and may be abnormal in only the most severe poisonings.
3. Cholinesterase (ChE) activity tests are useful only in organophosphate and carbamate poisoning and are most effective when used in a monitoring program for applicators where baselines have been established. A person can have a 60% drop in ChE activity levels and still stay in “normal” ranges. A postexposure series of tests demonstrating a dip with recovery may be the only laboratory response elicited. ChE activity levels can also be affected by cocaine use and the taking of medications (3,7).

D. Research.

Whenever possible, physicians should learn the name of the chemical and its properties before embarking on nonemergency treatment. Sources include the MSDS, reference texts, poison control centers, telephone numbers on the pesticide container, TOXLINE, and MEDLINE.

IV. Treatment

A.

Mild poisonings are associated with few symptoms and normal vital signs. Moderate poisonings are associated with more severe symptoms, objective signs, and normal vital signs. Severe poisonings are associated with multiple complaints, objective signs, and unstable vital signs. Exercise caution as some pesticides may exhibit delayed onset of symptoms and signs.

B.

Mild and moderate poisonings can usually be evaluated and followed on an outpatient basis. Individuals who have suffered mild or moderate poisoning rarely require treatment other than reassurance, antiemetics for nausea and vomiting, and steroids for rash.

C.

Severe poisonings usually require hospitalization and intensive physiologic support. Decontamination should not be ignored in the hospital setting, and gastrointestinal lavage may be needed in cases of ingestion.

D.

Antidotes such as atropine, pralidoxime, vitamin K, and nicotinamide are rare. They may not be needed and should not be attempted unless the pesticide is identified.

E.

Elimination enhancement. Forced diuresis, exchange transfusion, and chelation are replete with complications and should only be considered when the patient's condition is severe, on an inpatient basis, and when the specific agent has been identified.

F.

Atropine is useful in organophosphate and carbamate poisoning when bradycardia causes hypotension or when secretions threaten respiration. The dosage is 0.5–2.0 mg IV every 20–30 minutes. The literature is replete with persons brought near death by inappropriate atropine administration. In severe cases, atropine may have to be administered serially for several days (3).

G.

In jurisdictions where required, reports must be made to the appropriate agencies.

V. Follow-up.

Serial examinations to follow chronic problems may be necessary, especially with neurologic and respiratory involvement. Work, impairments, and disability status must be documented. The possibility of fraud must be considered and documented if discovered (8).

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21.2
OCCUPATIONAL LUNG DISEASES

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John R. Wheat

Occupational lung diseases are caused by the inhalation of foreign substances into the lungs in the context of the occupational setting (1,2 and 3). Due to the common nature of these illnesses, family physicians are often the initial medical providers treating these patients. This initial medical encounter affords the family physician the opportunity not only to impact the health of an individual patient but to improve the work environment for a segment of the community. Family physicians are increasingly called on to treat these illnesses by virtue of their role as company physicians. The most common occupational lung diseases are asthma, hypersensitivity pneumonitis, pneumoconiosis (asbestosis, coal worker's pneumoconiosis, and silicosis), and work-related pulmonary infections. Because these patients may present with nonspecific or undifferentiated pulmonary symptoms, documentation of the nature and duration of exposure is essential. As these illnesses may present years after the occupational exposure, a detailed past medical and occupational history is required (4,5 and 6)

I. Occupational asthma

Occupational asthma is the most common occupational lung disease in the United States (4). This condition accounts for approximately 25%–50% of all occupational lung disease and is responsible for approximately 15% of all asthma cases. Occupational asthma is characterized by variable airflow limitation and bronchial hyperresponsiveness caused by conditions attributable to a particular work environment. Occupational asthma should be differentiated from work-aggravated asthma that persists away from the workplace but is worsened by workplace exposures. More than 250 compounds have been associated with occupational asthma. The most common of these are isocyanates, wood dust, dyes, irritant gases and fumes (e.g., chlorine and ammonia), flour, animal dander, and latex. Isocyanates (diisocyanates) are responsible for more cases of occupational asthma than any other single substance; approximately 5% of workers exposed to volatile isocyanates develop asthma (7). The diagnosis of occupational asthma can potentially have major socioeconomic effects on both the worker and the employer.

A. Diagnosis

of occupational asthma is based on the history, physical examination, and appropriate diagnostic testing. The most common symptoms of asthma are cough, wheezing, and shortness of breath, although wheezing may not always be present. Respiratory symptoms that occur within 1 hour after work begins or 6–8 hours later is consistent with but not diagnostic of

occupational asthma. Symptoms that worsen during the work week but improve during weekends or vacations are suggestive of occupationally induced asthma. Additional useful information includes exposure to substances known to cause occupational asthma. Because many products contain multiple chemicals, the Material Safety Data Sheet (MSDS) should be obtained from the company's safety officer and reviewed for known causative agents. The physical examination will ascertain whether the worker is wheezing or is noticeably short of breath, and, if possible, should be made while the patient is symptomatic in the workplace. The chest radiograph is useful in ruling out other pulmonary conditions. The peak expiratory flow rate (PEFR) is essential in determining whether a diminution in pulmonary function is occurring while the patient is at work. Initially, workers are asked to measure peak flows every 2–4 hours during waking hours for a period of 4 weeks. This measurement is performed with a peak flowmeter to obtain an objective measurement of pulmonary function. Workers who have decrease in peak flow rates while at work and normal baseline flow rates off the job have reversible airway disease. A standard spirometry and flow volume loop providing the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, and forced expiratory flow at 25%–75% of FVC (FEF_{25-75}) indicates whether preexisting pulmonary disease is present and determines the pattern of disease (obstructive or restrictive).Spirometry followed by bronchodilator therapy indicates whether there is a reversible component to the pulmonary function tests. A 15% increase in the FEV_1 following bronchodilatation suggests reactive airway disease. If neither peak flow nor spirometry measurement is adequate to ascertain the diagnosis of occupational asthma, then nonspecific or specific bronchial provocation should be considered. Nonspecific provocation involves a patient breathing a sequence of nebulized mists containing progressively increased concentrations of bronchoconstricting agents such as methacholine or histamine. A drop in the FEV_1 of more than 20% is considered a positive test. Pulmonary function testing may be obtained before, during, and after work to substantiate the history. Specific bronchoprovocation testing (SBPT) is considered a superior method for confirming the diagnosis of asthma secondary to a particular agent but is seldom used because of its complexity.

B. Treatment

of occupational asthma involves bronchodilator therapy including inhaled ß-agonists, corticosteroids, and mast cell membrane stabilizers. Noninhaled agents include leukotriene antagonists, theophylline, and systemic corticosteroids. Workers diagnosed with occupational asthma benefit from a multilevel approach to the disorder that may require engineering and administrative consultation to protect the worker from the offending agent. Personal protective equipment is also occasionally used, although this strategy is not as effective as engineering controls. The primary principle in managing this disorder is avoidance of the causative agent. Some cases of occupational asthma have been shown to be completely reversible with loss of hypersensitivity to the offending agent when complete avoidance occurred early in the course of the disease. However, other cases have progressed to chronic asthma that did not remit when exposure was continued beyond the early stages of disease.

C. Prevention

of occupational asthma is preferable to management of bronchospasm. Early detection of reversible airway disease may facilitate a plan to prevent chronic symptoms. Complete avoidance of the offending substance is the primary means of preventing recurrence of symptoms. This may be accomplished by transferring the worker from the specific area of causation. Alternatively, the work area may be changed, such as by making an open system into a closed system or by improving or redirecting the ventilation. Personal protective equipment and high-efficiency particulate air (HEPA) filters may be used in certain circumstances.

II. Hypersensitivity lung disease

encompasses a group of occupational lung diseases, which include hypersensitivity lung pneumonitis, organic toxic dust

syndrome, and irritant lung disease. Agricultural workers are at particularly increased risk for these disorders.

A. Hypersensitivity pneumonitis

(allergic alveolitis) is an interstitial granulomatous lung disease caused by repeated inhalation of antigens in organic dusts. These antigens are typically of fungal or animal protein origin. Farmer's lung is the prototypical hypersensitivity pneumonitis.

1. **Diagnosis** of this condition is suggested by a constellation of flu-like signs and symptoms including cough, fever, myalgias, malaise, dyspnea, and tachycardia within a few hours after exposure to an environmental antigen. Auscultation usually reveals expiratory rales, although wheezing is generally absent. Leukocytosis may be present and the chest radiograph may reveal diffuse infiltrates, miliary mottling, or bilateral acinar filling mimicking the appearance of pulmonary edema. Spirometry reveals decreased lung volumes with a decrease in vital capacity revealing a restrictive defect. Repeated exposures may cause recurrent pneumonitis accompanied by development of pulmonary fibrosis associated with a permanent decrease in pulmonary function.
2. **Treatment** consists of corticosteroids, oxygen, and bronchodilators. The symptoms generally peak in 8–12 hours with improvement over 24–48 hours, if there is no further antigenic exposure. Workers who have severe symptoms or hypoxemia require hospitalization for more aggressive treatment. Although most attacks of this illness are relatively mild, acute hypersensitivity pneumonitis can be fatal.
3. **Prevention** of recurrence of this illness requires avoidance of exposure to the precipitating antigen. Complete avoidance is warranted, but in some circumstances use of respirators will reduce exposure to relatively safe levels. It is important to identify this disorder to prevent development of a chronic pulmonary disease. It is believed that workers who have repeated bouts of subacute attacks are more likely to develop irreversible pulmonary fibrosis.

B. Organic toxic dust syndrome

is a condition in which workers develop cough, wheezing, shortness of breath, and fever after being exposed to moldy grain dust, wood chips, hay, and straw. This condition typically arises within hours after massive exposure to fungal spores. Workers may have fever, cough, myalgias, and chest tightness. Wheezing and rales may be heard on auscultation, and a significant restrictive pattern may be demonstrated by pulmonary function studies. The white blood cell count may be elevated. Symptoms clear in a few days. Although many of the clinical features of this illness resemble those of allergic alveolitis, organic toxic dust syndrome is a benign condition without long-term effects. Many farmers develop this condition every year, but few seek medical attention.

C. Irritant lung disease

is caused by toxic gases such as ammonia, chlorine, oxides of nitrogen (silo filler's disease), sulfur dioxide, ozone, and phosgene. Byssinosis is caused by exposure to cotton fibers and accompanying bacterial components (endotoxins and possibly lipopolysaccharides).

1. **Silo filler's disease** is the prototype of irritant lung diseases. Exposure to nitrogen dioxide, which exists in two forms in equilibrium (NO_2 and N_2O_4), causes direct alveolar injury as the nitrous dioxide is changed into nitric acid within the lung tissue. Nitrogen dioxide is produced by the curing process of fresh silage, by arc welding, and by the production and use of nitric acid.
    a. **Diagnosis** is facilitated by proving exposure to the nitrogen dioxide, which leads to cough with sputum production and dyspnea. In silo filler's disease, wheezing, tachypnea, and tachycardia can occur within 2 hours after exposure. In extreme instances, the patient can develop pulmonary edema and become cyanotic. The chest radiograph may demonstrate pulmonary edema, ill-defined nodular densities, or diffuse miliary mottling. Pulmonary function testing shows reduction in lung volumes associated with a decrease in diffusing

capacity. In most instances, there is a gradual improvement over 2–3 weeks that may be followed by relapse associated with fever, chills, and dyspnea. Death may occur from respiratory failure.

b. **Treatment** of severe illness requires aggressive respiratory support, including mechanical ventilation with high concentrations of inspired oxygen. Corticosteroids have been anecdotally shown to improve outcomes and should be given to all individuals who are symptomatic to decrease alveolar injury.
c. **Prevention** of silo filler's disease requires avoidance of fresh silage. Although 2 weeks is generally enough time for the nitrogen gasses to dissipate, there have been poisonings 6 weeks after silo filling. This is probably related to lack of ventilation. Personal protective devices are not a suitable means of protecting workers from this exposure.
d. **Byssinosis** is caused by exposure to cotton fibers and its contaminates. A similar illness is also seen in hemp and flax workers. Since the advent of increased manufacturing controls in the ginning process and yarn production, this disease has largely disappeared.
    a. **Diagnosis** should be suspected when a worker complains of chest tightness and shortness of breath on the first workday of the week. This is associated with a modest decline in ventilatory capacity over the week's first work shift. The chest radiograph is normal in early disease.
    b. **Management** of this illness is directed to controlling ambient dust concentrations. The National Institute of Occupational Safety and Health (NIOSH) has set standards for cotton dust concentrations in the workplace, the result of which has been the virtual elimination of this illness. For those workers who cannot avoid exposure, personal protective equipment can be used.

III. Pneumoconiosis

describes the group of pulmonary diseases caused by the deposition of particulate matter in the lungs. The International Labor Office (ILO) defines pneumoconiosis as “the accumulation of dust in the lungs and the tissue reaction to its presence.” The dusts that cause pneumoconiosis are asbestos, coal dust, silica, beryllium, graphite, aluminum, and others. Asbestos, coal dust, and silica have affected the largest number of workers. The ILO has standardized procedures for radiologic evaluation of pneumoconiosis, and the NIOSH National Coal Workers' Health Surveillance Program have adopted these standards along with specific certification requirements for radiologists.

A. Asbestosis

is caused by a naturally occurring fibrous mineral silicate. More than 27 million workers have been exposed to asbestos within the last 50 years, approximately half of whom are still living. It is estimated that approximately 3 million workers have continued occupational exposure to asbestos, primarily in the construction, building, maintenance, and custodial industries. Asbestos is still readily found in many products (e.g., older floor tiles and cement products) and in the insulation in older buildings. The latency period for the disease is generally 15–20 years. The main occupational exposures have been asbestos mining, asbestos removal, building demolition, textile and tile manufacturing, ship building, pipe fitting, and application of asbestos fireproofing and insulation. Although the use of asbestos in the United States has sharply decreased since the 1970s, the incidence of asbestos-related deaths has continued to climb. The incidence of mesothelioma, 80% of which is related to asbestos exposure, has continued to rise through the mid-1990s. The diseases associated with asbestos are asbestosis (a diffuse fibrotic condition of the lung), carcinoma of the lung, mesothelioma, and pleural lung disease (pleural plaques and pleural thickening).

1. **Diagnosis** is based on work exposure, pulmonary symptoms, and radiographic findings. The usual duration of exposure before disease development is greater than 1 year's duration occurring at least 15 years before the onset of symptoms. The initial symptom is a nonproductive

cough and shortness of breath associated with medium to coarse inspiratory rales. The radiologic features of asbestosis are pleural plaques, diffuse pleural thickening and calcification, diffuse pulmonary fibrosis, and small irregular opacities. Spirometry demonstrates reduced lung volumes with a restrictive pattern and impairment of gas exchange as measured by the diffusing capacity of carbon monoxide (DLco). The pulmonary fibrosis of asbestosis tends to be progressive, resulting in impairment of pulmonary function, dyspnea, and right heart failure.

2. **Treatment** of asbestosis is supportive, as there is no effective treatment.
3. **Prevention** of asbestosis is accomplished by controlling ambient asbestos dust and preventing workers from coming into direct contact with asbestos particles. This usually requires workers to wear protective suits and respirators when performing tasks such as removal of insulation. The 1995 Occupational Safety and Health Administration asbestos standard requires employers to provide medical surveillance for employees who work with or around asbestos for more than 30 days in a year.

B. Coal worker's pneumoconiosis (CWP)

is the medical term used to describe the pulmonary disease caused by the inhalation and deposition of carbonaceous dusts. Black lung is the term used in the Federal Coal Mine Health and Safety Act, which defines the coal miners' benefits program. Although the incidence of deaths from CWP has declined since its peak in 1972, there were 1,417 deaths in 1996 attributable to this disease. Even though dust control methods and worker protection (primarily respirators) have been emphasized, the nation's 50,000 underground coal miners are at risk for this disease. Coal dust can result in a spectrum of conditions, including simple coal workers pneumoconiosis, progressive massive fibrosis (PMF), chronic bronchitis, and emphysema.

1. **Diagnosis** of CWP is made based on occupational exposure to coal dust, symptoms, and radiologic findings. Coal dust targets macrophages and epithelial cells, which become activated, releasing reactive oxygen species, cytokines, and proteases that damage lung tissue. Simple coal workers' pneumoconiosis is usually asymptomatic, even though the chest radiograph may show rounded and irregular densities. At this stage, there is only a small decrease in ventilatory capacity. PMF is associated with increased radiologic nodularity, sometimes coupled with bullous emphysematous changes. Advanced disease is associated with both obstructive and restrictive impairment of lung function with decreases in FEV_1 and FVC, and decreased diffusion capacity.
2. **Treatment** of persons with CWP, PMF, and emphysema caused by coal dust is largely unsatisfactory, although standard bronchodilator therapy may be useful.
3. **Prevention** of diseases caused by coal dust requires use of dust control technology and respirators. Periodic medical examinations are now required of all coal mine workers. Workers who have early radiologic evidence of CWP (e.g., simple CWP) should be removed from the exposure, which effectively halts development of disease.

C. Silicosis

is a chronic fibrotic disease of the lungs caused by exposure to free crystalline silica. Compounds that contain silica are sand, quartz, and certain mining products. The disease is usually seen after 10–30 years of exposure. It may be seen in an accelerated pattern if exposure has been intense. Industrial sources of free silica include mining, stone work, sandblasting, foundry work, and glass manufacturing.

1. **Diagnosis** of early silicosis requires radiographs showing nodular densities 1–3 mm in diameter because early disease is asymptomatic. Spirometry is usually normal in early disease. Dyspnea and increased radiographic densities, primarily in the upper lung fields, herald disease progression. Hilar adenopathy may ensue, and lymph nodes may

become calcified. Spirometry in more advanced disease reveals decreased lung volumes with a restrictive defect. End-stage silicosis is characterized by progressive decline in pulmonary capacity with the development of fibrotic masses in the upper lung fields.

2. **Management** of silicosis is supportive. Workers with any degree of silicosis should be prevented from working in areas of silica dust, although the disease may progress despite this measure. It is not unusual for patients with silicosis to develop active tuberculosis.
3. **Prevention** of silicosis is accomplished by controlling exposure to silica dust through the use of strict environmental control techniques.

IV. Occupational lung infections

primarily affect farmers, veterinarians, microbiology laboratory technicians, sanitation workers, health care personnel, and heating ventilation/air conditioning workers. Pulmonary infections that may be contracted through work include tuberculosis, atypical mycobacteriosis, legionnaire's disease, histoplasmosis, psittacosis, brucellosis, and coccidioidomycosis.

A. Diagnosis

of occupational lung infections involves a detailed history of exposure, physical examination, chest radiograph, appropriate cultures, and serologic testing.

B. Treatment

of these infections requires precise diagnosis based on cultures and is usually amenable to standard treatment.

C. Prevention

of occupational lung infections may require respiratory protection in the presence of potential exposure.

V. Medical surveillance

for workers at risk for occupational lung disease is important for prevention and early recognition (8). The primary tools used for medical surveillance are the history (including a respiratory questionnaire), physical examination, spirometry, and chest radiograph. These measures help to determine which employees have early symptoms of disease and which employees are at increased risk because of preexisting lung disease. The most valuable measures from spirometry are FVC, FEV_1, and FEV_1/FVC. An FEV_1 less than 75% generally precludes respirator use. Workers who smoke are at increased risk for occupational lung disease and should be encouraged by both the physician and employer to stop smoking.

VI. Industrial hygiene

is the science of workplace environmental assessment and management of worker protection. Industrial hygienists are trained to evaluate the worksite for potential problems that effect worker health and develop strategies to protect the workers from potential harmful substances. Industrial hygienists are capable of quantitating harmful substances to determine if they meet U.S. government standards for workplace safety. A list of industrial hygienists can be found in January issues of the *American Industrial Hygiene Journal*.

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21.3
HEAT-RELATED SYNDROMES

Michael H. Bross

Heat-related syndromes occur when the effects of environmental and metabolic heat result in illness. When the ambient temperature rises above 95°F, the evaporation of sweat is the only effective means of heat dissipation. High humidity limits the evaporation of sweat. Dehydration, medications that limit sweating, poor conditioning, obesity, sleep deprivation, alcoholism, chronic disease, and advancing age all compromise the ability to tolerate heat load.

I. Minor syndromes

A. Heat cramps.

Patients complain of brief, intense cramps in severely stressed muscles. Workers and athletes are typically affected after profuse sweating from heavy exertion. Heat cramps respond well to rest and an oral electrolyte solution. Gradual heat acclimation, increased dietary salt, and ongoing fluid replacement are preventive measures.

B. Heat edema

refers to swelling of the feet and ankles that occurs with heat stress and prolonged sitting or standing. This condition is mostly seen in elderly, nonacclimatized individuals. Heat edema is a benign condition that responds well to leg elevation and support stockings. Diuretics should be avoided. Diagnostic workup for more serious conditions is warranted if additional symptoms occur.

C. Heat syncope

results when high temperatures and a dilated vascular space compromise venous return. Advanced age or dehydration are commonly present. Emergency department evaluation is usually indicated to rule out other illnesses. Medications, especially anticholinergic drugs and diuretics, are often contributory and should be adjusted. Management consists of oral or intravenous fluid replacement and close observation. Maintaining adequate hydration, rising gradually from lying or sitting positions, and wearing support hose all help to prevent recurrences.

II. Major syndromes

A. Heat exhaustion

1. **Clinical presentation.** Heat exhaustion symptoms include nausea, vomiting, headache, dizziness, muscle weakness, visual disturbances, profuse sweating, and cutaneous flushing.
2. **Diagnosis.** The heat exhaustion patient has a clear sensorium without neurologic findings. Core body temperature is often elevated, occasionally to extreme levels. Tachycardia, hyperventilation, and hypotension occur in serious cases.
3. **Management.** The patient must immediately be taken to a cool environment, have excess clothing removed, and be sponged with lukewarm water. Oral rehydration is tolerated in mild cases, with 1 L/h given for several hours. Serious cases are best transported to the nearest emergency medical facility. Hemoconcentration, azotemia, and oliguria are corrected by intravenous rehydration with a solution of dextrose in normal saline or dextrose in half-normal saline. Caution is advised in elderly patients to avoid fluid overload.

B. Exercise-associated hyponatremia

1. **Clinical presentation.** Endurance athletes and hikers, aware of the dangers of heat-related illness, may consume excessive fluids over several hours of exertion. Early hyponatremia symptoms include nausea, vomiting, headache, dizziness, incoordination, and mild confusion. Serious progressive symptoms are combative behavior, lethargy, seizures, and coma. Deterioration often occurs after exertion has ended and treatment has begun (1).

2. **Diagnosis.** Consider hyponatremia when a mental status change occurs. Examination typically reveals low or normal body temperature, stable blood pressure and pulse, moist mucous membranes, and no orthostatic hypotension. Low serum sodium is diagnostic, with symptoms typically occurring when the serum sodium falls below 130 mmol/L. Severe symptoms are associated with a serum sodium of less than 125 mmol/L.
3. **Management.** Fluid consumption should be limited until the situation can be clarified by a serum sodium. If heat exhaustion is also being considered, a bolus of 250 mL of normal saline is reasonable. The bolus will help heat exhaustion without worsening hyponatremia. Mild hyponatremia can be treated with fluid restriction ± normal saline. Severe symptomatic hyponatremia requires 3% NaCl at approximately 1 mL/kg per hour. Frequent blood monitoring is indicated to achieve a gradual rise in serum sodium, not to exceed 10 mmol/L over the first 24 hours.
4. **Complications.** Obtundation, seizures, and coma commonly occur with rapid-onset severe hyponatremia. Intensive care support may be necessary. Overly rapid correction of hyponatremia can result in central pontine myelinolysis, a condition characterized by quadriparesis, swallowing dysfunction, and mutism.

C. Heatstroke

1. **Clinical presentation**
   a. Classic heatstroke victims are elderly people with chronic diseases and limited mobility. During heat waves, these individuals become progressively dehydrated until the body's cooling mechanisms fail. The skin is hot and dry without sweating. Tachypnea, tachycardia, and hypotension are characteristic.
   b. Exertional heatstroke victims are active individuals who over exert themselves in the heat. Sweating may be profuse or absent. Circulation is often hyperdynamic with marked tachypnea.
2. **Diagnosis.** Heatstroke victims have a core body temperature of 40.5°C (105°F) or greater and acute neurologic findings. Core temperature may be lower after prehospital treatment. Neurologic abnormalities range from irritability and confusion to deep coma. Seizures are common.
3. **Management**
   a. Prehospital treatment. Heatstroke victims must be immediately cooled to a core temperature of 39°C (102°F) to avoid high mortality (2). Treatment consists of removing unnecessary clothing, spraying the body with lukewarm water, and enhancing airflow across the patient during transport to an emergency facility.
   b. Airway, breathing, and circulation. Respiratory assistance with intubation is often required for critically ill patients. Cardiac monitoring and oxygen are begun. Fluid resuscitation is started with dextrose in normal saline or dextrose in half-normal saline. Core temperature is measured with a flexible rectal probe. A Foley catheter is inserted to monitor urine output.
   c. Immediate cooling. Core temperature should be lowered at least 0.1°C/min to the target temperature of 39°C (102°F). Cooling can be accomplished by one of two methods.
      1. Evaporative cooling involves spraying the uncovered patient with lukewarm water and using fans to blow air across the body (3).
      2. Ice water baths consist of placing the patient in a tank of iced water, relying on the rapid conduction of heat into water. Shivering and agitation, more common in iced baths, is effectively treated with intravenous diazepam (Valium), 5 mg every 5 minutes.

d. Baseline tests include chest radiography, electrocardiography, cardiac isoenzymes, arterial blood gases, complete blood count, prothrombin time, fibrinogen level, blood chemistry profile, creatine kinase, urinalysis, and urine myoglobin.

e. Complications

1. Cardiovascular instability calls for intense monitoring with a Swan-Ganz catheter and a central line. For persistent hypotension with low cardiac index, low-dose isoproterenol infusion is appropriate (4).
2. Renal. Low or absent urine output, hematuria, and proteinuria are signs of renal injury. Rhabdomyolysis, a common complication of exertional heatstroke, results in dark urine, intense muscle pain, myoglobinuria, and high serum creatine kinase. Renal damage is addressed by administering fluids to maintain a high urine output (more than 50 mL/h). With myoglobinuria, urine alkalinization with sodium bicarbonate and mannitol 12.5–25.0 g is also helpful.
3. Hepatic injury is a consistent finding, with jaundice commonly occurring in 1–3 days.
4. Neurologic. Computed tomographic scanning of the head and possibly lumbar puncture are recommended for patients with persistent coma, seizures, or a focal neurologic deficit.
5. Hematologic. Serial clotting studies are indicated for patients with petechiae, purpura, hematemesis, or epistaxis. Early coagulopathies are treated with fresh frozen plasma and platelet transfusions. Disseminated intravascular coagulation remains a devastating complication. Heparin has been effective in some cases.
6. Respiratory. Increasing airway resistance, increasing pulmoary infiltration, and decreasing oxygen saturation characterize adult respiratory distress syndrome. Mechanical ventilation with positive end-expiratory pressure is helpful.

III. Prevention

A National Weather Service heat index of over 90°F is hazardous, with direct sunlight raising the value up to an additional 15°F. Physically impaired people and those taking medications that limit sweating should avoid the heat and drink plenty of liquids. Active people can minimize heat risk by gradually acclimating themselves to the heat over 10–14 days, drinking plenty of water before and during heat exposure, and wearing vapor-permeable light clothing. Endurance athletes and hikers should replenish fluid losses with frequent small quantities of fluid, not exceeding 0.5–1 L/h. A commercially available carbohydrate electrolyte beverage may be beneficial in the case of prolonged exertion (5).

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22.1
BACTERIAL ENDOCARDITIS PROPHYLAXIS

Bruce M. Bushwick

I. General considerations.

Bacterial endocarditis is an uncommon, serious infection of the endocardium, damaged or abnormal heart valves, or endothelium near congenital anatomical defects (endarteritis). It is believed to occur when people at risk experience transient bacteremia following traumatic manipulation of certain mucosal surfaces. There have been no satisfactory controlled clinical trials of antibiotic prophylaxis in humans. However, animal models, in vitro studies, and clinical experience suggest that morbidity and mortality can be reduced by the use of prophylactic antibiotics directed against endocarditis-associated bacteria (1). Because the infection is fatal if untreated, prevention is of utmost importance.

II. Clinical strategy.

The task of the family physician is as follows:

A.

Recognize the clinical conditions that increase the risk of developing endocarditis or endarteritis.

B.

Recognize the procedures known to cause transient bacteremia and predispose the patient at risk to develop endocarditis.

C.

Decide whether prophylactic antibiotics are indicated.

D.

Prescribe antibiotic therapy that is likely to suppress endocarditis-causing bacteria during the period of transient bacteremia.

E.

Educate the patient at risk.

III. Conditions associated with increased risk of endocarditis

(2)

A. High-risk conditions

1. Prosthetic cardiac valves, including bioprosthetic and homograft valves
2. Previous bacterial endocarditis, even in the absence of heart disease
3. Cyanotic congenital cardiac abnormalities, including but not limited to the following:
   a. Single-ventricle states
   b. Transposition of the great arteries
   c. Tetralogy of Fallot
4. Surgically constructed systemic pulmonary shunts or conduits

B. Moderate-risk conditions

1. Congenital cardiac abnormalities not noted in Section III.A.3 .
2. Rheumatic and other acquired valvular dysfunction
3. Hypertrophic cardiomyopathy
4. Mitral valve prolapse **with** valvular regurgitation and/or thickened leaflets

IV. Conditions not believed to predispose the patient to developing endocarditis

(risk is thought to be no higher than that of the general population) (2)

A.

Isolated secundum atrial septal defect

B.

Surgical repair without residua after 6 months of atrial septal defect, ventricular septal defect, or patent ductus arteriosus

C.

Previous coronary bypass graft surgery

D.

Mitral valve prolapse without valvular regurgitation (although thickening or redundancy of the valve leaflets may increase risk for men older than 45)

E.

Physiologic or functional heart murmurs

F.

Previous rheumatic fever or Kawasaki's disease without valvular dysfunction

G.

Cardiac pacemakers or implanted defibrillators

V. Bacteremia-producing procedures that predispose patients with high- or moderate-risk conditions to developing endocarditis

(2) (This list is not all-inclusive.)

A. Dental procedures

1. Professional cleaning
2. Dental extractions

3. Periodontal procedures
4. Tooth implantation or reimplantation of avulsed teeth
5. Root canals
6. Placement of antibiotic fibers or strips subgingivally
7. Initial placement or orthodontic bands but not brackets
8. Intraligamentary local anesthetic injections
9. Any procedure known to induce gingival or mucosal bleeding

B. Respiratory tract procedures

1. Tonsillectomy and/or adenoidectomy
2. Operations involving the respiratory mucosa
3. Rigid bronchoscopy

C. Gastrointestinal tract procedures

(Note: prophylaxis is optional for moderate-risk patients undergoing these.)

1. Sclerotherapy for esophageal varices
2. Esophageal dilatation of stricture
3. Endoscopic retrograde cholangiography with biliary obstruction
4. Biliary tract surgery
5. Operations involving the intestinal mucosa

D. Genitourinary procedures

1. Cystoscopy
2. Urethral dilatation
3. Urethral catheterization or surgery if urinary infection is present
4. Prostate surgery

E. Other procedures

1. Incision and drainage of infected tissue
2. Vaginal delivery in the presence of infection

VI. Procedures not typically associated with endocarditis

(2)

A. Dental procedures

1. Adjustment of orthodontic appliances
2. Filling cavities in decayed teeth
3. Injection of intraoral anesthesia
4. Shedding of primary teeth
5. Any procedure not likely to cause gingival bleeding

B. Surgical procedures

1. Tympanostomy tube placement
2. Endotracheal intubation
3. Flexible fiberoptic bronchoscopy with or without biopsy
4. Cardiac catheterization
5. Lower gastrointestinal endoscopy with or without gastrointestinal biopsy
6. Cesarean section
7. In the absence of infection: urethral catheterization, dilatation and curettage, uncomplicated vaginal delivery, therapeutic abortion, sterilization procedures, insertion or removal of intrauterine device.

VII. Prophylactic therapy

A.

Administer prophylactic antibiotics under the following circumstances:

1. To patients who have conditions associated with an increased risk of endocarditis and who undergo endocarditis-associated procedures
2. **Optionally**, to patients with **high-risk** conditions who undergo procedures not usually associated with endocarditis that involve the lower respiratory (including **flexible fiberoptic bronchoscopy**), genitourinary (including **vaginal hysterectomy** and **vaginal delivery**), or gastrointestinal tracts (including **transesophageal echocardiography** and **endoscopy**)
3. If clinical judgment warrants in circumstances not addressed in Section III and Section V .

B.

Prophylactic antibiotic choice and route of administration:

1. See Table 22.1-1 for specific prophylactic antibiotic recommendations.

A. Dental, Oral, Upper Respiratory Tract, or Esophageal Procedures in Adults
   1. Standard regimen
      a. Amoxicillin, 2.0 g PO 1 h before procedure
   2. Amoxicillin/penicillin allergic
      a. Azithromycin or clarithromycin, 500 mg PO 1 h before procedure *or*
      b. Clindamycin, 600 mg PO 1 h before procedure *or*
      c. Cephalexin or cefadroxil, 2.0 g PO 1 h before procedure[a]
   3. Unable to take oral medications
      a. Ampicillin, 2.0 g IV or IM within 30 min before procedure
   4. Unable to take oral medications and penicillin allergic
      a. Clindamycin, 600 mg IV within 30 min of starting procedure *or*
      b. Cefazolin, 1.0 g IM or IV within 30 min of starting procedure[a]

B. Genitourinary/Gastrointestinal Procedures in Adults
   1. Patients with high-risk conditions
      a. Ampicillin, 2.0 g IV or IM, plus gentamicin, 1.5 mg/kg IV (not to exceed 120 mg) within 30 min of starting procedure, then ampicillin, 1.0 g IV or IM 6 h later (or amoxicillin, 1 g PO)
   2. High-risk patients who are ampicillin/amoxicillin allergic
      a. Vancomycin, 1.0 g IV (over 1–2 h) completed within 30 min of starting procedure plus gentamicin, 1.5 mg/kg IV or IM (not to exceed 120 mg) within 30 min of starting procedure
   3. Patients with moderate-risk conditions
      a. Amoxicillin, 2.0 g PO 1 h before procedure or ampicillin, 2.0 g IV or IM within 30 min of starting procedure
   4. Patients with moderate-risk conditions who are allergic to ampicillin/amoxicillin
      a. Vancomycin, 1.0 g IV (over 1–2 h) completed within 30 min of starting procedure

C. Dose Modification for Pediatric Patients (Total Dose Not to Exceed Adult Dose)
   1. Initial doses
      a. Amoxicillin or ampicillin, 50 mg/kg
      b. Azithromycin or clarithromycin, 15 mg/kg
      c. Clindamycin, 20 mg/kg
      d. Gentamicin, 1.5 mg/kg
      e. Vancomycin, 20 mg/kg
      f. Cephalexin or cefadroxil, 50 mg/kg
      g. Cephazolin, 25 mg/kg
   2. Follow-up doses should be half of the initial dose

[a] Do not use cephalosporins in individuals with immediate-type hypersensitivity reactions (urticaria, angioedema, or anaphylaxis) to penicillins.
Adapted from Dajani AS, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 1997;277:1794–1801, with permission.

Table 22.1-1. Prophylactic therapy for prevention of bacterial endocarditis

2. When performing an endocarditis-associated procedure in the presence of infection, antibiotic choice should cover the most likely pathogen causing the infection, in addition to the general guidelines.
3. Consider parenteral route of administration for lower gastrointestinal or genitourinary procedures in high-risk patients. Other patients could receive oral prophylaxis.

VIII. Patient education and charting

A.

In patients who are at risk, an effective oral health program should be undertaken to minimize bacterial seeding through chronically inflamed tissues.

B.

Charts of at-risk patients should be clearly identified, and if desired, an outline of standard prophylactic medication can be attached to facilitate prescribing.

C.

When endocarditis prophylaxis is given, the patient should be told the rationale for treatment, risks, and benefits. Early signs and symptoms of endocarditis should be reviewed, such as unexpected fevers, night sweats/ chills, weakness, myalgias, arthralgias, or malaise, so that emergent infections can be rapidly identified and treated.

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22.2
MEDICATION USE DURING PREGNANCY

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In general, common sense suggests that medication use during pregnancy should be limited. Nevertheless, pregnant women sometimes present with clinical syndromes that may warrant drug therapy.

The U.S. Food and Drug Administration (FDA) has established five categories for drugs based on their potential for causing birth defects in infants born to women who use the drugs during pregnancy. The categories are as follows (1):

A.

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and fetal harm appears remote (e.g., *folic acid, levothyroxine*).

B.

Animal studies have not demonstrated a fetal risk, but there are no human studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in human studies (e.g., *amoxicillin, ceftriaxone*).

C.

Animal studies show adverse effects, and there are no controlled studies in women. Drugs should be given only if benefit outweighs the potential risk to the fetus (e.g., *labetalol, nifedipine,* and *omeprazole*).

D.

Positive evidence of human fetal risk exists, but benefits may outweigh risks in certain situations (e.g., *lithium, phenytoin,* and *propylthiouracil*).

E.

Studies or experience have shown fetal risk that clearly outweighs any possible benefits (e.g., *misoprostol, warfarin, isotretinoin*).

Drugs used in pregnancy and others that should be avoided are discussed here by system category. Commonly used herbal agents considered safe and those to avoid are listed at the end of the chapter. Most medications are followed by the FDA category in parentheses if available. *Clinicians who prescribe medications during pregnancy should observe the following guidelines: Try to avoid any medication during the first trimester. Use single, noncombination agents. Choose topical treatments (if available) over oral. Use the lowest effective dose. Remember, use medication only if the benefit appears to outweigh the risk.*

I. Allergy

A. Allergic rhinitis.

Allergic rhinitis can affect up to one third of women of childbearing age. First-line therapy includes intranasal cromolyn (B) (Nasalcrom) or beclomethasone (C) (Vancenase AQ, Beconase AQ). If symptoms are not controlled, then first-generation antihistamines, such as chlorpheniramine (B), 4 mg PO qid can be used. There are no controlled trials with the second-generation antihistamines, which include loratadine (B) (Claritin), cetirizine (B) (Zyrtec), and fexofenadine (C) (Allegra). Pseudoephedrine (C) (Sudafed), 30–60 mg PO qid has the best safety record if an oral decongestant is required.

II. Infectious disease

A. Colds (upper respiratory tract infection).

The best treatment is symptomatic management with fluids, humidity, and rest. If absolutely necessary, antihistamines such as chlorpheniramine (B) and triprolidine (C) appear to be the safest. If a decongestant is indicated, use a topical agent first. Pseudoephedrine (C), 30–60 mg PO every 6–8 hours, has the best safety record for an oral decongestant. Preparations containing guaifenesin (C) or dextromethorphan may be used for the management of cough (2). *Avoid* iodine-containing expectorants (e.g., potassium iodide) (D) because of the potential for thyroid toxicity in the newborn, and also *avoid* alcohol-containing products.

B. Sexually transmitted diseases

(3)

1. **Chlamydial infection.** Manage with amoxicillin (B), 500 mg PO tid for 7 days, or erythromycin base (B) (Eryc, E-Mycin), 500 mg PO qid for 7 days. Alternative regimen is azithromycin (B) (Zithromax), 1 g orally. Repeat culture 3 weeks after completion of antibiotic course. *Avoid* erythromycin estolate (Ilosone), doxycycline (D), and quinolones (C). (See also Chapter 19.7 .)
2. **Genital warts, external (condyloma acuminata).** Safe treatments during pregnancy include topical bi- or trichloroacetic acid weekly, cryotherapy, or liquid nitrogen. **Avoid** podophyllin (C), podofilox (C) (Condylox), and imiquimod (B) (Aldara).
3. **Gonorrhea (GC) (uncomplicated).** Treat patients for both GC and chlamydial infection with ceftriaxone (Rocephin) (B), 125 mg IM or cefixime (Suprax) (B), 400 mg PO single dose plus azithromycin (B), 1 gm orally. Women who cannot tolerate a cephalosporin should be administered a single 2-g dose of spectinomycin (B) IM. Reculture after treatment. *Avoid* quinolones and tetracyclines (see also Chapter 19.6).
4. **Herpes genitalis.** For severe first episode, late-onset disease in the second or third trimester, or disseminated herpes simplex virus infections, use of acyclovir (C) (Zovirax) appears justified. Famciclovir (Famvir) and valacyclovir (Valtrex) are two new agents with better absorption and both are classified as B. Doses vary with indication. If daily suppressive therapy at 36 weeks appears justified, use acyclovir, 400 mg PO bid.
5. **Pediculosis** (***P. humanus capitis* or "head lice," and *Phthirus pubis* or "crabs"**). Manage with topical permethrin 5% (B) (Elimite) or 1% (Nix) liquid. Wash hair, apply lotion for 10 minutes, then rinse. *Avoid* lindane (B) (Kwell) due to the potential for neurotoxicity and aplastic anemia (see also Chapter 16.3).
6. **Scabies** (***Sarcoptes scabiei***.) Manage with topical permethrin (B) (Elimite) 5% cream. Apply to entire skin from chin to toes. Leave on for 8–10 hours. *Avoid* crotamiton (C) (Eurax) and lindane (B) (Kwell) (see also Chapter 16.3).
7. **Syphilis.** Manage primary, secondary, and latent infection of less than 1 year 's duration with benzathine penicillin (B) (Bicillin LA), 2.4 million U IM. Higher doses are used in late latent or when the duration of disease is unknown. There is no alternative to penicillin in pregnancy. If there is a penicillin allergy, skin-test and desensitize if necessary. Follow patient with monthly Venereal Disease Research Laboratory (VDRL), and if there is a fourfold increase in titer, retreat (see also Chapter 19.5).

C. Urinary tract infection (uncomplicated).

Empirical treatment includes oral cephalexin (B) (Keflex), 500 mg tid, amoxicillin/clavulanate (B) (Augmentin), 250 mg tid, or nitrofurantoin (B) (Macrodantin), 50–100 mg qid (4). Treat for 7–10 days. Trimethoprim-sulfamethoxazole (C) (Bactrim, Septra) can also be used, but avoid near term due to risk of kernicterus. Obtain a repeat urine culture after treatment. *Avoid* quinolones (C), which are associated with fetal cartilage damage, and doxycycline (D) due to offspring teeth staining and maternal hepatotoxicity (see also Chapter 12.1 and Chapter 12.2).

D. Vaginitis

(see also Chapter 13.1)

1. **Bacterial vaginosis.** Manage with metronidazole (C) (Flagyl), 500 mg PO bid for 7 days or clindamycin (B) (Cleocin), 300 mg PO bid for 7 days. *Avoid* metronidazole in the first trimester. Use oral metronidazole and clindamycin, *not* topical in pregnancy.
2. **Candidiasis.** Treat with topical agents, such as clotrimazole (B) (Mycelex, Gyne-Lotrimin), miconazole (Monistat) (C), and terconazole (Terazol) (C) vaginal cream. Use vaginally every night for 7 days. *Avoid* oral fluconazole (Diflucan) (C) until more data are available.
3. ***Trichomonas vaginalis***. Metronidazole (C), 2 g or 500 mg PO bid for 7 days, is the treatment of choice. *Avoid* this agent in the first trimester. For symptomatic relief in the first trimester, try clotrimazole (B) suppositories.

III. Pulmonary disorders

A. Asthma.

Management of asthma in pregnant women differs little from management in nonpregnant patients. Medications that are safe to use in pregnancy include albuterol (C) (Ventolin, Proventil), cromolyn (B) (Intal), theophylline (C), and glucocorticoids (C). Whenever possible, treatment should be by inhalation rather than oral. During exacerbations, IV and oral glucocorticoids may be used in the usual manner. No published human data or consensus guidelines exist regarding the use of leukotriene D4 antagonists, zafirlukast (Accolate) (B) and montelukast (Singulair) (B), in pregnancy. Zileuton (C) should be *avoided* during pregnancy (see also Chapter 10.1).

B. Pneumonia (community acquired).

Streptococcus pneumoniae, Mycoplasma pneumoniae, and *Chlamydia pneumoniae* are the most common bacterial organisms. *Haemophilus influenzae* is commonly found in patients who smoke. For empirical outpatient treatment, use azithromycin (B) (Zithromax), 500 mg followed by 250 mg/d PO for 4 days. Alternative treatment includes cefuroxime (B) (Ceftin), 500 mg PO bid, amoxicillin/ clavulanic acid (Augmentin), 875/125 mg PO bid. These alternative antibiotics are *not* active against *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. *Avoid* clarithromycin (C), tetracycline (D), and quinolones (C) (see also Chapter 10.2).

IV. Gastrointestinal disorders

A. Nausea and vomiting.

Attempt conservative measures, including small frequent meals, a bland diet, and acupressure wristbands or acupressure on the volar surface of the forearm. Ginger tea up to 1 g/d (about 4 cups) may help. Initial medications include pyridoxine (A), 25 mg PO q8h, and phosphorated carbohydrate solution (Emetrol), 1–2 tablespoons PO every 15 minutes to 5 doses. Safe antiemetics include meclizine (B) (Antivert), 25–mg po q6h prn, promethazine (C) (Phenergan), 25 mg PO/IM/PR every 4–6 hours prn, or metoclopramide (B) (Reglan), 10 mg PO qid. Ondansetron (B) (Zofran) has been used in patients whose symptoms are refractory to other therapy.

B. Gastroesophageal reflux (GERD).

GERD can effect up to 50% of pregnant women. Treatment includes routine antireflux measures. Antacids and alginic acid (Gaviscon) are first-line agents. Antacids may interfere with iron absorption. H_2 receptor antagonists cimetidine (B) (Tagamet), 400 mg PO at bedtime, and ranitidine (B) (Zantac) 150 mg PO bid, have the most published data in terms of human experience. In refractory cases, omeprazole (C) (Prilosec) has been used, but more research is needed to assess its overall safety (see also Chapter 11.2).

C. Inflammatory bowel disease.

Active Crohn's disease and ulcerative colitis can have an adverse impact on pregnancy. First-line treatment in active disease is sulfasalazine (B) (Azulfidine), 500 mg PO qid, or mesalamine (B) (Asacol), 800 mg PO tid, and rectal or systemic glucocorticoids (5). Like other sulfonamides, sulfasalazine is considered category D near term because of the theoretical risk of kernicterus. Folic acid 1 mg PO bid is advised in women receiving sulfasalazine. Adverse fetal effects have been documented with the use of 6-mercaptopurine, azathioprine, and cyclosporine. Methotrexate (D) is *contraindicated*. Consultation with a gastroenterologist is warranted in active disease (see also Chapter 11.9).

V. Endocrine disorders

A. Diabetes.

Diet is the cornerstone of management. If medication is needed, insulin (B) is the drug of choice. Avoid oral hypoglycemics (see also Chapter 17.2).

B. Thyroid disorders

(see also Chapter 17.3)

1. **Hypothyroidism.** Oral levothyroxine (A), 0.1–0.20 mg/d, is the thyroid preparation of choice. Other preparations are associated with increased side effects.
2. **Hyperthyroidism.** Propylthiouracil (PTU) (D), 50–150 mg PO q8h is preferred over methimazole (Tapazole) (D), which has been associated with newborn scalp defects (aplasia cutis). Short-term use of a ß-blocker, such as propranolol (C) (Inderal), 20–40 mg PO q8h, or atenolol (D) (Tenormin, 50–100 mg PO qd), may be needed for initial symptom management to control maternal heart rate at 80–90 beats/min. Monitor for intrauterine growth retardation. The use of radioactive iodine (X) is *contraindicated.* Endocrinology consultation for management issues is recommended.

VI. Neurologic and psychiatric disorders

A. Headaches, migraine.

Nondrug therapies, such as relaxation, sleep, massage, ice packs, and biofeedback, should be tried first. If drug therapy is needed, the most acceptable analgesic is acetaminophen (B) (Tylenol), 1,000 mg at first sign of headache. An antiemetic may also be required, such as promethazine (C) (Phenergan) or metoclopramide (B) (Reglan). *Avoid* aspirin (C) and nonsteroidal anti-inflammatory drugs, especially in the last trimester (category D) due to risk of premature closure of ductus arteriosus. In severe cases, hydrocodone (C) and meperidine (C) may be given for short-term use only. Prophylactic treatment is rarely indicated. Ergotamine (D) and serotonin 5-HT_1 receptor agonists such as sumatriptan (C) are *contraindicated* in pregnancy (see also Chapter 6.1 .)

B. Depression.

Psychotherapy is considered first-line treatment for depression during pregnancy. Fluoxetine (Prozac) (C), 20 mg/d PO, appears to be relatively safe and should be the agent of first choice (6). The selective serotonin reuptake inhibitors (SSRIs) paroxetine (Paxil) (C) and sertraline (Zoloft) (B) also appear safe, but data on humans are limited. Long-term effects on the fetus/infant after the use of SSRIs in pregnancy is unknown. Many of the older antidepressants, such as amitriptyline (D), imipramine (D), and phenelzine (C), are considered teratogenic and should be avoided. There are no data based on controlled testing in humans for bupropion (B), venlafaxine (C), and nefazodone (C) (see also Chapter 5.2).

VII. Herbal agents

(see also Chapter 22.3)

A.

Herbal agents generally recognized as safe (GRAS) for use as a food supplement by the FDA include chamomile, garlic, ginger, and ginseng (7).

B.

Herbal agents to avoid in pregnancy include but are not limited to black and blue cohosh, cascara, chondroitin, dong quai, dihydroepiandrosterone, echinacea, feverfew, ginkgo, goldenseal, St. John's wort, wild yam, and valerian.

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22.3
HERBAL MEDICINE

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Jodi A. Chaffin

I. Background

A.

The use of herbs by patients in the United States exploded after Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994. This legislation designated numerous botanical products as *dietary supplements*. Dietary supplements are not approved by the Federal Drug Administration (FDA) and are prohibited from having a therapeutic (drug) claim. A therapeutic claim relates to the diagnosis, treatment, cure, or prevention of a disease. However, product labels and advertising can make statements of nutritional support as long as they do not claim to cure a sick person or affect the course of disease. DSHEA authorized the FDA to issue “good manufacturing practice” regulations; however, such regulations are not yet official, so the responsibility for producing quality products rests with the manufacturer. The quality of the final product is dependent on a number of factors, including growing and harvesting conditions, plant parts used, extraction methods used, and dosage form. Adulteration of herbal dietary supplements with pharmaceuticals, such as steroids and benzodiazepines, and metals, such as arsenic and lead, has occurred. Currently, the FDA's postmarketing surveillance program, “Med Watch,” wherein health professionals make reports to the FDA about product problems or adverse events, is the only form of regulation.

1. **Variety.** Herbs come in a variety of forms: whole fresh, dried powders, teas, juices, tinctures, standardized extracts, essential oils, and isolated components (1,2 and 3). Standardizing to single constituent markers is an attempt to produce a quality product. For example, the standardized extract for St. John's wort is 0.3% hypericin. However, the evaluation of herbal products on store shelves has shown that there is variability in the standardized ingredient despite claims of quality.
2. **Dosing.** The dosing of herbal dietary supplements is highly variable and depends on the production method and the dosage form of the specific supplement. For example, you can find black cohosh, an herbal dietary supplement used for menopause, in the following forms: tablet, standardized to the marker, 27-deoxyacteine: 1–2 mg daily; powdered rhizome: 40–200 mg daily; tincture (1:10 preparation in 60% alcohol): 0.4–2 mL daily; fluid extract (1:1 preparation): 3–4 mL twice daily; solid (dry powdered) extract (4:1 preparation): 250–500 mg daily; alcohol-based extracts, 40%–60% (v/v).

B.

Herbs have been in use for thousands of years throughout the world. In Germany, herbs are more regulated and part of conventional medical training. Much of the research that we currently have on herbs comes from other countries. Many studies exist, but most of these are not the double-blind, placebo-controlled trials that are done on pharmaceuticals before bringing them to patients. Currently, the National Institutes of Health funded research on a variety of herbs and dietary supplements. However, the reality is that it is impossible to patent what your neighbor can grow in his or her back yard. Therefore, little financial incentive exists to do the kind of research on herbs that is done with pharmaceuticals.

Patients use herbs and other dietary supplements to both prevent and manage disease and often take them concurrently with prescription medications. Studies show that patients often do not tell their physicians what herbs they are taking. Physicians are encouraged to ask about herbs and other dietary supplements when inquiring about a patient's medications.

Table 22.3-1. Some commonly used herbal products: uses and precautions[a]

Herb	Most common uses	Dose	Interactions/precautions/contraindications
Black cohosh *Cimicifuga racemosa*	Used to manage the symptoms of menopause, best studies in Germany for up to 6 mo. Used for premenstrual symptoms and dysmenorrhea, less well studied. Used to induce menses, poor studies	Clinical studies have used a commercially prepared standardized extract from Germany, Remifemin, 20-mg tablet BID	Maximum effect achieved in 4–8 wk. Limit use to 6 mo (German Commission E). Evidence of estrogenic activity is conflicting. German in vitro studies show that Remifemin amplifies tamoxifen's induced proliferation inhibition on the estrogen receptors of breast cancer cells. However, the following are uncertain: (a) if black cohosh has estrogen-like protection for osteoporosis or cardiovascular diseases; (b) if black cohosh can be combined with hormone replacement therapy; (c) if patients with a uterus need progesterone protection for endometrial cancer prevention. Contraindicated in pregnancy and breast-feeding. Side effects: mild GI Black cohosh is not blue or white cohosh.
Echinacea *Echinacea angustifolia* or *E. pallida* or *E. purpurea*	Used orally to prevent or treat URIs. Limited studies suggest nonspecific immune stimulant activity. Used topically for wound healing in burns and abscesses.	Dosing depends on *Echinacea* species, plant part, and extraction process. Echinacea root extract of 1:5 tincture with 50% ethanol is indicated in Germany for the supportive treatment of flu-like infections at a dose equivalent to 900 mg of crude drug daily. Echinacea juices are indicated for the supportive treatment of recurrent upper and lower respiratory infections at a dose of 6–9 mg/d.	German Commission E recommendations: (a) limit use to 8 consecutive weeks; (b) discourage use in individuals with immune or autoimmune illnesses, such AIDS, HIV infection, multiple sclerosis, and tuberculosis. (Controversial because no studies demonstrate or confirm this.) Avoid in patients allergic to Asteraceae/Compositae family (ragweed, chrysanthemums, marigolds, daisies, etc.). Anaphylactic reactions have occurred. In Germany, intravenous formulations may compromise diabetes control. Not demonstrated in oral echinacea formulations. May inhibit oocyte fertilization and alter sperm DNA and should be avoided in couples attempting to conceive. Side effects: some GI
Garlic *Allium sativum*	Used for lowering mild hypertension and cholesterol.	One raw clove per day. Prolonged cooking will inactivate the ingredients thought to be beneficial. Benefits in studies from garlic in pill form have been conflicting because different processes have been used to prepare garlic pills, resulting in pills with different pharmacologic actions.	Safe in amounts consumed in food. Some products may have antithrombotic activity, so avoid use in patients taking anticoagulants. Can lower blood glucose in diabetics. Undesirable garlic taste and smell can occur even with so-called "odorless" products.

Ginkgo *Ginkgo biloba*	Used to improve memory in mild to moderate dementia (good studies). Less evidence, but possibly effective for use in peripheral vascular disease, reversing SSRI-induced sexual dysfunction (men and women), and treatment for depression in the elderly. Claims to improve mental alertness and overall brain function are unsubstantiated.	120–240 mg/d of concentrated standardized extract.	Side effects include mild GI complaints, headache, dizziness, palpitations, and allergic skin reactions. Large doses might cause restlessness, diarrhea, nausea, vomiting, lack of muscle tone, and weakness. Bleeding is often mentioned as a side effect of ginkgo, but very few cases have been reported. Until further studies are performed, patients on NSAIDS, aspirin, or anticoagulants should avoid ginkgo. To avoid transient headache and dizziness, start with low dose and increase over 8 wk.
Ginger *Zingiber officinale*	Used for motion sickness and joint pain, studies show possible effectiveness. Used to reduce postoperative nausea and vomiting, conflicting evidence. Prevention and treatment of chemotherapy-induced nausea, no conclusive data. Use for nausea in pregnancy is controversial, no conclusive evidence of safety.	For motion sickness: 1-g tablet or capsule 30 min prior to travel, then 1/2 g every 4 h. Maximum dose 4 g/d	Caution in patients with gallstones, ginger increases flow of bile. Large doses can cause heartburn. Inhibits platelet aggregation: clinical significance and/or potential interaction with anticoagulants, unknown.
Ginseng Several species, e.g., *Panax ginseng*	Used to improve the body's response to stress. Called an "adaptogen." Many studies of poor quality.	Preparations vary widely.	When considering reports of adverse reactions, keep in mind that ginseng has been the most commonly adulterated herbal product in the United States Reports of adverse reactions include breast tenderness in women; nervousness, excitation, heart palpitations, insomnia, and increased blood pressure; postmenopausal bleeding. Germany recommends limiting duration of use to 3 mo because of the possibility of hormone-like or hormone-inducing effects. Antiplatelet effects, be careful with blood-thinning drugs. May have hypoglycemic effects.

Kava *Piper methysticum*	Used for anxiety, restlessness, stress and muscle relaxant, poor studies.	Extracts standardized to 30% or 70% kava lactones. Doses vary, usually 100–300 mg/d.	May reduce reaction time while driving. Alcohol should not be consumed concomitantly. May have additive CNS depressant effects with prescription tranquilizers, muscle relaxants, valerian, St. John's wort. No evidence for physical dependence. Heavy, prolonged use can result in dermatitis. High doses can result in a drunken-like state. Avoid in pregnancy, lactation, and depression.
Ma huang *Ephedra sinica*	Commonly used today in the United States as an appetite suppressant. Primary active ingredient is the alkaloid ephedrine. Ephedrine produces amphetamine-like actions: stimulates CNS, produces mydriasis, enhances myocardial contraction and heart rate, causes bronchodilation, decreases GI motility, and stimulates peripheral vasoconstriction with an associated rise in blood pressure.	The FDA recommends using ephedra-containing products for a maximum of 7 d and in amounts not exceeding 8 mg of ephedrine every 6 h or 24 mg/d. (Much more is consumed if patients follow the instructions for Metabolife.)	Not recommended for weight loss. The FDA issued warnings against the use of ephedra as an appetite suppressant and advises that intake over the recommended amount may result in heart attack, stroke, seizure, or death. The FDA prohibits the marketing of ephedrine with other CNS stimulants, such as caffeine and yohimbine. However, herbal weight loss products package ma huang with guarana, a caffeine-containing herb.
Milk thistle *Silybum marianum*	Fruit and seed promoted for treatment of acute and chronic liver conditions by the German Commission E. Studies show likely effective when used orally for dyspeptic complaints, bile duct inflammation, and treating toxic, inflammatory, or chronic liver conditions (cirrhosis due to hepatitis, alcohol, or drugs, etc.).	Daily dose of 200–400 mg standardized by the amount of silymarin extract (70%–80%).	No serious adverse effects have been seen with milk thistle. Can cause an allergic reaction in individuals sensitive to the Asteraceae/Compositae family (ragweed, chrysanthemums, marigolds, daisies, etc.) Silymarin decreases elevated serum transaminase laboratory values.

Saw palmetto *Serenoa repens*	Used for the symptoms of BPH. Clinical studies provide evidence of moderate scientific quality that commercial extracts of saw palmetto are more effective than placebo in relieving lower urinary tract symptoms of BPH, frequency, urgency, dysuria, nocturia, and impaired urinary flow. Improvement of symptoms can take up to 2 months of treatment.	Daily dose 320 mg or 160 mg bid of a commercial liposterolic extract standardized to 70%–95% free fatty acids.	No reported side effects or drug interactions. Contrary to earlier warnings, saw palmetto has no significant effect on serum prostate-specific antigen levels. It does not affect overall prostate size, but shrinks the inner prostatic epithelium and may have anti-inflammatory and antiandrogen properties. Studies show no side effects or drug interactions, but be aware of potential α-adrenergic or endocrine blocking effects. Simultaneous use with prescription medications to treat BPH like finasteride is not recommended.
St. John's wort *Hypericum perforatum*	Orally for mild to moderate depression Topically, oil preparations used for bruises, burns and neuralgia.	Adults: Up to 1,000 mg daily, standardized to 0.3% Commercial products available in whole-herb form; also standardized to hypericin and hyperforin.	Superior to placebo and as effective as low-dose TCAs and possibly as effective as SSRIs. Associated with fewer side effects than synthetic antidepressants Do not use in pregnancy: historical records include St. John's wort in herbal formulas for inducing abortion. Animal studies show slight uterine effects.
		Pediatric: 200–400 mg/d. German Commission E does not recommend use in children younger than 12 yr.	Possibly increases photosensitivity in patients with fair complexions. Reports suggest that St. John's wort extracts are potent inducers of hepatic enzymes. St. John's wort can decrease plasma cyclosporine levels (reports of transplant rejections); reduce serum digoxin, theophylline, and amitriptyline levels; decrease protease inhibitors (indinavir); and decrease the effectiveness of warfarin. Breakthrough bleeding in women on oral contraceptive pills; unknown if this results in contraceptive failure.
Dietary supplements			
Creatine	Used to increase physical muscle performance during brief, high-intensity exercise or work	Dose: 20–30 g/d for 1 wk max., then 3 g/d maintenance	Creatine is present in red meat and is synthesized in the body from arginine, glycine, and methionine. It is metabolized to creatinine. Vegetarians, those without a large dietary intake of creatine, and untrained athletes gain the most advantage. Side effects include mild GI and muscle cramping. Dehydration is a risk because creatine causes muscles to retain water. Therefore, hydration is important when using creatine. The effects of chronic creatine administration have not been adequately studied.

Chromium	May benefit patients with type 2 diabetes mellitus who are chromium deficient but use limited because currently no reliable diagnostic test exists to determine chromium deficiency. Potentiates insulin action, increasing insulin receptor sensitivity. American Diabetes Association says, "The only known circumstance in which chromium replacement has a beneficial effect on glycemic control is for people who are chromium deficient as a result of long-term parenteral nutrition. However, it appears that most people with diabetes are not chromium deficient and therefore chromium supplementation has no known benefit." (1998)	Currently don't know the content of chromium in the U.S. diet or how to monitor chromium levels or status. Studies have looked at doses of 175–1000 µg/d. The recommended daily allowance is 50–200 µg. Chromium picolinate is the most easily absorbed form.	Studies show benefit in gestational and type 2 diabetes mellitus. In 19 randomized controlled trials in which individuals received between 175 and 1,000 µg/d chromium for duration of 6–64 wk, there was no evidence of any toxic effects. Lowers the hyperglycemia caused by steroids. No adverse reactions reported.
Glucosamine sulfate	Used to manage pain, inflammation and to retard or reverse degenerative joint changes in osteoarthritis.	500 mg tid. Takes at least 1 mo to see results. Although chondroitin sulfate and glucosamine sulfate are frequently marketed together, there is no evidence that the combination has greater benefit than either product alone.	Compared head to head with NSAIDs and shown to be as effective, with fewer side effects. Takes longer to achieve benefit with glucosamine, but benefits persist longer. Few side effects; possible constipation. Animal studies show increases insulin resistance: clinical significance unknown. Many of the "joint mixtures" also contain potassium.
Omega-3 fatty acids	Used for a variety of inflammatory-related conditions	Fish oil: Doses vary, 1–4 g/d; capsules typically contain EPA and DHA fish oil.	Adverse effects: Some of the supplements have other vitamins and minerals added. When used with anticoagulants, NSAIDs, and aspirin, can increase bleeding risk. Lowers blood sugar.

Flax seed oil Fish oil	Insufficient evidence Likely effective for modest antihypertensive effect and decreased mortality after myocardial infarction (29%–42%). Has been shown with one fish meal a day or fish meal as well as fish oil capsules. American Heart Association recommends use with triglycerides >1,000. Possible effectiveness: Rheumatoid arthritis: modest but significant improvements in joint symptoms and decreases the amount of NSAIDs needed. GI: lowers relapse rate of Crohn's. GU: treat painful menses, to prevent recurrent miscarriage associated with antiphospholipid antibodies. To treat symptoms of chronic fatigue syndrome; to reduce albuminuria in individuals with diabetic nephropathy; when taken orally with other therapy for bipolar disorder. Pulmonary: lowers smokers' risk of chronic obstructive pulmonary disease. It has been suggested that depletion of omega-3 fatty acids may be of etiologic importance in depression, aggression, schizophrenia, and other mental and neurologic disorders. Studies are ongoing. Ineffective for asthma, lupus, atopic dermatitis, psoriasis	Flax seed oil: 1 tbs of oil or capsule bid-tid. Oil must be refrigerated and cannot be used in cooking. Polyunsaturated fatty acid—precursor.	Potential side effects: fishy odor, GI upset. May increase bleeding time. Increase in calories and weight gain May increase LDL cholesterol in some individuals (meta-analysis and summary of trials showed an average of 4 g/day increased LDL by 5%–10%) May decrease immune response. Unrefined fish oil preparations may contain pesticides.

* Other possibilities to include with reasonable studies of effectiveness are grape seed extract, valerian, and coenzyme Q10.
BPH, benign prostatic hypertrophy; CNS, central nervous system; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; URI, urinary tract infection.

II. Some commonly used products.

Table 22.3-1 lists most common uses and precautions/contraindications/interactions for herbal dietary supplements. There are a variety of dosing forms available for each of these products in stores. We have limited doses to the form and dosage used in the best studies.

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3. *The Review of Natural Products by Facts and Comparisons.* St. Louis: Wolters Kluwer, 1999.

Web Addresses

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US Pharmacopeia: http://www.usp.org/

FDA: http://vm.cfsan.fda.gov./

22.4
PAIN MANAGEMENT

Janey M. Purvis

I. Overview

A.

Pain is one of the most common presenting complaints. Pain may be acute or chronic, and may be related to trauma, disease, or operative procedures. Up to 30% of Americans have chronic pain at any time. Common sites of chronic pain are low back, joint, neck, head, abdomen, pelvis, and peripheral nerves (postherpetic and trigeminal neuralgia). Chronic pain is 1.5 times more common in women, increases with age, and more than two thirds of those with chronic pain experience pain in two or more sites.

B.

Pain has an enormous impact on the patient's physical, psychological, social, and occupational functioning. Chronic pain is associated with increased psychiatric disorders and socioeconomic hardships. Society is affected by loss of productivity and excessive health care expenditures.

C.

Desite well studied guidelines and effective treatments, acute and chronic pain remain grossly under-treated. Pain management is now a priority for healthcare advisory and regulatory boards.

D.

Barriers to adequate pain management include: 1) lack of knowledge in the use of opioids (narcotic analgesics); 2) concerns about opioid safety and side

effects; 3) concerns about dependence, addiction and abuse of controlled substances; and 4) fears of regulatory scrutiny.

II. Pain assessment

A.

The standardized assessment of pain remains underutilized and is essential to guide treatment. Pain assessment scales are used for acute and chronic pain. They are simple, have proven valid for measuring pain despite its complex nature, and are most accurate and reliable if patient reported. The Numeric Pain Scale is most commonly used, but the Visual Analog Scale or the Wong-Baker Face Pain Scale may be used for children, elderly, or semiconscious patients who may give less reliable responses (Fig. 22.4-1).

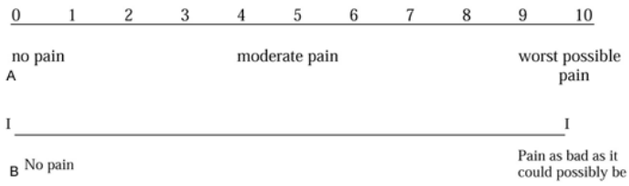

FIG. 22.4-1. Pain assessment scales. A: 0–10 numeric pain intensity scale. B: Visual analogue scale.

III. Acute pain.

Definition: “Normal, predicted physiological response to an adverse chemical, thermal, and mechanical stimulus and is associated with surgery, trauma and acute illness. Generally time limited.…”(1).

A.

Acute pain management goals are to relieve patient discomfort while facilitating recovery.

B.

A flexible and practical treatment plan must be discussed with the patient and family in the acute or preoperative setting. Specialist consultation is required if spinal analgesia, complex neural blockade, or continuous analgesic infusion is considered. Postoperative patient-controlled analgesia (PCA), self-administration of intravenous opioids, is effective and well accepted. Preemptive pain treatment for surgery is effective in the reduction of postoperative pain.

C.

Acute pain is managed predominantly by medications alone. Other modalities, such as immobilization, ice, heat, massage, relaxation, and transcutaneous electrical nerve stimulation (TENS), may be helpful.

D.

Opioid addiction, tolerance, dependence, and abuse (see chronic pain) are rare in acute pain settings.

E.

Initial pain intensity assessment based on pain scales will guide management. Regular reassessment must be performed and documented at appropriate intervals and after each intervention.

F.

The World Health Organization (WHO) Analgesic Ladder provides a basis for pain management depending on intensity level. If used appropriately, 80%–90% of pain is controllable. Dosing should be scheduled regularly; however, as acute pain wanes, smaller doses or weaker analgesics are used (Table 22.4-1).

Step 1: Mild pain (0–3 on Pain Assessment Scale)
Nonopioid
± adjuvant
Step 2: Moderate pain (4–6 on Pain Assessment Scale)
Weak opioid + nonopioid
± adjuvant
Step 3: Severe pain (7–10 on Pain Assessment Scale)
Strong opioid + nonopioid
± adjuvant

Table 22.4-1. The World Health Organization Analgesic Ladder

IV. Chronic pain

A.

Definition: “a pain state which is persistent and in which the cause of the pain cannot be removed or otherwise treated.… May be associated with a long-term incurable or intractable medical condition or disease” (1).

B.

Chronic pain is no longer felt to be prolonged acute pain. Recent advances in the neurobiology of chronic pain reveal profound changes in pain information processing by sensitized peripheral and central neurons, resulting in altered detection, sensitivity, activation, excitation, and inhibition of the

pain pathways. What triggers these changes is unclear. Pain perception is modulated by emotional and psychological aspects, also known to have a neurobiologic basis.

C.

Management goals are to improve function and quality of life. Management plans must be individualized and include patient education, medication, physical and psychological therapies.

D.

Initial evaluation includes a complete history and physical examination, noting prior investigations, surgical procedures, consultations, treatments, and responses. Pain assessment includes pain intensity (based on pain scales), duration, character, location, relief and stimulus factors. Assessment includes the impact of pain on sleep, psychological status, physical, personal, social, and occupational functioning.

E.

Medication management is based on the WHO Analgesic Ladder (Table 22.4-1). Adjuvant medications play a key role in management due to their analgesic properties, ability to enhance analgesic effects, and effectiveness for specific symptoms such as sleep disorders, depression, and neuropathicpain (pain described as burning, shooting, or lancinating, generally less responsive to opioids).

F.

Chronic opioid use requires careful consideration. *Addiction* is defined as a neurobehavioral syndrome with genetic and environmental influences that results in psychological dependence on the use of substances for their psychic effects and is characterized by compulsive use despite harm. Research shows that addiction risk in pain treatment is low (i.e., less than 20%, decreasing to 10% when a narcotic contract is used and increasing with a history of drug addiction or alcoholism). Consultation with an addiction specialist may be indicated. *Drug dependence*is a state of neuroadaptation that is characterized by the emergence of a withdrawal syndrome if drug use is stopped or decreased abruptly, or with antagonist administration. It is an expected result of opioid use. *Tolerance* is a physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce the same effect or a reduced effect is observed with a constant dose. Dependence or tolerance does not equate with addiction. *Abuse* is the use of a drug for nonmedicinal purposes, which causes harm to the self or others. An opioid contract, signed by patient and physician, defines the prescribing conditions (who writes the prescriptions, the dispensing pharmacy, rules regarding lost or stolen scripts, telephone requests, early refills, escalating drug use, and the repercussions of breaking the contract).

G.

Regulatory agencies and state boards now emphasize appropriate, effective pain management. Pain may be managed with controlled substances without fear of discipline by adhering to the following guidelines. The physician must (a) perform a complete evaluation, as in IV.D above, with thorough documentation, including indications and justification for chronic opioid use; (b) document a treatment plan, investigations, and responses to interventions; (c) document and sign the discussion of the risks and benefits of drug use (material risk notice) and develop a narcotic contract, especially if

addiction risk is high; (d) periodically review and revise the treatment plan; (e) refer to a specialist for evaluation and treatment suggestions (required in some states); (f) maintain accurate and complete records that are accessible and available for review; and (g) comply with state Drug Enforcement Administration (DEA) rules.

H.

Psychological treatments include therapy for depression and anxiety (up to 60% of chronic pain patients), cognitive behavioral therapy, goal setting, and relaxation techniques (biofeedback, yoga, meditation, and hypnosis).

I.

Physical treatments include physical therapy, manipulation, exercise, and TENS.

J.

Surgical therapies include nerve blocks, trigger point injections, and spinal infusions.

K.

Alternative therapies, such as acupuncture, reflexology, and chiropracty, are increasingly popular.

L.

Pain clinics are increasing in number in the United States and elsewhere. They use a multidisciplinary approach to pain management and are proving to be cost effective. Referral to a pain clinic is indicated if the patient is very difficult to manage, treatments have proven ineffective, or for consultant advice.

V. Pharmacologic therapy

A. Nonopioids

(nonsteroidal anti-inflammatory drugs, NSAIDs)

1. All NSAIDs are effective for mild to moderate pain. If ineffective at maximum dose, change drug or progress to step 2 medications.
2. NSAIDs adversely affect the kidney, gastrointestinal mucosa, and coagulation. Risk increases in patients with congestive heart failure, renal or liver dysfunction, and in those older than 75 years.
3. Chronic use can cause gastritis, peptic ulcer disease, and renal insufficiency. Gastrointestinal complications are higher in patients older than 60 years, those with prior peptic ulcer disease, and those who use steroids chronically. Consider cytoprotection in long-term use. Gastric side effects are lower with cyclooxygenase-2 (Cox-2) inhibitors (Vioxx and Celebrex), but decreased renal effects, although suggested, have not yet been established (Table 22.4-2).

NSAID	Usual dosage	Maximum dose/d	Comments
Acetylsalicylic acid (aspirin, Empirin)	325–650 mg q4h	4,000 mg	R,G
Celocoxib (Celebrex)	100 mg bid	400 mg	CI sulfa allergy
Choline magnesium trisalicylate (Trilisate)	1,000–1,500 mg bid	3,000 mg	S
Diclofenac–misoprostol (Arthrotec)	50/200 mg tid	225 mg diclofenac	CI in pregnant
Ibuprofen (Motrin, Advil, Nuprin)	400–600 mg tid-qid	2,400 mg	S
Indomethacin (Indocin, Indocin SR)	25–50 mg tid SR 75 mg bid	200 mg	R, S, G
Ketorolac (Toradol)	10 mg q4–6h	40 mg	G, up to 5 d
Ketorolac (IM/IV)	15–30 mg q6h	120 mg	G, up to 5 d
Nabumetone (Relafen)	1 g qd-bid	2 g	
Naproxen (Naprosyn, Aleve, Anaprox)	250–500 mg bid	1,500 mg	S,G
Rofecoxib (Vioxx)	25–50 mg qd	50 mg	S
Salsalate (Disalcid, Salflex)	1,000 mg bid-tid	3,000 mg	G
Acetaminophen (Tylenol, Panadol, Tempra)	325–650 mg q4h	4,000 mg	R,S,G; liver toxicity in healthy adults > 10 g, caution with heavy alcohol use, safe in pregnancy and renal dysfunction, safe with stable mild liver disease.

CI, contraindicated; G, generic available; NSAID, nonsteroidal anti-inflammatory drug; R, rectal dosing available; S, suspension available.

Table 22.4-2. Commonly prescribed NSAIDs and dosages

B. Weak opioid + nonopioid

1. The maximum allowable dose of the nonopioid component limits the amount of the combination drug that can be used.
2. Dose is titrated to effect and side effects. Constipation is inevitable. Treat preemptively with a bowel program. Respiratory depression tends to be short lived, is antagonized by pain, and occurs in the opioid naïve. Nausea and sedation resolve over time, recur with dose increases (Table 22.4-3).

Codeine (DEA III)
+ ASA:
Empirin #3 (325/30) 1–2 tabs q4h
Empirin #4 (325/60) 1–2 tabs q4h
+ Acetaminophen:
Tylenol #2 (300/15) 1–2 tabs q4h, G
Tylenol #3 (300/30) 1–2 tabs q4h, G
Tylenol #4 (300/60) 1–2 tabs q4h, max. 6 tabs qd, G
Hydrocodone (DEA III)
+ ASA:
Lortab ASA (500/5) 1–2 tabs q4h
+ Acetaminophen:
Hyco-pap (500/5) 1–2 tabs q4–6h
Lorcet 10/650 1 tab q4–6h, max. 6qd
Lorcet HD (500/5) 1–2 tabs q6h, max. 8qd
Lorcet Plus (650/7.5) 1–2 tabs q6h, max. 6qd
Lortab (500/2.5) 1–2 tabs q4–6h, max. 8qd
Lortab 10 (500/10) 1–2 tabs q4–6h, max. 8qd
Lortab (7.5/500) 1–2 tabs q4–6h, max. 8qd
Lortab (5/500) 1–2 tabs q4–6h, max. 8qd
Vicodin (500/5) 1–2 tabs q4–6h, G
Vicodin E-S (750/7.5) 1 tab q4–6h
Vicodin HP (660/10) 1 tab q4–6h, G
+ Ibuprofen:
Vicoprofen (7.5/200) 1 tab q4–6h
Oxycodone (DEA II)
+ ASA:
Percodan (325/4.5) 1 tab q6h
Percodan-Demi (325/2.25) 1–2 tabs q6h
+ Acetaminophen:
Percocet (325/5) 1–2 tabs q4–6h
Roxicet (325/5) 1 tab q6h, G
Tylox (500/5) 1 tab q6h, G
Propoxyphene (DEA IV) (Has abuse potential and no analgesic advantage over non-opioids, few indications for use.)
+ Acetaminophen:
Darvocet-N50 (325/50) 2 tabs q4h, G
Darvocet-N100 (650/100) 1 tab q4h
Tramadol (Ultram) nonopioid for moderate to severe pain, 50–100 mg q4–6h, max. 400 mg qd; caution in elderly, renal and liver dysfunction; avoid in opiate dependent; seizures may occur with antidepressants.

ASA, acetylsalicylic acid; DEA II, high addiction potential; DEA III, moderate; DEA IV, minimal; G, generic preparation available.

Table 22.4-3. Scheduled drugs based on addiction potential

C. Opioids

1. “Cornerstone of therapy for moderate to severe pain” (5).
2. Caution in decreased renal function and elderly.
3. Chronic use may lead to addiction, tolerance, dependence, or abuse.
4. Regular dosing with long acting agent is best for constant chronic pain, with short acting agent for breakthrough, acute, or episodic pain.
5. Oral and transdermal routes are easiest for chronic pain.
6. Appropriate dose is that which relieves pain (no maximal dose).
7. Meperidine (Demerol) is not recommended due to short action, production of toxic metabolite, and poor oral efficiency.
8. Starting doses are lower than equianalgesic doses given below.
9. All DEA II (Table 22.4-4)

	Equianalgesic doses		
Drug	Oral	Parenteral	Comments
Morphine	30 mg q3–4h	10 mg SC/IM/IV q4h	R 10–20 mg q4h, S,G
Long acting (MS Contin, Oramorph)	15–30 mg q8–12h	N/A	Do not cut/chew/crush
Codeine	60 mg q3–4h	75 mg SC/IM q3–4h	
Oxycodone (Roxicodone)	30 mg q3–4h	N/A	S,G
Long acting (OxyContin)	10 mg q12h	N/A	Increase dose q1–2d
Hydrocodone	30 mg q3–4h	N/A	
Hydromorphone (Dilaudid)	7.5 mg q3–8h	1.5 mg IV/SC/IM q3–4h	R,G
Levorphanol (Levo-Dromoran)	4 mg q6–8h	2 mg SC q6–8h	G, half-life 6h
Methadone (Dolophine, Methadose)	20 mg q6–8h	10 mg SC/IM q6–8h	G, potent, inexpensive
Fentanyl (Duragesic), transdermal	25–100 μg q72h, start at 25, increase q3–6d, rotate sites, takes 12 h;		
Actiq transmucosal lozenges	600 μg lozenge, max. 4qd		

Agonist–antagonists: Pentazocine (Talwin) and butorphanol (Stadol) have limited use due to limited effectiveness, short action, associated dysphoria, and abuse potential. G, generic preparation available; R, rectal dosing available; S, suspension available.

Table 22.4-4. Equianalgesic doses (DEA II)

D. Adjuvant medications

1. Antidepressants. Use to manage depression, anxiety, sleep disturbance, and neuropathic pain. May have some analgesic properties. Role of selective serotonin reuptake inhibitors is unclear.
   a. Amitriptyline (Elavil): start at 25–75 mg qhs, up to 300 mg qd.
   b. Desipramine (Norpramin): start at 25–50 mg qhs, up to 300 mg qd. Lower side effects than other tricyclic antidepressants.

2. Anticonvulsants
   a. Gabapentin (Neurontin): start at 300 mg qhs, up to 1,200 mg tid. Effective for neuropathic pain.
   b. Carbamazepine (Tegretol): start at 100 mg bid, up to 400 mg tid. Complete blood count at initiation of drug, at 3 and 6 months.
   c. Baclofen (Lioresal): muscle relaxant:, start at 5 mg tid, maximum 20 mg tid.
   d. Capsaican (Zostrix) 0.75% topical: apply tid-qid. May cause burning, erythema, or hyperalgesia.

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Internet Sites

1. http://www.painmed.org/

2. http://www.aapainmanage.org/

3. www.medsch.wisc.edu/painpolicy

4. www.fsmb.org/pain.htm.

22.5
TERMINAL CARE

Marc Tunzi

Jessica H. Muller

Everybody dies. The aim of terminal care is to make this last transition in life as easy as possible for dying patients and their families. Physical, psychological, and social problems should be prevented, when possible, and managed actively, when not (1). Death is not failure; inattentiveness to dying patients is failure. Terminal care generally refers to the medical care of patients with a life expectancy of 6–12 months or less. Many aspects of terminal care planning apply to everyone but especially to geriatric patients and to patients with chronic diseases. Similarly, certain aspects of terminal care symptom and problem management apply to patients who may be severely ill but are not yet considered terminal.

I. Communication and planning issues

B. Break bad news in a quiet, unhurried, comfortable setting.

Find out what patients know, and how much they want to know, before delivering information in a sensitive but straightforward manner, using clear language. Check for patients' understanding and emotional response. Schedule follow-up (2).

C. The goals of care

for terminal patients and their families are to maximize comfort and function and to minimize pain and suffering. Achievement of these goals relies on effective communication and planning.

1. Discuss the goals of care with competent patients. When possible, patients should be empowered to control their treatment and to resolve conflicts regarding incompatible goals of care.
2. Discuss treatment goals with families and friends after discussing them with patients first. Exceptions to this are when it is not possible to communicate directly with patients (see Section I.B.4) and when patients explicitly want family present for the discussion.
3. Be sensitive to cultural differences in terminal care values and practices. In addition to encouraging patients and families to consider community resources and pastoral care, clinicians must be sensitive to how their own social, moral, and religious values influence their life-and-death decision making.

4. “Be there.” All patients and families experience a wide range of emotions during the dying process. Anger, denial, depression, and bargaining are typical reactions (3). In addition, personal psychosocial problems, interpersonal family relationships, and the timeline of the death (whether chronic or acute) all influence how patients and families react. The physician's presence and validation of these reactions can be therapeutic for all involved.

D. Ethical planning issues.

Addressing patients' desires about terminal care and life-sustaining treatment should be part of health care maintenance performed during regular office visits. These issues may be introduced as a sort of “informed consent” for the future by making such statements as, “I discuss life-sustaining treatments and advance directives, such as the living will and the power of attorney for health care, with all my patients; do you have any questions about them” or “I discuss medical values with all my patients; have you ever discussed them with your family”

1. Personal values ultimately guide patient decision making. Patients must be asked whether they want to live at all costs or whether they might compromise some life expectancy for a better quality of life. They must also weigh a variety of other potentially competing values, such as maintaining mobility and physical independence, maintaining the ability to think clearly and communicate with others, being treated in accordance with their religious beliefs, not becoming a burden on family, and avoiding unnecessary pain and suffering.
2. Advance directives are written or oral instructions given that enable patients to guide their future health care decisions in the event that they cannot do so themselves.
   a. Living wills are documents that allow patients to choose one of two or three scenarios for their terminal care (choices vary by state): Do everything medically possible to maintain life; do no extra ordinary intervention but maintain comfort and allow death to occur “naturally”; or do no extraordinary intervention but continue nutrition and hydration in addition to other comfort care. In most states, laws require a patient to be diagnosed as terminal (prognosis less than 6–12 months) by two physicians for a living will to be legally binding.
   b. Durable powers of attorney for health care (DPAHC) are legal documents that enable patients to appoint another specific individual (known as a proxy, agent, or surrogate) to make decisions for them, should they be unable to do so for themselves. These documents are most effective when patients and their surrogates have thoroughly discussed treatment options so that the standard of substituted judgment may be applied (see Section I.B.4). Patients do not need a lawyer to complete a DPAHC.
   c. Oral directives are the most common kind of advance directives and are often sufficient in guiding terminal care decisions. Unfortunately, the legal benefits of oral directives to family and friends vary by state and may not be upheld in cases of a family dispute or family-physician disagreement. Oral directives to physicians, on the other hand, *when clearly documented in the medical record*, are usually honored by the courts. This documentation should include a description of the patient's medical condition and clear evidence of the patient's decision-making capacity (see Section I.B.3) (4).
3. Medical decision-making capacity refers to the ability to make a rational decision on medical treatment options. Capacity should be viewed on a sliding scale; a patient may have the ability to understand and make decisions about some treatment options but not others, and should be reevaluated for each pending decision. Determining capacity requires assessment of a patient's ability to accept responsibility for making the treatment decision; to understand the medical situation

and prognosis; to understand the alternatives for care; to communicate a clear decision from those alternatives; and to discuss how the decision fits his or her general goals and values. Appropriate questions include, “What can you tell me about your condition” “What is your understanding of this treatment and why do you think it is right for you” “What can you tell me about the alternatives we've discussed”

4. Surrogacy. When an individual does not have medical decision-making capacity, surrogate decisions must be made. When possible, a legal surrogate, appointed by the patient in a DPAHC, should make decisions. A living will or other clearly documented advance directive may also guide care. When these are not available, surrogate decision makers should generally follow the traditional family hierarchy: spouse, parents or children, siblings, other relatives, and friends. The two standards most often used for making surrogate decisions are substituted judgment (“If the patient were still able to make decisions for herself, what would she want in this situation”) and best interests (“What do you think is the best thing to do for the patient, all things considered”). Of the two, substituted judgment is usually thought to be superior, although it requires intimate knowledge of the patient to be accurate. It also produces less guilt because it focuses the decision-making process back on the patient and away from the family.

II. Medical care issues

B. Symptom and problem management

should focus on comfort and function, not on achieving a particular physiologic effect. Information about symptoms must be solicited; patients may be too afraid, proud, weak, or tired to divulge symptoms on their own but will usually discuss them if asked (5).

1. **Pain** should be prevented, when possible (e.g., pain due to bedsores or futile treatments), and treated promptly, when not (also see Chapter 22.4). Before treating, however, other symptoms should be assessed as well; sometimes “pain” is really anxiety, fatigue, loneliness, nausea, constipation, or other condition. When prescribing pain medications, low-potency agents should be used first and advanced quickly as needed. Side effects (epigastric burning, nausea, constipation, unwanted sedation) should be monitored closely. Both duration of action and the best delivery system (liquid, pill, tablet, rectal suppository, transdermal) should be carefully considered. The routine use of pain medication in terminal patients is much more effective than “as needed” (prn) use and is preferred. Drug dependency is not an issue. As-needed pain medication should be reserved for pain above a patient's baseline. Medication choices include acetaminophen, 650–1,000 mg PO q4–6h; ibuprofen, 600 mg PO tid, or other nonsteroidal anti-inflammatory agent; acetaminophen with codeine, 30–60 mg PO q4–6h; acetaminophen with hydrocodone, 5–10 mg PO q4–6h; acetaminophen with oxycodone, 5–10 mg PO q4–6h; slow-release oxycodone (OxyContin), 10–40 mg PO q12h; hydromorphone (Dilaudid), 2–4 mg PO or 3 mg PR q6–8h; morphine sulfate syrup, 10–15 mg PO q4h; slow-release oral morphine (MS Contin, Oramorph SR), 30–60 mg PO bid; fentanyl (Duragesic) patch, 25–100 µg/h q72h; or fentanyl transmucosal lozenge (Actiq), 200–1,600 µg qid.
2. **Agitation and anxiety** may be due to hypoxemia, pain, or a specific patient fear (see Chapter 5.1). Treatment, when needed, will depend in part on the patient's other symptoms: Some pain and nausea medications, for example, may also be anxiolytic. Treatment may also depend on how much sedation is wanted. Medication choices for treating anxiety and agitation include diphenhydramine, 25–50 mg PO tid-qid; short-acting benzodiazepines, such as lorazepam, 1–2 mg PO, or alprazolam, 0.25–0.5 mg PO bid-qid; sedating antidepressants, such as amitriptyline, 10–100 mg PO at bedtime, or trazodone, 50–100 mg PO

bid-tid; and neuroleptics, such as haloperidol, 1–5 mg PO bid-tid, thioridazine (Mellaril), 25–50 mg PO bid-tid, risperidone (Risperdal), 0.5–4 mg PO bid, or olanzapine (Zyprexa), 2.5–10 mg PO qd.

3. **Nausea and vomiting** may be due to constipation or gastritis, diets of excessive volume, or diets that may have become intolerable (e.g., dairy products). Choices for antinausea medication include prochlorperazine (Compazine), 5–10 mg PO qid or 25 mg per rectum (PR) bid-tid; metoclopramide (Reglan), 5–10 mg PO qid; or ondansetron (Zofran), 4–8 mg PO, via tablets or solution, q12h. Droperidol (Inapsine), 0.5–2.0 mg IV or IM, or ondansetron 4 mg IV over 2–5 minutes may be used for refractory vomiting.
4. **Constipation** may occur naturally, be caused by bowel obstruction, or be caused by opiate medications. If tolerated, increasing dietary fiber, either naturally or with supplements such as psyllium, may help. Phenolphthalein (Ex-Lax, Feen-a-Mint) and magnesium (Milk of Magnesia) laxatives should not be used on a long-term basis. The osmotic laxative lactulose, 15–30 mL per day, may be used intermittently. Other medications include stool softeners, such as docusate sodium (Colace), 100 mg PO 1–2 times per day; motility agents, such as metoclopramide (see Section II.A.3) or bisacodyl (Dulcolax), 10 mg PO or PR 1–2 times per day; and enemas.
5. **Bladder problems.** Urinary retention may be treated with intermittent catheterizations, a chronic indwelling catheter, cholinergic agents such as bethanecol (Urecholine), 10–50 mg PO tid-qid, or α-adrenergic antagonists such as terazosin (Hytrin), 1–5 mg PO at bedtime. Xylocaine jelly should be considered for catheter changes. Condom catheters are not recommended. Assessment of urinary spasm should begin with evaluation for the possibility of overdistention. Symptoms may be managed with anticholinergic agents, such as oxybutynin (Ditropan), 5 mg bid-tid PO, or tolterodine (Detrol), 1–2 mg PO bid.
6. **Dyspnea** is best treated with supplemental oxygen. Morphine sulfate (see Section II.A.1) may also be used to decrease the sensation of air hunger. Antibiotics for respiratory infections may or may not be indicated to decrease sputum and thereby increase comfort. Respiratory secretions, sometimes known as the “death rattle” in patients shortly before death, may be diminished by decreasing hydration or by administration of atropine or scopolamine, 0.2–1.0 mg sublingual or subcutaneous q4–6h.
7. **Nutrition.** Few activities and treatments provoke as many emotions as those associated with nutrition. Food is often seen as a sign of life and hope, and not eating or withholding nutrition is seen as representative of despair or abandonment. Nonetheless, alert terminal patients should control their own dietary intake. Studies have not shown that forced feeding prolongs life; in fact, for some cancers, increased feeding may speed the rate of cancer growth. Decisions on the use of tube feedings or hyperalimentation in patients who are unable to eat should be guided by the concept of benefits versus burdens (see Section II.B.2). Potential benefits of nutrition in terminal patients include maintaining and increasing strength and function. Potential burdens include increasing patient anxiety by forcing food and the risks of gastric distention and aspiration. Alert patients who are anorectic should be evaluated for pain control, oral candidiasis, depression, and constipation. Symptoms of dry mouth may be managed with glycerine swabs or mouthwash or cautious use of viscous lidocaine (Xylocaine). Thirst may be relieved with ice chips or sips of water.

C. Ethical treatment issues

1. **Do not resuscitate (DNR) order** refers to the withholding of cardiopulmonary resuscitation (CPR) in the event of a cardiac or pulmonary arrest. Before writing a DNR order, the patient's clinical condition and

prognosis, a description of what CPR entails, and an estimate of the patient's likely chance for survival should be discussed with the patient and family and documented in the medical record. Studies suggest that when CPR is attempted, approximately 14% of patients survive to discharge and 86% die acutely. Certain groups have a much lower survival: The elderly have a survival rate ranging from 0% to 6.5%, and patients with metastatic cancer or sepsis have a survival of essentially zero (4). Patients who choose not to be resuscitated should be reassured that other treatments will not be affected by this decision. If not already completed, advance directives should be addressed. Patients who are still at home should be advised that if an ambulance is called and emergency medical services personnel respond, CPR may be automatically initiated; depending on the clinical situation, these patients and families should be instructed to call their physician or hospice or home health nurse first. Orders for “slow codes,” or non-aggressive or time-limited CPR, are inappropriate. However, orders specifically foregoing one aspect of CPR (e.g., a do-not-intubate order) may be appropriate in certain clinical situations.

2. **Withholding versus withdrawing care.** There is no ethical difference between withholding and withdrawing care that cannot or has not achieved its desired effect. Psychologically, however, it usually *feels* different to withdraw care. Clear communication about expectations is critical. The judicious use of treatment time trials may also be helpful. If a particular treatment is tried over a predetermined, fixed period of time and if at the end of that time the desired outcomes are not achieved, the treatment may be discontinued without guilt. In general, the concept of “benefits versus burdens” should guide decisions on the appropriateness of care. This involves engaging the patient, family, and health care team in listing the pluses and minuses of an intervention and weighing them against each other to determine use.
3. **Determination of futility** depends on who decides what is futile: the patient, the family, or the physician. A treatment might be physiologically futile but extremely important to a patient's sense of hope or to a family's ability to gather together. On the other hand, a patient or a family who strongly values life at all costs might insist on an intervention that clearly has no benefit but does have great burdens (e.g., administering chemotherapy to a patient with metastatic cancer who is now failing medical therapy for sepsis). If clear communication with the patient and family does not resolve disagreements regarding futile care, an ethics consultation should be obtained (see Section II.B.4). Alternatively, care may be transferred to another physician who feels able to meet the patient's or family's treatment requests.
4. **Ethics consultation** should be considered whenever there are persistent disagreements or conflicts in patient care. In some hospitals, consultation is performed by an ethics committee, whereas in others, it is performed by a professional clinical ethicist. Decisions about DNR status and withholding or withdrawing care are the most common reasons for requesting an ethics consultation.
5. **Euthanasia and physician-assisted suicide** are beyond the scope of this manual. However, if a patient inquires about them, the opportunity should be used to explore the reasons behind the request. Often, these patients have great fears about pain, isolation, or becoming a physical or financial burden to their families. Some may have treatable depression. Others may simply need a clarification of their medical problems and a discussion of their medical care plans.

D. Home and hospice care

1. Home health services may include nursing assessment of the patient's clinical status and home environment; teaching about medications and other treatments, diagnosis, and prognosis; social services evaluation

of financial issues and individual or family counseling needs; and occupational and physical therapy evaluation and treatment.

2. Hospice programs provide a full spectrum of interdisciplinary, team-based services for dying patients and their families. In addition to the usual home care services, hospice emphasizes the terminal process itself, particularly addressing pain control, pastoral care, and bereavement support for the family. Hospice is considered appropriate for a patient who has progressively lost weight, suffered a significant reduction in function, been repeatedly hospitalized for symptom management, or whose disease has progressed to a point where the family is experiencing great stress in providing the necessary care. To be eligible for hospice, patients must have a survival prognosis of less than 6–12 months, and patients and families must decline further aggressive treatment. Although most hospice care is home based, reasons to consider short-term inpatient hospice care include providing a respite for the family, intervening in a home or family crisis situation, or providing intensive symptom management for pain, nausea, vomiting, and other acute problems.

E. Determination of death

1. Traditionally, death has been clinically defined as the absence of spontaneous pulse and blood pressure (no circulatory function) and the absence of spontaneous breathing (no respiratory function). Often, the absence of pupillary responses (no brain function) is added.
2. Brain death criteria have been established in most states because intensive care life support systems may physiologically sustain certain organs even after a patient's cerebral functions have been permanently lost. These clinical criteria generally include coma that is documented to be irreversible (i.e., not due to drugs or hypothermia), absence of motor function and reflexes (though spinal cord reflexes may still be intact), and absence of brain stem function, established by apnea and the lack of pupillary and oculovestibular reflexes (6).

   Electroencephalograms may be confirmatory but are not usually required. However, some hospitals do require formal neurologic consultation before allowing a patient to be declared brain dead. Organ transplantation is sometimes an issue with brain-dead patients whose other organs remain viable. In these cases, death should first be declared by a physician clearly unassociated with the transplant team, and the discussion of organ donation should follow.

3. Persistent vegetative state (PVS) refers to the condition wherein patients have no obvious cortical function but do have residual brain stem activity that allows them to maintain circulatory and respiratory functions and many neurologic reflexes. Clinically, these patients still have a heart beat, can still breathe, can still constrict their pupils, and may posture with pain or loud noise; however, they are unable to think, actually feel pain, or have any awareness or purposeful activity. The diagnosis requires repeated examinations and neurologic consultation. Improvement and survival are virtually zero after 3 months of PVS resulting from anoxic brain injury (e.g., after cardiac arrest) or after 12 months of PVS resulting from a traumatic brain injury. *Very* rare recoveries have been reported, however (7). The treatment provided to patients in PVS should be based on advance directives, if present, and clear and honest family discussions if not. Although it may be completely appropriate to withhold or withdraw medical interventions from patients in PVS, mandatory withholding and withdrawal really involves the complex issue of futility (see Section II.B.3) and is not universally accepted.

III. Bereavement and follow-up issues

B. Autopsy

should be considered when the physician or the patient's family wants certainty about the cause of death to confirm the clinical diagnosis,

evaluate the level of response to a particular treatment, or be reassured that care was appropriate and death unavoidable. Legally, the local coroner's office must be notified when an individual dies without medical attendance, when the attending physician is unable to state the cause of death, or when death follows an accident or injury, including suicide or homicide. Asking about autopsies should be simple and direct, emphasizing the considerations outlined previously. The discussion should follow family notification of the death and preferably occur in person (though, in most states, consent for autopsy may be obtained over the phone). If an autopsy is performed, a family conference should be arranged afterward to discuss the findings. The costs of an autopsy are usually not covered by health insurance plans. However, many hospitals provide autopsies as a quality control measure at no charge.

C. Family follow-up issues

focus on promoting the tasks of bereavement, which include feeling sadness and pain, accepting the reality of the loss, and redirecting time and energy from caring for the deceased to other activities. Reassuring family members that they will not be abandoned, normalizing their reactions, and encouraging open communication are all helpful. Appropriate comments include “It's OK to feel both sad and angry” and “Death *is* hard to understand; have you talked with your family or minister about how you're dealing with things”

D. Physician follow-up issues.

The death of a patient who has had a very complicated course of disease or with whom the physician has developed a close relationship is often a great personal loss. Complicating this loss may be a sense of guilt or personal failure. Just as family and friends must grieve to recover, physicians too should be allowed to grieve by discussing a patient's death with staff, colleagues, or their own families, if appropriate. Attending a patient's funeral service should be considered a means of both assisting the physician's own grief work and showing support for the patient's family.

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