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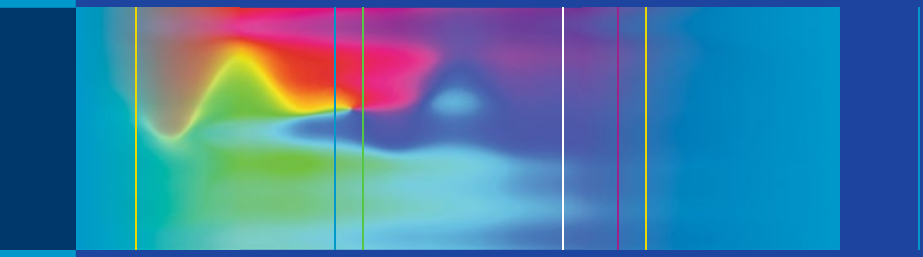

Pocket Guide to Critical Care Pharmacotherapy

Second Edition

Springer

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This handbook is dedicated
to my wife, Maria,
my children, Theodore
Thomas, Eleni Thalia,
and Pantelia "Lia" Zoe, and
my mother, Eleni.
I am grateful for your
collective understanding
of my professional
commitment.

John Papadopoulos

Preface

Critical care medicine is a cutting-edge medical field that is highly evidence-based. Studies are continuously published that alter the approach to patient care. As a critical care clinician, I am aware of the tremendous commitment required to provide optimal evidence-based care. *Pocket Guide to Critical Care Pharmacotherapy* covers the most common ailments observed in critically ill adult patients. I utilize an algorithmic, easy-to-follow, systematic approach. Additionally, I provide references and web links for many disease states, for clinicians who want to review the available literature in greater detail.

The contents of this handbook should be utilized as a guide and in addition to sound clinical judgment. Consult full prescribing information and take into consideration each drug's pharmacokinetic profile, contraindications, warnings, precautions, adverse reactions, potential drug interactions, and monitoring parameters before use.

Every effort was made to ensure the accuracy of *Pocket Guide to Critical Care Pharmacotherapy*. The author, consulting editor, and publisher are not responsible for errors or omissions or for any consequences associated with the utilization of the contents of this handbook.

New York, NY, USA — John Papadopoulos, BS, PharmD, FCCM, BCNSP

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Advance Cardiac Life Support

Table 1.1 ACLS pulseless arrest algorithm

- Basic life support (BLS) algorithm—emphasis on maintaining cardiac/cerebral perfusion through early, high-quality chest compressions with minimal interruption, rapid defibrillation when appropriate, and avoiding delays in establishing a definitive airway and excessive ventilation. Use of vasopressors and antiarrhythmic agents is deemphasized
  - Check the carotid pulse for 5–10 s
  - If no pulse within 10 s, start **high-quality** cardiopulmonary resuscitation (CPR) with chest compressions
  - Push hard and fast (at least 100 compressions/min) at a depth of at least 2 in.
  - Allow full chest recoil after each compression
  - Minimize interruptions in CPR (any interruption > 10 s) including pulse checks
  - One CPR cycle is equal to 30 compressions then two breaths (30:2)
    - Five cycles administered every 2 min
    - If possible, compressor should change every 2 min
  - Avoid excessive ventilation leading to harmful elevations in intrathoracic pressure
  - Continuous chest compressions with advanced airway. Administer 8–10 breaths per minute for cardiac arrest or 10–12 breaths per minute for respiratory arrest, and check rhythm every 2 min
  - The AHA recommends continuous waveform capnography (in addition to bedside assessment) as the most reliable method of confirming correct endotracheal tube placement
    - End tidal CO_2 ($PETCO_2$) less than 10 mmHg indicates poor blood flow and unlikely return of spontaneous circulation (ROSC); improvement in CPR quality is advised

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_1,

Table 1.1 (continued)

- A sustained abrupt rise in $PETCO_2$ (especially to normal values of 35–40 mmHg or greater) is usually indicative of ROSC and a rhythm/pulse check is advisable
- If intra-arterial diastolic pressure is less than 20 mmHg, then attempt to improve CPR quality

- ROSC—pulse/BP, $PETCO_2$ greater than 40 mmHg, spontaneous waves if using arterial line
- Give oxygen when available
- Attach defibrillator/monitor as soon as possible
- Assess rhythm → shockable rhythm?
  - Ventricular fibrillation/pulseless ventricular tachycardia (shock advised)—proceed to Table 1.2
  - Pulseless electrical activity (no shock)—proceed to Table 1.3
  - Asystole (no shock)—proceed to Table 1.4

Data from *Circulation*. 2010;122:S640–S65

Table 1.2 Ventricular fibrillation/pulseless ventricular tachycardia algorithm

- Basic life support (BLS) algorithm → give **high-quality** cardiopulmonary resuscitation (CPR) stopping only for shock delivery, brief rhythm checks, brief pulse checks if organized rhythm, and to facilitate placement of an advanced airway
- Give oxygen
- Give one unsynchronized shock
  - Biphasic (device specific): 120–200 J (if unknown use 200 J)
  - Monophasic: 360 J
- Immediately after the shock, resume CPR for five cycles (about 2 min)
- When vascular access established (intact PVL > emergent PVL, interosseous [IO] access > emergent CVL), administer vasopressor during CPR (before or after the shock)
  - Epinephrine 1 mg intravenous push (IVP) or IO, repeat every 3–5 min
  - Vasopressin 40 units IVP/IO × one dose only, may replace the first or second dose of epinephrine
- Check rhythm after five cycles (about 2 min) of CPR. Shockable rhythm—repeat shock using equivalent or higher energy
- Resume CPR immediately after the shock
  - Consider antiarrhythmics (before or after the shock)
    - Amiodarone 300 mg IVP/IO × one dose (first-line agent)
      - May administer one repeat dose of 150 mg IVP/IO in 3–5 min
    - Lidocaine 1–1.5 mg/kg IVP/IO × one dose, then 0.5–0.75 mg/kg IV every 5–10 min to a maximum of 3 mg/kg. May consider if amiodarone is not available
    - Magnesium 1–2 g in 10 mL of D5W IVP/IO over 5 min for torsades de pointes or severe hypomagnesemia

(continued)

Table 1.2 (continued)

- Resume CPR immediately for five cycles (about 2 min)
- Repeat cycles of shock (if persistent VF/pulseless VT) and epinephrine administration as aforementioned every 3–5 min
- If ROSC, then proceed with post-cardiac arrest care

Data from *Circulation*. 2010;122:S640–S65

Table 1.3 Pulseless electrical activity algorithm

- Review most frequent causes (*see* Table 1.12). Hypovolemia and hypoxia are the two most common causes of PEA arrest
- Basic life support (BLS) algorithm → give **high-quality** cardiopulmonary resuscitation (CPR)
- Epinephrine 1 mg intravenous push (IVP) or intraosseous (IO), repeat every 3–5 min
- Vasopressin 40 units IVP/IO × one dose only, may replace the first or second dose of epinephrine
- Check rhythm after five cycles (about 2 min) of CPR. If shockable rhythm then proceed with the VF/VT algorithm in Table 1.2
- The AHA has removed atropine from the 2010 guidelines, as it is unlikely to have a therapeutic benefit
- If ROSC, then proceed with post-cardiac arrest care

Table 1.4 Asystole algorithm

- Validate the rhythm (look for loose leads, low signal, loss of power)
- Identify and correct an underlying cause if present
- Basic life support (BLS) algorithm → give **high-quality** cardiopulmonary resuscitation (CPR)
- Epinephrine 1 mg intravenous push (IVP) or intraosseous (IO), repeat every 3–5 min
- Vasopressin 40 units IVP/IO × one dose only, may replace the first or second dose of epinephrine
- Check rhythm after five cycles (about 2 min) of CPR. If shockable rhythm then proceed with the VF/VT algorithm in Table 1.2
- The AHA has removed atropine from the 2010 guidelines, as it is unlikely to have a therapeutic benefit
- The AHA recommends against attempted pacing in the 2010 guidelines, as it is unlikely to have a therapeutic benefit
- An initial defibrillation may be warranted if it is unclear if the rhythm is fine VF or asystole
- If ROSC, then proceed with post-cardiac arrest care

Table 1.5 Bradycardia algorithm (slow [heart rate < 50/min] or relatively slow)

- Assess airway, breathing, and signs/symptoms of bradycardia
- Give oxygen if hypoxemic (maintain oxygen saturation ≥ 94 %)
- Monitor blood pressure, pulse oximetry, and establish IV access
- Obtain and review 12-lead electrocardiogram (ECG)
- Consider causes and differential diagnosis

Serious signs or symptoms owing to bradycardia are present

- Atropine 0.5 mg intravenous push (IVP) every 3–5 min up to a total of 0.04 mg/kg or 3 mg total
  - Administer every 3 min in urgent circumstances
  - Use 1 mg doses in obese patients to avoid paradoxical bradycardia
  - Will not work in denervated transplanted hearts
- Transcutaneous pacing: provide analgesia and/or sedation if benefit outweighs any risk; set the demand rate to 60 beats/min; set the current milliamperes output to 2 mA above the current at which consistent electrical and mechanical capture is achieved
- Dopamine continuous IV infusion 2–10 mcg/kg/min
- Epinephrine continuous IV infusion 2–10 mcg/min
- Consider glucagon 2–10 mg IV bolus followed by a 2–10 mg/h continuous IV infusion in β-adrenergic blocker or calcium channel blocker-induced bradycardia not responsive to atropine
- Prepare for possible transvenous pacing if the above measures are ineffective

Table 1.6 Tachycardia algorithm overview (heart rate > 100/min)

Evaluate patient

- Assess airway, breathing, and signs/symptoms of tachycardia
- Give oxygen if hypoxemic (maintain oxygen saturation ≥ 94 %)
- Establish IV access
- Obtain 12-lead electrocardiogram (ECG)
- Identify and treat etiology
- Questions to address:
  - Is the patient unstable or stable?
  - Are there serious signs or symptoms as a result of the tachycardia?
    - Including hypotension, hypoperfusion, heart failure, angina, pre-syncope/syncope, acute dyspnea, or hypoxemia
    - Ventricular rates less than 150/min rarely are responsible for serious signs or symptoms
  - Is the rhythm regular or irregular?
  - Is the QRS complex narrow or wide? What is the morphology if wide?

(continued)

Table 1.6 (continued)

Unstable patient (serious signs or symptoms)

- Prepare for immediate synchronized cardioversion (*see* Table 1.10)

Stable patient (no serious signs or symptoms as a result of the tachycardia)

- *Atrial fibrillation/atrial flutter*
  - Evaluate
    - Cardiac function (i.e., can the patient tolerate negative inotropic medications?)
    - Suspicion or known of Wolff–Parkinson–White Syndrome (WPW)
    - Duration (less than or greater than 48 h)
  - *See* atrial fibrillation/atrial flutter algorithm (Table 1.7)
    - Rate control
    - Rhythm control
    - Consider early anticoagulation
- Narrow-complex tachycardias (QRS < 0.12 s)
  - *See* Table 1.8
- Stable wide-complex tachycardia with a regular rhythm
  - If ventricular tachycardia or uncertain rhythm (*see* Table 1.9)
  - If SVT with aberrancy, give adenosine (*see* Table 1.8)
- Stable wide-complex tachycardia with an irregular rhythm
  - If atrial fibrillation with aberrancy (*see* Table 1.7)
  - If atrial fibrillation with WPW (*see* Table 1.7)
  - If polymorphic ventricular tachycardia (*see* Table 1.9)

Table 1.7 Management of stable atrial fibrillation/atrial flutter

	Rate control	*Rhythm control (duration ≤ 48 h)*
Normal cardiac function	• β-adrenergic blockers • Diltiazem • Verapamil	• Consider synchronized cardioversion or • Amiodarone • Ibutilide • Flecainide • Propafenone • Procainamide
EF < 40 %	• Digoxin • Diltiazem (with caution) • Esmolol (with caution) • Amiodarone	• Consider synchronized cardioversion *or* • Amiodarone

(continued)

Table 1.7 (continued)

	Rate control	*Rhythm control (duration ≤ 48 h)*
WPW	• Synchronized cardioversion *or* • Amiodarone • Flecainide • Procainamide • Propafenone • Sotalol	• Synchronized cardioversion or • Amiodarone • Flecainide • Procainamide • Propafenone • Sotalol **Avoid!** • Adenosine • β-adrenergic blockers • Calcium channel blockers • Digoxin

EF Ejection fraction, *WPW* Wolff–Parkinson–White syndrome

Notes:

Use only one medication initially for rate or rhythm control (endpoint = desired goal, maximum advisable total dose given, or untoward side effects). When utilizing both IV and enteral drug delivery, be aware of onset/duration of action to avoid excessive dosing leading to hypotension and/or bradycardia. Occasionally, two agents may need to be utilized; combination therapy with a calcium channel blocker + β-adrenergic blocker may increase the incidence of hypotension and bradycardia

- Duration of atrial fibrillation/atrial flutter > 48 h or unknown
  - Electrical or chemical cardioversion in a patient without adequate anticoagulation may cause embolization of atrial thrombi
  - No synchronized cardioversion if clinically stable
  - Delay electrical cardioversion
  - Provided therapeutic anticoagulation for 3 weeks, cardiovert *electrically* (if rhythm control is desired), then continue therapeutic anticoagulation for 4 more weeks
  - Early cardioversion alternative
    - Begin heparin IV continuous infusion
    - Perform transesophageal echocardiogram (TEE) to exclude atrial clot
    - If negative, cardiovert *electrically* within 24 h
    - Continue therapeutic anticoagulation for 4 weeks

TABLE 1.8 Management of narrow complex stable supraventricular tachycardia (QRS < 0.12 s)

- Attempt therapeutic/diagnostic maneuver if *regular* rhythm with observation of continuous rhythm strip or ECG, to inhibit sinus node and AV conduction and diagnose sinus tachycardia, atrial flutter or atrial tachycardia or "break" AV nodal reentrant rhythm (AVNRT). If *irregular* rhythm, proceed to Table 1.7
  - Attempt vagal stimulation (e.g., carotid massage, valsalva maneuver)
  - If unresponsive to vagal maneuvers, give adenosine 6 mg rapid intravenous push (IVP) over 1 s. If no diagnosis/conversion without evidence of sinus/AV node slowing (AHA states within 1–2 min, **author's and editor's experience is that adenosine is more rapidly effective**), give a second dose of 12 mg rapid IVP over 1 s. The patient should be warned of common transient flushing, dyspnea, and chest discomfort; adenosine may exacerbate bronchoconstriction in patients with asthma
  - If converts, most commonly AVNRT
  - If no conversion, diagnose sinus tachycardia, atrial flutter, or paroxysmal atrial tachycardia

Paroxysmal (re-entry) supraventricular tachycardia (recurrent/ refractory to vagal stimulation or adenosine)

- Ejection fraction (EF) preserved
  - Calcium channel blocker
  - β-adrenergic blocker
  - Digoxin
  - Synchronized cardioversion (if refractory)
  - Consider procainamide, amiodarone, and sotalol
- EF less than 40 %
  - Digoxin
  - Amiodarone
  - Diltiazem (cautious use)
  - Esmolol (cautious use)

Ectopic or multifocal atrial tachycardia

- EF preserved
  - No synchronized cardioversion!
  - Calcium channel blocker
  - β-adrenergic blocker
  - Amiodarone
- EF < 40 %
  - No synchronized cardioversion!
  - Amiodarone
  - Diltiazem (cautious use)
  - Esmolol (cautious use)

(continued)

Table 1.8 (continued)

Junctional tachycardia
- EF preserved
  - No synchronized cardioversion!
  - Amiodarone
  - β-adrenergic blocker
  - Calcium channel blocker
- EF < 40 %
  - No synchronized cardioversion!
  - Amiodarone

Table 1.9 Management of stable ventricular tachycardia

If suspicion of SVT with aberrancy, the AHA suggests that a diagnostic/therapeutic trial of adenosine is reasonable. **Verapamil** is **contraindicated** for regular wide-complex tachycardia unless known SVT with aberrancy

Monomorphic ventricular tachycardia
- Normal cardiac function
  - Amiodarone
  - Lidocaine
  - Procainamide
  - Sotalol
- Impaired cardiac function (ejection fraction < 40 %)
  - Amiodarone
  - If persistent, use synchronized cardioversion

Polymorphic ventricular tachycardia
- Use unsynchronized cardioversion if unstable/pulseless
- Normal baseline QT-interval and normal cardiac function
  - Treat ischemia
  - Correct electrolyte abnormalities (i.e., hypokalemia and hypomagnesemia)
  - β-adrenergic blockers
  - Lidocaine
  - Amiodarone
  - Procainamide
  - Sotalol
- Normal baseline QT-interval and impaired cardiac function (ejection fraction < 40 %)
  - Amiodarone
  - Synchronized cardioversion if persistent and stable
- Prolonged baseline QT interval (torsades de pointes?)
  - Correct electrolyte abnormalities (i.e., hypokalemia and hypomagnesemia)
  - Discontinue any medication that can prolong the QT-interval (*see* Table 2.11)
  - Magnesium

(continued)

Table 1.9 (continued)

- Overdrive pacing
- Isoproterenol (avoid if known familial long QT-interval syndrome; can use β-adrenergic blockers in these cases)
- Lidocaine
- Synchronized cardioversion if persistent and stable

Table 1.10 Synchronized cardioversion algorithm for the management of symptomatic tachycardia

- If ventricular rate is more than 150/min, prepare for immediate synchronized cardioversion
  - May administer brief antiarrhythmic trial based on specific arrhythmia
- Immediate cardioversion is generally not needed if ventricular rate is ≤ 150/min
- Consider sedation when possible
  - Diazepam, midazolam, or etomidate with or without a narcotic analgesic (e.g., morphine or fentanyl)
- Have bedside access to:
  - Pulse oximeter, IV line, suction device, and intubation equipment

Synchronized cardioversion

- For monomorphic ventricular tachycardia, paroxysmal supra-ventricular tachycardia (SVT), atrial fibrillation, atrial flutter
  - Treat polymorphic ventricular tachycardia (wide complex and irregular rate) as ventricular fibrillation (*see* Table 1.9)
- Narrow complex and regular rate: 50–100 J
- Narrow complex and irregular rate: 120–200 J if biphasic or 200 J if monophasic
- Wide complex and regular rate: 100 J
- Wide complex and irregular rate: do not synchronize, treat with defibrillation doses
- Resynchronize after **each** cardioversion
- If there is no response to the initial shock, then increase the joules in a step-wise fashion
- Administer unsynchronized shocks if it is unclear whether monomorphic or polymorphic VT in an unstable patient

Cardioversion procedure

- Turn on defibrillator
- Attach monitor leads to patient and ensure proper display of patient's rhythm
- If using electrode pads (AHA recommendation), may omit previous step, apply pads and ensure the monitor is reading "pads" or "paddles." Press the "Sync" control button to synchronize the defibrillator
  - Look for markers on R waves indicating synchronized mode
  - If needed, adjust monitor gain until synchronized markers occur with each R wave

(continued)

Table 1.10 (continued)

- If using paddles, apply gel to paddles and position appropriately
- Select appropriate energy level
- Position electrode pads on patient **or** apply gel to paddles
- Position paddles on patient's sternum and apex (apical/posterior position is acceptable)
- Announce to team members "Charging defibrillator—stand clear"
- Press charge button on apex-paddle (right hand)
- When the defibrillator is charged announce to team members
  - "I am going to shock on three."
    - "One—I am clear"
    - "Two—you are clear"
    - "Three—everybody is clear"
- Apply 25 lbs of pressure if using paddles
- Press the discharge buttons simultaneously and hold until shock delivered (may take longer in irregular rhythm (e.g. atrial fibrillation)
- If defibrillating, CPR continues until "clear." Do not perform a pulse or rhythm check after shock delivery. Resume chest compressions immediately
- If tachycardia persists, adjust the energy dose according to the algorithm

Cardioversion pearls

- Data demonstrate that four pad positions (anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular) are equally effective to treat atrial or ventricular arrhythmias
- Anterolateral position is a reasonable default (**editor prefers anterior-right infrascapular position for atrial fibrillation**)
- Resynchronize after each synchronized cardioversion before repeating
- If the initial shock terminates VF but this arrhythmia recurs, deliver shocks at the previously successful energy level
- To avoid myocardial damage, the interval between shocks should be ≥ 1 min
- Remove any medication patches, wipe the area clean, then place the electrode pads/paddles
- If a hairy chest prohibits appropriate electrode pad/paddle placement, either quickly pull of the electrode pads to remove some hair or quickly shave the area with a razor if available. Then use a new set of electrode pads
- Wipe any water off the patient's chest before attaching the electrode pads or placing paddles
- Place electrode pads or paddles to either side (not directly on top) of an implanted defibrillator or pacemaker, then follow the normal steps for operating the external defibrillator

Table 1.11 Common drugs utilized during ACLS

Drug	*Adult dose*	*Comments*
Adenosine	• 6 mg rapid IVP over 1 s • 12 mg rapid IVP may be administered in 1–2 min needed	• Follow each dose with a 20 mL IV flush of normal saline and elevate the arm immediately • Decrease dose if administered through a central line, to patients with transplanted hearts, or concomitant dipyridamole therapy to 3 mg • Caffeine and theophylline may antagonize the effect of adenosine • Patients should be warned of common but transient flushing, dyspnea, and chest discomfort • May exacerbate bronchoconstriction in patients with asthma
Amiodarone	• *Cardiac arrest:* 300 mg IVP/IO. Additional 150 mg IVP/IO in 3–5 min if needed • *SVT/wide-complex tachycardia (stable):* 150 mg IV over 10 min. May repeat 150 mg every 10 min as needed	• Rapid infusion followed by a continuous IV infusion of 1 mg/min for 6 h, then 0.5 mg/min for 18 h • Use cautiously with other drugs that prolong the QT-interval • IV diluent (polysorbate 80) may contribute to hypotension • Contains 37.3 % iodine by weight • Maximum 24 h dose is 2.2 g • Familiarize yourself with common drug–drug interactions

(continued)

TABLE 1.11 (continued)

Drug	*Adult dose*	*Comments*
Atropine	• *Bradycardia:* 0.5–1 mg IVP every 3–5 min	• Dose every 3 min in severe clinical conditions • Doses ≤0.5 mg may cause bradycardia in obese patients; use 1 mg doses • Use cautiously in the setting of an acute myocardial infarction • Can be given through endotracheal tube at 2–2.5 times the recommended dose
Digoxin	• Total intravenous loading dose is usually between 0.5 and 1 mg • Administered as follows: ○ 50 % of loading dose initially, followed by 25 % every 6 h for two doses • Inject over 1–5 min	• Dose based on ideal body weight • Decrease loading dose in end stage renal disease, uncontrolled hypothyroidism, or patients on quinidine by 30–50 % • Correct hypokalemia, hypomagnesemia, and hypercalcemia before initiating therapy • May monitor the digoxin level at least 4–6 h after an intravenous loading dose regimen is complete. This will not reflect steady-state concentrations but may be used to assess the adequacy of the loading dose regimen. Digoxin distributes greater into heart tissue than blood; when evaluating any digoxin level, always assess the heart first then the blood • Digoxin-like immunoreactive substances (found in patients with heart failure, end stage renal disease, liver disease, or third trimester of pregnancy) may cross-react with certain digoxin immunoassays and may result in a false elevation of levels • Familiarize yourself with common drug–drug interactions

Diltiazem	• 0.25 mg/kg IV over 2 min • If response is inadequate after 15 min, may administer 0.35 mg/kg IV over 2 min • May initiate a continuous IV infusion of 5 mg/h. Rate may be increased in 5 mg/h increments up to 15 mg/h if needed	• Hypotension and bradycardia may be seen if combined with a β-adrenergic blocker • Familiarize yourself with common drug–drug interactions
Epinephrine	• *Cardiac arrest:* 1 mg IVP/IO (10 mL of a 1:10,000 solution) every 3–5 min • *Profound bradycardia:* 2–10 mcg/min continuous IV infusion • *Bronchodilator*: 0.1–0.5 mg SQ (0.1–0.5 mL of a 1:1,000 solution) every 10–15 min until adequate response	• Greater than 1 mg doses may contribute to post-resuscitation myocardial and neurological dysfunction but may be used in β-adrenergic blocker or calcium channel blocker overdoses • Can be given through an endotracheal tube at 2–2.5 times the recommended dose • 1:1,000 is equal to 1 mg/mL and used for IM administration • 1:10,000 is equal to 0.1 mg/mL and used for IV administration
Esmolol	• Loading dose: 500 mcg/kg over 1 min • Followed by 50 mcg/kg/min. May increase every 5–10 min by 50 mcg/kg/min increments up to a maximum of 200 mcg/kg/min	• Use cautiously and avoid the loading dose if tenuous hemodynamics • Should be administered through a central line if concentrations greater than 10 mg/mL are utilized • Monitor total volume administered with the continuous infusion

(continued)

TABLE 1.11 (continued)

Drug	*Adult dose*	*Comments*
Isoproterenol	• 2 mcg/min continuous IV infusion • Use lower doses in patients who are elderly or have ischemic heart disease (e.g., 0.5 mcg/min)	• Use with extreme caution • Temporary agent for torsades de pointes before transvenous pacing
Lidocaine	• *Cardiac arrest or stable rhythm:* 1–1.5 mg/kg IVP/IO. May repeat in 5–10 min with 0.5–0.75 mg/kg IVP/IO. May follow bolus with a continuous IV infusion of 1–4 mg/min. If arrhythmia reappears during continuous IV infusion, may bolus with 0.5 mg/kg and reassess	• Maximum dose is 3 mg/kg IVP/IO • Decrease continuous IV infusion dose in patients with hepatic or left ventricular dysfunction • Monitor drug levels with prolonged infusions (>24 h) • Can be given through tracheal tube at 2–2.5 times the recommended dose
Magnesium sulfate	• *Cardiac arrest (torsades de pointes):* 1–2 g diluted in D5W 10 mL IVP/IO • *Stable torsades de pointes:* 1–2 g diluted in 50 mL D5W IV over 5 min followed by a continuous IV infusion of 0.5–1 g/h	• Use cautiously in patients with renal dysfunction, myasthenia gravis, or concomitant digoxin therapy
Sodium bicarbonate	• 1 mEq/kg IVP • Repeat with 0.5 mEq/kg every 10 min as needed	• Not recommended for routine use in cardiac arrest patients • May be useful for cardiac arrest associated with tricyclic antidepressant overdose, hyperkalemic states, or severe (non-lactic acid) metabolic acidosis

		• Use arterial blood gases to guide therapy • May increase tissue and central venous acidosis during CPR and may transiently falsely elevate $PETCO_2$ • Complete correction of base deficit should be avoided
Vasopressin	• 40 units IVP/IO (one dose only)	
Verapamil	• 2.5–5 mg IVP over 2 min • May administer a second dose of 5–10 mg 15–30 min after the initial dose, if inadequate response. Maximum total dose is 20 mg IVP	• Use cautiously in patients with left ventricular dysfunction

IVP Intravenous push, *SQ* Subcutaneous, *CPR* Cardiopulmonary resuscitation

Notes:

1. Pharmacological agents play a secondary role to electric cardioversion in unstable patients
2. Priorities for drug access are: intravenous > intraosseous > endotracheal
3. Intravenous route: a peripheral IV is preferred for drug administration, unless a central line is already present; administer intravenous drugs by rapid bolus followed with a 20 mL flush of intravenous fluid; elevated the extremity above the level of the heart for 10–20 s if peripheral venous access is utilized during resuscitation
4. Intraosseous route: any drug or fluid given intravenously can be given intraosseously
5. Endotracheal route: atropine, epinephrine, lidocaine and vasopressin can be administered through the endotracheal tube at 2–2.5 times the recommended intravenous dose diluted with 5–10 mL of normal saline or sterile water; technique—stop CPR, administer medication beyond the tip of the endotracheal tube, follow with five quick insufflations to aerosolize the drug, and then resume CPR
6. All antiarrhythmic agents can be proarrhythmogenic. Sequential use of more than one agent can result in an adverse drug event. Do not use more than one antiarrhythmic agent unless absolutely necessary. Electric cardioversion is preferred over a second antiarrhythmic agent if the initial agent fails

Table 1.12 Pulseless electrical activity: causes (HATCH H_2MO ppH) and management

Condition	*Evidence*	*Management*
Hypovolemia	Flat neck veins, narrow complex	Intravenous fluids
Acidosis	Arterial blood gases	Sodium bicarbonate, hyperventilation
Tension pneumothorax[a]	History, tracheal deviation unequal breath sounds, unilateral hyper resonance to percussion	Needle decompression for **ANY** suspicion
Cardiac tamponade[a]	History, emergent bedside Echocardiogram results	Pericardiocentesis
Hypoxia	ABG, central cyanosis Compromised airway	Ventilation, BVM to definitive airway, oxygen therapy, positive end expiratory pressure (PEEP)
Hyperkalemia	History, bizarre wide QRS Complexes to sine wave medications	*See* hyperkalemia—low threshold to treat as often rapidly reversible pathway (Table 14.6)
Hypokalemia	History, wide QRS complex	Replete potassium
Myocardial infarction	History, electrocardiogram (ECG), cardiac enzymes	Acute coronary syndrome pathway (Tables 2.4 and 2.5)
Overdose	History, physical exam	Drug-specific
Pulmonary embolism[a]	History, emergent bedside Echocardiogram results	*See* pulmonary embolism pathway
Auto-**P**EEP[a]	Especially in asthma/ COPD, excessive ventilation during CPR, ventilator or BVM > spontaneous	Allow complete exhalation, treat airway disease
Hypothermia	Low core body temperature	Raise body temperature

[a]Causes of obstructive shock should be entertained in patients with PEA/asystole with absent or low levels of $PETCO_2$ after placement of invasive airway

Table 1.13 Pharmacological management of anaphylaxis/anaphylactoid reactions

- Stop infusion of culprit drug where possible
- Assess airway and cardiopulmonary status
- Place patient in a supine position; elevate lower extremities if hypotensive.
- Administer oxygen at high flow rates if hypoxic (e.g., 6–10 L/min)
- Rapid fluid resuscitation with a crystalloid or a colloid if hypotensive (large volumes may be required)
- Epinephrine
  - Shock or threatened airway/respiratory failure: 0.1–0.5 mg IVP (1–5 mL of a 1:10,000 solution) over 5 min. May repeat in 5–10 min and as needed or start a continuous IV infusion at 2–10 mcg/min
  - Condition not life-threatening or no vascular access: 0.3–0.5 mg IM (0.3–0.5 mL of a 1:1,000 solution). May repeat in 5–10 min as needed for three total doses
- Antihistamines
  - Diphenhydramine 25–50 mg IV over 5 min q6h
- Histamine$_2$-receptor antagonists
  - Famotidine 20 mg IV over 2 min q12h, ranitidine 50 mg IV over 5 min q8h, or cimetidine 300 mg IV over 5 min q6h (must adjust dose of each drug with renal impairment)
  - H_2-receptor antagonism without concomitant H_1-receptor antagonism may result in a negative inotropic and chronotropic response
- Hydrocortisone 50–100 mg (or other equivalent dose corticosteroid) IV q6–8h
- If bronchospasm present, use albuterol nebulization 2.5–5 mg every 20 min for 3 doses
- If upper airway edema/stridor, use racemic epinephrine nebulization 0.5 mL every 3–4 h as needed
  - Epinephrine solution for inhalation—1 % (10 mg/mL or 1:100) solution
  - Low threshold for early intubation and mobilization of resources needed to perform a surgical airway
- If in shock, use epinephrine or norepinephrine continuous IV infusion for hemodynamic support in conjunction with fluid resuscitation

Chapter 2
Cardiovascular

Table 2.1 Thrombolysis in myocardial infarction (TIMI) grade flows

TIMI grade	*Definition*
0	No perfusion; no antegrade flow beyond point of occlusion
1	Penetration without perfusion; failure of contrast medium to move out of the area of occlusion
2	Partial perfusion; passage of contrast medium through obstruction but at a slow rate of clearance
3	Complete perfusion; prompt antegrade flow distal to the obstruction and adequate clearance of contrast medium

Table 2.2 TIMI risk score for STEMI

Markers

- Age ≥75 years (3 pts), 65–74 years (2 pts), < 65 years (0 pts)
- Diabetes mellitus, hypertension, or angina (1 pt)
- Systolic blood pressure < 100 mmHg (3 pts)
- Heart rate > 100/min (2 pts)
- Killip Class II–IV (2 pts)
- Weight < 67 kg (1 pt)
- Anterior ST-segment elevation or LBBB (1 pt)
- Time to treatment > 4 h (1 pt)

Numbers of markers designate risk of all cause 30-day mortality

- 0: 0.8 %
- 1: 1.6 %
- 2: 2.2 %
- 3: 4.4 %
- 4: 7.3 %

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_2,

Table 2.2 (continued)

- 5: 12.4 %
- 6: 16.1 %
- 7: 23.4 %
- 8: 26.8 %
- 9–14: 35.9 %

Data from http://www.mdcalc.com/timi-risk-score-for-stemi

Notes:
With an increasing risk factor score, progressively greater benefit is seen with:

- Enoxaparin versus unfractionated heparin
- Tirofiban versus placebo
- Invasive strategy versus conservative strategy

Independent predictors of early death from STEMI include age, Killip class, time to reperfusion, cardiac arrest, tachycardia, hypotension, anterior infarct location, prior infarction, diabetes mellitus, smoking status, renal function, and biomarker findings

Table 2.3 Acute pharmacological management of unstable angina and non-ST elevation myocardial infarction with an initial invasive angiographic strategy

*Antiplatelet pharmacotherapy for an **initial invasive** approach (angiography +/– stent)*

- Patients with UA/NSTEMI at medium or high risk who an invasive strategy is selected should receive dual antiplatelet therapy on presentation (**note**: prasugrel should only be given at the time of angiography/PCI)
- Platelet function testing to determine platelet inhibitory response on $P2Y_{12}$ receptor inhibitor therapy may be considered. Role of genotyping in the clinical management of patients has not been established
- Aspirin (if no evidence of allergy)
  - 162–325 mg (non-enteric coated) chew and swallow immediately, followed by 81 mg enterally daily (indefinitely); inquire about prehospital administration of aspirin
    - If history of aspirin-induced bleeding or bleeding risk factors present, may use a lower initial dose (i.e., 81 mg daily)
    - A loading dose followed by a maintenance dose of clopidogrel, prasugrel, or ticagrelor in patients who are not able to take aspirin; dual $P2Y_{12}$ receptor inhibitor therapy is **not** recommended
  - Dual therapy with a $P2Y_{12}$ receptor inhibitor is recommended with **one** of the following regimens (either clopidogrel, prasugrel, or ticagrelor [**note**: the ACCF/AHA does not rank these agents in order of preference]):

(continued)

Table 2.3 (continued)

- Clopidogrel
  - 600 mg enterally before or at the time of PCI followed by 75 mg daily for at least 12 months; a shorter duration should be considered if increased bleeding risk
    - 75 mg twice daily for 6 days, then 75 mg daily may be considered in patients not at high risk for bleeding
    - Review medication profile for potential drug–drug interactions
  - In patients whom an initial invasive approach is planned and if bivalrudin is selected as the anticoagulant during PCI:
    - 300 mg enterally for one dose at least 6 h earlier than PCI, followed by 75 mg daily for 12 months in addition to aspirin pharmacotherapy
      - Do not use combination therapy in patients at high risk of bleeding or if the need for urgent CABG cannot be excluded
- Prasugrel
  - 60 mg enterally at the time of PCI (no later than 1 h after PCI) followed by 10 mg daily for at least 12 months; a shorter duration should be considered if increased bleeding risk
    - Prasugrel should not be administered routinely in patients with UA/NSTEMI before angiography
  - Potentially harmful in patients with a prior history of stroke and/or transient ischemic attacks
  - Patients <60 kg may be at increased risk for bleeding with a 10 mg daily regimen; consider lowering the dose to 5 mg daily
  - Generally not recommended in patients ≥75 years except in high-risk situations (e.g., diabetes or prior myocardial infarction); if utilized consider lowering the dose to 5 mg daily
- Ticagrelor
  - 180 mg enterally before or at the time of PCI followed by 90 mg twice daily for at least 12 months; a shorter duration should be considered if increased bleeding risk
  - The recommended concomitant aspirin dose to be used is 81 mg daily
  - Should be avoided in patients with a prior history of intracranial hemorrhage
- Glycoprotein IIb/IIIa inhibitors (given during angiography)
  - PCI dosing not provided
  - The use of upstream (at presentation and before angiography) glycoprotein IIb/IIIa inhibitors may be considered in high-risk patients (e.g., elevated troponin levels, diabetes, or significant ST-segment depression). Administered, in addition to aspirin and a $P2Y_{12}$ receptor inhibitor; may be administered just before PCI

(continued)

Table 2.3 (continued)

- Either eptifibatide or tirofiban can be administered for initial early treatment in addition to aspirin and clopidogrel or ticagrelor plus an anticoagulant before diagnostic angiography
  - Either low molecular weight heparin (LMWH), fondaparinux or heparin in *intermediate to high-risk patients* in whom an invasive management strategy is planned (*see* Table 2.3 for risk assessment)
  - Eptifibatide can be continued for 12–18 h after angiography
  - Tirofiban can be continued up to 18 h after angiography
- If bivalirudin is chosen as the anticoagulant, can omit administration of an IV glycoprotein IIb/IIIa inhibitor
- Glycoprotein IIb/IIIa inhibitors are not recommended in patients with a low risk for ischemic events (i.e., TIMI risk score ≤ 2) or who are at high risk for bleeding
- Abciximab is not indicated in patients in whom PCI is not planned

Anticoagulant pharmacotherapy for an **initial invasive** approach

- One anticoagulant should be added to antiplatelet therapy
- Bivaliruin (given during angiography)
  - Peri-PCI dosing not provided
  - Can continue at a dose of 0.25 mg/kg/h up to 72 h if given before diagnostic angiography
- Unfractionated heparin (given during angiography)
  - Peri-PCI dosing not provided
  - May be combination with antiplatelet pharmacotherapy for at least 48 h
  - After PCI dosing: weight-based dosing to achieve an activated partial thromboplastin time (aPTT) between 50 and 70 s (**note:** some institutions titrate heparin to anti-Factor Xa levels)
    - 60–70 units/kg IV bolus (4,000 units maximum), followed by 12–15 units/kg/h continuous IV infusion (1,000 units/h maximum)
  - Nomogram for adjusting the heparin infusion

aPTT (s)	Rebolus	Stop infusion	Change infusion
<35	80 units/kg	–	↑ by 4 units/kg/h
35–49	40 units/kg	–	↑ by 2 units/kg/h
50–70	–	–	–
71–90	–	–	↓ by 2 units/kg/h
>90	–	1 h	↓ by 3 units/kg/h

    - If patient is obese, utilize an adjusted body weight for heparin dosing
      - Adjusted body weight = ideal body weight + 0.3 (actual body weight – ideal body weight)
    - Check aPTT every 6 h until stable then every 12–24 h
  - Use beyond 48 h is indicated in patients with refractory or recurrent angina or a large infarction

(continued)

Table 2.3 (continued)

- Low molecular weight heparins
  - Enoxaparin may be preferred over unfractionated heparin in intermediate to high-risk patients (*see* Table 2.3 for risk assessment)
  - Enoxaparin
    - 1 mg/kg SQ every 12 h for 2–8 days
    - Adjust dose if CrCl < 30 mL/min. Consider avoiding if CrCl < 15 mL/min
  - Fondaparinux
    - 2.5 mg SQ q24h for up to 8 days
    - Contraindicated if CrCl < 30 mL/min
    - Per guidelines, if used during PCI, it must be coadministered with another anticoagulant with anti-Factor IIa activity
- Warfarin with concomitant aspirin and $P2Y_{12}$ receptor inhibitor therapy may be considered if clinically indicated but is associated with an increased risk of bleeding
  - May be used if patients are intolerant to $P2Y_{12}$ receptor inhibitor therapy
  - Goal INR = 2–2.5 with concomitant aspirin therapy or dual antiplatelet therapy
  - Goal INR = 2.5–3.5 without antiplatelet therapy

Anti-ischemic pharmacotherapy

- β-adrenergic blockers
  - Early intravenous β-adrenergic blockers are to be used with extreme caution, strictly avoided in patients with evidence or significant risk of developing hemodynamic instability, heart failure or bradyarrythmias
  - Oral β-adrenergic blockers should be given in the first 24 h in the absence of contraindications
  - Avoid early if cocaine-induced acute coronary syndrome (relative contraindication)
    - Metoprolol
      - 5 mg IV every 5 min for three total doses (if hypertensive, hyperdynamic, or tachydysrhythmia present and risk factors for cardiogenic shock are not present [e.g., age > 70 years, SBP < 120 mmHg, HR > 110/min]). Usually start with oral β-adrenergic blocker therapy within 24 h
      - Step-down to or initiate 25–50 mg enterally q6–12h
    - Propranolol
      - 1 mg slow intravenous push (IVP), repeated every 5 min; not to exceed a total of 5 mg (if hypertensive, hyperdynamic, or tachydysrhythmia present and risk factors for cardiogenic shock are not present [as above])
      - An alternative dosing regimen may be 0.1 mg/kg in three divided doses every 2–3 min. Do not exceed a rate of 1 mg/min

(continued)

Table 2.3 (continued)

- Contraindications to β-adrenergic blockers
  - Bradycardia (heart rate < 60/min), systolic blood pressure < 100 mmHg, severe left ventricular dysfunction with pulmonary edema, second-degree or third-degree heart block, PR-interval >0.24 s, evidence of hypoperfusion, or active asthma
  - Avoid β-adrenergic blockers with intrinsic sympathomimetic activity (e.g., acebutolol, pindolol)
- Nitroglycerin
  - Sublingual 0.4 mg tablets every 5 min × three doses on presentation (inquire about prehospital administration of nitroglycerin) in the presence of ongoing ischemia. Initiate intravenous pharmacotherapy if chest pain persists
  - Start continuous IV infusion at 5–10 mcg/min and titrate using 5–10 mcg/min increments until symptoms resolve or systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) falls by ≥ 30 mmHg from baseline. Usual maximum dose = 200 mcg/min; indicated in the first 48 h
  - Avoid in patients with:
    - Right ventricular infarction
    - If presenting SBP is < 90 mmHg or ≥ 30 mmHg below baseline MAP
    - Presence of profound bradycardia or tachycardia
    - Recent use (within 24 h of sildenafil or vardenafil or within 48 h of tadalafil) of a phosphodiesterase-5 inhibitor for erectile dysfunction (or pulmonary hypertension)
  - Use beyond 48 h is indicated in patients with persistent angina or pulmonary congestion
  - Dilates large coronary arteries and collateral vessels
  - Some intravenous preparations contain significant amounts of ethanol

Adjuvant pharmacotherapy

- Angiotensin converting enzyme inhibitors (ACE-I)—(oral therapy within 24 h after presentation)
  - Greatest benefit in patients with left ventricular dysfunction (ejection fraction [EF] < 40 %), anterior wall infarction, or pulmonary congestion. Use without these conditions is still warranted
  - Angiotensin receptor blockers if allergic or intolerant to ACE-I (data with valsartan and candesartan)
  - Start with low doses and increase as tolerated
- Statins
  - Commence therapy within 24–96 h after admission (i.e., atorvastatin 80 mg enterally daily)
  - If patient is on a statin before admission, continue therapy during admission to avoid rebound phenomenon

(continued)

Table 2.3 (continued)

- Morphine
  - 2–5 mg IV over 5 min every 5–30 min as needed
- Oxygen therapy
  - Administer to patients with an $SaO_2 < 90$ % or respiratory distress
  - Little justification for use beyond the first 2–6 h in the uncomplicated patient
- Sodium nitroprusside (dilates ***only*** large coronary arteries and ***not*** collateral vessels)
  - **May cause coronary steal**. Avoid general utilization in patients with acute coronary syndromes. If therapy is indicated, use in combination with nitroglycerin, as this agent dilates large coronary arteries and collateral vessels

Data from *http://circ.ahajournals.org/content/early/2013/04/29/CIR.0b013e31828478ac.full.pdf*
Circulation 2012;126:875–910

Table 2.4 Acute pharmacological management of ST-elevation myocardial infarction (noninvasive or conservative strategy)

Fibrinolytic pharmacotherapy (in the absence of contraindications)

- Indicated for patients with ischemic symptoms of ≤12 h in duration in whom, primary PCI cannot be performed within 120 min of first medical contact, and 12-lead electrocardiogram (ECG) evidence of:
  - ST-elevation >0.1 mV in at least two contiguous precordial leads or at least two adjacent limb leads
  - New (or presumed new) left-bundle-branch block
  - A true posterior wall infarction
    - May manifest as tall R waves in the right precordial leads and ST-segment depression in leads V_1–V_4
  - Some beneficial evidence exists to support administration times of up to 24 h after symptom onset in patients with continuous ischemic symptoms
- Alteplase, reteplase, or tenecteplase preferred over streptokinase in:
  - Patients with symptom duration ≤ 6 h
  - Anterior wall infarction (large area of injury)
- Administration within 30 min of arrival into the healthcare system recommended
- Exclude contraindications (*see* Table 2.7)

Agents for IV administration

- Alteplase (tPA)
  - 15 mg IV bolus followed by 0.75 mg/kg continuous IV infusion (not to exceed 50 mg) over 30 min, followed by 0.5 mg/kg continuous IV infusion (not to exceed 35 mg) over 1 h; total dose not to exceed 100 mg.

(continued)

Table 2.4 (continued)

- Reteplase (rPA)
  - 10 units IV push over 2 min followed 30 min later with another 10 units IV push over 2 min (administer a normal saline flush with each dose)
- Tenecteplase (TNKase)—single dose IV push over 5 s
  - <60 kg—30 mg
  - 60–69.9 kg—35 mg
  - 70–79.9 kg—40 mg
  - 80–89.9 kg—45 mg
  - ≥90 kg—50 mg
- Streptokinase
  - 1.5 million units continuous IV infusion over 30–60 min using a ≥0.5 μm in-line filter
  - Monitor for any signs of an allergic reaction
  - Antibodies remain for at least 3–6 months after administration

Evidence of improvement

- Relief of presenting signs and symptoms
- Sustained hemodynamic and electrical stability
- A reduction of at least 50 % of the ST-segment elevation on follow-up ECG obtained 60–90 min after fibrinolytic therapy

*Adjuvant antiplatelet pharmacotherapy **after** fibrinolytic therapy*

- Aspirin 162–325 mg X 1 dose followed by 81–325 mg daily indefinitely (81 mg is the preferred maintenance dose)
- Clopidogrel
  - ≤75 years: 300 mg loading dose followed by 75 mg daily for at least 14 days and up to 1 year
  - >75 years: no loading dose, give 75 mg followed by 75 mg daily for at least 14 days and up to 1 year

*Adjuvant anticoagulant pharmacotherapy **after** fibrinolytic therapy*

- Unfractionated heparin (given with fibrinolytics)
  - Should receive for a minimum of 48 h and preferable the duration of initial hospitalization (up to 8 days or until potential revascularization)
  - As adjunct therapy to the use of alteplase, reteplase, or tenecteplase
    - 60 units/kg IV bolus (4,000 units maximum), followed by 12 units/kg/h continuous IV infusion (1,000 units/h maximum)
  - For patients receiving streptokinase
    - Recommended if patient is at high risk for systemic thromboembolism (anterior wall infarction, heart failure, left ventricular thrombus, atrial fibrillation, previous embolism)
  - Weight-based dosing to achieve an activated partial thromboplastin time (aPTT) between 50 and 70 s (**note**: some institutions titrate heparin to anti-Factor Xa levels)
    - 60–70 units/kg IV bolus (4,000 units maximum), followed by 12–15 units/kg/h continuous IV infusion (1,000 units/h maximum)

(continued)

Table 2.4 (continued)

- Nomogram for adjusting the heparin infusion

aPTT (s)	Rebolus	Stop infusion	Change infusion
<35	80 units/kg	–	↑ by 4 units/kg/h
35–49	40 units/kg	–	↑ by 2 units/kg/h
50–70	–	–	–
71–90	–	–	↓ by 2 units/kg/h
>90	–	1 h	↓ by 3 units/kg/h

  - If patient is obese, utilize an adjusted body weight for heparin dosing
    - Adjusted body weight = ideal body weight + 0.3 (actual body weight – ideal body weight)
  - Check aPTT every 6 h until stable then every 12–24 h
  - For patients receiving *concomitant* fibrinolytic pharmacotherapy, check an aPTT 3 h after heparin initiation
- Use beyond 48 h is indicated in patients with refractory or recurrent angina or a large infarction

- Enoxaparin for up to 8 days or until revascularization
  - If < 75 years: 30 mg IV bolus followed in 15 min by 1 mg/kg SQ q12h (**note**: maximum of 100 mg for the first two doses)
    - Adjust maintenance dose to q24h if CrCl < 30 mL/min; consider avoiding if CrCl < 15 mL/min
  - If ≥ 75 years: no bolus; 0.75 mg/kg SQ q12h (**note**: maximum of 75 mg for the first two doses)
    - Adjust maintenance dose to q24h if CrCl < 30 mL/min; consider avoiding if CrCl < 15 mL/min
- Fondaparinux for up to 8 days or until revascularization
  - 2.5 mg IV, then 2.5 mg SQ daily starting on the following day
  - Contraindicated of CrCl < 30 mL/min

*Adjuvant antithrombotic therapy **after** PCI performed **after** fibrinolytic therapy*

- Aspirin
  - Count any loading dose administered with fibrinolytic therapy (before PCI) followed by 81–325 mg daily indefinitely (81 mg is the preferred maintenance dose)
- Clopidogrel
  - 300 mg loading dose if PCI performed ≤ 24 h after fibrinolytic therapy (if not loaded previously)
  - 600 mg loading dose if PCI performed > 24 h after fibrinolytic therapy (if not loaded previously)
  - Maintenance dose is 75 mg daily for at least 30 days and up to 1 year with a bare-metal stent or at least 1 year with a drug-eluting stent

(continued)

TABLE 2.4 (continued)

- Prasugrel
  - May be used in place of clopidogrel in a patient who has not received a previous loading dose of clopidogrel at the time of fibrinolytic administration
  - 60 mg loading dose if PCI performed > 24 h after a fibrin-specific agent (e.g., tenecteplase, reteplase, alteplase)
  - 60 mg loading dose if PCI performed > 48 h after a non-fibrin-specific agent (e.g., streptokinase)
  - Maintenance dose is 10 mg daily for at least 30 days and up to 1 year with a bare-metal stent or at least 1 year with a drug-eluting stent
  - Should not be administered in patients with a history of prior stroke or transient ischemic attack
- Heparin
  - Continue through PCI and maintain therapeutic activated clotting time of 250–300 s (HemoTec device) or 300–350 s (Hemochron device) taking into account if a GP IIb/IIIa receptor antagonist is utilized
- Enoxaparin
  - Additional dosing is not needed if the last administered dose was within 8 h; administer 0.3 mg/kg IV if the last administered dose was between 8 and 12 h earlier
- Fondaparinux is not recommended as the sole anticoagulant in PCI; a concomitant agent with activity against clotting Factor IIa should be administered

*Adjuvant antiplatelet pharmacotherapy **after** PCI performed (only)*

- Platelet function testing to determine platelet inhibitory response on $P2Y_{12}$ receptor inhibitor therapy may be considered. Role of genotyping in the clinical management of patients has not been established
- Aspirin (if no evidence of allergy)
  - 162–325 mg (non-enteric coated) chew and swallow immediately, followed by 81–162 mg (81 mg daily preferred) enterally daily indefinitely; inquire about prehospital admission of aspirin
    - If history of aspirin-induced bleeding or bleeding risk factors present, use lower doses (i.e., 81 mg daily)
    - A loading dose followed by a maintenance dose of clopidogrel, prasugrel, or ticagrelor in patients who are not able to take aspirin; dual $P2Y_{12}$ receptor inhibitor therapy is **not** recommended
  - Dual therapy with a $P2Y_{12}$ receptor inhibitor is recommended with **one** of the following regimens (either clopidogrel, prasugrel, or ticagrelor [**note**: the ACCF/AHA does not rank these agents in order of preference])

(continued)

Table 2.4 (continued)

- Clopidogrel
  - 600 mg enterally before or at the time of PCI followed by 75 mg daily for up to 1 year; a shorter duration should be considered if increased bleeding risk
  - 75 mg twice daily for 6 days, then 75 mg daily may be considered in patients not at high risk for bleeding
  - Review medication profile for potential drug–drug interactions
- Prasugrel
  - 60 mg enterally at the time of PCI (no later than 1 h after PCI) followed by 10 mg daily for at least 1 year; a shorter duration should be considered if increased bleeding risk
  - Potentially harmful in patients with a prior history of stroke and/or transient ischemic attacks
  - Patients < 60 kg may be at increased risk for bleeding with a 10 mg daily regimen; consider lowering the dose to 5 mg daily
  - Generally not recommended in patients ≥ 75 years except in high-risk situations (e.g., diabetes or prior myocardial infarction); if utilized consider lowering the dose to 5 mg daily
- Ticagrelor
  - 180 mg enterally before or at the time of PCI followed by 90 mg twice daily for at least 1 year; a shorter duration should be considered if increased bleeding risk
  - The recommended concomitant aspirin dose is 81 mg daily
  - Should be avoided in patients with a prior history of intracranial hemorrhage
- Glycoprotein IIb/IIIa inhibitors (given during angiography; in conjunction with heparin or bivalirudin in selected patients)
  - PCI dosing is not provided
  - Administered in addition to aspirin and a $P2Y_{12}$ receptor inhibitor; may be administered just before PCI.
  - Either eptifibatide or tirofiban can be administered for initial early treatment in addition to aspirin and clopidogrel or ticagrelor plus an anticoagulant before angiography
    - Eptifibatide can be continued for 12–18 h after angiography
    - Tirofiban can be continued up to 18 h after angiography
  - If bivalirudin is chosen as the anticoagulant, can omit administration of an IV glycoprotein IIb/IIIa inhibitor
  - Abciximab is not indicated in patients in whom PCI is not planned; may be administered via intracoronary route

*Adjuvant anticoagulant pharmacotherapy **after** PCI performed (**only**)*

- One anticoagulant should be added to antiplatelet therapy
- Bivaliruin (given during angiography, with or without prior heparin)
  - Peri-PCI dosing not provided

(continued)

Table 2.4 (continued)

- Can continue at a dose of 0.25 mg/kg/h up to 72 h if given before diagnostic angiography
- Prefer over heparin and GP IIb/IIIa receptor antagonist in patients at a high risk for bleeding

- Unfractionated heparin (given during angiography)
  - Peri-PCI dosing not provided
    - May be combination with antiplatelet pharmacotherapy for at least 48 h with PCI
    - After PCI dosing: weight-based dosing to achieve an activated partial thromboplastin time (aPTT) between 50 and 70 s (**note:** some institutions titrate heparin to anti-Factor Xa levels)
    - 60–70 units/kg IV bolus (4,000 units maximum), followed by 12–15 units/kg/h continuous IV infusion (1,000 units/h maximum)
  - Nomogram for adjusting the heparin infusion

aPTT (s)	Rebolus	Stop infusion	Change infusion
<35	80 units/kg	–	↑ by 4 units/kg/h
35–49	40 units/kg	–	↑ by 2 units/kg/h
50–70	–	–	–
71–90	–	–	↓ by 2 units/kg/h
>90	–	1 h	↓ by 3 units/kg/h

    - If patient is obese, utilize an adjusted body weight for heparin dosing
      - Adjusted body weight = ideal body weight + 0.3 (actual body weight – ideal body weight)
    - Check aPTT every 6 h until stable then every 12–24 h
- Enoxaparin IV followed by SQ for up to 8 days or until revascularization
  - If age < 75 years: 30 mg IV bolus followed in 15 min by 1 mg/kg SQ q12h (**note**: maximum of 100 mg for the first two doses)
    - If age ≥ 75 years: no bolus, 0.75 mg/kg SQ q12h (**note**: maximum of 75 mg for the first two doses)
  - If CrCl < 30 mL/min, then q24h dosing (**note**: caution is advised in patients with impaired renal function); consider avoiding of CrCl < 15 mL/min
  - Preferred over unfractionated heparin if anticoagulation is required for greater than 48 h
- Fondaparinux IV followed within 24 h by daily SQ for up to 8 days or until revascularization
  - 2.5 mg IV, followed by 2.5 mg SQ daily starting on the following day
  - Fondaparinux is not recommended as the sole anticoagulant for primary PCI
  - Contraindicated if CrCl < 30 mL/min

(continued)

Table 2.4 (continued)

- Warfarin
  - Triple therapy should be restricted to patients with systemic venous thromboembolism or stent thrombosis; benefit should out-weight the bleeding risk.
  - Should be administered in patients with STEMI and atrial fibrillation with a $CHADS_2$ score ≥ 2, mechanical heart valves, or hypercoagulable state (i.e., DVT, PE, LV thrombus)
  - In patients with a large anterior wall infarction and significant left ventricular dysfunction, visible intracardiac thrombus, akinetic segment, or a history of a thromboembolic event
    - Administered to achieve an INR of 2–2.5 might be considered in patients receiving dual antiplatelet therapy
    - May be limited to 3 months in patients with LV dysfunction; repeat echocardiogram in 3 months to determine the duration of warfarin pharmacotherapy

Adjuvant anti-ischemic pharmacotherapy

- β-adrenergic blockers
  - *Avoid early* if cocaine-induced acute coronary syndrome
    - Metoprolol
      - 5 mg IV for every 5 min in three doses (if hypertensive, ongoing ischemia, hyperdynamic, or tachydysrhythmia present and risk factors for cardiogenic shock are not present [e.g., age > 70 years, SBP < 120 mmHg, HR > 110/min]). Usually start with oral β-adrenergic blocker therapy within 24 h in the absence of bradycardia, pulmonary congestion, or hypotension/hypoperfusion
      - Step down to 25–50 mg enterally q6–12h
    - Carvedilol 3.125 twice daily and titrate to 25 mg twice daily as tolerated every 3–5 days
    - Propranolol
      - 1 mg slow intravenous push (IVP), repeated every 5 min. Not to exceed a total of 5 mg
      - An alternative dosing regimen may be 0.1 mg/kg in three divided doses every 2–3 min. Do not exceed a rate of 1 mg/min
  - Contraindications
    - Bradycardia (heart rate <60 bpm), systolic blood pressure <100 mmHg, severe left ventricular dysfunction with pulmonary edema, second or third-degree heart block, PR interval > 0.24 s, evidence of hypoperfusion, active asthma. Patients with initial contraindications in the first 24 h should be reevaluated for the presence or absence of these contraindications
  - Avoid β-adrenergic blockers with intrinsic sympathomimetic activity (e.g., acebutolol, pindolol)

(continued)

Table 2.4 (continued)

- Nitroglycerin
  - Sublingual 0.4 mg tablets every 5 min × three doses on presentation. Initiate intravenous pharmacotherapy if chest pain persists
  - Start continuous IV infusion at 5–10 mcg/min and titrate using 5–10 mcg/min increments until symptoms resolve or systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) falls by ≥30 mmHg from baseline. Usual maximum dose = 200 mcg/min
  - Avoid in patients with:
    - Right ventricular infarction
    - If presenting systolic blood pressure (SBP) is <90 mmHg or ≥30 mmHg below baseline MAP
    - Presence of profound bradycardia or tachycardia
    - Recent use (within 24 h of sildenafil or vardenafil or within 48 h of tadalafil) of a phosphodiesterase-5 inhibitor for erectile dysfunction (or pulmonary hypertension)
  - Use beyond 48 h is indicated in patients with persistent angina or pulmonary congestion
  - Dilates large coronary arteries and collateral vessels
  - Some intravenous preparations contain significant amounts of ethanol

Adjuvant pharmacotherapy or device therapy

- Angiotensin converting enzyme inhibitors (ACE-I)—(oral therapy within 24 h after presentation)
  - Greatest benefit in patients with left ventricular dysfunction (ejection fraction <40 %), anterior wall infarction, or pulmonary congestion. Use without these conditions is still warranted
    - Use indefinitely in patients with left ventricular dysfunction
    - Use for 4–6 week in patients without left ventricular dysfunction unless another indication exists
    - Can utilize lisinopril, ramipril, trandolapril, or captopril
  - Angiotensin receptor blockers (ARBs) if allergic or intolerant to ACE-I
    - Can utilize valsartan
  - Start with low doses and increase as tolerated
- Calcium channel blockers (verapamil or diltiazem only)
  - May be utilized in situations where β-adrenergic blockers are ineffective or contraindicated
  - Do not use a calcium channel blocker in the setting of chronic heart failure, 2° or 3° atrioventricular block, or left ventricular dysfunction
- Aldosterone receptor blockade
  - Spironolactone 25 mg enterally daily or eplerenone 25 mg enterally daily
    - May increase spironolactone or eplerenone to 50 mg daily within 4 week

(continued)

Table 2.4 (continued)

- Indicated in patients on ACE-I or ARB pharmacotherapy with a left ventricular ejection fraction ≤ 40 % and either symptomatic heart failure or diabetes mellitus
  - Contraindications include serum potassium >5.5 mEq/L at initiation or a CrCl ≤ 30 mL/min. Eplerenone is a CYP3A4 substrate; monitor for drug–drug interactions
- Statins
  - Commence therapy within 24–96 h after admission (e.g., atorvastatin 80 mg enterally daily)
  - If patient is on a statin before admission, continue therapy during admission to avoid rebound phenomenon
- Morphine
  - 2–5 mg IV over 5 min every 5–30 min as needed
- Oxygen therapy
  - Administer to patients with an $SaO_2 < 90$ %
  - Little justification for use beyond the first 2–6 h in the uncomplicated patient
- Sodium nitroprusside (dilates ***only*** large coronary arteries and ***not*** collateral vessels)
  - **May cause coronary steal**. Avoid general utilization in patients with acute coronary syndromes. If therapy is indicated, use in combination with nitroglycerin, as this agent dilates large coronary arteries and collateral vessels
- Insulin infusions (very controversial)
  - Patient should have a continuous source of dextrose if infusing insulin
  - In patients with hyperglycemia with or without preexisting diabetes
  - During the first 24–48 h (especially in patients with a complicated course)
  - Maintain blood glucose between 80 and 150 mg/dL
    - Optimum range not delineated
    - Strict avoidance of hypoglycemia is advocated
- Docusate sodium 100 mg enterally every 8 h to prevent straining
- Anxiolytic medications as needed
- An intra-aortic balloon pump (IABP) may be utilized in a patient in cardiogenic shock secondary to mechanical complications (e.g., mitral regurgitation or VSD) or with precipitous decompensation. Routine use of IABP in conjunction with PCI or fibrinolysis in the setting of STEMI and cardiogenic shock is not warranted
- An implantable cardioverter-debrillator may be indicated before discharge in a patient who developed sustained VT/VF more than 48 h after the STEMI

Data from *http://circ.ahajournals.org/content/early/2013/04/29/CIR.0b013e31828478ac.full.pdf*
Chest 2004;126:549S–575S. *Lancet* 2005;366:1607–1621

Table 2.5 Considerations in patients with right ventricular infarctions

- Obtain right precordial leads in any patient with an inferior wall myocardial infarction
- Patients have an exaggerated preload dependence. Blood pressure may decrease in response to diuretics, nitroglycerin, morphine, or positive pressure ventilation
  - Judicious use of fluids to maximize preload
    - Excess fluid may be harmful (i.e., increase left shift of intraventricular septum during diastole, increase tricuspid regurgitation, increase RV wall/oxygen demand)
  - Avoid use of nitroglycerin, loop diuretics, and morphine (see above)
    - All can result in venous dilation with a resultant decrease in preload
- Restore atrioventricular synchrony if possible
- Reduce right-ventricular afterload, avoid hypoxemia and acidemia. Maintain normal FRC if intubated. Inotropic support with dobutamine/dopamine when necessary; IABP may be considered when significant LV dysfunction coexists
- Avoid hypoxemia, acidosis, and lung hyperinflation

Table 2.6 Contraindications to fibrinolytic therapy in patients with ST-elevation myocardial infarction

Absolute	*Relative*
• Active internal bleeding (except menses)	• Ischemic stroke >3 months
• Previous hemorrhagic stroke	• History of chronic, severe, uncontrolled hypertension
	• Uncontrolled hypertension on presentation (>180/110 mmHg)
• Atherothrombotic or cardioembolic cerebrovascular accident within 3 months	• Current use of anticoagulants in therapeutics doses
	• Known bleeding diathesis
• Known intracranial neoplasm (primary or metastatic), aneurysm, arteriovenous malformation	• Recent internal bleeding (within 2–4 weeks)
	• Recent major surgery (within 3 weeks)
• Suspected aortic dissection	• Recent trauma (within 2–4 weeks)
• Significant closed-head injury or facial trauma within 3 months	• Recent prolonged cardiopulmonary resuscitation (>10 min) with evidence of thoracic trauma
• Intracranial or intraspinal surgery within 2 months	
• Severe uncontrolled hypertension	• Noncompressible vascular punctures
• With streptokinase—administration within the past 6 months	• Active peptic ulcer disease
	• Pregnancy
	• Dementia

Table 2.7 Management of acute decompensated heart failure

Pulmonary edema only

- Furosemide 0.5–1 mg/kg IV push (adjust higher for reduced GFR)
- Morphine 2–4 mg IV, repeat prn
- Nitroglycerin sublingual/IV if hemodynamically stable
- Oxygen
- NIPPV-CPAP/BIPAP (if hypercapneic or excessive work of breathing)
- Intubation/PEEP-if unstable, fails NIPPV or has contraindications to NIPPV
  - PPV reduces LV preload, afterload, and oxygen consumption

Hypoperfusion state only

- Crystalloid/colloid to maximize LV preload while avoiding pulmonary edema. If a pulmonary artery catheter (PAC) is present, achieve a pulmonary capillary wedge pressure (PCWP) between 15 and 18 mmHg (average)
  - If cardiac index (CI) > 2.2 L/min/m^2 and patient improves clinically → observe
- If PCWP between 15 and 18 mmHg but hypoperfused
  - If adequate mean arterial pressure (MAP)
    - Dobutamine—2.5–10 mcg/kg/min continuous IV infusion up to 20 mcg/kg/min (monitor for hypotension)
    - Milrinone—0.2–0.75 mcg/kg/min continuous IV infusion
      - Loading dose of 50 mcg/kg over 10 min may be utilized but is frequently omitted
        - Avoid loading dose or administer 50 % if tenuous hemodynamics
      - Use lower doses in patients with renal dysfunction (i.e., 0.2 mcg/kg/min)
      - Limited experience with dobutamine and milrinone co-administration
    - Add nitroprusside if CI < 2.2 L/min/m^2 if clinical end point not achieved despite therapeutic dobutamine +/−milrinone
      - Nitroprusside—0.25–0.5 mcg/kg/min continuous IV infusion; increase in increments of 0.25–0.5 mcg/kg/min until desired hemodynamic effect. Usual doses up to 2–3 mcg/kg/min
        - **High-alert medication—read package insert before use**
- If inadequate MAP
  - Dopamine—2.5–20 mcg/kg/min continuous IV infusion. May require doses ≥10 mcg/kg/min for adequate BP response
  - Norepinephrine—start at 4 mcg/min and titrate to desired effect

(continued)

Table 2.7 (continued)

Pulmonary congestion and hypoperfusion

- If adequate MAP
  - Goal PCWP between 15 and 18 mmHg
  - Furosemide 0.5–1 mg/kg IV push (use with caution)
    - +/−morphine 2–4 mg IV (use with caution)
    - +/−nitroglycerin IV (use with caution)
      - Start continuous IV infusion at 5–10 mcg/min and titrate using 5–10 mcg/min increments until symptoms resolve or SBP < 90 mmHg or MAP falls by ≥ 30 mmHg from baseline. Usual maximum dose = 200 mcg/min
  - Dobutamine—2.5–10 mcg/kg/min continuous IV infusion up to 20 mcg/kg/min
  - Milrinone—0.2–0.75 mcg/kg/min continuous IV infusion
    - Loading dose of 50 mcg/kg over 10 min may be utilized
      - Avoid loading dose or administer 50 % if tenuous hemodynamics
    - Use lower doses in patients with renal dysfunction (i.e., 0.2 mcg/kg/min)
    - Limited experience with dobutamine and milrinone co-administration
- If inadequate MAP
  - Goal PCWP between 15 and 18 mmHg
  - Furosemide 0.5–1 mg/kg IV (use with caution)
    - +/−morphine 2–4 mg IV (use with caution)
  - Dopamine—2.5–20 mcg/kg/min continuous IV infusion. May require doses ≥10 mcg/kg/min for adequate BP response
  - Norepinephrine—start at 4 mcg/min and titrate to desired effect

TABLE 2.8 Vaughan Williams classification of antiarrhythmics

Type	*Drug*	*Automaticity*	*Conduction velocity*	*Refractory period*	*Blockade*
Ia[a]	Quinidine Procainamide[b] Disopyramide	↓	↓	↑	Sodium (intermediate)
lb	Lidocaine Mexiletine Tocainide	↓	0/↓	↓	Sodium (fast on–off)
Ic	Flecainide Propafenone[c] Moricizine	↓	↓↓	0	Sodium (slow on–off)
II	β-adrenergic blockers[d]	↓	↓	↑	β-adrenergic receptors
III[e]	Amiodarone[f] Sotalol[c] Ibutelide Dofelitide	0	0	↑↑	Potassium
IV	Verapamil Diltiazem	↓	↓	↑	Calcium

[a]Class I antiarrhythmics display different binding affinity for the sodium channel (C>A>B). They possess rate-dependence properties (i.e., sodium channel blockade is greatest at fast heart rates). Additionally, this class may increase defibrillation threshold (i.e., greater energy may be required for successful cardioversion)
[b]The *N*-acetyl procainamide (NAPA) metabolite blocks rapid potassium channels
[c]Has β-blocking properties
[d]Propranolol (at high doses) has been noted to have quinidine-like activity
[e]This class may decrease defibrillation threshold (i.e., less energy may be required for successful cardioversion)
[f]Has activity of all four Vaughan Williams classifications

TABLE 2.9 Antithrombotic pharmacotherapy for patients with new onset atrial fibrillation

***Note**: these recommendations apply for atrial flutter as well*

- **Use of a $CHADS_2$ score to assess thromboembolic risk and management**
  - Congestive heart failure (1 point)
  - Hypertension (1 point)
  - Age ≥ 75 years (1 point)
  - Diabetes mellitus (1 point)
  - Secondary (previous) TIA, CVA, or systemic embolic event prevention (2 points)
  - **Low-risk score = 0**—recommend no therapy rather than antithrombotic therapy. If a patient chooses therapy, suggest aspirin (81–325 mg over oral anticoagulation)
  - **Intermediate risk score = 1**—recommend oral anticoagulation over aspirin or no therapy. Combination therapy with aspirin and clopidogrel may be considered
  - **High-risk score ≥ 2**—recommend oral anticoagulant pharmacotherapy rather that no therapy, aspirin, or combination aspirin plus clopidogrel. Oral anticoagulant pharmacotherapy can include warfarin (goal INR of 2.5 [range 2–3]), dabigatran, rivaroxaban, or apixaban. For patients not candidates for oral anticoagulant pharmacotherapy, can recommend the combination of aspirin plus clopidogrel
  - **Note**: the $CHADS_2$-VASc score adds additional risk factors for stroke and may be utilized in parallel with the $CHADS_2$ score to assess for stroke risk and assist in management decisions; V-vascular disease (i.e., prior ACS or PVD); A-age 65–74 years; Sc-female gender
- Atrial fibrillation and mitral stenosis
  - Warfarin administered to achieve an INR of 2.5 (range 2–3). If not a candidate for oral anticoagulation, can recommend the combination of aspirin plus clopidogrel
- Atrial fibrillation and placement of an intracoronary stent
  - Triple therapy during the first month after a bare-metal stent or the first 3–6 months after a drug-eluting stent with warfarin administered to achieve an INR of 2.5 (range between 2 and 3) and aspirin plus clopidogrel. After this initial period of triple therapy, warfarin plus a single antiplatelet agent. **Note**: in patients with a $CHADS_2$ score of 0 or 1, can use dual antiplatelet therapy rather than triple therapy for the first 12 months
- Atrial fibrillation and ACS *without* intracoronary stent placement
  - Warfarin administered to achieve an INR of 2.5 (range between 2 and 3) plus single antiplatelet therapy for the first 12 months. If $CHADS_2$ score of 0, can recommend dual antiplatelet therapy for the first 12 months

(continued)

Table 2.9 (continued)

- Elective electrical or pharmacological cardioversion (≥48 h or unknown duration)
  - Warfarin administered to achieve an INR of 2.5 (range 2–3), dabigatran, or LMHW for at least 3 weeks before elective cardioversion and for at least 4 weeks after successful cardioversion. Decisions beyond 4 weeks should be based on risk-based recommendations for long-term anticoagulation
  - If duration less than 48 h, can perform electric or pharmacological cardioversion with intravenous unfractionated heparin or full dose low molecular weight heparin (LMWH) initiated at presentation then therapeutic anticoagulation for at least 4 weeks after successful cardioversion. Decisions beyond 4 weeks should be based on risk-based recommendations for long-term anticoagulation
- Emergency electrical or pharmacological cardioversion
  - Intravenous unfractionated heparin (goal activated partial thromboplastin time [aPTT] = 60 s [range 50–70 s]) started as soon as possible followed by 4 weeks of therapeutic anticoagulation. Decisions beyond 4 weeks should be based on risk-based recommendations for long-term anticoagulation

Data from *Chest* 2012;141:7S–47S

Table 2.10 Causes and management of acquired torsades de pointes

Factors that may exacerbate/precipitate

- Congenital
  - Jervell–Lange-Nielsen (autosomal dominant with congenital deafness)
  - Romano-Ward (autosomal dominant without deafness)
- Severe bradycardia (HR < 50/min), sinus node dysfunction, A-V block
- Cardiomyopathy, myocarditis, myocardial ischemia/ infarction
- Hypokalemia, hypomagnesemia, hypocalcemia
- Starvation, anorexia nervosa, and liquid protein diets
- Hypothyroidism, severe hypothermia
- Female sex
- Ion-channel polymorphisms

Medications (extensive list may be found at www.torsades.org)

- Antiarrhythmic agents
  - Quinidine, procainamide, disopyramide, sotalol, ibutilide, dofetilide, and amiodarone (less common)
- Anti-infectives
  - Clarithromycin, erythromycin, azithromycin, fluoroquinolones, pentamidine, amantadine, foscarnet, and voriconazole

(continued)

Table 2.10 (continued)

- Antipsychotics
  - Chlorpromazine, thioridazine, mesoridazine, quetiapine, ziprasidone, haloperidol, and risperidone
- Antidepressants
  - Amitriptyline, desipramine, doxepin, imipramine, and venlafaxine
- Others
  - Tamoxifen, droperidol, cisapride, tizanidine, probucol, quinine, methadone, levomethadyl, and ranolazine
- Review medication profile for drug–drug interactions (extensive lists may be found at www.drug-interactions.com)

Management

- Discontinue offending drug(s)
- Unsynchronized electric defibrillation if hemodynamically unstable
- Correct any electrolyte disorders (e.g., hypokalemia, hypomagnesemia)
- Magnesium IV (suppresses early after-depolarizations)
  - 1–2 g IV in 50 mL D5W over 2–5 min; may repeat dose in 15 min
  - Followed with 0.5–1 g/h continuous IV infusion (titrate dose to control torsades de pointes)
- Temporary transvenous overdrive pacing (goal HR = 100 beats/min)
- Pharmacological pacing
  - Isoproterenol (if available) 2–10 mcg/min continuous IV infusion (lower dose if patient has a history of coronary artery disease)
    - Titrate to increase heart rate (about 100/min) until torsades de pointes is suppressed
  - Epinephrine 2–10 mcg/min continuous IV infusion
    - Titrate to increase heart rate (about 100 beats/min) until torsades de pointes is suppressed
- Lidocaine (less effective than above interventions)
- Sodium bicarbonate may be useful if torsades de pointes is quinidine-induced
- Adrenergic agents are contraindicated in congenital long QT-interval syndromes; β-adrenergic blockade may be indicated

Table 2.11 Hypertensive crises

Hypertensive emergency (no absolute blood pressure range)

- Sudden increase in systolic and diastolic blood pressure associated with end-organ damage. Organ dysfunction is uncommon with a diastolic blood pressure ≤ 120 mmHg. The absolute level may not be as important as the rate of increase. Lower blood pressure threshold for treatment in pregnant patients (i.e., ≥ 150–170/105–110 mmHg or mean arterial pressure >110 mmHg)

Hypertensive urgency

- Severely elevated blood pressure without acute end-organ damage

End-organ damage examples

- Heart
  - Acute aortic dissection, acute pulmonary edema, left ventricular failure, angina, and acute coronary syndrome
- Brain
  - Intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and hypertensive encephalopathy
- Acute kidney injury, retinopathy, microangiopathic hemolytic anemia, and preeclampsia/eclampsia

Note: Although all of the above require modulation of blood pressure, acute HTN may be directly responsible for the end-organ damage in acute kidney injury/retinopathy (malignant HTN), hypertensive encephalopathy, ACS, pulmonary edema and preeclampsia

Diagnosis

- *Must* differentiate between hypertensive emergency and urgency
- History (previous crises, previous medications including OTCs and herbal medications, recreational drug use), physical examination (mandatory fundoscopic examination, blood pressure on all limbs), urinalysis, and electrolytes, blood urea nitrogen, creatinine, peripheral blood smear, complete blood count, electrocardiogram (ECG), chest X-ray, and head CT
- Identify etiology if possible

Goals of blood pressure reduction

- Initial goal is **not** to achieve a normal BP (except in acute aortic dissection)
- Reduce mean arterial pressure (MAP) by 20–25 % or to a diastolic blood pressure of 110 mmHg in hypertensive emergencies
- Reduce blood pressure gradually over 24–48 h in hypertensive urgencies

Notes: Placement of an arterial catheter is strongly recommended. Target should generally be the MAP (possible exceptions: ICH-systolic; preeclampsia-systolic most important; aortic dissection-dP/dT reflected in systolic and heart rate; ischemic stroke-guidelines use systolic and diastolic

(continued)

Table 2.11 (continued)

Hypertensive emergency	*Target/time to achieve goal*
• Acute aortic dissection	• SBP 100–120 mmHg and heart rate of 60 beats/min within 5–10 min
• Acute pulmonary edema	• MAP reduction within 15–30 min
• Hypertensive encephalopathy	• MAP reduction within 2–3 h
• Intracerebral hemorrhage	• BP 140/90 mmHg if there is no evidence or suspicion of elevated intracranial pressure. Time to achieve not well delineated (possibly within 3 h)
• Subarachnoid hemorrhage	• SBP between 140 and 160 mmHg within 3–6 h
• Catecholamine crisis	• MAP reduction within 2–6 h

Management of hypertensive emergencies (intravenous agents)

- Left ventricular failure and pulmonary edema
  - Drugs of choice—nitroprusside, nitroglycerin, fenoldopam, enalaprilat, and loop diuretics
  - Avoid—β-adrenergic blockers, non-dihydropyridine calcium channel blockers, and hydralazine
- Acute coronary syndromes
  - Drugs of choice—nitroglycerin, β-adrenergic blockers, enalaprilat, nicardipine (may be added), and fenoldopam (may be added)
  - Cautious—nitroprusside (coronary steal phenomenon)
  - Avoid—hydralazine, minoxidil, diazoxide, and calcium channel blockers in Q-wave myocardial infarction
- Acute aortic dissection
  - Drugs of choice—esmolol + nitroprusside, esmolol + nicardipine, and labetolol
  - Avoid—hydralazine, minoxidil, and diazoxide
- Catecholamine crises
  - Drugs of choice—nitroprusside, phentolamine, nicardipine, and benzodiazepines in alcohol withdrawal or cocaine intoxications
  - Avoid—monotherapy with β-adrenergic blockers (including labetolol)
- Hypertensive encephalopathy, ICH, and SAH
  - Drugs of choice—labetolol, nicardipine, nimodipine (in SAH), and fenoldopam
  - Avoid—nitroprusside, nitroglycerin, clonidine, methyldopa, propranolol, diazoxide, hydralazine, and minoxidil
- Acute renal failure/microangiopathic hemolytic anemia
  - Drugs of choice—nicardipine, fenoldopam
  - Avoid—nitroprusside, angiotensin converting enzyme inhibitors ACE-Is (except in sclerodermic renal crisis)

(continued)

Table 2.11 (continued)

- Preeclampsia/eclampsia
  - Drugs of choice—hydralazine, labetolol, and nicardipine
    - Hydralazine has a long history of safety in pregnancy; however, blood pressure lowering is unpredictable in timing and potency with a given intravenous dose (**author's opinion**)
  - Avoid—nitroprusside, angiotensin converting enzyme inhibitors [ACE-Is], angiotensin receptor blockers [ARBs], and loop diuretics

Management of hypertensive urgencies (oral agents)

- Clonidine—0.2 mg enterally in one dose, then 0.1 mg q1h as needed to a total dose of 0.6 mg
- Captopril—25 mg enterally in one dose, then 12.5–25 mg as needed
- Labetolol—200–300 mg enterally every 2–3 h

Data from *Chest* 2000;118:214–227. *Stroke* 2007;38:2001–2023 and Stroke 2012;43:1711–1737

Table 2.12 Management of catecholamine/vasopressin extravasation

- Stop catecholamine infusion, leave peripheral IV (PIV) in place, elevate extremity
- ***Infiltrate*** the involved area with phentolamine 5 mg (in 10 mL normal saline)
  - Use multiple small injections with a 27- or 30-gauge needle. Do not inject a volume that will result in skin swelling
  - Also, may inject a portion (use clinical judgment to determine dose) through the PIV as soon as the extravasation is noted
- Repeat 5 mg if no evidence of resolution within 30 min

Notes:

Vasopressor infusions (including vasopressin) should be given through a PIV placed definitively intravascularly in a large vein (e.g. antecubital vein) or preferably a CVL

If using a PIV, we suggest a protocolized extremity check to ensure frequent, periodic surveillance of the PIV infusion site and surrounding tissue to prevent/minimize tissue necrosis due to extravasation

If using a PIV, the clinical team should be educated on both complications/antidote of vasopressor extravasation

Extravasation of vasopressor delivered by the IO route has been reported

Table 2.13 Prevention of venous thromboembolism in the medical intensive care unit patient

Review risk factors for thromboembolism

- Age > 40 years, previous venous thromboembolism, chronic heart failure, acute respiratory failure, recent major surgery (within 2 weeks), confined air/ground travel (>6 h duration within 1 week of admission), inflammatory bowel disease, myocardial infarction, nephrotic syndrome, and ischemic stroke
- Hypercoagulable states
  - Malignancy, sepsis, antiphospholipid antibody syndrome, dysfibrinogenemia, DKA, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, and pregnancy/postpartum
  - Antithrombin, protein C, and protein S deficiencies
  - Factor V Leiden mutation, prothrombin 20210A gene mutation, and plasminogen activator inhibitor (PAI-1) excess
  - Heparin-induced thrombocytopenia
- Pharmacotherapy
  - Estrogen, megestrol, tamoxifen, and raloxifene
  - General anesthesia use > 40 min
- Vascular injury
  - Trauma, knee or hip surgery, and central venous access or in-dwelling femoral venous catheter, pregnancy/delivery
- Venous stasis
  - Immobility (including bedrest ≥ 3 days), paralysis, morbid obesity, varicose veins, and hyperviscocity syndromes, pregnancy

Risk stratification

- Patients should be classified as low, moderate, or at high risk depending on their medical condition and presence of risk factors

Prophylaxis

- Discontinue estrogen-containing products and megestrol based on clinical judgment
- **Low risk** or if there is a <u>contraindication</u> to pharmacotherapy
  - Early ambulation *or* graduated compression stockings and/or intermittent pneumatic compression devices (IPC)
- **Moderate risk**
  - Heparin 5000 units SQ q12h (*see* comment below)
- **High risk**
  - IPC + heparin 5000 units SQ q8h or a low molecular weight heparin or fondaparinux

Duration of prophylaxis

- Based on patient's acute medical condition and the presence or resolution of risk factors

Chest 2012;141:7S–47S

(continued)

TABLE 2.13 (continued)

Notes:

(a) Prophylaxis is not indicated if the patient has therapeutic pharmacological anticoagulation
(b) Pharmacotherapy should **not** be utilized if contraindications are present
(c) Patients who weigh ≥70 kg should generally receive heparin 5000 units SQ q8h if moderate risk or at high risk
(d) Patients on vasopressors may require higher doses of unfractionated heparin or a different mode of drug administration. Low molecular weight heparins and fondaparinux should be avoided
(e) In patients with a **creatinine clearance less than 30 mL/min**, unfractionated heparin may be preferred. If a low molecular weight heparin is utilized, may need to adjust dose and monitor periodic peak anti-Factor Xa levels to avoid drug accumulation; fondaparinux is contraindicated

TABLE 2.14 Acute management of a deep-vein thrombosis or pulmonary embolism

Deep-vein thrombosis

- Elevate and rest an acutely swollen leg
  - Routine bed rest should not be recommended as part of the standard of care
  - Early ambulation once anticoagulated
- In an acute deep-vein thrombosis or pulmonary embolism, a low molecular weight heparin or fondaparinux is preferred over unfractionated heparin (unless the patient is hemodynamically unstable or there is a predictable need for an invasive procedure)
- Heparin
  - 80 units/kg IV bolus followed by 15–18 units/kg/h continuous IV infusion based on activated partial thromboplastin time (aPTT). **Note:** some institutions titrate heparin to anti-Factor Xa levels
  - Nomogram for adjusting the heparin infusion

aPTT (s)	Rebolus	Stop infusion	Change infusion
<35	80 units/kg	–	↑ by 4 units/kg/h
35–49	40 units/kg	–	↑ by 2 units/kg/h
50–70	–	–	–
71–90	–	–	↓ by 2 units/kg/h
>90	–	1 h	↓ by 3 units/kg/h

    - If patient is obese, utilize an adjusted body weight for heparin dosing
      - Adjusted body weight = ideal body weight + 0.3 (actual body weight – ideal body weight)
  - Obtain aPTT every 6 h until stable, then every 12–24 h
  - Obtain anti-Factor Xa levels to guide therapy in patients who require large doses of heparin (i.e., >25 units/kg/h)

(continued)

Table 2.14 (continued)

- Low molecular weight heparins *(*adjust doses for renal dysfunction*)*
  - Enoxaparin
    - 1 mg/kg SQ q12h (maximum initial single dose = 160 mg)
  - Dalteparin
    - 100 units/kg SQ q12h (maximum initial single dose = 10,000 units)
  - Tinzaparin
    - 175 units/kg SQ q24h (maximum initial dose = 18,000 units/day)
- Fondaparinux (contraindicated if CrCl < 30 mL/min)
  - <50 kg—5 mg SQ Q24h
  - 50–100 kg—7.5 mg SQ q24h
  - >100 kg—10 mg SQ q24h
- Fibrinolytic therapy
  - Systemic or local fibrinolytic therapy reserved for patients who have limb-threatening thrombosis (phlegmasia cerulean alba dolens) despite appropriate anticoagulant therapy
  - Consider surgical or catheter-based venous thrombectomy if contraindications to fibrinolytic therapy exist
- Inferior vena cava (IVC) filter (consider use of a retrievable filter)
  - May be useful in patients with:
    - Contraindications to anticoagulation (e.g., serious bleeding risk, coagulopathic, thrombocytopenic, metastatic brain cancer, and fall risk)
    - Failure of anticoagulation
    - Low cardiopulmonary reserve (i.e., right-ventricular hypokinesis on echocardiogram) where an initial or repeat pulmonary embolism would be catastrophic
    - Large free-floating clot loosely attached to the inferior vena cava wall

Pulmonary embolism (PE)

- Not in shock and right ventricular dysfunction is absent
  - Manage as deep-vein thrombosis (DVT) protocol
- Not in shock and right ventricular systolic dysfunction is present
  - Manage as DVT protocol
  - Consider fibrinolysis, especially in patients with persistent or worsening respiratory failure and/or evidence of hypoperfusion with a low risk of bleeding
  - Consider IVC filter if significant lower extremity/IVC clot persists (**editor's opinion**)
  - Consider catheter-based embolectomy +/– IVC filter if large central pulmonary artery clot burden and persistent hypoxemia or right ventricular dysfunction (**editor's opinion**)

(continued)

Table 2.14 (continued)

- In shock (e.g., systolic blood pressure < 90 mmHg)
  - Definitive or presumptive diagnosis in the ICU with transesophageal echocardiogram
  - Cautious trial of volume expansion with a crystalloid in the absence of high right atrial pressure (CVP or jugular venous pressure); uncommon.
    - Excess fluid administration may worsen perfusion by increasing RV wall tension and ischemia, increasing tricuspid regurgitation, and decreasing LV compliance due to increased ventricular septal shift
  - Vasopressor
    - Norepinephrine (preferred agent)
    - RV perfusion pressure (MAP-CVP) and a higher MAP goal should be targeted (**editor's opinion**)
  - Inotropic support
    - Dobutamine (preferred agent)
    - If intubation necessary-inhaled nitric oxide (up to 40 ppm) is reasonable and cautious use of PEEP to normalize FRC without decreasing venous return (**editor's opinion**)
  - Fibrinolysis—in the absence of contraindications and the patient is in "compensated" shock (**author's opinion**)
    - Alteplase 100 mg IV over 2 h through a peripheral vein
    - Alteplase 0.6 mg/kg (maximum of 50 mg) over 2–15 min may be utilized if the patient is in cardiac arrest
    - Administer heparin without a loading dose when the aPTT $\leq 2 \times$ control after fibrinolysis
  - Surgical embolectomy
    - In the absence of contraindications and the patient is in "decompensated" shock with a central clot (**editor's opinion**)
    - Catheter-based embolectomy may be an alternative to IV fibrinolysis. Not enough data to support routine use; can be attempted if central clot and contraindications to fibrinolysis or cardio-pulmonary bypass (editor suggests procedure performed in OR or "hybrid" room)
    - Place an IVC filter

Data from *Chest* 2012; 141:7S–47S

Table 2.15 Management of an elevated international normalized ratio (INR) in patients receiving warfarin pharmacotherapy

INR < 4.5 with no significant signs of bleeding	• Hold or decrease next dose • Monitor more frequently • If held, resume lower dose when INR in the therapeutic range
INR ≥ 4.5–10 with no significant signs of bleeding	• Hold for next one or two dose(s) • Monitor more frequently • Resume lower dose when INR in the therapeutic range *If rapid reversal for surgery is needed* • Administer vitamin K_1 2.5–5 mg enterally • Administer an additional vitamin K_1 2.5 mg enterally if INR is still elevated after 24 h
INR ≥ 10 with no significant signs of bleeding	• Hold warfarin pharmacotherapy • Administer vitamin K_1 5 mg enterally ◦ Administer vitamin K_1 10 mg enterally if increased bleeding risk or rapid reversal is warranted ◦ INR will be reduced within 24 h ◦ Administer additional vitamin K_1 as needed • Monitor more frequently • Resume lower dose when INR in therapeutic range
Serious or life-threatening bleeding at any INR	• Hold warfarin pharmacotherapy • Administer vitamin K_1 10 mg IV over 30–60 min ◦ May be repeated in 12 h • Supplement with prothrombin complex concentrate (4-factor may be preferred) or fresh frozen plasma (15–20 mL/kg) • Recombinant factor VIIa may be considered as an alternative to prothrombin complex concentrate if the patient has a known history of heparin-induced thrombocytopenia

Data from *Chest* 2012; 141:7S–47S

Notes:

(a) When bleeding is not evident, the goal INR with intervention is to achieve a therapeutic INR (e.g., between 2 and 3; ***not*** 1)

(b) In patients with mild-to-moderate elevations in INR and no evidence of *major* bleeding, vitamin K_1 should be administered enterally. Subcutaneous administration should be avoided, as absorption is erratic. Additionally, intramuscular administration should also be avoided, as this route of administration has not been shown to be effective and may lead to hematoma formation in a patient who is excessively anticoagulated

(c) Investigate the reason for the elevated INR (e.g., compliance, drug–drug interactions, drug–herbal interactions, drug–nutrient interactions, dietary changes)

(continued)

TABLE 2.15 (continued)

(d) In patients who have bled and warfarin pharmacotherapy is re-initiated, consider lowering the intensity of anticoagulation
(e) If systemic anticoagulation is warranted after high dose of vitamin K_1 (i.e., 10 mg), then the use of unfractionated heparin or a low molecular weight heparin (LMWH) may be required until the effects of vitamin K_1 are reversed and the patient becomes responsive to warfarin pharmacotherapy
(f) The intravenous vitamin K_1 product is an aqueous colloidal solution that contains a polyoxyethylated castor oil diluent. An anaphylactoid reaction can occur if the intravenous rate exceeds **1 mg/min**

Chapter 3
Cerebrovascular

Table 3.1 General supportive care for patients with an acute cerebrovascular accident

- Rule-out clinical situations that may mimic a cerebral vascular accident (e.g., hypoglycemia, seizures, migraine with an aura, hypertensive or Wernicke's encephalopathy, CNS tumor, drug toxicity [e.g., lithium, phenytoin])
- Airway support and ventilatory assistance in patients with a depressed level of consciousness or airway compromise
- Supplemental oxygen in hypoxic patients (maintain oxygen saturation >94 %)
- Antipyretics and cooling devices for the management of fever
- Antihypertensive agents should be avoided unless the systolic blood pressure is >220 mmHg or the diastolic blood pressure is >120 mmHg (*see* Table 3.2 for management)
  - Patients who are otherwise eligible (except blood pressure) for alteplase should have their blood pressure lowered cautiously to a systolic ≤185 mmHg and a diastolic ≤110 mmHg. **Note**: once tPA is administered, the blood pressure must be maintained below 180/105 mmHg to limit the risk of ICH
- Treat hypotension with intravenous normal saline
- Avoid/treat hypoglycemia (<60 mg/dL)
- Control hyperglycemia
  - Target blood glucose levels 140–180 mg/dL
    - Optimal blood glucose range is not well delineated
    - Frequent monitoring of blood glucose levels and adjustments of insulin are required to avoid hypoglycemia

Data from *Stroke* 2013;44:1–87

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_3,

Table 3.2 Blood pressure management in the setting of an acute cerebrovascular accident

*Patient **not** eligible for alteplase*

- Systolic blood pressure (SBP) ≤220 mmHg or diastolic blood pressure (DBP) ≤120 mmHg
  - Observe (unless other end-organ damage present)
- SBP >220 mmHg or DBP between 121 and 140 mmHg
  - Aim for a 10–15 % reduction in MAP
  - Labetolol 10–20 mg IV over 1–2 min. May repeat or double every 10 min (maximum 300 mg)
  - Nicardipine 5 mg/h continuous IV infusion. Titrate by 2.5 mg/h increments every 5–15 min to a maximum of 15 mg/h
- DBP >140 mmHg
  - Aim for a 10–15 % reduction in mean arterial pressure (MAP)
  - Nitroprusside—0.25–0.5 mcg/kg/min continuous IV infusion; increase in increments of 0.25–0.5 mcg/kg/min until desired hemodynamic effect. Usual doses up to 2–3 mcg/kg/min. **High-alert medication**—read package insert before use

*Patient otherwise eligible for alteplase (**except for blood pressure**)*

- SBP >185 mmHg or DBP >110 mmHg confirmed by two consecutive measurements
  - Labetolol 10–20 mg IV over 1–2 min. May repeat X one dose
  - Nicardipine 5 mg/h continuous IV infusion. Titrate by 2.5 mg/h increments every 5–15 min to a maximum of 15 mg/h
  - If blood pressure is not *reduced* and *maintained* at target range (systolic ≤185 mmHg and diastolic ≤110 mmHg), **do not** administer fibrinolytic
    - Aggressive treatment to reduce and maintain blood pressure excludes patients from fibrinolytic eligibility. Patients that require sodium nitroprusside to control blood pressure may not be sufficiently stable to receive fibrinolytic pharmacotherapy
  - Blood pressure control during and after fibrinolytic administration is SBP <180 mmHg and DBP <105 mmHg

During and after fibrinolytic therapy

- Monitor blood pressure every 15 min for 2 h from the start of tPA, then every 30 min for 6 h, then every hour for 16 h
- If blood pressure increases above target range
  - DBP >140 mmHg
    - Nitroprusside—0.25–0.5 mcg/kg/min continuous IV infusion; increase in increments of 0.25–0.5 mcg/kg/min until desired hemodynamic effect. Usual doses up to 2–3 mcg/kg/min. **High-alert medication**—read package insert before use
  - SBP >180–230 mmHg or DBP between 105 and 140 mmHg
    - Labetolol 10–20 mg IV over 1–2 min. May repeat or double every 10 min (maximum 300 mg). Alternatively, a continuous IV infusion (2–8 mg/min) may be initiated after the initial bolus
    - Nicardipine 5 mg/h continuous IV infusion. Titrate by 2.5 mg/h increments every 5–15 min to a maximum of 15 mg/h
    - If blood pressure not controlled, may consider nitroprusside

Data from *Stroke* 2013;44:1–87

Table 3.3 Alteplase inclusion and exclusion criteria for cerebrovascular accident indication

Inclusion criteria

- Age ≥ 18 years
- Clinical diagnosis of an acute ischemic cerebrovascular accident (CVA) causing a measurable neurological deficit
- Ability to definitively establish the time of CVA onset
- Ability to begin alteplase therapy within 3 h (up to 4.5 h) of CVA onset
- Patient or family members understand the potential risks and benefits from treatment

Exclusion criteria

- Evidence of intracranial hemorrhage, subarachnoid hemorrhage, or a large area of cerebral edema, parenchymal hypodensities, or sulcal effacement on pretreatment head CT scan
- Head CT shows a multilobar infarction/hypodensity involving more than one-third of the cerebral hemisphere
- History of any intracranial hemorrhage
- Known arteriovenous malformation, aneurysm, or intracranial neoplasm
- Active internal bleeding
- Platelet count <100,000/mm^3
- Patient is coagulopathic or has received heparin within the past 48 h and has an elevated activated partial thromboplastin time (aPTT) greater than the upper limit of normal
- Patient is coagulopathic or has recently received an oral anticoagulant (e.g., warfarin) and has an elevated international normalized ratio (INR) > 1.7
- Current use (within 2 days [assuming normal renal and hepatic function]) of a direct thrombin inhibitor or direct factor Xa inhibitor with elevated sensitive laboratory tests
- History of any intracranial or intraspinal surgery, serious head trauma, or previous CVA within previous 3 months
- Recent arterial puncture at a non-compressible site or biopsy within previous 7 days
- Blood pressure >185/110 mmHg on repeated measurements
- Serum glucose < 50 mg/dL

Relative Exclusion Criteria—with careful consideration, patient may receive tPA despite one or more relative contraindications if the potential benefit outweighs risks

- Modified National Institute of Health Stroke Score (NIHSS) of > 25
- History of major surgery or serious trauma in the previous 14 days
- History of gastrointestinal or urinary tract hemorrhage within previous 21 days
- Seizure observed at stroke onset with postictal residual neurological impairments

(continued)

Table 3.3 (continued)

- Acute myocardial infarction within 3 months
- Rapidly improving or minor symptoms
- Current or recent pregnancy

*Additional exclusion criteria for tPA administration between **3** and **4.5** h after stroke onset*

Age ≥ 80 years old, taking oral anticoagulants regardless of INR, NIHSS > 25, or if the patient has a history of both stroke and diabetes mellitus

Note: patients on aspirin therapy before CVA onset can still receive tPA. No recommendations are made regarding other antiplatelet agents

Table 3.4 Modified National Institute of Health Stroke Scale

Item	*Name*	*Response*
1 A	Level of consciousness	0 = Alert
		1 = Drowsy
		2 = Obtunded
		3 = Unresponsive/coma
1 B	Orientation—2 questions	0 = Answers both correctly
	(e.g., month, age)	1 = Answers one correctly
		2 = Answers neither correctly
1 C	Commands—2	0 = Performs both tasks correctly
	(e.g., open and close eyes)	1 = Performs one task correctly
		2 = Performs neither task
2	Gaze	0 = Normal
		1 = Partial gaze palsy
		2 = Complete gaze palsy
3	Visual fields	0 = No visual loss
		1 = Partial hemianopia
		2 = Complete hemianopia
		3 = Bilateral hemianopia
4	Facial movement	0 = Normal
		1 = Minor facial weakness
		2 = Partial facial weakness
		3 = Compete unilateral palsy
5	Motor function (arm)	0 = No drift
	a. Left	1 = Drift before 5 s
	b. Right	2 = Falls before 10 s
		3 = No effort against gravity
		4 = No movement

(continued)

Table 3.4 (continued)

Item	*Name*	*Response*
6	Motor function (leg)	0 = No drift
	a. Left	1 = Drift before 5 s
	b. Right	2 = Falls before 5 s
		3 = No effort against gravity
		4 = No movement
7	Limb ataxia	0 = No ataxia
		1 = Ataxia in one limb
		2 = Ataxia in two limbs
8	Sensory	0 = No sensory loss
		1 = Mild sensory loss
		2 = Severe sensory loss
9	Language	0 = Normal
		1 = Mild aphasia
		2 = Severe aphasia
		2 = Global aphasia (mute)
10	Articulation	0 = Normal
		1 = Mild dysarthria
		2 = Severe dysarthria
11	Extinction or inattention	0 = Absent
		1 = Mild-loss of one sensory modality
		2 = Severe-loss of two sensory modalities

Table 3.5 Alteplase administration protocol for cerebrovascular accident indication

- *See* Table 3.3 for inclusion and exclusion criteria
- **0.9 mg/kg IV dose with a maximum of 90 mg total dose**
- Reconstitute with the accompanying 100 mL vial of sterile water diluent that accompanies tPA using the transfer device provided; gently swirl, **DO NOT** shake
- The reconstituted solution will have a 1 mg/mL concentration. After determining the correct dose, remove and discard the excess milligrams with a syringe and needle inserted into a peripheral area (away from the puncture site caused by the transfer device)
- With a syringe and needle inserted into a peripheral area (away from the puncture site caused by the transfer device), withdraw and administer 10 % of the dose intravenously over 1 min
- Administer remaining 90 % of the dose intravenously over 1 h. To ensure full delivery of any medication in the IV tubing, spike a 50 mL normal saline bag and run at the same rate to ensure that all the tPA remaining in the tubing is administered
- Door-to-needle time should be within 60 min from hospital arrival
- Admit patient to an intensive care or stroke unit for monitoring
- Monitor for changes in neurological status every 15 min during and after the infusion for 2 h, then every 30 min for the next 6 h, and then every hour until 24 h after treatment
- Monitor blood pressure every 15 min during and after the infusion for the first 2 h, then every 30 min for the next 6 h, and then every hour until 24 h after treatment. Increase frequency of monitoring if systolic blood pressure ≥180 mmHg or diastolic ≥105 mmHg
- No antiplatelet agents or anticoagulants should be administered for 24 h following the completion of alteplase infusion
- Maintain blood pressure <180/105 mmHg for 24 h following the completion of the alteplase infusion
- No arterial punctures or other invasive procedures for 24 h following the completion of the alteplase infusion
- Discontinue infusion and obtain emergent head CT scan if intracranial hemorrhage is suspected (*see* Table 2.6)
- Obtain follow-up head CT or MRI scan at 24 h before starting antiplatelet or anticoagulant pharmacotherapy

Table 3.6 Management of an alteplase-induced intracranial hemorrhage

- Discontinue alteplase infusion immediately
- Order immediate head CT scan without contrast
- Check complete blood count, prothrombin time, international normalization ratio, activated partial thromboplastin time, fibrinogen levels
- If intracranial hemorrhage is confirmed, administer 5–10 units of cryoprecipitate, evaluate laboratory results, and supplement blood products and platelets as deemed necessary (e.g., 2 units fresh frozen plasma [FFP], 6–8 units platelets)
  - Platelet dysfunction may be seen with fibrinolytic therapy
- Evaluate patient for possible aminocaproic acid therapy
- Obtain neurosurgery consult
- Nomogram for predicting 30-day mortality may be found in *Circulation* 1998;98:1376–1382

Table 3.7 Management of intracranial hypertension (intracranial pressure ≥20 mmHg)

General supportive measures

- Maintain cerebral perfusion pressure (CPP) between 60 and 80 mmHg
  - CPP = mean arterial pressure (MAP) − intracranial pressure (ICP)
  - Use fluids and/or vasopressors to elevate MAP if necessary
  - Maintain euvolemia (pulmonary capillary wedge pressure between 10 and 14 mmHg)
  - Administer packed red blood cells (PRBCs) if HCT <30 %
- Monitor for transient increases in ICP that occur with suctioning or bronchoscopy. Pretreatment with lidocaine IV may blunt this transient increase in ICP
- Seizure prophylaxis if warranted
- Adequate nutritional support
- Adequate pain control (i.e., morphine) and sedative use (i.e., propofol, benzodiazepine)
  - Effects on MAP and CPP should be monitored carefully

Interventions to decrease intracranial pressure

- Head-of-bed elevation at 30 %
- Maintain patient's head in straight position
- Avoid hyperthermia
  - Use antipyretics and cooling blanket where necessary
  - Therapeutic use of hypothermia is currently not recommended
- Hyperventilate to a goal between 30 and 35 mmHg
  - Hyperventilation to 25–30 mmHg for brief periods may be considered in refractory intracranial hypertension
  - Effect limited to 24 h
  - Avoid rapid increase in CO_2 (prevent rebound)

(continued)

Table 3.7 (continued)

- Mannitol (as a 15–20 % solution)
  - 1 g/kg IV bolus followed by 0.25 g/kg IV q6h
  - Use in-line 5 μm filter set
  - Maintain measured serum osmolality under 310–320 mOsm/kg
  - Contraindicated in severe renal impairment
  - Effect may be limited to 24 h
- Pentobarbital coma (in refractory cases)
  - Utilize a central line +/– pulmonary artery catheter
  - 10 mg/kg IV over 30 min followed by 5 mg/kg/h continuous IV infusion for 3 h (total loading dose is 25 mg/kg)
  - Loading dose followed by 1 mg/kg/h. Can titrate up to 3 mg/kg/h
  - Slow rate if patient becomes hypotensive during the loading or maintenance infusion
  - Maintain plasma levels between 30 and 40 mg/L
  - Taper dose if ICP well controlled for 24–48 h
  - **Note**: potent CYP 450 enzyme inducer
- Cerebrospinal fluid drain through ventriculostomy if hydrocephalus present
- Consider decompressive surgery
- No role for corticosteroids in cerebrovascular accidents or traumatic brain injury based on the available literature. May increase complication rate

Data from *Stroke* 2007;38:2001–2023 and *J. Neurotrauma* 2000;17:449–627

Chapter 4
Critical Care

Table 4.1 General drug utilization principles in intensive care

• Start with low doses and titrate carefully
• Discontinue any nonvital medication on ICU admission. Keep track of this intervention and restart medications as clinically necessary
• Avoid complete discontinuation of drugs with adverse withdrawal syndromes if not contraindicated (e.g., β-adrenergic blockers, clonidine, benzodiazapines, SSRIs, baclofen, etc.).
• Review medication profile daily for drug–drug interactions
• Anticipate common drug side effects
• Avoid intramuscular route of drug administration
• Avoid the subcutaneous and intramuscular route of drug administration in patients in any form of shock
• Avoid enteral route of drug administration in patients with shock when there is an intravenous formulation
• Oxygen is a "drug"—titrate inspired oxygen concentration to provide adequate systemic oxygen delivery, avoiding both hypoxic vasoconstriction and hyperoxic hypercarbia (e.g., 88–92 % in chronic hypercapneic patients)
• Use the lowest inspired oxygen concentration consistent with adequate tissue oxygenation in patients receiving/or having received bleomycin. May also apply to patients receiving amiodarone or chest radiotherapy.
• Water is a "drug"—ensure adequate intake to avoid dehydration (hypernatremia)
• Strict avoidance of hypoglycemia. Ensure an adequate source of dextrose in any patient receiving an insulin product
• Promote appropriate patient sleep–wake cycles
• Practice daily wake-up in patients receiving sedative medications
• Become familiar with the pharmacokinetic and pharmacodynamic principles of medications prescribed in ICU patients

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_4,

Table 4.1 (continued)

- Become familiar with the principles of safe writing rules as suggested by the Institute of Safe Medication Practice
- Be aware of common sound-alike medications
- Practice good hand hygiene
- Vaccinate carefully selected patients
- Obtain and review one's institution's antibiogram
- Always address the need for stress-ulcer prophylaxis, deep vein thrombosis (DVT) prophylaxis, and nutrition support

Table 4.2 Management of severe sepsis and septic shock[a]

*Resuscitation goals during the **first 6 h** (early goal-directed therapy)*

- Non-invasive strategies targeting early fulfillment of available clinical endpoints have been shown to be equally effective[b]
- Target central venous pressures between 8 and 12 mmHg (12–15 mmHg in intubated patients)—**all targets should be individualized based on patient/clinical situation** (e.g., need higher CVP in patients with increased abdominal pressure)
  - Use a crystalloid (normal saline or lactated Ringer's solution) as the initial fluid of choice. The initial fluid challenge should be a **minimum of 30 mL/kg within the first 3 h**; more rapid administration and greater amounts of fluid may be needed in some patients. Monitor for evidence of systemic or pulmonary edema
  - Can use albumin in fluid resuscitation when a patient requires substantial amount of crystalloid or prior to or during resuscitation if the patient develops significant increased abdominal pressure or pulmonary edema (**author's opinion**)
  - Hydroxyethyl starches should be **avoided**
- Target mean arterial pressure $\geq$ 65 mmHg (if elevated intra-abdominal pressure (IAP) or intracerebral pressure (ICP), target abdominal perfusion pressure (MAP-IAP) or cerebral perfusion pressure (MAP-ICP))
- Target urine output $\geq$ 0.5 mL/kg/h
- If elevated lactate levels, target resuscitation to normalize lactate levels
- Central venous (superior vena cava) or mixed venous oxygen saturation $\geq$ 70 % or > 65 %, respectively, using invasive strategy
  - A published study would support a mixed venous oxygen saturation of 65 % as similar to a central venous oxygen saturation of 70 %[c]
- Blood product administration only when hemoglobin concentrations decrease to < 7 g/dL to target a hemoglobin concentration between 7 and 9 g/dL. In patients with myocardial ischemia, acute hemorrhage, or severe hypoxemia, a goal-directed trial to higher hemoglobin concentrations may be warranted

(continued)

Table 4.2 (continued)

Diagnosis

- Diagnostic studies should be performed to identify the source of infection, causative pathogen, and any complications (e.g., abscess, empyema, infected intravascular catheter, etc.). A removable or drainable focus should be removed or drained
- After appropriate cultures have been obtained, initiate appropriate spectrum empiric antimicrobial therapy ***within the first hour*** of presentation. Consider combination pharmacotherapy targeting the most likely causative pathogens (based on possible sources, previous antimicrobials, immune status, recent stay in a health-care facility, etc.) and select antimicrobials that penetrate into the presumed source of sepsis
  - A published trial in bacteremic septic shock patients showed that each hour of delay in effective antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival by 7.6 %
- Reassess pharmacotherapy after 48–72 h and continue or streamline therapy based on microbiological data, clinical response, and clinical judgment

Vasopressors

- Use when an appropriate fluid challenge fails to restore adequate hemodynamics and organ perfusion or in the face of life-threatening shock when fluid challenge is in progress. Should generally be utilized in patients who have been adequately fluid resuscitated
- Intravenous choices (**central line preferred by author but controversial**)
  - Norepinephrine (**first-choice vasopressor**)
    - Start with 0.05 mcg/kg/min or 4 mcg/min continuous IV infusion and titrate to effect. Maximum dose approximately 125 mcg/min or 3 mcg/kg/min
  - Epinephrine (added to and potentially substituted for norepinephrine)
    - Start with 0.05 mcg/kg/min continuous IV infusion and titrate to effect. Dose range is 2–10 mcg/min
    - Doses under 0.05 mcg/kg/min may exacerbate hypotension
  - Vasopressin (**author's opinion—added to norepinephrine *before* epinephrine**)
    - May be considered in patients with refractory septic shock
    - Can be used as the first vasopressor in patients with malignant tachyarrythmias or active coronary ischemia (preferred over phenylephrine in these circumstances [**author's opinion**]); see below
    - 0.03 units/min (0.01–0.04 units/min) continuous IV infusion
      - Doses > 0.04–0.67 units/min have been associated with myocardial ischemia, decreased cardiac output, and cardiac arrest

(continued)

Table 4.2 (continued)

- Dopamine (**only in highly selected patients with a low-risk of tachyarrhythmias**)
  - 2.5–20 mcg/kg/min continuous IV infusion; may require doses above 10 mcg/kg/min for an adequate response
  - No role for low-dose (renal) dopamine
- Phenylephrine (**not recommended**)
  - Circumstances where it may be utilized include emergent 100 mcg boluses, norepinephrine-associated arrhythmias, known high cardiac output states, or salvage therapy
  - Start with 50 mcg/min continuous IV infusion and titrate to effect; maximum dose around 400 mcg/min

Inotropes

- Potentially useful in resuscitated patients with persistent evidence of systemic or organ hypoperfusion
- Increasing cardiac index to predefined supranormal levels has not been found to improve outcome
- Dobutamine
  - 2.5–10 mcg/kg/min continuous IV infusion up to 20 mcg/kg/min
  - May cause hypotension and tachycardia
- Milrinone
  - 0.2–0.75 mcg/kg/min continuous IV infusion; use lower doses in patients with renal dysfunction (i.e., 0.2 mcg/kg/min)
  - Loading dose of 50 mcg/kg over 10 min may be utilized
    - Avoid or administer 50 % if tenuous hemodynamics
  - Can be used cautiously as a primary inotrope or in combination with dobutamine
  - If utilized, may require starting or increased doses of a vasopressor (combination with vasopressin studied)

Corticosteroids

- Administer **only** if adequate fluid resuscitation and vasopressor therapy are **not** able to restore appropriate hemodynamic parameters
- Hydrocortisone 50 mg IV q6h or 100 mg IV q8h for 7 days if deemed appropriate (**note**: these recommended doses are the author's opinion). Some clinicians advocate dose tapering after shock resolution
- ACTH stimulation test is **not** recommended

Glycemic control

- Maintain blood glucose levels between 110 and 150 mg/dL (**author's opinion**)
  - Use a continuous IV infusion of insulin based on an institution-specific protocol
  - Should be used with a continuous enteral or intravenous source of dextrose
    - Aggressively avoid and treat hypoglycemia

[a]Data from *Crit Care Med.* 2013;41:580–637. [b]Data from *NEJM.* 2014;370: 1683–1693. [c]Data from *Int. Care Med.* 2004; 30:1572–1578. [d]Data from *Crit. Care Med.*

Table 4.3 Pain, agitation, and delirium guidelines[a]

Pain

- Evaluate location, intensity, characteristics, and aggravating/alleviating factors
  - Assess intensity by utilizing the Behavioral Pain Scale or the Critical Care Pain Observation Tool in patients whom motor function is intact and behaviors are observable; vital signs should not be used alone for pain assessment
  - Establish predetermined end points
- Methods of intravenous administration
  - Continuous IV infusion
  - Intermittent IV bolus
  - Patient-controlled analgesia in non-critically ill patients
  - As needed, method (e.g., prn) should be avoided if the patient has continuous analgesic requirements
- Patient hemodynamically unstable
  - Fentanyl 0.5–3 mcg/kg/h continuous IV infusion or 25–100 mcg IVP every 30–60 min
    - Less histamine release than morphine
- Patient hemodynamically stable
  - Fentanyl 0.5–3 mcg/kg/h continuous IV infusion or 25–100 mcg IVP every 30–60 min
  - Morphine 1–10 mg/h continuous IV infusion
    - For acute pain can administer 2–4 mg IVP every 1–2 h
    - Avoid prolonged use or high doses in patients with renal failure
  - Hydromorphone 0.5–3 mg/h continuous IV infusion
    - For acute pain can administer 0.2–0.6 mg IVP every 1–2 h
- **Avoid** meperidine, buprenorphine, butorphanol, and nalbuphine
- NSAIDs or acetaminophen may be used as adjunctive agents in the appropriate patient
- Reassess goals daily and titrate/taper dose to desired response (as the patient may accumulate the medication or become tolerant)
  - With downward titration, monitor for signs/symptoms of withdrawal
    - Tachycardia, hypertension, tachypnea, mydriasis, lacrimation, diaphoresis, rhinorrhea, piloerection, vomiting, diarrhea, yawning, muscle cramps, irritability, and anxiety

Agitation and Sedation

- Address etiology of agitation and/or anxiety
  - Sepsis, renal/liver failure, hypoxia, hypercarbia, pain, central nervous system infections, hypoglycemia, electrolyte imbalances, substance withdrawal, sleep deprivation and/or ventilator dysynchrony
    - If patient is sleep deprived, consider altering the patient's environment and possibly a nighttime sedative to promote an appropriate sleep–wake cycle

(continued)

Table 4.3 (continued)

- Establish predetermined end points using a valid and reliable sedation and agitation scale (*see* Table 4.4)
  - A light rather than a deep level of sedation is recommended; the target level of sedation will be patient dependent
  - Bispectral index monitoring may be of some value in patients who are deeply sedated and receiving neuromuscular blocking agents
- Optimize the environment and minimize lighting, noise, and frequent vital sign checks
- Methods of intravenous administration
  - Continuous IV infusion
  - Intermittent IV bolus
- Management of acute agitation (**non-benzodiazepine strategy**) in mechanically ventilated patients
  - Consider **analgesia-first sedation strategies**, as pain is common in the critical care setting
  - Propofol 5–50 mcg/kg/min continuous IV infusion (preferably through a central line)
    - **Nutritional considerations**: Contains soy bean oil, egg lecithin, and glycerol. Provides 1.1 kcal/mL of emulsion; may need to adjust nutritional regimen. One formulation contains EDTA. Prolonged therapy with the EDTA-containing product may decrease serum zinc levels. May need to monitor serum zinc levels and supplement. Monitor serum triglyceride levels with prolonged infusions
    - **Propofol infusion syndrome** has been described and may result in severe metabolic acidosis, cardiac dysrhythmias, cardiovascular collapse, rhabdomyolysis, and death. The risk may be increased with concomitant catecholamine infusions or when the dose exceeds 60–80 mcg/kg/min
  - Dexmedetomidine 1 mcg/kg IV over 10 min, followed by 0.2–0.7 mcg/kg/h continuous IV infusion; doses up to 1.5 mcg/kg/h have been utilized
    - Some clinicians omit the bolus dose or administer half the recommended amount; avoid if hemodynamically unstable
    - No decrease in respiratory drive; may have an analgesic effect, can be utilized adjunctively in GABA-withdrawal states
- If a benzodiazepine is warranted:
  - Midazolam 0.02–0.1 mg/kg/h continuous IV infusion (**note**: active metabolite may accumulate in patients with renal impairment)
  - Lorazepam 0.01–0.1 mg/kg/h continuous IV infusion or 1–4 mg IV every 4–6 h

(continued)

Table 4.3 (continued)

- Reassess goals daily and titrate/taper dose to desired response (as the patient may accumulate the medication or become tolerant)
  - With downward titration, monitor for signs/symptoms of withdrawal
    - Anxiety, agitation, delirium, diaphoresis, myoclonus, tremors, and seizures
  - Consider daily sedation interruptions as per hospital protocol
  - Use sedation protocols and checklists to facilitate sedation management
- The addition of a narcotic analgesic to a sedative may have additive effects. Monitor and titrate to desired level of sedation if used concomitantly

Delirium

- Use the Confusion Assessment Method for the ICU (Table 4.5) to evaluate the patient
- Have a high suspicion for sepsis
- If possible, discontinue any benzodiazepines, as they may be a risk factor for delirium
- Evaluate for reversible etiologies. Drugs that may cause delirium include:
  - Benzodiazepines, barbiturates, opioids, corticosteroids, dopamine agonists (e.g., amantadine, bromocriptine, levodopa, pergolide, pramipexole, ropinirole), H_2-receptor antagonists, anticholinergics (e.g., chlorpromazine, diphenhydramine, diphenoxylate, oxybutynin, prochlorpromazine, scopolamine, trihexyphenidyl), β-adrenergic blockers, methyldopa, carbamazepine, phenytoin, baclofen, cyclobenzaprine, lithium, metoclopramide, antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors), cefepime (in the setting of a low CrCl), older generation fluoroquinolones, and interleukin-2
- Haloperidol 1–2 mg slow IVP, followed by doubling the dose every 15–20 min until desired effect achieved. For maintenance regimen, add up total loading dose and administer 25 % enterally every 6 h; duration based on clinical judgment (**note: author's opinion**)
  - Monitor for QT-interval prolongation and extrapyramidal side effects
- Olanzapine 2.5–10 mg intramuscular or enteral daily may be an alternative to haloperidol. Start with 2.5 mg in elderly or debilitated patients
- Dexmedetomidine 1 mcg/kg IV over 10 min, followed by 0.2–0.7 mcg/kg/h continuous IV infusion; doses up to 1.5 mcg/kg/h have been utilized. Some clinicians omit the bolus dose or administer half the recommended amount; avoid if hemodynamically unstable

[a]Data from *Crit. Care Med.* 2013;41:263–306

Table 4.4 Riker sedation-agitation scale[a]

Score	*Description*	*Definition*
7	Dangerous agitation	Pulling at endotracheal tube (ETT), trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm down despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down with verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens with verbal stimuli or gently shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

[a]Data from *Crit. Care Med.* 1999;27:1325–1329

Table 4.5 Confusion assessment method for the diagnosis of delirium in intensive care unit patients[a]

Features	*Assessment variable*
1. Acute onset of mental status changes or fluctuating course	• Is there evidence of an acute change in mental status from baseline? • Did the abnormal behavior fluctuate during the past 24 h? • Did the sedation scale (e.g., Riker Sedation–Agitation Scale) or Glasgow Coma Scale fluctuate in the past 24 h?
2. Inattention	• Did the patient have difficulty focusing? • Is there a reduced ability to maintain and shift attention? • How does the patient score on the Attention Screening Examination (ASE)? ◦ Visual component ASE tests the patient's ability to pay attention through recall of 10 pictures ◦ Auditory component ASE tests attention through having the patient squeeze hands or nod whenever the letter "A" is called in a random letter sequence

(continued)

Table 4.5 (continued)

Features	*Assessment variable*
3. Disorganized thinking	• If the patient is already extubated from the ventilator, determine whether or not the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject • For patients still intubated, can the patient answer the following four questions correctly? ◦ Will a stone float on water? ◦ Are there fishes in the sea? ◦ Does 1 pound weigh >2 pounds? ◦ Can you use a hammer to pound a nail? • Was the patient able to follow questions and commands throughout the assessment? ◦ Are you having unclear thinking? ◦ Hold up this many fingers (examiner holds up two fingers in front of the patient) ◦ Now do the same thing with the other hand (examiner not holding up any fingers)
4. Altered level of consciousness (any level other than alert)	• Alert—normal, spontaneously fully aware of the environment, interacts appropriately • Vigilant—hyperalert • Lethargic—drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the examiner; becomes fully aware and appropriately interactive when prodded minimally • Stupor—difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interactive with the examiner; becomes incompletely aware and inappropriately interactive when prodded strongly; can be aroused only by vigorous and repeat stimuli and as soon as the stimulus ceases, stuporous subjects lapse back into the unresponsive state • Coma—unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the examiner, so that the interview is impossible even with maximal prodding

[a]Data from *Crit. Care Med.* 2001;29:1370–1379

Note: Patients are diagnosed with delirium if they have both features 1 and 2 *and* either 3 or 4

Table 4.6 Neuromuscular blocker use in the intensive care unit[a]

Indications

- Facilitate endotracheal intubation
  - Succinylcholine 1–1.5 mg/kg IV up to 150 mg total dose
  - Contraindications may include use in patients with a personal or family history of malignant hyperthermia, extensive/severe burns, myopathies with elevated creatine phosphokinase, penetrating eye injuries, pre-existing hyperkalemia, narrow-angle glaucoma, and disorders of plasma pseudocholinesterase
- Facilitate mechanical ventilation
  - Decrease oxygen consumption
- Control increased intracranial pressures
- Some data to support use in early ARDS to avoid unwanted patient effort that may contribute to ventilator-induced lung injury
- Control muscle spasms associated with tetanus

Sedation and analgesic pharmacotherapy must be optimized before the use of neuromuscular blockade (NMB)

- NMBs ***do not*** possess sedative, amnestic, or analgesic properties

If the patient is adequately sedated and there is still a need for continuous NMB then:

- Cisatracurium or atracurium can be utilized (especially if in the presence of renal and/or hepatic dysfunction)
  - Cisatracurium
    - 0.15–0.2 mg/kg IV bolus followed by 3 mcg/kg/min continuous IV infusion once recovery from the bolus dose is observed. Usual dose range between 0.5 and 5 mcg/kg/min
  - Atracurium
    - 0.4–0.5 mg/kg IV bolus followed by 9–13 mcg/kg/min continuous IV infusion once recovery from the bolus dose is observed
- Consider daily discontinuation of NMB and patient assessment if prolonged infusions are required

Monitor

- Train-of-four
  - Superficial nerves
    - Ulnar nerve—monitor response of the adductor pollicis (thumb)
    - Posterior tibial nerve—monitor flexion of the big toe and foot
    - Facial nerve—monitor contraction of the orbicularis oculi muscle
  - Target number of twitches depends on patient's condition and depth of sedation
    - Usually goal is 1/4 or 2/4 twitches
  - Percent receptor occupation and resultant NMB:
    - 3/4 twitches—80 % receptor occupation
    - 2/4 twitches—85 % receptor occupation
    - 1/4 twitches—85–90 % receptor occupation
    - 0/4 twitches—90–100 % receptor occupation

(continued)

Table 4.6 (continued)

- Clinical status and respiratory effort
- Visual and tactile assessment of muscle tone
- Clinical evidence of undersedation
  - Tachycardia, hypertension, piloerection, and diaphoresis
- Bispectral index (BIS) monitor
- Muscle weakness and damage
  - Check periodic creatine phosphokinase levels with prolonged infusions (especially if the patient is receiving concomitant corticosteroid pharmacotherapy)
    - Try to avoid this drug combination

Preventative strategies

- Appropriate deep vein thrombosis (DVT) prophylaxis
- Reposition patient as appropriate to prevent decubitus ulcer formation
- Ophthalmic ointment, drops, or taping the patient's eyelids shut to prevent keratitis and corneal abrasion

[a]Data from *Crit Care Med.* 2002;30:142–156

Table 4.7 Reversal of nondepolarizing neuromuscular blockers

Combination IV agents	*Dose when 3/4 TOF*	*Dose when 2/4 TOF*	*Dose when 1/4 TOF*
Edrophonium + Atropine	10 mg **(0.5–1 mg/kg)** + 7–14 mcg/kg	10 mg **(0.5–1 mg/kg)** + 7–14 mcg/kg	Do not use
Neostigmine + Glycopyrrolate	0.5–1 mg **(0.04 mg/kg [5 mg maximum])** +5 mcg/kg	1–1.5 mg **(0.07 mg/kg [5 mg maximum])** +10 mcg/kg	2–2.5 mg **(0.08 mg/kg [5 mg maximum])** +15 mcg/kg
Pyridostigmine + Glycopyrrolate	0.1 mg/kg + 5 mcg/kg	0.2 mg/kg + 10 mcg/kg	0.3 mg/kg + 15 mcg/kg

Notes:

1. TOF—train-of-four
2. Postpone reversal until a twitch is observed
3. Administer anticholinergic agent 1–2 min before acetylcholinesterase inhibitor
4. Doses are estimated based on recommended dosing ranges and TOF
   a. There is considerable difference of opinion regarding optimum dosage. In general, anesthesiology literature/references recommend higher doses ***(the bold text reflects anesthesia literature recommendations)***. Consult a clinician with expertise in this field in a situation of uncertainty
5. Up to a 60 min time to recovery with a long-acting neuromuscular blocker (i.e., pancuronium, doxacurium)
6. Up to a 30 min time to recovery with an intermediate-acting neuromuscular blocker (i.e., atracurium, cisatracurium, rocuronium, and vecuronium)

Table 4.8 Factors that alter the effects of neuromuscular blockers

Increase effect	*Decrease effect*
Clinical	*Clinical*
• Hypokalemia, hypocalcemia, hyponatremia, hypermagnesemia • Acidosis, hypothermia • Renal failure • Hepatic failure • Neuromuscular diseases	• Alkalosis • Hypercalcemia • Demyelinating lesions
Medications	*Medications*

• Anesthetics
  ○ Desflurane, enflurane, isoflurane, halothane
• Antimicrobials
  ○ Aminoglycosides, clindamycin, polymyxins, vancomycin
• Class I Antiarrhythmics
• β-adrenergic blockers
• Calcium channel blockers
• Dantrolene
• Lithium
	• Anticholinesterases
	• Calcium
	• Carbamazepine, phenytoin
	• Theophylline, caffeine

Table 4.9 Management of malignant hyperthermia[a]

Triggers

- Volatile inhalational anesthetics +/–
  - Desflurane, enflurane, halothane, isoflurane, and sevoflurane
- Succinylcholine

Management

- Discontinue offending agent
- Stabilize airway, breathing, and circulation
- Hyperventilate with 100 % oxygen
- Dantrolene IV
  - 2.5 mg/kg IV every 5–10 min as necessary up to a maximum of 10 mg/kg
  - Followed by 1–2 mg/kg enterally every 6 h for 72 h
- Cool patient
  - Evaporative cooling
    - Patient is repeatedly wetted down by sponging or spraying the skin with tepid water while a fan is blowing air across the body service
  - The effectiveness and safety of strategic ice packing (groin, axillae), whole body ice packing, and gastric or peritoneal lavage are controversial
  - Temperature management systems (i.e., Arctic Sun) may be utilized if available
  - Cooling efforts should continue until the core body temperature reaches 38 °C or 100.4 °F
  - Shivering (a common complication of cooling, which can add to heat generation) can be managed with:
    - Meperidine 25–50 mg IV × one dose; cautious use in patients with hepatic or renal disease or seizure predisposition
    - Lorazepam 1–2 mg IV q 4–6 h as needed
  - There is no role for acetaminophen or aspirin antipyretic pharmacotherapy
- Maintain intravascular volume status and urine output with normal saline
- Manage complications:
  - Rhabdomyolysis, arrhythmias, seizures, and disseminated intravascular coagulation (DIC)

[a]www.mhaus.org

TABLE 4.10 Use of packed red blood cell transfusions in critically ill patients[a]

Potential adverse effects of packed red blood cell (PRBCs) transfusions

- Immediate immunological complications
  - Anaphylactic/anaphylactoid reactions, transfusion-related acute lung injury (TRALI), hemolysis, platelet destruction, and fever
- Delayed immunological complications
  - Alloimmunization to red cells, white cells, and platelets
    - Delayed hemolytic reactions
  - Graft versus host disease
- Transfusion-related immunomodulation (TRIM)—leading to increased infection risk
- Hypothermia
- Infectious
  - Viral
    - Hepatitis B and C, HIV 1 and HIV 2, cytomegalovirus, HTLV I and HTLV II, and West Nile virus
  - Bacterial
    - *Yersinia enterocolitica, Babesia* spp., *Bartonella* spp., *Borrelia* spp., and *Brucella* spp.
  - Others
    - *Leishmania* spp., *Rickettsia*, *Parvovirus* spp., *plasmodia* and *Toxoplasma* spp., and prions
- Iron overload
- Metabolic complications
  - Hypocalcemia (owing to citrate binding)
  - Hyperkalemia
  - Metabolic alkalosis (citrate is a bicarbonate equivalent as is hepatically metabolized to bicarbonate)
- Volume overload (TACO—transfusion-associated cardiac overload)

Establish institution-specific guidelines with transfusion thresholds. Transfusion guidelines and triggers should account for an individual patient's ability to tolerate and compensate for an acute decrease in hemoglobin, based on signs and symptoms of impaired global and regional tissue oxygenation

Suggestions for the appropriately identified patient:

- Pacted red blood cells (PRBCs)
  - Controversy exists regarding the appropriate transfusion trigger
  - Hemoglobin trigger <7 g/dL in most intensive care unit patients
    - Goal between 7 and 9 g/dL
  - Suggested hemoglobin trigger <10 g/dL in patients **with**:
    - A significant cardiac history *and* evidence of current ischemia (no supportive evidence, trials are ongoing)
    - Acute severe bleeding
    - One paper[a] showed a survival benefit of a bundle which included target Hg ≥ 10 g/dL if SVO_2 endpoint not reached after fluid resuscitation in the first 6 h of therapy of severe sepsis/septic shock; later studies have shown no benefit using this transfusion strategy

[a]*NEJM* 1999;340:409–417

Table 4.11 Propylene glycol content of commonly utilized intravenous medications[a]

Chordiazepoxide	207 mg/mL
Conivaptan	300 mg/mL
Diazepam	414.4 mg/mL
Digoxin	414.4 mg/mL
Esmolol (2.5 g/10 mL ampule)	250 mg/mL
Etomidate	350 mg/mL
Hydralazine	103.6 mg/mL
Lorazepam (2 mg/mL)	830 mg/mL
MVI-12 (adult)	310.8 mg/mL
Nitroglycerin	310–518 mg/mL
Pentobarbital	414.4 mg/mL
Phenobarbital	702.4 mg/mL
Phenytoin	414.4 mg/mL
Trimethoprim/sulfamethoxazole	414.4 mg/mL

[a]Data from *Int. Care Med.* 2002;28:81–84

Note:

1. Chronic or large ingestions of propylene glycol have been associated with the development of hyperosmolar anion-gap metabolic acidosis, renal dysfunction, hemolysis, cardiac arrhythmias, and seizures
2. Monitor osmolar gap in patients receiving prolonged or high doses of above intravenous medications (e.g., lorazepam ≥10 mg/h infusion for >48 h)
3. A toxic propylene glycol plasma level breakpoint remains to be determined
4. Propylene glycol is partially excreted by the kidney unchanged and partially metabolized by hepatic alcohol dehydrogenase to lactic acid and pyruvate
5. Must evaluate volume of medication administered to determine total propylene glycol exposure. High-dose lorazepam (i.e., >10 mg/h), phenytoin loading doses, and phenobarbital are the most likely offenders

Table 4.12 Drug-induced fever

- Etiology probably multifactorial (i.e., hypersensitivity reactions, pharmacological action of the drug and/or metabolites, infusion-related, induced adrenal insufficiency, Jarisch-Herxheimer reaction following treatment of syphilis, brucellosis, schistosomiasis, or trypanosomiasis, or idiosyncratic)
- Rash, urticaria, visceral organ abnormalities (especially acute interstial nephritis), and peripheral eosinophilia may be seen
- Fever pattern may range in severity and perserverance; may cause a pulse-temperature deficit
- Resolution of fever may occur 72 h after the discontinuation of the offending agent

Medications

- Abacavir
- Allopurinol
- Anticholinergic agents (e.g., antihistamines, atropine, tricyclic antidepressants)
- Aspirin (severe overdose)
- Barbiturates, carbamazepine, and phenytoin (antiepileptic hypersensitivity syndrome)
- Bleomycin
- Amphotericin B, cephalosporins, penicillins, minocycline, nitrofurantoin, sulfonamide antimicrobials, and vancomycin
- Heparin
- Hydralazine, methyldopa, procainamide, and quinidine
- L-asparaginase, immunoglobulins, and interferons
- Vaccines
- Zonisamide
- Intravenous infusion-associated
  - Amphotericin B, bleomycin, and pentazocine

Note:

Drug-induced hyperthermia syndromes are covered separately

- Malignant hyperthermia (*see* Table 4.9)
- Neuroleptic malignant syndrome (*see* Table 12.2)
- Serotonin syndrome (*see* Table 12.3)
- Altered thermoregulation
  - Atropine, antihistamines, phenothiazines, and haloperidol
  - Amphetamines, cocaine, and ecstasy (methylene dioxymethamphetamine), monoamine oxidase inhibitors, theophylline, thyroxine
  - Baclofen withdrawal

Table 4.13 Pharmaceutical dosage forms that should not be crushed

- Any extended release preparation
  - CR—controlled-release
  - EC—enteric coated
  - LA—long-acting
  - SR—sustained release
  - TR—time release
  - SA—sustained action
  - SL—sublingual
  - XL—extended length
  - XR—extended release

Table 4.14 Stress-related mucosal damage prophylaxis protocol

Assess patient for the presence of risk factors

- Mechanical ventilation for >48 h
- Coagulopathy (i.e., thrombocytopenia or disseminated intravascular coagulation)
- Septic shock
  - Systolic blood pressure (SBP) < 90 mmHg or a mean arterial pressure (MAP) < 60 mmHg for >1 h or hypotension requiring vasopressor pharmacotherapy
- Head or spinal cord injury
- Major trauma
- Major surgery
- Burns (thermal injury) in >30 % of body surface area
- Renal failure
- Liver failure
- High-dose corticosteroid therapy (e.g., hydrocortisone 200 mg/day or greater or its equivalent)

Suggested utilization guidelines

- Lack of enteral access
  - Intravenous H_2-receptor antagonist (preferred) or intravenous proton pump inhibitor (PPI)
- Presence of an NGT or PEG or patient can take PO
  - Enterally administered H_2-receptor antagonist, sucralfate, or PPI
- Presence of a transpyloric feeding tube
  - H_2-receptor antagonist or PPI
- Convincing evidence on the efficacy of enteral nutrition in the prevention of stress-related mucosal damage is not available

(continued)

Table 4.14 (continued)

Dosing and administration guidelines

- H_2-receptor antagonists (adjust all doses for renal impairment)
  - Famotidine: 20 mg IV or enterally q12h
  - Ranitidine: 150 mg enterally q12h or 50 mg IV q6h
  - Nizatidine: 150 mg enterally q12h
  - Cimetidine: 300 mg IV or enterally q6h
- Proton pump inhibitors (consider q12h dosing for better pH control)
  - Omeprazole: 20–40 mg enterally daily
  - Esomeprazole: 20–40 mg enterally daily or q12h
  - Lansoprazole: 30 mg enterally or IV daily
  - Pantoprazole: 40 mg enterally or IV daily or 12 h
  - Rabeprazole: 20 mg enterally daily
- Sucralfate 1 g enterally q6h
  - May be preferred in patients whose risk/attributable mortality of hospital-acquired pneumonia (HAP) is greater than upper gastrointestinal bleed. Data suggests a lower incidence of HAP when compared with H_2-receptor antagonist
  - May be less effective than H_2-receptor antagonist pharmacotherapy
  - Contains 207 mg aluminum/1 g. Avoid chronic use in patients with renal failure
  - Does not alter gastric pH

Duration of prophylaxis

- Reassess patient daily for the presence or absence of risk factors
- Consider discontinuing prophylaxis when the patient is discharged from the intensive care unit or if risk factors abate

Table 4.15 Therapeutic drug monitoring

Medication	*Goal steady-state levels*
Amikacin	• High concentration (once-daily) ◦ Peak—50–60 mcg/mL ◦ Trough—undetectable • Pneumonia (standard dosing) ◦ Peak—25–30 mcg/mL ◦ Trough—4–5 mcg/mL • Bacteremia (standard dosing) ◦ Peak—20–25 mcg/mL ◦ Trough—4–5 mcg/mL • Urinary tract infection (standard dosing) ◦ Peak—15–16 mcg/mL ◦ Trough—3–4 mcg/mL • Goal peak = 8–12 × MIC pathogen • Obtain peak 30–60 min after a dose • Obtain trough 30 min before a dose
Carbamazepine	• 4–12 mcg/mL • Obtain trough concentrations for routine monitoring
Digoxin	• Chronic heart failure—0.5–9 ng/mL • Atrial fibrillation—1.5–2 ng/mL • May check a level 4 h after an IV dose or 6 h after an enteral dose • Obtain trough concentrations for routine monitoring
Gentamicin	• High concentration (once daily) ◦ Peak—18–20 mcg/mL ◦ Trough—undetectable • Pneumonia (standard dosing) ◦ Peak—8–10 mcg/mL ◦ Trough—1 mcg/mL • Bacteremia (standard dosing) ◦ Peak—5–8 mcg/mL ◦ Trough—1 mcg/mL • Urinary tract infection (standard dosing) ◦ Peak—5 mcg/mL ◦ Trough—1 mcg/mL • Endocarditis (standard dosing) ◦ Peak—3–5 mcg/mL ◦ Trough—1 mcg/mL • Goal peak = 8–12 × MIC pathogen • Obtain peak 30–60 min after a dose • Obtain trough 30 min before a dose

(continued)

Table 4.15 (continued)

Medication	*Goal steady-state levels*
Lidocaine	• 1–5 mcg/mL • Check a level if therapy is continued beyond 24 h or if a patient has LV dysfunction or hepatic impairment • Has two active metabolites that are renally cleared
Phenobarbital	• 15–40 mcg/mL • Levels obtained within 1–2 weeks after the initiation of therapy do not reflect steady-state concentrations • Once steady-state is achieved, levels can be obtained irrespective of when the dose is administered
Phenytoin/ Fosphenytoin	• 10–20 mcg/mL ◦ 1–2 mcg/mL for free drug • Some patients may need levels up to 25 mcg/mL • Time to achieve steady-state may be prolonged • May obtain a level 2 h after an IV load to assess the adequacy of the dose, then again within 2–3 days • May obtain a level 4 h after an IM load with fosphenytoin • Obtain trough concentrations for routine monitoring • Equation to adjusted measured phenytoin levels in the setting of hypoalbuminemia ◦ Adjusted phenytoin level = measured phenytoin level/(0.2 × serum albumin) + 0.1 • Equation to adjust measured phenytoin levels in the setting of CrCl ≤ 10 mL/min (+ /– hypoalbuminemia) ◦ Adjusted phenytoin level = measured phenytoin level/ (0.1 × serum albumin) + 0.1 ◦ May need to monitor free phenytoin levels
Theophylline	• 5–15 mcg/mL • Levels above 15 mcg/mL can predispose a patient to toxicity • Obtain a level 24 h after the initiation of a continuous IV infusion of aminophylline, then daily until stable • Obtain trough concentrations for routine monitoring of enteral theophylline products • Has active metabolites that are renally cleared

(continued)

Table 4.15 (continued)

Medication	*Goal steady-state levels*
Tobramycin	• High concentration (once daily) ◦ Peak—18–20 mcg/mL ◦ Trough—undetectable • Pneumonia (standard dosing) ◦ Peak—8–10 mcg/mL ◦ Trough—1 mcg/mL • Bacteremia (standard dosing) ◦ Peak—5–8 mcg/mL ◦ Trough—1 mcg/mL • Urinary tract infection (standard dosing) ◦ Peak—5 mcg/mL ◦ Trough—1 mcg/mL • Goal peak = 8–12 × MIC pathogen • Obtain peak 30–60 min after a dose • Obtain trough 30 min before a dose
Valproic acid	• 50–100 mcg/mL • Obtain trough concentrations for routine monitoring
Vancomycin	• Most indications ◦ Trough—15–20 mcg/mL • Urinary tract infections ◦ Trough—10–15 mcg/mL • Obtain trough 30 min before a dose

Table 4.16 Select antidotes for toxicological emergencies

Acetylcysteine (NAC)

- Used in acetaminophen intoxication
  - If ≤8 h from the time of acute ingestion and patient "at risk" based on the level
  - Can be utilized after the 8-h time frame in acetaminophen intoxications, in potentially other hepatotoxic ingestions or indeterminate causes of acute hepatic failure
- IV dose
  - 150 mg/kg over 60 min, followed by 50 mg/kg over 4 h, followed by 6.25 mg/kg/h for 16 h. Total dose is 300 mg/kg over 24 h
  - Alternative IV regimen: 140 mg/kg followed in 4 h by 70 mg/kg q4h × 17 additional doses
  - Use intravenously if unable to administer enterally or if the patient is in acute hepatic failure
- Enteral dose
  - 140 mg/kg followed in 4 h by 70 mg/kg q4 h × 17 additional doses. Repeat any enteral dose if the patient vomits within 1 h of administration

(continued)

Table 4.16 (continued)

- Treatment duration may vary based on clinical presentation
  - Consider a longer course of treatment if initiation of NAC is delayed beyond 8 h of acetaminophen ingestion
- Use IV product with caution in patients with a history of asthma

DigiFab (Digibind no longer available)

- Used in cardiac glycoside intoxication. The information below pertains to **digoxin** intoxication
- Indications:
  - Life-threatening dysrhythmia
  - Digoxin level ≥ 10 ng/mL
  - Ingestion of ≥ 10 mg
  - Potassium level > 5 mEq/L (secondary to digoxin toxicity)
  - Lower thresholds in elderly patients
- IV dose (**3 different methods** to determine the number of vials required in the setting of digoxin intoxication)
  - #1—(Serum concentration in ng/mL × body weight in kg)/100
  - #2—(Milligrams of digoxin ingested)/0.5
  - #3—Acute ingestion—20 vials; start with 10 vials then administer the remaining 10 vials if needed, to avoid a febrile reaction. Chronic ingestion—6 vials
  - Round vial number up to the nearest whole vial
- Administer over 30 min
  - May bolus if cardiac arrest is imminent
- Plasma levels are not useful after administration. Monitor the patient clinically
- Monitor for rebound toxicity in patients with renal impairment
- Monitor for CHF exacerbation and hypokalemia
- Contraindicated if known hypersensitivity to sheep products, papaya, or papain; administer if the perceived benefit outweighs the potential risk

Flumazenil

- Used in benzodiazepine, zaleplon, and zolpidem intoxications
- Indications:
  - Central nervous system depression with normal vital signs and normal electrocardiogram
- Avoid use if:
  - Seizure history
  - Chronic benzodiazepine use
  - Concomitant TCA intoxication
  - Concomitant arrhythmogenic or epileptogenic ingestant
  - Use carefully in patients with known alcohol dependence or panic attacks
  - Above unknown
  - In these settings may precipitate refractory status epilepticus

(continued)

Table 4.16 (continued)

- Dose (for suspected overdose)
  - 0.2 mg over 30 s. If still lethargic, give 0.3 mg over 30 s. May administer 0.5 mg every 60 s to a maximum cumulative dose of 3 mg. Patients with a partial response to 3 mg may need additional titrated doses up to 5 mg. Consider an alternative diagnosis if the patient does not respond to 5 mg. May initiate a continuous IV infusion of 0.1–1 mg/h in the event of resedation (**note**: benzodiazepine's half-life is longer than flumazenil's half-life)
- Does not reliably reverse respiratory or cardiac depression
- Monitor for rebound benzodiazepine intoxication

Glucagon

- Used in β-adrenergic blocker and calcium channel blocker intoxication
- Dose
  - 2–10 mg IV bolus followed by 3–10 mg/h continuous IV infusion
- Monitor for tachyphylaxis, gastrointestinal side effects, or hyperglycemia/hypoglycemia

Methylene blue (*see* Table 8.3)

Naloxone

- Used in opiate intoxication. Limited efficacy in clonidine intoxication
- Dose
  - 0.4 mg IV over 30 s every 2–3 min as needed to a maximum dose of 10 mg in the presence of life-threatening cardiopulmonary depression. Use 0.1 mg increments or lower doses (0.04 mg) in opioid-dependent patients, patients with cardiovascular disease, or if the clinical situation is not life-threatening. Consider an alternative diagnosis if the patient does not respond to a 10 mg total dose. May initiate a continuous IV infusion at 2/3 the reversal dose in patients who experience rebound toxicity (opiate's half-life is longer than naloxone's half-life)
- Use with caution in patients with cardiovascular disease or acute pulmonary edema
- Monitor for signs of opioid withdrawal in opioid-dependent patients

Octreotide

- Used in sulfonylurea and quinine intoxication (secondary after glucose administration)
- Dose
  - 50 mcg IV/SQ q6h
  - Role for continuous IV infusion?
- Monitor for hypoglycemia and hyperglycemia

Protamine sulfate

- Used in unfractionated heparin (UFH) and low molecular weight heparin (LMWH) intoxication
  - Fully reverses UFH
  - Reverses approximately 60 % of LMWHs (excluding fondaparinux)

(continued)

Table 4.16 (continued)

- Dose
  - UFH—1 mg protamine/100 units UFH
    - Must estimate amount of UFH in circulation (use a 60 min half-life)
    - If an anti-Factor Xa or aPTT level is prolonged 2–4 h after the first dose of protamine sulfate, may administer an additional 0.5 mg of protamine sulfate per 100 units UFH if needed
    - Example
      - Patient on UFH 1,000 units/h continuous IV infusion has a major bleed. Method to estimate UFH burden:
        - From the previous hour—1,000 units remaining
        - From 2 h ago—500 units remaining
        - From 3 h ago—250 units remaining
        - Total estimated circulating UFH that needs to be reversed = 1,750 units
        - Dose of protamine = 17.5 mg
  - Enoxaparin—1 mg of protamine/1 mg enoxaparin to a maximum of 50 mg
    - Dose may depend on the lapsed time after LMWH administration (e.g., 0.5 mg protamine per 1 mg enoxaparin to a maximum of 50 mg if greater than 8 h has passed since the last administered dose)
  - Dalteparin or tinzaparin—1 mg protamine/100 units dalteparin or tinzaparin to a maximum of 50 mg
    - Dose may depend on the lapsed time after LMWH administration (e.g., 0.5 mg protamine per 100 units dalteparin or tinzaparin to a maximum of 50 mg if greater than 8 h has passed since the last administered dose)
  - **Maximum single dose of protamine sulfate is 50 mg in any 10-min period**
    - Weak anticoagulant when excessively dosed (decreases factor VIII levels)
  - Administer protamine sulfate dose slowly over 10 min
- Risk factors for an adverse event
  - Previous protamine exposure (e.g., during coronary artery bypass graft, or NPH insulin products containing protamine zinc) or fish allergy (salmon)
- Monitor for heparin rebound (may occur within 8–18 h)

Pyridoxine (see Table 10.1)

Hydroxocobalamine (Cyanokit®)

- Used in cyanide poisonings (before sodium nitrite followed by sodium thiosulfate)
  - 5 g IV over 15 min. In severe poisonings and based on clinical response, a second dose of 5 g may be administered over 15 min to 2 h

(continued)

TABLE 4.16 (continued)

Sodium nitrite followed by sodium thiosulfate

- Used in cyanide (including from sodium nitroprusside) intoxication
  - Dose of sodium nitrite is 300 mg or 4–6 mg/kg IV over 2 min. 150 mg or 50 % of the previous dose may be given if signs of cyanide toxicity reappear
  - Dose of sodium thiosulfate is 12.5 g or 150–200 mg/kg IV over 2 min. 6.25 g or 50 % of the previous dose may be given if signs of cyanide toxicity reappear
- The purpose of sodium nitrite (or amyl nitrite in the absence of IV access) is to produce methemoglobin, which binds cyanide with greater affinity than mitochondrial cytochromes. In the presence of decreased oxygen carrying capacity, as in combined exposures to cyanide and carbon monoxide (e.g., some fires), sodium nitrite can be detrimental and should be avoided

Vitamin K_1 (*see* Table 2.16)

Chapter 5
Dermatology

Table 5.1 Drug-induced dermatological reactions

Angioedema
- Alteplase, angiotensin converting enzyme inhibitors, atracurium, β-lactams, heparin, iron (parenteral), losartan, and streptokinase

Erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis
- Allopurinol, barbiturates, carbamazepine, cephalosporins, cyclophosphamide, ethambutol, fluconazole, ibuprofen, lamotrigine, macrolides, nitrofurantoin, penicillins, phenytoin, propranolol, quinolones, sulfonamide antimicrobials, sulindac, tetracyclines, thiazides, valproic acid, and vancomycin

Maculopapular eruptions
- Allopurinol, barbiturates, benzodiazepines, captopril, carbamazepine, erythromycin, fluoroquinolones, isoniazid, NSAIDs, penicillins, phenothiazines, phenytoin, rifampin, sulfonamides antimicrobials, and tetracyclines

Photosensitivity reactions
- Amantadine, amiodarone, barbiturates, benzodiazepines, carbamazepine, chlorpromazine, fluoroquinolones, furosemide, NSAIDs, promethazine, psoralens, quinidine, simvastatin, sulfonamide antimicrobials, sulfonylureas, tetracyclines, and thiazides

Skin discoloration
- Blue—amiodarone (blue-gray), FD&C dye no. 1, and methylene blue
- Red—anticholinergic agents (e.g., antihistamines, atropine, tricyclic antidepressants, scopalamine), disulfiram, hydroxocobalamin, and vancomycin
- Yellow—β-carotene

(continued)

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Table 5.1 (continued)

Systemic lupus erythematosis
• Carbamazepine, chlorpromazine, ethosuximide, hydralazine, isoniazid, methyldopa, minocycline, penicillamine, phenylbutazone, phenytoin, procainamide, quinidine, thiazides, and valproic acid
Urticaria
• Albumin, aminophylline, aspirin, heparin, insulin, metoclopramide, NSAIDs, muromonab-CD3 (OKT3), opiates, penicillins, propafenone, quinidine, senna, sulfonamide antimicrobials, and vancomycin

Chapter 6
Endocrinology

Table 6.1 Management of diabetic ketoacidosis and hyperosmolar hyperglycemic state

- Identify precipitating factors
  - Infection, acute coronary syndrome, cerebrovascular accidents, trauma, noncompliance with insulin pharmacotherapy, new-onset diabetes mellitus, and medications (e.g., corticosteroids and sympathomimetics)
- Prepare a comprehensive flow sheet with vitals, laboratory data, fluid type and rates, insulin rates, and other treatments
- Correct fluid abnormalities
  - Upon presentation: **normal saline** infused at 15–20 mL/kg/h (providing 1–1.5 L in the first hour), then 4–14 mL/kg/h for most patients
    - Use clinical variables (e.g., blood pressure, heart rate, skin temperature) to target euvolemia; urine output may not be reliable in the hyperglycemic patient
    - Monitor for hyperchloremic metabolic acidosis
  - If serum sodium rises above 145–150 mEq/L, switch to hypotonic fluid replacement (i.e., 0.45 % saline). Lactated Ringer's solution may prolong ketoacid production by promoting alkalinization
    - Serum sodium may rise with insulin and isotonic saline fluid administration; estimate the corrected serum sodium concentration at presentation:
      - Add 1.6 mEq/L to the measured serum sodium for every 100 mg/dL rise in blood glucose > 200 mg/dL
  - When blood glucose falls to ≤ 200 mg/dL, switch to D5W, D5W/1/2 NS, or D5W/NS depending on plasma sodium concentration

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_6,

Table 6.1 (continued)

- Regular insulin
  - Do not initiate insulin therapy if the serum potassium < 3.5 mEq/L. Maintain potassium levels between 4 and 5 mEq/L during insulin infusion therapy
  - Prepare 100 units of regular insulin in 100 mL normal saline (new tubing should be primed with 20 mL of the infusion)
  - Use an ideal body weight to dose insulin in obese patients
  - Bolus with **0.1 units/kg** IV, then **0.05–0.1** units/kg/h continuous IV infusion
    - Consider withholding the insulin bolus in the setting of shock until resuscitation is underway; rapid lowering of blood glucose can precipitate worsening of the hypovolemia state
    - If blood glucose does not decrease by at least 10 % in the first hour, administer 0.14 units/kg regular insulin bolus then adjust the continuous infusion
  - Goal is to reduce blood glucose by 50–150 mg/dL/h. Use an institution dose adjustment protocol to titrate the insulin infusion
  - Continue the insulin infusion until acidosis is corrected (i.e., anion gap closes)
    - Maintain blood glucose between 150 and 200 mg/dL
  - Monitor blood glucose every hour. Once blood glucose is within the range of 150–200 mg/dL on three consecutive measurements and the anion gap closes, monitor blood glucose every 2 h
    - If hypoglycemia develops in the setting of continued ketoacidosis, lower the insulin infusion and administer glucose infusions to maintain euglycemia. **Do not stop the insulin infusion**
  - Monitor anion gap as often as necessary (e.g., every 4 h)
- **Transition to long acting insulin** (e.g., insulin glargine) once ketoacidosis has resolved, blood glucose ≤ 200 mg/dL, and the patient is eating. Different methods exists; one example is provided below:
  - Initiate long acting insulin **2 h** prior to stopping the insulin infusion, then daily at the same time each day
  - Estimate total daily dose of insulin: when the decision is made to transition, evaluate the last 7 insulin drip rates and omit the 2 highest rates; add the 5 lowest insulin drip rates and multiply by 4 = **total daily dose** of insulin
  - Divide the **total daily dose** of insulin proportionally into the **basal** and **prandial bolus** components (**note**: patient may also need prandial correctional insulin)
  - **Basal** insulin: **total daily dose** divided by 2 = units of insulin glargine SQ q24h (**note**: maximal initial dose of 50 units daily)
  - **Prandial bolus**: **total daily dose** divided by 6 = units of insulin aspart SQ before each meal

(continued)

Table 6.1 (continued)

- Hypoglycemia management
  - If blood glucose < 70 mg/dL and the patient has normal mental status and is able to swallow, administer glucose 40 % oral gel 15 g PO q10 min prn; repeat blood glucose measurement in 15 min
  - If blood glucose < 70 mg/dL and the patient is NPO or if < 100 mg/dL and the patient has an altered mental status, administer dextrose 50 % 50 mL IVP q10 min prn; repeat blood glucose in 10 min
- Monitor and correct potassium, phosphorus, and magnesium
- Bicarbonate therapy (if desired)
  - No proven benefit except for concomitant symptomatic hyperkalemia
  - Goal is to increase the pH > 7.2
  - Monitor arterial or venous pH hourly
  - Do not overcorrect pH as acetoacetate and β-hydroxybutyrate are metabolized to bicarbonate
- Administer all intravenous medications in saline where possible
- Monitor for evidence of cerebral edema, noncardiogenic pulmonary edema, acute respiratory distress syndrome, hyperchloremic metabolic acidosis, and vascular thrombosis

Table 6.2 Management of thyrotoxic crisis and myxedema coma

Thyrotoxic crisis

- Supportive care
  - Control hyperthermia with acetaminophen and cooling blanket
    - Avoid aspirin, as it may increase free T_4 and T_3 levels by interfering with plasma–protein binding
  - Fluid resuscitation
- Propylthiouracil (preferred thionamide, as it blocks peripheral conversion of $T_4 \rightarrow T_3$)
  - 200 mg enterally every 4–6 h. Reduce dose once signs/symptoms are controlled. Usual maintenance dose is 100–150 mg q8h
  - Alternative—methimazole 30 mg enterally every 6–8 h. Reduce dose once signs/symptoms are controlled. Usual maintenance dose is 15–60 mg daily in three equally divided doses
- Lugol's solution 10 drops or 1 mL in water q8h
  - Alternative—saturated solution of potassium iodide (SSKI) 5–10 drops in water q8h
  - Use iodine solutions at least 1–2 h after a thionamide
- β-adrenergic blockers
  - Adjust dose to achieve heart rate ≤ 100 beats/min
  - Cautious use in setting of heart failure related to systolic dysfunction
  - Propranolol 0.5–1 mg slow intravenous push (IVP) up to a total of 5 mg, then 20–80 mg enterally q6h
  - Esmolol may be utilized if a rapid short-acting agent is needed
- Hydrocortisone 100 mg IV q8h or 50 mg IV q6h until adrenal suppression is excluded. Also blocks peripheral conversion of $T_4 \rightarrow T_3$
- Consider plasmapheresis if intractable symptoms

(continued)

Table 6.2 (continued)

Myxedema coma

- Supportive care
  - Rewarm passively with a blanket; active rewarming may cause distributive shock
  - Treat hypotension with fluids and vasopressor support. Consider adrenal insufficiency
  - Manage hyponatremia if present
- Levothyroxine (T_4) 200–500 mcg IV bolus followed by 75–100 mcg/day
  - Reduce dose in patients with coronary artery disease
- Liothyronine (T_3) 25–50 mcg IV bolus. Use 10–20 mcg IV bolus in patients with coronary artery disease. Subsequent doses (e.g., 2.5–10 mcg IV q6–8 h) should be administered between 4 and 12 h after the initial bolus dose and continued until signs and symptoms resolve
- Role for dual T_3 and T_4 therapy is uncertain
- Hydrocortisone 100 mg IV q8h or 50 mg IV q6h until adrenal insufficiency is excluded
- *Low threshold for empiric antimicrobial therapy*

Chapter 7
Gastrointestinal

Table 7.1 Management of acute non-variceal upper gastrointestinal bleeding[a]

Address etiology
Risk factors for rebleeding
- Clinical
  - Prolonged hypotension
  - Age > 65 years
  - Fresh blood in emesis, in nasogastric aspirate, or on rectal examination
  - Evidence of active bleeding
  - Large transfusion requirements
  - Low initial hemoglobin
  - Coagulopathy
  - Concomitant diseases (e.g., hepatic, renal, and neoplasm)
- Endoscopic
  - Ulcers > 1–2 cm in size
  - Site of bleeding
    - Posterior lesser gastric curvature or posterior duodenal wall
  - Evidence of stigmata of recent hemorrhage
    - Spurting vessel
    - Oozing vessel
    - Non-bleeding visible vessel (NBVV)
    - Ulcer with an adherent clot

Management
- Appropriate fluid resuscitation (**note**: do not over resuscitate)
- Placement of a nasogastric tube in the appropriate patient
  - Benefits may include
    - Potential reduction in risk of massive aspiration if placed initially in an awake patient

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_7,

Table 7.1 (continued)

- Facilitates endoscopic view
- May help gauge activity and severity of bleeding

- Urgent endoscopy (within 24 h of presentation)
- Histamine$_2$-receptor antagonists are ***not*** recommended
- Pantoprazole IV
  - In patients with evidence of stigmata of recent hemorrhage
  - May be initiated prior to endoscopy
  - 80 mg IV over 2 min followed by 8 mg/h continuous IV infusion for up to 72 h
  - Step-down to oral/enteral proton pump inhibitor (high-dose) once stable (e.g., pantoprazole 40 mg bid or esomeprazole 40 mg bid)
  - Esomeprazole or lansoprazole may be utilized as alternative intravenous agents
- Oral/enteral proton pump inhibitor
  - In patients with a flat spot or clean ulcer base
- Octreotide 50 mcg IV bolus followed by 50 mcg/h continuous IV infusion for 3–5 days
  - In patients with evidence of a spurting or oozing vessel who are at the highest risk of rebleeding (**author's opinion**)[b]
- *Helicobacter pylori* testing and treatment where appropriate

[a]Data from *Ann. Intern. Med.* 2003;139:843–857
[b]Data from *Ann. Intern. Med.* 1997;127:1062–1071

Table 7.2 Causes of diarrhea in the intensive care unit patient[a]

Medications
- Antimicrobials (noninfectious)
- Sorbitol-containing solutions
  - Guaifenesin, theophylline, and valproic acid
- Prokinetic agents
  - Metoclopramide and erythromycin
- Histamine$_2$-receptor antagonists, proton pump inhibitors, magnesium-containing enteral products, and misoprostol
- Digoxin, procainamide, and quinidine

Enteral nutrition formulas (especially hyperosmotic formulas)

Infectious
- *Clostridium difficile*, *Staphylococcus aureus*, and *Candida* spp.
- Uncommon—*Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia* spp., and enteropathogenic *Escherchia coli*

Others
- Fecal impaction, ischemic bowel, pancreatic insufficiency, and intestinal fistulae
- Gastrointestinal neoplasm
  - Vasoactive intestinal polypeptide secreting tumors

[a]*Am. J. Gastroenterol.* 1997;92:1082–1091. *Hepatology* 1998;27:264–272

Table 7.3 Managing the complications of cirrhosis

Supportive measures

- Abstinence from alcohol
  - Alcohol withdrawal prophylaxis or treatment
- Nutrition support
  - Protein restriction should not be routinely utilized
- Corticosteroid therapy for patients with alcoholic hepatitis (steatonecrosis) with or without hepatic encephalopathy
  - Maddrey score or discriminant function = 4.6 (patient's prothrombin time – prothrombin time control) + total bilirubin
    - If the score is ≥ 32 and/or the patient is encephalopathic, consider administering prednisone or prednisolone (the active form of prednisone) if there is no evidence of an upper gastrointestinal tract hemorrhage or an active infection
  - 6 weeks of prednisone or prednisolone therapy and taper
    - For example, 40 mg enterally bid × 1 week, 40 mg enterally daily × 1 week, 20 mg enterally daily × 2 weeks, and 10 mg enterally daily × 2 weeks. Alternative regimen is 40 mg enterally daily for 4 weeks followed by a taper
- More data on etanercept, infliximab, and pentoxifylline are needed before any recommendations can be made

Ascites (serum ascites albumin gradient ≥ 1.1 g/dL)

- Reduced sodium intake (≤2 g/day)
- Fluid restriction not necessary unless serum sodium < 120–125 mEq/L
- Diuretics
  - Spironolactone 50–200 mg enterally daily
  - Furosemide 20–80 mg enterally daily
    - Monitor for excessive diuresis
  - 100 mg spironolactone/40 mg furosemide ratio to maintain normokalemia. Doses may be adjusted every 3–5 days up to a maximum of spironolactone 400 mg/day and furosemide 160 mg/day. Single morning doses increase patient compliance
  - Amiloride may be a less effective alternative to spironolactone
    - 5–20 mg/day
  - Once edema has resolved, maintain weight loss (should not exceed 0.5 kg/day)
  - Stop diuretic pharmacotherapy if serum creatinine acutely rises > 2 mg/dL, the patient becomes encephalopathic, or serum sodium decreases below 120 mEq/L despite fluid restriction

Tense ascites

- Large-volume paracentesis
  - If removing > 5 L of fluid, consider albumin volume expansion to prevent hemodynamic compromise, rapid reaccumulation of ascites, dilutional hyponatremia, or hepatorenal syndrome
    - Replace with 8–10 g albumin/L of ascitic fluid removed

(continued)

Table 7.3 (continued)

- Avoid large-volume paracentesis in patients with preexisting hemodynamic compromise, acute renal insufficiency, active infection, or active upper gastrointestinal bleed. Cautious large-volume paracentesis in patients with tense ascites *and* respiratory compromise or evidence of abdominal compartment syndrome

- High-dose diuretics until loss of ascitic fluid
  - Spironolactone up to 400 enterally daily
  - Furosemide up to 160 enterally daily

Refractory ascites

- Serial therapeutic paracentesis (as above under tense ascites)
- Transjugular intrahepatic porto-systemic shunt (TIPS)
- Peritoneovenous shunt
- Liver transplantation

Hepatic encephalopathy (acute)

- Precipitating factors
  - Infection, constipation, metabolic alkalosis, hypokalemia, excessive dietary protein intake, gastrointestinal hemorrhage, hypoxia, or hypovolemia
  - Drugs with sedative properties (e.g., benzodiazepines)
- Management
  - Address precipitating factors
  - Protein restriction in patients with grade III or IV hepatic encephalopathy
    - Limit to 40 g/day or 0.5 g/kg/day and provide appropriate nonprotein calories
      - Add protein back in 20 g increments every 3–5 days once acute hepatic encephalopathy improves and until protein caloric goal is achieved (usually 0.8–1 g/kg/day)
    - Specialized enteral formulas may have a role in carefully selected patients
      - Nutrihep, hepatic-aid, and hepatamine (IV)
    - Vegetable protein better tolerated than animal protein
      - Contains less aromatic amino acids
  - Lactulose
    - 30–60 mL enterally every 2 h until defecation, then 15–30 mL enterally q6–12h, titrated to achieve 2–3 soft stools per day
    - In NPO patients, a retention enema can be utilized
      - 300 mL lactulose syrup in 700 mL water **or** 150 mL lactulose syrup in 350 mL water held for 30–60 min q6–8h
  - Rifaximin 550 mg enterally q12h (usually in combination with lactulose)
  - Neomycin 0.5–1 g enterally q6h (has fallen out of favor)
    - Duration should be $\leq$2 weeks to avoid systemic accumulation and renal toxicity

(continued)

Table 7.3 (continued)

- Metronidazole 500 mg enterally q8h can be a substitute for neomycin
- Zinc sulfate 220 mg enterally q8–12 h (efficacy questionable)
  - Zinc is a cofactor for ammonia metabolism
  - Presence of malnutrition and diarrhea can lead to zinc deficiency

Hepatorenal syndrome—type 1 (rapid, progressive decline in renal function)

- Avoid NSAIDs and nephrotoxins
- Assess patient for prerenal azotemia and hold diuretic therapy
- Fluid resuscitate if evidence of volume depletion
- **In patients with spontaneous bacterial peritonitis**:
  - Albumin IV 1.5 g/kg on day 1, then 1 g/kg on day 3
- Consider midodrine 7.5 mg enterally q8h + octreotide 100 mcg IV/SQ q8h
  - Administer with concomitant albumin volume expansion
- 1 g/kg IV on day 1, followed by 20–40 g/day
- Titrate to appropriate volume status and central venous pressure
  - Goal is to increase mean arterial pressure (MAP) by 15 mmHg
- Can increase midodrine to a maximum of 12.5 mg enterally q8h
- Can increase octreotide to a maximum of 200 mcg IV/SQ q8h
- Can use octreotide in combination with phenylephrine in patients without enteral access
  - Duration of therapy is 5–20 days
- End point of therapy
  - Decrease serum creatinine to < 1.5 mg/dL
- Consider large-volume paracentesis if any evidence of abdominal compartment syndrome is secondary to tense ascites
- Liver transplantation

Spontaneous bacterial peritonitis (SBP)

Treatment

- Albumin IV 1.5 g/kg on day 1, then 1 g/kg on day 3 to decrease renal failure and mortality
- Antimicrobial pharmacotherapy usually for 7–10 days
- Should target *Enterobacteriaceae* and *streptococci*
- β-lactam/β-lactamase inhibitor combinations, third or fourth-generation cephalosporins, or a fluoroquinolone
- Must inquire about previous antimicrobial use and evaluate for bacterial resistance

Secondary prophylaxis

- Long-term daily fluoroquinolone or trimethoprim/sulfamethoxazole

Primary prophylaxis

- Risk factors
  - Low ascitic fluid protein level (≤1 g/dL) or serum total bilirubin > 2.5 mg/dL

(continued)

Table 7.3 (continued)

- Either short-term inpatient therapy or long-term daily therapy with either a fluoroquinolone or trimethoprim/sulfamethoxazole

Variceal hemorrhage

- Secure airway
- Fluid resuscitation (avoid hypervolemia or over-resuscitation)
- Low threshold for invasive monitoring
- Emergent endoscopy
  - Antimicrobial prophylaxis if ascites/cirrhosis present preferably before endoscopy
  - β-lactam/β-lactamase inhibitor combinations, third or fourth-generation cephalosporin, trimethoprim/sulfamethoxazole, or a fluoroquinolone for 7 days
- Band ligation
- Octreotide 50 mcg IV, followed by 50 mcg/h continuous IV infusion for 5 days
  - Consider tapering infusion on day 5 to prevent rebound increase in splanchnic pressures
- Vasopressin + nitroglycerin IV ***(octreotide preferred pharmacotherapy)***
  - Vasopressin 0.2–0.8 units/min continuous IV infusion
  - Nitroglycerin counteracts systemic vasoconstrictive effects of vasopressin
- Pantoprazole IV ***(questionable benefit)***
  - 80 mg IV over 2 min followed by 8 mg/h continuous IV infusion for up to 72 h
- Step down to oral/enteral proton pump inhibitor once stable
- Esomeprazole or lansoprazole may be alternative intravenous agents
- Sclerotherapy (not commonly utilized)
  - Ethanolamine, sodium tetradecyl sulfate, sodium morrhuate, and polidocanol
- Endoscopic-refractory cases
  - Balloon tamponade followed by TIPS or surgical porto-systemic shunt may be indicated
- Secondary prophylaxis[a]
  - Propranolol or nadolol
  - Increase dose until the heart rate decreases by 25 % or to 60–70 beats/min
  - Dose propranolol carefully in patients with a recent TIPS procedure because of increased enteral bioavailability
- Endoscopic monitoring with intervention every 1–2 weeks until varix/varices has/have healed, then every 3–6 months
- Evaluate for liver transplantation
- Balloon tamponade
- TIPS

[a]Detailed recommendations in *NEJM* 2001;345(9):669–681

Table 7.4 Drug-induced hepatotoxicity[a]

Autoimmune
- Diclofenac, fenofibrate, lovastatin, methyldopa, minocycline, nitrofurantoin, phenytoin, and propylthiouracil

Cholestasis
- Amiodarone, ampicillin, amoxicillin, captopril, chlorpromazine, ceftriaxone, erythromycin estolate, estrogen products, methimazole, nafcillin, rifampin, sulfonamide antimicrobials, and sulfonylureas

Fibrosis
- Amiodarone, methotrexate, methyldopa, and hypervitaminosis A

Hepatocellular damage
- Acetaminophen, bosentan, diclofenac, isoniazid, lovastatin, methyldopa, niacin, nefazodone, phenytoin, propylthiouracil, rifampin, trazodone, valproic acid, and venlafaxine

Immunoallergic reactions
- Allopurinol, amoxicillin/clavulanic acid, dicloxacillin, erythromycin derivatives, halothane, phenytoin, and trimethoprim/sulfamethoxazole

Steatonecrosis
- Alcohol, amiodarone, didanosine, l-asparaginase, piroxicam, stavudine, tamoxifen, tetracycline derivatives, valproic acid, and zidovudine

Veno-occlusive disease
- Azathioprine, cyclophosphamide, nicotinic acid, tetracycline, and vitamin A

[a]*NEJM* 203;349:474–485

Table 7.5 Drug-induced pancreatitis

Allergic
- Angiotensin converting enzyme inhibitors, azathioprine, mercaptopurine, mesalamine, sulfasalazine, sulfonamide antimicrobials, and tetracyclines

Direct toxic effect
- Didanosine, l-asparaginase, lamivudine, metformin, pentamidine, statins, stavudine, sulindac, valproic acid, and zalcitabine

Hypertriglyceridemia mediated
- Estrogens, furosemide, hydrochlorothiazide, interferon alfa-2b, isotretinoin, propofol, and protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir)

Spasm of the sphincter of Oddi
- Octreotide, and opiates

Chapter 8
Hematology

Table 8.1 Drug-induced hematological disorders

Agranulocytosis
- β-lactam antimicrobials, chloramphenicol, chloroquine, clindamycin, dapsone, doxycycline, flucytosine, ganciclovir, isoniazid, metronidazole, nitrofurantoin, pyramethamine, rifampin, streptomycin, sulfonamide antimicrobials, vancomycin, and zidovudine
- Acetazolamide, captopril, ethacrynic acid, furosemide, hydralazine, methazolamide, methyldopa, procainamide, thiazide diuretics, and ticlopidine
- Allopurinol, aspirin, carbamazepine, chlorpropamide, clomipramine, clozapine, colchicine, desipramine, gold salts, imipramine, levodopa, penicillamine, phenothiazines, phenytoin, propylthiouracil, and sulfonylureas

Aplastic anemia
- Acetazolamide, allopurinol, aspirin, captopril, carbamazepine, chloramphenicol, chlorpromazine, dapsone, felbamate, gold salts, metronidazole, methimazole, penicillamine, pentoxifylline, phenothiazines, phenytoin, propylthiouracil, quinidine, sulfonamide antimicrobials, sulfonylureas, and ticlopidine

Hemolysis (oxidative)
- Benzocaine, β-lactams, chloramphenicol, chloroquine, dapsone, hydroxychloroquine, methylene blue, nitrofurantoin, phenazopyridine, rasburicase, and sulfonamide antimicrobials

Hemolytic anemia
- β-lactam antimicrobials, gatifloxacin, indinavir, isoniazid, levofloxacin, nitrofurantoin, ribavirin, rifabutin, rifampin, silver sulfadiazine, streptomycin, sulfonamide antimicrobials, and tetracyclines
- Acetazolamide, amprenavir, captopril, hydralazine, hydrochlorothiazide, methyldopa, procainamide, quinidine, ticlopidine, and triamterene
- Levodopa, methylene blue, phenazopyridine, quinine, and tacrolimus

(continued)

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Table 8.1 (continued)

Megaloblastic anemia
- Azathioprine, chloramphenicol, colchicine, cyclophosphamide, cytarabine, 5-fluorodeoxyuridine, 5-fluorouracil, hydroxyurea, mercaptopurine, metformin, methotrexate, phenobarbital, phenytoin, primidone, proton pump inhibitors, pyrimethamine, sulfasalazine, and vinblastine

Methemoglobinemia
- Benzocaine, cetacaine, EMLA cream, lidocaine, prilocaine, and procaine
- Chloroquine, dapsone, methylene blue (doses ≥4 mg/kg), nitrofurantoin, phenazopyridine, primaquine, rasburicase, and sulfonamide antimicrobials
- Nitrates (e.g., amyl nitrate and nitroglycerin) and nitroprusside

Thrombocytopenia
- Amphotericin B products, β-lactam antimicrobials, isoniazid, linezolid, rifampin, sulfonamide antimicrobials, and vancomycin
- Abciximab, aminophylline, amiodarone, amrinone, aspirin, carbamazepine, chlorpromazine, danazol, diltiazem, eptifibatide, heparin, histamine$_2$-receptor antagonists, low molecular weight heparins, methyldopa, milrinone, procainamide, quinidine, quinine, NSAIDs, thiazide diuretics, ticlopidine, tirofiban, and valproic acid

NSAID Nonsteroidal anti-inflammatory drugs

Table 8.2 Management of heparin-induced thrombocytopenia[a]

- Discontinue all heparin and low molecular weight heparin sources
  - Intravenous, subcutaneous, flushes, and heparin-coated catheters
- Monitor for evidence of thrombosis
- Avoid low molecular weight heparins (high cross-reactivity)
- Avoid warfarin monotherapy during the acute phase of heparin-induced thrombocytopenia (HIT)
  - Has been associated with paradoxical venous limb gangrene and skin necrosis. If warfarin has been initiated at the time HIT is recognized, reverse with vitamin K_1 (5–10 mg enterally or intravenously × 1 or 2 doses)
- Avoid platelet transfusions
- Aspirin and inferior venacaval filters are not considered adequate therapies
- Pharmacotherapy
  - Direct thrombin inhibitors (DTIs) for a minimum of 5–7 days or until the platelet count has risen to normal values
    - Argatroban dosing—can use actual body weight (**note**: lower doses are suggested than what is recommended in the prescribing information)

(continued)

Table 8.2 (continued)

- 0.5 mcg/kg/min continuous IV infusion if the patient is critically ill
- 1.5 mcg/kg/min continuous IV infusion if the patient is not critically ill and the BMI < 30
- 1 mcg/kg/min continuous IV infusion if the patient is not critically ill and the BMI ≥ 30
- Monitor activated partial thromboplastin time (aPTT) 2 h after the start of the continuous infusion; goal aPTT is between 50 and 85 s
- Decrease dose in patients with hepatic impairment; read the prescribing information before use

- Lepirudin 0.4 mg/kg IV bolus, followed by 0.15 mg/kg continuous IV infusion
  - Monitor aPTT 4 h after the start of the continuous infusion
  - Decrease dose in patients with renal impairment; read the prescribing information before use
  - Antibodies develop in 30 % after initial and 70 % after repeat exposure. Fatal anaphylaxis has been reported after sensitization
- Alternative agents
  - Bivalirudin: Used as an alternative to heparin during cardiopulmonary bypass in patients with a history if HIT
  - Fondaparinux
  - Danaparoid (10 % cross-reactivity)
    - Not available in the United States

- Avoid interruptions of pharmacotherapy

- Ultrasonography of the lower limbs
- **Conversion to warfarin and duration of therapy**
  - HIT with or without evidence of thrombosis
    - Convert to oral warfarin pharmacotherapy once the platelet count has returned to baseline values (**preferably > 150 × 10^9/L**). Continue for at least 30 days in patients without evidence of thrombosis (optimal duration is not known but one author recommends at least 2–3 months of warfarin. [b]Continue for at least 3–6 months in patients with evidence of thrombosis
      - Determine baseline international normalized ratio (INR) and aPTT on DTI monotherapy
      - Start with warfarin ≤ 5 mg dose
      - Identify the desired INR target (e.g., 1.5–2 point increase)
      - Avoid overshooting target INR. Small doses of vitamin K may be administered if a patient develops a supratherapeutic INR
    - Overlap with parenteral therapy for a minimum of 5 days or until the INR has been in the therapeutic range for *2* consecutive days

(continued)

Table 8.2 (continued)

- After the desired overlap and target INR has been reached, withhold the DTI and recheck the INR and aPTT in 2–4 h. Prolonged cessation may be required if the patient initially required a low-dose DTI infusion. If the INR is between 2 and 3 and the aPTT is at/near baseline, the DTI can be discontinued
  - The argatroban package insert advises overlapping with warfarin aiming for an INR ≥ 4. Once achieved, check package insert for directions
- Further anticoagulation may be required based on original indication for heparin
  - Duration as per indication

[a]Data from *Chest* 2012;141:7S–47S
[b]Data from *Blood* 2003;101(1):31–37

Table 8.3 Management of methemoglobinemia

Determine etiology
- Medications
  - Benzocaine, cetacaine, EMLA cream, lidocaine, prilocaine, and procaine
  - Chloroquine, dapsone, methylene blue (doses ≥ 4 mg/kg), nitrofurantoin, phenazopyridine, primaquine, rasburicase, and sulfonamide antimicrobials
  - Nitrates (e.g., amyl nitrate and nitroglycerin) and nitroprusside
- Chemical agents
  - Aniline dyes, antipyrine, benzene derivatives, chlorates, and chlorobenzene
  - Dinitrophenol, dinitrotoluene, trinitrotoluene, naphthalene, and nitric oxide
  - Paraquat, phenol, and silver nitrate
  - Smoke inhalation
- Foods high in nitrates or nitrites
- Well water contaminated with fertilizer (nitrates)
- Hereditary
  - NADH methemoglobin reductase deficiency
  - Hemoglobin M (histidine replaced with tyrosine in heme)

Management of acquired methemoglobinemia
- Supportive care
  - Oxygen, intubation if necessary
  - Decontamination if indicated
- Action level is patient-specific
  - ≥ 20 % methemoglobin level in symptomatic patients
  - ≥ 30 % methemoglobin level in asymptomatic patients

(continued)

Table 8.3 (continued)

- Patients with heart disease, pulmonary disease, central nervous system disease, or anemia should be treated at lower methemoglobin thresholds
- Conversion rate (with removal of offending agent) of methemoglobin back to hemoglobin is about 15 % per hour

- Withdrawal of offending agent
- Dextrose infusion
  - Needed for NADH and NADPH synthesis (Emden-Meyerhof and hexose monophosphate shunt pathways, respectively)
- Methylene blue
  - 1–2 mg/kg IV over 5 min
  - Flush with 15–30 mL of normal saline
  - Repeat dose of 1 mg/kg IV over 5 min in 30–60 min if needed
  - Cooximetry cannot be used to follow initial response, because methylene blue is detected as methemoglobin
  - Use cautiously in patients with known G6PD deficiency
    - May precipitate a Heinz body hemolytic anemia or methemoglobinemia
    - May be ineffective, as NAPDH is required to convert methylene blue to leukomethylene blue (reducing agent)
    - Lower doses (i.e., 0.3–0.5 mg/kg increments) may be utilized with careful monitoring in life-threatening situations
- Adjunctive pharmacotherapy in dapsone-induced methemoglobinemia
  - Cimetidine 300 mg IV or enterally q6h
    - Duration depends on dapsone half-life (~20–30 h but prolonged with cimetidine use) and methemoglobin levels
    - Prevents formation of hydroxylamine (oxidizing) metabolite of dapsone
  - Ascorbic acid has a questionable role
- Blood transfusions may be indicated with methemoglobin levels ≥ 50 % and evidence of tissue hypoxia

Causes of an inadequate response to methylene blue

- Persistent effects of oxidizing agent
- G6PD deficiency
- Presence of sulfhemoglobinemia
- NADH methemoglobin reductase deficiency
- Presence of hemoglobin M

Management

- Exchange transfusions?
- Hyperbaric oxygen therapy?

Ann. Emerg. Med. 1999;34:646–656

Chapter 9
Infectious Diseases

Table 9.1 Common causes of fever in intensive care unit patients

- Pneumonia
- In-dwelling catheters
- Pressure sores
- *Clostridium difficile* colitis
- Sinusitis (in patients with a nasogastric tube)
- Acalculous cholecystitis
- Pancreatitis
- Venous thromboembolism
- Drug fever (refer to Table 4.12)

Table 9.2 Prevention of hospital-acquired and ventilator-associated pneumonia

Nonpharmacological

- Avoid tracheal intubation if possible
- Avoid nasal intubation
- Removal of nasogastric and endotracheal tubes when appropriate
- Shorten duration of mechanical ventilation
- Avoid gastric overdistention (<250 mL)
- Subglottic suctioning (questionable efficacy)
- Drain ventilator circuit condensate
- Use of heat and moisture exchangers
- Avoid unnecessary ventilator circuit changes/manipulation
  - Unless visually contaminated with blood, emesis, or purulent secretions
- Semirecumbent positioning (between 30° and 45°, even during patient transport)

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_9,

Table 9.2 (continued)

- Maintain appropriate endotracheal cuff pressure
- Formal infection control program
- Appropriate hand washing and/or use of ethanol-based hand sanitizers
  - Note that the ethanol-based hand sanitizers are not sporicidal

Pharmacological

- Avoid unnecessary antimicrobials
- Short-course antimicrobials
- Avoid unnecessary stress ulcer prophylaxis that alters gastric pH
  - Sucralfate does not alter gastric pH
- Vaccinations in the appropriate patients
  - *Streptococcus pneumonia*, *Haemophilus influenzae*, and influenza virus
- Avoid unnecessary red blood cell transfusions

Data from *Crit. Care Med.* 2004;32:1396–1405

Table 9.3 Management of hospital-acquired and ventilator-associated pneumonia

- Obtain appropriate cultures and sensitivities
- Calculate clinical pulmonary infection score (refer to Table 9.4)
- Early invasive diagnosis of ventilator-associated pneumonia (VAP) utilizing either broncho-alveolar lavage or protected specimen brush techniques may improve outcome by facilitating identification of the causative pathogen or facilitating diagnosis of extrapulmonary infections
- Initiate early, aggressive, and empiric intravenous therapy
  - Target all likely organisms
    - Must know common prevalent organisms and resistance patterns in your institution and intensive care unit
  - Early-onset hospital-acquired pneumonia
    - Occurring 2–4 days after acute care hospital admission
    - Commonly associated with antibiotic-sensitive bacteria
    - *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *oxacillin-sensitive Staphylococcus aureus*
      - Unless risk factors for infection owing to potentially antibiotic-resistant bacteria
  - Late-onset hospital-acquired pneumonia
    - Occurring ≥ 5 days after acute care hospital admission
    - Usually antibiotic-resistant bacteria
    - Oxacillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Enterobacter* spp., and *Klebsiella pneumoniae*

(continued)

Table 9.3 (continued)

- Ventilator-associated pneumonia
  - Nosocomial bacterial pneumonia developing in patients on mechanical ventilation
  - *Early-onset* (within 48–72 h after mechanical intubation)
    - Antibiotic-sensitive bacteria
    - Unless risk factors for infection owing to potentially antibiotic-resistant bacteria
  - *Late-onset* (>72 h after mechanical intubation)
    - Antibiotic-resistant bacteria
    - Oxacillin-resistant *S. aureus, P. aeruginosa, Acinetobacter* sp., *Enterobacter* sp., and *K. pneumoniae*
- Antimicrobial pharmacotherapy (combination therapy)
  - Oxacillin-resistant *S. aureus* coverage
    - Vancomycin
      - Target trough levels between 15 and 20 mcg/mL (to increase pulmonary penetration)
    - Linezolid
      - In patients who have received a recent course of vancomycin and/or are critically ill (based on a high APACHE II score)
  - Broad Gram-negative coverage including *P. aeruginosa*
    - Recommend initial combination therapy to increase probability of having at least one drug that covers the likely pathogen (**author's opinion**)
    - Piperacillin-tazobactam, cefepime, or meropenem *plus either:*
      - An aminoglycoside (consider high-concentration [once-a-day] dosing in patients with a creatinine clearance above 30 mL/min) *or*
      - Levofloxacin (750 mg IV q24h and adjust for creatinine clearance)
- Stream-line antimicrobial therapy based on clinical judgment, patient response, and microbiological data
- Consider short-course therapy (8 days) based on clinical judgment and patient response
  - May not apply to pneumonias caused by *P. aeruginosa* or *Acinetobacter* spp.

Data from:
Am. J. Resp. Crit. Care Med. 2005;171:388–416
Drugs 2003;63(20):2157–2168
Chest 2002;122:2183–2196
JAMA 2003;290:2588–2598

Table 9.4 Clinical pulmonary infection score (CPIS) calculation

Temperature (°C)
- 36.5–38.4 = 0 points
- 38.5–38.9 = 1 point
- >39 or <36 = 2 points

Blood leukocyte count (mm^3)
- 4000–11,000 = 0 points
- <4000 or >11,000 = 1 point
- Bands > 50 %, add 1 additional point

Tracheal secretions
- Absent = 0 points
- Nonpurulent = 1 point
- Purulent = 2 points

Oxygenation (PaO_2/FIO_2 in mmHg)
- >240 = 0 points
- Presence of ARDS = 0 points
- ≤240 = 2 points

Pulmonary radiography
- No infiltrate = 0 points
- Diffuse or patchy infiltrate = 1 point
- Localized infiltrate = 2 points

Progression of pulmonary infiltrate
- No progression = 0 points
- Radiographic progression = 2 points
  - Exclude ARDS and pulmonary edema

Tracheal aspirate cultures (semiquantitative analysis of pathogenic bacteria)
- No growth, rare or light quantity = 0 points
- Moderate or heavy quantity = 1 point
- Same pathogenic bacteria seen on Gram-stain, add 1 additional point

Data from:
Am. J. Resp. Crit. Care Med. 2000;162:505–511
Am. Rev. Resp. Dis. 1991;143:1121–1129
Note:
– CPIS score > 6 is the threshold for suspected pneumonia
– At baseline, assess the first five variables
– At 72 h, assess all seven variables

Chapter 10
Neurology

Table 10.1 Management of convulsive status epilepticus

Identify etiology

- Cerebrovascular accident, subarachnoid hemorrhage, intracerebral hemorrhage, central nervous system tumor or infection, head trauma, autoimmune encephalopathy, and pre-eclampsia/eclampsia
- Low antiepileptic drug levels, drug overdose (e.g., cocaine, isoniazid, theophylline, phenothiazine), ethanol related, and drug withdrawal
- Cerebral hypoxia/anoxia, hypoglycemia, hyponatremia, hypernatremia, hypomagnesemia, hypocalcemia, and hypercalcemia (rare)

Management

- Airway/breathing/circulation (ABCs)
- Oxygen by nasal cannula or mask
  - Consider endotracheal intubation if respiratory assistance is needed
- Obtain appropriate laboratory tests
  - Complete blood count, serum chemistries, arterial blood gases, and antiepileptic blood levels
  - Urine and blood toxicological panel
- Manage complications
  - Hyperthermia, metabolic acidosis, arrhythmias, cerebral edema, and rhabdomyolysis
- Thiamine (unless patient is known to be euglycemic)
  - 100 mg IV administered ***before*** dextrose
- Dextrose 50 % (unless patient is known to be euglycemic)
  - 50 mL IV

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_10,

TABLE 10.1 (continued)

- Lorazepam (**preferred initial benzodiazepine**)
  - 0.1 mg/kg IV (up to 4 mg per dose)
  - Do not exceed an infusion rate of 2 mg/min
  - May repeat in 5–10 min
  - May administer IM in patients without IV access (maximum 3 mL per IM injection)
  - Patients on chronic benzodiazepine pharmacotherapy may require higher doses
- Diazepam
  - 0.15 mg/kg IV (up to 10 mg per dose)
  - May repeat in 5 min
  - Do not exceed an infusion rate of 5 mg/min
  - Duration of effect is typically less than 20 min
  - May administer IM in patients without IV access (maximum 3 mL per IM injection)
- Phenytoin
  - 15–20 mg/kg IV
  - Do not exceed a rate of 50 mg/min
    - Do not exceed a rate of 25 mg/min in elderly patients or in the presence of atherosclerotic heart disease or conduction abnormalities
    - The infusion rate can be slowed if the seizure terminates or if an arrhythmia develops
  - If seizure persists, some experts administer an additional 5 mg/kg IV before advancing to the next line of pharmacotherapy
  - Target acute level 15–18 mcg/mL
    - Measure level 2 h after the initial loading dose
  - Equation to adjusted measured phenytoin levels in the setting of hypoalbuminemia
    - Adjusted phenytoin level equal to measured phenytoin level/ $(0.2 \times \text{serum albumin}) + 0.1$
  - Equation to adjust measured phenytoin levels in the setting of creatinine clearance ≤ 10 mL/min +/−hypoalbuminemia
    - Adjusted phenytoin level = measured phenytoin level/ $(0.1 \times \text{serum albumin}) + 0.1$
  - Begin phenytoin maintenance dose 12 h after the loading dose if indicated

(continued)

Table 10.1 (continued)

- Fosphenytoin (in place of phenytoin)
  - 15–20 mg PE/kg IV
  - Administered at a rate of 100–150 mg PE/min *(can give faster than phenytoin)*
  - May administer IM in patients without IV access (maximum 3 mL per IM injection)
  - If seizure persists, some experts administer an additional 5 mg PE/kg IV before advancing to the next line of pharmacotherapy
  - Target acute phenytoin level 15–18 mcg/mL
    - Measure level 2 h after the loading dose
  - Begin ***phenytoin*** maintenance dose 12 h after the loading dose
- Levetiracetam
  - 1,000–3,000 mg IV
  - Administer at an infusion rate of 2–5 mg/kg/min
- Lacosamide
  - 200–400 mg IV
  - Administer at an infusion rate of 200 mg over 15 min
- Valproate
  - 20–40 mg/kg IV
  - Administer at an infusion rate of 3–6 mg/kg/min
  - May give an additional 20 mg/kg IV
  - Use with caution in patients with traumatic head injury
- Phenobarbital
  - 20 mg/kg IV
  - Do not exceed a rate of 50–100 mg/min
    - Use slower infusion rates in elderly patients
    - The infusion rate can be slowed if the seizure terminates
  - Target level 15–40 mcg/mL
  - Give until seizure stops or until full dose administered
  - May repeat 10–20 mg/kg IV if needed in 20 min
  - May cause hypotension and respiratory depression
    - Some experts would mechanically intubate the patient if a loading dose of phenobarbital is required

Refractory status epilepticus (patient must have a protected airway)

- Search for an acute or progressive etiology
- Midazolam
  - 0.2 mg/kg IV, followed by 0.05–2 mg/kg/h continuous IV infusion
  - CYP450 enzyme induction from phenytoin, fosphenytoin, or barbiturates may decrease effect
  - Titrate to maintain burst suppression on electroencephalogram (EEG) or seizure cessation

(continued)

Table 10.1 (continued)

- Propofol
  - 1–2 mg/kg IV, followed by 20–50 mcg/kg/min continuous IV infusion
    - Reduce dose gradually 12 h after seizure cessation
  - CYP450 enzyme induction from phenytoin, fosphenytoin, or barbiturates may decrease effect
  - Titrate to maintain burst suppression on electroencephalogram (EEG) or seizure cessation
- Pentobarbital
  - 5 mg/kg IV over 1 h, followed by 0.5–5 mg/kg/h continuous IV infusion
  - Administration rate should not exceed 50 mg/min
  - May give an additional 5–10 mg/kg IV over 1 h
  - Target level 20–40 mcg/mL
  - If breakthrough seizure, 5 mg/kg IV bolus, then increase the rate by 0.5–1 mg/kg/h
  - Titrate to maintain burst suppression on electroencephalogram (EEG) or seizure cessation
- Ketamine or inhaled anesthetic agents in refractory cases
- Administer vitamin B_6 (pyridoxine) in the setting of isoniazid toxicity
  - 1 g pyridoxine IV for each gram of isoniazid to a maximum of 5 g or 70 mg/kg
    - Repeat if necessary
  - Alternative IV dosing regimen: 0.5 g/min until seizure stops or maximum dose is reached. When seizure stops, administer the remaining dose over 4–6 h

Data from:
Neurocrit Care. 2012;17:3–23
J. Neurol. 2003;250:401–406
JAMA 1993;270:854–859

Table 10.2 Medications that may exacerbate weakness in myasthenia gravis

- Aminoglycosides, bacitracin, clindamycin, erythromycin, polymixins
- Drugs with anticholinergic properties
  - Diphenhydramine, phenothiazines, trihexyphenidyl and tricyclic antidepressants
- Disopyramide, quinidine, quinine, phenytoin, procainamide
- β-adrenergic blockers, calcium channel blockers
- Colchicine, cisplatinum, lithium, penicillamine
- Magnesium-containing products (avoid hypermagnesemia)
- Neuromuscular blockers

Chapter 11
Nutrition

Table 11.1 Nutrition assessment

Body weight calculations

- Assess body mass index (weight in kg/height in m^2)
  - Underweight: < 18.5
  - Normal weight: 18.5–24.9
  - Overweight: 25–29.9
  - Obese: 30–39.5
  - Extremely obese: ≥ 40
- Assess actual body weight (ABW)
  - Normal: 90–120 % ideal body weight (IBW)
  - Mild malnutrition: 80–89 % IBW
  - Moderate malnutrition: 70–79 % IBW
  - Severe malnutrition: ≤ 69 % IBW
  - Overweight: > 120 % IBW
  - Obese: ≥ 150 % IBW
  - Extremely obese: ≥ 200 % IBW
- IBW
  - Male = 50 kg + (2.3 × number of inches over 5 ft)
  - Female = 45.5 kg + (2.3 × number of inches over 5 ft)
  - **Use this weight for nutritional calculations in obese or extremely obese patients**
- If ABW is less than IBW, use ABW

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_11,

Table 11.1 (continued)

Assessing daily caloric and protein needs

- Predictive equations such as the Harris–Benedict equation may be utilized to estimate caloric needs (**note**: predictive equations should be used with caution, as they may provide a less accurate measure of energy requirements than indirect calorimetry; these equations may be even less predictive in the obese or extremely obese patients)
  - Males
    - (66 + 13.7 [wt in kg] + 5 [height in cm] − 6.8 [age]) × AF × IF
  - Females
    - (655 + 9.6 [wt in kg] + 1.8 [height in cm] − 4.7 [age]) × AF × IF
  - Activity factors (AF)
    - Out of bed: 1.3
    - Fever: 1.13
  - Injury factors (IF)
    - Infection: 1.2–1.8
    - Surgery: 1.2–1.8
    - Pancreatitis: 1–1.8
    - Burns or head trauma: up to 2
- Protein needs assessment
  - Usual: 0.8 g/kg/day
  - Renal failure: < 0.6 g/kg/day
  - Hemodialysis patients: 0.8–1.2 g/kg/day
  - Continuous renal replacement therapy: 1.2–1.5 g/kg/day
  - Liver failure: 0.5–1 g/kg/day
  - Critically ill patients: 1.2–2 g/kg/day
  - Burn patients: 2–3 g/kg/day
- **Simple alternative to the Harris-Benedict or predictive equations**
  - Maintenance or mild stress
    - Total calories: 20–25 kcal/kg
    - Nonprotein calories: 15–20 kcal/kg
    - Daily protein needs: 0.5–1 g/kg
  - Mild-to-moderate stress (minor infection, disease exacerbation)
    - Total calories: 25–30 kcal/kg
    - Nonprotein calories: 20–25 kcal/kg
    - Daily protein needs: 1–1.5 g/kg
  - Moderate-to-severe stress (sepsis, major surgery, burns)
    - Total calories: 30–35 kcal/kg
    - Nonprotein calories: 25–30 kcal/kg
    - Daily protein needs: 1.5–2 g/kg (>2 g/kg for burn patients ≥ 30 % body surface area)
- **Feeding approach in the critically ill obese patient**
- Permissive underfeeding is recommended

(continued)

Table 1.11 (continued)

- If BMI > 30, the target energy requirement is either 22–25 kcal/kg/day based on ideal body weight or 11–14 kcal/kg/day based on actual body weight
- If BMI between 30 and 40, provide protein ≥ 2 g/kg based on ideal body weight; if BMI > 40 provide protein ≥ 2.5 g/kg based on ideal body weight
- Nonprotein calorie to nitrogen ratio (NPC/N)
  - Nitrogen = grams of protein/6.25
  - Maintenance NPC/N ratio: 150:1
  - Stress NPC/N ratio: 90–120:1

Macronutrients

- Carbohydrates
  - Provides 3.4 kcal/g parenterally and 4 kcal/g enterally
  - Should not exceed 5 mg/kg/min parenterally; can result in:
    - Increased carbon dioxide production
    - Hyperglycemia
    - Lipogenesis
    - Cholestasis (increased total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transferase)
- Lipids
  - Provides 10 kcal/g
  - Do not exceed 1 g/kg/day or 60 % of total calories
  - Do not administer in patients with egg allergies
  - Adverse effects include
    - Dyspnea, chest pain, palpitations, chills
    - Headaches, nausea, fever
    - Cholestasis (increased total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transferase)
- Protein
  - Provides 4 kcal/g
  - In critically ill patients, may give protein calories in excess of energy requirements in order for this macronutrient to be utilized for tissue repair and synthesis (**author's opinion**)
    - i.e., give total calories as nonprotein calories

Data from *JPEN*. 2009;33:277–316

Table 11.2 Principles of parenteral nutrition

Indications

- Inability to absorb nutrients from the gastrointestinal tract
  - Small bowel resection, severe diarrhea, intractable vomiting, bowel obstruction, fistulas
  - Critically ill patients with nonfunctioning GI tract
    - Sepsis, trauma, cancer, severe pancreatitis
- Hyperemesis gravidarum
- Severe malnutrition

Routes

- Peripheral vein
  - May use in patients without large nutritional requirements and not fluid restricted
  - Should not exceed 900 mOsm/L solutions
    - Amino acids provide 10 mOsm/g
    - Dextrose provides 5 mOsm/g
    - Lipids provides 0.71 mOsm/g (product specific)
  - Complications may include thrombophlebitis
- Central vein
  - May use in patients who require parenteral nutrition for > 7 days
  - Must be administered through a central vein
    - Subclavian or internal jugular vein
  - Must verify catheter placement

Initiating

- Determine caloric needs (refer to Table 11.1)
  - 50 % estimated caloric needs the first day
  - 75–100 % estimated caloric needs by the second to third day
- Determine protein needs
- Determine route
- Titrate macronutrients based on:
  - Substrate tolerance
  - Patient's body weight
  - Biochemical markers (e.g., prealbumin), although the value of this practice is not validated
  - 24-h urine urea nitrogen collection in critically ill patients

Discontinuing

- When discontinuing parenteral nutrition, it is important to taper over several days to prevent hypoglycemia
- If parenteral nutrition is stopped abruptly, replace with a dextrose 10 % in water solution and infuse at the same parenteral nutrition rate

Table 11.3 Select drug–nutrient interactions

- Phenytoin
  - Caseinate salts found in enteral nutrition formulas may reduce bioavailability (mechanism not well delineated)
  - Protocol
    - Hold feeds 1–2 h before and after administration
    - Flush enteral feeding tube with 20 mL water or saline
    - Administer dose
    - Adjust enteral feeding rate to maintain the same 24-h volume
- Warfarin
  - Vitamin K content of enteral nutrition formulas may affect pharmacological activity. Monitor and titrate dose to maintain therapeutic international normalized ratio (INR)
- Medications with a decreased bioavailability if administered concomitantly with enteral nutrition formulas
  - Azithromycin, fluoroquinolones, ketoconazole, isoniazid, penicillin, rifampin, tetracycline
  - Didanosine, indinavir, stavudine, zidovudine
  - Aledronate, risedronate, levodopa

Table 11.4 Strategies to minimize aspiration of gastric contents during enteral nutrition

- Start desired enteral nutrition product at 20 mL/h
  - Increase every 6 h by 20 mL/h increments until goal rate is achieved
- Check gastric residuals every 8–12 h
  - Keep ≤ 250–500 mL
- Use continuous infusion instead of intermittent bolus feeding
- Elevate head of bed by a 30–45° angle
- Consider continuous subglottic suctioning in mechanically ventilated patients
- Optimizing oral health
- The use of blue food coloring and methylene blue should be avoided, as it has low sensitivity and has been associated with adverse patient outcomes

If high gastric residuals

- Prokinetic agents
  - Metoclopramide
    - 5–10 mg IV every 6–8 h (adjust for renal impairment)
  - Erythromycin
    - 250 mg IV or enterally every 6–8 h for ≤ 5 days
- Minimize use of narcotic analgesics wherever possible
  - Enteral naloxone (parenteral product)
    - 1–2 mg **enterally** every 6 h may decrease the gastrointestinal effects of opioid analgesics without reversing the systemic analgesic effects; monitor for opioid withdrawal
- Transpyloric or small bowel feeding
  - Positioning the tip of the feeding tube past the ligament of Treitz may be more effective than postpyloric placement in high-risk patients

JPEN. 2009;33:277–316. *Chest* 2004;125:793–795

Chapter 12
Psychiatric Disorders

Table 12.1 Management of alcohol withdrawal

Refer to the clinical institute withdrawal assessment for alcohol scale (CIWA-Ar)

- A validated 10-item assessment tool used to monitor the severity of withdrawal and monitor pharmacotherapy
  - A score of ≤8 corresponds to mild withdrawal
  - A score between 9 and 15 corresponds to moderate withdrawal
  - A score of more than 15 corresponds to severe withdrawal and at increased risk of seizures and delirium tremens

Supportive care

- Intravenous fluids
- Correct any electrolyte abnormalities
- Thiamine 100 mg intravenously/enterally daily
  - Administer before glucose administration to prevent precipitation of Wernicke's encephalopathy
- Multivitamin daily (source of folate)
- Avoid phenothiazines and haloperidol, as both may lower the seizure threshold

Benzodiazepine pharmacotherapy

- Fixed dose regimens
  - Administered at specific intervals with additional doses given as needed
  - Chlordiazepoxide 50–100 mg enterally every 6 h for 1 day, 25–50 mg every 6 h for 2 days then continue to taper for a total of 7 days
  - In patients with significant liver dysfunction, lorazepam or oxazepam may be preferred
  - This regimen is useful in patients at high risk of major withdrawal or history of withdrawal seizures or delirium tremens

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_12,

Table 12.1 (continued)

- Loading dose strategy
  - Diazepam 10–20 mg intravenously/enterally initially to provide sedation
  - Titrate additional doses every 5–15 min until goal achieved
    - Can double the dose until the appropriate level of sedation is achieved
    - Maximum dose is not clear; some experts have utilized diazepam doses above 200 mg
  - Then allow the drug level to taper through metabolism
- Symptom-triggered regimens
  - Administered only when the CIWA-Ar score is ≥ 9. May administer with a lower threshold (i.e., CIWA-Ar score < 9) if there is a history of withdrawal seizures
    - Administer diazepam 5–10 mg IV/enterally initially. Measure the CIWA-Ar score 1 h after the initial and each subsequent dose of diazepam. Adjust dose based on severity of symptoms
    - Alternative may be chlordiazepoxide 25–50 mg intravenously/enterally every hour as needed
  - This approach may result in less total medication and more rapid detoxification

Other pharmacotherapy for alcohol withdrawal symptoms

- Phenobarbital
- Ethanol (enteral)

Adjuvant pharmacotherapy

- Sympatholytics
  - β-adrenergic blockers, dexmedetomidine, or clonidine may be utilized in conjunction with benzodiazepines in patients with coronary artery disease who may not tolerate adrenergic excess
- Benzodiazepine-refractory delirium tremens
  - Consider propofol pharmacotherapy, as it agonizes GABA-A receptors and antagonizes NMDA receptors. Patient must have a protected airway
  - Phenobarbital can be used as an alternative

Anticonvulsant pharmacotherapy for status epilepticus (uncommon—consider alternative etiology)

- Low threshold for airway protection and mechanical ventilation
- Benzodiazepines
- Phenytoin
- Propofol

CIWA-Ar Clinical Institute Withdrawal Assessment for Alcohol-Revised, *GABA* γ-Aminobutyric acid, *IV* Intravenous, *NMDA* *N*-methyl D-aspartate

Data from

Br. J. Addict. 1989;84:1353–1357

Am. Fam. Physician 2004;69:1443–1450

NEJM 2003;348:1786–1795

Crit. Care Med. 2000;28:1781–1784

Table 12.2 Management of serotonin syndrome

Precipitating medications (usually when utilized in combination or inadequate washout period)

- Serotonin reuptake inhibitors
  - Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
  - Clomipramine, imipramine, nefazodone, trazodone, venlafaxine
  - Dextromethorphan, meperidine, pentazocine
  - Amphetamine, cocaine, fenfluoramine, dexfenfluoramine, methylphenidate, sibutramine, St. John's wort
  - Dolasetron, granisetron, ondansetron, palonosetron
- Enhance serotonin release
  - Methylenedioxymethamphetamine (MDMA or ecstasy), mirtazapine
- Serotonin receptor agonists
  - Buspirone, ergot alkaloids, lithium, lysergic acid diethylamide (LSD)
- Serotonin precursor
  - L-tryptophan
- Impair serotonin breakdown
  - Monamine oxidase inhibitors
    - Linezolid
    - Clorgiline, isocarboxizid, moclobemide, phenelzine, selegiline, tranylcypromine

Signs and symptoms

- Typically start within minutes to hours after ingestion
- Usually resolve within 12–24 h with cessation of precipitating agent or supportive therapy but can be prolonged with long half-life drugs
- Assess for the presence of the following clinical features
  - Agitation, altered mental status, delirium, diaphoresis, diarrhea, and hyperactive bowel sounds
  - Hyperreflexia (L > U extremities), hyperthermia, and incoordination
    - Poorly treated hyperthermia may lead to metabolic acidosis, rhabdomyolysis, elevated aminotransferases, seizures, renal failure, and disseminated intravascular coagulation (DIC)
  - Myoclonus (inducible or spontaneous), muscular hypertonicity, shivering, tremor, akathesia, tachycardia, mydriasis, and ocular clonus
  - Severe symptomatology may mask other clinical features

Management depends on the severity of illness

- Discontinue offending agent(s)
- Supportive care
  - Fluids to replace hyperthermia-induced and gastrointestinal losses
  - Hemodynamic support if necessary

(continued)

Table 12.2 (continued)

- Rapid external cooling for hyperthermic patients
  - Fans, cooling blankets, and tepid water baths
  - Temperature management systems (i.e., Arctic Sun) may be utilized if available
  - No role for antipyretic pharmacotherapy
- Intravenous benzodiazepine to decrease muscle rigidity and agitation
- Cyproheptadine
  - *Mild-to-moderate cases:* 4 mg enterally q8h
  - *Severe cases:* 12 mg enterally in one dose, then 2 mg every 2 h as symptoms continue. Once signs and symptoms are controlled, convert to 8 mg enterally q8h
  - Duration patient and precipitating-agent specific
- Avoid
  - Physical restraints (may be associated with isometric muscle contractions and worsening of hyperthermia)
  - Propranolol (may worsen autonomic instability)

Data from
NEJM 2005;352:1112–1120
Am. J. Resp. Crit. Care Med. 2002;166:9–15
Ann. Emerg. Med. 1996;28:520–526
Am. J. Psychiatry 1991;148:705–713

Table 12.3 Management of neuroleptic malignant syndrome

Precipitating medications
- Typical and atypical antipsychotic medications (D_2-receptor antagonists)
  - Clozapine, haloperidol, olanzapine, phenothiazines, quetiapine, risperidone, thioxanthenes
  - Parenteral agents may have a higher incidence
- Droperidol, metoclopramide, prochlorperazine, promethazine, venlafaxine
- Abrupt withdrawal of dopamine agonists
  - Amantadine, bromocriptine, levodopa

Signs and symptoms
- Altered consciousness
- Autonomic instability (e.g., labile blood pressure, tachycardia, diaphoresis, and incontinence)
- Hyperthermia
- Rigidity (lead-pipe)
- May occur within the first few weeks of pharmacotherapy or with rapid increases in dosage regimens
- Once neuroleptic malignant syndrome (NMS) develops, signs and symptoms may escalate over 24–72 h and may have a prolonged clinical course

(continued)

TABLE 12.3 (continued)

Management

- Discontinue offending agent
- Rapid external cooling
  - Fans, cooling blankets, and tepid water baths
  - Temperature management systems (i.e., Arctic Sun) may be utilized if available
  - Antipyretic pharmacotherapy is not effective
- Fluids
  - To replace hyperthermia-induced losses
- Intravenous benzodiazepine to decrease muscle rigidity
- Bromocriptine 2.5–5 mg enterally q8h (can be increased to 30–45 mg/day)
- Dantrolene IV (role and benefit not well defined in the management of NMS)
  - 2.5 mg/kg IV every 5–10 min as necessary up to a maximum of 10 mg/kg
  - Then, 1–2 mg/kg enterally q6h for 72 h
- Other interventions
  - Restart medication (e.g., levodopa) if episode is believed to be a result of drug withdrawal
  - Anticholinergic agents should not be abruptly withdrawn but use may be a confounding variable in the setting of hyperthermia
  - Electroconvulsive therapy may be useful in drug-refractory cases
  - Non-depolarizing neuromuscular blockers may be useful in severe, refractory cases
  - If antipsychotic pharmacotherapy is still warranted
    - Wait until 1–2 weeks after symptoms have resolved
    - Initiate therapy with an agent from a different class
    - Select a low-potency or atypical agent and adjust therapy using the lowest possible dose

Data from
Psychiatric Quarterly. 2001;72:325–336

Chapter 13
Pulmonary

Table 13.1 Management of chronic obstructive pulmonary disease

Management of stable disease

- **Note**: read the goldcopd guidelines for a detailed explanation of airflow limitation risk, characteristics, and spirometric classifications (Gold 1–4)
- Gold 1—mild disease
  - $FEV_1/FVC < 70$ %
  - $FEV_1 \geq 80$ % predicted
  - **Patient A Group**: add a short-acting anticholinergic **or** a short-acting $beta_2$ agonist prn (e.g., ipratropium or albuterol); alternative can include a long-acting anticholinergic (e.g., tiotropium or aclidinium) **or** a long-acting $beta_2$-agonist (e.g., salmeterol or formoterol) **or** a combination of both a short-acting anticholinergic and a short-acting $beta_2$ agonist; theophylline may be an option
  - Smoking cessation programs, physical activity, flu, and pneumococcal vaccination
- Gold 2—moderate disease
  - $FEV_1/FVC < 70$ %
  - $FEV_1 < 80$ % and ≥ 50 % predicted
  - **Patient B Group**: add a long-acting anticholinergic **or** a long-acting $beta_2$ agonist; alternative can include both a long-acting anticholinergic and a long-acting $beta_2$ agonist; other possible options can include a short-acting anticholinergic and a short-acting $beta_2$ agonist or theophylline
  - Smoking cessation programs, pulmonary rehabilitation, physical activity, flu, and pneumococcal vaccination

(continued)

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Table 13.1 (continued)

- Gold 3—severe disease
  - $FEV_1/FVC < 70$ %
  - $FEV_1 < 50$ % and ≥30 % predicted
  - **Patient C Group**: add an inhaled corticosteroid (e.g., beclomethasone, budesonide, fluticasone) **and** a long-acting $beta_2$ agonist **or** a long-acting anticholinergic; alternatives can include a long-acting $beta_2$ agonist **and** a long-acting anticholinergic **or** a long-acting anticholinergic **and** a phosphodiesterase-4 inhibitor (e.g., roflumilast) **or** a long-acting $beta_2$ agonist **and** a phosphodiesterase-4 inhibitor; other possible options can include a short-acting anticholinergic **and/or** a short-acting $beta_2$ agonist **or** theophylline
  - Smoking cessation programs, pulmonary rehabilitation, physical activity, flu, and pneumococcal vaccination
- Gold 4—very severe disease
  - $FEV_1/FVC < 70$ %
  - $FEV_1 < 30$ % predicted or presence of chronic respiratory failure or right heart failure
  - **Patient D Group**: add an inhaled corticosteroid **and** a long-acting $beta_2$ agonist **and/or** a long-acting anticholinergic; alternatives can include inhaled corticosteroids **and** a long-acting $beta_2$ agonist **or** a long-acting anticholinergic **and/or** a phosphodiesterase-4 inhibitor; other possible options can include a short-acting anticholinergic **and/or** a short-acting $beta_2$ agonist **or** theophylline
  - Smoking cessation programs, pulmonary rehabilitation, physical activity, flu, and pneumococcal vaccination
  - Add long-term oxygen therapy if chronic respiratory failure

Management of acute exacerbations

- Oxygen therapy
- Nebulized short-acting bronchodilator therapy (e.g., albuterol and ipratropium)
- Consider intravenous aminophylline if needed
- Systemic corticosteroid therapy
  - Prednisone 40 mg enterally daily or equivalent for 5 days
- Antimicrobials therapy if increased dyspnea, sputum volume or sputum purulence or if acute respiratory failure requiring mechanical ventilation
  - Cover *Streptococcus pneumoniae, Hemophilus influenza, Moraxella catarrhalis*; evaluate for multi-drug resistance pathogen risk factors (including MRSA)
  - Evaluate antimicrobial use in the past 3 months to determine possible pathogen and the optimal empiric antimicrobial regimen

Data from www.goldcopd.org

Table 13.2 Management of acute asthma exacerbations

Initial assessment

- Impending or actual respiratory arrest
  - Intubation and mechanical ventilation with 100 % oxygen to achieve oxygen saturation ≥ 90 % (>95 % in pregnancy)
  - Albuterol 2.5–5 mg nebulized every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously (need an Aeroneb Solo mesh nebulizer device for administration)
  - Ipratropium 500 mcg nebulized every 20 min for 3 doses, then as needed for up to 3 h; can continue if the patient is admitted into an ICU
  - Methylprednisolone 60–125 mg IV every 6–8 h
  - Magnesium 2 g IV over 20 min × 1 dose
- FEV_1 or PEF < 40 % (severe exacerbation)
  - Oxygen to achieve oxygen saturation ≥ 90 % (>95 % in pregnancy)
  - Albuterol 2.5–5 mg nebulized every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously (need an Aeroneb Solo mesh nebulizer device for administration)
  - Ipratropium 500 mcg nebulized every 20 min for 3 doses, then as needed for up to 3 h; can continue if the patient is admitted into an ICU
  - Prednisone 40–60 mg enterally in a single or divided dose(s) every 12–24 h
  - Magnesium 2 g IV over 20 min × 1 dose may be considered
- FEV_1 or PEF ≥ 40 %
  - Oxygen to achieve oxygen saturation ≥ 90 % (>95 % in pregnancy)
  - Albuterol 2.5–5 mg nebulized every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed. A metered dose inhaler with a spacer or chamber device may also be utilized (4–8 puffs every 20 min for 3 doses then every 1–4 h as needed)
  - Ipratropium 500 mcg nebulized every 20 min for 3 doses. A metered dose inhaler with a spacer or chamber device may also be utilized (8 puffs every 20 min for up to 3 doses)
  - Prednisone 40–60 mg enterally in a single or divided dose(s) every 12–24 h if no immediate response to bronchodilators

Repeat assessment

- For patients who cannot use or do not benefit from inhaled bronchodilators (i.e., severe airflow obstruction)
  - Epinephrine (1:1000): 0.3–0.5 mg (0.3–0.5 ml of the 1:1000 solution) IM every 20 min for up to 3 doses
  - Terbutaline 0.25 mg SQ/IM every 20 min for up to 3 doses (in place of epinephrine; **do not** use both agents)

(continued)

TABLE 13.2 (continued)

Notes

- Make frequent (every 1–2 h) objective assessments of the response to pharmacotherapy
- The dose-response curve for $beta_2$ agonists is shifted to the right with increased levels of bronchoconstriction. This explains the need for higher and more frequent doses during an acute asthma exacerbation.
- The dose of bronchodilator can be gradually reduced based on both symptomatic and objective improvement until the patient returns to pre-exacerbation use of short-acting $beta_2$ agonist pharmacotherapy
- Discontinue long-acting $beta_2$ agonist therapy during the acute phase of treatment
- Levalbuterol may be utilized if the patient experiences tachycardia or tremors with albuterol
- Comparison of an MDI and a spacer with nebulizer delivery has demonstrated comparable improvement in asthma symptoms
- Consider discontinuation of ipratropium pharmacotherapy after the acute phase of treatment, as it is unlikely that it will provide any additional benefit
- The optimal dose of systemic corticosteroids is not known; the effect of intravenous versus enteral administration is identical
- The use of methylxanthines have not been shown to be effective in the management of acute asthma exacerbations
- Antimicrobials should be reserved for patients with evidence of an acute bacterial respiratory tract infection
- Avoid drugs that cause histamine release (e.g., morphine sulfate, codeine, atracurium, metocurine, mivacurium, tubocurarine)
- If sedation is required, consider either propofol (preferred) or ketamine, as both drugs are weak bronchodilators
- The routine use of heliox (helium-oxygen) cannot be recommended

Data from www.ginasthma.org

Table 13.3 Drug-induced pulmonary diseases

Cough
• Angiotensin converting enzyme inhibitors
Eosinophilic pulmonary infiltration
• Nitrofurantoin, penicillin, sulfonamide antimicrobials
• Aspirin, NSAIDs
• Amiodarone, bleomycin, captopril, chlorpromazine, chlorpropamide, imipramine, methotrexate, phenytoin
Noncardiogenic (permeability) pulmonary edema
• Heroin, methadone, morphine, propoxyphene
• Naloxone, nalmefene, salicylates
• Bleomycin, cyclophosphamide, mitomycin, vinblastine, interleukin-2
Pneumonitis
• Amiodarone, docetaxel, gold compounds, nitrofurantoin, paclitaxel
Pulmonary fibrosis
• Bleomycin, busulfan, carmustine, cyclophosphamide, methotrexate, mitomycin, radiation therapy
• Amiodarone, methysergide, nitrofurantoin

Chapter 14
Renal

Table 14.1 Contrast-induced nephropathy prevention strategy[a]

Risk factors

- Creatinine clearance < 60 mL/min/1.73 m^2 (stages III–V chronic kidney disease), diabetes mellitus (with renal insufficiency), hypertension, chronic heart failure, cirrhosis, nephrosis, age > 75 years, cholesterol emboli syndrome, multiple myeloma (questionable)
- Hypovolemia, intraprocedural volume depletion, use of large volumes of contrast, intra-aortic balloon pump
- Urine albumin/creatinine ratio > 30, proteinuria
- Concurrent nephrotoxin use (e.g., aminoglycosides, polymixins, amphotericin B, foscarnet, cyclosporine, tacrolimus, NSAIDs)
- Other medications (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics)
- Intra-arterial contrast administration may have a higher prevalence than the intravenous route

Prevention strategies

The first preventative strategy is to address any reversible risk factor(s)[b]

- **Saline hydration**
- Ensure euvolemia and good urine output
- Use if there are no contraindications to volume expansion
- Hold diuretics the day before and of the procedure
- Isotonic saline preferred over 0.45 % saline
  - Start 2 h (up to 12 h in high-risk patients) before procedure
    - 1 mL/kg/h
  - Continue for at least 6 h after the procedure
  - Target urine output around 150 mL/h

(continued)

J. Papadopoulos, *Pocket Guide to Critical Care Pharmacotherapy*, DOI 10.1007/978-1-4939-1853-9_14,

TABLE 14.1 (continued)

- **Sodium bicarbonate** found to be more effective than isotonic saline hydration[c]; some clinicians have questioned this trial's methodology
  - Sodium bicarbonate 3 amps in 1 L D5W
  - 3 mL/kg/h for 1 h before contrast
  - 1 mL/kg/h for 6 h after the procedure

Choice of contrast agent

- Use nonionic and either low or iso-osmolar products
  - E.g., iodixanol
- Use the least amount of volume to complete the procedure
  - A total volume that is >5 mL/kg divided by the patient's serum creatinine in mg/dL is associated with increased risk of nephropathy
- Avoid studies that are closely spaced. Optimal time not well delineated; prudent to wait a few days between studies when possible

Pharmacotherapy

- N-acetylcysteine (NAC)
  - 600 mg enterally every 12 h (24 h before and 24 h after the procedure)
    - For emergent procedures, 1 g of NAC administered 1 h before and 4 h after the procedure may have some value[d]
  - Intravenous
    - 150 mg/kg in 500 mL DSW over 30 min before the procedure, followed by 50 mg/kg in 500 mL DSW over 4 h following the procedure[e]

Limited if any value based on the available literature

- Forced diuresis with either a loop diuretic or mannitol
- Renal dose dopamine
- Aminophylline/theophylline (adenosine receptor antagonists)
- Calcium-channel blockers
- Fenoldopam
- Hemodialysis or hemofiltration

[a]Data from *NEJM.* 2006;354:379–386; *Crit Care Clin.* 2005;21:261–280
[b]A risk prediction table can be found in *NEJM.* 2006;354:379–386
[c]Data from *JAMA.* 2004;291:2328–2334
[d]Data from *J Interv Cardiol.* 2004;17(3):159–165
[e]Data from *J Am Coll Cardiol.* 2003;41(12):2114–2118

Table 14.2 Pharmacological management of acute kidney injury

Fluid control (must assess patient's volume status)
In "stable" patients with oliguric acute kidney injury (AKI): medical therapy (for pH, K^+, fluid control = HD = CVVH)
- Hypovolemic
  - Administer crystalloid fluid resuscitation
- Volume overloaded
  - Concentrate intravenous medications
  - Evaluate maintenance fluids
  - Concentrate parenteral nutrition
  - Use concentrated enteral nutrition products

Avoid and/or discontinue nephrotoxins wherever possible
Diuretic pharmacotherapy (strict avoidance of intravascular volume depletion)
- Loop diuretics (**dose depends on severity of renal insufficiency**)
  - Furosemide intermittent IV
    - Infusion rate ≤ 4 mg/min for doses > 40 mg
    - 40–200 mg intravenous administration
      - If net hourly diuresis is ≥ 1 mL/kg/h and pharmacotherapeutic end point is achieved, then no further diuretic
      - If net hourly diuresis is ≥ 1 mL/kg/h and pharmacotherapeutic end point is not achieved, then continue same dose every 6 h
      - If net hourly diuresis is < 1 mL/kg/h, double the previous dose of diuretic and administer within 2 h; **maximum single dose is 200 mg**
        - Consider combining with a distal tubule acting diuretic (i.e., chlorothiazide IV or metolazone PO) to overcome the "ceiling" effect
  - Furosemide continuous IV infusion
    - 40–200 mg intravenous bolus X 1
    - Initiate at 0.1 mg/kg/h continuous IV infusion (can be adjusted based on GFR)
      - Increase hourly by 0.1 mg/kg/h increments until net hourly diuresis is ≥ 1 mL/kg/h
      - Maximum infusion rate is 0.4–0.5 mg/kg/h or **40 mg/h**
      - Continue until pharmacotherapeutic end point is achieved
        - Consider combining with distal tubule acting diuretic (i.e., chlorothiazide IV or metolazone PO) to overcome the "ceiling" effect if large doses of furosemide are required
- Thiazide diuretics
  - Potentiates the effects of a loop diuretic
  - Chlorothiazide
    - 500–1,000 mg IV every 12 h (works even in the setting if reduced GFR [**author's and editor's opinion**])

(continued)

Table 14.2 (continued)

- In "sulfa" allergic patients:
  - Identify the implicated agent and the severity of the reaction
  - Ethacrynic acid may be a safe alternative to furosemide
    - 40 mg furosemide = 50 mg ethacrynic acid
  - Refer to the following review article on sulfonamide allergies[a]

Management of diuretic-resistant edema

- Evaluate excessive sodium intake
  - Dietary, intravenous fluids, medications (e.g., ticarcillin, metronidazole)
- Switch to parenteral diuretic pharmacotherapy
- Increase dose of loop diuretic
- Consider continuous infusion of a loop diuretic
- Consider combining the loop diuretic with a thiazide diuretic
- Discontinue medications that may decrease renal blood flow
  - E.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers, NSAIDs
- Combine loop diuretic with albumin 25 % (data supporting efficacy is limited)
  - Albumin 12.5–25 g IV every 8–12 h
  - May be warranted in patients with hypoalbuminemia (<2.5 g/dL)

[a] *Ann. Pharmacother.* 2005;39:290–301

Table 14.3 Management of acute uremic bleeding

- Acute hemodialysis not effective
- Packed red blood cell transfusion (PRBCs)
  - Goal hematocrit ≥ 28–30 % (patient specific)
  - Higher hematocrit may improve platelet-vessel wall interaction
- Cryoprecipitate (in life-threatening hemorrhage)
  - 10 units every 12–24 h
  - To replenish von Willebrand factor (vWF)
- Desmopressin
  - 0.3 mcg/kg IV over 15–30 min
  - May repeat every 12 h for 2–3 total doses
    - Will increase endothelial release of vWF
    - Tachyphylaxis develops with repeat doses; activity may return after a 3-day drug-free period
- Conjugated estrogen in severe cases
  - 0.6 mg/kg IV daily for 5 days

Table 14.4 Drug-induced renal diseases

Functional acute kidney injury (abnormal intrarenal hemodynamics that can be potentiated by hypovolemia or effective arterial volume depletion)
- Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, NSAIDs

Glomerular disease
- Gold, hydralazine, NSAIDs
- Chlorpropamide, penicillamine, phenytoin, quinidine

Interstitial nephritis
- Acute allergic
  - β-lactam antimicrobials, erythromycin, nitrofurantoin, rifampin, sulfonamide antimicrobials, vancomycin
  - Diuretics (all classes), NSAIDs
- Chronic
  - Cyclosporine, ifosfamide, lithium

Obstructive nephropathy
- Intratubular crystallization
  - Acyclovir, foscarnet, indinavir, sulfonamide antimicrobials
  - Acetazolamide, ascorbic acid, methotrexate, triamterene
- Outflow obstruction
  - Anticholinergic agents, disopyramide
- Nephrolithiasis
  - Allopurinol, indinavir, sulfadiazine, topiramate, triamterene, zonisamide
- Rhabdomyolysis
  - Azathioprine, colchicine, doxylamine, niacin (in combination with a statin), statins

Papillary necrosis
- Acetaminophen

Pseudorenal failure (increase in blood urea nitrogen or serum creatinine without a change in glomerular filtration rate)
- Increase protein catabolism
  - Corticosteroids, tetracyclines
- Impairs proximal tubular secretion of creatinine
  - Cimetidine, pyrimethamine, trimethoprim
- Interactions with laboratory assay (Jaffe method)
  - Ascorbic acid
  - Cephalosporins (e.g., cefaclor, cefazolin, cefoxitin, cephalexin, cephalothin)

Tubular damage
- Acute tubular necrosis
  - Aminoglycosides, amphotericin B, carboplatin, cisplatin, foscarnet, intravenous contrast dyes, drugs associated with rhabdomyolysis
- Osmotic damage
  - Dextrans, hetastarch, mannitol, intravenous immunoglobulins that contain sucrose

Table 14.5 Management of acute hypocalcemia (serum calcium < 8.5 mg/dL)

- Animal models of critical illness suggest ionized hypocalcemia is universal and treatment to achieve normal levels associated with increased mortality (author suggests treating symptomatic patients only)
- Correct serum calcium in the presence of hypoalbuminemia
  - Corrected serum calcium (mg/dL) = measured serum calcium (mg/dL) + 0.8 (4 g/dL–measured serum albumin [g/dL])
  - Measure ionized calcium levels (normal 4–5.2 mg/dL or 1–1.3 mmol/L)
    - **Preferred approach in critically-ill patients**
- Evaluate and manage etiology
  - Check parathyroid hormone (PTH), vitamin D and precursors, magnesium, and phosphate levels
  - Pharmacological causes of decreased ionized calcium may include excess infusions of citrate, EDTA, lactate, fluoride poisoning, foscarnet, cinacalcet, bisphosphonates, or unrelated increase in serum phosphate or decrease in serum magnesium levels
- Symptomatic (e.g., dysrhythmias, hypotension, tetany, and seizures)
  - Usually associated with an ionized calcium level < 2.8 mg/dL or < 0.7 mmol/L
  - Calcium chloride 1 g (10 mL of a 10 % solution) IV over 5–10 min
    - Contains 272 mg/13.6 mEq elemental calcium per gram product
    - **Severe desiccant → must give through a central line**
  - Calcium gluconate 1–3 g (10–30 mL of a 10 % solution) IV over 5–10 min
    - Contains 93 mg/4.5 mEq elemental calcium per gram product
    - Preferred product for peripheral venous administration
  - Measure serum calcium every 6 h during acute therapy
  - A continuous IV infusion of 0.3–2 mg/kg/h may be initiated to achieve and maintain normocalcemia if warranted (see critically ill setting above)
  - Change to enteral therapy once serum calcium is ≥ 8.5 mg/dL or ionized calcium normalizes
  - Use cautiously in patients on digitalis glycoside pharmacotherapy
  - Correct concomitant hypomagnesemia
  - Initiate calcitriol 0.25 mcg enterally daily if suspect vitamin D or PTH deficiency
  - If present and clinically feasible, treat acute severe hyperphosphatemia before calcium administration (i.e., with phosphate binders and/or with hemodialysis in acute tumor lysis syndrome)

(continued)

Table 14.5 (continued)

- Asymptomatic
  - Enteral calcium 1–3 g daily
  - Various salts
    - Carbonate: 250 mg elemental calcium per 500 mg tablet
    - Citrate: 200 mg elemental calcium per 950 mg tablet
    - Gluconate: 90 mg elemental calcium per 1 g tablet
    - Lactate: 60 mg elemental calcium per 300 mg tablet
  - Calcium citrate and gluconate do not require an acidic medium for maximal bioavailability (i.e., appropriate salt with concomitant acid suppressive therapy)

Table 14.6 Management of acute hypercalcemia (serum calcium > 12 mg/dL)

- Identify and manage etiology (e.g., hyperparathyroidism, malignancy, excessive vitamin D effect)
  - Drug-induced causes can include:
    - Thiazide diuretics, calcium-containing antacids, vitamin D, lithium
- Intravenous 0.9 % saline (if no contraindications are present)
  - 200–300 mL/h initial therapy (patient-specific)
  - 100–200 mL/h once patient is adequately hydrated
  - Maintain urine output between 100 and 150 mL/h
- Potassium and magnesium supplementation
- Loop diuretics
  - Patient must be euvolemic before use and remain as such
    - Any resulting hypovolemia may increase serum calcium by promoting tubular calcium reabsorption
  - E.g., furosemide 40–80 mg IV (1 mg/kg) every 2–4 h
- Salmon calcitonin 4 units/kg SQ every 12 h
  - Onset within 1–2 h (effects on bone and calciuretic)
  - A test dose should be considered before therapy is initiated
    - In a tuberculin syringe dilute 10 units in 1 mL 0.9 % saline
    - Inject 1 unit (0.1 mL) intradermally on the flexor surface of the forearm
      - The appearance of erythema or a wheal within 15 min indicates a positive reaction, and calcitonin salmon should not be administered
  - If an inadequate response is observed after 1–2 days, may increase the dose to 8 units/kg SQ every 12 h
  - Tachyphylaxis may develop (limit use to 48 h)

(continued)

TABLE 14.6 (continued)

- Bisphosphonate
  - Slow onset (1–2 days)
  - Use cautiously in patients with renal insufficiency
  - Etidronate 7.5 mg/kg IV over 2–4 h for 3–5 days
  - Pamidronate 60–90 mg IV × 1 dose over 2 h
    - 60 mg for calcium levels ≤ 13.5 mg/dL
    - 90 mg for calcium levels > 13.5 mg/dL
  - Zoledronate 4 mg IV in one dose over 15 min (preferred agent-associated with increased events than pamidronate but no difference in severe renal toxicity)
- Other agents
  - Gallium nitrate 200 mg/m^2/d by continuous IV infusion for ≤ 5 days
    - May be superior to bisphosphonates for humoral hypercalcemia of malignancy (PTHrp)
  - Glucocorticoids (for hypercalcemia associated with increased vitamin D activity)
    - Prednisone 20–40 mg enterally daily or equivalent in hypervitaminosis D, lymphoma or granulomatous disease-related
  - Chelating agents (rarely used)
    - EDTA 10–50 mg/kg over 4 h up to a maximum of 3 g in 24 h
- Hemodialysis with calcium-free dialysate
  - In life-threatening situations or if the patient is anuric

TABLE 14.7 Management of acute hypokalemia (serum potassium <3.5 mEq/L)

- Evaluate etiology
  - Drug-induced may include:
    - Diuretics, laxatives
    - Sympathomimetics (including inhaled/nebulized B_2-adrenergic agonists), theophylline, caffeine
    - Penicillin, ampicillin, nafcillin, ticarcillin, aminoglycosides, amphotericin B
    - Cisplatin
- Symptomatic or severe hypokalemia (<2.5 mEq/L)
  - 10–20 mEq over 1 h
  - Repeat as necessary until serum potassium normalizes
  - Electrocardiogram monitoring is indicated when infusion rates exceed 10 mEq/h
  - Doses > 20 mEq/h should be administered through a central line
    - Catheter tip should not be extended into the right atrium
  - Maximum rate is 40 mEq/h

(continued)

Table 14.7 (continued)

- Parenteral product should be mixed with saline instead of dextrose diluents
  - To prevent insulin-mediated intracellular shift of potassium during the infusion
- If cardiac arrest from hypokalemia is imminent, give an initial infusion of 2 mEq/min, followed by another 10 mEq IV over 5–10 min. Document in medical chart that rapid infusion is intentional owing to life-threatening situation. Once the patient is stabilized, reduce the infusion to gradual replacement[a]

- Asymptomatic
  - Increase dietary intake
    - Figs, dates, prunes, bananas, oranges, kiwis, mangos
    - Avocados, lima beans, vegetables
  - Salt substitutes (usually with potassium phosphate)
  - Potassium chloride 20–40 mEq enterally daily
    - Adjust dose to maintain normokalemia
  - Consider concomitant utilization of a potassium-sparing diuretic (e.g., spironolactone, amiloride, triamterene) if renal losses because of a loop or thiazide diuretics

[a]Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2000;102(8):I218

Table 14.8 Management of acute hyperkalemia (serum potassium ≥5.5 mEq/L)

Agent	*Comments*
Calcium gluconate (20–30 mL) of a 10 % solution over 2–5 min (peripheral line) or Calcium chloride (10 mL) of a 10 % solution over 2–5 min (central line)	• Administer if abnormal electrocardiogram (ECG) or anticipating rapidly rising potassium level • Repeat every 30 min until ECG normalizes • Avoid if suspected digitalis toxicity. If severe symptomatic hyperkalemia and concomitant digoxin toxicity, treat with DigiFab prior to infusing calcium if time permits • Onset: 1–2 min • Duration: 10–30 min

(continued)

TABLE 14.8 (continued)

Agent	*Comments*
Sodium bicarbonate 45–50 mEq IV over 5 min	• Administer if abnormal ECG or pre-existing nonorganic metabolic acidosis • Onset: 30–60 min • Duration: 2–6 h • Repeat dose in 30 min if needed
Regular insulin 10 units IV over 5–10 min	• Onset: 15–30 min • Duration: 2–6 h
Dextrose 50 % 50–100 mL IV over 5–10 min	• Withhold if blood glucose > 250 mg/dL • Onset: 15–30 min • Duration: 2–6 h
Furosemide 40–80 mg (1 mg/kg) IV over 2–5 min	• Onset: 15 min • Duration: 6 h
Albuterol 10–20 mg nebulized over 10 min	• Second-line pharmacotherapy • Onset: 30 min • Duration: 1–6 h
Sodium polystyrene sulfonate 15–60 g in 20 % sorbitol suspension enterally. As an enema, prepare 50 g in 70 % sorbitol plus 100 mL tap water. This solution should be retained for 30–60 min	• Enteral route more effective • Onset: 1–2 h • Duration: variable • Repeat every 4–6 h as needed
Hemodialysis (3–4 h)	• Use in patients with endstage renal disease or if life-threatening emergency • Onset: immediate • Duration: variable

Notes:
Treatment depends on degree of hyperkalemia and presence/severity of signs and symptoms (often irrespective of actual serum potassium level). *Mild:* 5.5–6 mEq/L (no ECG changes)—furosemide and sodium polystyrene sulfonate. *Moderate:* 6.1–7 mEq/L (peaked T waves on ECG)—insulin, glucose, sodium bicarbonate, albuterol, furosemide, and sodium polystyrene sulfonate. *Severe:* > 7 mEq/L (prolongation of conduction and widened QRS on ECG)—calcium, insulin, glucose, sodium bicarbonate, albuterol, furosemide, and sodium polystyrene sulfonate. Monitor serum potassium levels every 2 h until normalizes

Table 14.9 Management of acute hypomagnesemia (serum magnesium <1.4 mEq/L)

- Evaluate etiology
  - Drug-induced may include:
    - Thiazides, loop diuretics
    - Aminoglycosides, amphotericin B
    - Cyclosporine, tacrolimus, foscarnet, pentamidine
    - Cisplatin, ethanol
- Symptomatic or severe (≤1 mEq/L)
  - Magnesium sulfate 1–2 g IV over 15–30 min, repeat as needed to correct serum magnesium level
  - If seizures are present, administer 2 g IV over 2–5 min
- Asymptomatic or level > 1 mEq/L
  - Magnesium oxide 300 mg enterally every 6–8 h
  - Milk of magnesia 5 mL every 6–8 h
  - Adjust dose until serum magnesium normalizes
  - Cautious dosing in patients with renal dysfunction

Table 14.10 Management of acute hypermagnesemia (serum magnesium >2 mEq/L)

- Evaluate etiology
  - Drug-induced may include:
    - Magnesium administration (IV [e.g., management of preeclampsia], enteral, enemas)
      - Milk-alkali syndrome
    - Theophylline, lithium
- Symptomatic
  - Calcium chloride (central line) 5–10 mL of a 10 % solution or calcium gluconate (peripheral line) 10–20 mL of a 10 % solution over 5–10 min
    - Repeat every hour as needed
  - Forced diuresis in patients with adequate renal function
    - 0.9 % saline
    - Furosemide 1 mg/kg IV X dose
      - Subsequent dosing based on clinical response
      - May cause hypocalcemia, which may worsen the signs and symptoms of hypermagnesemia
  - Hemodialysis
  - Supportive care
    - Vasopressors, cardiac pacing, or mechanical ventilation

TABLE 14.11 Management of acute hyponatremia (serum sodium <135 mEq/L)

Determine serum osmolality

- Serum osmolality$_{mOsm/kg} = 2(Na_{mEq/L}) + glucose_{mg/dL}/18 + BUN_{mg/dL}/2.8 + ETOH_{mg/dL}/4.6$

Isotonic hyponatremia (275–290 mOsm/kg)

- Pseudohyponatremia caused by hyperlipidemia or paraproteinemias
  - Seen if serum sodium is measured by flame photometry
  - Less common today with the use of ion (sodium) specific electrodes (but if lab dilutes sample prior to measurement, serum sodium will still be artifactually low)

Hypertonic hyponatremia (≥290 mOsm/kg)

- Excess effective osmoles in the extracellular fluid
  - Hyperglycemic state or use of mannitol
    - For every 100 mg/dL rise in serum glucose, the serum sodium decreases by 1.6 mEq/L (on average)
  - Suspect unmeasured osmoles if the osmolar gap is >15 mOsm/kg

Hypotonic hyponatremia (≤275 mOsm/kg)

- **Hypovolemic state (physical exam rarely reliable in distinguishing hypovolemia versus euvolemia)**
  - Urine sodium <10 mEq/L (in the absence of a diuretic effect): considered extrarenal losses
    - Gastrointestinal: vomiting, nasogastric suctioning, diarrhea
    - Skin: fever and burns
    - Third-spacing: sepsis and pancreatitis
  - Urine sodium ≥20 mEq/L: consider renal losses
    - Diuretic use
    - Adrenal insufficiency
    - Salt-wasting nephropathy
    - Cerebral salt-wasting syndrome (existence controversial)
- **Euvolemic state**
  - Urine osmolality <100 mOsm/kg (anti-diuretic hormone [ADH] suppressed)
    - Psychogenic polydipsia (excess water after excreting osmoles [e.g., normal endogenous or exogenous] in dilute urine)
    - Beer potomania syndrome or "tea and toast" diet (excess water after excreting osmoles [minimal endogenous and no exogenous] in dilute urine)
    - Reset osmostat in patients with excess free water (never severe)
  - Urine osmolality ≥100 mOsm/kg (ADH present)
    - Excess water after excreting osmoles (e.g., normal) in "inappropriately" concentrated urine
    - SIADH (should distinguish between cerebral salt-wasting syndrome in which patients are volume-contracted [existence controversial])

(continued)

Table 14.11 (continued)

- Causes
  - Pulmonary disease (e.g., pneumonia, empyema), small-cell lung cancer
  - Central nervous system infections, trauma, stroke
  - Pain, severe nausea, pituitary surgery
  - Psychiatric disease (i.e., medications, excess water intake)
  - Postoperative state (pain, nausea, morphine)
  - Psychiatric medications (antipsychotics, TCAs, SSRIs, SNRIs, MAOIs)
  - Anti-epileptics (carbamazepine, lamotrigine, oxcarbazepine, VPA)
  - Chemotherapy (cyclophosphamide, vinblastine, vincristine)
  - Bromocriptine, chlorpropamide
  - Vasopressin, desmopressin, oxytocin, ecstasy
  - NSAIDs, morphine
- Hypothyroidism
- Adrenal insufficiency (primary and secondary)
- Reset osmostat (see above)

- **Hypervolemic state**
  - Urine sodium < 10 mEq/L (sodium avid)
    - Chronic heart failure, cirrhosis, nephrotic syndrome
  - Urine sodium ≥ 20 mEq/L
    - Renal failure

Management

- Depends on the rapidity of onset and severity of symptoms
  - Rapidly correct to begin to normalize brain cell edema if **severe symptoms** are present (depressed mentation, seizures, respiratory failure), continue to correct at a moderate rate for less severe symptoms (nausea, anorexia, headache), slowly correct if asymptomatic (brain cells not edematous)—**all targets/limits should be interpreted in the individual context to avoid precipitation of an osmotic demyelination syndrome**
  - Menstruant women are at greatest risk for significant morbidity and mortality related to hyponatremia and any related correction
  - Can raise the serum sodium at a rate of **1 mEq/L/h or more for the first 1–5 h** in patients with **severe symptoms**. A **4–6 mEq/L** increase is almost always enough to reverse **severe symptoms** and can be safely accomplished rapidly (*Chest.* 2013;144(2):672–679) with minimal/no increase in the serum sodium for the remainder of the first 24 h. The 2014 Clinical Practice Guidelines on the Diagnosis and Treatment of Hyponatremia suggest a 5 mEq/L rise in the first hour or until severe symptoms resolve, whichever comes first, with a correction limit of 10 mEq/L in the first 24 h and 8 mEq/L over the next 24 h and until a serum sodium of 130 mEq/L is achieved (*Nephrol Dial Transplant*. 2014;2(29):ii1–ii29)

(continued)

Table 14.11 (continued)

- In rare instances where severe symptoms persist after a 5 mEq/L rise (patients with hyperacute increases in water intake over a few hours [e.g. primary polydipsia, marathon runners, use of MDMA] are felt to be at very low risk for osmotic demyelination syndrome), it may be reasonable to continue to increase sodium by 1 mEq/L/h until symptoms resolve or rise at a maximum of 10 mEq/L per 24 h, while investigating other causes of symptoms/signs

- *Acute symptomatic* (**usual serum sodium < 120 mEq/L**)
  - Address etiology and stop any offending medication(s)
  - Regardless of volume status, treat with 0.9 % or preferably 3 % saline (see calculation example below) until signs and symptoms resolve; **note**: 3 % saline can be administered through a peripheral line if central access is not available
  - Cause-specific treatment can be instituted once signs and symptoms have resolved
    - Risk factors for developing osmotic demyelination syndrome (ODS) include an initial serum sodium ≤ 105 mEq/L, concomitant hypokalemia, liver disease, alcoholism, and malnutrition. Correcting chronic (>48 h) hyponatremia (<120 mEq/L) by greater than 10–12 mEq/L in the first 24 h or greater than 18 mEq/L in 48 h is also a risk factor
    - **Under critical conditions (i.e., transtentorial herniation) a 30–60 mL bolus of 23.4 % saline (through a central-line) or a 250 mL bolus of 3 % saline may be administered to increase the serum sodium concentration by 5 mEq/L (*Neurology*. 2008:70(13):1023–1029)**
  - Patients should be treated in an advanced setting (e.g., ICU)
  - Monitor serum sodium at least every 2–4 h and urinary osmolality and sodium every 4–6 h for the first 24 h
  - Potassium is equivalent osmotically to sodium and repletion will raise the sodium level
  - If the serum sodium corrects too rapidly and stabilization or a decrease in serum sodium is wanted, urinary water losses may be matched/exceeded with a trial of D5W (avoid hyperglycemic osmotic diuresis (often unsuccessful—[**editor's opinion**])
  - **Desmopressin 2–4 mcg IV X 1** dose may be administered to halt water diuresis allowing the serum sodium to fall (*Clin J Am Soc Nephrol.* 2008;3(2):331–336); see above for potential target/limits
  - Calculate sodium deficit (SD)
    - SD = (delta ≤ 6 mEq/L) × (patient's weight in kg × Vd)
      - Vd for males = 0.6 L/kg
      - Vd for females = 0.5 L/kg

(continued)

Table 14.11 (continued)

- **Example calculation**
  - A 65-year-old male patient (70 kg) presents with a serum sodium of 110 mEq/L and seizures. How much intravenous 3 % saline (513 mEq/L) should this patient receive?
    - Determine volume required
      - (delta 5 mEq/L) × (0.6 × 70 kg) = 210 mEq
      - 513 mEq/1000 mL = 210 mEq/x
        - $x = 409$ mL of 3 % saline required to correct a delta of 5 mEq/L
    - Determine 3 % saline infusion rate
      - 409 mL/5 $mEq_{(\Delta Na)} = x/1$ mEq (**maximum hourly increase**)
        - x = 82 mL maximum per hour
        - Therefore initiate 3 % saline at 80 mL/h
    - Seizures cease after a total of 2 h
      - At this point the patient received 160 mL of 3 % saline
      - 409 mL–160 mL = 249 mL remaining over 22 h or 11 h
        - Therefore reduce rate to 20 mL/h for 11 h then stop
  - Important to note that these formulas do not account for ongoing solute and water losses
- Hypovolemic state
  - Utilize 0.9 % (isotonic) saline (154 mEq/L and 308 mOsm/L)
  - Using 1/3 the dose of 3 % saline may allow sodium and volume correction to be more closely "matched", avoiding potentially dangerous rapid sodium correction due to normal water diuresis in euvolemia (must regulate initial rate of serum sodium correction)
- Euvolemic state
  - Rule out adrenal insufficiency, hypothyroidism or renal failure (treat if present)
  - SIADH
    - If urine osmolality is ≤ 300 mOsm/L, may use 0.9 % saline if mild signs and symptoms (i.e., headache, nausea, vomiting, weakness)
    - If urine osmolality exceeds 300 mOsm/L, add a loop diuretic (e.g., furosemide 40 mg IV every 6 h) to 0.9 % saline or use 3 % saline (513 mEq/L and 1,026 mOsm/L)
    - Utilize 3 % saline for severe signs and symptoms (i.e., altered mental status, coma, seizures)
      - 0.9 % isotonic saline will **worsen** hyponatremia if urine osmolality is high
    - If asymptomatic, restrict fluid to 1–1.2 L/day (enteral and parenteral); increasing osmolar intake (high protein diet and/or sodium chloride [NaCl] tablets) will potentiate the rise in serum sodium and/or allow more liberal fluid intake

(continued)

Table 14.11 (continued)

- Conivaptan may be utilized in carefully selected patients
  - Loading dose—20 mg IV over 30 min X 1dose. Evaluate response and need for additional doses or continuous IV infusion
  - The loading dose may be followed by a continuous IV infusion of 20 mg over 24 h. May titrate to a maximum of 40 mg/day if inadequate response. Total duration of therapy not to exceed 4 days
- Hypervolemic state
  - Fluid restriction to between 1–1.2 L/day
  - Utilize a loop diuretic
  - Utilize 3 % saline (513 mEq/L and 1,026 mOsm/L) plus a loop diuretic for severe signs and symptoms
  - Conivaptan may be considered

Table 14.12 Management of acute hypernatremia (serum sodium >145 mEq/L)

Hypovolemic hypernatremia (loss of water and sodium [water ≥ sodium])

- Renal losses
  - Diuretics, mannitol, glucosuria
- Extrarenal losses
  - Excessive sweating, osmotic diarrhea, vomiting, nasogastric suctioning
- Management
  - If postural hypotension present
    - Normal saline
      - Change to hypotonic saline or dextrose 5 % in water to correct free water deficit once intravascular replete
  - Primarily water depletion
    - Hypotonic saline or dextrose 5 % in water

Euvolemic hypernatremia (loss of water)

- Renal losses
  - Central or nephrogenic diabetes insipidus
- Extrarenal losses
  - Insensible pulmonary or skin losses
- Management
  - Water replacement as dextrose 5 % in water
  - Central diabetes insipidus
    - Vasopressin
      - 5–10 units SQ every 6–12 h (dosage range 5–60 units/day)
      - Continuous IV infusion regimen: 0.0005 units/kg/h; double dose as needed every 30 min to a maximum of 0.01 units/kg/h

(continued)

Table 14.12 (continued)

- Desmopressin
  - 2–4 mcg IV/SQ daily administered as a single daily dose or in two divided doses
  - 10–40 mcg in 1–3 divided doses intranasally daily
- Notes:
  - Adjust morning and evening doses separately to consider diurnal variation in water excretion
  - Adjust dose based on urine output, urine osmolality, and serum sodium

◦ Nephrogenic diabetes insipidus
- Sodium restriction (<2,000 mg/day)
  - Consider dietary, fluid, or medication sodium sources
- Hydrochlorothiazide 25 mg enterally every 12–24 h (may work in central diabetes insipidus)
- Amiloride 5–10 mg enterally daily if lithium-related
- Indomethacin 50 mg enterally every 8 h (may work in central diabetes insipidus)

Hypervolemic hypernatremia (water and sodium gain [sodium ≥ water])

- Sodium overload
  - E.g., sodium-rich medications, sodium bicarbonate, hypertonic IV fluids, nutrition, enemas, dialysis, plasma products (sodium citrate content)
- Management
  - Loop diuretics (e.g., furosemide 40 mg IV every 6 h) and water replacement as dextrose 5 % in water

Calculating water deficit and general management principles

- Water deficit = Vd (weight in kg) × ([patient's serum sodium/140]–1)
  - Vd for males = 0.6 L/kg
  - Vd for females = 0.5 L/kg
- Administer half of deficit over 24 h, then remainder over next 1–2 days
- Goal should be a serum sodium < 145 mEq/L
  - Monitor serum sodium every 2–3 h over the first 24 h
- Serum sodium in acute-onset hypernatremia may be lowered by 1 mEq/L/h
- Serum sodium in slow-onset hypernatremia may be lowered by 0.5 mEq/L/h
- **Sodium decrease should be ≤ 6 mEq/L in the first 24 h**
- Rapid correction may result in cerebral edema, seizures, osmotic demyelination syndrome, or death
- In the setting of hyperglycemia, use the corrected serum sodium to estimate free water deficit
  - Add 1.6 mEq/L to the measured serum sodium for every 100 mg/dL rise in serum glucose above 200 mg/dL (average)
- The above water deficit equation does not take into consideration of continuous free water losses (i.e., insensible, renal, or gastrointestinal)

Table 14.13 Management of acute hypophosphatemia (<2 mg/dL)

- Intravenous pharmacotherapy
  - Intravenous formulations contain either sodium 4 mEq/mL or potassium 4.4 mEq/mL with 3 mmol/mL phosphate
  - Symptomatic and severe hypophosphatemia (≤1 mg/dL)
    - 0.25 mmol/kg (ideal body weight) over 6 h, repeat as necessary
    - Higher doses (0.3–0.5 mmol/kg) can be carefully utilized in critically ill patients with severe symptoms, an explanation for phosphate wasting, and good renal function
  - Symptomatic and moderate hypophosphatemia (between 1 and 2 mg/dL)
    - 0.15 mmol/kg (ideal body weight) over 6 h, repeat as necessary
  - Monitor for hypernatremia or hyperkalemia, hypocalcemia, and metastatic soft tissue deposition of calcium-phosphate crystals
- Enteral supplementation
  - Neutra-Phos (Na-7 mEq, K-7 mEq, and PO_4^- 250 mg) per packet
  - Neutra-Phos K (K-14.25 mEq and PO_4^- 250 mg) per capsule
  - K-Phos Neutral (Na-13 mEq, K-1.27 mEq, and PO_4^- 250 mg) per tablet
  - Initiate pharmacotherapy with PO_4 750–1,500 mg/day in three divided doses
    - Reduce dose and monitor carefully in patients with renal impairment

Table 14.14 Management of hyperphosphatemia (>5 mg/dL)

- Severe hyperphosphatemia, presenting as hypocalcemia and tetany should be treated with hemodialysis and possibly careful intravenous calcium administration (**see management of hypocalcemia**)
- Dietary and phosphorus-containing medication restriction
  - Protein restrict to 0.6–0.8 g/kg/day
  - Foods high in phosphorus include:
    - Diary products, cola beverages, beer, dried beans, peanut butter
  - Avoid phosphate-containing laxatives (e.g., Fleet's Phospho-Soda), sodium or potassium phosphate solutions, avoid hypervitaminosis D
- Phosphate binders
  - Administer just before or with a meal to maximize effects
  - Calcium salts (acetate, carbonate, citrate)
    - Dose of elemental calcium should not exceed 1.5–2 g/day and plasma calcium levels should not exceed 9.5 mg/dL (to avoid coronary artery calcification resulting from excess calcium)
    - First-line agents (except when patient has concomitant hypercalcemia)
    - Titrate dose to achieve normophosphatemia

(continued)

Table 14.14 (continued)

- Calcium carbonate requires an acidic medium for solubility
  - H_2-receptor antagonists and proton pump inhibitors may affect solubility
- Calcium citrate should not be administered with aluminum-containing compounds. Concomitant administration may increase systemic bioavailability of aluminum and predispose to toxicity
- May place patients at risk for vascular calcification
  - Combine with sevelamer if high-dose calcium salts are required to correct hyperphosphatemia

- Sevelamer
  - Initiate therapy with 800 mg enterally tid with meals (up to 1,600 mg tid)
  - Use in patients who have concomitant hypercalcemia and/or a calcium/phosphate product > 55
- Aluminum-containing solutions
  - More potent than sevelamer
  - 15–45 mL enterally every 8 h
  - Avoid concomitant use with citrate-containing products
  - Avoid chronic use (>1 month)
    - If chronic use is required in patients with end-stage renal disease, monitor serum aluminum concentrations every 3 months

Table 14.15 Management of acute primary metabolic acidosis (pH < 7.35)

Determine etiology (bicarbonate loss or nonvolatile acid gain)

- Anion gap metabolic acidosis ($AG = Na - [Cl + HCO_3]$)
  - **MUDPILES**
    - **M**ethanol
    - **U**remia
    - **D**iabetic ketoacidosis
      - Alcoholic or starvation ketoacidosis
    - **P**araldehyde
    - **I**soniazid or iron (lactic acidosis)
    - **L**actic acidosis
      - Type A (associated with tissue hypoxia)
        - Cardiogenic/distributive/obstructive/hypovolemic shock
        - Carbon monoxide poisoning
        - Severe hypoxemia, severe anemia
        - Seizures
        - Limb or intestinal ischemia
        - Drugs associated with methemoglobinemia (see Table 8.1)

(continued)

Table 14.15 (continued)

- Type B (associated with tissue hypoxia)
  - Acute leukemia, acute lymphoma, sarcomas, hepatoma, mesothelioma
  - Short-bowel syndrome (D-lactic acidosis [lab does not measure])
  - Liver or kidney disease (decreased clearance)
  - Diabetes mellitus
  - Thiamine deficiency, pyruvate dehydrogenase deficiency
  - Mitochondrial disease, congenital enzyme deficiencies
  - Metformin, salicylates, iron, isoniazid
  - Reverse transcriptase inhibitors
  - Cyanide poisoning (including nitroprusside-related)
  - Carbon monoxide poisoning
  - Early acetaminophen overdose
  - Epinephrine, theophylline toxicity
- **E**thylene glycol, methanol, ethanol ingestion
- **S**alicylates
- Alkalemia (absolute or relative)—*NEJM*. 1998;329:819–826.
- Other—toluene in advanced renal failure

- Hyperchloremic (nonanion gap) metabolic acidosis
  - Consumption/loss of bicarbonate
    - Gastrointestinal losses (e.g., diarrhea, fistula, ileostomy, ureterosigmoidostomy)
    - Dilutional (administration of nonalkali fluids [i.e., normal saline, D5W])
    - Toluene (glue sniffing) toxicity—in the absence of advanced renal failure
    - Renal losses (e.g., proximal [Type II] renal tubular acidosis [RTA])
      - Complication of carbonic anhydrase inhibitor or topiramate pharmacotherapy
      - Heavy metals (e.g., cadmium, mercury, lead)
      - Outdated tetracycline (Fanconi's syndrome)
      - Nephrotic syndrome, multiple myeloma, Wilson's disease, amyloidosis
      - Responsive to sodium bicarbonate 10–15 mEq/kg/day
  - Decreased renal acid excretion
    - Distal (Type I) RTA—hypokalemic (secondary hypoaldosteronism)
      - Systemic lupus erythematosus, Sjogren's syndrome, multiple myeloma, obstructive uropathy, cirrhosis, sickle cell disease
      - Hypercalcemia, amphotericin B, toluene
      - Responsive to sodium bicarbonate 1–3 mEq/kg/day

(continued)

Table 14.15 (continued)

- Distal (Type IV) RTA—hyperkalemic (hyporeninemic hypoaldosteronism)
  - Diabetic or HIV nephropathy, analgesic abuse nephropathy, cyclosporine nephropathy, chronic interstitial nephritis
  - Pharmacologically exacerbated by angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-adrenergic blockers, spironolactone, eplerenone, heparin, NSAIDs
  - Manage hyperkalemia (dietary restriction)
  - Responsive to sodium bicarbonate 1–3 mEq/kg/day
    - May need concomitant fludrocortisone, kayexalate, or loop diuretic pharmacotherapy to manage hyperkalemia
- Accumulation of exogenous acid
  - Ammonium chloride, hydrochloric acid, arginine monohydrochloride, toluene
  - Parenteral nutrition (amino acid salts), arginine

Management

- Address etiology
- **Sodium bicarbonate**
  - May be utilized in:
    - Severe hyperchloremic metabolic acidosis (pH < 7.2 or serum HCO_3 < 8 mEq/L)
    - Bicarbonate losing states
    - Salicylate toxicity
    - Convincing data in lactic acidosis is lacking (type A lactic acidosis-no benefit/potential harm [*Chest*. 200;117(1):260–267
      - Manage underlying etiology
      - Utilize if associated symptomatic hyperkalemia
      - May be warranted in very severe metabolic acidosis
  - Goal:
    - pH > 7.2 or HCO_3 between 8 and 10 mEq/L
    - Do not normalize these parameters
    - These goals may minimize an "overshoot" metabolic alkalosis
      - Remember that acetoacetate, β-hydroxy butyrate, and lactic acid are bicarbonate "equivalents"
  - Calculate bicarbonate deficit (BD) to determine dose
    - $BD = (8 - \text{patient's serum } HCO_3) \times 0.5$ (ideal body weight)
    - Administer as an intravenous infusion over 1–4 h
    - Follow-up with arterial blood gases to determine correction and need for additional sodium bicarbonate therapy

(continued)

Table 14.15 (continued)

- Tromethamine (THAM)
  - Acts as a proton acceptor
    - Combines with H^+ from carbonic acid to form bicarbonate and a cationic buffer
    - May increase intracellular pH
    - Dose of $0.3\,N$ THAM (mL) = 1.1 ([ABW in kg] × [goal HCO_3– patient's HCO_3]) administered intravenously over 1–6 h using a large peripheral vein or central vein
      - Additional doses determined by base deficit
    - Contraindicated in patients with renal failure (protonated form must be renally excreted), chronic respiratory acidosis or salicylate toxicity
    - Monitor for hyperkalemia and hypoglycemia

Table 14.16 Management of acute primary metabolic alkalosis (pH > 7.45)

Determine etiology (loss of H^+ [or chloride-rich fluid] or gain of HCO_3^- rich fluid)

- Chloride-responsive or volume-depleted states (urinary chloride concentration < 10 mEq/L)
  - Diuretic pharmacotherapy (renal H^+/chloride losses, secondary hyperaldosteronism, renal ammoniagenesis)
    - E.g., loop diuretics, thiazides
  - Gastrointestinal losses (H^+/chloride losses)
    - Vomiting, nasogastric suctioning, secretory diarrhea (villous adenoma or laxative abuse)
  - Respiratory losses in patients with cystic fibrosis
  - Mild-to-moderate potassium depletion (renal ammoniagenesis)
  - Posthypercapneic acidosis
- Chloride-unresponsive (urinary chloride concentration > 20 mEq/L)
  - Excess mineralocorticoid activity (renal H^+ losses, hypokalemia-induced renal ammoniagenesis)
    - E.g., Bartter's, Gitelman's, Cushing's, or Liddle's syndromes
    - Primary or secondary hyperaldosteronism
    - Black licorice (glycyrrhizic acid) consumption
  - Severe potassium (K < 2 mEq/L) or magnesium (Mg < 1 mEq/L) depletion (renal ammoniagenesis, renal H^+ losses, and stimulated renal bicarbonate reabsorption)
- Indeterminate
  - Excessive alkali administration
    - Bicarbonate, acetate, citrate, lactate
    - Milk-alkali syndrome
  - High-dose penicillin therapy (e.g., ticarcillin)

(continued)

Table 14.16 (continued)

Management

- Address etiology
- Chloride-responsive or volume-depleted states
  - Intravenous normal saline (to address volume depletion)
  - Potassium, magnesium, or calcium chloride replacement if warranted
  - Arginine monohydrochloride or ammonium chloride if no hepatic insufficiency
  - Upper gastrointestinal losses
    - H_2-receptor antagonists, proton pump inhibitors
  - If patient is euvolemic, potassium-repleted, or volume intolerant
    - Acetazolamide 250–500 mg IV/enterally every 12 h × 2–4 doses
      - Rarely, may lead to a small rise in PCO_2 in patients with chronic respiratory acidosis; cautious use in severe lung disease
      - Contraindicated in liver failure (impairs ureagenesis)
      - Contraindicated in salicylate toxicity, unless serum alkalinization is maintained
  - If alkalosis persists or if pH > 7.6 or HCO_3 > 45 mEq/L
    - Hydrochloric acid
      - HCl dose in mEq = 0.5 (IBW) × (patient's serum HCO_3–38)
      - 0.1 *N* HCl = 100 mEq/L
      - 0.2 *N* HCl = 200 mEq/L
      - Administer through a central line at ≤ 0.1–0.2 mEq/kg/h
        - Cautious use in severe lung disease; avoid producing acidemia
      - Discontinue infusion when the arterial pH reaches 7.5
    - Arginine monohydrochloride
      - 10 g/h continuous IV infusion
      - Discontinue infusion when the arterial pH reaches 7.5
      - Do not administer in patients in septic shock
    - Ammonia chloride has a limited role
  - Hemodialysis using a low-bicarbonate dialysate
- Chloride-unresponsive
  - Potassium, magnesium replacement
  - Excessive mineralocorticoid activity
    - Decrease dose or change corticosteroid to one with less mineralocorticoid activity (e.g., dexamethasone)
    - Bartter's or Gitelman's syndrome
      - Spironolactone, amiloride, or triamterene
    - Liddle's syndrome
      - Amiloride or triamterene
    - Decrease/eliminate exogenous alkali administration

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