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)