Toxicology

Steven E. Pass, Pharm.D., FCCP, FCCM, FASHP, BCPS

Texas Tech University Health Sciences Center

School of Pharmacy

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Learning Objectives

1. Review the epidemiology for acute poisonings in the United States.
2. Distinguish the common clinical toxidromes associated with acute poisonings.
3. Describe the general management of a patient with an acute overdose.
4. Assess the gastric decontamination strategies for an acute overdose.
5. Evaluate the options for the management of selected toxins.
6. Assess a patient with clinical acute overdose, and develop a patient care plan according to current evidence.
7. Review the adverse effects and monitoring of the poisoned patient.

Abbreviations in This Chapter

ED	Emergency department
HIET	Hyperinsulinemic euglycemic therapy
ICU	Intensive care unit
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 38-year-old woman with type 2 diabetes mellitus is admitted for confusion and altered mental status. She has an active prescription for glipizide 10 mg by mouth twice daily, but she is unable to respond to further questioning. Her vital signs are as follows: blood pressure (BP) 115/65 mm Hg, heart rate (HR) 68 beats/minute, respiratory rate (RR) 15 breaths/minute, and temperature 98.6°F. Her point-of-care glucose level is 45 mg/dL, and she is given 50 mL of 50% dextrose in water intravenously twice. Her follow-up point-of-care glucose level is 50 mg/dL after the first dose and 57 mg/dL after the second dose, with no improvement in symptoms. Which is the most appropriate intervention at this time?
   A. Dextrose.
   B. Glucagon.
   C. Octreotide.
   D. Sodium bicarbonate.

2. A 56-year-old man is admitted to the intensive care unit (ICU) after a β-blocker overdose. After the administration of 2 L of 0.9% sodium chloride and 3 g of calcium gluconate, his vital signs are as follows: BP 70/40 mm Hg, HR 52 beats/minute, and RR 22 breaths/minute. Which therapy is most appropriate at this time?
   A. Glucagon 5 mg.
   B. Atropine 1 mg.
   C. Insulin 0.1 unit/kg.
   D. Dopamine 2 mcg/kg/minute.

3. A 76-year-old woman is admitted to the emergency department (ED) with the chief concern of decreased mental status. Her vital signs are as follows: BP 118/72 mm Hg, HR 57 beats/minute, and RR 17 breaths/minute. She is experiencing nausea, but her physical examination is otherwise normal. Her husband is concerned that she may not be taking her medications properly. Given her presentation, which common toxidrome is most likely in the patient?
   A. Anticholinergic.
   B. Cholinergic.
   C. Opioid.
   D. Sympathomimetic.

4. A 38-year-old woman is admitted to the ICU after a suspected overdose of risperidone. She was initially hypotensive, but she was stabilized after the administration of two 500-mL boluses of lactated Ringer solution. Her BP is now 118/77 mm Hg, HR 75 beats/minute, and RR rate 16 breaths/minute. A 12-lead electrocardiogram (ECG) shows QT prolongation (corrected QT interval [QTc] = 480 milliseconds), and her chemistry panel is significant for a bicarbonate of 24 mEq/L, potassium of 3.1 mEq/L, and magnesium of 1.8 mg/dL. Which intervention is most appropriate at this time?

A. Potassium chloride 20 mEq every hour for two doses.
B. Activated charcoal 50 g.
C. Magnesium sulfate 2 g.
D. Lorazepam 2 mg.

5. A 48-year-old man is admitted to the medical floor for community-acquired pneumonia. His medical history is significant for hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD), and he reports occasional alcohol use. He is initiated on levofloxacin 750 mg intravenously daily and nebulizer treatments with albuterol and ipratropium. Twenty-four hours after admission, he is increasingly more confused and has nausea and vomiting. His vital signs are stable: BP 115/68 mm Hg, HR 122 beats/minute, RR 21 breaths/minute, and temperature 99.7°F. The team is concerned about possible alcohol withdrawal and asks for recommendations for initial therapy. Which is the most appropriate treatment for this patient?

A. Lorazepam 2 mg intravenous push every 4 hours as needed according to the patient's Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA) score.
B. Phenobarbital 65 mg by mouth every 8 hours as needed according to the patient's CIWA score.
C. Propofol continuous infusion.
D. Clonidine 0.1 mg by mouth every 12 hours.

6. A 57-year-old male patient on the medical floor is incorrectly administered a dose of methadone 40 mg by mouth that was written for the patient in the adjoining bed. Two hours later, the nurse finds him unresponsive with the following vital signs: BP 105/67 mm Hg, HR 61 beats/minute, RR 8 breaths/minute, and temperature 98.7°F. The nurse calls for the rapid response team, and as the team pharmacist, you are asked for a recommendation. Which treatment is most appropriate at this time?

A. Activated charcoal 50 g.
B. Naloxone 0.04 mg intravenously.
C. Whole bowel irrigation.
D. 1 L of 0.9% sodium chloride.

7. A 56-year-old female patient is admitted to the ED after an intentional overdose of 25 amlodipine 10-mg tablets. She is given activated charcoal 50 g, 2 L of 0.9% sodium chloride, and 3 g of calcium gluconate. Her current vital signs are as follows: BP 90/50 mm Hg, HR 107 beats/minute, RR 17 breaths/minute, and temperature 98.7°F. Serum chemistries are as follows: Na 141 mEq/L, K 2.5 mEq/L, Cl 101 mEq/L, HCO_3 24 mEq/L, blood urea nitrogen (BUN) 19 mg/dL, serum creatinine (SCr) 0.9 mg/dL, and glucose 215 mg/dL. The ED physician wants to initiate hyperinsulinemic euglycemic therapy (HIET). Which is most appropriate to initiate first with respect to HIET?

A. Give insulin 1 unit/kg.
B. Give 50 mL of 50% dextrose in water.
C. Warn the physician that full effects may take up to 30 minutes.
D. Give 20 mEq of potassium chloride intravenously every hour for four doses.

8. The patient in the previous question is not responding to HIET initiation. Her BP remains low at 70/40 mm Hg, and her HR is now 58 beats/minute. Which is most appropriate to initiate at this time?

A. Norepinephrine.
B. Isoproterenol.
C. Epinephrine.
D. Intravenous fat emulsion.

I. EPIDEMIOLOGY

A. Population-based: The American Association of Poison Control Centers releases an annual report based on all the cases submitted by the 55 regional poison centers to the National Poison Data System (Clin Toxicol 2013;51:949-1229).
   1. In 2012, 2,275,141 human exposures were reported. Fatalities were reported in 1190 cases.
   2. The most common site of exposure was a residence (93.6%), followed by a workplace (1.58%) and a school (1.26%).
   3. Most of the reported cases (1,402,937) occurred in children, defined in the report as younger than 20 years. To add perspective, 1,242,908 reported cases were reported in children younger than 12 years.
   4. The most common reasons associated with these exposures were unintentional (80.1%), intentional (16%), and adverse reaction (2.6%). Of note, therapeutic errors accounted for 280,269 (12.3%) of all cases. The scenarios reported for therapeutic errors included inadvertent double-dosing (28.7%), incorrect medication administered (15.7%), incorrect dose (13.6%), doses administered too close in time (9.7%), and inadvertent exposure to another person's medication (8.3%).
   5. Routes of exposure included ingestion (83.4%), dermal (7%), inhalation/nasal (6%), and ocular (4.3%). The fatal exposures were mostly by ingestion (77.2%), followed by inhalation/nasal (7.8%) and parenteral (4.6%).

B. Management-based
   1. Only 27% of exposures were managed in a health care facility, with 69.2% being managed at the site of the occurrence.
   2. Gastric decontamination was employed in more than half of all exposures (56%); however, antidotes were given in only 18.4% of the exposures.
      a. The most common gastric decontamination strategy was the use of activated charcoal (2.5% of total exposures), followed by other emetic agents (0.58%), cathartics (0.54%), gastric lavage (0.15%), and whole bowel irrigation (0.08%).
      b. Looking at trends in specific gastric decontamination strategies, ipecac use has declined from about 15% of all cases in 1985 to only 0.01% of all cases in 2012. Use of activated charcoal has also declined, from a high of 7.7% of all cases in 1995 to only 2.5% of all cases in 2012.

Table 1. Top 5 Most Common Medication-Related Toxic Exposures in 2012

Most Common Medication-Related Exposures	% of Total Cases
All human exposures	
1. Analgesics	11.6
2. Sedatives/hypnotics/antipsychotics	6.05
3. Antidepressants	4.05
4. Cardiovascular drugs	3.87
5. Antihistamines	3.61
Adult exposures (> 20 yr of age)	
1. Analgesics	12.5
2. Sedatives/hypnotics/antipsychotics	10.9
3. Antidepressants	6.5
4. Cardiovascular drugs	5.8
5. Alcohols	4.8

Table 1. Top 5 Most Common Medication-Related Toxic Exposures in 2012 *(continued)*

Most Common Medication-Related Exposures	% of Total Cases
Pediatric exposures (< 5 yr of age)	
1. Analgesics	9.9
2. Vitamins	4.3
3. Antihistamines	3.9
4. Antimicrobials	2.7
5. Gastrointestinal preparations	2.6

yr = year(s).

Information from: Mowry JB, Spyker DA, Cantilena LR, et al. 2012 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th annual report. Clin Toxicol 2013;51:949-1229.

II. GENERAL MANAGEMENT

A. The primary treatment strategy for the management of a toxic exposure should focus on stabilizing the patient, with an emphasis on the ABCs (airway, breathing, and circulation). Patients should be monitored for vital signs (HR, RR, temperature, and oxygen saturation) and changes in mental status.

B. Supportive care should be based on specific patient symptoms and may include the administration of intravenous fluids, supplemental oxygen, and advanced airway management. Additional tests such as a 12-lead ECG, chest radiograph, or electroencephalogram may be required.
   1. Use of "coma cocktail" preparations is controversial and therefore not routinely recommended because they should not replace or substitute for a thorough analysis of the patient (JEMS 2002;27:54-60). Formulations vary, but they typically contain one or more of dextrose, thiamine, folate, and naloxone. Below is an overview of the common additives, a rationale for use, and potential controversies.
      a. 50% dextrose 25–50 mL is administered to treat hypoglycemia; it is recommended to perform point-of-care blood glucose testing to confirm before administration.
      b. Thiamine 100 mg is administered to prevent Wernicke encephalopathy; however, this condition can be quickly recognized, and several doses are typically required to effectively treat it.
      c. Naloxone 0.04–2 mg is administered to reverse respiratory depression secondary to opiate overdose; however, this is recommended in unconscious patients, preferably after a urine toxicology screen is done.

C. Ingestions
   1. A thorough physical examination should be performed.
   2. A medication history and reconciliation should be done, including all prescription medications, over-the-counter agents, and herbal products.
   3. The history of the ingestion should be determined, if possible, including the following elements (Ann Emerg Med 1999;33:735-56):
      a. Timing and route of the exposure, the possible agents involved and the strengths and amounts, and the potential intent of the patient
      b. History from the prehospital care providers and/or family members or other patient advocates
      c. Onset and progression of any symptoms

4. Some providers advocate for the use of toxidromes (Table 2), which are a collection of symptoms that occur with particular classes of toxic agents. Toxidromes may help in the identification of the toxic agent and assist in care by helping providers anticipate additional symptoms. Although they may be very useful in the care of an acute poisoning, it is recommended to use them with caution because some symptoms may overlap with other classes of toxins or may be absent altogether.

Table 2. Common Toxidromes

Toxidrome	Signs and Symptoms
Anticholinergic	Mydriasis, tachycardia, anhidrosis, dry mucous membranes, hypoactive bowel sounds, altered mental status, delirium, hallucinations, urinary retention, flushing, hyperthermia
Cholinergic	Diarrhea, diaphoresis, involuntary urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation, salivation, confusion, central nervous system depression, tachycardia, hypertension, fasciculations, muscle weakness
Opioid	Sedation, miosis, decreased bowel sounds, decreased respirations, bradycardia, hypotension
Sympathomimetic	Agitation, delirium, myoclonus, mydriasis, tachycardia, hypertension, hyperthermia, diaphoresis

Adapted from: Holstege CP, Borek HA. Toxidromes. Crit Care Clin 2012;28:180-98. Critical care clinics by W.B. Saunders. Reproduced with permission from: W.B. Saunders in the format reuse of a book/textbook through Copyright Clearance Center.

5. Drug screens are used in acute toxic ingestions, the most common of which is the qualitative urine screen. This method tests for the presence of a substance, but it cannot detect the amount of the substance present. If a toxin is known, a quantitative drug screen may be used to confirm the exact amount present. Although urine drug screens may vary by institution, they may include amphetamines, barbiturates, benzodiazepines, cocaine, opiates, THC (marijuana), and tricyclic antidepressants (TCAs). Urine screens are not considered comprehensive; therefore, the presence of additional agents should be tested (e.g., acetaminophen, salicylates).
   a. A negative screen does not exclude the presence of a toxic substance, especially if the presumed agent is not present on the screen. Many agents are not identified by their designated screen; this is especially an issue with standard amphetamines, benzodiazepines, and opiate screens.
   b. A positive test also does not necessarily confirm the diagnosis because another agent may be present but at levels below a detectable threshold. In addition, a positive test does not indicate that the patient is intoxicated on the particular substance (e.g., cocaine is positive for 3 days; however, its effects last only a few hours).

Patient Case

1. A 53-year-old man (height 74 inches, weight 97 kg [215 lb]) arrives in the ED confused and disoriented. He is unable to provide any information about his condition or medical history. Vital signs are as follows: BP 85/50 mm Hg, HR 120 beats/minute, RR 28 breaths/minute, and temperature 99.2°F. On physical examination, an unmarked pill bottle is found in his pocket. Two tablets remain, and a possible drug overdose is suspected. Which is most appropriate to do first for this patient?

   A. Send a quantitative urine drug screen.
   B. Stabilize the patient's airway, breathing, and circulation.
   C. Order a coma cocktail.
   D. Try to identify the tablets in a drug database.

III. GASTRIC DECONTAMINATION/ENHANCED ELIMINATION

A. Many strategies for gastric decontamination are used to try to remove toxins or prevent further absorption. No particular strategy is preferred to another; each has certain advantages and disadvantages, and the risks and benefits must be considered before use. Consensus statements from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists recommend against the routine use of any decontamination strategy but suggest that these strategies play a role in individualized care after a poison exposure.

B. Ipecac
   1. Ipecac is no longer manufactured in the United States because of concerns for safety and ability to improve outcomes for patients who have been poisoned.
   2. Mechanism of action is to induce vomiting through irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone in the medulla
   3. Ipecac was previously recommended for gastric decontamination outside the health care environment (home, schools, etc.) and was successful in returning 40%–50% of gastric contents.
   4. Once considered both safe and effective, more recent guidelines recommend ipecac to be given only under a specific recommendation from a poison control center, ED physician, or other qualified medical personnel when all the following conditions are met (Clin Toxicol 2005;43:1-10; Clin Toxicol 2013;51:134-9):
      a. No specific contraindication exists for use
      b. There is a substantial risk of serious toxicity to the patient
      c. No alternatives are available or considered effective to reduce the toxin absorption
      d. A delay of more than 1 hour is expected before arrival to a medical facility
      e. Use of ipecac will not adversely affect a more definitive treatment option

C. Gastric Lavage
   1. Gastric lavage is performed by inserting a larger-bore catheter tube (36–40 French for adults and 24–28 French for children) with several holes at the distal end into the stomach. Aliquots of warmed tap water are then instilled until there is clearing of aspirated fluid.
   2. The efficacy is highly variable and diminishes over time; therefore, it is optimal to perform within 60 minutes of ingestion
   3. Recent guidelines emphasize that gastric lavage has not been proven to decrease the severity of illness, improve recovery times, or improve outcomes (Clin Toxicol 2013;51:140-6).
   4. Should be considered only for life-threatening ingestions when it can be safely performed within 30–60 minutes
   5. Even in life-threatening overdoses, it may not be beneficial. Gastric lavage should not be performed routinely, if at all, for the treatment of the patient who is poisoned. In the rare situation when it might be appropriate, clinicians should consider treatment with activated charcoal or observation and supportive care in place of gastric lavage (Clin Toxicol 2013;51:140-6).
   6. Contraindications for gastric lavage include patients with craniofacial abnormalities, concomitant head trauma, unprotected airway, and increased risk of and severity for aspiration and those at risk of gastrointestinal (GI) hemorrhage or perforation. Patients with decreased consciousness require oral or nasal intubation before the procedure.
   7. Complications associated with gastric lavage include aspiration, laryngospasm, perforation of the esophagus or stomach, arrhythmias, fluid imbalance, hyponatremia, and small conjunctival hemorrhages.

D. Cathartics
   1. Used to reduce the transit time of toxins and hence absorption, as well as in combination with charcoal to decrease constipating effects
   2. Cathartics have conflicting data regarding decreased transit time in the GI tract and have no data to support an improvement in patient outcomes (J Toxicol Clin Toxicol 2004;42:243-53).
   3. Cathartic use is not recommended; if used, it should be limited to a single dose.
   4. Contraindications to cathartic use include absence of bowel sounds, recent GI surgery, intestinal perforation or obstruction, hypotension, electrolyte disturbances, and renal insufficiency (for magnesium-based cathartics).
   5. Complications include nausea, dehydration, hypotension, and sodium and magnesium imbalances.

E. Activated Charcoal
   1. Activated charcoal is an adsorbent that works by binding the toxin throughout the GI tract to reduce systemic absorption. Although activated charcoal binds most substances, Table 3 lists the agents for which activated charcoal is NOT recommended.
      a. Acids and alkalis should be avoided because vomiting can be damaging, and the charcoal may cause discoloration of the stomach lining and therefore interfere with endoscopy.
      b. Alcohols bind poorly; therefore, large doses are needed, which are difficult to ingest.
      c. Cyanide will bind, but not with as much activity as other substances. Because the toxic dose of cyanide is so small, normal doses of activated charcoal may be effective.
      d. Hydrocarbons may lead to a significant risk of aspiration.
   2. It is optimal to administer activated charcoal within 60 minutes of the toxin ingestion to maximize efficacy.
   3. Disadvantages include the potential for aspiration in patients who have reduced consciousness or who are otherwise unable to protect their airway and the potential for developing an intestinal obstruction.
   4. Doses are often mixed with juices or carbonated beverages to improve their palatability.
   5. If significant nausea occurs, it is recommended to administer an antiemetic. When choosing an antiemetic, potential drug and symptom interactions should be considered as well.
   6. Complications include aspiration, accidental administration into the lung, emesis, constipation, and gastric obstruction.
   7. Contraindications include unconscious state or otherwise unable to protect the airway without endotracheal intubation and recent GI surgery
   8. Multidose activated charcoal is a method described to enhance the elimination of certain toxins. It has not been shown to be more effective in reducing morbidity or mortality than single-dose charcoal, but it may be administered to enhance elimination in life-threatening ingestions caused by medications that undergo significant enterohepatic recirculation with active enterohepatic metabolites (J Toxicol Clin Toxicol 1999;37:731-51).

Table 3. Agents for Which Activated Charcoal Is Not Recommended

Substance	**Examples**
Acids	Mineral acids, boric acid
Alcohols	Ethanol, methanol, ethylene glycol
Alkalis	Cleaning solutions, bleach, dishwasher detergents, lye
Carbamates	Neostigmine, physostigmine, insecticides
Cyanide	Cyanogen chloride, hydrogen cyanide, potassium cyanide, sodium cyanide
Hydrocarbons	Gasoline, kerosene, petroleum oils

Table 3. Agents for Which Activated Charcoal Is Not Recommended *(continued)*

Substance	Examples
Metals	Arsenic, iron, lead, lithium, mercury
Organic solvents	Acetic acid, acetone, ethylene glycol, glycerin, toluene
Organophosphates	Insecticides (malathion, parathion), herbicides, antihelminthic drugs (trichlorfon)

F. Whole Bowel Irrigation
   1. Whole bowel irrigation is a strategy for cleansing the bowel to remove potential toxins by administering an osmotic polyethylene glycol solution.
   2. May be useful in potentially life-threatening ingestions of medications with long half-lives, sustained-release dosage forms, or enteric-coated formulations. Specifically useful for certain toxic substances not adsorbed by activated charcoal (e.g., lithium and iron). May also be beneficial for iron overdoses and for packers or stuffers of illicit substances
   3. Contraindications include bowel obstruction, perforation, or ileus and in recent bowel surgery. A kidney-ureter-bladder radiograph may be used to rule out these contraindications.

G. Urine Alkalinization
   1. Urine alkalinization is a strategy for enhancing the elimination of toxins by increasing the urine pH to levels of 7.5 or greater with the administration of sodium bicarbonate or sodium acetate (J Toxicol Clin Toxicol 2004;42:1-26).
   2. Specific substances that may benefit from this strategy include salicylates, phenobarbital, chlorpropamide, and other weak acids with intrinsic urinary clearance.
   3. Contraindications include acute and chronic renal failure and preexisting heart disease.
   4. Complications include hypokalemia, hypernatremia, hypocalcemia, cerebral vasoconstriction, and coronary vasoconstriction.
   5. To administer urine alkalinization, it is recommended to check baseline blood chemistries, electrolyte levels, and an arterial blood gas and to correct any fluid or electrolyte deficits (especially potassium).
   6. Monitoring includes urine pH every 15–30 minutes until the goal pH level of 7.5–8.5 is achieved, followed by every hour; serum potassium levels, central venous pressure, and arterial blood gases should be measured hourly.

Table 4. Common Dosage Strategies for General Decontamination and Enhanced Elimination

Decontamination/ Elimination Strategy	Pediatric Dosing	Adult Dosing
Gastric lavage[a]	10-mL/kg aliquots, followed by return of an equal amount	200- to 300-mL aliquots, followed by return of an equal amount
Cathartics		
Magnesium citrate:	4 mL/kg	240 mL
Sorbitol:	4.3 mL/kg (35% solution)	1–2 mL/kg (70% solution)

Table 4. Common Dosage Strategies for General Decontamination and Enhanced Elimination *(continued)*

Decontamination/ Elimination Strategy	Pediatric Dosing	Adult Dosing
Activated charcoal Single dose	Up to 1 yr of age: 0.5–1 g/kg (usually 10–25 g) 1–12 years: 0.5–1 g/kg (usually 25–50 g)	> 12 years and adults: 25–100 g[b]
Multidose	0.5–1 g/kg (25–50 g), followed by 0.25–0.5 g/kg (10–25 g) every 4 hr	50 g, followed by 25–50 g every 4 hr
Whole bowel irrigation[c]	9 mo to 6 yr: 500 mL/hr 6–12 yr: 1000 mL/hr	> 12 and adults: Goal is 2000 mL/hr (initiated at 500 mL/hr and doubled every 30 min)
Urine alkalinization[d]	25–50 mEq intravenously over 1 hr	225 mEq intravenously over 1 hr

[a]Sterile water or 0.9% sodium chloride; may repeat until the return fluid is clear and absent of particulate matter.

[b]Upper limit may vary depending on the capacity of the stomach.

[c]Polyethylene glycol electrolyte lavage solutions; dose until the rectal effluent is clear or the desired effect has been achieved.

[d]Sodium bicarbonate solution: additional boluses can be given hourly (or begin a continuous infusion at this hourly rate) to maintain a urine pH of 7.5–8.5.

hr = hour(s); min = minute(s); mo = months.

IV. ACETAMINOPHEN

A. Background
   1. Acetaminophen is consistently one of the most common toxic drug exposures.
   2. Acetaminophen ingestions of 4 g or greater may cause injury in select patients. In general, acute doses of 150 mg/kg or 10 g in adults and 200 mg/kg in children are considered toxic. It is recommended that doses exceeding this threshold be managed in a health care facility.
   3. The mechanism of toxicity is caused by the active metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which can lead to oxidant cell injury, hepatic failure, and death.
   4. Around 90% of acetaminophen undergoes phase II conjugation to glucuronide and sulfate conjugates that are excreted in the urine. An additional 2% is excreted unchanged in the urine. The remaining amount (8%–10%) is converted by cytochrome P450 (CYP2E1) to NAPQI. NAPQI is normally converted by glutathione to cysteine conjugates, which are renally excreted. In an overdose, the sulfation and glucuronidation pathways become saturated, leading to glutathione depletion and a subsequent buildup of NAPQI (Clin Liver Dis 2013;17:587-607).

B. Clinical Presentation – Four clinical phases are associated with an acetaminophen toxicity (time intervals are estimated and may vary with individual patients).
   1. Phase I occurs within the first 24 hours after ingestion. Patients may present with minimal or no signs of distress. Potential signs and symptoms include nausea, vomiting, diaphoresis, and anorexia.

2. Phase II occurs 24–48 hours after exposure and is marked by initial damage to the hepatocytes. Patients may present with right upper quadrant pain, increases in liver transaminases, elevated total bilirubin concentrations, and prolonged prothrombin time.
3. Phase III occurs 72–96 hours after initial exposure and is the peak of the hepatotoxic effects. Patients may present with lactic acidosis, acute renal failure, acute pancreatitis, and fulminant hepatic failure, as evidenced by jaundice, extensive coagulopathies, hypoglycemia, and hepatic encephalopathy.
4. Phase IV occurs about 1 week after exposure and marks the recovery phase if the patient survives phase III.

C. Treatment
1. The goal of treatment is to prevent the development of hepatic toxicity and reduce mortality.
2. Gastric decontamination with a single dose of activated charcoal can be considered if the patient presents within the first hour after exposure, is not vomiting, and has no alterations in mental status.
3. Antidote therapy is recommended with acetylcysteine. The mechanism of action for acetylcysteine is to increase the synthesis and bioavailability of glutathione, substitute for glutathione by binding to the reduced sulfur group of NAPQI, and supply a substrate for sulfation, thereby increasing the non-toxic metabolism.
4. Guidelines suggest that acetylcysteine treatment should be administered to patients within the first 8 hours of exposure if they can be stratified as being at possible or probable risk of hepatotoxicity by the Rumack-Matthew nomogram (Figure 1). If patients cannot be stratified either because of unknown time of ingestion or inability to perform acetaminophen serum assays, they should receive acetylcysteine if any of the following conditions apply: increased alanine aminotransferase (ALT) concentration, serum acetaminophen levels greater than 20 mcg/mL, or history of chronic ingestions exceeding 4 g/day with an elevated serum ALT concentration (Ann Emerg Med 2007;50:292-313).
   a. This includes patients presenting more than 24 hours postingestion with evidence of hepatotoxicity.
   b. Limitations to the use of the Rumack-Matthew nomogram include the following (Ann Emerg Med 2007;50:292-313):
      i. Presentation more than 24 hours postingestion
      ii. An unknown or unreliable history of ingestion
      iii. Overdoses with extended-release formulations
      iv. Chronic or repeated supratherapeutic ingestions
      v. Patients with preexisting hepatic disease, chronic alcohol use, or concurrent medications metabolized by the CYP system
5. Intravenous acetylcysteine is preferred because of its decreased overall administration time (21 hours vs. 72 hours for oral) and minimal GI adverse effects. If the commercially available intravenous acetylcysteine formulation is not available and cannot be obtained in a timely fashion, poison control centers can be contacted for instructions on compounding the inhalational acetylcysteine formulation for intravenous use. It is not recommended to use this strategy except for emergency situations.
6. Oral acetylcysteine is dosed for 18 total doses; doses may be repeated if emesis occurs within 1 hour of a dose. To improve palatability, doses may be diluted in juice or carbonated beverages in a covered cup with a straw. Antiemetics may be administered if significant nausea or vomiting occurs.
7. Although treatment guidelines recommend 18 total doses of acetylcysteine administered over 72 hours for oral acetylcysteine therapy and 20 hours of the intravenous infusion of acetylcysteine, many poison control centers recommend early discontinuation (or prolonged therapy) if the following conditions are met (Dart, 2007):
   a. Serum acetaminophen concentrations are undetectable or less than 10 mcg/mL
   b. ALT levels normal (60 IU/L or less) or improving. Some clinicians also advocate an INR (international normalized ratio) of 1.3 or less.
   c. The patient is clinically improved

8. Adverse effects (intravenous): Anaphylactoid reactions (rash, urticarial, pruritus), hyponatremia, hypervolemia, seizures (pediatric patients with unadjusted volume)
9. Adverse effects (oral): Nausea, vomiting, anaphylactoid reactions (rare)
10. Medication errors may occur because of the complex dosing regimens (Ann Pharmacother 2008;42:766-70). Common errors include delays in therapy, incorrect dosages, and incorrect infusion rates.

D. Monitoring
   1. Patients should be monitored for improvement in vital signs and mental status.
   2. The following laboratory values should be monitored periodically for improvement as well as for potential worsening.
      a. ALT, aspartate aminotransferase (AST), total bilirubin, and prothrombin time
      b. BUN and SCr
      c. Serum electrolytes
      d. Fulminant hepatic failure: Serum bicarbonate, serum lactate, arterial blood gas, serum glucose, and ammonia levels

Table 5. Acetylcysteine Dosage

Route	Dose
Oral	**Loading dose:** 140 mg/kg **Maintenance doses:** 70 mg/kg every 4 hr for a total of 17 doses (72 hr)
Intravenous	**Loading dose:** 150 mg/kg (max 15 g[a]) in 200 mL of 5% dextrose in water infused over 60 min **Maintenance dose:** 50 mg/kg (max 5 g[a]) in 500 mL of 5% dextrose in water infused over 4 hr followed by 100 mg/kg (max 10 g[a]) in 1000 mL of 5% dextrose in water infused over 16 hr Patients weighing less than 40 kg require reduced volume administration

[a]Acetadote has not been well studied in patients weighing more than 100 kg; dose limits are recommended by the manufacturer.

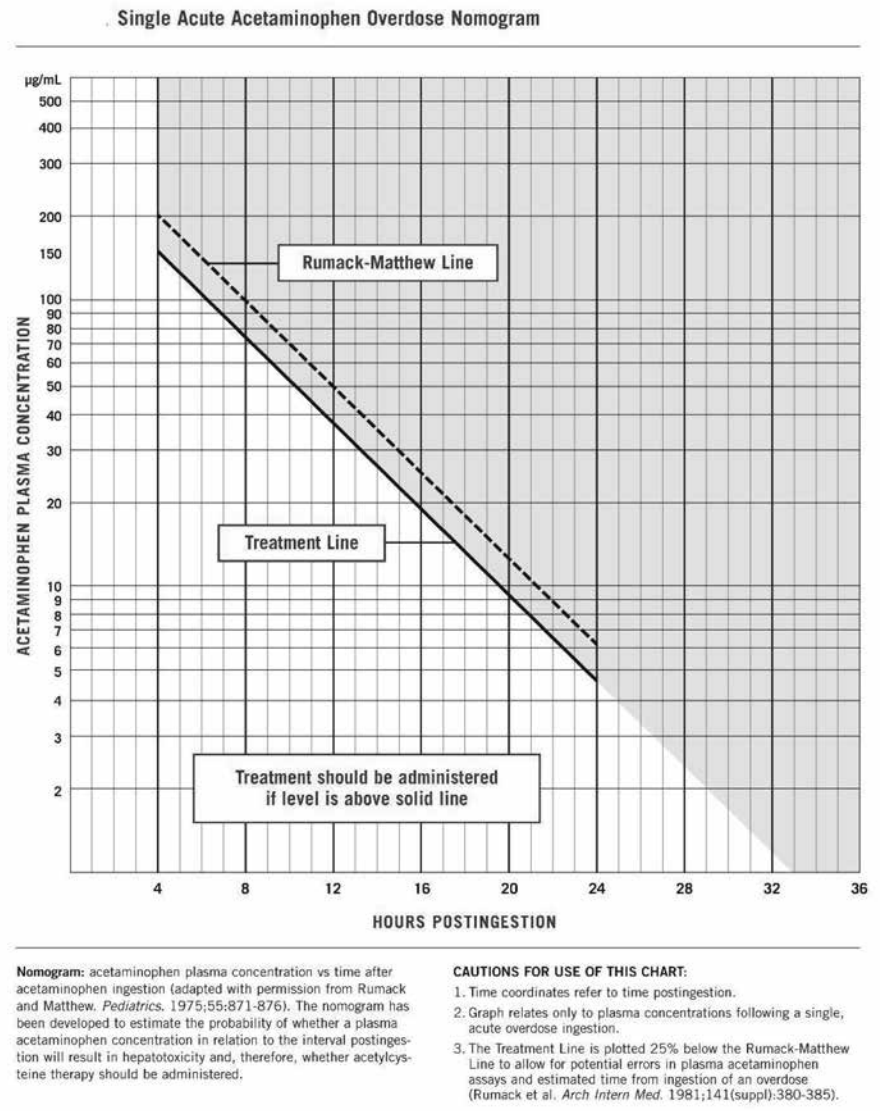

Figure 1. Rumack-Matthew nomogram.

Reprinted from: Tylenol for Healthcare Professionals. Guidelines for the Management of Acetaminophen Overdose. McNeil Consumer & Specialty Pharmaceuticals. Available at www.tylenolprofessional.com/acetaminophen-safety/overdose-management.html. Accessed December 1, 2014.

Patient Case

Questions 2 and 3 pertain to the following case.
A 42-year-old woman (height 66 inches, weight 79.2 kg [176 lb]) presents to the ED with the chief concern of flu-like symptoms. Her symptoms include headache, congestion, severe nausea and vomiting, abdominal pain, and some confusion. She has been taking acetaminophen 500-mg caplets as needed for her symptoms, but she just ran out of the bottle she purchased yesterday. On presentation, she is alert and oriented. Her vital signs are as follows: BP 135/90 mm Hg, HR 83 beats/minute, RR 18 breaths/minute, and temperature 101.8°F. An acetaminophen level on admission was 100 mcg/mL, AST 560 IU/L, and ALT 310 IU/L. The physician wants to begin general management.

2. Which general management strategy is most indicated for this patient?
   A. 10% magnesium citrate 240 mL per tube once.
   B. Continued stabilization of the patient.
   C. Gastric lavage.
   D. Charcoal 50 g per tube once.

3. Which is the most appropriate treatment for her acetaminophen toxicity?
   A. Give acetylcysteine 11,200 mg oral bolus, followed by 5600 mg orally every 4 hours for 17 doses.
   B. Give acetylcysteine 11,200 mg intravenous bolus, followed by 5600 mg intravenously every 4 hours for 12 doses.
   C. Give acetylcysteine 12,000 mg intravenously over 1 hour, followed by 4000 mg intravenously over 4 hours; then 8000 mg intravenously over 16 hours.
   D. Acetylcysteine therapy is not indicated in this patient.

V. SALICYLATES

A. Background
   1. Salicylates as a single agent (not in combination with other agents) accounted for 18,949 overdoses and 27 deaths in 2012.
   2. These numbers, which include overdoses of both adult and pediatric formulations of acetylsalicylic acid, are often underreported because of the nonrecognition of these products as a potential cause.

B. Clinical Presentation
   1. The mechanism of toxicity for salicylates is through the interference with aerobic metabolism owing to the uncoupling of mitochondrial oxidative phosphorylation, leading to increases in anaerobic metabolism, which causes a significant lactic acidosis (Emerg Med Clin North Am 2007;25:333-46). This also leads to hypoglycemia because of glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids.
   2. Salicylates are readily absorbed in the stomach and small intestine and are then conjugated with glycine in the liver to the active component, salicylic acid. In overdoses, the liver cannot metabolize the excess drug, and most is then excreted unchanged by the kidneys (Postgrad Med 2007;121:162-8).
   3. The most common clinical symptoms associated with a salicylate overdose are hyperventilation (respiratory alkalosis), tinnitus, and GI irritation. Symptoms may vary depending on the serum salicylate level; however, these may be low to normal early in the presentation (Postgrad Med 2007;121:162-8):
      a. Serum level less than 30 mg/dL: Asymptomatic

b. Serum level 15–30 mg/dL: Therapeutic levels
c. Serum level 30–50 mg/dL: Hyperventilation, nausea, vomiting, tinnitus, dizziness
d. Serum level 50–70 mg/dL: Tachypnea, fever, sweating, dehydration, listlessness
e. Serum level greater than 70 mg/dL: Coma, seizures, hallucinations, stupor, cerebral edema, dysrhythmias, hypotension, oliguria, renal failure
f. Acute salicylate toxicity is typically associated more with the GI symptoms; chronic toxicity is more associated with the central nervous system (CNS)-type symptoms.
g. Absorption may be delayed because of gastric pylorospasm, bezoar formation, or enteric-coated formulations; therefore, these ranges should be used with caution because they may not correlate with actual symptoms (Am J Emerg Med 2010;28:383-4).

C. Treatment
1. There is no antidote for salicylate poisoning; the goals of therapy are to limit the additional absorption of salicylates and to provide supportive care.
2. Gastric decontamination with a single dose of activated charcoal is recommended if the patient is alert and not vomiting.
   a. Multidose may be considered (25 g every 3 hours without sorbitol) if there is evidence of further absorption and if the patient has active bowel sounds.
3. Administer intravenous crystalloid fluids to maintain BP.
4. Administer intravenous glucose for hypoglycemia or significant neurologic symptoms.
5. Urine alkalinization is recommended to enhance renal elimination and increase the glomerular filtration rate.
   a. Administration strategies that have been described in the literature:
      i. Administer 250 mL of sodium bicarbonate 8.4% over 1 hour; then administer additional 50-mL boluses as needed to maintain a goal urine pH range of 7.5–8.5.
      ii. Administer 150 mL of sodium bicarbonate 8.4% in 1 L of 5% dextrose in water at 2–3 mL/kg/hour to maintain a urine output of 1–2 mL/kg/hour.
   b. Oral bicarbonate is not recommended because it may enhance salicylate absorption.
   c. Discontinue once the serum salicylate concentrations are less than 30 mg/dL or there is a resolution of clinical symptoms.
6. Replace serum potassium concentrations, if necessary.
7. Consider hemodialysis for any of the following (Postgrad Med 2007;121:162-8):
   a. Acute renal insufficiency
   b. End-organ damage (severe pulmonary edema, seizures, rhabdomyolysis)
   c. Altered mental status
   d. Deterioration of clinical status
   e. Severe acid-base disturbances

D. Monitoring
1. Patients should be monitored for up to 24 hours because of the possibility of delayed or impaired absorption.
2. Monitor RR and support as needed; caution is advised if intubation is required to support breathing because of a requirement for an increased minute ventilation (Am J Emerg Med 2010;28:383-4).
3. During urine alkalinization, monitor for signs and symptoms of fluid overload, hypernatremia, hypokalemia, and worsening alkalemia.

Patient Case

4. A 62-year-old man presents to the ED with the chief concern of nausea, tachypnea, and flu-like symptoms. He is alert and oriented and is able to communicate that his symptoms have been worsening for the past 2 days. He has been taking a combination cold product, which he thinks has helped. His medical history is significant for a stroke, for which he takes aspirin 325 mg by mouth daily, and hypertension, for which he takes amlodipine 5 mg by mouth daily. His vital signs are as follows: BP 135/82 mm Hg, HR 78 beats/minute, RR 29 breaths/minute, and temperature 100.2°F. Arterial blood gas results are as follows: pH 7.52, P_{CO_2} 25, and HCO_3 20 mEq/L. A salicylate level is sent, which is 25 mg/dL. Which treatment management strategy is most indicated for this patient?

   A. Sodium chloride infusion.
   B. Urgent endotracheal intubation.
   C. Sodium bicarbonate infusion.
   D. Hemodialysis.

VI. OPIOIDS

A. Background
   1. Opioids as a single agent (not in combination with other agents) accounted for 44,281 overdoses and 117 deaths in 2012 because of non-combination opioid products. The Centers for Disease Control and Prevention reported 14,800 deaths caused by prescription opioid painkillers in 2008.
   2. The most common agents associated with a toxicologic event were tramadol, oxycodone, methadone, morphine, and buprenorphine.
   3. The most common agents associated with a toxicologic death were methadone, oxycodone, morphine, and tramadol.
   4. Opioids act at the mu, delta, and kappa opioid receptors, although mu is responsible for most of the opioids' clinical effects.

B. Clinical Presentation
   1. The most common clinical symptoms associated with opioid overdose are respiratory depression (defined as less than 12 breaths/minute), coma, miosis, and hypoactive bowel sounds.
   2. Additional findings may include stupor, hepatotoxicity, acute renal failure, rhabdomyolysis, compartment syndrome, hypothermia, and seizures (N Engl J Med 2012;367:146-55).
   3. Diagnostic workup (Pharmacotherapy: A Pathophysiologic Approach, 9e. New York: McGraw-Hill, 2014):
      a. 12-lead ECG to test for QT prolongation – Methadone may cause QT prolongation and potentially torsades de pointes.
      b. Arterial blood gas to monitor for respiratory acidosis
      c. Standard chemistry panel for electrolyte and glucose abnormalities – Creatinine kinase (CK), BUN, and SCr for signs of rhabdomyolysis
      d. Pulse oximetry

C. Treatment
   1. Stabilize the airway, provide supplemental bag-valve mask breaths if needed, and administer supplemental oxygen. Establishment of an airway, if needed, by endotracheal intubation
   2. Administer intravenous crystalloid fluids to maintain BP.

3. Gastric decontamination with a single dose of activated charcoal is recommended if the patient presents within the first hour after exposure and is awake with an intact airway. Whole bowel irrigation can be considered for extended-release formulations or for packers or stuffers of illicit substances (including ingestion of fentanyl patches).
4. Antidote therapy (N Engl J Med 2012;367:146-55):
    a. Naloxone is a competitive antagonist at the opioid receptor.
    b. The intravenous route is preferred, but naloxone is also effective through the intramuscular, intranasal, inhalational, or intrapulmonary route.
    c. Onset of action of intravenous naloxone is 2 minutes with a duration of 30–120 minutes.
    d. Dosing may be affected by the specific opioid agent and dose, affinity for the mu-receptor, and patient weight.
    e. Initial dose is 0.04 mg in adult patients and 0.1 mg/kg in pediatric patients; if no response, the dose is increased every 2–3 minutes to 0.5 mg, 2 mg, 4 mg, and 10 mg, followed by 15 mg
    f. It is recommended that a continuous infusion be initiated at a dose of two-thirds the effective bolus dose per hour (0.04–4 mg/hour) for patients requiring subsequent naloxone doses to sustain effect (Ann Emerg Med 1986;15:566-70).
    g. Adverse effects are rare and may be more related to a return of sympathetic response to opioid withdrawal.
    h. If no effect is seen, consider other causes such as secondary or alternative agents.

D. Monitoring – Observe respiratory status and vital signs for a minimum of 4–6 hours after the last dose of naloxone or discontinuation of the continuous infusion.

VII. ALCOHOLS (METHANOL AND ETHYLENE GLYCOL)

A. Background
1. Alcohol poisonings (methanol and ethylene glycol) are not as common as poisonings with other substances, accounting for 2.8% of all cases in 2012 (National Poison Data System), but they can be serious and potentially fatal.
2. Methanol is commonly found in products such as windshield washer fluid, antifreeze, brake and carburetor fluids, and cooking products.
3. Ethylene glycol is commonly found in products such as antifreeze, de-icing solutions, refrigerants, and brake fluids.
4. Toxicity of both agents is caused by the breakdown to toxic metabolites by alcohol dehydrogenase and aldehyde dehydrogenase.
    a. Methanol is converted to formaldehyde and then to formic acid, which results in an anion gap acidosis and ocular toxicity.
    b. Ethylene glycol is converted to glycoaldehyde and then to glycolic acid, followed by glyoxylic acid and, eventually, oxalic acid. Glycolic acid results in an anion gap acidosis and CNS toxicity. Oxalic acid results in CNS toxicity and renal toxicity because of the formation of calcium oxalate crystals.

B. Clinical Presentation
1. Common symptoms include inebriation, altered mental status, nausea, vomiting, hematemesis, nystagmus, and depressed reflexes. In rare cases of ethylene glycol toxicity, patients may present with tetany caused by hypocalcemia.
2. Early in therapy, an osmolar gap will be present, but this will diminish as the parent compound is metabolized.
    a. As the osmolar gap declines, the anion gap will rise, resulting in a significant metabolic acidosis.

b. Calculations:
   i. Osmolar gap:
   (sodium x 2) + (glucose/18) + (BUN /2.8)
   ii. Osmolar gap with ethanol ingestion:
   (sodium x 2) + (glucose/18) + (BUN/2.8) + (ethanol/4.6)
   iii. Osmolar gap with methanol ingestion:
   (sodium x 2) + (glucose/18) + (BUN/2.8) + (methanol/3.2)
   iv. Osmolar gap with ethylene glycol ingestion:
   (sodium x 2) + (glucose/18) + (BUN/2.8) + (ethylene glycol/6.2)
   v. Anion gap:
   $Na - (Cl + HCO_3)$

3. Methanol and ethylene glycol serum concentrations may be monitored to determine severity and to guide therapy in conjunction with an anion gap metabolic acidosis. Often, the ability to obtain these serum concentrations is not readily available and may take several hours to perform; therefore, therapy should not be delayed.

C. Treatment (Figure 2 on page 2-253)
1. Treatment is focused on blocking the toxic alcohol metabolism and allowing it to be excreted unchanged in the urine.
2. Gastric lavage may be considered within the first hour after ingestion (Crit Care Clin 2012;28:661-771). The efficacy of this other decontamination modality has not been established.
3. Fomepizole is the preferred antidote because of its predictable response, ease of dosing, and lack of contraindications to use.
   a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.
   b. After 48 hours, fomepizole induces its own metabolism, requiring dosage increases.
   c. Therapy is discontinued when methanol/ethylene glycol levels are less than 20 mg/dL. If the patient is still symptomatic with a normal pH, further workup is warranted, and hemodialysis may be indicated.
   d. Hemodialysis increases the clearance of fomepizole; therefore, doses must be administered every 4 hours during hemodialysis.
   e. Adverse effects may include headache, nausea, dizziness, abdominal pain, hypotension, and bradycardia.
   f. Oral administration has been shown to be effective and may be considered if intravenous access cannot be established (Clin Toxicol 2008;46:181-6).
4. Ethanol may be administered by diluting 95% alcohol for intravenous, oral, or per-tube administration.
   a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.
   b. Alcohol dehydrogenase has a higher affinity for ethanol.
   c. Intravenous alcohol preparations are no longer commercially available and must be compounded.
   d. Disadvantages include frequent monitoring and ICU admission in some institutions.
   e. Adverse effects include CNS depression, nausea, vomiting, abdominal pain, polyuria, and hypoglycemia (especially in children).
5. Hemodialysis should be considered if the clinical condition deteriorates, as evidenced by:
   a. Methanol/ethylene glycol level greater than 50 mg/dL
   b. Significant metabolic acidosis
   c. Development of acute renal failure or visual disturbances (methanol)
   d. Development of significant electrolyte abnormalities

6. Additional therapies
    a. Pyridoxine and thiamine
        i. Serve as cofactors in the metabolism of the toxic metabolites of ethylene glycol to non-toxic metabolites
        ii. Pyridoxine promotes the metabolism of glyoxylate to glycine
        iii. Thiamine promotes the metabolism of glycolic acid to a non-toxic metabolite; also used to prevent or treat Wernicke-Korsakoff syndrome
    b. Folinic acid
        i. Serves as a cofactor in the metabolism of the toxic metabolites of methanol to non-toxic metabolites. May reduce formate accumulation and reduce the development of metabolic acidosis ingestion (Crit Care Clin 2012;28:661-771).
        ii. Folic acid may be used if folinic acid is unavailable.
    c. Dextrose
        i. Recommended to check a point-of-care level before administration (Crit Care Clin 2012;28:661-771).
        ii. Administer 50 mL of 50% dextrose in water if 70 mg/dL or less or if testing is unavailable.
    d. Magnesium – Recommended to administer 1–2 g intravenously for hypomagnesemia
    e. Antiseizure medications
        i. Benzodiazepines are the preferred agent to treat seizures.
        ii. Other options include benzodiazepines, phenobarbital, propofol, and phenytoin.

D. Monitoring
    1. Patient should be closely monitored for resolution of clinical symptoms and return of baseline mental status.
    2. Monitor serum electrolytes and blood glucose periodically.
    3. Arterial blood gases with a goal of pH greater than 7.2
    4. Methanol/ethylene glycol levels with a goal of less than 20 mg/dL

Patient Cases

5. A 35-year-old man is admitted to the ED appearing inebriated. He is alert, but oriented only to person. His vital signs are BP 122/80 mm Hg, HR 82 beats/minute, and RR 25 breaths/minute. His serum ethanol concentration is 20 mg/dL, and his ethylene glycol concentration is 100 mg/dL. Which is the most appropriate therapy at this time?

    A. Fomepizole.
    B. Ethanol infusion.
    C. Thiamine.
    D. Activated charcoal.

6. A patient with methanol intoxication is initiated on fomepizole treatment, together with hemodialysis. After the 15-mg/kg bolus dose is given, which would be best for adjusting the maintenance fomepizole doses during dialysis?

    A. 10 mg/kg every 12 hours.
    B. 20 mg/kg every 12 hours.
    C. 10 mg/kg every 4 hours.
    D. 20 mg/kg every 4 hours.

VIII. ALCOHOL WITHDRAWAL

A. Background
   1. Alcohol withdrawal is a relatively common consequence of ICU admission.
   2. The strongest risk factor is a history of alcohol withdrawal.

B. Clinical Presentation
   1. Withdrawal symptoms typically occur within 8 hours after blood alcohol levels decrease, peak at 72 hours, and are markedly reduced at 5-7 days (N Engl J Med 2014;371:2109-13).
   2. Common symptoms include tremors, diaphoresis, nausea, vomiting, and abnormal vital signs, including hypertension, tachycardia, hyperthermia, and tachypnea (Am J Emerg Med 2013;31:734-42).
   3. Additional symptoms categorized as moderate to severe withdrawal include:
      a. Alcoholic hallucinations are typically auditory, visual, or tactile and may last up to 6 days.
      b. Alcohol withdrawal seizures (tonic-clonic) typically occur within 72 hours.
      c. Delirium tremens is a severe and potentially life-threatening symptom that may develop within 72 hours. Includes autonomic hyperactivity, confusion, delirium, psychosis, hallucinations, and seizures

C. Treatment
   1. The goal of therapy is to keep the patient safe, alleviate and prevent the progression of symptoms, and treat comorbidities (Crit Care Med 2010;38(suppl):S494-S501).
   2. Benzodiazepines are the primary agents used in treatment.
      a. Lorazepam and diazepam are preferred because of their more predictable effects; lorazepam is typically recommended because of its shorter half-life.
      b. Chlordiazepoxide is not recommended in the acute setting.
      c. Symptom-triggered therapy is preferred because it reduces benzodiazepine use, duration of mechanical ventilation, and duration of ICU stay.
      d. Scheduled treatment may be necessary if symptoms are severe or difficult to control.
   3. Ethanol – Use of ethanol to control alcohol withdrawal is controversial and is not routinely recommended.
   4. Phenobarbital
      a. Barbiturate with sedative, hypnotic, and antiseizure activity – Mechanism of action is by increasing the binding of γ-aminobutyric acid (GABA) to $GABA_A$ receptor and prolonging the chloride channel opening
      b. Potential second-line agent if benzodiazepines fail to adequately control symptoms
      c. May increase the efficacy of benzodiazepines when used in combination by increasing the binding to the $GABA_A$ receptor
   5. Clonidine: Mechanism of action is the α_2-receptor agonist that helps control the catecholamine surge associated with withdrawal that is responsible for elevations in BP and HR
   6. Baclofen: Mechanism of action is a selective GABA receptor agonist that reduces the signs and symptoms of alcohol withdrawal
   7. Propofol
      a. Mechanism of action is a general anesthetic through $GABA_A$ receptor agonism and NMDA (*N*-methyl-d-aspartate) receptor antagonism
      b. Useful for controlling delirium and preventing seizures
   8. Dexmedetomidine
      a. Mechanism of action is the α_2-receptor agonist, which may help control BP, HR, and delirium.
      b. May reduce overall benzodiazepine requirements
   9. Supportive care: Alcohol-dependent patients are often nutritionally deficient and at risk of Wernicke encephalopathy and hypomagnesemia.

D. Monitoring
   1. Clinical Institute Withdrawal Assessment for Alcohol Scale (revised version) (CIWA-Ar) to determine the severity of symptoms and treatment
   2. Vital signs every 2–4 hours
   3. Electroencephalogram for sustained seizure-related activity

Table 6. Agents for Treatment of Alcohol Withdrawal

Agent	Suggested Starting Dose	Suggested Interval/Infusion Dose Range
Diazepam	5–20 mg	Every 6–8 hr
Lorazepam	2–4 mg	Every 4–6 hr
Phenobarbital	65–130 mg	Every 15–20 min until symptoms are controlled
Clonidine	0.1–0.3 mg	Every 8–12 hr
Baclofen	10 mg	Every 8–12 hr
Propofol	10–20 mcg/kg/min	20–70 mcg/kg/min
Dexmedetomidine	0.1–0.3 mg/kg/hr	0.5–1 mg/kg/hr
Multivitamin	10 mL IV or 1 tablet	Once daily for 2–3 days
Thiamine	100–500 mg	Once daily for 2–3 days
Magnesium	1–2 g	Replacement based on serum concentrations

IV = intravenously.

IX. B-BLOCKERS AND CALCIUM CHANNEL BLOCKERS

A. Background
   1. Cardiovascular agents accounted for more than 100,000 toxic exposures in 2012 and were the second leading cause of death.
   2. Two of the most common cardiovascular agents involved in toxic exposures are β-blockers (24,465 cases and 13 deaths in 2012) and calcium channel blockers (11,910 cases and 24 deaths in 2012).

B. Clinical Presentation
   1. β-Blocker overdoses are characterized by hypotension, bradycardia, and prolonged atrioventricular conduction.
   2. Calcium channel blocker overdoses are characterized by hypotension, prolonged atrioventricular conduction, bradycardia, lethargy, hyperglycemia, and depressed consciousness.

C. Treatment
   1. Consider gastric lavage or activated charcoal if patients present within 1–2 hours of overdose. Whole bowel irrigation is recommended for delayed presentation or for sustained- or extended-release formulations.
   2. Maintenance of hemodynamic stability
      a. Goal of therapy is a mean arterial pressure greater than 65 mm Hg or systolic blood pressure greater than 90 mm Hg.
      b. Administer isotonic fluids (0.9% sodium chloride or lactated Ringer solution) at 20–30 mL/kg or colloidal solutions (e.g., albumin 5% 250 mL).

c. Administer intravenous calcium chloride or calcium gluconate
   i. Calcium chloride 1–2 g (central line is preferred; however, bolus doses may be administered in a peripheral line if needed)
   ii. Calcium gluconate 3–6 g. Repeat dose may be given every 15–30 minutes; may also consider continuous infusion at 0.3–0.7 mEq/kg/hour
d. Treat symptomatic bradycardia:
   i. Atropine 0.5 mg intravenously; if no response, proceed to the following options
   ii. Glucagon 5–10 mg (50–150 mcg/kg) intravenous push over 1 minute. If HR and symptom response is achieved from the bolus, may consider a continuous intravenous infusion initiated at the same rate as the bolus dose that achieved response
      (a) Stimulates adenylate cyclase, which increases intracellular cAMP (cyclic adenosine monophosphate), leading to increased inotropy, chronotropy, and cardiac conduction
      (b) Adverse effects include nausea, vomiting, and hyperglycemia.
      (c) Use with caution with decreased mental status because of possible aspiration or airway obstruction.
   iii. Norepinephrine continuous infusion initiated at 1–3 mcg/minute and titrated to response
   iv. Dopamine continuous infusion at 5–10 mcg/kg/minute and titrated to response (maximum of 20 mcg/kg/minute)
   v. Phenylephrine continuous infusion at 20–40 mcg/minute and titrated to response
   vi. Epinephrine continuous infusion at 1 mcg/minute and titrated to response
   vii. Transcutaneous or transvenous pacing or intra-aortic balloon pumps
e. Hyperinsulinemic euglycemic therapy (HIET)
   i. Mechanism of action:
      (a) Insulin increases the plasma levels of ionized calcium, improves the hyperglycemic acidotic state, improves the myocardial use of carbohydrates, and exerts an independent inotropic effect (Am J Crit Care Med 2007;16:498-503).
      (b) Dextrose prevents the development of hypoglycemia after insulin administration.
      (c) Potassium prevents the development of hypokalemia after insulin administration.
      (d) Onset of action is as soon as 5 minutes; however, it may take up to 30 minutes for full effects to be seen.
   ii. Dosing (Am J Health Syst Pharm 2006;63:1828-35; Clin Toxicol 2011;49:277-83):
      (a) If baseline glucose is less than 200 mg/dL, administer 50 mL of 50% dextrose in water – May consider an infusion of 5%–10% dextrose to maintain a serum glucose concentration greater than 100 mg/dL
      (b) If baseline potassium is less than 2.5 mEq/L, administer 40 mEq of potassium chloride intravenously – Hypokalemia is uncommon; however, it is recommended to replace potassium if serum levels fall below 2.8–3 mEq/L during treatment.
      (c) Bolus 1 unit/kg of regular insulin intravenously, followed by a continuous intravenous infusion at 0.5–1 unit/kg/hour; increase rate every 10 minutes to a maximum of 10 units/kg/hour
   iii. Adverse effects: Hypoglycemia, hypomagnesemia, and hypokalemia
   iv. Monitoring:
      (a) Vital signs every 15–60 minutes with a goal mean arterial pressure greater than 65 mm Hg and an HR greater than 50 beats/minute
      (b) Serum glucose every 15 minutes; then every 30–60 minutes once stable to target serum levels greater than 100 mg/dL
      (c) Serum potassium every hour during the insulin infusion; then every 6 hours to target levels of at least 3.5–4 mEq/L

f. Intravenous lipid emulsion
   i. Mechanism of action is not well known; however, it is thought to be owing to a combination of binding lipid-soluble agents and the provision of free fatty acids that increase cardiac energy and intracellular calcium.
   ii. Improves HR and reduces mortality as an individual treatment or in combination with other therapies
   iii. Dosing: Administer an intravenous bolus of 1.5 mL/kg (usually 100 mL) of 20% lipid emulsion (Intralipid), followed by an intravenous infusion of 0.25–0.5 mL/kg/minute over 60 minutes.
   iv. Adverse effects may include pancreatitis, interference with laboratory results, and fat embolism.
   v. Drug interactions are not well known.

Table 7. Treatment Options for β-Blockers and Calcium Channel Blocker Toxicity

Indication	Treatment	Dose	Comments
↓ Cardiac contractility	HIET	1 unit/kg of regular insulin + 0.5-g/kg dextrose IV bolus; then 0.5–1 unit/kg/hr of regular insulin + 0.5 g/kg/hr dextrose continuous IV infusion	1. Initiate HIET simultaneously with calcium, glucagon, or norepinephrine 2. If blood glucose is > 400 mg/dL (22 mmol/L), omit dextrose bolus 3. Titrate dextrose infusion to maintain blood glucose 100–250 mg/dL (5.5–14 mmol/L) 4. Monitor blood glucose every 20–30 min until stable; then every 1–2 hr 5. K^+ replacement not needed unless < 2.5 mEq/L
	10% calcium gluconate	0.6-mL/kg IV bolus; then 0.6- to 1.5-mL/kg/hr IV continuous infusion	1. Calcium chloride can be substituted but requires central IV access 2. Used primarily for CCB toxicity but can also be considered for BB toxicity
	Glucagon	50- to 150-mcg/kg (3–10 mg) IV bolus; then 50- to 150-mcg/kg/hr continuous IV infusion	Used primarily for BB toxicity but can also be used for CCB toxicity
	Norepinephrine	Titrate to age-appropriate SBP	Administered by central IV access
↓ Peripheral resistance	Norepinephrine	Titrate to age-appropriate SBP	Administered by central IV access
HR < 50 beats/min	Glucagon	50- to 150-mcg/kg (3–10 mg) IV bolus; then 50- to 150-mcg/kg/hour continuous IV infusion	Used primarily for BB toxicity but can also be used for CCB toxicity
	Norepinephrine	Titrate to age-appropriate SBP	Administered by central IV access
	Cardiac pacing		Target HR is 60 beats/minute
QRS > 120 milliseconds	Sodium bicarbonate	1- to 2-mEq/kg IV bolus	Can repeat for recurrent QRS widening

BB = β-blocker; CCB = calcium channel blocker; HIET = hyperinsulinemic euglycemic therapy; IV = intravenous; SBP = systolic blood pressure.

Reprinted with permission from Elsevier from: Kerns W II. Management of beta-adrenergic blocker and calcium channel antagonist toxicity. Emerg Med Clin North Am 2007;25:309-31.

Patient Case

Questions 7 and 8 pertain to the following case.
A 52-year-old man is admitted to the ED with concerns about dizziness and headache. His vital signs are as follows: temperature 98.9°F, BP 87/50 mm Hg, and HR 58 beats/minute. His wife reports that he has a history of hypertension and that he was recently given a diagnosis of being in the early stages of Alzheimer disease. She has brought his medications with her; the 1-month supply was refilled 2 days ago: a bottle of diltiazem CD 120 mg/day (7 tablets remaining) and a bottle of donepezil 5 mg once daily (28 tablets remaining).

7. Which decontamination strategy would provide the most benefit?
   A. Charcoal 25 g every hour until his BP improves.
   B. Ipecac 30 mL followed by 240 mL of water.
   C. Polyethylene glycol-electrolyte solution 1500 mL/hour until the rectal effluent is clear.
   D. Magnesium citrate 240 mL, followed by 240 mL of water.

8. Which antidote would be best to administer first?
   A. Calcium chloride 1 g intravenously over 1 minute.
   B. Glucagon 5 mg intravenously over 1 minute.
   C. Atropine 1 mg intravenously over 1 minute.
   D. Epinephrine 1 mg intravenously over 1 minute.

X. DIGOXIN

A. Background
   1. The cardiac glycosides accounted for 2525 toxic exposures and 18 deaths in 2012.
   2. Mechanism of action is inhibition of the sodium-potassium adenosine triphosphatase pump and suppression of the atrioventricular node.
   3. Because of its narrow therapeutic index, toxicity has been reported in as many as 35% of patients receiving digoxin (Postgrad Med 1993;69:337-9).
      a. The normal therapeutic range is 0.8–2.1 ng/mL (may vary by laboratory and/or institution).
      b. Toxicity may be related to an acute ingestion or may be an issue with chronic dosing or renal dysfunction.
   4. Risk factors for digoxin toxicity include renal failure, advanced age, ischemic heart disease, left ventricular dysfunction, electrolyte imbalances (hypokalemia, hypomagnesemia, hypercalcemia), and hypothyroidism (Postgrad Med 1993;69:337-9).

B. Clinical Presentation
   1. Cardiac effects associated with digoxin toxicity include heart block, tachyarrhythmias, and bradyarrhythmias. More specific examples include fascicular tachycardia, ventricular bigeminy, and ventricular tachycardia (Am J Cardiol 1992;69:108G-119G).
   2. Non-cardiac effects associated with digoxin toxicity include nausea and vomiting, lethargy, headaches, confusion, and visual disturbances.

C. Treatment
   1. Consider decontamination strategies if patients present within 2 hours of overdose.
      a. Multidose activated charcoal is beneficial because of the enterohepatic recirculation of digoxin. Load 50–100 g; then either 10 g/hour, 10–20 g every 2 hours, or 40 g every 4 hours (Postgrad Med 1993;69:337-9).
      b. Colestipol or cholestyramine is an effective drug-binding alternative to charcoal, but it may not be useful in acute toxicity (Am J Cardiol 1992;69:108G-119G).
      c. Hemodialysis is not considered effective.
   2. Correct serum electrolyte abnormalities.
      a. Correct serum potassium concentration to a goal of 3.5–4 mEq/L.
      b. Correct serum magnesium concentration to a goal of 1.5–2.2 mg/dL.
      c. Correct serum calcium concentration to a goal of 8.5–10.5 mg/dL.
   3. Treat symptomatic bradyarrhythmias with atropine 0.5 mg or transcutaneous pacing.
   4. Digoxin immune antigen-binding fragments (Fab)
      a. Antibodies that bind to digoxin molecules that are then renally excreted
      b. Indications for use in acute intoxications (Crit Care Clin 2012;28:527-35):
         i. Life-threatening arrhythmias: Asystole, ventricular fibrillation or tachycardia, complete heart block, symptomatic bradycardia
         ii. Evidence of end-organ damage (e.g., renal failure, altered mental status)
         iii. Hyperkalemia (greater than 5–5.5 mEq/L)
      c. Products:
         i. Digibind: 38 mg per vial
         ii. DigiFab: 40 mg per vial
      d. Dosing:
         i. If amount is unknown: 10–20 vials for acute toxicity or 6 vials for chronic toxicity
         ii. If the amount of digoxin ingested is known:
             dose (vials) = total body load (0.8 x mg of digoxin ingested)/0.5
         iii. If digoxin level is known:
             dose (vials) = [serum digoxin level (ng/mL) x weight (kg)]/100
      e. Adverse effects include heart failure exacerbation, atrial fibrillation, orthostatic hypotension, hypokalemia, and phlebitis.

D. Monitoring
   1. Monitor vital signs every 30–60 minutes initially. Goal HR of greater than 60 beats/minute and asymptomatic
   2. Monitor serum potassium levels hourly for at least the first 6 hours.
   3. Additional serum digoxin levels are not recommended after the administration of Fab. A rapid rise in serum concentrations is expected because of the mechanism of the Fab-digoxin complex. Repeat serum digoxin concentrations may be checked 24 hours after the initial treatment if Fab is not administered.

XI. ANTIDEPRESSANTS

A. Background
   1. Antidepressants accounted for more than 106,000 toxic exposures and 38 fatalities in 2012.
   2. The most common agents involved in toxic exposures were the selective serotonin reuptake inhibitors (SSRIs) and the TCAs
   3. SSRIs block the reuptake of serotonin at the presynaptic neuron.

4. Patients with SSRI overdoses are often asymptomatic with self-limiting effects (Emerg Med Clin North Am 2007;25:477-97). The most common adverse effects may include drowsiness, tremor, altered mental status, nausea and vomiting, tachycardia, hypotension, seizures, and QRS- or QT-interval prolongation.
5. TCAs exert many effects, including blocking the reuptake of norepinephrine and serotonin at the presynaptic neuron, blocking muscarinic cholinergic receptors, blocking antihistamine effect, and, to a lesser degree, blocking α-adrenergic receptors.
6. Individuals with TCA overdoses may present with the following adverse effects (Emerg Med Clin North Am 1994;12:533-47):
    a. Cardiovascular: Hypo- or hypertension, tachy- or bradycardia, increased QRS or QT interval, atrioventricular-conduction block, complete heart block
    b. Respiratory: Hypoventilation, crackles, hypoxia
    c. Neurologic: Delirium, lethargy, seizures, coma
    d. Other: Hyperthermia, dry mucous membranes, urinary retention, blurred vision

B. Treatment
1. There are no specific antidotes for antidepressant overdoses; general supportive care is recommended, with a focus on airway, breathing, and circulation.
2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure (Emerg Med Clin North Am 2000;18:637-54).
3. Administer crystalloid or colloids fluids to maintain BP and HR, with the goal of a systolic blood pressure greater than 90 mm Hg and an HR greater than 60 beats/minute.
    a. Norepinephrine, dopamine, or epinephrine may be used if fluid resuscitation alone is unsuccessful.
    b. Dopamine may not be an effective agent because endogenous norepinephrine stores are depleted in an overdose.
4. Sodium channel blockade
    a. Alkalinization of blood to a pH of 7.45–7.55 is recommended for the TCAs. Requires frequent monitoring of arterial pH (varies by effect, but as often as every 15–30 minutes)
    b. Administer sodium bicarbonate.
        i. Recommended bolus dose of 1 mEq/kg (minimum 50 mEq)
        ii. May repeat bolus every 15 minutes until ECG stabilized or arterial pH goal achieved
        iii. May consider a continuous infusion of hypertonic saline for patients refractory to sodium bicarbonate
    c. Proposed indications for sodium bicarbonate include (Chest 2008;133:1006-13):
        i. QRS greater than 100–120 milliseconds
        ii. Wide complex tachycardia
        iii. Cardiac arrest
        iv. Right bundle-branch block
        v. Refractory hypotension
5. Replace serum electrolytes if QT prolongation
6. Seizures should be managed with benzodiazepines. Phenobarbital may be considered if the patient is refractory to benzodiazepines and has a stable BP.

C. Monitoring – Patients should be monitored for clinical improvement for at least 6–8 hours and for a minimum of 24 hours for more severe adverse effects or with citalopram or escitalopram (because of the longer half-lives of these agents).
1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB and troponins, BP, HR
2. Monitor for signs and symptoms of respiratory depression with RR and pulse oximetry.

D. Serotonin Syndrome
   1. Excessive serotonin concentrations lead to overstimulation of serotonin-1A and serotonin-2A receptors in the central and peripheral nervous systems (Emerg Med Clin North Am 2007;25:477-97).
   2. Adverse effects include altered mental status, autonomic instability (hyperthermia, tachycardia, hypertension, arrhythmias), and neuromuscular changes (hyperreflexia, increased rigidity).
   3. Diagnosis is made according to clinical findings; many clinicians support the use of the Hunter Serotonin Toxicity Criteria (QJM 2003;96:635-42). By this method, patients have likely serotonin toxicity if they have taken a serotonergic agent and one of the following criteria are present:
      a. Spontaneous clonus
      b. Inducible clonus PLUS agitation or diaphoresis
      c. Ocular clonus PLUS agitation or diaphoresis
      d. Tremor PLUS hyperreflexia
      e. Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus
   4. Treatment should focus on supportive care; symptoms typically resolve within 24–48 hours.
      a. Discontinue the offending agent.
      b. Benzodiazepines should be administered as first line for agitation and muscle rigidity.
      c. Cyproheptadine 8–12 mg by mouth should be administered for agitation and muscle rigidity as an adjunct to benzodiazepines.

Patient Case

9. A 21-year-old man is admitted to the ED after taking 30 citalopram 20-mg tablets about 2 hours ago. His vital signs are as follows: BP 125/85 mm Hg, HR 77 beats/minute, RR 15 breaths/minute, and temperature 98.7°F. Which is the best intervention for this patient?

   A. Administer lorazepam 2 mg intravenously to prevent seizure activity.
   B. Closely monitor the patient for the development of any toxic effects.
   C. Recommend a cooling blanket to prevent serotonin syndrome–related hyperthermia.
   D. Order a 12-lead ECG to monitor for cardiac conduction disturbances.

XII. ATYPICAL ANTIPSYCHOTICS

A. Background
   1. The atypical antipsychotic agents accounted for more than 40,000 toxic exposures and 15 fatalities in 2012.
   2. These agents are classified primarily as having D_2-dopaminergic receptor and serotonin-2A receptor antagonism. Additional effects include antagonism of the α_1- and histamine-1 receptors.
   3. Adverse effects associated with the atypical antipsychotics are typically self-limiting.
      a. More severe adverse effects may include CNS depression, tachycardia, hypotension, and QT prolongation.
      b. Less severe adverse effects include dizziness, drowsiness, miosis, blurred vision, urinary retention, and CNS excitation.

B. Treatment
   1. There are no specific antidotes for the atypical antipsychotics; general supportive care is recommended, focusing on airway, breathing, and circulation.

2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure if no contraindications exist (J Emerg Med 2012;43:906-13).
3. Administer crystalloid to maintain BP with a goal of a systolic blood pressure greater than 90 mm Hg and an HR greater than 60 beats/minute.
    a. Consider vasopressors if fluid resuscitation is inadequate.
    b. Because of the α-receptor antagonist activity of these agents, norepinephrine or phenylephrine is preferred if vasopressors are needed.
4. Administer sodium bicarbonate if QRS prolongation (quetiapine overdose only)
5. Replace serum electrolytes; especially magnesium and potassium, if QT prolongation. Magnesium replacement is recommended for membrane stabilization in patients with a QTc greater than 500 milliseconds and normal serum magnesium levels.
6. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
7. Lipid emulsion therapy may be effective because of the high lipophilicity of these agents and may be considered if more traditional treatment means are unsuccessful (J Emerg Med 2012;43:906-13). Administer an intravenous bolus dose of 1.5 mL/kg of 20% intralipid over 2–3 minutes, followed by a continuous intravenous infusion of 15 mL/kg over 60 minutes, if necessary.

C. Monitoring: Patients should be monitored for clinical improvement for at least 8–12 hours.
1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
2. Monitor for respiratory depression with RR and pulse oximetry.
3. Monitor renal function with urine output, BUN, and SCr.

XIII. LITHIUM

A. Background
1. Lithium was associated with around 7000 toxic exposures and two deaths in 2012.
2. Mechanism of action is through an influence on serotonin and norepinephrine reuptake, inhibition of the phosphatidylinositol cycle, and inhibition of the post-synaptic D_2 receptor.
3. Adverse effects associated with lithium include:
    a. Acute overdose:
        i. GI: Nausea, vomiting, diarrhea
        ii. CNS: Confusion, tremor, myoclonus, seizures, coma
        iii. Cardiovascular: T-wave inversion, ventricular arrhythmias
        iv. Acute renal failure
    b. Acute or chronic overdose:
        i. Endocrine: Hypothyroidism, myxedema coma
        ii. Nephrogenic diabetes insipidus

B. Treatment
1. There are no specific antidotes for lithium; general supportive care is recommended, focusing on airway, breathing, and circulation.
2. Gastric decontamination is not typically recommended. Activated charcoal is not effective for lithium overdoses; whole bowel irrigation may be useful for sustained-release formulations.
3. Administer crystalloid to maintain BP, with a goal of systolic blood pressure greater than 90 mm Hg.
    a. Consider vasopressors if fluid resuscitation is not adequate.
4. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation

5. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
6. Lithium overdoses are primarily managed with hemodialysis or continuous replacement therapy.
    a. Saline infusions may be administered if there are no contraindications to fluid therapy (goal is a serum sodium level of 140–145 mEq/L). Lithium clearance is reduced in hyponatremia.
    b. Intermittent hemodialysis may require several sessions to fully remove lithium levels because of the rebound of lithium levels that occurs after dialysis sessions.
    c. Suggested indications for the use of hemodialysis include (Chest 2005;133:1006-13):
        i. Severe toxicity (severe altered mental status or seizures)
        ii. Renal failure (will be unable to eliminate lithium)
        iii. Lithium concentrations greater than 2.5 mmol/L in chronic exposures
        iv. Lithium concentrations greater than 4 mmol/L in acute exposures

C. Monitoring – Patients should be monitored for clinical improvement for at least 8–12 hours.
1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
2. Monitor for respiratory depression with RR and pulse oximetry.
3. Monitor renal function with urine output, BUN, and SCr.
4. Monitor baseline lithium levels and then every 6 hours after until levels have decreased to less than 1.5 mmol/L (normal 0.6–1.2 mmol/L).

Patient Case

10. A 24-year-old woman is brought to the ED by her roommate. She has been in a normal state of health, but the roommate is concerned because she "seems really out of it." According to the roommate, the patient had an appointment with the physician today, and she had been given a prescription to refill olanzapine 5 mg by mouth daily, but the bottle is empty. On physical examination, she is alert and oriented x 3, but she dozes off several times. Her vital signs are stable, and a 12-lead ECG shows sinus tachycardia. Which intervention is most appropriate for this patient?

    A. Lactated Ringer solution 500 mL.
    B. 8.4% sodium bicarbonate 50 mL.
    C. Lorazepam 2 mg.
    D. Clinical monitoring for 6 hours.

XIV. ORAL HYPOGLYCEMICS

A. Background
1. Oral hypoglycemics accounted for around 14,000 toxic exposures and 10 fatalities in 2012.
2. The most common oral hypoglycemic involved in toxic exposures is metformin, followed by the sulfonylureas and the thiazolidinediones.
3. The most serious adverse effects were reported with the sulfonylureas; however, most fatalities were associated with metformin.

B. Clinical Presentation
1. Clinical signs and symptoms include hypoglycemia (not with metformin), nausea, vomiting, dizziness, tachycardia, and diaphoresis.
2. More severe adverse effects include seizures, palpitations, tachyarrhythmias, electrolyte abnormalities, and metabolic (lactic) acidosis.

C. Treatment (Figure 3 on page 254)
   1. Stabilization of the airway, breathing, and circulation
   2. Identifying the causative agent is important because specific treatment will vary by the agent involved.
   3. Consider gastric decontamination with single-dose activated charcoal if patients present within 1 hour of overdose.
   4. Observe clinically asymptomatic patients for a minimum of 8 hours (Am J Health Syst Pharm 2006;63:929-38).
   5. For symptomatic patients or blood glucose less than 60 mg/dL, treat with glucose:
      a. Conscious patients: Administer 8 oz of an oral carbohydrate (such as juice, non-diet sodas, or milk) or oral glucose tablets or gels.
      b. Unconscious patients: Administer intravenous dextrose, 0.5–1 g/kg
      c. Repeat doses may be required; consider a continuous infusion of dextrose if needed. Glucose levels should be monitored often (every 15–60 minutes) until stable.
      d. Use caution to avoid overcorrection of serum glucose.
   6. Octreotide
      a. Mechanism of action is a somatostatin analog that inhibits the secretion of insulin.
      b. Primarily studied in sulfonylurea overdose, but considered a treatment option for all oral hypoglycemic toxic exposures
      c. Adverse effects include headache, dizziness, nausea, abdominal pain, and sinus bradycardia.
   7. Glucagon
      a. Mechanism of action is stimulation of gluconeogenesis.
      b. May trigger additional insulin secretion, leading to a secondary hypoglycemia
      c. May provide a benefit in prehospital settings when oral or intravenous options are not available, but is not routinely recommended
      d. Not recommended in pediatric patients, in malnourished patients, or for sulfonylurea toxic exposures
   8. Sodium bicarbonate
      a. Indicated for severe metformin-associated lactic acidosis
      b. 1–2 mEq/kg or 50–200 mEq of 8.4% sodium bicarbonate intravenously
   9. Hemodialysis or continuous renal replacement therapy may be necessary to enhance metformin clearance in severe cases.

D. Monitoring
   1. Regular assessment of vital signs and mental status (Emerg Med J 2006;23:565-7)
   2. Measure capillary blood glucose at a minimum of every hour for 24 hours with a goal of greater than 70 mg/dL.
   3. Measure BP hourly, especially after octreotide administration.

Patient Case

11. As the pharmacist in the ICU satellite, you receive a call from a distressed nurse about a patient in the cardiac step-down unit. The patient was found unconscious, and on investigation, it was discovered that he had received a glyburide 20-mg tablet 1 hour earlier that was meant for another patient. The patient has stable vital signs, but his point-of-care blood glucose level is 37 mg/dL. Which intervention is most appropriate at this time?

    A. 8 oz of milk by mouth.
    B. 50 mL of 50% dextrose in water intravenously.
    C. Octreotide 100 mcg subcutaneously.
    D. Glucagon 1 mg intramuscularly.

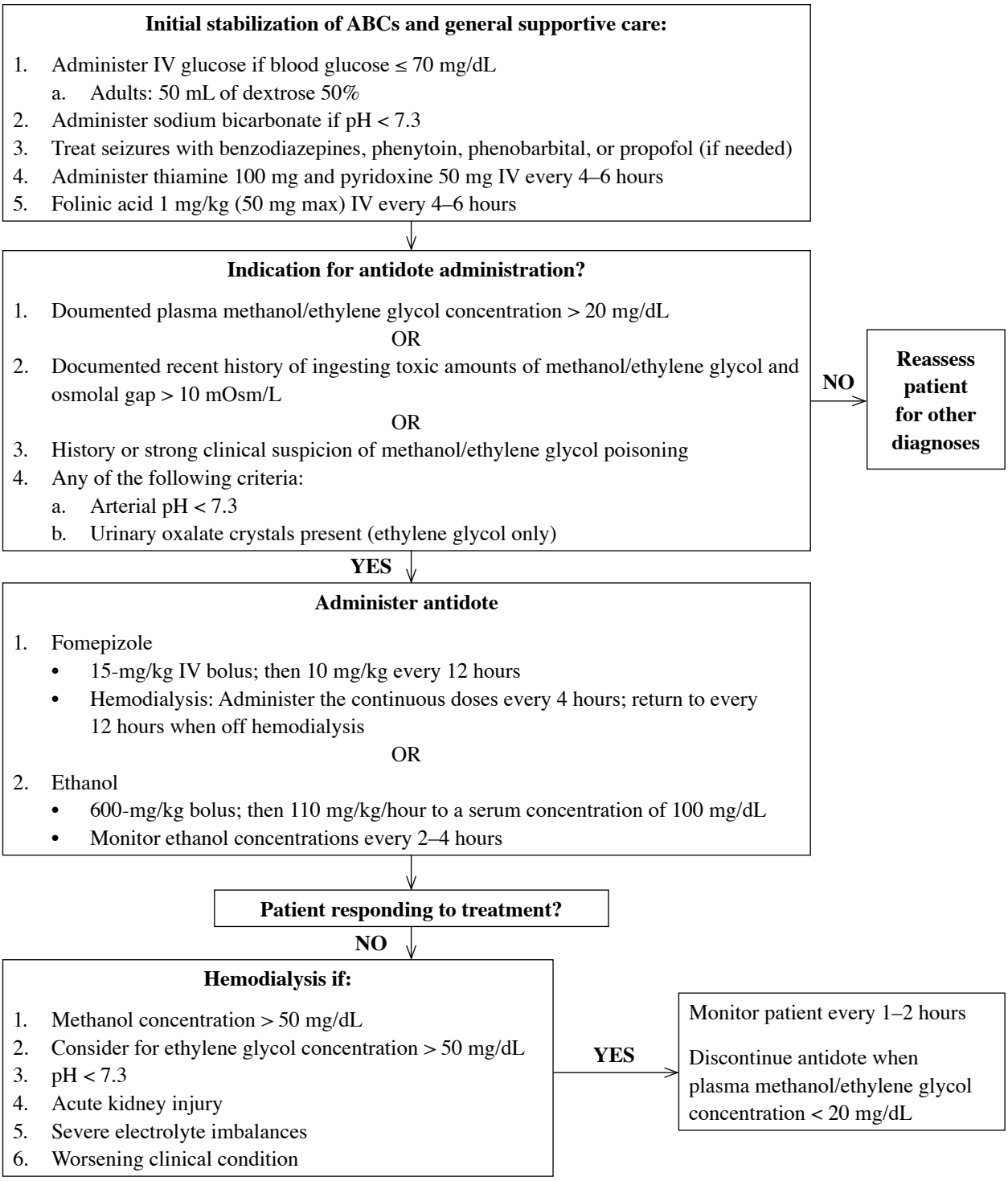

Figure 2. Treatment algorithm for the management of an acute alcohol poisoning.

ABC = airway, breathing, and circulation; IV = intravenous.

Information from: Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol 2002;40:415-46; and Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. J Toxicol Clin Toxicol 1999;37:537-60.

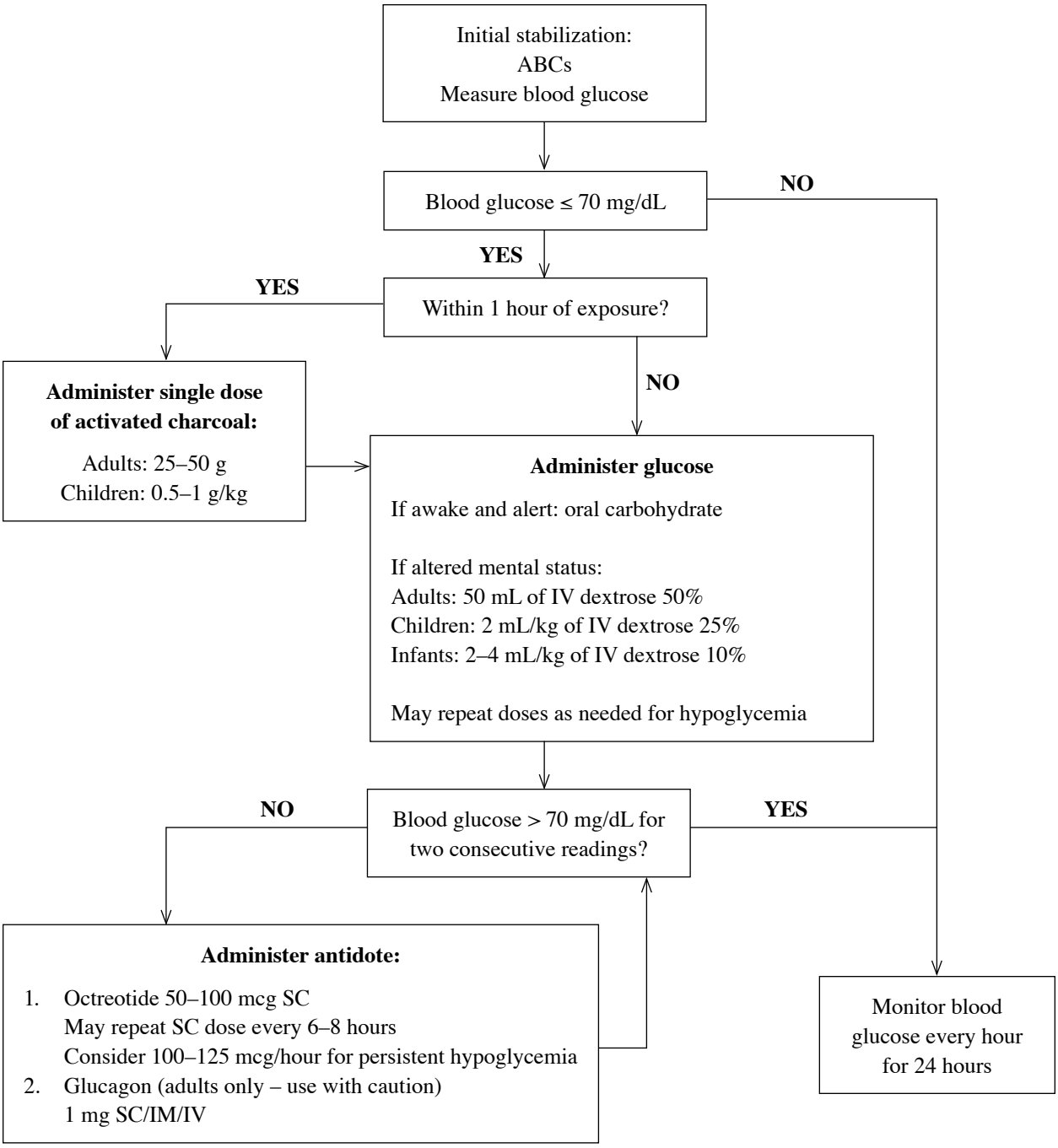

Figure 3. Treatment algorithm for the management of an oral hypoglycemic agent poisoning.

ABC = airway, breathing, and circulation; IM = intramuscularly; IV = intravenous(ly); SC = subcutaneously.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

The most important first step in all drug overdose cases is to try to stabilize the patient's airway, breathing, and circulation. This may involve the use of supplemental oxygen or advanced airway management, establishment of intravenous access, and administration of intravenous fluids. Once the patient is stable, the process of identifying the suspected toxin can begin. This may include thoroughly examining the patient, speaking with family or first responders, and communicating with the patient's physicians and pharmacies. Blood and urine samples may be sent for quantitative or qualitative toxicologic assays. A coma cocktail may provide some benefit, but a clear cause should be established before considering its use.

2. Answer: B

The patient is experiencing symptoms of an acute acetaminophen overdose, and stabilizing the patient, together with providing good supportive care, is indicated until a determination for additional therapy can be made. Typical decontamination strategies may provide benefit, but they have not been definitively shown to improve patient outcome. Magnesium citrate (and cathartics as a whole) is not considered an effective decontamination strategy. Gastric lavage is of most benefit within the first 60 minutes of exposure, and the potential adverse effects outweigh any potential benefit. Similarly, single-dose charcoal requires more rapid administration.

3. Answer: C

The patient is considered at high risk of developing hepatic damage from acetaminophen and requires therapy with intravenous acetylcysteine. The dose of intravenous acetylcysteine is as follows (doses are calculated using actual body weight): loading dose: 150 mg/kg in 200 mL of 5% dextrose in water over 60 minutes; maintenance dose: 50 mg/kg in 500 mL of 5% dextrose in water over 4 hours, followed by 100 mg/kg in 1000 mL of 5% dextrose in water over 16 hours. Oral dosing of acetylcysteine is not a viable option because of the patient's severe nausea and vomiting. Compounding of the intravenous formulation is also not recommended when the intravenous formulation is available.

4. Answer: C

This patient has an acute salicylate overdose. Although his serum salicylate concentrations are in the therapeutic range, he has symptoms consistent with salicylate toxicity, as evidenced by his nausea, tachycardia, and respiratory alkalosis. He is currently stable, but his serum salicylate concentrations may continue to rise; therefore, enhanced elimination with serum bicarbonate is the best option. His vital signs, which are stable, should be monitored for changes; however, although he is not experiencing signs of significant dehydration, he would benefit from the fluid administration of sodium bicarbonate. Sodium chloride would be more beneficial if his vital signs were more unstable. His RR, which is elevated, should be monitored; however, he is alert and able to communicate and therefore does not need intubation at this time. He is also not indicated for hemodialysis because of his moderate symptoms, but this could be considered if his condition deteriorates.

5. Answer: A

The most appropriate therapy for an ethylene glycol intoxication is fomepizole. An ethanol infusion is a possible treatment option, but it is not preferred because of the difficulties in dosing and adverse effects. Activated charcoal is not an option for gastric decontamination because it is not effective for alcohols. Thiamine is a cofactor in the metabolism of ethylene glycol, but it would not be preferred to administer thiamine before fomepizole.

6. Answer: C

After the initial bolus of fomepizole, 10 mg/kg should be administered every 12 hours. Because of the increased clearance of fomepizole during hemodialysis, the frequency is changed to every 4 hours during dialysis. When dialysis is completed, the dose returns to 10 mg/kg administered every 12 hours. There is no indication for a dose increase.

7. Answer: C

The best treatment option for this patient is whole bowel irrigation because of the extended-release formulation of diltiazem. Ipecac is not recommended because it may impede treatment with more effective treatment options and because it is no longer manufactured in the United

States. A cathartic would not be useful in this situation; guidelines recommend its use only in combination with other decontamination strategies, not as a single agent. Activated charcoal may provide some benefit, but similar to ipecac, the time interval is not known, and diltiazem does not undergo enterohepatic recirculation.

8. Answer: A

There are several potential antidotes for a calcium channel blocker overdose. Calcium is the most effective, and it should be given by bolus, followed by continuous infusion if needed. Glucagon is not an effective antidote and is therefore not an option for this patient. Atropine is effective for symptomatic bradycardia caused by the calcium channel blocker, but the dose should be 0.5 mg. Epinephrine is an alternative to glucagon, but it requires administration by continuous infusion.

9. Answer: D

Most of the SSRIs are relatively safe, and many patients will present as asymptomatic after an overdose. However, there is a potential for patient's developing serious adverse effects such as serotonin syndrome, seizures, and cardiac toxicity. Although this patient is stable and has no specific concerns, it is recommended to check a 12-lead ECG to measure for QRS- or QT-interval prolongation and treat with sodium bicarbonate, if necessary. A benzodiazepine should be administered if muscle rigidity develops, but it should not be used as a prophylactic measure. It is recommended that the patient be observed for at least 6–8 hours. Measures should be performed to reduce hyperthermia if a serotonergic syndrome develops, but this should be treated with measures to reduce muscle activity (i.e., sedation or chemical paralysis), not by applying measures to enhance surface cooling.

10. Answer: D

Although the patient appears to have taken an overdose of olanzapine, she is experiencing only mild symptoms. The best intervention would be to monitor her for 6 hours for the progression of her symptoms or development of additional complications. Intravenous fluids would be appropriate if the patient has dehydration or hypotension. Sodium bicarbonate is indicated for QRS prolongation and is not warranted at this time. Olanzapine does not cause seizures; therefore, lorazepam would not be indicated.

11. Answer: B

The most appropriate intervention at this time is to give the patient intravenous dextrose. Oral glucose is a viable option, but it cannot be administered to an unconscious patient without oral access. Octreotide should be reserved for use if the administration of a glucose solution fails to raise the blood glucose above 70 mg/dL for two consecutive readings. Glucagon is a potential option for treatment, but because the patient has intravenous access, the intramuscular route would not be preferred.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The best option for this patient right now is to administer octreotide 50–100 mcg subcutaneously. The patient has not responded to two doses of intravenous dextrose, as evidenced by point-of-care glucose concentrations less than 70 mg/dL; therefore, additional doses of dextrose are not indicated. Although glucagon is also a potential option, it is not recommended for sulfonylurea exposures. Sodium bicarbonate is indicated only for metformin-induced metabolic acidosis.

2. Answer: A

Any of the options listed in this question are possible treatments for a patient with a β-blocker overdose who is not responding to the administration of intravenous fluids and calcium. The optimal choice ultimately involves efficacy and appropriate dosing. Glucagon is an option, and it should be dosed at 5–10 mg initially. Atropine is an option for the patient's bradycardia, but the initial recommended dose is 0.5 mg. Dopamine is an option for the treatment of hypotension and bradycardia, but the correct dose would be the initiation of an infusion at 5–10 mcg/kg/minute titrated to effect. Hyperinsulinemic euglycemic therapy may be preferred in this setting; however, the correct bolus dose is 1 unit/kg.

3. Answer: B

Given the patient's presentation and the common toxidromes, the most likely scenario is a cholinergic agent. The patient is experiencing bradycardia with a normal BP and RR, has a decrease in mental status, and is experiencing nausea. Although not an absolute, anticholinergics and sympathomimetics are more commonly associated with tachycardia. Similarly, opioids are typically associated with a decrease in respirations.

4. Answer: A

The patient is experiencing QT prolongation after an atypical antipsychotic overdose. It is important to stabilize the patient by administering sodium bicarbonate and electrolyte replacement. Her potassium level is low, requiring replacement. Although her magnesium level is normal, it should be monitored; however, her magnesium level does not require replacement at this time because her QTc is less than 500 milliseconds. Because the time interval of the overdose is not known, there is limited benefit for activated charcoal. Lorazepam is not indicated for prophylaxis of seizure activity.

5. Answer: A

This patient has the clinical signs and symptoms of alcohol withdrawal. Management should focus on the patient's safety and controlling his symptoms, and treatment should be administered using a symptom-triggered therapy strategy. The primary agents used to control symptoms are the benzodiazepines, and lorazepam is a good option. Barbiturates such as phenobarbital are typically reserved for patients who do not respond to benzodiazepine therapy because of benzodiazepine's long elimination half-life and stronger sedative effects. Clonidine is a potential option, especially because this patient has borderline hypertension, but oral dosing may be difficult with his level of confusion. Propofol should be avoided in non-intubated patients.

6. Answer: B

The patient is experiencing an unintended opioid overdose, as evidenced by the decreased RR and decreased consciousness. Administration of the antidote, naloxone, is the best option. Because 2 hours have passed since the methadone dose was given, there is limited usefulness for activated charcoal at this time, and it would not be advisable to administer it to an unconscious patient without an established airway. Whole bowel irrigation is also not useful in this situation because it is too late to prevent drug absorption together with the airway safety concern. Administration of intravenous fluids would be beneficial to improve BP but should not be administered in this case before naloxone.

7. Answer: D

The patient is not responding to the initiation of intravenous fluids and calcium gluconate, so HIET is warranted. Because of the patient's low serum potassium levels, it is critical to replace this before administering insulin. The patient's glucose level is greater than 200 mg/dL, so additional glucose need not be given at this time. Full effects may take up to 30 minutes to be seen, but this should not prevent the initiation of HIET.

8. Answer: A

The patient is not responding to the initiation of intravenous fluids and calcium, so the most appropriate option at this time is to initiate a vasopressor agent. From the choices listed, the best first option is norepinephrine initiated at 4 mcg/minute and titrated to the desired effect. Epinephrine is also a possible option, but it would be recommended if the patient were not responding to increasing doses of norepinephrine. Isoproterenol has only a β-agonist effect; although it would increase HR, it would have no effect on increasing BP and might in fact lower BP. Intravenous lipid emulsion is a potential therapy, but it is typically administered in a patient with severe decompensation caused by a lipophilic medication who is not responding to fluids or vasopressors.