Antidote Use in the Critically Ill Poisoned Patient

David P. Betten, MD*
Rais B. Vohra, MD†
Matthew D. Cook, DO‡
Michael J. Matteucci, MD†‡
Richard F. Clark, MD†

The proper use of antidotes in the intensive care setting when combined with appropriate general supportive care may reduce the morbidity and mortality associated with severe poisonings. The more commonly used antidotes that may be encountered in the intensive care unit (*N*-acetylcysteine, ethanol, fomepizole, physostigmine, naloxone, flumazenil, sodium bicarbonate, octreotide, pyridoxine, cyanide antidote kit, pralidoxime, atropine, digoxin immune Fab, glucagon, calcium gluconate and chloride, deferoxamine, phytonadione, botulism antitoxin, methylene blue, and Crotaline snake antivenom) are reviewed. Proper indications for their use and knowledge of the possible adverse effects accompanying antidotal therapy will allow the physician to appropriately manage the severely poisoned patient.

The use of antidotes for poisonings has been explored for thousands of years. The vast majority

of these treatments have long since fallen out of favor because they were found to offer little or no benefit and in many cases produce significant detrimental effects. Strychnine, cocaine, and other stimulants, for example, were commonly used in the 1920s and 1930s for barbiturate overdoses. Their inherent toxicity and the low mortality rate associated with barbiturate poisonings treated with supportive care alone led to their eventual dismissal [1]. Antidotes commonly used today, when administered in conjunction with aggressive supportive care, are often able to decrease the severity and duration of symptoms while possessing safety profiles more benign than their predecessors. In certain circumstances, when used promptly and appropriately, their use may be life saving.

The infrequent presentation of individuals requiring particular antidotes and the relatively high cost of antidotes has resulted in many hospitals carrying inadequate quantities of some of the more commonly used antidotes [2,3]. Antidote stocking guidelines were recently established by a multidisciplinary panel of 12 health care professionals. Sixteen antidotes were unanimously identified by the consensus panel for stocking (Table 1) [4]. Hospitals not possessing these antidotes should at the minimum have pre-identified neighboring health care centers that will readily be able to transport these antidotes on an emergency basis.

The following is a brief review of some of the more commonly used antidotes that may be used in the intensive care setting. Given the complexity of management of severely poisoned patients and subtleties in the use of many antidotes, further consultation with a medical toxicologist or poison center (national poison center hot line: 1-800-222-1222) should be considered. The management of acute and chronic heavy metal poisonings (arsenic, lead, mercury, etc) is not addressed, and the reader is referred to several excellent reviews pertaining to

Table 1. Consensus Stocking Guidelines of 20 Commonly Encountered Antidotes for Hospitals That Accept Emergency Admissions as Determined by an Expert Multidisciplinary Panel [4]

Recommended for Stocking	Consensus Not Reached for Routine Stocking	Not Recommended for Routine Stocking
N-acetylcysteine	Flumazenil	Black widow antivenin
Crotalid snake antivenin	Physostigmine	Ethylenediamine tetraacetic acid
Calcium gluconate/chloride		
Sodium bicarbonate		
Cyanide antidote kit		
Deferoxamine		
Digoxin immune Fab		
Dimercaprol		
Atropine		
Ethanol		
Fomepizole		
Glucagon		
Methylene blue		
Naloxone		
Pralidoxime		
Pyridoxine		

appropriate indications for treatment and methods of administration of common chelation agents [5-9].

Acetaminophen Poisoning

Acetaminophen misuse is responsible for more hospitalizations following overdose than any other common pharmaceutical agent. Although acetaminophen possesses an outstanding safety profile at therapeutic doses, a rapid course of progressive hepatic failure leading to death may occur following large overdoses when treatment is delayed. It has been estimated that 450 deaths annually and nearly 40% of all cases of acute liver failure in the United States are secondary to the inappropriate use of acetaminophen [10,11]. Toxicity occurs as a result of acetaminophen's metabolism via cytochrome p450 to *N*-acetyl-p-benzoquinoneimine (NAPQI). At therapeutic doses of acetaminophen, NAPQI is detoxified by glutathione to nontoxic conjugates; however, with excess dosing and exhaustion of glutathione reserves, NAPQI accumulates, initiating a cascade of events capable of producing hepatocyte damage and fulminant hepatic failure.

N-acetylcysteine

N-acetylcysteine (NAC) prevents NAPQI-induced hepatoxicity through several mechanisms: (1) NAC functions as a glutathione (GSH) precursor that may increase GSH availability as well as provide inorganic sulfate that promotes acetaminophen metabolism through the nontoxic sulfation pathway. (2) NAC directly converts NAPQI to nontoxic cysteine and mercaptate conjugates. (3) NAC reduces NAPQI back to acetaminophen, where it may be further eliminated by other nontoxic routes. In the setting of progressive hepatic failure, NAC may offer further benefit as a result of its nonspecific antioxidant effects and free radical scavenging properties in addition to NAC-mediated improvement in microvascular perfusion [12,13].

When administered early (<8 hours) after acute ingestion, NAC is almost completely effective in preventing significant hepatotoxicity. The benefit of this antidote is lessened beyond 8 hours following overdose as glutathione stores become further depleted [14]. Treatment should be initiated immediately for any suspected toxic acetaminophen ingestion beyond 8 hours. Current US Food and Drug Administration (FDA)–approved treatment options include either oral or intravenous NAC. Oral NAC is administered as a 140 mg/kg loading dose followed by 70 mg/kg every 4 hours for an additional 17 doses for any patient with a toxic ingestion as plotted on the Rumack-Matthew nomogram. Should signs of progressive hepatic damage be present after this 72-hour period, treatment with NAC may still be of some benefit and should be continued until a definitive clinical and laboratory improvement is noted. Success has been demonstrated with a shortened treatment duration of oral NAC in several studies when administered to appropriate candidates [15-17]. Early NAC discontinuation

should be considered only after a minimum of at least 20 hours of oral NAC administration when no further acetaminophen is detectable in the serum and hepatic transaminases and prothrombin times are normal.

Intravenous NAC has been used throughout Europe, Canada, Australia, and portions of the United States for more than 2 decades with success demonstrated in treatment durations of 20 to 48 hours [18-20]. Intravenous NAC recently gained FDA approval in the United States for patients treated within 8 to 10 hours following an acute toxic acetaminophen ingestion. It is administered as a 140-mg/kg loading dose over 15 minutes followed by a 50-mg/kg infusion over 4 hours, concluding with a 16-hour infusion of 100 mg/kg. When intravenous NAC is initiated beyond 8 to 10 hours postingestion, it should be continued beyond the 20-hour infusion if needed until acetaminophen is no longer measurable and transaminases are normal or returning to normal.

The indication and duration of NAC therapy in chronic acetaminophen poisoning are less clearly defined. Healthy adults can likely tolerate at least 7 g of acetaminophen over 24 hours without risk of hepatotoxicity. Individuals with underlying liver disease, HIV, or malnutrition may be at increased risk with smaller ingestions. Treatment should be considered with greater than 4 g per day in this population if there is any laboratory evidence of hepatotoxicity or if serum acetaminophen concentrations are elevated (>10 mg/L). Treatment of individuals meeting these criteria is reasonable given the uncertainty of the ingestion, the difficulty in predicting who will develop subsequent hepatic damage, and the lack of clinical studies that address chronic overdose management [21]. Treatment with NAC, either orally or intravenously, should continue until acetaminophen is not detected and transaminases and prothrombin time are normal or normalizing.

Death following single acute acetaminophen ingestions in children less than age 5 has not been reported despite extremely elevated acetaminophen levels and delays in treatment onset. A predominance of the sulfation pathway (which produces nontoxic metabolites), increased glutathione reserves, and improved regenerative capabilities of young livers are theorized to account for this protective effect [22]. Misdosed infants and children with acute febrile illnesses who experience chronic acetaminophen poisoning are not afforded a similar protection and appear to be an at-risk group [23]. Those receiving greater than 75 mg/kg/day should have laboratory evaluation performed and treatment with NAC initiated if transaminase abnormalities are present or acetaminophen levels are elevated.

N-acetylcysteine given orally is often poorly tolerated due to its "rotten egg" sulfur smell. High-dose antiemetics may be needed to prevent emesis. Any NAC dose vomited within 1 hour from ingestion should be readministered. If vomiting is present and persistent beyond 8 hours following acetaminophen ingestion, intravenous NAC should be strongly considered. Intravenous NAC has been used effectively and relatively safely throughout the world for more than 20 years [19]. Anaphylactoid reactions with intravenous NAC may occur as a dose- and rate-related effect; however, these reactions are generally minor (pruritis, vomiting) and usually respond to antihistamines and a slowing of the NAC infusion rate [20,24]. Major adverse effects and death following intravenous NAC administration are exceedingly rare and are most commonly related to rapid intravenous loading in patients with underlying airway disease or in the case of NAC dosing errors [25,26].

Toxic Alcohol Poisoning

Ingestions of methanol and ethylene glycol are inebriating to the central nervous system but are otherwise nontoxic prior to their enzymatic conversion by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALD) to their acidic metabolites. ADH and ALD convert methanol to formate, a retinal toxin causing visual defects and papilledema [27-29]. Ethylene glycol is metabolized by ADH and ALD to glycolic acid and later to oxalic acid, which precipitates with calcium in renal tubules and other tissues [30]. Each of these metabolites is acidic, and their accumulation results in a "wide anion gap" acidosis. This acidosis may be delayed for several hours after initial ingestion because of delayed metabolism, especially in the presence of ethanol. Poisoning with other alcohols such as propylene glycol and isopropanol is intoxicating but does not require antidotal therapy, because their metabolites generally do not lead to irreversible organ toxicity.

Fomepizole/Ethanol

The goal of antidotal therapy in toxic alcohol poisoning is to prevent metabolism of the parent compounds to their toxic metabolites. Competitive inhibition of ADH can be achieved by administration of either ethanol or 4-methylpyrrazole (fomepizole) (Fig 1). When given early following methanol or ethylene glycol ingestion, these antidotes are completely protective against metabolic conversion; however, once metabolism has occurred, supportive
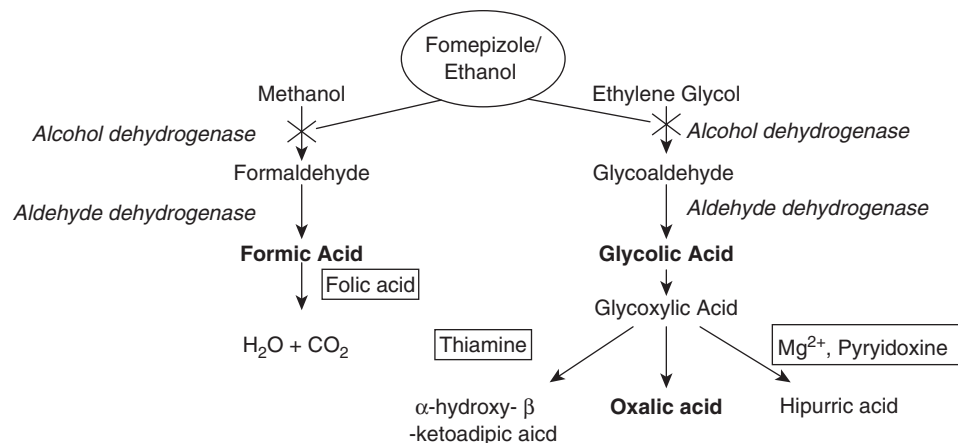
Fig 1. Competitive enzymatic inhibition of alcohol dehydrogenase by fomepizole and ethanol prevents metabolism of methanol and ethylene glycol to toxic metabolites (bold type). Enzymatic cofactor supplementation (boxes) may offer greater rate of metabolism to nontoxic metabolites.

care, treatment of acidosis with sodium bicarbonate, and enhancement of elimination of the toxic metabolites with hemodialysis are required to attenuate injury [29,31,32].

Because serum levels of methanol and ethylene glycol are often unavailable immediately, antidotal therapy for toxic alcohol poisoning is often indicated in the presence of surrogate markers of toxicity. The presence of an unexplained serum osmolar gap or a high anion gap metabolic acidosis should prompt the consideration of toxic alcohol poisoning. Significant toxic alcohol poisoning may occur even with a "normal" osmolar gap given the interindividual variability of baseline osmolar gaps. This is particularly true with ethylene glycol poisoning. The presence of urinary crystals and urine fluorescence (occasionally seen because of fluorescene present in many antifreeze products) following ethylene glycol ingestion can aid in the diagnosis when present but is unreliable and may be absent even with high-level exposures.

Treatment with ethanol or fomepizole should be administered to all patients with a history concerning for methanol or ethylene glycol ingestion and those with documented levels of 20 mg/dL or greater of either agent. Treatment should also be considered in the setting of large anion gap metabolic acidosis or significant osmolar gaps of uncertain etiology. Antidotal treatment of toxic alcohol poisoning should be continued until the levels of methanol or ethylene glycol are below 20 mg/dL and clinical symptoms of toxicity are resolving [28,30]. Given the long half lives of methanol (43-54 hours) and ethylene glycol (14-18 hours) during ethanol and fomepizole administration, hemodialysis should be considered for plasma toxic alcohol

levels greater than 50 mg/dL. Further indications for dialysis include deteriorating vital signs despite intensive supportive care, metabolic acidosis (pH <7.25) refractory to sodium bicarbonate administration and supportive care, renal failure, and severe electrolyte derangements. All patients should receive supplemental cofactors (discussed below).

Ethanol is administered as a 10% solution in D5W and should be infused to maintain a serum concentration of 100 to 150 mg/dL. The loading dose is 600 to 700 mg/kg over 30 minutes, followed by a maintenance infusion of 66 mg/kg/h (for nondrinkers) to 154 mg/kg/h (for chronic drinkers) [33]. Hourly serum ethanol concentrations are required to titrate the infusion rate for the desired level. During dialysis, the maintenance dose of ethanol should be increased to 169 to 257 mg/kg/h (higher rates for chronic ethanol abusers) because ethanol will also be removed. Oral dosing with ethanol can be initiated in the rare circumstance that neither intravenous ethanol nor fomepizole is available; the suggested initial oral loading dose is 4 ounces of 80-proof whiskey (40% ethanol by volume) [28,30].

Fomepizole is a potent ADH inhibitor, displaying an affinity that is 500 times that of ethanol and 5000 to 10 000 times that of methanol and ethylene glycol [32]. Fomepizole is more expensive than ethanol but offers a more desirable side effect profile [34]. It does not cause inebriation, hypoglycemia, hyperosmolarity, or vasodilation. It is not metabolized and therefore will not further deplete reduced nicotinamide adenine dinucleotides (NADH) or generate more acid as the metabolism of ethanol would. No serum levels of fomepizole are necessary to guide dosing [31]. The loading dose is 15 mg/kg, followed by 4 maintenance doses at 10 mg/kg. Thereafter, the

maintenance dose should be increased to 15 mg/kg to offset an increased rate of degradation of fomepizole [35,36]. Hemodialysis removes a significant proportion of circulating fomepizole, necessitating a decrease in the maintenance-dosing interval to 4 hours during the procedure [27,33]. Alternatively, a continuous infusion of 1.5 mg/kg/h has been reported to achieve a therapeutic level of fomepizole during hemodialysis [28,30].

Following toxic alcohol poisoning, certain vitamins can function as cofactors, potentially maximizing degradation of the alcohol to nontoxic metabolites (Fig 1). For methanol toxicity, folic acid or folinic acid (leucovorin) at a daily dose of 1 mg/kg intravenously (IV) should be given to all patients [36]. For patients with suspected ethylene glycol toxicity, administration of pyridoxine (50 mg IV every 6 hours), thiamine (100 mg daily by oral or IV routes), and magnesium (usually 2 g daily by oral or IV routes) is recommended.[36] The mechanism by which these cofactors reduce the toxic effects caused by methanol and ethylene glycol is not well understood; thus, their use should be considered an adjunctive measure with fomepizole, ethanol, and, if needed, hemodialysis. Sodium bicarbonate can correct severe acidosis and slow central nervous system (CNS) penetration of the injurious metabolites but does not stop their generation or enhance elimination.

Antimuscarinic Poisoning

Anticholinergic drugs competitively block muscarinic acetylcholine receptors in the CNS, in terminal parasympathetic synapses, and on the salivary and sweat glands. These agents typically produce the "antimuscarinic toxidrome" characterized by tachycardia, mydriasis, dry, flushed skin, urinary retention, dry mucosae, ileus, and confused delirium with mumbling speech, seizures, hallucinations, and agitation [37,38]. Many compounds can induce the antimuscarinic syndrome, including antihistamines, tricyclic antidepressants (TCAs), antiparkinsonian agents, typical and atypical antidepressants, and atropine-like alkaloids in *Datura stramonium* and *Atropa belladonna* plant species.[39,40,41]

Physostigmine

Reversal of antimuscarinic symptoms is achieved with the use of physostigmine. Physostigmine is a tertiary carbamate that reversibly disables acetylcholinesterase, increasing levels of acetylcholine in both central and peripheral sites [39,40,42,43]. In recent decades, enthusiasm for this agent has waned because of concerns of precipitating seizures and reported cardiotoxicity in the setting of TCA overdose [44-48].

Diagnostic use of physostigmine can be considered in patients with altered mental status and signs of antimuscarinic toxicity. Complete reversal of signs and symptoms (particularly altered mental status) after physostigmine administration suggests the presence of antimuscarinic toxicity. The therapeutic use of physostigmine is recommended by some authors to reverse life-threatening tachycardia, hyperthermia, or severe agitation resulting from antimuscarinic toxicity; however, this agent should be used only as a therapeutic adjunct to conventional treatments for these conditions [41].

Although in past decades physostigmine had been administered safely to thousands of TCA-poisoned patients, convulsions and dysrhythmias following physostigmine have been described in multiple case reports of TCA overdose [45,46,47,49]. These reports are difficult to interpret because TCAs are proconvulsants by themselves in overdose. Pentel [44] reported 2 individuals who developed seizures before, and asystole following, physostigmine administration. Both individuals were relatively bradycardic before administration of physostigmine, and 1 had a first-degree atrioventricular block. Another case series reported a single convulsion among 39 patients given diagnostic physostigmine for varying antimuscarinic substance ingestions; this patient had also convulsed prior to physostigmine administration [50]. These and other similar reported cases suggest that physostigmine-related complications can be avoided through careful selection of patients without high-risk characteristics, such as electrocardiographic (ECG) evidence of TCA overdose. We suggest that contraindications to the use of physostigmine include QRS or QTc prolongation, relative bradycardia or intraventricular conduction block, a cardiotoxic TCA ingestion (generally at least 1 g), or underlying seizure disorder.

In adults, the standard dose of physostigmine is 1 to 2 mg IV given by slow push (1 mg over 1-2 minutes) in a monitored setting. The use of benzodiazepines prior to physostigmine administration is recommended by some clinicians to reduce the risk of adverse drug reactions. Lack of complete reversal after 4 mg makes antimuscarinic toxidrome an unlikely cause of altered mental status. The onset of effect occurs within 5 to 20 minutes, and duration is 45 minutes to 1 hour. Antimuscarinic toxicity returns often with milder severity once the antidote's effects wane [42].

The clinician must be prepared to recognize and treat cholinergic effects that may occur following physostigmine administration, such as emesis, hypersalivation, bradycardia, diaphoresis, diarrhea, bronchorrhea, and bronchospasm. Less commonly, nicotinic effects of fasciculations, weakness, and paralysis may be present as well. Severe bradycardia or bronchorrhea should be treated with atropine (one-half the physostigmine dose), which should be readily available. Seizures are generally brief and self-limited and should be treated with standard doses of benzodiazepines.

Opioid Poisoning

The term *opioids* encompasses the naturally occurring opiate compounds from the poppy plant (*Papaver somniferum*) as well as synthetic and semisynthetic compounds that have similar clinical effects [49]. Opioids are potent agonists of the μ, κ, and δ receptors in the CNS [51]. Sedation and hypoventilation are among the most common symptoms of overdose. Complications of opioid overdose include hypoxic injury to virtually any organ system, rhabdomyolysis, intestinal ileus, nerve compression injury, intravenous injection-related infectious diseases, and a poorly understood phenomenon of noncardiogenic pulmonary edema [52-54].

Naloxone

Naloxone is a synthetic antagonist of opioid receptors and reverses apnea in opioid overdose. The onset of action is almost immediate after intravenous, intramuscular, intranasal, or endotracheal dosing, and the duration of effect is 1 to 4 hours [55,56].

Suspected or known opioid toxicity with demonstrable respiratory depression (rate <8/min) is the primary indication for naloxone. The smallest dose that effectively restores respiratory drive should be administered. The required intravenous dose is typically 0.04 to 0.4 mg, although administration by other routes or following overdose of high-potency synthetic compounds such as fentanyl or propoxyphene may require higher doses [51]. If there is no increase in respiratory drive after administration of 10 mg of naloxone, a search should continue for alternative etiologies of CNS depression. Recurrent or prolonged sedation, such as can be the case in methadone intoxication, may require treatment with continuous intravenous infusion of two thirds of the initial effective dose per hour [57]. Patients must be monitored for recurrence of respiratory depression for at least 2 hours after the last dose of naloxone prior to medical clearance [51,55,58].

Serious adverse events after even high doses of naloxone are extremely rare. However, naloxone should be cautiously used in a patient with normal respirations, even when opioid overdose is suspected. Opioid-dependent patients may experience withdrawal after naloxone administration and become only more agitated and dysphoric [59]. Use of naloxone may also "unmask" the toxicity of coingestants, such as TCAs, and concurrently abused substances (a popular drug combination is heroin with cocaine, also termed a "speedball") [51]. Naloxone has been rarely reported to induce noncardiogenic pulmonary edema following infusion, but these reports also suggest the possibility of pre-existing acute lung injury prior to naloxone administration [51,60].

Long-acting opioid antagonists (nalmefene, naltrexone) have similar effects but longer durations of action (nalmefene 4-6 hours; naltrexone 10-24 hours) than naloxone [51,61]. Long-acting opioid reversal agents are not appropriate first-line antidotes because undesirable withdrawal symptoms can persist for several hours. Furthermore, a prolonged observation period after the last dose may be necessary because life-threatening effects of opioid toxicity may recur after naltrexone or nalmefene have been metabolized [61].

Benzodiazepine Poisoning

Poisoning with benzodiazepine compounds is generally marked by mild to moderate sedation but most often follows a benign course. However, when these agents are combined in overdose with other sedating compounds such as ethanol, they can cause respiratory arrest and severe morbidity [62]. Symptoms of benzodiazepine poisoning include decreased responsiveness, hyporeflexia, hypothermia, hypotension, and respiratory depression. Significant derangements in vital signs are not consistent with benzodiazepine overdose. A paradoxical excitatory reaction may rarely accompany the therapeutic use of benzodiazepines for procedural sedation [63]. Benzodiazepines have a specific binding site on the γ-aminobutyric acid (GABA) type A receptor complex in the CNS, a chloride channel that causes neuronal hyperpolarization [64]. Binding of benzodiazepines increases the frequency of channel opening when GABA (the major inhibitory neurotransmitter in the CNS) binds at a separate site on the complex [65].

Table 2. Medications Commonly Associated With QRS Prolongation Due to Impaired Sodium Channel Influx [4]

Tricyclic antidepressants	
Carbamezapine	
Diphenhydramine	Quinidine
Propoxyphene	Procainamide
Cocaine	Flecainide
Thioridazine	Encainide
Mesoridazine	Amantadine
Fluoxetine	Quinine

Flumazenil

Flumazenil is a competitive antagonist at the benzodiazepine site on the GABA-A receptor complex [66]. By preventing the binding of benzodiazepines, flumazenil decreases the inward chloride current; the subsequent neuronal depolarization reverses CNS and respiratory depression [64,66]. It is effective in reversing sedation of benzodiazepine and non-benzodiazepines that share activity at the benzodiazepine receptor, such as zolpidem [64,67-69]. It is also effective in the treatment of paradoxical excitatory reactions to benzodiazepines [63].[63] Intravenous flumazenil induces reversal in 5 to 10 minutes and has a duration of action of 15 to 245 minutes in healthy adults. Patients with hepatic failure may have a prolonged response to flumazenil [70,71]. Repeat doses may be required to treat ingestions of compounds with prolonged effects.

In adults, the starting dose of flumazenil to reverse benzodiazepine-induced sedation is 0.2 mg IV. If the initial dose of flumazenil is ineffective, it can be followed by 0.3- to 0.5-mg doses every minute as needed up to a maximum of 3 mg [72]. Lack of any response after this dose makes coma attributable to benzodiazepines highly unlikely. A continuous flumazenil infusion of 0.1 to 0.5 mg/h may be needed to prevent resedation in some cases [73]. Following flumazenil discontinuation, patients should be observed for several hours to ensure that resedation from longer acting benzodiazepines does not occur.

Flumazenil is well tolerated and effective in sedated patients with isolated benzodiazepine overdose. In chronic users and those with physical dependence on benzodiazepines, flumazenil can precipitate withdrawal symptoms and seizures [74]. Flumazenil has caused convulsions in patients with head injury, those with underlying seizure disorders, and those who have coingested proconvulsant drugs, such as TCAs, and should be avoided in these populations [74,75]. Should seizures occur following flumazenil administration, high-dose benzodiazepines or barbiturates may be needed to stop further seizure activity. The diagnostic use of flumazenil for coma of unknown cause must be weighed against the possibility of precipitating seizures or withdrawal symptoms in high-risk patients.

Cardiac Sodium Channel Poisoning

Tricyclic antidepressants are the classic example of agents causing toxicity by inhibiting rapid sodium channel influx in the cardiac conduction system. Cardiac toxicity results from a slowing of cardiac action potentials by slowing sodium channel influx in phase 0. This leads to a delay in depolarization resulting in electrocardiogram QRS and QT prolongation and an increased risk of ventricular dysrhythmias. Similar sodium channel blocking effects on the heart can be seen in overdose with numerous other substances that should be evaluated and treated in a similar fashion (Table 2) [76].

Sodium Bicarbonate

Sodium bicarbonate should be considered for the management of toxic ingestion of all substances with sodium channel effects and evidence of cardiac toxicity. The effectiveness of this agent is a result of both the increased sodium concentration produced and increased serum alkalinization. Tricyclic antidepressants are weak bases. As a result, serum alkalinization will increase the proportion of non-ionized drug. The non-ionized TCA form may have a greater distribution throughout tissue, causing a greater proportion of drug to move away from the cardiac conductive system, resulting in less sodium channel blockade. Alkalinization also accelerates recovery of sodium channels by neutralizing the protonation of the drug-receptor complex [77,78]. This results in a more rapid movement of the neutral form of the drug away from the sodium channel receptor. A similar benefit of serum alkalinization can be duplicated with controlled hyperventilation [79].

Increased extracellular sodium concentrations produced by sodium bicarbonate may produce a more rapid sodium channel influx by way of an increased sodium concentration gradient [80]. Experimental models testing alkalinization with sodium free buffers for TCA toxicity were not as effective as sodium bicarbonate in reducing cardiotoxicity. A role for hypertonic saline administration has been proposed in the setting of persistent cardiotoxicity and QRS prolongation when alkalinization has been optimized

(pH 7.45-7.55), although controlled trials supporting this in humans are lacking [81].

Administration of sodium bicarbonate should be considered in individuals with cardiac conduction delays, ventricular dysrhythmias, or hypotension when the ingestion of a sodium channel-blocking drug is suspected. QRS durations of greater than 160 milliseconds are typically implicated in cases that progress into ventricular dysrhythmias and in which seizure activity is most likely to develop [82]. Treatment with sodium bicarbonate should be considered with QRS duration greater than 100 to 120 milliseconds, because this affords an ample margin of safety should an individual quickly decompensate. An R wave in lead aVR greater than or equal to 3 mm has been found to be equally predictive of individuals who may develop ventricular dysrhythmias [83]. In addition, sodium bicarbonate appears to be of some benefit in improving blood pressure and cardiac output in hypotensive patients with narrow complex rhythms following tricyclic antidepressant ingestions [84]. Although capable of reversing cardiac conduction sodium channel effects, sodium bicarbonate is unable to affect other TCA properties such as seizures, anticholinergic toxicity, and α-adrenergic receptor antagonism and thus should be considered as only part of TCA overdose management.

Sodium bicarbonate is most typically administered as a 50-mL ampule of 8.4% solution. The amount of sodium bicarbonate necessary for reversal of cardiotoxicity in these cases may vary. In the setting of QRS widening or hypotension, 2 ampules administered over 1 to 2 minutes is an appropriate starting dose. The serum pH of the patient should be closely monitored, with a goal of 7.45 to 7.55. Serial blood gas analyses may be needed to guide further treatment. If QRS widening remains or recurs, additional sodium bicarbonate ampules should be infused if the goal pH has not been exceeded. Death from TCA toxicity occurs generally within the first 1 to 2 hours, making continuous infusions of sodium bicarbonate unnecessary in most situations. In addition, bolus infusions of sodium bicarbonate may be more appropriate to rapidly raise extracellular sodium concentrations. Alkalinization can be discontinued with hemodynamic stability and resolution of ECG abnormalities.

Oral Hypoglycemic Poisoning

Sulfonylureas and meglitinides are widely used for treatment of non-insulin-dependent diabetes mellitus, and together they account for the majority of cases of drug-induced hypoglycemia. These drugs act similarly by depolarizing pancreatic β-islet cells, triggering exocytosis of preformed insulin and resulting in facilitated end-organ glucose uptake [85-87]. In overdose, or in the absence of adequate food intake, sulfonylureas can cause prolonged, life-threatening hypoglycemia [88]. Onset of sulfonylurea-induced hypoglycemia is typically within 8 hours of ingestion, with hypoglycemic effects lasting 6 to 72 hours depending on the agent ingested [89-91]. The shorter acting meglitinides typically take effect in less than 1 hour, with hypoglycemic effects lasting 1 to 4 hours [91,92]. Case reports and animal studies, however, have found prolonged hypoglycemic effects of 6 to 24 hours following meglitinide ingestion [93,94]. Although there are few data on meglitinide overdose, treatment options are expected to be similar to sulfonylureas.

Dextrose

Any patient who overdoses with an oral hypoglycemic agent should be observed for a minimum of 8 hours, during which glucose levels should be monitored every 1 to 2 hours [90]. Patients should be allowed to eat and drink freely during this observation period. If hypoglycemia occurs, patients should receive IV dextrose as a bolus (D50W or D25W) or infusion (D10W or D5W) in order to maintain euglycemia. Overly aggressive dextrose administration leading to hyperglycemia may result in further pancreatic insulin release and rebound hypoglycemia [85,86]. Prolonged hypertonic dextrose (>10%) infusion through a peripheral IV site is not recommended because phlebitis may occur. Any patient with hypoglycemia requiring IV dextrose following sulfonylurea or meglitinide overdose should be admitted and observed for a minimum of 24 hours [90,92]. Patients should be monitored for several hours after discontinuation of IV dextrose to ensure no recurrence of hypoglycemia.

Octreotide

Octreotide is a long-acting, synthetic somatostatin analogue [95]. In the setting of oral hypoglycemic agent overdose, octreotide potently and selectively binds to somatostatin receptors on pancreatic β-islet cells, decreasing insulin secretion to near basal rates and inhibiting rebound hypoglycemia [96-99]. Octreotide is well absorbed via subcutaneous or IV routes and has a duration of action of approximately 6 to 12 hours. Diazoxide, previously used with regularity for sulfonylurea-induced hypoglycemia, is less efficacious and is associated with

more frequent adverse side effects (hypotension, tachycardia, nausea, and vomiting) than octreotide, and it is now rarely used [95,100].

Octreotide is indicated for cases of oral hypoglycemic agent–induced hypoglycemia after initial control of hypoglycemia with IV dextrose or when hypoglycemia is refractory to dextrose therapy [91]. Adults may receive 50 μg and children 1 μg/kg IV or subcutaneously every 6 to 12 hours as needed [90,101]. Octreotide has been found to be superior to IV dextrose and diazoxide in maintaining euglycemia and has decreased or eliminated the need for IV dextrose in simulated human sulfonylurea overdoses [95]. Patients should be monitored for recurrence of hypoglycemia for 24 hours or more after the last octreotide dose in cases of long- acting sulfonylurea overdose [98,102]. Adverse effects following administration include nausea, vomiting, diarrhea, crampy abdominal pain, injection site pain, dizziness, fatigue, flushing, headache, and hyperglycemia [103].

Isoniazid Poisoning

Isoniazid (isonicotinic hydrazide, INH) has been used for the treatment and prophylaxis of tuberculosis since 1952 [104]. It is rapidly absorbed after oral ingestion with peak blood concentrations and toxic effects occurring within 1 to 6 hours [105]. INH toxicity is a result of its ability to produce a deficiency of pyridoxal-5-phosphate, the active form of pyridoxine and a required cofactor for glutamic acid decarboxylase (GAD). In the absence of functional GAD, glutamic acid is unable to be converted to GABA, the primary CNS inhibitory neurotransmitter. Following INH overdose, decreased production and activity of GABA on postsynaptic receptors result in seizures and metabolic acidosis secondary to seizure-induced lactic acidosis [106]. INH-induced seizures may be prolonged and refractory to GABA agonists such as benzodiazepines [104,107]. Coma is another prominent feature of INH overdose, the exact mechanism of which is yet to be defined [108,109].

Pyridoxine

Pyridoxine is a water-soluble essential vitamin that has no known metabolic effects by itself [110,111]. Pyridoxine must be converted to the active pyridoxal-5-phosphate before it can act as a coenzyme for the decarboxylation of glutamic acid to GABA [110,111]. When administered at appropriate doses, exogenous pyridoxine is able to replenish INH-depleted pyridoxine and pyridoxal-5-phosphate stores and stop further seizures. Paradoxically, repletion of pyridoxine stores reverses both the CNS excitatory (seizure) and inhibitory (coma) effects of INH [112,113].

Intravenous pyridoxine is indicated for the treatment of INH-induced seizures and coma. When the amount of INH ingested is known, 1 g of pyridoxine per gram of INH ingested should be administered immediately. If the amount of INH ingested is unknown, an empiric dose of 5 g of pyridoxine is suggested in adults, or 70 mg/kg (maximum 5 g) in children. Should seizures persist, the initial dose should be repeated every 20 minutes until the desired effect is achieved [114]. Pyridoxine should be mixed in 50 to 100 mL of 5% dextrose in water and may be administered at a rate of 0.5 g/min [114,115]. With appropriate pyridoxine dosage administration, desired effects should be evident within minutes [112,113,116]. A prophylactic IV dose of 5 g of pyridoxine has been suggested for asymptomatic patients who present within 2 hours of a significant INH ingestion, but the efficacy of this therapy has not been studied [107].

Pyridoxine hydrochloride for IV administration is supplied in 1-mL vials containing 100 mg/mL [115]. Given the high doses that may be needed and the manufacturer's packaging of just 100 mg/vial, 50 to 150 or more vials may be required to adequately treat INH-poisoned patients. Many hospitals lack adequate IV pyridoxine to treat even 1 severely intoxicated individual [117]. In the event IV pyridoxine is unavailable, the oral form may be crushed and administered orally as a slurry at a similar dosage to the IV form [114]. Pyridoxine should be administered concomitantly with benzodiazepines because a synergistic anticonvulsive effect has been demonstrated in animal studies [118].

Pyridoxine may also have an antidotal role in poisonings by monomethylhydrazine, a structurally similar substance to INH found in the Gyromitra mushrooms and rocket fuel that is capable of producing toxicity similar to INH [104]. Large acute (IV) and chronic (oral) pyridoxine overdoses have been associated with isolated sensory neuropathies in a stocking-glove pattern; however, this should not be of concern in the acute management of the above poisonings [110,119].

Cyanide Poisoning

Exposure to cyanide occurs through various routes including inhalation (hydrogen cyanide), ingestion (sodium and potassium cyanide salts, laetrile,

plant-derived cyanogenic glycosides), and intravenous administration of cyanide-containing medications (nitroprusside). Cyanide rapidly diffuses into tissues and binds to the cytochrome oxidase complex, disrupting the mitochondrial electron transport chain. The result is inhibition of oxidative phosphorylation and cellular hypoxia leading to anaerobic metabolism, metabolic acidosis, seizures, coma, cardiovascular collapse, and death. Clinical effects frequently occur rapidly following cyanide exposure; however, compounds such as acetonitrile and propionitrile may result in delayed toxicity as parent compounds are hepatically converted to cyanide [120-122].

Cyanide Antidote Kit

The current FDA-approved antidote kit for cyanide poisoning consists of amyl nitrite, sodium nitrite, and sodium thiosulfate (Taylor Pharmaceutical/ Akorn Inc, Decatur, IL).[123] Amyl nitrite and sodium nitrite induce methemoglobinemia by oxidizing iron in hemoglobin from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form. This ferric iron rapidly removes cyanide from cytochrome oxidase forming cyanomethemoglobin and restoring cellular respiration. Cyanomethemoglobin reacts with thiosulfate to form thiocyanate, a reaction catalyzed by the enzyme rhodenase. Thiocyanate is renally excreted leaving methemoglobin free to bind more cyanide [124,125]. Whereas both nitrites and thiosulfate are individually protective in cyanide poisoning, when used together they appear to have synergistic effects [124,126]. Nitrite-induced vasodilation may improve end-organ perfusion and has been suggested as an alternative mechanism contributing to the apparent effectiveness of the cyanide antidote kit [127].

Immediate empiric use of the cyanide antidote kit should be strongly considered for patients with suspected exposure to cyanide, especially those who are unresponsive or with significant acidosis. Nitrites should be used cautiously in smoke inhalation victims because concomitant methemoglobinemia and carboxyhemoglobinemia may severely worsen oxygen-carrying capacity [128]. In such cases, sodium thiosulfate may be safely given without prior nitrite therapy [129]. It has been suggested that the danger of sodium nitrite treatment following smoke inhalation is overestimated because carboxyhemoglobin may clear more rapidly than methemoglobinemia develops. Potential benefits and risks of treatment should be considered prior to treatment initiation [130]. Rapid (or even recommended) infusion rates of sodium nitrite may cause hypotension, and vasopressor support may be required [128,131]. Prophylactic

sodium thiosulfate (10 mg of thiosulfate per 1 mg of nitroprusside) is recommended during rapid and prolonged nitroprusside infusions (>3 µg/kg/min).[132]

Amyl nitrite pearls may be crushed into gauze and held near the patient's mouth and nose or under the lip of an oxygen mask for inhalation (30 seconds of each minute) while IV access is obtained. Once IV access is established, sodium nitrite may be administered as 10 mL of 3% solution (300 mg) for adults, or 0.2 to 0.33 mL/kg (maximum 10 mL) for children at 2.5 mL/min [123,124]. A lower dose may be necessary in anemic patients to avoid severe methemoglobin effects [124]. Co-oximetry should be used to monitor and maintain methemoglobin levels below 30% [124]. Pulse oximetry readings are inaccurate in methemoglobin-poisoned patients and will plummet even further following methylene blue administration. After sodium nitrite infusion, sodium thiosulfate may be administered IV as 50 mL of 25% solution (12.5 g) for adults or 1.65 mL/kg (maximum 50 mL) for children [124]. If initial patient response is inadequate, repeat doses of sodium nitrite and thiosulfate (half of the initial doses) may be given 30 minutes later [124].

Hydroxocobalamin, Hyperbaric Oxygen, and Normobaric Oxygen

Hydroxocobalamin, a cobalt-containing cyanide chelator, has been used safely and effectively in combination with thiosulfate outside the United States since 1970 and is reviewed in detail elsewhere [133]. Hyperbaric oxygen therapy for isolated cyanide toxicity remains an unproven and controversial modality [134]. Its use is reserved for cases of concomitant carbon monoxide and cyanide exposure. Normobaric oxygen administration, however, enhances the antidotal effects of nitrites and thiosulfate in animal studies of cyanide poisoning [134,135].

Cholinergic Poisoning

Cholinergic agents include acetylcholinesterase (AChE) inhibitors such as carbamate and organophosphorus (OP) insecticides, and organophosphorus nerve agents used in chemical warfare (sarin, soman, tabun, VX). These agents are well absorbed by ingestion, dermal contact, and inhalation [136].

Organophosphorus insecticides and nerve agents deposit a phosphoryl group at the active site of AChE, binding and disabling this enzyme. The resulting accumulation of acetylcholine (ACh) causes parasympathetic muscarinic (salivation, lacrimation,

urinary incontinence, diarrhea, diaphoresis, emesis, bronchorrhea, bronchoconstriction, bradycardia, and miosis), parasympathetic nicotinic (muscle weakness, fasciculations, and paralysis), sympathetic nicotinic (tachycardia, mydriasis), and CNS (delirium, seizures, coma) effects [136137]. Eventually, OP-bound AChE is spontaneously dealkylated in a process called "aging," at which time the OP-AChE bond becomes irreversible and regeneration of AChE is required. The aging process takes minutes to weeks depending on the offending agent but is typically faster with the OP nerve agents [138].

Carbamate insecticides bind reversibly to AChE through a process called carbamylation and do not cause aging of the enzyme [136,139]. In addition, carbamates do not readily cross the blood-brain barrier, thus producing cholinergic symptoms that are typically less prominent than OP poisonings [136].

Atropine

Atropine reverses the muscarinic effects of cholinergic poisoning. The primary goal and endpoint of atropine therapy in cholinergic poisoning are reversal of bronchorrhea and bronchoconstriction [140]. Atropine competitively antagonizes postsynaptic muscarinic ACh receptors but has no effect at the nicotinic receptors responsible for muscle weakness, fasciculations, and paralysis [140]. Atropine can terminate seizures in cholinergic-poisoned patients and should be administered in conjunction with benzodiazepines for this purpose [141-143].

Cholinergic-poisoned adults should receive an initial IV atropine dose of 1 to 5 mg. This can be repeated every 2 to 3 minutes until reversal of bronchorrhea and bronchospasm occurs. A continuous IV infusion may be required in severe poisonings (0.5-1 mg/h). Children should receive 0.05 mg/kg IV initially, followed by repeat doses every 2 to 3 minutes or continuous infusion (0.025 mg/kg/h) as needed [136]. Atropine therapy should be continued for at least 24 hours to allow metabolism and excretion of the cholinergic agent [144]. Large doses of atropine may be required in some cases (hundred to thousands of milligrams), so hospital supplies may be exhausted with just 1 severely poisoned patient [145]. Overly aggressive atropinization may cause antimuscarinic delirium, hyperthermia, and muscle twitching [144,146].

Pralidoxime

Pralidoxime (2-PAM) is the only FDA-approved AChE reactivator for OP poisoning. If administered prior to AChE aging, pralidoxime can hydrolytically cleave the OP-AChE complex, freeing the enzyme to degrade accumulated Ach [147]. Unlike atropine, pralidoxime may help reverse both muscarinic and nicotinic effects of OP poisoning [148]. The clinical efficacy of oximes remains controversial [149]. Pralidoxime is indicated early as adjunctive therapy to atropine for poisonings with OPs [136,137]. Because AChE aging does not occur with carbamate poisonings, pralidoxime is not expected to benefit these patients. However, when identification of the offending agent is not possible, concurrent therapy with both atropine and pralidoxime is recommended [136-150].

Suggested dosing regimens for pralidoxime vary. Adults may receive 1 to 2 g and children 25 to 50 mg/kg (maximum 2 g) by IV bolus over 15 to 30 minutes [136,137,151]. The initial bolus may be repeated in 1 hour if muscle fasciculations or weakness persists [147]. Continuous IV infusion may also be used and will be necessary in severe cholinergic poisonings [137,151].

The MARK-1 Kit and Benzodiazepines

The MARK-1 intramuscular autoinjector kits (Meridian Medical Technologies, Columbia, MD), originally designed for battlefield use by OP nerve agent–exposed soldiers, are now available to civilian emergency medical system responders. These kits are FDA-approved for general use in OP poisonings [140]. The adult kits contain 2 mg of atropine and 600 mg of pralidoxime in separate spring-loaded, pressure-activated autoinjectors. Pediatric autoinjectors containing 0.25 to 1 mg of atropine are also available. Benzodiazepines have demonstrated effectiveness in terminating OP-induced seizures and muscle fasciculations and may increase survival when coadministered with atropine and pralidoxime [141-143]. Diazepam 10-mg autoinjectors are sold separately from the MARK-1 kits.

Cardiac Glycoside Poisoning

Cardiac glycoside toxicity is characterized by cardiac, gastrointestinal, and neurologic dysfunction [152-154]. Digoxin and digitoxin are responsible for nearly all cardiac glycoside exposures; however, multiple plant species (lily of the valley, red squill, oleander, foxglove, yew) and animal species (Colorado river toad) contain structurally similar glycosides and may result in toxicity following ingestion or exposure [155].

The various manifestations of toxicity result from the glycoside binding and inhibition of sodium-potassium-adenosine triphosphatase (Na-K-ATPase) on cellular membranes. Clinical effects can include high-grade atrioventricular (AV) block, hyperkalemia, ventricular irritability with ventricular tachycardia or fibrillation, bidirectional ventricular tachycardia, paroxysmal atrial tachycardia with block, sinus bradycardia, confusion, color vision perceptual difficulty, and vomiting [156,157].

Anti-digoxin Antibody Fragments (Digibind®, DigiFab®)

Anti-digoxin Fab fragments consist of sheep-derived immunoglobulin G (IgG) antibodies that are cleaved and purified to isolate the antigen-binding fragment (F-ab, or Fab) [158]. This Fab fragment binds rapidly to free (unbound) digoxin in the serum and extracellular fluid. This results in a redistribution of digoxin out of tissue and away from Na-K-ATPase on cell membranes [159,160]. Improvements in cardiac disturbances, hyperkalemia, and extracardiac symptoms should be notable within 20 to 90 minutes following administration of the anti-digoxin antibody [152,156,161]. The digoxin-antibody complex circulates without dissociating until it is renally eliminated or proteolytically metabolized [161]. Up to 12% of patients may not respond to anti-digoxin Fab fragments because of inadequate dosing, underlying cardiac disease, or irreversible multiple organ failure at the time of therapy [156,162].

In the setting of cardiac glycoside toxicity, dysrhythmias, electrolyte derangements (especially hypomagnesemia), and dehydration should be addressed with standard measures, with a few notable exceptions. Hyperkalemia should be treated with insulin and dextrose, sodium bicarbonate, and cation exchange resins (sodium polystyrene sulfate) as well as digoxin-specific Fab fragments. Intravenous calcium should be cautiously administered, if at all, because intracellular calcium concentrations are usually elevated from the Na-K-ATPase poisoning. Further calcium administration has been reported to predispose to cardiac arrest, but these reports are not well documented or reproduced experimentally [163]. Ventricular irritability should be treated with Vaughn-Williams class IB agents such as lidocaine. Class IA agents such as procainamide and quinidine are contraindicated in this setting because they depress contractility and have prodysrhythmic effects. Atropine can be administered at standard doses for bradycardia or AV blockade.

Indications for the use of anti-digoxin Fab fragments include life-threatening cardiac dysrhythmias, high-grade AV blockade, serum potassium greater than 5 mEq/L, acute ingestion of greater than 10 mg of digoxin in an adult (4 mg in a healthy child), or steady-state serum concentration of >15 ng/mL [160]. Because unbound digoxin is more easily bound prior to tissue penetration, the early empiric use of digoxin-specific Fab fragments is recommended if a severe ingestion is suspected [159].

Each 40-mg vial of anti-digoxin Fab fragments can bind approximately 0.5 mg of digoxin [159]. When a known amount is ingested, the total amount of biologically available drug can be calculated assuming a bioavailability of 80% for digoxin. For example, if 10 mg is ingested, 8 mg needs to be neutralized. Because each vial of Digibind® binds 0.5 mg of the digoxin, a total of 16 vials would be indicated.

If the digoxin steady-state serum concentration is available (approximately 4-6 hours postingestion), the number of required vials of anti-digoxin antibody fragments can be calculated using digoxin's volume of distribution of 5 L/kg with the following formula:

$$\text{Vials} = \frac{[\text{digoxin serum concentration (ng/mL)} \times 5 \text{ L/kg} \times \text{patient weight (kg)}]}{[1000 \times 0.5 \text{ mg/vial}]}$$

Empiric treatment recommendations made by drug manufacturers for suspected ingestions of unknown digoxin quantities suggest an initial dose of 10 vials for acute ingestions and 3 vials for chronic toxicity. The clinical utility of anti-digoxin Fab fragments in poisonings by cardiac glycosides other than digoxin and digitoxin, such as those found in plants like oleander, has only been studied in animal models and a few human case reports [164,165]. Given the structural similarity of these related glycoside compounds and their potential toxicity, the administration of 10 to 20 vials of digoxin Fab fragments should be considered in symptomatic cases.

An ultrafiltration-based free digoxin assay must be used to evaluate the concentration of free (not Fab-bound) digoxin molecules in the serum following therapy with anti-digoxin Fab fragments [156,159,166]. Total digoxin levels may be falsely elevated following digoxin-antibody Fab fragment administration and should not be used as an indication for additional treatment. Delayed recrudescence of high free digoxin levels may occur attributable to late redistribution from the tissue compartment, but this is rarely of clinical importance. The safety profile for digoxin-specific Fab fragments is well established with less than a 1% rate of allergic reactions [165,167].

β-Adrenergic Receptor Blockers

β-adrenergic receptor blockers are frequently used for rate control and hypertension. They act by blocking receptors of a variety of cell types including myocytes, vascular smooth muscle, and cardiac pacemaker cells. Normally, the binding of the β-agonist stimulates a G-protein to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which activates phosphokinase A. This activation causes increased opening of cell membrane calcium channels, increased release of calcium from the sarcoplasmic reticulum, and improved function of myofibrillar proteins [168]. Blocking of the receptor leads to decreased inotropy and chronotropy, causing hypotension, bradycardia, and mental status depression. Several antidotes, including glucagon, calcium, and hyperinsulinemia-euglycemia, have been used with varying success for β-adrenergic receptor blocker poisoning. Whereas glucagon is discussed below, calcium and hyperinsulinemia-euglycemia will be presented in the calcium channel blocker poisoning section.

Glucagon

Glucagon is an endogenous polypeptide that has a role in maintaining plasma glucose levels by acting as a counterregulatory hormone to insulin [169]. It is used for hypoglycemia, β-adrenergic receptor blocker poisoning, and calcium channel blocker poisoning. Glucagon binds to a specific cell membrane receptor that stimulates the conversion of ATP to cAMP with the same resultant effects as β-adrenergic receptor agonists [170]. Because of its unique receptor, glucagon can bypass the blocked β-adrenergic receptor.

The dose of glucagon required in the treatment of β-adrenergic receptor blocker poisoning is much greater than that needed to treat hypoglycemia. For these poisonings, glucagon is administered as an intravenous bolus of 5 to 10 mg in adults (50 μg/kg in children). The effects may occur within minutes and last approximately 15 minutes [171]. Rebolusing with higher doses may be required for adequate clinical response. An intravenous infusion of 1 to 10 mg/h should be started if initial boluses are effective because of glucagon's short half-life and may be required for up to 48 hours [168]. The most common side effects of glucagon are nausea and vomiting. Both hyperglycemia and hypoglycemia can occur with this therapy, and blood glucose levels should be closely monitored.

Calcium Channel Antagonist Poisoning

Calcium channel antagonists are commonly prescribed for the treatment of hypertension or for rate control in the setting of atrial fibrillation. They work by blocking calcium influx into cells, resulting in decreased contractility, tone, and conduction of action potentials through the atrioventricular node. There are 3 classes of calcium channel antagonists: phenylalkylamines (Verapamil) and benzothiazepines (Diltiazem) have more cardiac specific actions, whereas dihydropyridines (Amlodipine) have more peripheral effects [170]. However, specificity is frequently lost with high-dose poisonings. Symptoms of poisoning include bradycardia and hypotension. Antidotal therapies include glucagons, calcium, and hyperinsulinemia-euglycemia.

Calcium

The administration of calcium salts should be the first choice in symptomatic calcium channel antagonist poisoning. Although human case reports are conflicting on the efficacy of this therapy, animal studies are generally supportive of its use [172]. The relative safety of intravenous calcium infusions is also favorable compared with other proposed antidotes for these cases. Calcium gluconate can be given via peripheral intravenous access, whereas calcium chloride requires central venous access for administration because of its caustic effects. Increased extracellular calcium is thought to lead to an increased concentration gradient, driving calcium intracellularly [170]. The effect may be short-lived and the condition may require additional therapy.

Each 10-mL ampule of calcium gluconate (1 g) contains 90 mg of elemental calcium, whereas 10 mL of calcium chloride (1 g) contains 272 mg of elemental calcium [173]. Usual adult dosing begins with 30 to 60 mL of calcium gluconate or 10 to 20 mL of calcium chloride with repeated doses every 15 to 20 minutes to keep the serum calcium in the high- normal range [170]. Some toxicologists recommend pushing serum calcium concentrations higher than normal in refractory cases. Hypercalcemia can occur with overzealous treatment and can lead to nausea, vomiting, and myocardial depression.

Hyperinsulinemia-Euglycemia

Hyperglycemia in the setting of calcium channel blocker poisoning is relatively common. Calcium

channel blockers have been shown to decrease cellular uptake of glucose and free fatty acids and shift oxidation from fatty acids to carbohydrates [174]. Several animal studies and case series have demonstrated the benefit of insulin in this setting [174-177]. Intravenous insulin has an onset of action of approximately 10 to 15 minutes [174]. Insulin improves glucose uptake and myocardial oxygen delivery in addition to increasing inotropy [175]. This therapy also seems to improve peripheral vascular resistance [176].

Hypotension refractory to calcium or glucagon treatment in the setting of calcium channel blockade or β-adrenergic receptor blockade warrants consideration of insulin and glucose therapy. A bolus dose of insulin, 1 IU/kg IV, may be administered, followed by an insulin infusion at a rate of 0.5 to 1.0 IU/kg/h titrated to effect. Capillary blood glucose should be monitored every 20 minutes for the first hour and then at hourly intervals [172]. A 10% dextrose infusion should be titrated to keep the capillary blood glucose in the 150 to 200 mg/dL range. Potassium should also be closely monitored.

Iron Poisoning

Iron poisoning produces a rapidly progressive course of multiple organ failure. Severe poisonings occur typically with ingestions greater than 60 mg/kg of elemental iron [178]. Absorption of excess iron results predominantly from profound irritant effects on the gastrointestinal (GI) tract. Free iron can then be absorbed through this damaged GI mucosa and can produce direct hepatocyte damage, impaired coagulation, iron-mediated cardiac depressant effects, and renal failure. Profuse vomiting, diarrhea, gastrointestinal blood loss (hematemesis, hematochezia), hypotension, and a profound metabolic acidosis may be seen following large toxic ingestions.

Deferoxamine

Deferoxamine is derived from *Streptomyces pilosus* and possesses a high affinity and specificity for ferric iron (Fe^{3+}). Free iron and iron transported between transferrin and ferritin may be bound or chelated by deferoxamine while having little effect on iron contained in hemoglobin, hemosiderin, or ferritin [179]. Deferoxamine administration should be considered following iron poisoning in the presence of hypotension and signs of progressive shock, repetitive vomiting, metabolic acidosis,

serum iron levels >500 µg/dL, or a general toxic appearance [180]. Because plasma iron absorption is variable with levels that peak in the first 2 to 6 hours following ingestion, treatment should not be withheld from individuals with levels <500 µg/dL with signs of severe toxicity because peak serum iron levels may be unknown [181]. If free iron is present in circulation on deferoxamine administration, the iron-ferrioxamine complex will be cleared by the kidneys and will appear as red or "wine" colored urine. The presence of this "vin rose" urine can then be used as a guide to duration of therapy, because urine color normalizes as potentially toxic free iron is removed from the bloodstream.

Deferoxamine is administered intravenously initially at 5 to 10 mg/kg/h and should be rapidly titrated up to 15 mg/kg/h. Supportive care with intravenous fluids and vasopressors is imperative with signs of progressive shock because deferoxamine is unable to reverse pretreatment iron-mediated effects. In addition, deferoxamine is able to chelate a relatively small portion of the total unbound plasma iron following large ingestions. One hundred milligrams of deferoxamine is capable of chelating just 8.5 g of elemental iron [182]. Infusions of greater than 15 mg/kg/h of deferoxamine (maximum manufacturer-recommended dose) have been given successfully but should be done with caution given deferoxamine-induced hypotension (mediated by histamine release) that can occur at higher doses in patients already prone to hypotension [183]. Higher dose deferoxamine has also been associated with acute lung injury when infused for greater than 24 hours [184]. Deferoxamine discontinuation is recommended by 24 hours with signs of clinical improvement. Deferoxamine and chronic iron overload, in addition, have also been implicated in several cases of *Yersinia enterocolitica* sepsis. This bacterium requires iron as a growth factor but lacks the ability to solubilize the element and transport it intracellularly. The combination of excess iron and deferoxamine may therefore encourage the growth of *Yersinia* species given its ability to rapidly proliferate in this high iron concentration environment. Severe diarrhea and septic-appearing signs and symptoms beginning several days following deferoxamine treatment should prompt consideration of *Yersinia* sepsis [185].

Discontinuation of deferoxamine is appropriate with resolution of metabolic acidosis, when clinical improvement is noted, and urine color is returning to normal [180]. With some laboratory colorimetric assays, serum iron levels, it should be noted, may be falsely lowered in the presence of deferoxamine. This may limit the usefulness of monitoring iron

concentrations as an end point for therapy [186]. Deferoxamine should not be withheld in pregnancy because neither iron nor deferoxamine will cross the placenta very well [187]. Poor fetal outcomes following iron poisoning occur in the presence of maternal hemodynamic compromise [188].

Oral Anticoagulant Poisoning

Anticoagulants function by disabling the complex coagulation pathway resulting in an inability to generate thrombin and subsequent fibrin clot. Disruption of the intrinsic pathway (heparin) and the extrinsic pathway (warfarin and "warfarinlike" substances) may result in potentially life-threatening complications such as gastrointestinal, intracranial, and retroperitoneal hemorrhage [189]. Oral anticoagulants include short-acting agents, such as warfarin, and the long-acting anticoagulant rodenticides (LAARs) or "superwarfarins," which include difenacoum and brodifacoum. Therapeutic misadventures, drug interactions that inhibit warfarin metabolism, and intentional rodenticide ingestions result in the majority of anticoagulant poisoning. Intentional overdoses with heparin are rare. Cases of heparin toxicity typically involve inappropriately high heparin dosages administered to hospitalized infants. The use of the reversal agent protamine may be considered in these rare circumstances and is reviewed elsewhere [190].

Phytonadione (Vitamin K_1)

Vitamin K_1 administration is used for xenobiotic-induced alterations of the extrinsic coagulation pathway, typically seen following ingestions of warfarin or LAARs. Oral anticoagulants irreversibly inhibit vitamin K reductases, enzymes responsible for maintaining adequate quantities of vitamin K quinol, the active form of vitamin K [191-193]. Vitamin K quinol is a required cofactor for the carboxylation reaction, which produces active forms of coagulation factors II, VII, IX, and X. In its absence, these factors become depleted, evident by prolonged prothrombin times (PT) and International Normalized Ratio (INR) abnormalities when falling to 25% of normal values [194].[194]

Vitamin K_1 reversal of PT and INR may be evident after several hours, typically taking 8 to 24 hours to return to baseline values [195,196]. Vitamin K_1 is available for administration as oral and parenteral (intramuscular, subcutaneous, IV) formulations. Oral

vitamin K_1 possesses no real adverse effects and should be considered the route of choice in individuals able to tolerate enteral administration. The intravenous form of vitamin K_1 has a slightly faster onset of action than oral vitamin K_1; however, this benefit should be weighed against its potential toxicity evident by numerous cases of anaphylactoid reactions that have been reported even with proper administration [197]. Intramuscular injections may produce hematomas in highly anticoagulated individuals and should be administered with caution. The onset of vitamin K_1 effect may take several hours, even with IV vitamin K_1; therefore, coadministration of fresh frozen plasma, which contains active clotting factors, should be strongly considered with active bleeding or significantly elevated INRs (>20) for rapid coagulopathy reversal [198].

Treatment duration requirements with vitamin K_1 are variable. Warfarin has a half-life of approximately 35 hours; therefore, treatment with vitamin K_1 will typically be required for at least 3 to 5 days to maintain adequate stores of clotting factors [198]. LAARs may need treatment for up to several months given their prolonged enzyme inhibitory capabilities [199]. Individuals requiring chronic anticoagulation who experience therapeutic errors make up a special population, because only partial reversal of a coagulopathy may be necessary to avoid complications from their underlying medical problem. Consensus guidelines for this patient subset have been established by the American College of Chest Physicians [200].

Half-lives of exogenously administered vitamin K_1 suggest that dosing may be necessary 3 to 4 times daily to maintain adequate supplies of clotting factors [201]. Treatment with 50 to 100 mg orally 3 to 4 times per day for >6 months has been needed following large LAAR ingestions [202]. Factor VII levels, which possess the shortest half life (5 hours) of the affected clotting factors, as well as the INR, are typically used to guide the duration and dosage of vitamin K_1 needed [194,203]. Following rodenticide ingestion, prophylactic treatment is not recommended. INR and PT should be assessed 2 to 3 days following ingestion to determine if prolonged therapy may be warranted. Prophylactic treatment will not allow this determination to be made until the effects of exogenously administered vitamin K_1 have worn off. Small amounts of ingested LAARs typically do not require prolonged treatment. A 1-time ingestion of less than 1 box of rodenticide has been shown to be unlikely to produce any clinically significant coagulopathy, even in small children [203,204].
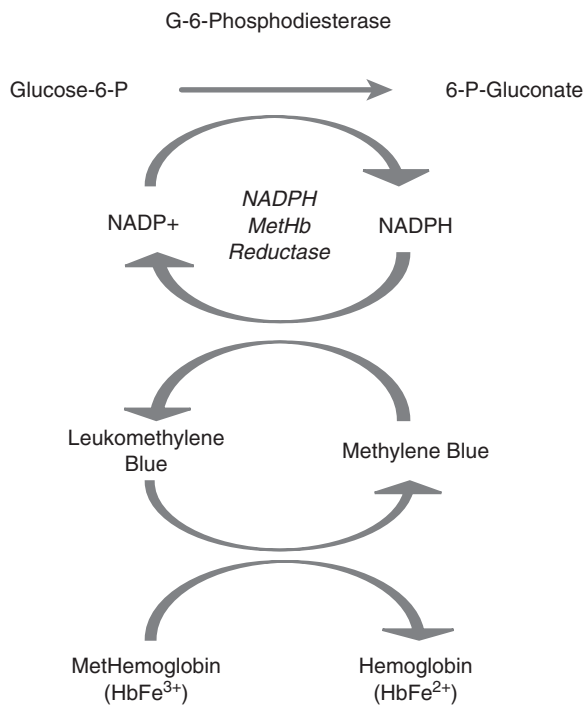
G-6-Phosphodiesterase

Glucose-6-P → 6-P-Gluconate

NADP+ · NADPH

NADPH MetHb Reductase

Leukomethylene Blue · Methylene Blue

MetHemoglobin $(HbFe^{3+})$ · Hemoglobin $(HbFe^{2+})$

Fig 2. Reduction pathway of methemoglobin (MetHb) to hemoglobin. Methylene blue is nonenzymatically converted to leukomethylene blue, which is dependent on adequate production of reduced nicotinamide adenine dinucleotides phosphate (NADPH) by the hexose monophosphate shunt. NADP+ = oxidized nicotinamide adenine dinucleotide phosphate.

Botulism

Botulism is a paralytic illness caused by the toxin produced by *Clostridium botulinum*. It is primarily caused by ingestion of foodstuffs contaminated with the toxin, although it may also result from *C botulinum* contamination of infections incurred during subcutaneous injection ("skin-popping") of illicit substances [205]. *C botulinum* toxin is also a potential biological weapon [205]. Seven botulinum toxins have been identified, but only 3 are commonly implicated in human illness (A, B, and E) [206]. The toxin acts by blocking the release of acetylcholine at the neuromuscular junction, leading to flaccid paralysis [205]. Signs and symptoms develop within 12 to 36 hours and include nausea and vomiting, difficulty swallowing, facial weakness, double vision, and descending muscular weakness and paralysis that can progress to respiratory failure. The cause of death is usually respiratory insufficiency. The diagnosis is primarily clinical, but serum assays can be sent for confirmation.

Botulism Antitoxin

Antitoxin acts by binding to free botulinum toxin, preventing its uptake into the neuron. It needs to be administered as soon as the diagnosis is considered, because only toxin that has not entered neurons will be bound. Treatment with antitoxin within 24 hours of exposure has been shown to reduce the overall duration of symptoms [207]. Waiting for confirmatory tests may result in severe, otherwise preventable disease [206,207].

Several antitoxin preparations are available from state health departments or the Centers for Disease Control and Prevention (CDC). The most common preparations are bivalent (A and B), which have 7500 IU of type A and 5000 IU of type B antitoxin, and trivalent (A, B, and E), which have 7500 IU of type A, 5500 IU of type B, and 8500 IU of type E antitoxin [207]. Monovalent (E), pentavalent (A, B, C, D, and E) and heptavalent (A, B, C, D, E, F, and G) preparations are also available in special circumstances. Once a case of botulism is suspected, the clinician should first contact the state health department. If this is not satisfactory, the CDC can be contacted at 770-488-7100 (24 hours).

The trivalent antitoxin is administered as an initial dose of 1 vial every 2 to 4 hours for 3 to 5 doses depending on the severity of symptoms. Each vial is diluted 1:10 in normal saline and infused slowly. The other preparations are administered in a similar fashion. The antitoxins are immunoglobulin preparations from horses, and hypersensitivity reactions occur in approximately 9% of those treated [208]. A skin test prior to antidote administration is recommended by some clinicians; however, its use is controversial given the high rate of false-negative and false-positive results associated with equine serum skin testing. Despite this relatively high rate of hypersensitivity reactions, antitoxin should be administered when reasonable suspicion of botulinum poisoning is present given its potential for significant morbidity and mortality. Diphenhydramine (50 mg IV) should be administered as pretreatment, and an epinephrine infusion should be available for immediate use at the bedside should signs of anaphylaxis occur [207].

Methemoglobinemia

Methemoglobinemia refers to the oxidation of hemoglobin ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). The ferric iron does not bind oxygen but increases the oxygen affinity of the remaining normal heme groups and shifts the oxyhemoglobin dissociation

curve to the left, leading to cellular hypoxia [209]. In normal healthy individuals, <1% of hemoglobin is in the Fe^{3+} state. Reduction to the ferrous form is continually taking place via NADH-cytochrome b5 reductase (major pathway) and reduced nicotinamide adenine dinucleotides phosphate (NADPH) methemoglobin reductase (minor pathway). Exposure to various oxidizing agents may produce elevated methemoglobin concentrations, overwhelming the body's reducing capabilities and eventually leading to increased methemoglobin levels and progressive symptomatology.

Methylene Blue

Methylene blue is the standard antidote for methemoglobinemia. Methylene blue acts rapidly, reversing methemoglobinemia within 30 minutes of administration. Within red blood cells, NADPH-methemoglobin reductase reduces methylene blue to leukomethylene blue, which then nonenzymatically donates an electron to methemoglobin, reducing the heme molecule (Fig 2) [210]. Methylene blue is regenerated in this reaction and is then acted on again by NADPH- methemoglobin reductase. This reaction depends on production of NADPH and may have limited effectiveness in patients deficient in glucose-6-phosphate dehydrogenase (G6PD), a key enzyme in the NADPH-generative monophosphate shunt [211].

The use of methylene blue should be based on the clinical appearance of the patient. Methylene blue is typically recommended for methemoglobinemia levels of 20% or greater; however, some individuals may tolerate levels of 40% or higher. Treatment at lower methemoglobin levels should be initiated in patients with symptoms of chest pain, anxiety, or tachycardia or with a history of cardiac, pulmonary, or CNS disease [210]. Methylene blue is dosed at 1 to 2 mg/kg IV over 5 minutes and may be repeated at 1 mg/kg IV if there is no improvement after 30 minutes [209]. Pulse oximetry readings are inaccurate in methemoglobin-poisoned patients and will plummet even further following methylene blue administration. Certain methemoglobin-producing agents, such as dapsone, may typically require repeat dosing of methylene blue because of its prolonged half-life and methemoglobin-inducing metabolites [212]. In doses higher than 7 mg/kg or in G6PD individuals, methylene blue can induce hemolysis [213]. Treatment with exchange transfusions may be warranted in these unusual circumstances. Intravenous infusion can be irritating to the blood vessel, and extravasation of methylene blue can lead to local tissue damage [210].

Snake Envenomations

An estimated 8000 snake envenomations occur in the United States each year. The pit vipers (Family Viperidae), including rattlesnakes (Crotalidae), cottonmouths (water moccasins), and copperheads (Agkistrodons) account for the vast majority of bites (95%) and occur in all states with the exception of Maine, Alaska, and Hawaii [214]. Effects of envenomation are divided into 4 categories: (1) local effects such as pain, swelling, ecchymoses, blistering, and tissue necrosis; (2) hematoxic effects including thrombocytopenia, hypofibrinogenemia, and hypoprothrombinemia; (3) neurotoxic effects including paresthesias and fasciculations; and (4) anaphylaxis, or the rare occurrence of immediate cardiovascular collapse secondary to presumed intravascular venom release [215].

Despite tremendous amounts of fear surrounding snake envenomations, death is a very rare occurrence in the United States, with an estimated 5-15 fatal bites occurring each year [216]. Rattlesnake envenomations are generally considered capable of producing more severe symptoms than cottonmouths and copperheads [217]. Antivenoms for the neurotoxic Eastern Coral Snake and exotic nonnative species are not typically available to most hospitals, and immediate contact with a poison control center is recommended to locate these products when necessary. Venom is not always injected into a victim every time a rattlesnake bite occurs. Approximately 20% of bites are "dry bites" in which no venom is injected into the victim and symptoms do not occur [218]. These cases require no therapy other than typical wound care. Individuals showing no evidence of venom effects after 12 hours of observation are unlikely to develop any subsequent toxicity, with the exception of those sustaining bites from the Mojave rattlesnake, in which case local symptoms may be minimal and neurological features may be delayed up to 24 hours from the time of envenomation [219].

Crotalinae Polyvalent Immune Fab (CroFab®)

CroFab® is the only currently manufactured snake antivenom in the United States. This ovine-derived antivenom is prepared by purifying IgG antibody fragments from sheep inoculated with venom from the cottonmouth, eastern and western diamondback, and Mojave rattlesnake. The similarity among venom components of pit vipers allows for cross-reactivity and neutralization of venom from other North

American species. The elimination of the antigenic "Fc" portion of the IgG molecule from the purified sheep sera with papain leaves a specific Fab fragment antivenom and creates a less immunogenic product. This results in a lower incidence of both immediate and delayed hypersensitivity reactions.

Crofab® is indicated to treat any local or systemic signs of envenomation such as pain, swelling, fasciculation, paresthesias, or measured hematologic abnormalities such as thrombocytopenia, hypofibrinoginemia, or prothrombin time elevations. Initial dosing consists of 4 to 8 vials depending on symptom severity. Additional antivenom therapy after this initial dosing should continue without delay until swelling progression is halted and pain subsides. Hematological and neurological abnormalities may be less responsive to antivenom administration especially if administered more than 24 hours after the envenomation. Laboratory evidence of coagulopathy may persist for several days after the bite and become refractory to further antivenom administration.

Recurrence of symptoms following initial control with Fab antivenom may occur hours to days later and may require the administration of additional antivenom [220]. Consideration of repeated 2-vial dosing every 6 hours for 3 additional doses is recommended by the manufacturer to prevent these recurrent effects; however, the benefit of these prophylactic doses has not been well studied. Children will require antivenom doses equal to those of adults because total venom inoculation (amount requiring antivenom neutralization) is independent of patient size or weight. Each vial of CroFab® should be reconstituted with 10 mL of sterile water and mixed by continuous gentle swirling. This should be further diluted in 250 mL of 0.9% normal saline and administered within 4 hours. The initial dose should proceed slowly over the first 10 minutes at a 25 to 50 mL/h rate with careful observation for any allergic reaction. If no such reaction occurs, the infusion rate may be increased to the full 250 mL/h rate until completion.

Crotaline Polyvalent Antivenom (Antivenin Crotalidae Polyvalent®)

Antivenin Crotalidae Polyvalent® is an equine-derived antivenom that has been used in the United States since 1954. Production of this antivenom has largely stopped, and its availability is only sporadic from reserve supplies. This product consists of whole serum immunoglobulins (IgG) derived from horses immunized with venom from the eastern and western diamondback rattlesnakes, the tropical rattlesnake, and fer-de-lance, the latter 2 being found in Central and South America. Because the product is an equine-derived antivenom consisting of both the Fc and Fab portions of the immunoglobulin, the risk of both immediate and delayed hypersensitivity reactions is higher. Treatment with H_1- and H_2-blocking agents, corticosteroids, and subcutaneous or intravenous epinephrine may be needed if immediate allergic reactions occur and should be readily available at the time of antivenom initiation. The routine use of skin testing prior to administration of the equine IgG antivenom is advocated by some authors; however, false-positive and false-negative skin tests are common [221]. A review of 26 patients treated with equine antivenom therapy found 23% developing immediate hypersensitivity reactions, with delayed reactions (serum sickness) in 50% [222]. Because of this high rate of adverse reactions, crotaline Fab antivenom appears to be a safer alternative for the treatment of all US pit viper envenomations.

Conclusion

The proper use of antidotes in the intensive care setting, when combined with aggressive supportive care, may significantly reduce the morbidity and mortality associated with many severe poisonings. Readily available access to these antidotes, a basic understanding of the indications for their usage, and knowledge of the potential for adverse effects will allow the intensivist to appropriately implement early treatment for many common intentional and unintentional poisonings. Many poisonings are rarely seen even in academic intensive care units, and therefore the intensivist is encouraged to consult with the experienced regional medical toxicologist.

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