INTRODUCTION

“What is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison” (1). This observation of the dose–response relationship made by Paracelsus in the 16th century holds today. One need not look farther than basic elements of oxygen or water to see that all substances can act as a poison at a specified dose. Medical toxicology, the care of poisoned patients, was recognized as a medical subspecialty in 1992 and today all 50 states are served by poison control centers; pioneered by the first in Chicago in 1953 (2). The American Association of Poison Control Centers (AAPCC) maintains the National Poisoning and Exposure Database (NPED) and includes comprehensive data from every case reported to poison centers throughout the United States. In 2013, the AAPCC received over 2 million reports of human exposures, including 20,749 major effects, as defined by life-threatening exposures or those causing significant disability, and 2,477 deaths (3).

The key principle in managing the poisoned patient is summarized by the phrase “treat the patient, not the poison.” Patient stabilization is a priority, starting with addressing airway compromise, breathing difficulty, and circulatory problems. Significant vital sign abnormalities or oxygen desaturation should be addressed immediately, and a bedside serum glucose concentration should be rapidly obtained in any patient with an abnormal neurologic examination. Hypoglycemia, while common and easy to correct, can be life threatening if diagnosis is delayed or missed (see section on antidiabetic medications). Additionally, an electrocardiogram (ECG) should be obtained in most cases of suspected poisoning, as several well-defined exposures may produce characteristic ECG changes (tricyclic antidepressants), life-threatening dysrhythmias via direct myocardial effect (cocaine or lidocaine) or by electrolyte abnormality (hydrofluoric acid [HF]).

A thorough physical examination will help identify the presence of a toxic syndrome, or “toxidrome.” The classic toxic syndromes (Table 151.1) can be differentiated based on vital signs, mental status, pupil size, presence (or absence) of peristalsis, diaphoresis, and urinary retention. The physician should keep in mind that toxic syndromes are archetypes that may be affected by coexisting exposures or disease processes, muddying the clinical picture. For example, the practice of “speedballing” (concurrent heroin and cocaine abuse) might result in small, normal, or large pupils. Though identification of a toxic syndrome will not specifically identify the exact poison responsible, it will somewhat guide therapy. For instance, the presence of a sedative–hypnotic toxic syndrome (overdose) warrants support of the airway, whether the condition is a result of ethanol or diazepam abuse.

A comprehensive history should attempt to identify the specific xenobiotic exposure, the amount, the time and reason for exposure, and general medical history. At times, a specific antidote may be warranted (Table 151.2). When the history is limited, laboratory studies and physical examination alone may be helpful in guiding appropriate therapy. Electrolyte abnormalities complicate many severe poisonings, and as a result, serum chemistries are warranted for all critically ill patients. Arterial blood gas analysis and aminotransferases should be judiciously used as well. A routine urine toxicologic screen, however, rarely aids in management as it focuses on select drugs of abuse and has a high rate of false positives and negatives. Even a true-positive result is not necessarily helpful; the cocaine assay, while remarkably specific, will remain positive for days after the clinical effects have subsided. By way of contrast, the acetaminophen concentration should be obtained following all overdoses where self-harm was intended. In one series, 1 in 365 individuals with suicidal ingestion had a potentially hepatotoxic acetaminophen concentration despite a history negative for acetaminophen ingestion (4).

The classification of the severity of the exposure (minor, moderate, major) is based on outcome and is closely tied to the nature of the poisoning, not necessarily the initial appearance of the patient. The need for ICU monitoring is determined by three general factors: (a) hemodynamic stability and clinical presentation, (b) characteristics of the specific xenobiotic, the substance introduced to the body, and (c) hospital unit capabilities (5).

All patients with significant laboratory abnormalities, hemodynamic or neurologic compromise, dysrhythmias, or conduction abnormalities should be admitted to the ICU. Pre-existing medical conditions such as severe liver or renal insufficiency, congestive heart failure, or pregnancy may also influence disposition. Sustained-release products, potentially lethal doses, or xenobiotics that may cause dysrhythmias or require a therapy that has the potential for adverse effects (i.e., high-dose atropine for organophosphate poisoning) have the potential to cause rapid clinical deterioration, and for this reason, require ICU admission for even asymptomatic patients. Finally, the capabilities of the hospital as a whole influence the disposition of the patient. Time-consuming nursing activities, such as hourly glucose checks or continuous drug infusions, may not be possible on general inpatient floors.

Throughout this chapter, a number of exposures (whether dermal, oral, ophthalmic, or inhalation) and their pathophysiology, clinical presentation, and management will be discussed. For the purpose of consistency, a toxin will be defined as a xenobiotic produced by a plant, animal, or fungi, while a drug or pharmaceutical refers to a commercially produced xenobiotic.

NONOPIOID ANALGESICS

In 2013, the American Association of Poison Centers NPED received 298,633 reports of exposures involving analgesics (3).
Acetaminophen Poisoning

Acetaminophen is estimated to be responsible for 51% of all cases of acute liver failure in the United States (6). Acetaminophen ingestions require ICU admission when hepatotoxicity is established. The analgesic effects of acetaminophen are mediated by central cyclo-oxygenase (COX)-2 and prostaglandin synthase inhibition (7). The metabolism of acetaminophen occurs principally in the liver and less than 5% of acetaminophen is eliminated unchanged in the urine. Ninety percent of absorbed acetaminophen undergoes hepatic conjugation with either glucuronic acid or sulfate to produce inactive metabolites. The remainder (5% to 15%) is oxidized by the cytochrome P450, forming N-acetyl-p-benzoquinoneimine (NAPQI), a toxic oxidant (8). Thiol-containing compounds, such as reduced glutathione, are used as electron donors to detoxify NAPQI.

<table>
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<tr>
<th>TABLE 151.1 Toxidromes</th>
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<td><strong>Group</strong></td>
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<tr>
<td>Anticholinergic</td>
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<tr>
<td>Cholinergic</td>
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<tr>
<td>Ethanol, sedative-hypnotic</td>
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<tr>
<td>Opioid</td>
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<tr>
<td>Sympathomimetic</td>
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<tr>
<td>Withdrawal from ethanol or sedative-hypnotic</td>
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<td>Withdrawal from opioids</td>
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The extensive availability of these drugs contributes to their prevalence in both suicidal ingestions and unintentional pediatric ingestions. Although they are generally safe when used correctly, the widely held misconception that these pharmaceuticals are harmless undoubtedly contribute to their potential for causing harm.

<table>
<thead>
<tr>
<th>TABLE 151.2 Selected Antidotes with Common Doses</th>
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<tr>
<td><strong>Xenobiotic</strong></td>
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<td>------------------------</td>
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<tr>
<td>Acetaminophen</td>
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<td>Calcium channel blockers</td>
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<td>Cholinergic compounds</td>
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The single dose of acetaminophen generally thought to produce toxicity is at least 150 mg/kg (8). In overdose, absorption of acetaminophen may be delayed, although peak absorption generally occurs at 2 hours, and rarely after 4 hours (9,10). Absorption may be expected to be further delayed in the presence of peristalsis-decreasing opioid or anticholinergic co-ingestants, or if the acetaminophen is formulated for extended release. In overdose, metabolism by sulfation becomes saturated, and the formation of NAPQI exceeds which can be detoxified by available glutathione (11). Because the toxic metabolite is formed in the liver, hepatic toxicity is the key clinical feature. N-acetylcysteine (NAC), the key to management of acetaminophen poisoning, acts as a precursor to glutathione synthesis, a substrate for sulfation; it directly binds to NAPQI itself; and enhances the reduction of NAPQI to acetaminophen (12).

Clinical Manifestations

Acute acetaminophen toxicity has been divided into four clinical stages (13). Not every untreated patient will advance through each of these stages. Spontaneous improvement is possible at any point, but the stages of toxicity serve as a useful guide to the progression of symptoms. During stage I, the patient is either asymptomatic or has nonspecific clinical findings (nausea, vomiting, malaise), and no laboratory abnormalities are recognized. Stage II begins with the onset of liver injury, generally within 24 hours but always within 36 hours of ingestion (14). Initial laboratory findings include elevated aminotransferases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), but progress to signs of hepatic dysfunction, including prolonged prothrombin time (PT), metabolic acidosis, and hypoglycemia. Stage III represents the time of peak hepatotoxicity, usually 72 to 96 hours from ingestion. While AST and ALT may ultimately exceed 10,000 IU/L, creatinine, lactate, phosphate, and PT are better indicators of prognosis. Fatalities usually occur within 3 to 5 days of ingestion. When death does not occur, hepatic recovery is referred to as stage IV. Hepatic regeneration will be histologically and functionally complete in survivors.

Management

Decontamination with activated charcoal should be considered if significant co-ingestants are suspected. N-acetylcysteine is the key to managing acetaminophen poisoning and is available for both oral and intravenous (IV) administration. The oral protocol for acute ingestions is a 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours for a total of 72 hours. The IV regimen is 150 mg/kg over 45 minutes, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours. Both regimens have equal efficacy for simple acute ingestion, but the IV regimen has the advantage of a shorter course, and is the only route that has been studied adequately in patients with hepatic failure. Unlike oral NAC, however, parenteral NAC carries the risk of anaphylactoid reactions. The duration and route of treatment should be determined by the patient presentation.

For simple, acute ingestions, the serum acetaminophen concentration should be plotted against the number of hours following ingestion on the Rumack–Matthew nomogram to determine whether treatment with NAC is necessary (15). The treatment line is a sensitive, but not specific, predictor of hepatotoxicity. The currently recommended line intersects 150 μg/mL at 4 hours, incorporating a 25% safety margin over the original nomogram line, which was itself nearly 100% sensitive for predicting hepatotoxicity. When the concentration at a specific time is plotted above the line, treatment is required. When treatment is initiated within 8 hours of ingestion, NAC has complete efficacy in preventing hepatotoxicity (16), and so should be started immediately when the laboratory result for the acetaminophen concentration is not expected to be available within 8 hours of the initial ingestion. Once the serum acetaminophen concentration is available, the decision whether to continue NAC can be reassessed based on the nomogram (Fig. 151.1). When there is uncertainty with regard to the exact time of ingestion, the physician should use the most conservative estimate (i.e., the earliest possible time) when using the nomogram. The risk of inadvertently failing to treat because of an incorrect history is mitigated by the safety margin associated with the nomogram.

The literature is less clear on the indications for the use of NAC for hepatotoxicity following suspected chronic acetaminophen use. The vast majority of people who take acetaminophen have no adverse clinical manifestations. Clinical trials involving daily dosing of 4 g of acetaminophen in both alcoholics and nonalcoholics showed that patients either have normal aminotransferase concentrations or very minor increases (17,18). Despite its safety, hepatotoxicity from chronic use occurs. Because chronic acetaminophen use often occurs in the setting of comorbid conditions, the diagnosis can be difficult to establish with certainty. NAC should be administered to all patients with suspected acetaminophen hepatotoxicity until the diagnosis has been excluded.

The nomogram cannot be used for patients who present more than 24 hours after ingestion. In such cases, NAC should be started immediately upon presentation. If the patient has both an undetectable acetaminophen concentration and normal aminotransferases, acetaminophen overdose is highly
unlikely, and NAC need not be continued. If either acetaminophen or aminotransferase concentrations are elevated (even minimally so), the patient should be administered 20 hours of IV NAC. Following the treatment period, aminotransferase and acetaminophen concentrations should be obtained again; at this point, if the aminotransferase concentrations are only minimally elevated, the patient was either minimally poisoned or acetaminophen was not the cause of the liver damage.

When acetaminophen-induced hepatotoxicity is encountered, IV NAC should be administered as described above, but the maintenance dose should be continued until clinical improvement, liver transplantation, or death occurs. Even in the presence of fulminant hepatic failure, IV NAC has been shown to decrease mortality, cerebral edema, and the need for vasopressors (19).

**Hepatic Transplantation**

The long-term complications of a transplant are significant, and those who survive acetaminophen poisoning without transplant will make a complete recovery. Under ideal conditions, the clinician could immediately determine which patients would survive without transplant and which would not, so that the appropriate patients could be candidates for a liver transplant before irreversible clinical deterioration; in practice, it is not always clear. Several prognostic criteria are available. The King’s College Hospital Criteria suggest that pH less than 7.3 after resuscitation or the combination of PT more than 100, creatinine more than 3.3 mg/dL, and grade III or IV encephalopathy are predictive of death in the absence of a transplant (20). Alternatively, a 48-hour serum phosphate concentration more than 1.2 mmol/L has also been shown to be sensitive and specific for predicting the need for transplant and the probability of death from acetaminophen hepatotoxicity (21). Presumably, a low or normal phosphate concentration is an evidence that the phosphate is being utilized by hepatocytes for adenosine triphosphate (ATP) generation.

**SALICYLATES AND OTHER NONSTERoidal ANTI-INFLAMMATORY DRUGS**

The nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available both with and without prescription for relief of inflammation, pain, and fever. Salicylates are a subgroup of NSAIDs that have unique features of toxicity and require distinct management. In this chapter, we will use the term NSAID to refer to non-salicylate NSAIDs.

The therapeutic effects of salicylates and NSAIDs result from the inhibition of COX, a mediator of prostaglandin synthesis. In general, they are renally eliminated. Because they are designed to promote fast relief, therapeutic doses of the immediate-release drugs produce significant concentrations within an hour. However, when taken in overdose or as enteric-coated or sustained-release formulations, absorption may be delayed and maximal serum concentrations may not be observed for hours after the ingestion.

In addition to these effects, salicylates also uncouple oxidative phosphorylation, meaning that some of the proton gradient across the mitochondrial matrix is dissipated in the formation of heat, rather than ATP, forcing the production of lactate. As a result, ICU admission is required when patients present with metabolic acidosis and hemodynamic instability, or if they require bicarbonate infusion or frequent measurements of salicylate concentration.

**Salicylate Poisoning**

**Clinical Manifestations**

Acute salicylate poisoning may cause epigastric pain, nausea, and vomiting. Salicylates induce hyperventilation (both tachypnea and hyperpnea) by direct stimulation of the brainstem respiratory center (22). Neurologic signs and symptoms of salicylate poisoning range from mild to severe, and include tinnitus, delirium, coma, and seizure. The initial feature of toxicity is primary respiratory alkalosis. A primary metabolic acidosis is characterized by the presence of lactic acid, ketocids, and salicylic acids (23); the net result is an increased anion gap metabolic acidosis. The simultaneous presence of a respiratory alkalosis and metabolic acidosis can be difficult to interpret. Because the respiratory alkalosis initially predominates in adults, the presence of an acidemia or even normal pH indicates advanced poisoning.

Chronic salicylate poisoning presents with the same signs and symptoms as acute poisoning, but typically occurs in elderly patients taking supratherapeutic amounts of salicylate to treat a chronic condition. Chronic poisoning can be a challenging diagnosis to establish because it is often not suspected. Elderly salicylate-poisoned patients presenting with metabolic acidosis and an altered sensorium may be initially misdiagnosed with sepsis, dehydration, or cerebrovascular accident (CVA) if a salicylate concentration is not obtained.

Serum salicylate concentrations only correlate loosely with toxicity because the principal site of poisoning is the central nervous system (CNS). The threshold for toxicity is usually considered to be 30 mg/dL when tinnitus develops. Chronically poisoned patients have a lower salicylate concentration for the same degree of illness because much of their total body burden has redistributed into the CNS. The degree of poisoning is determined by evaluating the serum concentration in the context of the patient's clinical appearance, laboratory results, and acuity of the ingestion.

**Management**

The key principles for management of salicylate poisoning are to minimize absorption, speed elimination, and minimize redistribution to tissues. Gastric emptying should only be attempted if a significant amount of drug is expected to be present in the stomach. Activated charcoal, 1 g/kg, should be administered every 4 hours if it can be given safely. Salicylates cause pylorospasm and may form concretions in overdose, leading to delayed absorption. Multiple-dose activated charcoal (MDAC) not only prevents delayed absorption, but also may speed up the elimination of salicylates by disrupting the enteroenteric circulation of the drug (24). Serum chemistry, venous or arterial blood gas analysis, and salicylate concentration should be obtained every 2 hours until the salicylate concentration demonstrates an interval decrease.

Moderately poisoned patients (increased anion gap or a salicylate concentration >40 mg/dL) should also have blood and urine alkalineized with sodium bicarbonate. As a weak acid
(pKa 3.5), salicylates will be ionized in an alkaline environment and “trapped” (i.e., unable to passively move through lipid membranes). Ionization prevents salicylate in the proximal tubule from diffusing into the plasma and salicylate in the plasma from diffusing into tissues, such as the brain (25). Alkalization can be achieved with an infusion of sodium bicarbonate of 150 mEq in 1 L of D5W at twice the maintenance rate. The urine pH should be maintained from 7.5 to 8.0 and systemic arterial pH between 7.45 and 7.55. Close attention should be paid to potassium repletion, as low serum potassium will cause preferential reabsorption of potassium over hydrogen ions in the proximal tubule and compromise attempts to alkalize the urine (26). Endotracheal intubation and sedation should be avoided whenever possible. The tachypnea and hyperpnea of salicylate poisoning do not necessarily represent “tiring,” and produces a helpful alkalosis. When intubation is unavoidable, patients should be administered 1 to 2 mEq/kg of bicarbonate prior to the procedure, intubated quickly, and hyperventilated afterward to avoid respiratory acidosis (27).

Early consultation with a nephrologist is recommended for seriously ill patients. Extracorporeal elimination is reserved for patients who are very ill, those who cannot tolerate alkalization, or those with serum concentrations so elevated that their clinical status is expected to deteriorate. We recommend hemodialysis for severe acid–base disturbances, mental status changes, inability to tolerate alkalization (renal failure or congestive heart failure), and serum salicylate concentrations of 100 mg/dL after acute poisoning and 60 mg/dL in chronic poisoning (Table 151.3).

**TABLE 151.3 Indications for Hemodialysis in Salicylate Poisoning**

- Renal failure
- Congestive heart failure (relative)
- Acute lung injury
- Persistent central nervous system disturbances
- Progressive deterioration in vital signs
- Severe acidosis or electrolyte imbalance, despite appropriate treatment
- Hepatic compromise with coagulopathy
- Salicylate concentration (acute) > 100 mg/dL or (chronic) >60 mg/dL


NSAID Poisoning

**Clinical Manifestations**

NSAIDs are considered safer than salicylates in therapeutic dosing. While chronic NSAID use is associated with interstitial nephritis, nephritic syndrome, or analgesic nephropathy, acute overdose can cause gastric injury and is sometimes accompanied by a reversible azotemia caused by vasoconstriction from decreased prostaglandin production (28). In severe overdose, the most consequential effects are elevated anion gap metabolic acidosis, coma, and hypotension (29).

**Management**

Activated charcoal should be administered if the patient presents within several hours of overdose. Good supportive care is the mainstay of therapy after NSAID overdose. NSAID elimination is not increased with alkalization and NSAIDs’ high degree of protein binding precludes removal with hemodialysis. Hemodialysis has, however, been used to correct acidemia and electrolyte abnormalities in patients with multiorgan system failure.

**PSYCHIATRIC MEDICATIONS**

Psychiatric medications represent a disproportionate number of poisonings in the United States. Antidepressants, antipsychotics, and sedative–hypnotics accounted for more than 20% of all deaths reported to poison control centers in 2013, while accounting for only 5.9% of total exposures (3).

**Antipsychotic Poisoning**

The antipsychotics are categorized as either typical or atypical. The typical antipsychotics, which include haloperidol, chlorpromazine, and thioridazine, antagonize dopamine primarily at the D2 receptor. The newer, atypical, medications are exemplified by clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, which have less dopaminergic antagonism and more serotoninergic effects than the typical antipsychotics. When antipsychotic medications produce coma, conduction abnormalities, or hyperthermia, these patients require ICU admission.

**Clinical Manifestations**

All antipsychotics produce sedation in overdose, though respiratory depression is usually not consequential. The drugs have varying degrees of muscarinic and α-adrenergic antagonism, often resulting in tachycardia and moderate hypotension (30). Many of the typical antipsychotics have type-IA antidyssrhythmic properties; most of the typical and a few of the atypical drugs (notably ziprasidone) can cause QTc prolongation and *torsades de pointes* (31,32). Management of overdose of the antipsychotics generally only requires supportive care.

**Neuroleptic Malignant Syndrome**

The dopamine antagonism required for control of psychosis can cause a group of distinct movement disorders that range in severity from mild to life threatening. These conditions—dystonia, akathisia, parkinsonism, tardive dyskinesia, and neuroleptic malignant syndrome (NMS)—are more likely to occur in the presence of the typical antipsychotics, although the atypical antipsychotics can cause them as well. The first four conditions mentioned above are of less concern to the intensivist than NMS, and will not be discussed.

NMS is characterized by the presence of altered mental status, muscular rigidity, hyperthermia, and autonomic dysfunction (33). While symptoms usually begin within weeks of starting treatment, they do occur in individuals that are taking the drug on a chronic basis. Risk factors include young age, male gender, extracellular fluid volume contraction, use of high-potency antipsychotics, depot drug preparations, concomitant lithium use, rapid increase in dose, or simultaneous use of multiple drugs (32). Diagnosis is not always clear because there is no reference standard. Other diagnoses to consider include infection, environmental hyperthermia, hyperthyroidism, serotonin syndrome, ethanol and sedative–hypnotic withdrawal, sympathomimetic intoxication, and anticholinergic intoxication.
Management of NMS begins with immediate treatment of life-threatening hyperthermia. Ice-water immersion and paralysis by neuromuscular blockade should not be delayed if temperature is more than 106°F (41.1°C). In instances of environmental hyperthermia, a delay of cooling longer than 30 minutes has been associated with significant morbidity and mortality (34). Benzodiazepines should be titrated to sedation and muscle relaxation. When present, rhabdomyolysis, electrolyte disorders, and hypotension should be aggressively treated.

Bromocriptine, a centrally acting dopamine agonist given at 2.5 to 10 mg three to four times a day, may be of theoretical benefit even though it is not well studied and may take days to control symptoms. After evidence of clinical improvement, bromocriptine should be decreased by no more than 10% a day since decreasing the dose too rapidly may precipitate a relapse of NMS. We do not recommend dantrolene, the drug of choice for malignant hyperthermia, in the management of NMS.

**Benzodiazepine Poisoning**

Benzodiazepines are widely used for their sedative, anxiolytic, and anticonvulsant properties, which are moderated by the frequency of opening of γ-aminobutyric acid (GABA)-mediated chloride channels in the CNS (35). In overdose, these drugs produce somnolence, coma, and minimal decreases in blood pressure, heart rate, and respiratory rate.

**Management**

Management of benzodiazepine overdose is supportive. Care of the comatose patient should focus on supporting the airway and blood pressure while waiting for the drug to be eliminated. There is a limited role for flumazenil, a competitive benzodiazepine antagonist; flumazenil can precipitate withdrawal in individuals who are tolerant to benzodiazepines and induce seizures in those with seizure disorders (36,37). Flumazenil may be indicated in patients without tolerance to benzodiazepines, such as children, who suffer from benzodiazepine overdose. When indicated, flumazenil should be given intravenously, 0.1 mg/min, up to 1 mg and can be repeated if the clinical response is inadequate. Because the duration of the effect of flumazenil is shorter than the effect of the benzodiazepine, recurrence of symptoms should be expected.

If there is any doubt as to whether the patient has tolerance to benzodiazepines, flumazenil should not be administered. Benzodiazepine poisoning can be managed effectively and safely with supportive care only, but benzodiazepine withdrawal precipitated by flumazenil can be life threatening.

**Cyclic Antidepressant Poisoning**

Until the introduction of the selective serotonin reuptake inhibitors (SSRIs), the cyclic antidepressants (CAs) were the principal pharmacologic treatment available for depression. In 2013, 13,037 CA exposures were reported to the AAPCC, with tricyclic antidepressants accounting for 2.27% of total fatalities (3). While the CAs differ slightly from each other in their receptor affinities, they can be treated as a group.

The CAs are usually absorbed within hours of ingestion, although the antimuscarinic effects may delay absorption in overdose. The drugs also exhibit α-adrenergic antagonism, inhibition of reuptake of norepinephrine, and anticholinergic properties. Acting as type-IA antidysrhythmics, CAs block sodium entry into myocytes during phase 0 of depolarization. Acute ingestions of 10 to 20 mg/kg of most CAs can cause significant poisoning (38).

**Clinical Manifestations**

Important CNS effects include lethargy, delirium, coma, and seizures. Tachycardia and hypotension develop early in toxicity. The IA antidysrhythmic properties cause prolongation of the QRS interval. CAs also produce a characteristic rightward shift of the axis in the terminal portion of the QRS, best seen as an R wave in the terminal 40 milliseconds of lead aVR (Fig. 151.2) (39). Serum drug concentrations may be obtained but do not correlate well with toxicity (40).

**Management**

Gastrointestinal decontamination should be considered in every patient. If the history suggests a recent large ingestion, activated charcoal should be administered and gastric lavage may be attempted. The ECG is the most important diagnostic test when managing CA overdose. A terminal 40-millisecond QRS axis of 130 to 270 degrees discriminated patients with CA toxicity from those without toxicity in one study (41). While the terminal 40-millisecond QRS axis is a good indicator of exposure, QRS duration is a better indicator of severity of poisoning. In another series, no patients with QRS less than 160 milliseconds had ventricular dysrhythmias and no patients with a QRS duration less than 100 milliseconds had seizures (40).

Sodium bicarbonate should be administered if the QRS duration is 100 milliseconds or more. Both the high sodium concentration and alkaline pH of sodium bicarbonate solution are responsible for its salutary effects. The sodium load increases the sodium gradient across the poisoned myocardial sodium channel, resulting in a narrowing of the QRS complex. The bicarbonate raises the pH, reducing CA binding to the sodium channel. Sodium bicarbonate should be administered as a 1- to 2-mEq/kg bolus during continuous ECG monitoring. If the complex narrows, sodium bicarbonate can be administered as an infusion. If the complex remains unchanged, the diagnosis of CA poisoning should be reconsidered. The sodium bicarbonate infusion may be performed by adding 150 mEq of bicarbonate to 1 L of D5W and infusing at twice the maintenance rate, with an arterial pH target of 7.50 to 7.55. Occasional repeat boluses of 1 to 2 mEq/kg may
be necessary. Hypertonic sodium chloride (3% NaCl) may be indicated when the QRS complex widens and the serum pH precludes further alkalinization. Hyperventilation may be used to induce alkalemia in intubated CA-poisoned patients and in those who cannot tolerate the fluid or sodium load from sodium bicarbonate. Although hyperventilation did not have an effect in one experimental model, it has been used clinically with success (42,43).

Seizures should be rapidly controlled as they will cause a metabolic acidosis, which will lead to even more avid binding of the CA to the cardiac sodium channels and potentially worsen cardio toxicity. Benzodiazepines can be safely administered or, alternatively, propofol or barbiturates are also appropriate. Phenytoin, a type-IA antidyssrhythmic, may worsen cardiac toxicity and is therefore not indicated (44).

If hypotension persists despite fluid resuscitation and vasopressors become necessary, norepinephrine may be superior to dopamine because intracellular catecholamines may be depleted. Therapy should continue until vital signs and ECG improve. In most instances, CA poisoning results in a rapid deterioration within hours of overdose. Unless there has been a significant secondary injury (such as from shock), those who survive to 24 hours are expected to make a complete recovery. Because of avid CA protein binding, hemodialysis is deemed ineffective.

**Lithium Poisoning**

Lithium is used in the treatment of bipolar affective disorders. Of 6,610 exposures reported to the AAPCC, 2.3% were classified as major or fatal (3). Patients will require ICU admission when they have signs of CNS toxicity, do not tolerate fluid therapy, or have serum concentrations more than 2 mmol/L, which may result in rapid deterioration.

Lithium is thought to increase serotonin release and increase receptor sensitivity to serotonin, as well as modulate the effects of norepinephrine on its second-messenger system (45). Lithium is freely filtered by the glomerulus, 80% of which is reabsorbed, with 60% occurring in the proximal tubule (46). Immediate-release preparations produce peak serum concentrations within hours, but sustained-release lithium may not peak for 6 to 12 hours. Acute toxicity occurs when an individual without a body burden of lithium takes a supratherapeutic dose of the drug. Chronic toxicity is usually the result of decreased elimination of the drug in a patient who is receiving a fixed dose (e.g., after developing renal insufficiency). Acute-on-chronic toxicity occurs when a patient with a pre-existent total body drug takes a supratherapeutic dose. The generally accepted therapeutic range of lithium is 0.6 to 1.2 mmol/L, although in both overdose and therapeutic dosing, clinical signs and symptoms may serve as a better guide than the serum concentration.

**Diagnosis**

In acute toxicity, a large ingestion of lithium—a gastrointestinal irritant—will initially cause gastrointestinal symptoms, such as vomiting and diarrhea. Neurotoxicity—which is clinically more significant—will be delayed until the drug has been absorbed and is redistributed into the CNS. In chronic toxicity, gastrointestinal symptoms may be completely absent. Neurotoxicity manifests itself as disorders of movement and alterations in mental status. In very mild toxicity, only a fine tremor will be present, but in more advanced poisoning, fasciculations, hyperreflexia, dysarthria, and nystagmus may be seen as well (46). Mental status changes range from confusion to coma and seizures (47).

Nephrogenic diabetes insipidus and hypothyroidism occur following chronic therapeutic lithium use, but are not features of overdose. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a chronic neurologic disorder with many of the same features of lithium neurotoxicity. The distinction is that SILENT persists even when the body burden of lithium is eliminated. The mechanism is not completely elucidated but may involve demyelination. SILENT has been reported both as a result of chronic therapeutic use and as a sequela of lithium intoxication (48).

**Management**

Since lithium does not bind to activated charcoal, it should only be considered when a mixed overdose is suspected (49). When sustained-release preparations are ingested, whole bowel irrigation has been shown to decrease serum lithium concentration (50); whole bowel irrigation can be performed by administering 2 L of polyethylene glycol orally every hour (25 mL/kg/hr in children) until the rectal effluent is clear. After both acute and chronic toxicities, IV fluids should be given to optimize intravascular volume, as volume-depleted patients will have a decreased glomerular filtration rate and increased reabsorption of lithium. When fluid deficits are restored, 0.9% saline can be administered at twice the maintenance rate or approximately 200 mL/hr in adults to aid in elimination of lithium.

Lithium can be removed by hemodialysis due to its low volume of distribution and limited protein binding. Although hemodialysis can only remove the lithium residing in the vascular compartment, the elimination of serum lithium will allow the remaining intracellular lithium to redistribute into the plasma. Thus, although lithium concentrations may rebound following dialysis, the tissue burden has actually decreased. The indications for dialysis are not universally agreed upon. Hemodialysis should be performed when there are signs of significant end-organ damage, when lithium cannot be eliminated without dialysis, or when the serum concentration is elevated such that severe toxicity is highly likely. We recommend dialysis when there is significant CNS toxicity such as clonus, obtundation, coma, or seizures; when a patient with milder toxicity cannot eliminate lithium sufficiently (renal insufficiency) or tolerate saline resuscitation (congestive heart failure); or in the presence of a serum lithium concentration more than 4.0 mmol/L following acute poisoning, or more than 2.5 mmol/L following chronic poisoning. Since repeat dialysis may be necessary, the clinician should reapply the above criteria 4 hours after dialysis is completed to determine if dialysis should be repeated.

A common clinical pitfall is to deny dialysis to patients with an elevated lithium concentration and signs of toxicity because consecutive lithium concentrations have shown a small decrease. The clinician concludes that the lithium will eventually be eliminated without dialysis, so dialysis should not be helpful. Unfortunately, duration of exposure to the toxic lithium levels may predispose the patient to SILENT. In other words, it is better to be exposed to a neurotoxin for a few hours than a few days. While this area is not adequately studied, it seems prudent to hemodialyze these patients.
TOXICOLOGIC BRADYCARDIA

In 2013, the AAPCC NPED reported 101,544 exposures to cardioactive medications including digoxin, β-adrenergic antagonists, and calcium channel blockers (CCBs), and accounted for 10.67% of total exposure fatalities that year (3). These xenobiotics have a narrow therapeutic index, drawing a fine line between therapeutic dosing and poisoning. The individuals who take these medications usually have underlying cardiovascular disease, making management of overdose even more challenging.

Digoxin Poisoning

Digoxin is a cardioactive steroid derived from the foxglove plant. Though digoxin and digitoxin are the only pharmaceuticals in the class, plants such as oleander, yellow oleander, dogbane, and red squill contain cardioactive steroids with similar toxicity. While some of these plants cause a great deal of morbidity worldwide, this chapter will deal primarily with digoxin, which causes more morbidity than any other cardioactive steroid in North America.

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Digoxin has multiple therapeutic and toxic cardiovascular effects, all of which result from inhibition of the Na⁺-K⁺-ATPase. The Na⁺-K⁺-ATPase extrudes sodium from the myocardial cell, creating a sodium gradient that drives Na⁺-Ca²⁺-antiporters to move calcium extracellularly. The inhibition of the Na⁺-K⁺-ATPase by digoxin increases intracellular Ca²⁺, which therapeutically triggers Ca²⁺-mediated Ca²⁺ release from the sarcoplasmic reticulum (SR); this is commonly called Ca-mediated Ca release (Fig. 151.3).

Digoxin also slows conduction through the sinoatrial (SA) and atrioventricular (AV) nodes, probably through direct and vagally mediated mechanisms (51). In therapeutic use, digoxin decreases heart rate and increases inotropy. In overdose, the

increased intracellular Ca\(^{2+}\) brings the cell closer to threshold, resulting in increased automaticity.

Digoxin does not exert its therapeutic and toxic effects until it redistributes from the serum into the myocardium. Digoxin has a large volume of distribution, precluding elimination by hemodialysis, and is mostly eliminated renally, although there is some hepatic metabolism. The maximal effect from a therapeutic dose of digoxin is seen at 4 to 6 hours when administered orally and 1.5 to 3 hours when given intravenously.

**Clinical Manifestations**

Digoxin poisoning can be either acute or chronic. Acute toxicity occurs when an individual without a tissue burden of digoxin ingests a supratherapeutic dosage of the drug. Chronic toxicity usually occurs when an individual on a fixed dose of the drug loses the ability to excrete it effectively. Both syndromes have similar cardiovascular manifestations, but acute toxicity may feature more prominent gastrointestinal symptoms. Acute poisoning may result in nausea, vomiting, and abdominal pain, whereas chronic poisoning develops more insidiously. In addition to gastrointestinal symptoms, chronic poisoning may present with weakness, confusion, or delirium (52,53).

Bradycardia with a preserved blood pressure typically occurs in digoxin toxicity. The ECG is the most important test in establishing the diagnosis. Because digoxin has multiple cardiac effects, there is no single ECG manifestation that is consistently seen in patients with digoxin toxicity. The most common rhythm disturbance reported is the presence of ventricular ectopy (54). The ECG could potentially exhibit increased automaticity from elevated resting potential, conduction disturbance from AV and SA nodal block, both, or neither. The ectopy may degrade into ventricular tachycardia or ventricular fibrillation. If conduction disturbance predominates, the ECG may demonstrate sinus bradycardia or varying degrees of AV block.

The laboratory provides clues to toxicity. The therapeutic range for digoxin is usually reported as 0.5 to 2.0 ng/mL. Serum digoxin concentration should be interpreted in the context of the history and ECG. Digoxin is a cardiototoxic, and serum concentrations do not necessarily reflect the degree of poisoning. Digoxin requires several hours to redistribute from the serum to the tissues. Shortly after an acute ingestion, the serum concentration may overestimate toxicity, while a mild increase in serum concentration of a patient chronically on digoxin may underestimate the high extent of the increased tissue burden.

Serum potassium concentration is a better predictor of illness following acute ingestions. A study of 91 digitoxin-poisoned patients performed in the pre–digoxin-specific antibody fragment era found no mortality when the potassium concentration was less than 5.0 mEq/L and 50% mortality when the potassium concentration was 3.0 to 5.5 mEq/L (55).

**Management**

Because acute toxicity can cause vomiting, activated charcoal and gastric lavage may be of limited value. Atropine can be given intravenously in 0.5-mg doses for bradycardia, although it is probably not important to “correct” the heart rate if the blood pressure is preserved. If necessary, potassium should be supplemented. Hypokalemia inhibits the function of the Na\(^{+}\)–K\(^{-}\)–ATPase, and thereby exacerbates digoxin poisoning. A pitfall in managing digoxin-poisoned patients is the administration of calcium in response to the recognition of hyperkalemia.

When hyperkalemia is the result of an increase in total body burden of potassium, such as in renal failure, calcium is the treatment of choice. However, calcium administration is not recommended in the setting of digoxin poisoning where extracellular distribution of potassium is the result of a poisoned Na\(^{+}\)–K\(^{-}\)–ATPase, nor an increase in total body potassium. Under these circumstances, increasing extracellular calcium may accentuate toxicity.

**Digoxin-Specific Immune Fragments**

Administration of digoxin-specific antibody fragments (Fab) is the most important intervention in digoxin-poisoned patients. Fab are prepared by cleaving the Fc fragment from IgG. The resulting Fab fragments are much less immunoreactive than the whole IgG antibodies. In a large series, digoxin-specific antibody fragments caused allergic reaction in 0.8% of patients (56).

Digoxin-specific Fab should be administered to anyone with digoxin-induced cardiotoxicity, a serum potassium concentration of 5.0 mEq/L or more after an acute overdose, or a serum digoxin concentration 15 ng/mL or more at any time or 10 ng/mL or more at 6 hours postingestion (57).

Digoxin-specific Fab are given by IV infusion and dosed according to serum concentration (Table 151.4). In the presence of suspected severe toxicity, treatment should not be dependent on nor await serum digoxin concentration results. The first clinical effect of Fab should be seen within 20 minutes and a maximal response within several hours (58). Following immune-specific antibody fragment administration, the serum digoxin concentration determined by most laboratories will be a total digoxin concentration, which will include the antibody-bound digoxin. The result will be a very elevated value without clinical utility. The determination of free digoxin concentration, which is available at some institutions, would not be affected.

**β-Adrenergic Antagonist and Calcium Channel Blockers**

**β-Adrenergic Antagonist Overdose**

β-Adrenergic receptors are coupled to G-proteins, which activate adenyl cyclase, resulting in increased production of ATP from cyclic adenosine monophosphate (cAMP). The cAMP activates protein kinase A (PKA), which initiates a series of phosphorylations. Phosphorylation of L-type calcium channels on cell membranes increases intracellular calcium, which

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**TABLE 151.4 Digoxin-Specific Fab Dose Calculation**

When serum digoxin concentration (SDC) known

\[ \text{No. of vials} = \left( \frac{\text{SDC (ng/mL)} \times \text{patient weight (kg)}}{100} \right) \times 10 \]

When SDC unknown, dose known

\[ \text{No. of vials} = \frac{\text{amount ingested (mg)}}{0.5 \text{mg/vial}} \]

When both SDC and dose unknown (acute poisoning)

Empiric therapy

10-20 vials (adult or pediatric)

When both SDC and dose unknown (chronic poisoning)

Empiric therapy

Adult: 3-6 vials

Pediatric: 1-2 vials
allows more activation of the SR and further calcium release, causing muscle contraction. The calcium influx also brings pacemaker cells closer to threshold (59).

Most of the β-adrenergic antagonists are exclusively metabolized or biotransformed in the liver and then renally eliminated. The exception is atenolol, which is exclusively renally eliminated.

**Clinical Manifestations**

All β-adrenergic antagonists have the potential to produce bradycardia and hypotension in a dose-dependent fashion. However, there are subtle differences among the agents in terms of receptor selectivity (α-, β₁-, and β₂-adrenergic receptors), lipid solubility, membrane-stabilizing activity, and potassium channel blockade that result in varied clinical manifestations.

Drugs with α- and β-adrenergic antagonist effects, such as labetalol and carvedilol, produce more hypotension and afterload reduction. The more β₁-selective drugs, including metoprolol and atenolol, have less potential for β₁-related adverse effects such as bronchospasm. The more lipid-soluble β-adrenergic antagonists, such as propranolol, penetrate the CNS more readily, causing obtundation or seizures prior to hemodynamic collapse (60). Membrane-stabilizing activity, similar to type-I antidysrhythmic activity, produces lengthening of the QRS interval, tachydysrhythmias, and hypotension. The membrane-stabilizing effect is usually associated with propranolol and other lipid-soluble drugs, although it has been observed after overdose with others (61,62). Sotalol and acebutolol can produce QTc prolongation due to potassium channel blockade, which may result in torsades de pointes (63).

**Calcium Channel Blocker Overdose**

The CCBs are formulated as both immediate and sustained release, but in overdose, the effects of either type may be prolonged. The CCBs undergo hepatic metabolism. There are three major classes of CCBs: dihydropyridines (including amlodipine, nifedipine, and others ending with the suffix “-pine”), phenylalkylamines (verapamil), and benzothiazepine (diltiazem). In practice, it is more clinically useful to divide them into two classes: the dihydropyridines and the nondihydropyridines. All of the drugs inhibit the function of L-type calcium channels. The dihydropyridines have greater affinity for calcium channels in vascular smooth muscle than the myocardium (64).

**Clinical Manifestations**

The most consequential clinical features of CCB overdose are cardiovascular. All of the CCBs produce hypotension, but effects on heart rate and contractility vary based on the class of the particular drug. As a result, they cause hypotension with a reflex tachycardia. Diltiazem, in contrast, produces little peripheral blockade, but does suppress contractility and conduction through the SA and AV nodes, resulting in bradycardia and decreased inotropy. These cardiac effects can be much more difficult to treat than the peripheral vasodilation of the dihydropyridines. In severe poisoning, heart block or complete cardiovascular collapse results. Verapamil, which is active in the peripheral vasculature and in the myocardium, produces a combination of the effects of the dihydropyridines and diltiazem. For this reason, verapamil is considered to be the most dangerous of the CCBs, although any of them can cause death in overdose.

CCBs have effects outside the cardiovascular system. The blockade of L-type calcium channels in pancreatic β-islet cells, where they trigger the blockade of insulin release, may result in hyperglycemia (65).

**Management**

Patients who initially present without symptoms of β-adrenergic antagonists or CCB overdose may rapidly become very ill. Patients with these overdoses should be taken very seriously and treated aggressively. Many antidotes have been investigated, with varying degrees of clinical success. In the treatment of β-adrenergic antagonist and CCB overdose do not benefit from removal with hemodialysis. There is no single antidote for either β-adrenergic antagonists or CCBs. The optimal treatment consists of a combination of the treatments described below.

Gastrointestinal decontamination should be considered in all patients. Gastric lavage may be indicated if there are pills still expected to be in the stomach—usually in the first hour or two after ingestion; activated charcoal should be administered. Whole bowel irrigation with polyethylene glycol is indicated for patients with a history of ingesting sustained-release drugs.

The initial management for hypotension will be IV crystalloid fluid. Although IV atropine, 0.5 to 1 mg, may be given for bradycardia, studies of atropine efficacy in CCB toxicity are not definitive (66). Calcium has a role not only in CCB toxicity, but also for β-adrenergic antagonist poisoning (67,68). Increasing extracellular calcium helps to overcome calcium channel blockade and increase intracellular calcium, typically with greater improvement in blood pressure than heart rate. The ideal dosing of calcium is not yet established. An IV bolus of 13 to 25 mEq of Ca²⁺ (10 to 20 mL of 10% calcium chloride or 30 to 60 mL of 10% calcium gluconate) can be followed by repeat boluses or an infusion of 0.5 mEq/kg/hr of Ca²⁺ (69); calcium concentration should be closely monitored.

Glucagon, an endogenous polypeptide hormone released by pancreatic α-cells, has significant inotropic effects mediated by its ability to activate myocyte adenylate cyclase, effectively bypassing the β-adrenergic receptor (70). Because calcium channel opening occurs “downstream” from adenylate cyclase, glucagon may not be as effective for overcoming calcium channel blockade. Glucagon should be given intravenously, at an initial dose of 3 to 5 mg (50 μg/kg in children), up to 10 mg. The total initial dose that produces a response should be given hourly as an infusion (59). Glucagon may cause hyperglycemia or vomiting, but neither complication should limit the therapy if it is effective.

Hyperinsulinea/euglycemia therapy should be instituted early in patients with moderate to severe poisoning. Insulin is a positive inotrope and may independently increase Ca²⁺ entry into cells (71) and allow the myocardium, which usually relies on fatty acids, to use more carbohydrate for metabolism (72). Although the ideal dose is not known, we recommend an IV bolus of 1 unit/kg, followed by an infusion of 0.5 to 1 unit/kg/hr. The initial bolus should be preceded by a 1-g/kg bolus of dextrose, followed by a 0.5-g/kg/hr infusion of dextrose to maintain euglycemia titrated to subsequent glucose concentrations. Although some clinicians are understandably apprehensive about using a dose of insulin that is 10-fold greater than the typical diabetic ketoacidosis regimen, the regimen has been demonstrated to have utility in both clinical and animal testing (73,74).

In severe poisoning, all of the above measures should be performed, as well as institution of inotropes and vasoactive...
drugs. Intra-aortic balloon counterpulsation should also be considered if cardiac output is severely compromised. These patients may be ideal for this procedure because, unlike with most other causes of cardiogenic shock, their cardiac output can recover in a relatively short period of time.

**Controversies**

Intravenous lipid emulsion (ILE) therapy, a component of total parenteral nutrition, has been proposed as an adjunctive therapy for β-adrenergic antagonist and CCB toxicity in critically ill patients; the exact mechanism is poorly understood. Theories include the induction of an intravascular “lipid sink,” or alternative lipid binding surface for the xenobiotic, effectively inactivating a percentage of the drug; evidence is limited to animal models and case reports. Clinical trials are lacking (75). ILE infusion may be considered after all alternative supportive methods—calcium, glucagon, fluids, insulin, vasopressors—have been attempted.

**TOXIC ALCOHOL POISONING**

The term toxic alcohols refers in particular to methanol and ethylene glycol, which are the most important chemicals in the class because they are both of high potential toxicity and wide availability. In 2013, the NPED received 6,600 reports of exposure to ethylene glycol, including 2.9% classified as major or fatal, and 1,784 exposures to methanol, with 1.3% major or fatal (3). When suspected, toxic alcohol poisoning requires ICU admission.

Methanol is commonly found in windshield wiper fluid, ethylene glycol in automobile antifreeze, and isopropanol is a ubiquitous topical disinfectant. The toxic alcohols are readily absorbed and have a volume of distribution similar to total body water. Both the parent compounds and the toxic metabolites are dialyzable. It is not the toxic alcohols themselves that produce significant toxicity, but their metabolites. Methanol and ethylene glycol are metabolized in a stepwise fashion by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to the clinically important metabolites: formic acid (methanol) and glycolic, glyoxylic, and oxalic acid (ethylene glycol) (Figs. 151.4 and 151.5). Isopropanol is less clinically consequential, as it is converted by ADH to acetone, which is an end product rather than a substrate of ALDH.

Because ADH preferentially metabolizes ethanol over all other alcohols, no significant metabolism of toxic alcohols will occur while high concentrations of ethanol are present. When ADH is inhibited, the parent compounds are eliminated very slowly without metabolism. In the absence of ADH, ethylene glycol is renally eliminated with a half-life of 8.5 hours while methanol, which is eliminated as a vapor, has a half-life of 30 to 54 hours (76–78).

**Clinical Manifestations**

The initial physical examination may be unremarkable. All of the toxic alcohols can produce significant CNS depression, and a compensatory tachypnea may be present if there is a metabolic acidosis. Acetone, generated from ADH metabolism of isopropanol, produces nausea, hypotension, hemorrhagic gastritis, and tachycardia, but these are not usually life threatening (79). Formate, a methanol metabolite, can produce blindness from toxicity to the retina and optic nerve (80). Ethylene glycol may cause nephrotoxicity in cases where oxalic acid, the primary metabolite, precipitates as calcium oxalate crystals in the renal tubules (81).


Standard laboratory studies can suggest—but not establish or exclude—the diagnosis of toxic alcohol poisoning. Metabolites of methanol or ethylene glycol may cause an elevated anion gap metabolic acidosis. The hallmark laboratory finding of isopropanol poisoning is ketonemia without acidosis. The osmolar gap, the difference between the measured and unmeasured osmoles, may be increased when the serum contains toxic alcohol osmoles. A very high osmolar gap does suggest the presence of toxic alcohol, whereas a low or normal gap does not exclude the presence of ethylene glycol or methanol. There is a great population variation in the “normal” osmolar gap, from −10 to 10, such that very high concentrations of toxic alcohols might not be apparent when the gap is calculated (82).

Other tests, such as fluorescence of the urine or the presence of calcium oxalate crystals in the presence of ethylene glycol poisoning, are neither sensitive nor specific (83). Since fluorescence is added to some brands of ethylene glycol–based antifreeze in order to facilitate detection of radiator leaks, some authors suggest the use of a Woods lamp to detect urine for fluorescence as a screen for ethylene glycol. However, in one study of a large group of children not exposed to ethylene glycol, almost all of them had urinary fluorescence (84). Because of the limitations in these laboratory studies, treatment should be started empirically as soon as the diagnosis is considered.

Management

There are several clinical presentations that suggest poisoning with a toxic alcohol, and each requires different management considerations. The first type of patient presents without acidosis and either a history of ingesting ethylene glycol or methanol or a very elevated osmolar gap. The physician should immediately begin an ADH inhibitor and obtain toxic alcohol concentrations, when available. Later, the decision to continue treatment or begin hemodialysis can be made based on the presence of a toxic alcohol in a high concentration. If the result is not expected in a timely manner, dialysis should be presumptively performed.

The second scenario is the patient who presents with an unexplained elevated anion gap metabolic acidosis that is not explained by the presence of lactate, ketoacids, or uremia. In such cases, the diagnosis should be considered, and ADH inhibition and hemodialysis should be instituted. One test that is very helpful in this scenario is a serum ethanol concentration. As long as there is elevated ethanol concentration present in the serum, toxic alcohols cannot be converted into their metabolites. Therefore, if a patient has a very elevated ethanol concentration, his or her elevated anion gap metabolic acidosis cannot be explained by toxic alcohol poisoning, unless the ethanol was consumed only hours after the ingestion of the toxic alcohol.

If a serum toxic alcohol concentration is available, the diagnosis can be established rapidly, and management is straightforward. From clinical experience, if the serum concentration of methanol is less than 25 mg/dL (or ethylene glycol <50 mg/dL) and there is no metabolic acidosis, treatment is not necessary. If treatment is required, the clinician must determine whether to use an ADH inhibitor alone or in conjunction with hemodialysis. There are two important considerations when determining whether hemodialysis is necessary. The first concern is the presence of toxic metabolites such as formate. Although these metabolites cannot easily be measured directly, the presence of a metabolic acidosis suggests that some of the parent compound has already been metabolized to a toxic metabolite, and dialysis should be employed. The second consideration is the duration of time needed to eliminate the toxic alcohol without dialysis. The half-life of methanol is approximately 2 days when ADH is inhibited. If the initial serum concentration is 200 mg/dL, about 6 days in an ICU may be necessary to reach a concentration of 25 mg/dL. In contrast, if dialysis were performed, the patient may only require a day of hospitalization, depending on the reason for ingestion of the alcohol.

The two ADH inhibitors available are fomepizole and ethanol. While considerably more expensive than ethanol, fomepizole is the treatment of choice. Fomepizole is administered by empiric weight–based dosing, while ethanol infusion requires serum concentrations to be obtained frequently. Unlike ethanol, fomepizole does not cause CNS or respiratory depression. Fomepizole should be given as a 15 mg/kg IV loading dose, followed in 12 hours by 10 mg/kg every 12 hours for 48 hours. If continued dosing is required, the infusion rate should be increased to 15 mg/kg. When fomepizole is unavailable, ethanol should be given intravenously, or orally if necessary. We recommend a loading dose of ethanol at 0.8 g/kg over 20 to 60 minutes, followed by an initial infusion of 100 mg/kg/hr (85).

The goal of ethanol therapy is to maintain an ADH inhibitory concentration of 100 mg/dL. The serum ethanol concentration should be obtained frequently and the rate adjusted accordingly. ADH blockade should continue during hemodialysis; fomepizole should be dosed every 4 hours and ethanol should be administered at a rate of 250 to 350 mg/kg/hr (85). Several hemodialysis sessions may be needed to remove the toxic alcohol, depending on the initial concentration. Symptoms of isopropanol can usually be managed with fluids and supportive care alone, although rarely, hemodialysis may be indicated.

Folate is a cofactor in the conversion of formic acid to a nontoxic metabolite, and thiamine and pyridoxine assist in transforming toxic metabolites following ethylene glycol poisoning. Therefore, 1 to 2 mg/kg of folic acid should be given every 4 to 6 hours in the first 24 hours of methanol poisoning, and thiamine hydrochloride (100 mg IM or IV) and pyridoxine (100 mg/d IV) should be administered for ethylene glycol poisoning. It is reasonable to administer sodium bicarbonate to a target pH of 7.2 to shift the equilibrium from formic acid to the less toxic formate.

CHOLINERGIC POISONING

Acetylcholine is the neurotransmitter found throughout the parasympathetic nervous system, in the sympathetic nervous system at the level of the ganglia and sweat glands, and at the neuromuscular junction (Fig. 151.6). The cholinergic syndrome describes the condition of excess acetylcholine characterized by the sum of the parasympathetic, somatic, and sympathetic effects. Cholinergic compounds are used as medications, pesticides, and weapons. In 2013, the AAPCC received reports of 3 fatalities and 13 major effects related to organophosphate and carbamate insecticides (3). The World Health Organization estimates that at least 1 million unintentional poisonings and 2 million suicide attempts occur annually worldwide from these insecticides (86).

Acetylcholine is inactivated in the synapse by acetylcholinesterase (AChE). Inhibition of AChE causes an excess of the neurotransmitter in the synapse. The two most important
classes of AChE inhibitors are the carbamates and the organic phosphorous compounds. The carbamates inactivate AChE by carbamylation, while the organic phosphorous compounds do so by phosphorylation. The carbamates and organic phosphorous compounds are both absorbed by ingestion, by inhalation, and through skin. Organic phosphorous compounds exhibit “aging,” whereby the reversible inhibition of AChE becomes permanent. Aging can take minutes to days, depending on the particular compound. Carbamates, however, spontaneously hydrolyze from the active site of AChE and do not age. ICU admission is required for those with respiratory compromise, hemodynamic instability, or the need for administration of large amounts of atropine.

**Clinical Manifestations**

Many of the carbamates have peak concentrations within 40 minutes following ingestion and may be almost completely eliminated from the serum within days (87–89). They are not particularly lipophilic and do not readily cross the blood–brain barrier, resulting in a predominance of peripheral symptoms (90).

In contrast, after ingestion, peak concentrations of the organic phosphorous compounds have been reported at 6 hours (91). Many of these agents are activated in the liver, resulting in a further delay to peak action. They are also generally very lipophilic and redistribution from fat allows measurable serum concentrations for up to 48 days (88,89). Their lipophilicity results in the demonstration of both peripheral and CNS clinical effects (90).

Diagnosis is often established by recognition of the muscarinic signs: salivation, lacrimation, urination, defecation, bradycardia, bronchorrhea, and bronchospasm. Acetylcholine initially acts as an agonist, but in excess becomes an antago-nist at the neuromuscular junction, producing weakness, fasciculations, and paralysis. Simulation of nicotinic receptors at the sympathetic ganglia produces tachycardia and mydriasis.

AChE inhibitor poisoning is a clinical diagnosis. Although red blood cell cholinesterase and butyrylcholinesterase are inhibited by carbamates and organic phosphorous compounds, their activity may remain depressed after clinical signs and symptoms have resolved. There may be a clinical role for these tests in mild cases when the diagnosis is unclear. Electromyography (EMG) may be a sensitive indicator of toxicity before clinically apparent symptoms have occurred (92).

**Management**

The first management priorities involve ensuring a secure airway and decontaminating the patient’s skin to protect caregivers and prevent further absorption. After initial stabilization, atropine should be administered. The presence of tachycardia is not a contraindication to atropine. The goal of “atropinization” is reversal of the muscarinic symptoms. Although red blood cell cholinesterase and butyrylcholinesterase are inhibited by carbamates and organic phosphorous compounds, their activity may remain depressed after clinical signs and symptoms have resolved. There may be a clinical role for these tests in mild cases when the diagnosis is unclear. Electromyography (EMG) may be a sensitive indicator of toxicity before clinically apparent symptoms have occurred (92).
Oximes are used to supplement antimuscarinic therapy. The oximes improve both muscarinic and nicotinic signs, primarily by restoring activity to phosphorylated AChE. Since oximes will not restore activity once aging has occurred, they must be administered early in the clinical course of AChE inhibitor poisoning. Oxime therapy is recommended for both organic phosphorous compounds and carbamates because oximes may have salutary effects following carbamate poisoning and because the toxic agent in question is not always known with certainty. Even in carbaryl poisoning, adequate atropinization overcomes any deleterious effect of pralidoxime (93). Pralidoxime (2-PAM) is the oxime most frequently available in the United States. Administer 1 to 2 g IV over 30 minutes (20 to 40 mg/kg in children, to a maximum of 2 g). Significant poisoning may require a continuous infusion of 500 mg/hr (10 to 20 mg/kg/hr in children, up to adult dose) (94).

Diazepam should be administered to patients severely poisoned by organic phosphorous compounds. Although human data are not available, animal studies show a survival benefit possibly unrelated to the GABAergic effects of diazepam (95). Because severely poisoned patients will require endotracheal intubation, diazepam can be administered very safely.

Delayed Manifestations

In the acute setting, the physician should be vigilant for recurrence of cholinergic signs after apparent resolution and for a distinct form of toxicity called the intermediate syndrome. The intermediate syndrome—so called because it occurs after acute, but before delayed, toxicity—may occur 24 to 96 hours after organic phosphorous poisoning and consists of upper body weakness, cranial nerve palsies, and areflexia. The syndrome appears to be self-limited, but can last up to 30 days and be severe enough to require intubation (96,97). We recommend continuing pralidoxime infusion at 500 mg/hr when this diagnosis is considered.

Delayed toxicity may occur days after apparent resolution of symptoms due to redistribution of the agent from fat stores. Discharge can be considered when the patient has been asymptomatic without additional treatment for 1 to 2 days (98).

**CYANIDE POISONING**

Cyanide salts are widely available and may be used in suicidal or homicidal poisoning. Because jewelers, laboratory workers, and industrial workers often have ready access to cyanide, a relationship to these industries may be an important historical clue. Cyanide poisoning should also be considered in all fire victims, as it is released when carbon fibers undergo combustion.

Cyanide poisoning most frequently occurs after the ingestion of a cyanide salt or inhalation of the gas hydrogen cyanide. In both forms, cyanide is rapidly absorbed. The most important toxic effect of cyanide is inhibition of cytochrome oxidase in the electron transport chain (99). Despite the presence of oxygen, cells cannot offload electrons from nicotinamide adenine dinucleotide (NADH) to oxygen, and generate ATP, resulting in anaerobic metabolism and producing lactic acid. Small quantities of cyanide are detoxified by the enzyme, rhodanese, which catalyzes the transfer of sulfur from thiosulfate, yielding thio-cyanate. Poisoning results when this system is overwhelmed by large concentrations of cyanide.

**Clinical Manifestations**

The history may be very helpful in establishing the diagnosis. Cyanide should be considered in anyone who rapidly loses consciousness after ingestion or inhalational exposure. Signs and symptoms resemble those of hypoxia: headache, lethargy, seizures, and coma in the absence of cyanosis.

**Management**

Cyanide poisoning requires treatment before laboratory confirmation is available, so treatment must be instituted based on clinical suspicion. As soon as cyanide poisoning is considered, 100% oxygen should be administered, IV access established, and fluids given. The remainder of treatment depends on the route of exposure.

Because the symptoms of cyanide poisoning are similar to those associated with hypovolemia or carbon monoxide poisoning, the diagnosis is difficult to establish with certainty. Laboratory studies will show a lactic acidosis. In one series, a plasma lactate concentration more than 8 mmol/L in patients with clinical suspicion of poisoning was 94% sensitive and 70% specific for cyanide toxicity (100). An older cyanide antidote kit consisted of amyl nitrite, sodium nitrite, and sodium thiosulfate. Sodium thiosulfate, the final component of the kit, functions by providing substrate to rhodanese, facilitating conversion of cyanide to thiocyanate. The dose is 50 mL in adults and 1.65 mL/kg in children, and the drug may be repeated in 2 hours at half the initial dose if symptoms persist. Hydroxocobalamin is largely replacing the older kit as the antidote of choice in cyanide poisoning. Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B₁₂) (101). In animal models, it has synergism with thiosulfate (102). Hydroxocobalamin should be given IV at 70 mg/kg (to a maximum of 3 g) in a separate infusion site from thiosulfate.

**CYANIDE, THIOCYANATE, AND NITROPRUSSIDE**

Nitroprusside contains an iron molecule coordinated to five cyanide molecules and one nitric oxide. Cyanide molecules are slowly liberated after nitroprusside is infused, but usually at a rate that can be detoxified by endogenous pathways. Risk factors for accumulation of cyanide are prolonged infusion, high infusion rate, and poor nourishment. If the diagnosis is suspected, the infusion should be discontinued and hydroxocobalamin and thiosulfate administered. A more likely complication of nitroprusside use is thiocyanate toxicity. Thiocyanate, which does not cause any symptoms at low concentrations, is cleared renally. Bioaccumulation occurs in patients with impaired renal function, causing delirium, hallucinations, seizures, and rash. In patients receiving more than 2 μg/kg/min of nitroprusside, and in those with renal insufficiency, serum thiocyanate concentrations should be checked after 48 to 72 hours of infusion. The infusion should be discontinued if the thiocyanate concentration is more than 10 mg/dL (103). Dialysis can be effective for thiocyanate accumulation, but should be reserved for only the most severely compromised patients (104).
METHEMOGLOBINEMIA

Methemoglobinemia results from the formation of dyshemoglobin, which is caused by inappropriate oxidation of heme iron. Under normal conditions, iron in deoxyhemoglobin remains in the reduced ferrous state, Fe²⁺, and the heme is available to bind oxygen. After oxygen binds, iron assumes the oxidized ferric state, Fe³⁺. Methemoglobin, which is normally formed in small quantities, is seen when a hemoglobin iron moiety is exposed to oxidative stress and converted to the ferric state in the absence of binding oxygen. Methemoglobin is unable to bind oxygen and increases the affinity of normal hemoglobin for oxygen. Thus, the result of methemoglobin formation is decreased oxygen delivery and a leftward shift in the oxygen dissociation curve. Due to the physiologic systems available to reduce methemoglobin to functional hemoglobin, low-level methemoglobin production may be a protective mechanism against oxidant damage to erythrocytes. The most important mechanism of methemoglobin reduction is catalyzed by the enzyme, methemoglobin reductase (cytochrome b₅ reductase), using NADH generated from the Embden–Meyerhof glycolytic pathway. Congenital methemoglobinemia is a rare condition caused by methemoglobin reductase deficiency (105). This enzyme is also relatively deficient until approximately 4 months, making infants prone to methemoglobin formation (106).

Most individuals with methemoglobinemia can be treated and discharged from the emergency department. Patients with methemoglobinemia may require ICU admission when it recurs following initial treatment, either from continued absorption of an inducer or continued metabolism of a drug to a methemoglobin inducer.

Clinical Manifestations

Although the diagnosis of methemoglobinemia is commonly confirmed by co-oximetry, it can be established presumptively based on symptoms and signs, and via pulse oximetry. Symptoms of methemoglobinemia are those associated with hypoxia. The severity of symptoms is determined by the concentration of methemoglobin and the patient’s underlying comorbidities. At low concentrations of methemoglobin (0% to 15%), patients may be asymptomatic, and as concentrations rise (20% to 50%), patients may manifest decreased exercise tolerance and dyspnea. At higher concentrations (50% to 70%), metabolic acidosis, seizures, and coma result. Concentrations greater than 60% or 70% can cause death in previously healthy individuals (107).

Pulse oximetry aids in diagnosis before co-oximetry has been obtained. Methemoglobin interferes with pulse oximetry in a somewhat predictable manner (108). Pulse oximetry reads absorbance of light at two wavelengths (660 and 940 nm), so chosen because they are the best to distinguish the absorption spectra of oxyhemoglobin and deoxyhemoglobin. Based on the ratio of absorption between the two wavelengths, the pulse oximeter uses an algorithm to estimate the percentage of total hemoglobin as oxyhemoglobin. Methemoglobin, however, has greater absorption than either oxyhemoglobin or deoxyhemoglobin at those wavelengths. When it is present in modest concentrations, the pulse oximeter will no longer be able to meaningfully calculate oxygen saturation. In a dog model, increasing methemoglobin concentrations caused the pulse oximeter oxygen saturation (SpO₂) to decrease and then plateau at 84% to 86%. In the clinical setting, methemoglobin does not produce this straightforward plateau in SpO₂, but does consistently generate readings between 70% and 90% (107). The oxygen saturation derived from the arterial blood gas analysis is not measured in the same fashion as SpO₂, and will not reflect the methemoglobin concentration. The oxygen saturation from an arterial blood gas analysis is a calculated saturation based on the PaO₂, and should be normal in the setting of methemoglobinemia. A difference between the SpO₂ and arterial blood gas–calculated oxygen saturation may suggest methemoglobinemia.

Methemoglobin Inducers

Acquired methemoglobinemia is most frequently seen after exposure to a drug, although it can also be found in infants without drug exposure who are ill with a metabolic acidosis or diarrhea (109,110). The drugs that have been associated with methemoglobin formation are extensive. Dapsone, nitrates, nitrates, benzocaine, and sulfonamides are consistently implicated in producing methemoglobinemia (Table 151.5) (111). It is not entirely clear why some individuals develop methemoglobinemia after exposure to these drugs and others

<table>
<thead>
<tr>
<th>TABLE 151.5 Common Causes of Methemoglobinemia</th>
</tr>
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<tbody>
<tr>
<td>HEREDITARY</td>
</tr>
<tr>
<td>• Hemoglobin M</td>
</tr>
<tr>
<td>• Cytochrome b₅ reductase deficiency</td>
</tr>
<tr>
<td>ACQUIRED</td>
</tr>
<tr>
<td>• Medications</td>
</tr>
<tr>
<td>• Amyl nitrate</td>
</tr>
<tr>
<td>• Benzoicaine</td>
</tr>
<tr>
<td>• Dapsone</td>
</tr>
<tr>
<td>• Lidocaine</td>
</tr>
<tr>
<td>• Nitric oxide</td>
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<tr>
<td>• Nitroglycerin</td>
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<tr>
<td>• Phenacetin</td>
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<tr>
<td>• Phenazopyridine</td>
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<tr>
<td>• Procaine</td>
</tr>
<tr>
<td>• Quinones</td>
</tr>
<tr>
<td>• Sulfonamides</td>
</tr>
<tr>
<td>• Other xenobiotics</td>
</tr>
<tr>
<td>• Aniline dye derivatives</td>
</tr>
<tr>
<td>• Butyl nitrite</td>
</tr>
<tr>
<td>• Chlorobenzene</td>
</tr>
<tr>
<td>• Fire</td>
</tr>
<tr>
<td>• Food adulterated with nitrates</td>
</tr>
<tr>
<td>• Food high in nitrates</td>
</tr>
<tr>
<td>• Isobutyl nitrite</td>
</tr>
<tr>
<td>• Naphthalene;</td>
</tr>
<tr>
<td>• Nitrate</td>
</tr>
<tr>
<td>• Nitrite</td>
</tr>
<tr>
<td>• Nitrobenzene</td>
</tr>
<tr>
<td>• Nitrous gases</td>
</tr>
<tr>
<td>• Silver nitrate</td>
</tr>
<tr>
<td>• Trinitrotoluene</td>
</tr>
<tr>
<td>• Well water (nitrates)</td>
</tr>
<tr>
<td>PEDIATRIC</td>
</tr>
<tr>
<td>• Reduced NADH methemoglobin reductase activity in infants</td>
</tr>
<tr>
<td>• (&lt;4 months of age)</td>
</tr>
<tr>
<td>• Associated with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia</td>
</tr>
</tbody>
</table>

do not. Although there is clearly a dose–response effect, host factors such as coexisting medical illness and metabolic variables play a role in methemoglobin development.

Management
When cyanosis is recognized and methemoglobinemia is considered, administer 100% oxygen by nonbreather mask. Unless the patient is asymptomatic, methylene blue should be administered intravenously, 1 to 2 mg/kg over 5 minutes. Methylene is reduced by nicotinamide adenine dinucleotide phosphate (NADPH) to leukomethylene blue. Leukomethylene blue, in turn, reduces methemoglobin to hemoglobin. Clinical improvement should be seen within minutes of administration. Because the medication itself has a blue color, oxygen saturation reported by pulse oximetry may transiently worsen. A repeat dose of methylene blue may be required if the methemoglobin concentration is high or if there is ongoing oxidative stress.

Some authors recommend against giving methylene blue, an oxidizing agent, to individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with this condition suffer from hemolytic anemia when exposed to drugs that create oxidative stress. Because G6PD is required to activate methylene blue, a deficiency in the enzyme may lead to a lack of efficacy of the antidote. The administration of methylene blue is appropriate when clinically indicated unless there is a strong history of G6PD deficiency. In such cases, hyperbaric oxygen (HBO) or exchange transfusion should be considered. If the G6PD-deficient patient presents with severe methemoglobinemia, methylene blue should be administered and the patient monitored closely for hemolysis.

Both dapsone and its hydroxylamine metabolites are responsible for methemoglobin formation. The cytochrome P450 conversion of dapsone to these metabolites is inhibited by cimetidine (112). Cimetidine should be administered intravenously, 300 mg every 6 hours, to patients with dapsone-induced methemoglobinemia.

CARBON MONOXIDE POISONING

In their latest annual report, the AAPCC received more than 14,289 reports of carbon monoxide (CO) exposure, including 157 major effects and 60 fatalities (3). These figures, while very concerning, underestimate morbidity and mortality from carbon monoxide, which is considered the leading cause of poisoning death in the United States. Carbon monoxide results from the incomplete combustion of carbonaceous fuels and is tasteless, odorless, and colorless. The initial clue to the presence of CO in the home may be the alarm from a CO detector. During natural disasters, when electricity is unavailable, people may use generators indoors, allowing CO from exhaust to permeate the home. Even when a home heater is used appropriately, it can lead to CO poisoning if the outflow is obstructed. In automobiles, a functioning catalytic converter minimizes the release of CO. Other internal combustion engines, such as lawn mowers, Zambonis, and outboard motors on boats, do not usually have catalytic converters and can cause CO poisoning. Methylene chloride, an important source of CO that is not a product of combustion, is hepatically metabolized to CO by the liver. Methylene chloride is used as a paint stripper and can be absorbed dermally, inhalationally, or by ingestion (113). Unlike other sources of CO poisoning, where carboxyhemoglobin begins to decline as soon as the patient is removed from the exposure, peak carboxyhemoglobin concentration will occur hours after exposure to methylene chloride as the parent compound is metabolized to CO.

Carbon monoxide is a hemotoxin, a neurotoxin, a cardiac toxin, and an inhibitor of cytochrome oxidase. It binds to hemoglobin with greater affinity than oxygen, and causes a leftward shift of the oxyhemoglobin dissociation curve, causing a decrease in delivery of oxygen to cells. Although the formation of carboxyhemoglobin can impair oxygen delivery sufficiently to cause mortality, inhibition of oxygen delivery alone does not fully explain why carboxyhemoglobin concentrations of 50% are often fatal whereas a similar degree of anemia might be well tolerated. The formation of carboxyhemoglobin is inadequate to explain the chronic cardiac and neurologic sequelae of CO. Carbon monoxide inhibition of cytochrome oxidase persists for days after carboxyhemoglobin concentration has normalized (114) and is associated with damage to the brain endothelium, resulting in lipid peroxidation (115,116). It also binds to myoglobin with high affinity, making it a direct skeletal and cardiac muscle toxin (117).

CO poisoning does not usually require ICU admission; this is only necessary for patients who are comatose or obtunded, those with signs of cardiotoxicity, and those with significant burns or other comorbidities.

Clinical Manifestations
Initially, patients complain of headache, nausea, and dizziness. Because of the vague nature of the complaints, CO poisoning may be misdiagnosed as a viral illness. The diagnosis should be considered when more than one person in a home presents with the same symptoms. Alteration in mental status, coma, seizures, and syncope are signs of severe poisoning. Indicators of tissue hypoxia, such as tachypnea, tachycardia, and ECG changes, may be seen as well. Carbon monoxide can cause dysrhythmias or an acute MI (118); the intensity of signs and symptoms is related to the duration and severity of exposure, and comorbid conditions. Pulse oximetry will interpret carboxyhemoglobin as hemoglobin, so the SpO2 will be falsely normal (119). For those who survive an acute CO exposure, there may be significant chronic neurologic and cardiovascular effects. Delayed neurologic sequelae (DNS) follow the resolution of initial symptoms, sometimes days to weeks later, and include dementia, movement disorders, and memory impairment (120).

Diagnosis
The diagnosis of CO poisoning is aided by obtaining the carboxyhemoglobin concentration, which can be taken from either a venous or arterial sample. The normal carboxyhemoglobin concentration is less than 5%, but smokers may have a concentration of up to 10% (121). Carboxyhemoglobin concentrations are an indicator of exposure, but do not correlate with the degree of toxicity (122). When there is a delay from exposure to measurement of carboxyhemoglobin, the concentration loses further value as a clinical tool. This is more likely if the patient has been receiving supplemental oxygen, which decreases the half-life of carboxyhemoglobin.
In patients with chest pain, shortness of breath, palpitations, or neurologic deficits indicating severe exposure, an ECG should be performed and serum cardiac markers obtained. Pregnancy status should be determined in women of childbearing age. Elevated serum cardiac markers during moderate and severe acute toxicity predict long-term mortality (123). The pathophysiology of chronic cardiovascular effects of carbon monoxide poisoning probably involves CO poisoning of cardiac myoglobin, but needs further study.

Within 12 hours of exposure, changes on a computed tomography (CT) scan of the brain may be seen. Characteristic findings include symmetric, low-density changes in the globus pallidus, putamen, and caudate nuclei (124). A normal CT scan is a good prognostic indicator. In a series of 18 patients, a negative CT within 1 week of admission was associated with good outcome (125).

**Management**

As soon as the diagnosis is considered, the patient should be administered 100% oxygen, and the carboxyhemoglobin concentration should be obtained. Without supplemental oxygen, studies have found that the half-life of carboxyhemoglobin in blood is 4 to 6 hours. With oxygen, it has been noted to range from 1 to 2 hours (126). Thus, oxygen is the mainstay of therapy in CO poisoning. When considering pregnant women exposed to CO, any disturbance in maternal oxygen delivery will be magnified in the fetus as fetal circulation relies on maternal oxyhemoglobin for oxygenation. Even though fetal hemoglobin has less affinity for CO than adult hemoglobin, there is a high incidence of fetal CNS damage and spontaneous abortion after severe maternal poisoning (127,128). In contrast, pregnant women who have lesser exposures have normal pregnancies and deliver healthy children (129). We recommend treating these patients similarly to those who are not pregnant.

**Controversies**

The use of HBO for CO poisoning is controversial. Many clinicians do not advocate its use. Whereas the animal data and case series suggest a benefit, large randomized clinical trials report mixed results. Some trials show a benefit for HBO in preventing neurologic sequelae, and some do not indicate any difference (for a detailed review of the literature, see Tomaszewski et al. [126]). While HBO decreases CO half-life faster than normal pregnancies and deliver healthy children (129). We recommend treating these patients similarly to those who are not pregnant.

**Clinical Manifestations**

The lack of oral burns does not exclude significant esophageal injury, nor does the presence of oral lesions guarantee visceral burns. The physical examination following caustic ingestion can be deceiving. A series of pediatric patients found visceral burns in 37.5% of patients without oral burns and 50% of patients with oral burns (137). Drooling, odynophagia, and abdominal pain are common findings following significant caustic exposure. However, a series of acid ingestions noted abdominal pain or tenderness in less than half of patients with gastric injury (134).

Pulmonary aspiration may lead to coughing and respiratory distress. Absorption of acid from the stomach may cause acidemia following ingestion. Alkalis are not systemically absorbed in consequential amounts, but a metabolic acidosis may be present if significant injury has occurred.
Management

Endoscopy should be performed in all adult patients presumed to have significant exposures in order to establish the severity of the burn. If endoscopy is normal, the patient can be safely discharged, while patients with severe injury are rapidly stabilized and referred for surgical care before their condition worsens. Endoscopy should be performed as early as possible, ideally within 12 hours. Wound strength is the weakest between 5 days and 2 weeks postinjury, when the perforation risk is the greatest. The exception to universal endoscopy may be a subset of pediatric exposures based upon a series of 79 patients younger than 20 years of age when no serious esophageal injuries were found in patients who lacked stridor or the combination of vomiting and drooling (138). Another group of investigators found no lesions in asymptomatic pediatric patients (139).

The presence of endoscopic evidence of perforation mandates immediate surgery. Other indications for operative repair include pleural effusions, ascites, and a serum pH less than 7.2 (140). If endoscopy demonstrates grade I injury, the patient can be started on a soft diet and the diet advanced as tolerated. The presence of grade II esophageal burns with gastric sparing warrants placement of a nasogastric tube under direct visualization. More severe injury may require parenteral nutrition or a jejunostomy. Silicone rubber esophageal stents have been used to prevent stricture (141).

Administer antibiotics that cover anaerobic bacteria and gram-positive and gram-negative aerobic organisms as soon as perforation is considered. Piperacillin/tazobactam is an appropriate choice, as is levofloxacin and clindamycin. Corticosteroids have been recommended to help prevent scarring and stricture formation in grade II lesions; randomized controlled trials have provided conflicting results. A recent meta-analysis could not find a benefit for the administration of corticosteroids following exposure to caustics (142).

HYDROFLUORIC ACID EXPOSURE

HF is a weak acid with important tissue-corrosive properties. HF and ammonium bifluoride have numerous industrial uses. HF dissolves metal oxides and glass, making it useful in rust removal and glass etching. It penetrates deeply into tissues before dissociating into protons and fluoride ions. Although the protons cause some damage, the most important toxic effects result from fluoride ions binding the divalent cations (143). The consumption of these cations leads to neuropsychiatric pain and cell death. HF ingestions and exposures resulting in electrolyte abnormalities require ICU admission.

Clinical Manifestations

HF produces a clinical syndrome distinct from the caustic agents and requires specific therapy. In small dermal exposures, HF produces severe pain with limited dermal findings. Large exposures by any route, including dermal, can produce severe hypocalcemia and death.

Most unintentional HF exposures are dermal. The severity of the exposure is determined by the duration of exposure, concentration, and extent of surface area exposed. Solutions with low fluoride concentration may cause severe pain beginning hours after the exposure, with a very unremarkable physical examination. An area that appears normal or merely mildly erythematous may be extremely painful. High-concentration industrial preparations may cause immediate pain, with hyperemia and ulceration (144). Similarly, ophthalmic exposures result in pain, chemosis, and damage to conjunctiva and corneal epithelium (145).

The most consequential effects of HF poisoning are systemic. Systemic toxicity can result from ingestions or dermal exposures. Dermal exposures to concentrated HF covering as little as 2.5% body surface area have resulted in systemic toxicity, although typical fatal dermal exposures are larger (146,147). Fluoride ions scavenge divalent cations, causing life-threatening hypocalcemia and hypomagnesemia. Hyperkalemia may be seen as well (148). The ECG may reflect these electrolyte abnormalities. Lengthening of the QRS and QT intervals or presence of peaked T waves may be early indicators of toxicity. The proximal cause of death is usually dysrhythmias; ventricular fibrillation and sudden cardiac arrest have been described (149,150).

Management

The most important concern in small dermal injuries is pain control. The mainstay of therapy is calcium gluconate. The calcium derives its efficacy from binding fluoride ions. Calcium chloride should only be used topically. Other analgesics and regional anesthesia are not contraindicated, but calcium has the advantage of halting tissue damage in addition to providing pain relief. Following decontamination with water, calcium gluconate gel should be applied to the injured area. If the hands are involved, the gel can be held in contact by placing it in a sterile glove and putting the glove on the hand. Prepare the gel by mixing 25 mL of 10% calcium gluconate in 75 mL of water-based lubricant (151). If the wound is located in an area where compartment syndrome is not a concern, 0.5% calcium gluconate can be injected intradermally, 0.5 mL/cm² (147). If these techniques fail to give relief, consider intra-arterial calcium gluconate. The obvious advantage of this route is that calcium can be administered directly and by continuous infusion to the affected area. Add 10 mL of 10% calcium chloride to 40 mL of 0.9% sodium chloride and infuse over 4 hours (152). In the case of ingestion, a nasogastric tube should be carefully placed and any material in the stomach should be aspirated and followed by instillation of a calcium solution. The benefits of this practice are not established, but it seems reasonable in view of the severity of the ingestion and the relative safety of the intervention.

IV calcium and magnesium should be given liberally, and electrolytes should be obtained hourly. Calcium can be administered as calcium gluconate or calcium chloride. One gram of calcium gluconate contains 4.5 mEq of elemental calcium, and 1 g of calcium chloride contains 13.6 mEq. Both calcium salts can produce vasodilation and dysrhythmias when administered too quickly. IV calcium should be administered no faster than 0.7 to 1.8 mEq/min (153). One patient required 267 mEq of calcium over 24 hours (154,155). Dysrhythmias should be expected in severely poisoned patients. Place defibrillator pads on the patient and perform continuous cardiac monitoring. When systemic toxicity occurs, electrolyte abnormalities are most severe in the first several hours of toxicity. Those who
have no signs or symptoms of systemic toxicity for 24 hours can be transferred to a lower level of care.

**ANTIDIABETIC AGENT EXPOSURE**

Diabetes is characterized by an inability to maintain normal blood glucose concentration due to deficiency of insulin, resistance to insulin, or a combination of both. The medications used to treat diabetes are collectively known as *antidiabetic agents*, while a subset of these drugs are properly called *hypoglycemic agents*. The hypoglycemics include insulin and those drugs that promote the release of endogenous insulin. In 2013, the AAPCC received reports of 12,179 exposures to sulfonylureas and biguanides, including 68 major exposures and 12 deaths (3).

The sulfonylureas, meglitinides, and thiazolidinediones are very highly protein bound, and thus not amenable to extracorporeal removal. Insulin and metformin are completely renally eliminated, while most of the sulfonylureas have active hepatic metabolites with urinary excretion of both active metabolites and the parent drug. By far, the most important pharmacokinetic parameter of the hypoglycemics is duration of action, which may be greatly increased in overdose. Insulin is available in multiple forms. In therapeutic subcutaneous doses, Inspro has onset of action within an hour and duration of action of less than 5 hours. Ultralente insulin, the longest-acting insulin commonly used, does not take effect for 4 to 6 hours but lasts as long as 36 hours (156). Regular insulin, lente, and NPH fall in between Lispro and Ultralente insulin. In overdose, the formation of depots of the drug in tissues can slow release and greatly prolong the duration of action. The vascularity of the site of injection will also influence the duration of hypoglycemia. The sulfonylureas generally have a duration of action of 12 to 24 hours in therapeutic doses. Chlorpropamide, a first-generation sulfonylurea, may promote insulin release for up to 12 to 24 hours in therapeutic doses. Lispro has onset of action within an hour and duration of action of less than 5 hours. Ultralente insulin, the longest-acting insulin commonly used, does not take effect for 4 to 6 hours but lasts as long as 36 hours (156). Regular insulin, lente, and NPH fall in between Lispro and Ultralente insulin. In overdose, the formation of depots of the drug in tissues can slow release and greatly prolong the duration of action. The vascularity of the site of injection will also influence the duration of hypoglycemia. The sulfonylureas generally have a duration of action of 12 to 24 hours in therapeutic doses. Chlorpropamide, a first-generation sulfonylurea, may promote insulin release for up to 72 hours (157). Meglitinides, intended to prevent postprandial hyperglycemia, induce insulin release for only 1 to 4 hours. There are not yet enough data on their pharmacokinetics in overdose, but it appears likely that duration of action would be increased in overdose.

**Clinical Manifestations**

The most important signs and symptoms of the aptly classified hypoglycemics are manifestations of decreased serum glucose. In one study, the serum glucose threshold for symptoms of hypoglycemia was 78 mg/dL in poorly controlled diabetics and 53 mg/dL in nondiabetics (158). Manifestations of hypoglycemia can be classified as either autonomic or neuroglycopenic. The former result from an increase in counterregulatory hormones (e.g., epinephrine), while the latter are due to a lack of glucose substrate available for the brain. The autonomic symptoms include tremor, diaphoresis, hunger, and nausea. Neuroglycopenic features of hypoglycemia can manifest as almost any conceivable neurologic deficit, including coma, agitation, seizure, hemiplegia, or mild confusion. Typically, the autonomic symptoms precede neuroglycopenic symptoms, thereby serving as a warning of hypoglycemia before the brain is deprived of a critical level of glucose. However, the autonomic symptoms may be blunted or absent in diabetics or patients taking β-adrenergic antagonists (159). The onset and duration of hypoglycemia is unpredictable after overdose. Of less clinical importance, the hypoglycemics can also produce electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypophosphatemia (160). These are reported more frequently in very large insulin overdoses (161).

Metformin does not produce hypoglycemia itself, but is often formulated with drugs that do, such as glipizide or glyburide. Metformin and its biguanide predecessor, phenformin, are associated with lactic acidosis. The biguanides promote anaerobic metabolism and inhibit lactate metabolism (162). Lactic acidosis is rare, but is more likely in the setting of liver disease, renal insufficiency, heart failure, other acute illness, or acute overdose (163,164). Hepatotoxicity is reported from the therapeutic use of thiazolidinediones and acarbose, but there are limited data on acute overdose of these drugs (165,166).

**Management**

A rapid bedside serum glucose concentration should be obtained as soon as hypoglycemia is considered. If the diagnosis of hypoglycemia is established, 1-g/kg IV dextrose should be given. Because high concentrations of dextrose can be irritating, children should receive 25% dextrose solution and infants 10% dextrose solution. As soon as a normal mental status is restored, the patient should be fed. Each 50-mL vial of 50% dextrose supplies 100 kcal of short-lived simple carbohydrate. In contrast, a meal will supply hundreds of “sustained-release” kilocalories. Glucagon should not be administered unless IV access is delayed and the patient cannot be fed. Glucagon will not be effective in patients with depleted glycogen stores.

If hypoglycemia recurs after it is initially corrected, the treatment is determined by the causative agent. Recurrent insulin-induced hypoglycemia should be treated with a dextrose infusion. Administer a 10% to 20% solution and titrate to maintain glucose in a normal range; a 5% dextrose solution is inappropriate for glucose maintenance.

Octreotide, a somatostatin analogue, is indicated for hypoglycemia following sulfonylurea use. Octreotide should be given subcutaneously, 50 μg every 6 hours (4 to 5 μg/kg/d in divided doses in children). Dextrose alone might not be sufficient to manage sulfonylurea-induced hypoglycemia. Because sulfonylureas potentiate endogenous β-islet cell insulin release, supplemental dextrose will induce more insulin release, with transient corrections and subsequent recurrence of hypoglycemia. Octreotide inhibits the β-islet cell calcium channel, inhibiting sulfonylurea-induced insulin release (167,168). There are no significant adverse effects of short-term octreotide use. Octreotide should be continued for 24 hours. After octreotide is discontinued, the patient should be observed for 24 hours. There are limited data in the literature regarding meglitinide toxicity. With a mechanism of action similar to the sulfonylureas, the meglitinides are shorter acting. Based on their shorter duration of action, we would expect they would be less likely to produce recurrent hypoglycemia, but we have no data to support this assumption. Until we have more experience with overdose of these drugs, it is prudent to manage meglitinide overdose similarly to sulfonylureas.

Metformin-associated lactic acidosis should be considered in patients taking an overdose of metformin, children exposed to more than one or two tablets, and those patients who take metformin therapeutically who also have renal insufficiency,
hepatic insufficiency, heart failure, or another acute illness. The diagnosis is established by obtaining serum chemistry, lactate concentration, and serum pH. The primary therapy is supportive. Although the role of bicarbonate in metformin-associated lactic acidosis is unclear, supplemental bicarbonate should be used to maintain the pH above 7.1. Although metformin is highly protein bound, hemodialysis can be used to correct refractory acidosis (169).

Adults who present with a history of sulfonylurea overdose and children who may have been exposed to sulfonylureas should be observed for 24 hours, even in the absence of hypoglycemia. Similarly, patients who present with hypoglycemia from long-acting forms of insulin should be observed for 24 hours as well.

NATURAL TOXINS

This brief discussion focuses on a few important plants that might necessitate intensive care management. In 2013, there were 48 reported major outcomes and 2 deaths resulting from plant exposure (3).

Belladonna Alkaloids

Plants such as jimsonweed (Datura stramonium) contain numerous anticholinergic compounds. They are used recreationally, often in the form of teas, for their hallucinatory effects. Toxicity is identified by the presence of anticholinergic symptoms: tachycardia; hyperthermia; dry, flushed skin; urinary retention; and agitation. One hundred jimsonweed seeds contain nearly 6 mg of atropine and similar alkaloids (170). In addition to supportive care, physostigmine can be given when the diagnosis is relatively certain. Physostigmine is administered 1 to 2 mg IV slowly over 5 minutes, and should be discontinued and the diagnosis reconsidered if cholinergic symptoms develop. If there is improvement or no change in the patient’s condition, physostigmine can be readministered after a 10- or 15-minute delay.

Nicotine and Nicotine-Like Alkaloids

Nicotine poisoning occurs from inhaled, transdermal, and ingested nicotine. A dose of 1 mg/kg can be lethal in an adult (171). A cigarette contains 13 to 30 mg of nicotine, but most of it is not delivered to the smoker when the cigarette is used as intended. The largest portion of the nicotine is pyrolyzed but not inhaled. As much as 5 to 7 mg of nicotine remains in the cigarette butt, a potentially lethal dose for a child (172). Workers handling tobacco can be poisoned from nicotine as well (173). Signs and symptoms of nicotine toxicity result from activation and then inhibition (from overstimulation) of nicotinic receptors. Gastrointestinal signs include nausea, vomiting, and diarrhea. Early cardiovascular toxicity involves hypertension from nicotinic stimulation of the sympathetic ganglia, but hypotension eventually occurs. The most important signs and symptoms result from nicotinic agonist effects at the neuromuscular junction. Early toxicity causes fasciculation, which gives way to paralysis. Management is supportive. Vasoactive agents may be necessary to maintain blood pressure, and intubation may be indicated to support respiration during paralysis.

Cicutoxin

Cicutoxin is found in Cicuta spp. such as water hemlock. The toxin is found throughout the plant, which is often eaten by adults who misidentify it as wild parsley, turnip, or parsnip (174). The mechanism of cicutoxin poisoning is unclear. Early symptoms are primarily gastrointestinal and begin soon after ingestion. Later, cicutoxin can cause status epilepticus, renal failure, and rhabdomyolysis (175).

Sodium Channel-Altering Plants

Aconitine, from Aconitum spp., opens sodium channels, increasing cellular excitability (174,176). Increased sodium influx delays repolarization, which in turn delays conduction. Slow conduction of peripheral nerves can lead to decreased sensation, weakness, paralysis, and CNS seizures. Vagal and cardiac myocyte sodium channel effects lead to bradycardia, AV block, increased automaticity, or asystole. Aconitine is found in Aconitum napellus (monkshood) and Chinese herbal remedies. Management is supportive; gastrointestinal decontamination should be performed. Cardiac complications have been successfully managed with a ventricular assist device (177).

Mushrooms

Thirty-one major outcomes and one death from mushroom ingestions were reported to poison control centers in 2013 (3). The vast majority of mushroom exposures do not result in significant morbidity, and most of the fatalities that occur are caused by only a few of the many mushroom species in North America. Identification of mushrooms is challenging and best left to the mycologist. However, because each of the clinically important toxic mushrooms causes a distinct clinical syndrome, the physician should be able to identify the toxicologic manifestations of several mushrooms. Mushroom toxins have been divided into 10 groups (178). We will discuss the most common exposures and those most likely to require ICU care.

Gastrointestinal Toxin–Containing Mushrooms

Most reported exposures are to mushrooms containing gastrointestinal toxins. Hundreds of types of mushrooms fall into this category. The most notable clinical feature of ingestion of these mushrooms is the development of vomiting and diarrhea within several hours of ingestion. With few exceptions, mushrooms that cause gastrointestinal symptoms within 6 hours belong to this category and will not cause life-threatening symptoms. The early onset of vomiting following exposure to gastrointestinal toxin–containing mushrooms clinically differentiates them from the cyclopeptide-containing mushrooms. Treatment of exposure to these mushrooms is supportive, and symptoms are generally self-limited. These mushrooms rarely lead to toxicity requiring ICU admission.

Cyclopeptide-Containing Mushrooms

Historically, mortality from these mushrooms is high, although improvements in critical care have improved the prognosis. The most prominent member of this group is Amanita phalloides and other Amanita species. Amanita phalloides contains numerous cyclopeptides, but the most important are a group called the amatoxins. Amatoxins are heat stable and present in lethal concentrations in mushrooms as small as 20 g (178).
Amatoxins cause endocrine, renal, and CNS injury, but the hepatic effects are the most consequential. Patients will be asymptomatic for the first few hours after ingestion, progressing in 5 to 24 hours to watery diarrhea. Hepatic toxicity is evident on day 2 with elevations in bilirubin, ALT, and AST; signs of fulminant hepatic failure such as encephalopathy and coagulopathy follow. Hypoglycemia results not just from hepatic failure, but from direct pancreatic toxicity (179). Cyclopeptides may also cause decreased levels of thyroid hormone and increased calcitonin.

Because patients do not seek help until symptoms develop, it is not uncommon for patients to present to a healthcare facility with volume depletion and early hepatic injury. Good supportive care and prevention of secondary complications are the keys to management. Activated charcoal should be administered 1 g/kg every 2 to 4 hours in order to adsorb any toxin remaining in the gut and interrupt the potential enterohepatic circulation (180). Many therapies to mitigate hepatotoxicity have been investigated, with no substantial or reproducible evidence of efficacy.

Although there are no data to support its use in Amanita poisoning, NAC effectively treats hepatic failure from other hepatotoxins, such as acetaminophen. Administer NAC intravenously, according to the acetaminophen protocol. Continue the final infusion until the patient expires, definitively recovers, or receives liver transplant.

Silibinin, extracted from milk thistle, improved hepatic markers and mortality in a dog model of Amanita poisoning, but was not found beneficial in a meta-analysis of human studies (181). Legalon SIL is an investigational silibinin derivative available in the United States for patients suspected of ingesting Amanita mushrooms. The loading dose of Legalon SIL is 5 mg/kg IV over 1 hour, followed by a maintenance dose of 20 mg/kg IV as a continuous infusion over 24 hours. Legalon SIL can be obtained by calling the 24-hour, toll-free hotline: 1-866-520-4412.

High-dose penicillin had some effectiveness in a dog model of Amanita poisoning, possibly by blocking hepatocyte uptake of amatoxin (182). Therapy includes IV penicillin G, 1 million units/kg/d in divided doses (183). The criteria for liver transplantation have not been clearly established. Transplantation is not without risk, and those who survive fulminant hepatic failure from Amanita without transplantation are expected to make a full recovery. Ideally, the decision to transplant should be delayed until it is clear the patient will not recover. Some consider transplantation for those with encephalopathy and prolonged PT, persistent hypoglycemia, metabolic acidosis, increased serum ammonia, aminotransferases, and hypofibrinogenemia (178). Patients should be referred to transplantation centers early in their clinical course so that they may be listed early, and transport should be avoided when they are gravely ill.

**Gyromitrin-Containing Mushrooms**

*Gyromitra* mushrooms are found throughout the United States. These mushrooms contain gyromitrin (N-methyl-N-formyl hydrazone), which is hydrolyzed to monomethylhydrazine (MMH). MMH inhibits the formation of pyridoxal-5’-phosphate (PLP), an enzyme cofactor synthesized from pyridoxine (vitamin B6). Of great importance, PLP is a cofactor for glutamic acid decarboxylase, the enzyme in the CNS that converts glutamate to GABA. Inhibition of PLP by monomethylhydrazine results in excessive excitation relative to inhibition.

The initial phase of toxicity, occurring 5 to 10 hours after ingestion, is manifested by nonspecific clinical features including nausea, vomiting, diarrhea, and headache, and ultimately leads to intractable seizures (178). Patients ingesting *Gyromitra* spp. should receive activated charcoal, 1 g/kg. Seizures may not respond to benzodiazepines alone. If *Gyromitra* spp. ingestion is considered, or if a patient presents with seizures after mushroom ingestion, pyridoxine 70 mg/kg IV should be given. Pyridoxine serves as substrate for pyridoxine phosphokinase, allowing some PLP to be generated despite inhibition by MMH.

**Allenic Norleucine–Containing Mushrooms**

The nephrotoxic *Amanita smithiana* contains the amino acid toxins allene norleucine (amino-hexadienoic acid) and possibly 1–2–amino-4-pentynoic acid (178). All known exposures to these mushrooms have occurred in the Pacific Northwestern United States. These serve as important exceptions to the “rule” that mushrooms that cause early gastrointestinal toxicity do not cause significant end-organ damage later.

Initial symptoms, which include nausea, vomiting, diarrhea, and abdominal cramping, may begin within an hour of ingestion. The most important clinical features of toxicity develop later. Acute renal failure, indicated by elevations in blood urea nitrogen (BUN) and creatinine, manifest 4 to 6 days after ingestion (184).

Activated charcoal should be administered when patients present after ingesting mushrooms from the Pacific Northwest. Management of nephrotoxicity is supportive. Patients who required hemodialysis underwent the procedure two to three times per week for approximately 1 month (178).

**Orellanine- and Orellinine-Containing Mushrooms**

*Cortinarius orellanus*, found in North America, contains the toxin orelanine, which is converted by photochemical degradation to another toxin, orellinine (178). Orelanine and orellinine are important causes of mushroom-induced nephrotoxicity. Orelanine is activated by the P450 system. These molecules generate oxidative damage by sustained redox cycling.

Symptoms begin 24 to 36 hours after ingestion. Patients report headache, chills, polydipsia, nausea, and vomiting. Early laboratory findings of hematuria, leukocyturia, and proteinuria indicate interstitial nephritis. Later, renal failure develops, characterized histologically by tubular damage and fibrosis of tubules with relative glomerular sparing (185,186). Hepatotoxicity is an uncommon feature.

Management is supportive. Administer activated charcoal if patients present early. Some patients will rapidly improve, whereas others require chronic hemodialysis (187).

**OTHER RESOURCES**

This chapter is intended to be a review of common and consequential xenobiotic exposures. *Goldfrank’s Toxicologic Emergencies* (McGraw-Hill, 2015) contains a more comprehensive review of all the substances discussed here. The regional poison center (1-800-222-1222) is an excellent resource for further information and recommendations specific to your patient.
Owing a great deal to the success of prevention measures, significant poisonings are relatively rare events. In 2013, of the 2.1 million human exposures reported to the AAPCC, only 1,218 were fatal. Although this figure underestimates total poisoning, it represents a very small number of patients per hospital per year. Because each ICU sees a paucity of these patients, many critical care physicians do not see enough of them to develop familiarity with their care. We encourage close collaboration between ICU physicians, regional poison centers, and toxicologists to provide the best possible care to poisoned patients.

Key Points

- Classic toxic syndromes can be differentiated based on vital signs, mental status, pupil size, presence of peristalsis, diaphoresis, and urinary retention.
- A comprehensive history should include, when available, the specific xenobiotic exposure, the size of exposure, reason, and time of ingestion.
- Serum glucose and ECGs are essential initial bedside tools in the assessment of the poisoned patient.
- Serum chemistries are warranted in all critically ill patients.
- Routine urine toxicologic screens rarely aid in management.
- Treat the patient not the poison.
- Stabilize airway, breathing, and circulation first.
- Specific antidotes may be warranted.
- Hemodynamic or neurologic instability, potential for dysrhythmias, ingestion of sustained release products, or ingestion of potentially lethal dose are indications for ICU admission.

References


