CHAPTER 67 ■ SUBSTANCE ABUSE AND WITHDRAWAL: ALCOHOL, COCAINE, OPIOIDS AND OTHER DRUGS

S. SUJANTHY RAJARAM • JANICE L. ZIMMERMAN

Ethanol, illicit drugs, and prescription drugs used for nonmedical purposes are a significant medical as well as social problem. The 2005 National Survey on Drug Use and Health found that 22.7% of Americans, or 55 million individuals, were binge drinkers, which includes 16 million heavy drinkers (five or more drinks on the same occasion at least 5 different days in the prior 30 days) (1). Pain relievers were used nonmedically by 4.7 million Americans, and 3.5 million used stimulants or cocaine. Casual or habitual use of these drugs contributes to acute and chronic illness. Substance abuse also underlies many forms of injury, including vehicular accidents, falls, near-drowning, thermal injuries, homicide, and suicide. Other critical illnesses may be impacted by either substance use or substance withdrawal. This chapter will cover acute toxicity and withdrawal syndromes related to ethanol, cocaine, opioids, and other selected drugs likely to be of importance to the critical care practitioner.

ETHANOL

Alcohol abuse and alcoholism (a dependence on alcohol) are major social, economic, and public health problems throughout the world. Alcoholism is the third leading cause of death in the United States and it reduces life expectancy by 10 to 12 years. Men who imbibe more than 14 drinks per week or four drinks at one time or women who have more than seven drinks per week or three drinks at one time are at risk for alcohol abuse and dependence (a standard drink is one 12-ounce beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits). Ethanol is rapidly absorbed in unaltered form from the stomach and small intestine. The presence of food (especially milk and fatty foods) in the stomach delays absorption, whereas the presence of water enhances absorption. Ethanol diffuses freely into body tissues. It is primarily metabolized in the liver. Less than 10% is excreted by the lungs or kidneys or through the skin. Several hepatic enzyme systems independently metabolize ethanol to acetaldehyde. The primary degradation pathway is in the hepatic cytosol by alcohol dehydrogenase, with nicotinamide adenine dinucleotide (NAD) as a cofactor. Acetaldehyde generated by this process is in turn metabolized through the Krebs cycle to carbon dioxide and water with 7 kcal/kg liberated in this process. Most people can metabolize about 150 mg of ethanol per kilogram body weight per hour. This is equivalent to about 12 ounces of beer or 1 ounce of 90-proof whiskey.

Acute Toxicity

Common features of acute ethanol intoxication are shown in Table 67.1. Intoxication with ethanol depends on the rate of rise of the blood alcohol level and the length of time the level is maintained. Blood alcohol levels of 20 to 30 mg/dL are often associated with a mild euphoria, delayed reaction time, decreased inhibition, and alteration in judgment. Most people exhibit gross intoxication at levels above 150 mg/dL. Opiates often develop at levels above 300 mg/dL, and death may result from respiratory depression, aspiration, or cardiovascular collapse when levels exceed 400 to 500 mg/dL (2).

Ethanol is a sedative-hypnotic drug and exerts its primary effects on the central nervous system (CNS). Patients can present with altered consciousness, agitation, euphoria, slurred speech, ataxia, stupor, and coma. Awareness of the environment (e.g., heat or cold exposure) and perception of pain are diminished. Ethanol may depress the respiratory center and lead to hypventilation and respiratory arrest. Although seizures are more common in alcohol withdrawal, they may also occur with acute intoxication.

Acute ethanol intoxication is often associated with an increased heart rate and cardiac output, whereas prolonged intoxication may be associated with depressed myocardial contractility (3). Acute intoxication can also be associated with a variety of cardiac arrhythmias, especially atrial fibrillation (“holiday heart” syndrome). Cutaneous vessels dilate, whereas splanchnic vessels constrict. Increased sweating associated with cutaneous vasodilation may account for the decrease in core temperature often associated with acute ethanol intoxication.

Metabolic problems related to alcohol ingestion can be life threatening. Alcohol enhances the urinary excretion of phosphate and magnesium that can result in clinically significant hypophosphatemia and hypomagnesemia. The chronic alcoholic patient often has decreased glycogen stores, and because alcohol also inhibits hepatic gluconeogenesis, profound hypoglycemia may occur. A variety of acid-base disturbances are seen in acute alcoholic intoxication. Depression of the respiratory center in the severely intoxicated person may result in respiratory acidosis. Nausea and vomiting may cause hypokalemia and metabolic alkalosis. The presence of a
significant metabolic acidosis or elevated lactate should prompt a search for conditions other than alcohol intoxication.

Ethanol ingestion may cause acute gastritis and gastrointestinal (GI) bleeding. Alcoholics have an increased incidence of peptic ulcer disease and pancreatitis. Acute alcohol intoxication may precipitate alcoholic hepatitis in the chronic user. All bone marrow cell lines are suppressed by alcohol ingestion. Suppression of antidiuretic hormone by ethanol causes diuresis and may lead to profound hypovolemia, especially if there is associated nausea, vomiting, or diarrhea.

Assessment and Treatment of Acute Intoxication

Treatment of acute ethanol intoxication is primarily supportive, but a careful examination is needed to detect complications. The first priority is assessment and stabilization of the airway and ventilation. The respiratory rate, depth of respirations, \( \text{SpO}_2 \), mental status, gag reflex, and presence of vomitus should be rapidly evaluated. An arterial blood gas should be obtained if hypoxemia is a concern but is not obvious on clinical examination. Intubation is indicated in the obtunded or comatose patient who is unable to protect his or her airway and when hypoxia has occurred or is likely. Positive pressure ventilation should be instituted to correct arterial hypoxemia and respiratory alkalosis. If the patient presents with altered mental status, \( 30 \) to \( 100 \) mg of thiamine and \( 25 \) g of glucose should be administered intravenously. If the patient responds to the administration of glucose or if blood glucose levels are low, a continuous infusion of glucose should be given. Intravenous naloxone may be administered if concomitant opioid use is suspected. Hypotension should be treated initially with volume resuscitation. GI bleeding should be considered in the hypotensive patient and further assessment may include a rectal examination and insertion of a nasogastric tube. GI decontamination is of limited utility because the majority of alcohol is already absorbed. ethanol is not adsorbed by activated charcoal, but charcoal may be administered if ingestion of other toxic drugs is suspected. Hypothermia should be corrected. Fluid, electrolyte, and acid-base disturbances are corrected, depending on the clinical presentation. A creatine phosphokinase (CPK) level may be warranted in the patient with trauma or prolonged muscle compression to evaluate for rhabdomyolysis. An ethanol blood level may be helpful in documenting the severity of intoxication and estimating the duration of impairment. A low ethanol level in the setting of a patient with a depressed level of consciousness should prompt an evaluation for other etiologies. A chest radiograph is often necessary to assess for evidence of aspiration or other complications such as pneumonia. Consider obtaining computed tomography of the head if there is any suspicion of subdural hematoma or other intracranial injury. Hemodialysis has been used in cases of massive ethanol ingestion (4).

The chronic alcoholic may also develop alcoholic ketoadidosis (3). This condition is typically preceded by binge drinking followed by a period of abstinence for 1 to 3 days with nausea, vomiting, and insufficient nutrient intake. The liver produces excessive ketones in response to starvation, which results in an anion gap acidosis. Pancreatitis is frequently present in these patients. The blood glucose may be low or high in this setting but is rarely above \( 300 \) mg/dL. Uncontrolled glucose intolerance is present. The condition responds to volume replacement and administration of glucose. Insulin is not needed. Thiamine should be administered before glucose to avoid precipitation of acute beriberi and Wernicke-Korsakoff syndrome.

Alcohol Withdrawal

Chronic excessive alcohol ingestion depresses central \( \alpha \) and \( \beta \) receptors and potentiates the inhibitory neurotransmitter \( \gamma \)-aminobutyric acid (GABA). The brain adapts with a functional increase in N-methyl-D-aspartate (NMDA) receptors, which are part of an excitatory system. When alcohol consumption stops, the excess excitatory receptors and removal of the inhibitory effects mediated by GABA contribute to the hyperadrenergic state that causes the symptoms seen in alcohol withdrawal.

Alcohol withdrawal syndromes occur in dependent patients during the initial period of abstinence. In hospitalized patients,
TABLE 67.2
STAGES OF ALCOHOL WITHDRAWAL AND TREATMENT

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Time frame</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremulousness</td>
<td>Onset within hours</td>
<td>Benzodiazepines (oral or IV)</td>
</tr>
<tr>
<td>Hyperactivity, tremor</td>
<td>Peak 10–30 h</td>
<td>Supportive measures</td>
</tr>
<tr>
<td>Diaphoresis, nausea</td>
<td>Subside in ∼40 h</td>
<td>Quiet environment</td>
</tr>
<tr>
<td>Mild tachycardia, hypertension</td>
<td></td>
<td>Thiamin, folate, vitamins</td>
</tr>
<tr>
<td>Clear sensorium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Onset 6–48 h</td>
<td>Lorazepam 2–4 mg IV, repeat as needed</td>
</tr>
<tr>
<td></td>
<td>Peak 13–24 h</td>
<td>Diazepam 10–20 mg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive measures as above</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Onset 8–48 h</td>
<td>Benzodiazepines (oral or IV)</td>
</tr>
<tr>
<td></td>
<td>May last 1–6 d</td>
<td>Supportive measures as above</td>
</tr>
<tr>
<td>Auditory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tactile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium Tremens</td>
<td>Onset 60–96 h &amp; 48–72</td>
<td>Benzodiazepines IV as needed</td>
</tr>
<tr>
<td>Coarse tremors, agitation</td>
<td></td>
<td>Diazepam</td>
</tr>
<tr>
<td>Altered sensorium (delusions, hallucinations, confusion)</td>
<td></td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Fever, tachycardia</td>
<td></td>
<td>Magnesium sulfate</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Time after last drink.

symptoms of alcohol withdrawal may occur in up to 40% of those who drink excessive amounts of alcohol (6). Prevention of alcohol withdrawal syndromes has been shown to improve morbidity and mortality and shorten hospital and intensive care unit (ICU) length of stay (7). Four stages of alcohol withdrawal have been described (8), but symptoms are a continuum of neuropsychiatric and hemodynamic manifestations. Patients may manifest one or more of these syndromes on presentation or develop additional manifestations and progress from less severe to more severe stages while hospitalized (Table 67.2). A key distinction is to determine if the patient has an intact or altered sensorium.

Assessment of the severity of withdrawal is needed to determine appropriate treatment. Although the revised Clinical Institute Withdrawal Assessment—Alcohol Scale (CIWA-Ar) is often used for assessment, it has less applicability in critically ill patients (9). Patients with minor withdrawal symptoms can usually be treated with intravenous or oral benzodiazepines. Benzodiazepines act as an alcohol substitute to dampen the excitatory neuronal activity, and additional benefits include prevention of seizures and delirium tremens. The choice of benzodiazepine in hospitalized patients may depend on severity of hepatic dysfunction, desired duration of action, and available routes of administration. All benzodiazepines are effective when appropriate doses are used. Fixed dosing and symptom-triggered regimens have been used effectively. Fixed dosing may be more appropriate in critically ill patients until other conditions have stabilized. Treatment duration beyond 7 days is seldom required.

Although benzodiazepines are clearly superior to placebo in treating alcohol withdrawal, it is difficult to draw conclusions regarding the efficacy of benzodiazepines compared to β blockers, clonidine, carbamazepine, and valproic acid due to heterogeneity of clinical trials. Many trials are conducted in outpatients and have limited applicability to hospitalized and critically ill patients (10,11). Hallucinosis also responds well to benzodiazepines. Intravenous ethanol may be an option for alcohol withdrawal treatment or prophylaxis (12). However, it is not recommended for routine use due to dosing variability and lack of established efficacy (13). Other agents such as clonidine and β-blockers have been reported to be effective for minor withdrawal symptoms but their use is less common. Clonidine and β-blockers do not prevent the development of delirium. All patients with alcohol withdrawal should receive supportive measures in addition to pharmacologic intervention. Thiamine (vitamin B₁) should be given intravenously or orally to prevent Wernicke encephalopathy. Magnesium sulfate may be needed to correct hypomagnesemia.

Seizures

Approximately 5% to 10% of patients with untreated mild alcohol withdrawal symptoms progress to seizures. Patients who have been drinking heavily for only a few years but have several detoxification admissions are at higher risk of seizures than patients with long drinking histories but fewer detoxification admissions. Previous nonalcohol-related admissions also increase the risk of alcohol withdrawal seizures. This association has been termed the “kindling effect.” According to the kindling hypothesis, each withdrawal episode is an irritative phenomenon to the brain. The accumulation of multiple episodes lowers the seizure threshold (14). Most alcohol withdrawal seizures are brief and self-limited in duration. Alcohol
withdrawal seizures are usually generalized tonic-clonic but focal seizures may also occur. Multiple seizures (two to six episodes) occur in approximately 60% of patients and within a 12-hour period. It may be difficult to distinguish withdrawal seizures from a pre-existing seizure disorder or new onset of a nonalcohol-related seizure. Other causes of seizures such as hypoglycemia, metabolic abnormalities, trauma, infection, and other drug intoxication must be considered. A computed tomography (CT) scan of the head should be obtained for new-onset seizure, persistent neurologic deficits, or evidence or suspicion of trauma. Alcohol withdrawal seizures can be terminated with benzodiazepines (15). Intravenous lorazepam or midazolam is commonly used. If the seizure terminates with-out intervention, a benzodiazepine should be administered as soon as possible to prevent subsequent seizures. The risk of a recurrent seizure is 1.3% to 24% (16). Lorazepam (2 mg) significantly reduces the risk of recurrent seizure, whereas phenytoin has no effect (16,17). Less than 3% of patients develop status epilepticus and they should be treated with benzodiazepines or propofol. Phenytoin is not as effective.

Delirium Tremens

Delirium tremens (DT) is the most severe manifestation of alcohol withdrawal and these patients should be cared for in an ICU setting. Untreated DT carries a mortality of 15%, but mortality declines to 1% if treated. The accumulation of multiple prior withdrawal episodes leads to more severe DT with each episode (14). Patients with DT have more severe autonomic hyperactiv-ity than milders cases of withdrawal and manifest delirium that may fluctuate. Some patients with severe withdrawal symptoms may need intubation during treatment. Fluid requirements may be increased due to increased insensible losses (fever, diaphore-sis) and lack of oral intake. High-dose intravenous benzodi-azepines (diazepam, lorazepam, midazolam) administered at frequent intervals or as a continuous infusion are needed to control the hyperadrenergic symptoms. Dosing should be indi-vidualized to achieve light somnolence (18). Benzodiazepines bind at the GABA-benzodiazepine receptor, and once these recep-tors are saturated, additional drug cannot bind. Patients may tolerate high doses of benzodiazepines but do not necess-arily benefit from them (19). Caution is advised when ad-ministering high doses of intravenous lorazepam or diazepam over long periods of time as the propylene glycol diluent may result in a lactic acidosis (20). Daily dose reductions of 25% can be initiated after the second or third day of treatment. Propofol infusions may be useful for patients who are refrac-tory to benzodiazepines. Propofol has dual activity similar to alcohol (GABA agonist and NMDA antagonist properties) that may explain its efficacy. Propofol has a rapid onset of action, sedation, and anticonvulsive properties (6,21). Other sedative-hypnotic drugs such as paraldehyde and barbiturates are effec-tive in treating DT but are not commonly used. Neurolep-tic agents are inferior to benzodiazepines and should not be used as single agents for treatment of DT (18). Neuromuscular blockers may be considered to control agitation when high-dose sedatives are not effective. Cardiac monitoring is neces-sary to detect arrhythmias early and institute therapy. Torsade de points may develop due to hypomagnesemia or prolonga-tion of the QTc interval and should be treated aggressively with intravenous magnesium sulfate. Beta blockers may be needed to treat hypertension or tachycardia but they should not be ad-ministered to treat delirium. Propranolol may worsen delirium. Thiamine supplementation (100 mg/day) is recommended for 3 days.

DT usually lasts 2 to 5 days, but in 5% to 10% of cases, DT lasts greater than a week. Elderly alcoholics have a longer withdrawal period with more symptoms than younger alco-holics (23). A small percentage of patients remain delirious for several weeks and require continuing treatment. Be aware, however, that after head trauma, a subdural hematoma can evolve subacutely in the alcoholic patient. Repeat imaging of the brain may be warranted after stabilization of a course of pro-tracted delirium to rule out a slowly accumulating subdural hematoma (19).

Cocaine

Cocaine (benzoylmethylecgonine) is an alkaloid derived from leaves of Erythroxylon coca. It is the second most commonly used illicit drug and the most frequent cause of drug-related deaths. Eighteen- to twenty-five-year-olds are the most com-mon users, although it is abused by younger and older individ-uals (1).

Cocaine is available in two forms. Cocaine hydrochloride is prepared by dissolving alkaloidal cocaine in hydrochloric acid resulting in a white water-soluble powder, crystals, or granules. This form of cocaine is used intranasally (snorting), orally, or intravenously. The other available form of cocaine is free base or crack cocaine. Heating cocaine hydrochloride in sodium bicarbonate or ammonia makes the hard crystallized cocaine base called crack because of the popping sound it makes when heated (24). Smoking crack cocaine has become a widespread practice due to the rapid absorption across the alveolar sur-face. Both forms of cocaine are readily absorbed from all body mucosal surfaces. The peak effects of cocaine range from 1 to 90 minutes depending on the route of administration. Inhal-a-tional and intravenous use result in the most rapid peak effects and shortest duration of action. Cocaine is rapidly metabolized by hepatic and plasma cholinesterases and nonsynaptic hy-drolysis to ecygone methyl ester and benzoylecgonine, which are excreted in urine. The urinary excretion of unchanged co-caine ranges from 1% to 15%. The route of administration does not affect metabolic excretion patterns appreciably and half-lives of most metabolites range from 45 to 90 minutes (23). Subjective rating of euphoria declines within minutes after constant concentrations are achieved, demonstrating rapid desensitization and acute tolerance (26). Duration of positive urinary metabolites is somewhat dependent on the assay tech-nique, the activity of plasma cholinesterases, and the duration and dosing of cocaine use.

Cocaine's lipophilic nature, compounded with rapid dis-tribution into and out of the CNS, suggests a highly abu-sive profile (rush and crash) and increased incidence of kin-dling. The major neurochemical actions of cocaine are CNS stimulation with release of dopamine; inhibition of neuronal norepinephrine and dopamine uptake, resulting in generalized sympathetic nervous system stimulation; release of serotonin or blockade of serotonin reuptake; and inhibition of sodium current in neuronal tissue, resulting in a local anesthetic effect (27).
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Toxicity
Numerous morbidities have been associated with acute and chronic cocaine use (Table 67.3). Complications of particular interest to intensivists are discussed below.

Cardiovascular
Cocaine increases the heart rate, blood pressure, and left ventricular contractility, leading to an increase in myocardial oxygen demand (28). The increased demand may combine with underlying coronary artery disease, vasoconstriction, platelet aggregation, or in situ thrombus formation to produce ischemia and infarction. Chronic cocaine use also accelerates atherosclerosis (29). Apart from structural changes in epicardial vessels, wall thickening is described in the intramyocardial small coronary arteries in people with cocaine-induced chest pain (30).

Chest pain is the most common cocaine-associated complication in patients who present for medical care. All patients presenting with chest pain should be questioned regarding cocaine use. Myocardial ischemia can occur with all routes of abuse with no relation to the dose or chronicity of use. The onset of chest pain often occurs temporally related to the use of cocaine. However, chest pain may occur hours to days after the last use of cocaine. Electrocardiograms are often abnormal in patients presenting with cocaine-associated chest pain (31, 32). Myocardial infarction may be present with a normal or abnormal electrocardiogram. Conversely, electrocardiograms may suggest acute ischemia in the absence of infarction due to j-point elevation or repolarization changes (32). Cardiac troponins are more specific for assessing myocardial injury than creatine kinase-MB, which may be elevated due to skeletal muscle injury (33). Myocardial infarction is reported to occur in approximately 6% to 7% of patients and occurs with normal coronary arteries and in the presence of significant atherosclerotic disease (32,34,35). Periods of silent ischemia are common in chronic users of cocaine, as shown by Holter tests and during periods of withdrawal (36). Dilated cardiomyopathy, myocarditis, and congestive heart failure can occur secondary to chronic cocaine use (37).

Cocaine is arrhythmogenic when taken in large quantities because of catecholamine effects. The arrhythmias are usually transient and resolve when cocaine is metabolized. Sinus tachycardia, supraventricular tachycardia, atrial fibrillation, premature ventricular beats, ventricular tachycardia, ventricular

<table>
<thead>
<tr>
<th>TABLE 67.3</th>
<th>CLINICAL MANIFESTATIONS OF COCAINE USE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANESTHETIC EFFECTS</strong></td>
<td><strong>RESPIRATORY</strong></td>
</tr>
<tr>
<td>Localized numbness</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Central neuronal depression</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Coma</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td><strong>Pulmonary vascular occlusion, pulmonary infarction</strong></td>
</tr>
<tr>
<td>Euphoria</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Tremor</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td>Sleeplessness</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
</tr>
<tr>
<td>Euphoria</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td>Headache</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Seizures</td>
<td><strong>RESPIRATORY</strong></td>
</tr>
<tr>
<td>Stroke</td>
<td><strong>Pulmonary edema</strong></td>
</tr>
<tr>
<td>Transient ischemic events</td>
<td><strong>Pulmonary hypertension</strong></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td><strong>Respiratory arrest</strong></td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
<td><strong>Pulmonary vascular occlusion, pulmonary infarction</strong></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td><strong>Central neuronal depression</strong></td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td><strong>Euphoria</strong></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Myocardial ischemia and infarction</td>
<td><strong>RESPIRATORY</strong></td>
</tr>
<tr>
<td>Myocarditis</td>
<td><strong>Pulmonary edema</strong></td>
</tr>
<tr>
<td>Aortic dissection or rupture</td>
<td><strong>Pulmonary hypertension</strong></td>
</tr>
<tr>
<td>Sudden death</td>
<td><strong>Respiratory arrest</strong></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td><strong>Pulmonary vascular occlusion, pulmonary infarction</strong></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td><strong>Central neuronal depression</strong></td>
</tr>
<tr>
<td>Vasculitis</td>
<td><strong>Euphoria</strong></td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
</tr>
<tr>
<td>Induction of renal atherogenesis</td>
<td><strong>Euphoria</strong></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Renal infarction</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td>Scleroderma renal crisis</td>
<td>Hemoptysis</td>
</tr>
</tbody>
</table>

Cardiomyopathy, supraventricular tachycardia, atrial fibrillation, premature ventricular beats, ventricular tachycardia, ventricular
fibrillation, bundle branch block, asystole, and torsade de pointes may occur.
Elevation of blood pressure occurs due to the acute effects of cocaine, but it is usually self-limited. Sustained elevations of blood pressure suggest the presence of chronic hypertension or another complication (e.g., intracranial process).

Central Nervous System
In large doses, cocaine may cause a generalized impairment of neuronal impulse transmission leading to CNS depression, coma, respiratory depression, and respiratory arrest. At low doses, stimulation is the common feature of cocaine use. The euphoria produced by cocaine is the principal reason for its abuse. Excessive CNS stimulation can occur and is manifested by tremulousness, agitation, sleeplessness, paranoia, and frank psychosis. Aggressive and assaultive behavior can occur in cocaine overdose.

Seizures can be induced, even on the first exposure, because cocaine lowers the threshold for seizures. Cocaine-related seizures are usually brief and self-limited, occurring soon after taking cocaine, although the interval between last use of cocaine and onset of seizures can be several hours (39). Sustained or repeated seizure activity suggests an additional complication such as hyperthermia, intracranial hemorrhage, metabolic abnormality, or massive intake of cocaine.

Cocaine use is associated with ischemic cerebrovascular accidents as well as transient ischemic attacks (39-41). Radiologic studies have demonstrated cerebral vasoconstriction as well as vessel thrombosis with cocaine (41,42). Although most symptoms occur during or immediately after cocaine use, neurologic symptoms may occur within hours to several days after the last use. Subarachnoid, parenchymal, and intraventricular hemorrhage may occur within moments of drug use, possibly related to blood pressure elevation. Some patients have anatomic abnormalities such as vascular malformation or aneurysm that may be amenable to specific therapy (39,43,44). Cerebral atrophy, predominantly in the temporal-frontal regions, has been noted in patients with chronic cocaine abuse (45).

Pulmonary
Pulmonary complications associated with cocaine are much less common than cardiovascular and cerebrovascular events but include a variety of conditions (46,47). Inhalation of cocaine, in contrast to IV use, has been demonstrated to cause bronchoconstriction (48). This response may be due to an irritant effect and may contribute to wheezing and exacerbations of asthma in cocaine users (49,50). Barotrauma (pneumothorax and pneumomediastinum) is reported secondary to snorting cocaine and crack inhalation (51). Noncardiogenic pulmonary edema may occur and is described more commonly with intravenous use of cocaine. Massive hemothorax with diffuse alveolar hemorrhage is a rare complication of unknown etiology and has been reported with smoking free-base cocaine and other routes of abuse. Other rare pulmonary toxicities, more commonly reported after inhalation of cocaine, include interstitial pneumonitis, pulmonary infiltrates with peripheral and/or lung eosinophilic prominence, and bronchiolitis obliterans (52). Septic pulmonary emboli and pulmonary vascular obstruction resulting from foreign body granulomas or angiographic thrombosis may develop as a consequence of IV cocaine use similar to IV heroin use (53).

Hyperthermia/Rhabdomyolysis
Hyperthermia may result from muscle hyperactivity or as a direct effect of cocaine on the hypothalamic temperature regulatory center. High ambient temperatures are associated with increased mortality from cocaine and hypertensin (51). Characteristics of several factors that play a role (54). Cocaine impairs sweating and cutaneous vasodilation as well as heat perception under conditions of heat stress (55). Cocaine-induced rhabdomyolysis is common and can lead to acute renal failure. Multiple factors such as hyperthermia, seizures, vasoconstriction with ischemia, excessive motor activity, concomitant use of other drugs, and even a direct toxic effect of cocaine may contribute to muscle injury. Myalgias and muscle tenderness are infrequently present. Seizures, hypotension or hypertension, arrhythmia, coma, and cardiac arrest identify a subgroup of patients who are prone to severe rhabdomyolysis (56,57).

Other Toxicities
Intestinal ischemia, infarction, and perforation have been reported following ingested, intravenous, and inhaled cocaine (58,59). Patients may present with complaints of acute or chronic abdominal pain. Acute renal failure may be precipitated by rhabdomyolysis, but other etiologies may include accelerated hypertension and glomerulonephritis (60). Rare cases of renal infarction have also been reported.

Diagnosis of Acute Intoxication
Patients with cocaine intoxication may present with a variety of primary complaints such as altered mental status, chest pain, syncope, palpitations, seizures, or attempted suicide (61). Characteristic findings of CNS stimulation such as agitation, mydriasis, sweating, hypertension, and tachycardia are often present. However, the effects of other drugs, the presence of complications, and delays in presentation may obscure the typical sympathomimetic manifestations. Other medical conditions such as meningitis, encephalopathy, epiglottis with status, and thyrotoxicosis may mimic cocaine intoxication (27). Confirmation of acute or recent cocaine exposure is made by urine toxicology testing.

Treatment for Acute Intoxication
Benzodiazepines are the pharmacologic agents of choice for control of cocaine-induced agitation. The agitation and psychosis of cocaine overdose usually can be managed with titrated doses of IV diazepam, 5 to 20 mg; lorazepam, 2 to 4 mg; or midazolam, 5 to 10 mg slowly. Haloperidol is not recommended as a first-line agent because of the lack of experimental support (62) and potential to lower the seizure threshold. Adequate hydration and correction of electrolyte abnormalities are important.

Cardiovascular
No large clinical trials have evaluated treatment strategies for cocaine-associated ischemia. Treatment of cardiac toxicity due to cocaine is directed at reversing physiologic effects that cause...
ischemia or arrhythmias. Aspirin should be administered as an antplatelet agent for suspected myocardial ischemia unless there is evidence of cerebral hemorrhage. Oxygen may also help to limit myocardial ischemia. Benzaodiazepines and nitroglycerin are considered first-line agents for relief of chest pain, but small clinical studies have yielded conflicting results on the benefit of combining the agents (63,64). Benzodiazepines decrease the blood pressure and heart rate, thus decreasing myocardial oxygen demand, and nitroglycerin may dilate coronary arteries or relieve vasoconstriction. Alpha blockers such as phentolamine have been recommended as a second-line treatment for unrelied pain, but are rarely needed (65). The use of $\beta$ blockers in the management of myocardial ischemia is debated. There is a potential concern of worsening vasospasm or hypertension due to unopposed stimulation of $\alpha$ receptors. Intra-coronary propranolol results in a small decrease in coronary artery diameter following intranasal cocaine, but $\beta$ blockers are not administered by this route or as soon after cocaine use in most patients (66). However, $\beta$ blockers have been used, particularly in the setting of myocardial infarction, without complications. Administration of $\beta$ blockers might be avoided in patients manifesting acute sympathomimetic findings, but the benefits of these agents should be considered in other patients with ongoing myocardial ischemia.

Most patients with cocaine-associated chest pain will not have infarction. Patients can be managed in chest pain or observation units similar to other chest pain patients (67). Low-risk patients with normal cardiac markers can be risk stratified safely with stress testing. Early therapy for cocaine-induced myocardial infarction should consist of oxygen, aspirin, and nitroglycerin as required for pain relief. If pain persists, patients with cocaine-induced myocardial infarction are candidates for reperfusion therapy. Primary percutaneous angiography is preferred in patients with evidence of ST-elevation myocardial infarction, especially when the diagnosis may be in doubt (65,68). Thrombolytic therapy has been safely used in cocaine-associated myocardial infarction and may be considered if invasive reperfusion is not available (69).

Arrhythmias associated with cocaine use are usually transient. Standard therapy should be considered for sustained arrhythmias unresponsive to control of pain and agitation. Although lidocaine is seldom used for ventricular arrhythmias, theoretical concerns of enhancing cocaine toxicity do not appear to be clinically significant (70). Sustained hypertension in acute cocaine intoxication is not common due to the short physiologic effects of the drug. Control of agitation with benzaodiazepines often results in resolution of hypertension. Intravenous labetalol is a reasonable option if the blood pressure needs to be lowered due to its $\alpha$- and $\beta$-blocking effects. Cocaine-intoxicated patients should be considered to have acute elevations in blood pressure, and unless there is documentation or clinical evidence of long-standing hypertension, there should be little concern about cerebral hypoperfusion with immediate lowering of blood pressure to normal levels (71).

**Central Nervous System**

Seizures induced by cocaine are best controlled with IV benzodiazepines. Other standard antiepileptics can be added for refractory cases. If neuromuscular blockers are used, brain seizure activity may persist unrecognized and, hence, warrants continuous electroencephalographic monitoring.

Interventions for ischemic strokes associated with cocaine use should be carefully considered. Since the etiology may involve vasococonstruction as well as thrombolic, the decision to use thrombolytic agents in patients presenting within 3 hours of symptom onset may be more difficult. Vascular imaging, if readily available, may be helpful. Blood pressure is not usually severely elevated, but if sustained hypertension is present, current guidelines should be followed for lowering blood pressure. Neurosurgical consultation should be sought for intracranial hemorrhages to evaluate for possible interventions. Patients with subarachnoid hemorrhage should be evaluated for vascular malformations that may be amenable to treatment.

**Pulmonary**

Most pulmonary toxicities associated with cocaine are managed with usual care or supportive care (46,47). Bronchospasm and asthma should be treated with inhaled $\beta$ agonists and corticosteroids if indicated. Pneumomediastinum can be followed without hospital admission for most patients. Small pneumothoraces may also resolve without intervention, whereas large pneumothoraces will require thoracostomy. Noncardiogenic pulmonary edema may require supplemental oxygen and mechanical ventilation but resolves within a few days unless other complications occur.

**Hyperthermia/Rhabdomyolysis**

Hyperthermia associated with cocaine use should be treated aggressively by rapid cooling (please see chapter discussing heat stroke). Control of coexisting agitation, psychosis, or seizures is essential to achieve and maintain cooling while avoiding brain, hepatic, and muscle cell destruction. There is no evidence that pharmacologic agents such as dimethane are of benefit in cooling patients with life-threatening hyperthermia.

Patients with hyperthermia, severe agitation or motor activity, seizures, and obtundation should be evaluated for rhabdomyolysis. Aggressive fluid resuscitation to replete the intravascular volume and enhance urine output should often be initiated prior to definitive diagnosis. Serial tests of electrolytes, renal function, and creatinine kinase values are needed to monitor the severity and response of rhabdomyolysis.

**Body Packers/Stuffers**

Individuals may ingest packets of cocaine or any illicit drug for the purpose of transport or concealment. Body stuffers swallow small amounts of drug (wrapped or unwrapped) in order to avoid arrest. In this circumstance, drugs are not prepared for passage through the GI tract and drug is frequently absorbed. Due to the smaller quantities of drug, toxicity is usually mild (71). In contrast, body packers swallow larger quantities of drug in multiple packets that are specially prepared for smuggling to withstand transit through the GI tract. Abdominal radiographs often show the location of the packets and allow tracking as they move through the GI tract. However, a negative result on plain abdominal radiograph does not rule out body packing, and an abdominal CT scan may be needed to visualize the packets (72).

Most body packers are asymptomatic and can be managed conservatively until the packets have been completely evacuated (72,73). Activated charcoal given every 4 to 6 hours can reduce the lethality of oral cocaine. Whole bowel irrigation may assist with passage of the packets. Body packers with signs and symptoms of drug toxicity, or ence degradation, or...
Opioids include all drugs (synthetic as well as natural) that have morphine-like properties and/or bind to opioid receptors. There are at least five opioid receptors with various physiologic roles including analgesia, ventilatory depression, drug dependence, bradycardia, dysphoria, hallucinations, sedation, and miosis. Opioids are classified as receptor agonists or antagonists. Some have combined properties because they stimulate one type of receptor and antagonize another. A classification of opioids is found in Table 67.4. Opioid dependence is characterized by repeated self-administration of drug and encompasses physiologic dependence and addictive behavior. Exposure to opioids causes neural changes that produce tolerance, dependence, and withdrawal (76).

Toxicity

Although all opioids are associated with toxicity, heroin use has been increasing and the purity has increased, resulting in overdoses and fatalities (77). Heroin is rapidly absorbed by all routes of administration, including intravenous, intranasal, intramuscular, subcutaneous (skin popping), and inhalation. Most fatal overdoses occur with IV administration. Intravenous fentanyl extracted from analgesic patches is also available via common routes of administration, including intravenous, intranasal, intramuscular, subcutaneous (skin popping), and inhalation. An opioid-induced release of histamine from mast cells can precipitate bronchospasm, urticaria, and pruritus. Other respiratory complications include aspiration of gastric contents, noncardiogenic pulmonary edema, asthma exacerbation (heroin), pulmonary hypertension, acute respiratory distress syndrome, and septic pulmonary emboli (53,79). Intravenously injected illicit opioids may be mixed with microscopic cellulose, talc, or cellulose. These fillers are capable of producing angiothrombosis and a foreign body granulomatous reaction in the lung.

A pronounced decrease in gastrointestinal peristalsis and increased ileocecal and anal sphincter tone are responsible for the constipation frequently seen with opioid use. Urinary retention may be caused by increased detrusor muscle tone. Local infections, endocarditis, and other systemic infections are especially common in the IV user.

### Treatment for Acute Intoxication

The most common cause of death in opioid overdose is ventilatory failure, and the immediate priority in acute opioid overdose is maintaining the airway, breathing, and circulation. Resuscitative measures include airway control, positive pressure ventilation, and intravenous fluids. Applying naloxone may reverse the primary toxic manifestations of opioids; naloxone also has a short duration of action and may cause withdrawal in chronic opioid users (76). Opioid dependence and withdrawal may require 3 to 7 days of therapy to prevent withdrawal symptoms. Most opioid overdose deaths occur within several hours of cessation of use, and naloxone may be less effective if administered too late. Patients who survive an opioid overdose require emergent surgical intervention (72).

#### Cocaine Withdrawal

Psychological and biochemical dependency on cocaine may be intense. Cocaine causes activation of the dopamine system and blocks dopamine uptake, especially in the pleasure centers of the brain (74). The brain becomes dopamine deficient, and even a short period of cocaine abstinence can result in a withdrawal state.

The clinical effects of cocaine withdrawal include depression, fatigue, irritability, sleep and appetite dysfunction, psychomotor agitation or retardation, and craving for more cocaine (25). A period of prolonged somnolence and decreased arousal can occur after binge use of cocaine and often necessitates evaluations to rule out complications associated with cocaine use (75). A supportive environment and professional drug counseling are warranted.

# Table 67.4

<table>
<thead>
<tr>
<th>CLASSIFICATION OF OPIOID AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPIOID AGONISTS</strong></td>
</tr>
<tr>
<td>Natural opium derivatives</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Semisynthetic opioids</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Oxycodeine</td>
</tr>
<tr>
<td>Synthetic opioids</td>
</tr>
<tr>
<td>Diphenoxylate</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Levorphanol</td>
</tr>
<tr>
<td>Loperamide</td>
</tr>
<tr>
<td>Meperidine</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Tramadol</td>
</tr>
<tr>
<td><strong>PURE OPIOID ANTAGONISTS</strong></td>
</tr>
<tr>
<td>Naloxone</td>
</tr>
<tr>
<td>Naltrexone</td>
</tr>
<tr>
<td><strong>AGONISTS-ANTAGONISTS</strong></td>
</tr>
<tr>
<td>Butorphanol</td>
</tr>
<tr>
<td>Nallbuphine</td>
</tr>
<tr>
<td>Pentazocine</td>
</tr>
</tbody>
</table>

**μ** and **κ** receptors in the brain, which cause CNS depression. Common clinical effects of these drugs are shown in Table 67.5.

The most worrisome feature of CNS depression is hyperventilation. Tidal volume decreases first, and then respiratory rate falls. Although less common, seizures may be associated with meperidine, propoxyphene, and tramadol toxicity or result from hyperventilation and hypoxemia due to other opioids. Arteriolar and venous dilatation with opioid use can precipitate preload reduction, a fall in cardiac output, and hypotension.

An opioid-induced release of histamine from mast cells can precipitate bronchospasm, urticaria, and pruritus. Other respiratory complications include aspiration of gastric contents, noncardiogenic pulmonary edema, asthma exacerbation (heroin), pulmonary hypertension, acute respiratory distress syndrome, and septic pulmonary emboli (53,79). Intravenously injected illicit opioids may be mixed with microscopic cellulose, talc, or cellulose. These fillers are capable of producing angiothrombosis and a foreign body granulomatous reaction in the lung.

A pronounced decrease in gastrointestinal peristalsis and increased ileocecal and anal sphincter tone are responsible for the constipation frequently seen with opioid use. Urinary retention may be caused by increased detrusor muscle tone. Local infections, endocarditis, and other systemic infections are especially common in the IV user.
intoxication is airway management and ventilation. If reversal of respiratory depression cannot be accomplished quickly with naloxone, intubation may be necessary. Naloxone, a pure opioid antagonist, reverses all of the opioid-induced CNS and ventilatory depressant effects. The dose required to reverse opioid effects depends on the amount and type of opioid administered. The initial dose of naloxone is 0.4 to 2 mg; the lower dose should be administered initially in patients suspected of chronic addiction to avoid precipitating acute withdrawal symptoms. Additional doses of naloxone can be given based on the patient’s response. Although intravenous administration is preferred, naloxone can be administered intramuscularly, by sublingual injection, or through an endotracheal tube. The goal of therapy is to restore adequate spontaneous respirations rather than complete arousal. Doses of naloxone up to 10 to 20 mg may be required in patients who have administered large quantities of opioids or opioids such as propoxyphene, pentazocine, methadone, and fentanyl. If CNS depression is not reversed by 20 mg of naloxone, alternate causes should be aggressively addressed (e.g., hypoglycemia, hypothermia, head trauma). Close observation of the patient after naloxone administration is warranted because its effects last approximately 60 to 90 minutes. The patient may require repeated bolus injections of naloxone or a continuous infusion to maintain adequate respirations, particularly with long-acting opioids. The dose for infusion is one half to two thirds of the initial naloxone dose that reversed respiratory depression given on an hourly basis. Adjustments of the dose should be made to achieve clinical end points and avoid withdrawal symptoms. Additional boluses may be required as the infusion is started. Nalmefene, a long-acting opioid antagonist, has also been used to treat opioid overdoses, but prolonged withdrawal symptoms are a concern (80).

Isotonic fluids should be administered for hypotension due to opioids. Patients with significant opioid toxicity should be observed for other potential complications including aspiration pneumonitis and noncardiogenic pulmonary edema. Noncardiogenic pulmonary edema is usually self-limited (24–36 hours) and managed with supportive care that may include intubation and mechanical ventilation (81). Seizures unresponsive to naloxone should be treated with intravenous benzodiazepines. Refractory seizures may suggest either body packing or another complication. The potential for acetaminophen toxicity should be considered in patients ingesting opioids formulated with acetaminophen.

### Acute Opioid Withdrawal

The chronic administration of exogenous opiates is thought to lead to diminished endogenous opioid peptides. When these exogenous opiates are discontinued, the patient can develop opioid withdrawal. The clinical manifestations of opioid withdrawal are outlined in Table 67.6. The onset of symptoms varies with the drug abused. Symptoms can begin within 6 to 12 hours of the last dose with short-acting opioids such as heroin and within 36 to 48 hours with long-acting opioids such as methadone. Opioid withdrawal is rarely life threatening and usually does not require intensive care.

### TABLE 67.5

**CLINICAL MANIFESTATIONS OF OPIOID INTOXICATION**

| CENTRAL NERVOUS SYSTEM | \-
|------------------------|
| Analgesia              | \-
| Apathy                 | \-
| Lethargy               | \-
| Seizures               | \-
| Coma                   | \-
| Ventilatory depression | \-
| Nausea                 | \-
| Emeis                  | \-
| Miosis                 | \-
| RESPIRATORY            | \-
|Histamine release—bronchospasm| \-
| Pulmonary edema        | \-
| CARDIOVASCULAR         | \-
| Arteriolar and venous dilation| \-
| Hypotension            | \-
| GASTROINTESTINAL       | \-
| Decreased peristalsis  | \-
| Decreased hydrochloric acid secretion| \-
| Constipation           | \-
| OTHER                  | \-
| Histamine release—urticaria, pruritus| \-
| Muscle rigidity (fentanyl)| \-
| Urinary retention      | \-

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### TABLE 67.6

**CLINICAL MANIFESTATIONS OF OPIOID WITHDRAWAL**

<table>
<thead>
<tr>
<th>EARLY</th>
</tr>
</thead>
</table>
| Yawning| \-
| Lacrimation| \-
| Rhinorrhea| \-
| Sneezing| \-
| Sweating| \-
| INTERMEDIATE |
| Restless sleep| \-
| Piloerection| \-
| Restlessness| \-
| Irritability| \-
| Anorexia| \-
| Flushing| \-
| Tachycardia| \-
| Tremor| \-
| Hyperthermia| \-
| LATE |
| Fever| \-
| Nausea| \-
| Vomiting| \-
| Abdominal pain| \-
| Diarrhea| \-
| Difficulty sleeping| \-
| Muscle spasm| \-
| Joint pain| \-
| Involuntary ejaculation| \-
| Suicidal ideation| \-

### Acute Opioid Withdrawal

The chronic administration of exogenous opiates is thought to lead to diminished endogenous opioid peptides. When these exogenous opiates are discontinued, the patient can develop opioid withdrawal. The clinical manifestations of opioid withdrawal are outlined in Table 67.6. The onset of symptoms varies with the drug abused. Symptoms can begin within 6 to 12 hours of the last dose with short-acting opioids such as heroin and within 36 to 48 hours with long-acting opioids such as methadone. Opioid withdrawal is rarely life threatening and usually does not require intensive care.
If it is necessary to control withdrawal symptoms, most opioids in sufficient dosage will alleviate symptoms. Methadone, buprenorphine, and clonidine have been used to treat acute opioid withdrawal. In addition, methadone and buprenorphine have been used to treat opioid addiction chronically. Methadone can cause constipation, respiratory depression, dizziness, sedation, nausea, and diaphoresis. Oral buprenorphine use is restricted in the United States to qualified physicians who treat opioid dependence. It has low toxicity in high doses, partly because its \( \mu \)-antagonistic effects limit the opioid effects of sedation, respiratory depression, and hypotension. Buprenorphine is more effective than clonidine and similar to methadone for management of opioid withdrawal (82).

Clonidine has also been used to suppress the autonomic effects of opioid withdrawal. Doses of 0.1 to 0.3 mg orally can suppress the signs and symptoms of opiate withdrawal within 24 hours and shorten acute withdrawal reactions by 3 to 4 days (83). Side effects are hypotension, drowsiness, dry mouth, and bradycardia.

**Heroin Body Packers**

Heroin body packers should be managed similar to cocaine body packers (see above). If there is evidence of systemic absorption from leaking packets, opioid toxicity should be treated with a continuous infusion of naloxone.

### AMPHETAMINES AND DERIVATIVES

Amphetamines, methamphetamines, and similar derivatives are the most commonly abused CNS stimulants along with cocaine. Although there are limited medical uses for these drugs (narcolepsy, attention deficit disorder, obesity), they are usually abused for the euphoric effects or to enhance performance. Amphetamines act by increasing release and inhibiting reuptake of dopamine and serotonin in the brain. Minor chemical substitutions can enhance the hallucinogenic properties of the drug. The ease of production of these drugs from readily available ingredients in clandestine laboratories has resulted in increased supply throughout the United States. Methamphetamine can be made from common ingredients such as rock salt, paint thinner, lantern fuel, battery acid, lye, ammonia, lithium, ether, rubbing alcohol, iodine, and cold medicines containing pseudoephedrine (84).

Methamphetamine in a crystalline form (commonly called ice, crank, glass, or crystal) is one of the most popular drugs in this class. It can be orally ingested, smoked, snorted, or injected intravenously. An amphetamine-like drug, 3,4-methylenedioxymethamphetamine, is a designer drug (commonly known as Ecstasy, XTC, or MDMA) that acts simultaneously as a stimulant and hallucinogen (85). It results in greater serotonin release in the brain with inhibition of serotonin reuptake. It is abused in pill or capsule forms that are orally ingested. MDMA use has been associated with rave parties and is more commonly abused by adolescents and young adults. Most amphetamines are detected on qualitative urine toxicology assays but a negative result does not rule out amphetamine intoxication or abuse.

#### Toxicty

In general, these drugs cause release of catecholamines, which result in a sympathomimetic/nerve transmitter. Amphetamines are often taken orally to escape the effects while the drug is known to have occurred. Further interventions are dependent on patient complaints and clinical findings. A careful assessment for complications should be made, including measurement of core temperature, obtaining an electrocardiogram (ECG), searching for evidence of trauma, and evaluating laboratory data for evidence of renal or hepatic dysfunction and rhabdomyolysis. IV hydration for possible rhabdomyolysis and hyperthermia and hypotension is warranted in individuals with known exertional dysfunction (86). Long-term use of these drugs may result in dilated cardiomyopathy and “meth mouth.” Meth mouth refers to a pattern of oral signs and symptoms of methamphetamine abuse, thought to include rampant caries and tooth fracture, leading to multiple tooth loss and edentulism (84). Burn injuries from methamphetamine laboratory explosions are associated with a higher incidence of inhalational injury and greater use of critical care resources (87).

Complications of MDMA use are usually a result of the drug effects and nonstop physical activity. The effects of MDMA last 4 to 6 hours. Medical complications include hyperthermia, hypertension, rhabdomyolysis, seizures, renal failure, arthralgia, headache, syncope, cerebral infarction/haemorrhage, hepatotoxicity, serotonin syndrome, and death (88). Hyponatremia and hypotension are relatively unique with this agent and the mechanisms leading to these complications are unknown.

#### Management

Management of amphetamine intoxication is primarily supportive. Gastric lavage is not recommended because absorption after oral ingestion is usually complete when patients present. Activated charcoal may be considered if a recent oral ingestion is known to have occurred. Further interventions are dependent on patient complaints and clinical findings. A careful assessment for complications should be made, including measurement of core temperature, obtaining an electrocardiogram (ECG), searching for evidence of trauma, and evaluating laboratory data for evidence of renal or hepatic dysfunction and rhabdomyolysis. IV hydration for possible rhabdomyolysis is warranted in individuals with known exertional dysfunction (86). Long-term use of these drugs may result in dilated cardiomyopathy and “meth mouth.” Meth mouth refers to a pattern of oral signs and symptoms of methamphetamine abuse, thought to include rampant caries and tooth fracture, leading to multiple tooth loss and edentulism (84). Burn injuries from methamphetamine laboratory explosions are associated with a higher incidence of inhalational injury and greater use of critical care resources (87).

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#### Withdrawal

Acute withdrawal from amphetamines is similar to cocaine and symptoms include fatigue, depression, anxiety, motor retardation, hyperactivity, and insomnia, increased eating, and drug craving (89). Although withdrawal is uncomfortable,


γ-HYDROXYBUTYRATE

γ-Hydroxybutyrate (GHB), a naturally occurring metabolite of GABA found in the brain, has limited clinical use in narcolepsy but is more commonly a drug of recreational abuse. It is one of several agents characterized as a “date rape” drug and it has been promoted to build muscle, improve performance, produce euphoria, and enhance sleep. The drug is usually available as a colorless, odorless liquid with a mild salty taste that is easy to mask in drinks. GHB is rapidly absorbed from the stomach (usually within 10–15 minutes) and readily crosses the blood–brain barrier where it interacts with GHB and γ-aminobutyric acid type B (GABA\(_B\)) receptors. Stimulatory effects occur from resulting increased dopamine levels in the brain and sedative effects by potentiation of endogenous opioids. γ-Butyrolactone (GBL), also known as 2(3H)-furanone-di-hydro, and 1,4-butanediol (BD), also called tetramethylene glycol, have been abused with the same adverse effects as GHB (90). Both agents are metabolized systemically to GHB.

Acute Toxicity

The manifestations of GHB toxicity are dose related and include agitation, coma, seizures, respiratory depression, and vomiting. Other effects include amnesia, tremors, myoclonus, hypotonia, hyperthermia, decreased cardiac output, and bradycardia. A dose of 20 to 30 mg/kg can produce euphoria and sleepiness and coma may result from doses of ≥40 to 60 mg/kg (91). Concomitant use of ethanol results in synergistic CNS and respiratory depressant effects. Deaths attributed to GHB and related agents usually result from respiratory depression, hypoxemia, or aspiration. GHB is not routinely detected by urine toxicology assays but can be detected in plasma or urine by gas chromatographic-mass spectrophotometric techniques. Rapid clearance precludes detection beyond 12 hours after a dose (91). Diagnosis is usually determined by the clinical course pending on the route of abuse, susceptibility of the user, and the manifestations are not dangerous. Patients may become suicidal during withdrawal and should be evaluated for this possibility. Symptoms may persist for months.

In patients requiring intubation and mechanical ventilation, symptoms can be expected to resolve within 2 to 96 hours unless complications such as aspiration or anoxic injury have occurred. The concomitant use of alcohol may prolong the CNS depression. Although physostigmine has been reported to awaken patients with GHB intoxication, its use is not recommended (92).

γ-Hydroxybutyrate Withdrawal

A sedative withdrawal syndrome following high-dose frequent use (every 1–3 hours) of GHB, GBL, and BD has been described (91, 93). Mild symptoms such as anxiety, insomnia, nausea, vomiting, and tremors begin within 6 hours of the last dose and may progress to severe delirium with autonomic instability (usually mild) requiring hospitalization and sedation. Patients may experience auditory, visual, and tactile hallucinations. The duration of symptoms requiring treatment may be as long as 2 weeks. Benzodiazepines are the initial choice for management and high doses may be required. Propofol and barbiturates have also been used successfully (91,93).

PHENCYCLIDINE

Phencyclidine (PCP) is a psychoactive drug used as a hallucinogen that can be administered by oral ingestion, nasal insufflation, smoking, or intravenous injection. PCP is a dissociative agent that blocks the NMDA receptors leading to an inhibition of sensory perception. Sympathomimetic effects result from inhibition of norepinephrine and dopamine reuptake.

Clinical Manifestations

Signs and symptoms reported with PCP use are variable depending on the route of abuse, susceptibility of the user, and concomitant drug use (94). Behavioral effects of PCP include coma, catatonia, psychosis, and confusion. Agitation may be intermittent and unexpected. Misperception of reality can lead to violent behavior, risk-taking behavior, and accidents resulting in trauma. Nystagmus (horizontal, vertical, and/or rotary) and miosis are characteristic findings with PCP intoxication along with ataxia. Medical complications can include hyperthermia, rhabdomyolysis, and seizures. Dystonic reactions occur rarely. PCP is usually detected on urine qualitative toxicology tests.

Management

Management of a patient with PCP intoxication includes control of agitation using a quiet, nonstimulatory environment and benzodiazepines as needed. Haloperidol may be beneficial for frank psychosis. Physical restraints are often needed until adequate sedation is achieved. Tachycardia and hypertension, if present, usually respond to control of agitation. Activated charcoal does adsorb PCP but most patients present after GI absorption is complete following oral ingestion. Although urinary acidification enhances PCP excretion, that intervention is not recommended. The possibility of rhabdomyolysis should be
evaluated and early fluid therapy should be considered while awaiting test results.

References


Chapter 68: ENVENOMATION

CRAG S. KITCHENS – Snakes Native to the United States • STEVEN A. SEIFERT – Snakes Non-Native to the United States • CLAUDIA L. BARTHOLD – Spiders and Scorpions • JENNIFER A. OAKES – Marine Envenomation

This review will discuss envenomation by snakes (both native and non-native to the United States), spiders, scorpions, and marine animals. Clinical and laboratory manifestations of envenomations are due to a spectacular array of substances that gain entry into the victim and cause symptoms. A great deal of attention has been paid to the biochemistry and mechanisms regarding venoms. As complex and varied as these are, one should expect that the symptoms and severity can range from mild to serious, or even be fatal, and the treatment can range from supportive to the administration of substances (antivenoms) meant to neutralize the activity of the venoms. Over the past 50 years, the scientific approach to understanding envenomation syndromes from folklore and anecdotal first-aid nostrums to an ever-growing and sophisticated scientific discipline.

SNAKES NATIVE TO THE UNITED STATES

Man has had a long and storied relationship with snakes, with references several millennia ago found in the third chapter of Genesis. Despite most references’ depiction of dread, the medical profession’s positive regard for snakes is attested by the universally accepted sign of the medical profession: a snake intertwined on the staff of Aesculapius. As clinical observation followed by clinical investigation accordingly, the health care professional must be prepared to deal with many common and non-native to the United States; other physicians’ styles may be less conservative; few will be more so. First, these facts not only underscore differences in therapeutic philosophy, but also acknowledge that there exists a considerable range in morbidity and mortality in envenomation based partly on the bitten host, but especially on the species of the offending reptile—we treat what we see. Second, one can deduce that there is no clear “standard of care.”

The second part of the chapter will address envenomation by snakes not native to the United States; other physicians’ styles may be less conservative; few will be more so. First, these facts not only underscore differences in therapeutic philosophy, but also acknowledge that there exists a considerable range in morbidity and mortality in envenomation based partly on the bitten host, but especially on the species of the offending reptile—we treat what we see. Second, one can deduce that there is no clear “standard of care.”

The second part of the chapter will address envenomation by snakes not native to the United States. Unfortunately, this separation sometimes is blurred by the increasing number of exotic snakes kept either professionally by herpetologists who work in zoos, research, or the pharmaceutical industry, or by amateurs who collect a variety of exotic poisonous snakes. Accordingly, the health care professional must be prepared to deal with a broad range of snake envenomations.

A mere century ago, the treatment of North American snakebites was shrouded in mystery, folklore, and old wives’ tales, and indeed, was not even considered a medical problem. As clinical observation followed by clinical investigation

68. Kolar H. The pharmacology and toxicology of “ecstasy” (MDMA) and related drugs. CMAJ. 2001;165:917.

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Coral Snake Envenomation

Coral snakes are rather small and brilliantly colored secretive reptiles. As opposed to most snakes, which prefer isolation, they are often found around newer housing projects and may be encountered in one’s garden or yard. By habit, they are not aggressive, supporting stories that children may play with them for hours to days without being bitten. Additionally, their anatomy is such that they cannot open their mouths as widely as the pit vipers, so they typically bite only at the tips of fingers or the webbed space between the thumb and first finger. Lacking the large fangs characteristic of pit vipers, puncture wounds are notoriously not prominent. Rather, if one squeezes the bite site, one may see minute, pinpoint accumulations of blood welling up from the tissue, indicating that the teeth of the coral snake have successfully worked their way into the subcutaneous tissue, thereby allowing the deposition of venom.

We have reported (2) a triad of risk factors that, in our opinion, if any two are present, warrant strong consideration for the infusion of three to five vials of antivenom: (a) the snake is positively identified as a coral snake; (b) there is a history of envenomation; and (c) one can observe pinpoints of blood following applied pressure to the bitten area. We typically do not administer antivenom for the presence of only one feature of this triad but typically observe the patient for about a day. The primary manifestation of envenomation is paralysis of the entire nervous system, with the primary threat to life being respiratory arrest, with or without aspiration pneumonia. Our local experience suggests that the natural history of those patients who develop respiratory arrest do so for approximately 7 to 10 days before the effects of the venom naturally abate. Mנטion is not affected. One must be able to support a totally flaccid patient for this period of time, with particular attention to maintenance of respiratory care and respiratory hygiene. Long-term sequelae following either successful treatment or the natural history of the envenomation syndrome may include several months of dysarthrias and paresthesias in the bitten extremity, but generally fade after several months to a year.

Antivenom Administration

The antivenom for coral snake envenomation supplied by Wyeth (Antivenin [Micrurus fulvius] [equine origin]) unfortunately is no longer being manufactured. As there are limited or no local tissue damage; therefore, the characteristic triad of immediate local pain, swelling, and discoloration characteristic of pit viper envenomation does not develop. It is accordingly possible to misconstrue a serious bite from a coral snake as one from either a “dry bite” by a venomous snake or a bite by a nonvenomous snake. This can lead to an unfortunate outcome.

Symptoms and Manifestations

Symptoms may be delayed up to 12 hours, yet are dangerous and can progress rapidly should they occur; therefore, patients should be observed for 24 hours to determine whether an envenomation has occurred.

As the venom is chiefly neurotoxic, neurologic signs and symptoms are declared in approximately the following ascending order and frequency: a mild numbness in the bitten extremity; and euphoria, often precipitously followed by cranial nerve symptoms, with diplopia being the one that the patient most often first notices, whereas a distinct flat dysarthria (similar to patients with myasthenia gravis) is the one that health care professionals usually first notice. Stridor, inability to swallow, and, finally, respiratory arrest may rapidly ensue. During progression from dysarthria to respiratory arrest, aspiration pneumonia is extremely common and comprises one of the major morbidities and mortalities of coral snake envenomation. Should cranial nerve involvement be noted to develop, it is important to prophylactically and preemptively intubate the patient in order to protect the airway.

Lacking the large fangs characteristic of pit vipers, puncture wounds are notoriously not prominent. Rather, if one squeezes the bite site, one may see minute, pinpoint accumulations of blood welling up from the tissue, indicating that the teeth of the coral snake have successfully worked their way into the subcutaneous tissue, thereby allowing the deposition of venom. We have reported (2) a triad of risk factors that, in our opinion, if any two are present, warrant strong consideration for the infusion of three to five vials of antivenom: (a) the snake is positively identified as a coral snake; (b) there is a history of envenomation; and (c) one can observe pinpoints of blood following applied pressure to the bitten area. We typically do not administer antivenom for the presence of only one feature of this triad but typically observe the patient for about a day. The primary manifestation of envenomation is paralysis of the entire nervous system, with the primary threat to life being respiratory arrest, with or without aspiration pneumonia. Our local experience suggests that the natural history of those patients who develop respiratory arrest do so for approximately 7 to 10 days before the effects of the venom naturally abate. Mентion is not affected. One must be able to support a totally flaccid patient for this period of time, with particular attention to maintenance of respiratory care and respiratory hygiene. Long-term sequelae following either successful treatment or the natural history of the envenomation syndrome may include several months of dysarthrias and paresthesias in the bitten extremity, but generally fade after several months to a year.
Pit Viper Envenomation

Genera

1. Crotalus: This family, Crotalidae, consists of three genera found within the United States. The largest genus, composed of some 15 to 20 species and subspecies, is Crotalus, the rattlesnakes. Rattlesnakes are distinctly New World animals. The rattle is composed of specialized scales that produce a rattling sound when the reptile shakes its tail. The most serious bites are those of two of the two largest snakes, namely the eastern diamondback rattlesnake (Crotalus adamanteus) and the western diamondback rattlesnake (Crotalus atrox).

2. Sistrurus: Two other species of rattlesnakes in the second genus, Sistrurus. Sistrurus catenatus (also known as the massasauga) is more frequently found in the upper Midwest west from western Pennsylvania and New York across to Michigan and Iowa. Sistrurus miliarius (also known as the pygmy rattlesnake) is seen chiefly in Florida and up into the Atlantic coast states. Both species of Sistrurus are smaller rattlesnakes with poorly developed rattles. Their bites are characterized by a very low morbidity and virtually zero mortality (1–4). We use antivenom only occasionally. (approximately 10% of the time) in pygmy rattlesnake bites.

3. Agkistrodon: The third genus of the family Crotalidae is Agkistrodon, which is composed of two species. The copperhead (Agkistrodon contortrix) is the most common pit viper from Georgia up through the Atlantic Coast states. In three reviews (7–9), antivenom was administered to only 0% to 11% of victims. Some practitioners may infuse antivenom more liberally in bites adjudged to be more serious than most. Agkistrodon piscivorus (commonly known as the water moccasin) is also in the Atlantic Coast states, in Florida, and westward through Alabama and Mississippi and into eastern Texas. Agkistrodon piscivorus is extremely venomous. Bites characteristically cause significant edema but virtually no mortality (7–9). Significant in vitro coagulation abnormalities are rare (9,10). We employ antivenom in only about 25% of victims of water moccasin envenomations and those chiefly for patients either at the extremes of age or with significant comorbidities.

Range of Venom Effects

Bites from these species of pit vipers vary enormously, from the least lethal with no documented deaths (Sistrurus miliarius—pygmy rattlesnake) to the most lethal (Crotalus adamanteus—eastern diamondback rattlesnake). The variability of the virulence is due to the variability of the venom. All pit viper venoms are very complex, containing upwards to 20 to 40 proteaceous substances, about half of which are enzymes that are designed to help spread the venom throughout the prey's tissues and to predigest the intended prey, and another equal number of nonezymatic proteins that have many other effects, including those on the autonomic nervous system. Indeed, pit viper venom is one of the most complex mixtures of poisons known to exist. Snake venom is best regarded as an offensive weapon to assist the animal rather than regarded as a defensive weapon against an accidental prey.

The complexity of the venom is demonstrated by its multiple effects. At one time, it was fashionable to describe venom as “neurotoxic” or “hematoxic,” but those notions tend to break down. It is fair to regard the venom of the coral snake to be chiefly, if not exclusively, neurotoxic. Several excellent reviews exist regarding the complex nature of pit viper venoms (11–19).

This mixture of venom components vary enormously not only within the family, but also within the genus and species. In fact, even within the same subspecies, there is considerable variation in the relative concentrations of various components in the venom. Even individual members of a species, kept over time, display variability in their venom pattern (20).

This is important when one considers the antivenom that is currently available. CroFab (Crotalidae polyvalent immune Fab [ovine] [FabAV], Therapeutic Antibodies, Inc., Nashville TN) is a mixture of Fab fragments prepared from purified immunoglobulins, produced by healthy sheep that have been repeatedly injected with venom from one of the following four snakes: Crotalus atrox, Crotalus adamanteus, Crotalus scutatu-

latae, or Agkistrodon piscivorus. The Fab fragments from all four preparations are then mixed together to produce a polyvalent mixture. As there are variable degrees of immunogenicity and responses from the sheep to the injection of multiple and variable components (antigens) within the venom of these four pit vipers, it should be realized that not all venom components will be neutralized to exactly the same degree. Because many of the venom principles within other species of this genus may be shared with other genera, there is a variable degree of crossover of the Fab antivenom against the venom of species to which the sheep was never exposed, such as Crotalus borridus atricaudatus, Sistrurus miliarius, and others. This no doubt explains, in part, the variability of the response of some envenomation.
syndromes from other snake bites to the same Fab antivenom. As an example, the author has had experience (unpublished data) with a patient envenomed by a pet mottled rock rattlesnake (Crotalus lepidus lepidus), a small and rather rarely offending reptile. The victim of this bite had essentially no salubrious response to repeated administrations of FabAV. One may deduce that there exist few Fab fragments directed against that snake’s individual venom pattern. On the other hand, the venom of the Southern Pacific rattlesnake (Crotalus bicinctus) is not injected into those sheep, yet envenomation by this reptile seems to respond well to FabAV (21).

Symptoms and Manifestations
The near-immediate onset of the triad of symptoms occurring in human victims of pit viper envenomation—namely, pain, swelling, and discoloration—supports the concept of disruption and digestion due to the venom. Digestive enzymes such as phosphatases, hyaluronidases, proteinases, phospholipases, and other substances dissolve connective tissue and proteins, and attack nerve endings (17,19). Edema is largely brought about by disruption of the endothelium of capillaries and lymphatics due to a variety of proteins that directly attack the endothelial integrity of the microcirculation. Discoloration results from extravasation of red cells through the disrupted microcirculation (19). A far smaller role in local hemorrhage is played by disruptions of the coagulation system, which is discussed in more detail below. Evidence for this concept is that while hemorrhage within soft tissues may be spreading and progressive, it is typically confined to the bony extremity and hemorrhage only rarely occurs systematically in victims of bites from snakes native to the United States; this is not always the case with bites from many snakes not native to this country. Pain, swelling, and discoloration (immediate to approximately 2 hours in the extremity) serve as excellent signs of envenomation. On the other hand, lack of pain, swelling, and discoloration usually indicate that the victim has been fortunate to be one of the 15% to 30% of pit viper victims in which the reptile did not inject venom. These victims of so-called “dry bites” clearly not only have not been fortunate, but also do not require antivenom. One pitfall and caveat is that some patients may be envenomed by a pit viper but fail to have any local signs of pain, swelling, or discoloration, yet may be clearly ill as attested by their prophase weakness, fasciculations, diaphoresis, hypotension, nausea, vomiting, diarrhea, mental status alterations (which include confusion and stupor), and the oft-mentioned “metallic taste” experienced by several victims. This situation occurs in approximately 5% to 10% of envenomation cases due to injection of the venom more or less directly into a vessel or a muscular bed rich in capillaries, such as the calf, or even more proximally in the great muscles of the legs or arms. It is often striking how few local signs there are other than puncture marks over these muscular areas in a patient who is clearly extremely ill. Many of the venom components that cause pain, swelling, and discoloration are neutralized by the currently available FabAV. A great many of these principles are shared within the Crotalidae family; however, not all are. The venom of some native snakes contains a principle that is quite myotoxic and this appears to be less promptly neutralized by FabAV. Reptiles that characteristically cause massive rhabdomyolysis with large elevations of the serum creatine phosphokinase (CPK)—including the CPK-MB band, but with no troponin assays—include the canebrake rattlesnake (Crotalus horridus atricaudatus) (22) of the eastern United States and the Mojave rattlesnake (Crotalus scutulatus) (23) of the desert southwest. Additionally, neurologic symptoms are more pronounced in the Mojave rattlesnake victim than in victims of most other Crotalidae species (24).

Clinical and Laboratory Findings
Coagulopathic findings, both clinical and laboratory, have always been of great interest to those who treat pit viper envenomations. Whereas some laboratory coagulation defects may be seen to some extent in most of the pit viper envenomations, they are by far most pronounced within the Crotalus genus and rarely encountered in the Agkistrodon venom (9,10) and, rarely, if ever, in the Sistrurus genera (10).

Laboratory coagulation abnormalities that have been described in bite victims of Crotalus subspecies have been most thoroughly studied in the bites from the eastern diamondback (Crotalus adamanteus) (10) and the western diamondback (Crotalus atrox) (16). The venom of these snakes contains a thrombin-like enzyme that has been referred to as crotalase. This enzyme rapidly and efficiently, yet partially, cleaves fibrinogen by cleaving the B-peptide off the β-subunit as does thrombin but, unlike thrombin, does not complete fibrinogen cleavage as it neither cleaves the A-peptide from the α-subunit nor activates factors V, VIII, or XIII. This partially clotted fibrinogen forms a loose gel that is exquisitely sensitive to any proteolytic activity, as visible thromboses or organ manifestations of systemic thromboses are not encountered. Also different from thrombin’s actions, crotalase neither activates platelets nor consumes antithrombin III. These are distinct and durable differentiating points from disseminated intravascular coagulation (DIC). In DIC, consumption of fibrinogen is typical but it is accompanied by severe depletion of platelets, factor V, factor VIII, occurs from the bite of some exotic snakes (15). Crotalase does not activate plasminogen directly (i.e., in vitro or in vivo) but does so indirectly, most likely by release of endothelial-secreted tissue plasminogen activator (tPA). Plasma levels of tPA spike in a reflex response to the deposition of the partially formed fibrin on the endothelial surface, and a brisk fibrinolysis occurs, attacking the extremely labile non-crosslinked, partially formed clot that produces massive quantities of circulating fibrin degradation products (FDPs), as essentially the total body fibrinogen complement (some 13 g) is nearly totally converted into FDPs within an hour (10). Crotalase is necessary in only extremely small amounts to totally defibrinogenate an adult human. This hypothesis is supported by three lines of evidence. The first is that even the most trivial bite from the smallest of eastern diamondbacks may be associated with total defibrinogenation, resulting in plasma fibrinogen levels less than 50 mg/dL. Therefore, the coagulation end point (visible fibrin clot) of routine coagulation tests, such as prothrombin time (PT) and partial thromboplastin time (PTT), is so impaired that many interpret this as the blood being “incoagulable,” which only seems true. Thrombin generation via the intact coagulation cascade is totally retained save for
the lack of the visible clot. Intact thrombin generation serves to afford intact hemostasis, despite incoagulable in vitro PTs and PTTs. Thrombin generation is sufficient to affect platelet adhesion at sites of wounds and, with even limited amounts of remaining fibrinogen, to secure a reasonable clot. This is also supported by the lack of systemic bleeding in the vast majority of defibrinogenated patients, as well as the impunity of insertion of central lines or even surgical procedures at the wound site.

A second line of evidence that crotalase need be present in only very small amounts is evidenced by an event termed “recurrence” (25,26). In this clinical situation, despite total arrest of the envenomation syndrome—as defined by a lack of progression of present swelling at the bite site, a lack of new swelling, cessation of nausea and vomiting, normalization of vital signs, and, at least temporarily, total correction of the PT and PTT (27)—after several days, the PT and PTT may revert to incoagulability as defibrinogenation recurs, most likely as a result of a pharmacodynamic and pharmacokinetic mismatch between venom principles and Fab antivenom. That is, antivenom fails to neutralize all of the injected venom, and also is cleared from circulation much more rapidly than venom components.

The third line of evidence is the astounding efficacy of re-administration of FabAV to re-reverse the recurrence of coagulopathy. It would appear that the circulatory release of crotalase with sudden defibrinogenation may be among the most sensitive markers of envenomation by either the eastern or western diamondback rattlesnake.

There is great and healthy debate of whether or not the recurrence syndrome could be treated (26). Patients who have been clinically stable for several days following prompt administration of FabAV may and usually do remain totally free of any symptoms, including any clinical signs of abnormal hemostasis, only to be found to have incoagulable PTs and PTTs as they are being prepared for hospital discharge.

A stumbling block for the majority of clinicians is drawing interpretations and conclusions based on their prior clinical experiences from clinical situations resulting in equally impaired PTs and PTTs, and then comparing those situations to this fairly benign defibrinogenation syndrome. Such examples may include the true, real, and quite obvious hemostatic disarray that may accompany greatly prolonged PTs and PTTs in patients with liver disease, warfarin overdose, DIC, hemophilia, or administration of heparin or other anticoagulants (28). These situations in which hemorrhage is quite obvious do not translate into the patient who is merely defibrinogenated. Defibrinogenation in this situation is rather more analogous to defibrinogenation following the therapeutic administration of plasminogen activators such as streptokinase or tPA. Whereas hemorrhage is experienced in approximately 1% of all patients who receive these therapeutic thrombolytic agents, it is heavily concentrated among older patients, hypersensitive patients, or those with prior central nervous system lesions such as strokes, trauma, metastatic disease, or primary tumors.

Treatment of true DIC is rather different and hinges on successful elimination of the underlying cause. Rather, the defibrinogenation syndrome is very easily and promptly reversed by the administration of fibrinogen in the form of approximately 8 to 10 units of cryoprecipitate and/or the readministration of FabAV. However, recurrence may happen yet again if unneutralized venom principles continue to enter the general circulation after the clearance of the additional antivenom. The clinical significance of recurrence, particularly as manifested by new or recrudescence of coagulation abnormalities from victims of North American pit vipers, is not at all evident. These recurrences have been best studied and defined as the result of study and follow-up of patients bitten by, particularly, rattlesnakes and administered FabAV. This was enabled because of the research, development, and observation from clinical protocol-driven prospective studies of patients treated with FabAV, which garnered the largest and most extensively followed group of patients (29). In fact, in retrospective studies, Bogdan et al. (30) found data showing that, among 334 consecutive patients treated for North American Crotalid bites, 112 exhibited coagulopathy. Of these, 31 had undergone coagulation testing sufficient to detect whether a recurrence occurred; of these 31, 14 (45%) had a recurrence of the coagulopathy to include severe hypofibrinogenemia or thrombocytopenia. Apparently, none of these patients experienced spontaneous hemorrhage despite these laboratory recurrences.

Boyer et al. (29), in studying FabAV-treated Crotalid envenomations in 38 patients, found that 20 (53%) had recurrence, persistent, or late coagulopathy, some occurring 13 days following envenomation and treatment. No patient experienced significant spontaneous bleeding. The most common severe, if not even dramatic, abnormality was incoagulable and/or extremely prolonged PTs or PTTs, all of which were due to severe selective defibrinogenation. Of their 20 patients, 16 were observed with no further FabAV treatment, and all fared well. Two patients who received supplemental doses of FabAV had prompt normal PTs and PTTs. Of interest, all their patients with defibrinogenation on presentation showed significant increases in their plasma fibrinogen levels following FabAV treatment, which is a major laboratory criterion for a therapeutic response to FabAV. One patient who was hypofibrinogenemic underwent a minor surgical procedure at a time that his fibrinogen was unmeasurable, and experienced hemorrhage limited to this surgical site. No blood products were administered. They suggested that for patients whose envenomation syndrome had included significant coagulopathy, repeat testing of the coagulation system for up to 2 weeks seemed appropriate, although which tests to order, what to do with these data, and whether the patient should remain hospitalized were not addressed.

Ruha et al. (31) studied 28 cases of rattlesnake envenomation in Arizona, noting that in some cases, despite initial control of coagulopathy, there was return of either coagulation defects and/or thrombocytopenia. As this was fairly benign, it was their opinion that one need not wait for total normalization of all the coagulation and platelet studies as a therapeutic end point for FabAV therapy. Oddeleye et al. (32) noted, in two cases of rattlesnake envenomation, that thrombocytopenia was difficult to reverse either with FabAV and/or platelet transfusions, and suggested that unless bleeding occurs, transfusion of platelets and blood products might best be withheld. Camilleri et al. (33) reported a crotaline envenomation with profound coagulopathy that was resistant to therapy, which they curtailed after 4 days of FabAV therapy, suggesting only close observation without further therapeutic intervention. Their patient was discharged home on day 12 with severe defibrinogenation, and apparently underwent spontaneous resolution sometime between day 17 and 37. They concluded that despite “critical value”
coagulopathies, if a patient is not bleeding and systemic and local manifestations of the bite have already been controlled, close observation without further therapeutic intervention is appropriate. Similar conservative conclusions were made from South American pit viper experiences by de Oliveira et al. (34) regarding their experience with Bothrops, and by San-Martins et al. (35) regarding the South American cascabel (Crotalus durissus), with both reports noting that, despite severe coagulation abnormalities, the clinical outcome did not seem to be linked to blood incoagulability; what few deaths occurred apparently were not thought due to venom-induced coagulation disturbances.

**Postmortem Findings**

Death from American pit viper envenomation is rare, and full autopsies are even rarer. Dart et al. (18) reviewed the few reports regarding 16 deaths out of about 1,000 cases of North American envenomations reported up to 1989. Central nervous system edema and hemorrhage were reported in a few cases, but cerebral hemorrhage was deemed the cause of death in only one. They speculated that the mortality rate from severe, complicated rattlesnake envenomation was approximately 1.4%, but were unable to more precisely construct an overall figure because so many cases, particularly mild cases, are not reported. They also opined that the exact cause of death may be difficult to determine, deducing that the most common cause was progressive shock leading to multiorgan failure and death hours to a few days later. Generalized edema from extravasation of fluid into the heart, lung, and brain was implicated. It appeared that edema was a result not of frank hemorrhage, but of the resultant effect of the toxins on the circulatory endothelial integrity and the microcirculation in particular. It was frequently noted in their review that delayed therapy and/or inadequate therapy, or even no antivenom therapy, seemed to be disproportionately encountered among fatal cases. They also opined that in patients to whom antivenom had been administered and died hours to days later, the primary cause included severe alteration in capillary permeability.

**Prehospital Treatment**

The key to good and effective therapy with minimal chance of loss of life, limb, or function is prompt transportation to a medical care facility. In areas where snakes are endemic, almost all hospitals have at least a modicum of antivenom available or close at hand. Calling the emergency room prior to arrival is reasonable if such does not delay transport.

Initial scene management is to prevent further bites and to calm the patient. If successful transport is anticipated within an hour, it is probably best to forgo any local therapy other than to gently splint the bitten extremity, keeping it at or slightly below heart level, and transport the patient to an appropriate health care facility. The use of topical cold packs may provide some relief of severe pain, if properly applied. Incising or excising the wound, the application of electrical currents, or other traumatic manipulations are contraindicated. Suction devices remove at best 2% of the venom load, are likely to be clinically insignificant, and, if used, should not delay transport. The use of a tourniquet with pressure sufficient to impede either arterial or venous flow is contraindicated. A lymphatic constricting band (ideally a blood pressure cuff inflated to 15 to 25 mm Hg, a band that allows a finger to pass easily beneath) or a properly applied pressure immobilization bandage may be considered if there are immediate life-threatening effects or a prolonged (greater than 1 hour) transport time. Any procedure that concentrates venom and slows its clearance from the bitten extremity, while used theoretically to decrease systemic manifestations, is likely to worsen local morbidity.

**Hospital Treatment**

Treatment of victims who have been envenomated by North American snakes will not be encountered by most physicians. If encountered, particularly if physicians are approaching their initial treatment of such victims, there is often an undue amount of anxiety, which is not well founded. Approximately 5,000 to 10,000 bites occur in the United States each year. Death from envenomation by North American pit vipers occurs only about five to ten times (0.1%) per year, representing approximately a 99.9% survival rate. Reasons for this fairly enviable situation, especially when compared to higher mortalities in other countries, include three facts. The first of these is that medical care is far more accessible than it is in many countries in which envenomations occur and for which survival is much less favorable, including the continents of Australia, South America, and the Indian subcontinent. Nearly anyone in the United States is within an hour of emergent care as opposed to many hours or several days in some parts of the world, and most facilities, at least in endemic areas, have antivenom on hand. A second reason is that the venoms of North American pit vipers do not cause true DIC with thrombosis and/or DIC-type bleeding, which may cause multiorgan failure, as is seen with many snakes, including those on the Indian subcontinent and especially Australia. Third is the employment of prompt and sound medical care, including fluid resuscitation and monitoring of vital signs, to maximize morbidity. Table 68.1 outlines the essentials of appropriate management of such patients.

**Immediate Management**

1. **Confront the bite:** First, confirm that the patient was bitten by a snake and, particularly, a venomous snake. With the exception of coral snake envenomation, this usually includes the presence of puncture wounds. Whereas snakes normally have two fangs, it is not uncommon to see snakes with one fang or even three or four, as their fangs mature and move.

**Table 68.1**

<table>
<thead>
<tr>
<th>INITIAL EVALUATION AND DIAGNOSTIC POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm patient was bitten by a venomous snake; determine snake species if possible.</td>
</tr>
<tr>
<td>Evaluate for local signs of envenomation:</td>
</tr>
<tr>
<td>☐ Pain</td>
</tr>
<tr>
<td>☐ Swelling</td>
</tr>
<tr>
<td>☐ Discoloration</td>
</tr>
<tr>
<td>Evaluate for systemic signs of envenomation:</td>
</tr>
<tr>
<td>☐ Alterations in vital signs, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>☐ Fasciculations</td>
</tr>
<tr>
<td>☐ Coagulation abnormalities</td>
</tr>
<tr>
<td>☐ Altered mental status</td>
</tr>
</tbody>
</table>
TABLE 68.2
CLINICAL CHARACTERISTICS OF ENVENOMATION THAT POTENTIALLY AID IN IDENTIFICATION OF OFFENDING CROTALUS SPECIES

<table>
<thead>
<tr>
<th>Common name</th>
<th>Scientific name</th>
<th>Distribution</th>
<th>Neurologic symptoms</th>
<th>Coagulopathic findings</th>
<th>Rhabdomyolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Diamondback</td>
<td>Crotalus adamanteus</td>
<td>Southeastern United States</td>
<td>+</td>
<td>Prolonged PT/PTT; nil</td>
<td>nil</td>
</tr>
<tr>
<td>Canebrake</td>
<td>Crotalus atrox</td>
<td>Eastern United States</td>
<td>nil</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Mojave</td>
<td>Crotalus scutulatus</td>
<td>Desert southwest United States</td>
<td>+++</td>
<td>nil</td>
<td>+++</td>
</tr>
<tr>
<td>Timber</td>
<td>Crotalus horridus</td>
<td>Eastern United States</td>
<td>++</td>
<td>Prolonged PT/PTT; nil</td>
<td>nil</td>
</tr>
</tbody>
</table>

PT, prothrombin time; PTT, partial prothrombin time.
++ = usually minimally present; +++ = usually moderately present; ++++ = usually extremely present; ++++ = always present.

One can occasionally augment identification of an offending snake by the symptom complex its bite produces, as is demonstrated in Table 68.2. The prognosis is generally species dependent, but also related to the time to presentation, time to antivenom administration, the health of the host, and other factors. Management will be based on a mixture of observed and anticipated symptoms and physical findings, as well as one’s prior experience in handling this emergency.

2. Determine the genus and species: Next, one should try to determine the family and/or genus and species of snake if at all possible. The majority of victims know not only precisely that they were in the same area as a venomous snake, but also the snake’s common name, yet still are compelled to taunt, toy with, kiss, or otherwise handle the venomous animal for reasons that are not clear. In such patients, snake identification is not difficult. Another 25% to 30% will bring the snake to the health care facility in conditions ranging from badly mutilated to quite alive. Identification by charts or consulting herpetologists or other experts is quite useful in determining the species of the snake, whereas it is not of much benefit for the victim if he or she cannot identify the type of snake that inflicted the bite. Whether by confusion or the desire to please, children will agree that the picture of nearly any snake presented to them is indeed the offending reptile. Several online links, such as [http://www.pitt.edu/~msc2/herp/SoNA.html](http://www.pitt.edu/~msc2/herp/SoNA.html), are available to assist identification.

3. Determine systemic signs and manifestations: Assuming the patient does have signs of local envenomation, next in order is to determine whether there are any systemic signs of envenomation, remembering the fact that no one dies of local envenomation, but only from systemic manifestations. As a general rule, in mild and moderate envenomations, the symptoms are due primarily to the local pain, swelling, and discoloration, which, while quite alarming, are not usually of a life-threatening nature. Systemic symptoms such as nausea, vomiting, diarrhea, and dysphoria, as well as fasciculations—particularly in Crotalus envenomations—do portend the possibility of a more serious outcome. Many coagulation abnormalities seen in Crotalus envenomations are often spectacular in their laboratory manifestations. Altered mental status to include a noticeable stupor and a metallic taste is often reported in serious envenomations.

4. Assign degree of severity: In attempting to assign a degree of severity from mild to moderate to severe, one must recognize several principles. The first is that the envenomation syndrome is progressive and, secondly, evaluation is ongoing and time dependent. Two patients may be bitten in the same manner. If the first patient is seen in 15 or 20 minutes after the bite, very few local signs of pain, swelling, or discoloration will be seen, whereas a similar patient requiring 2 hours to arrive for emergent care will have much more advanced and obvious pain, swelling, and discoloration, although with exactly the same prognosis. The corollary to that adage is that it is the rate of change in signs, symptoms, and other manifestations that is important. It is important not only in grading the severity of the bite, but also in grading the effect—or lack of effect—of the administration of antivenom.
Antivenom Administration

Because of the present lack of prospective, outcome-based studies, practices regarding perceived indications for the use of antivenom vary. Most practitioners will not administer antivenom to anyone without envenomation (“dry bites”) or to those who have minimal envenomation, particularly if it is by the Sistrurus species. Bites by the copperhead (Agkistrodon contortrix) are usually not treated (<9) with antivenom unless the patient is at the extremes of age or with many comorbid conditions. Envenomation by the water moccasin (Agkistrodon piscivorus) is notorious for a large amount of local edema but not much in the way of systemic symptoms and laboratory manifestations (10), and even less in the way of mortality. Their swelling can be so massive that, if untreated for any reason, bites of the hand may progress up the arm, chest wall, neck, face, and even abdomen; this is all reversible.

Severe envenomations are often apparent by the time they arrive at emergency care, primarily because of the rapidity with which the venom initially gains entry into the circulatory system. The corollary with that adage is that while it is common to see someone progress from minimum envenomation to moderate envenomation, it is quite rare to see one, in our experience, progress from moderate envenomation to severe envenomation. Rather, when they arrive—even within minutes of the event—severely envenomated patients may be considerably hypotensive with lethargy, nausea, and vomiting, and require immediate and aggressive therapy (Table 68.3). Suggested therapy is outlined in Table 68.4. At least one large-bore intravenous access site must be obtained and blood drawn for a variety of tests.

While one is evaluating the rate and degree of swelling, it is useful to outline the leading edge of proximal progression of the swelling with some type of ink pen. This may be more apparent by tactile rather than visual means. In this manner, one can observe whether the swelling is progressive. Whereas some relatively slow progression is tolerated—particularly if one elects not to treat the patient or if antivenom is not immediately available—more rapid swelling, particularly with concomitant systemic symptoms, usually justifies prompt and aggressive therapy.

In a situation involving our native reptiles, we do not administer antivenom in patients who have no envenomation; about 10% to 15% of people with minimal envenomation, half of those patients with moderate envenomation, and all patients with severe envenomation are administered antivenom.

The offending reptiles in one’s locale and the experience of those evaluating the patient will often override this simplification. Reasons for not administering antivenom to all, or nearly all, victims are several: (a) the extremely low mortality rate of envenomation by snakes native to the United States, (b) the—admittedly very low—rate (less than 0.01%) of serious and mild (14%) allergic reactions, (c) the modest rate (13%) of serum sickness–like late reactions (occurring typically 8–12 days after administration) to FabAV (1), and (d) the cost of antivenom treatment can easily exceed $50,000.

As antivenom is more efficacious the earlier it is administered, if the decision has been made to employ the drug, it should be done promptly. Control of the envenomation syndrome is adjudged by the slowing, or preferably the cessation, of progressive local swelling (27). One should not expect ex tant swelling to regress or any areas of local damage to the bite site such as a swollen or discolored area to regress, as such damage has already been done prior to the patient's treatment. Hemorrhagic bleb formation at the site of the bite is not an important sign in and of itself, although it generates much attention. These should be left alone or, if one thinks that bursting is imminent, the blebs should be topically sterilized and lanced, although this usually does not occur until the second or third day of the envenomation.

### TABLE 68.3
**SEVERITY OF ENVENOMATION BY PIT VIPERS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Frequency</th>
<th>Initial findings</th>
<th>FabAV vials in first 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>No envenomation</td>
<td>15%–30%</td>
<td>No local, systemic, or laboratory abnormalities 2 h after bite</td>
<td>0</td>
</tr>
<tr>
<td>Minimal envenom</td>
<td>20%–40%</td>
<td>Local and slowly progressive swelling without systemic or severe laboratory abnormalities</td>
<td>0–6</td>
</tr>
<tr>
<td>Moderate envenom</td>
<td>20%–40%</td>
<td>Rapidly progressive local swelling; systemic symptoms of nausea, vomiting, diarrhea, diaphoresis, fasciculations, moderate hypotension, and moderate hemostatic abnormalities, but without bleeding</td>
<td>6–18</td>
</tr>
<tr>
<td>Severe envenom</td>
<td>5%–10%</td>
<td>Severe systemic symptoms as above plus severe hypotension and lethargy; severe hemostatic abnormalities and possible bleeding</td>
<td>12–24 or more</td>
</tr>
</tbody>
</table>

### TABLE 68.4
**SUMMARY OF THERAPEUTIC MEASURES FOR PIT VIPER ENVENOMATION**

- Obtain IV access and administer crystalloid as indicated.
- Obtain CBC, PT, PTT, and platelet count every 6–12 h
- Estimate severity of envenomation:
  - Species of snake
  - Age, health status of victim
  - Rate of progression of signs/symptoms
- Administer FabAV per Table 68.3
- Follow rate of progression of signs/symptoms after FabAV administration.
- Determine tetanus vaccination status.
- Seek consultation from experts or a poison center (1-800-222-1222), especially if one is less experienced in treating snake envenomation.

CBC, complete blood count; PT, prothrombin time; PTT, partial thromboplastin time.
Compartment syndromes are seen very rarely, and indications for surgical intervention are justified by pressure measurements in only about 1% to 2% of all envenomated U.S. patients. The degree of swelling in and of itself is not a reliable sign of compartment syndrome given the elasticity of skin. More reliable signs are total lack of function and exquisite pain of the muscles contained within a compromised compartment, and often an intense hardness of the site owing to the nonelasticity of fascial tissue, which, while limiting swelling, allows pressure to increase as it is locked beneath the fascial plane. The palmar aspect of the hand and lateral compartment of the tibia may be so involved. Direct measurement of pressure within an anatomic compartment may be of use, and adequate antivenom therapy and elevation will usually result in normalization of pressures. Orthopedic consultation may be indicated, but in animal models, fasciectomy has not been shown to result in improved outcomes.

The mainstay for treatment for North American pit viper envenomation is ovine FabAV for bites in both adults and children (26,27). The Fab portions of sheep immunoglobulins are made by enzyme cleavage and elimination of the Fc fragment, which is regarded as the more immunogenic part of the intact immunoglobulin molecule, and by further enzymatic cleavage of the resulting Fab-β2. Pretreatment skin or conjunctival testing is neither required nor recommended prior to the administration of FabAV.

The small FabAV molecule has the theoretical advantage of a larger volume of distribution and the potential to neutralize more venom at the bite site. This has not been demonstrated clinically, however. On the other hand, as it has a more rapid distribution and a shorter half-life than IgG, periodic readministration during the initial treatment period is important. Search and development of a Fab(αβ') antisnake venom is currently under way. Fab(αβ') has a smaller volume of distribution and a longer circulating half-life, and thus may decrease the recurrence syndrome.

A more general rule of thumb for pit viper envenomation is that approximately half of the total swelling expected to occur does so within the first 2 hours of envenomation, and nearly all of it occurs by 12 hours after envenomation. This seems congruent with one study that involved timed rate of change in swelling (9). Accordingly, if a patient presents over 12 hours after the bite, it would be unusual to experience significantly more swelling, and most systemic symptoms should have occurred and abated. We rarely initiate administration of antivenom treatment more than 12 hours after a bite, and essentially never after 24 hours of the bite. One may initiate or continue antivenom administration after 24 hours in selected situations, such as in the management of continued coagulopathic effects or in the management of recurrence.

We hold that the derbigenination syndrome itself is not such a clear and present risk for spontaneous hemorrhage that its presence alone requires administration of antivenom, nor that its recurrence represents an established reason to readminister antivenom (10,26). As the literature and experience garnered thus far supports that derbigenination alone seems benign, the administration of blood products such as fresh frozen plasma (FFP) or cryoprecipitate is usually not warranted, even prior to a surgical procedure, as the risks of these blood products probably outweigh their (unproven) benefit. If one does encounter a patient with systemic hemorrhage, or should unacceptable bleeding follow a surgical procedure, administration of additional antivenom plus cryoprecipitate (eight to ten bags in an adult) is the treatment of choice. Likewise, other isolated, nonspecific coagulopathies (e.g., without bleeding) do not, in and of themselves, in our opinion, demand antivenom treatment (10).

Some species of snakes, particularly the timber rattlesnake (Crotalus borroridus borroridus), have a principle in their venom that causes significant thrombocytopenia, which appears rather resistant to reversal by antivenom therapy (37). If platelet counts are significantly falling and/or are less than 10,000 to 20,000 cells/μL, administration of (additional) antivenom and infusion of platelets may be indicated, particularly if there is evidence for systemic bleeding. In general, with most Crotalid envenomation, there is a mild thrombocytopenia in the range of 50,000 to 150,000 cells/μL that is thought to be due to passive entrapment of platelets within the previously described soft fibrin network and, as mentioned, does not support a diagnosis of DIC. The platelet count often will rebound within the day as the soft fibrin network is quickly cleaved by endogenously generated plasmin.

Surgical Procedures

A surgical procedure for the wound is rarely indicated, and there are several case series and experimental studies suggesting that surgical procedures correlate with a delayed outcome, some with a paradoxical increase in permanent loss of tissue, loss of anatomic function, and nonspecific stiffness (38–40). Antibiotics are generally not employed as they are of questionable assistance, and their routine use is not recommended (41,42). If there has been significant surgical manipulation of the wound in the field, as with repeated knife wounds, that stance may need to be reconsidered. Tetanus vaccination status should be ascertained as being up to date.

Observation

When observing the wound for any changes, it is best to have the extremity clearly visible so as not to compromise the evaluation; we do not advocate any covering dressings or wraps. Once the patient is at the hospital and receiving antivenom, the extremity should be elevated above the level of the heart. Monitoring is usually best performed in the emergency department, with subsequent admission to the intensive care unit (ICU), although ICU therapy should not be considered, in our opinion, as necessarily a standard of care. The usual length of hospitalization is 4 to 6 days. For up to 24 hours, we often observe patients—either in the emergency department or in the hospital—who are deemed to have no envenomation or mild envenomations, and who do not receive antivenom because of the very high incidence of concurrent inebriation, which would allow for the possibility of inaccurate history or incomplete evaluation and follow-up.

Prognosis

Nearly all North American pit viper bites result in some near-instantaneous local tissue destruction, which should not be expected to be totally absent or to resolve, even with the very best and most rapid care. Most edema and swelling that does occur after antivenom treatment lasts only for a month or two, with longer recovery times seen in older or debilitated patients. In general, there is a total return of function to the bitten extremity, although some patients can experience mild stiffness, atrophy, and weakness for up to a year or more (43,44). The
Snakes non-native to the United States

This section summarizes the epidemiology, pathophysiology, diagnosis, and treatment of non-native snake envenomations in the United States. Envenomations by reptile, amphibian, arthropod, or marine species not native to the United States pose special challenges to the provider. Clinicians are likely to be unfamiliar with the clinical spectrum of exotic envenomation and its current management. Antivenoms, if they exist, may not be available or may take many hours to locate and acquire. Zoos, aquariums, and academic institutions may possess non-native species for research and display. The problem is compounded by private collectors, whose existence is not usually known to their regional health care system until an exposure occurs. Policies and procedures governing acquisition, storage, handling, antivenom, and preparations for managing envenomations range from comprehensive to nonexistent.

Immediate Concerns

Major Problems

The severity and spectrum of effects in envenomation varies widely. A significant number of bites and stings do not result in envenomation. However, life-threatening effects may be seen and fatalities do occur. Identification to the species level of the envenomating organism is important in anticipation of effects and the selection of nonspecific and specific therapies. Antivenom may or may not be available for non-native species, and identification of the appropriate antivenom and its acquisition may require many hours. Other specific therapies may be available, and nonspecific therapies are directed at general classes of venom effects.

Epidemiology

There are about 3,000 snake species in the world, of which fewer than 300 are dangerous to humans (45). Venomous reptiles include the families Atractaspididae Colubridae, Crotalidae, Elapidae, Helodermatidae, and Hydrophidae (46). Between 40 and 50 non-native snake envenomations occur per year in the United States. Although non-native envenomations in the United States involve at least 77 separate species over the past decade, certain families, genera, and species are more commonly encountered. Cobras (family Elapidae) account for one third of all non-native venomous snake exposures, and 86% of Elapid. Naia naja, Naia murgusaria, and Ophiophagus hannah are the most commonly involved Elapid species. Viperids account for 46% of all non-native venomous snake exposures, with Bothrops, Bitis, and Lachesis genera accounting for 33%, 19%, and 11% of these, respectively. Bothrops goodmanni, Bothrops aschelgeli, Bitis gabonica, and Lachesis mutus are the most commonly encountered viperid species (47).

Pathophysiology

The venom glands of poisonous snakes are modifications of salivary glands (49). The venom of a single snake is a complex mixture of enzymes, nonenzymatic proteins and peptides, and other substances (50,51). These substances exert simultaneous toxic or lethal effects on the integumentary, hematologic, nervous, respiratory, muscular, and cardiovascular systems. The clinical picture also can be complicated by the effects of endogenous mediator release, such as histamine, cytokines, and nitric oxide (52). Some of these components may be found in all venomous snakes, with mixed clinical effects. The most important deleterious components of snake venom are shown in Table 68.5. Hyaluronidase is found in all venom and produces hydrolysis of connective tissue stroma, allowing the dispersion of other toxic components (53). Zinc-dependent metalloprotease enzymes damage vascular membranes and produce local and systemic hemorrhage (54,55). Phospholipases are found in most snake venoms, with a variety of effects (56), including destabilizing biologic membranes and abolishing the selective membrane ion channel permeability to ions such as calcium (56,57). Crotalid venom is rich in proteases, amino acidases, and phospholipases, and typically produces findings of cellular destruction, increased membrane permeability, and coagulation impairment. Coagulation abnormalities may result from multiple mechanisms, including consumption, aggregation or inhibition of platelets, or effects on the coagulation cascade, such as activation or inhibition of coagulation factors, procoagulant activity, detrinogenation, prohemoin action, collagenase-like activity, and other effects (58–60). Eclapid venoms vary widely among species but contain more neurotoxins and cardiotoxins (51), resulting in various expressions of nerve and cardiac toxicity. Sea snakes have venom similar to elapids.
Diagnosis and Monitoring

The spectrum of symptoms and signs produced in a victim by a given venomous snakebite varies with the species of snake, the natural variability in venom composition between snakes, and, in any given snake over time, the quantity of venom injected, bite location, and the age and health of the victim.

Size and Species

In general, larger snakes contain and deliver more venom, but fatal envenomations may result from juvenile snakes. Toxicities of the venom will depend on the species and other factors that affect venom production.

Quantity Injected

As many as 30% of Crotalid bites and 50% of Elapid bites may result in no envenomation (46,61). When venom is injected, the amount may be reduced by poor penetration of the fang or high tissue pressures, as in fingertips. The volume of available venom may also be reduced by recent previous feedings.

Bite Location

Tissues and anatomic areas with a low capacity for swelling, or which are functionally important, such the fingers or hand, are particularly at risk of both short- and long-term impairment. The destructive effects of proteolytic enzymes may directly damage tissues. Also, even where no true compartments exist, tissue pressures may be significantly elevated and vascular compromise may occur. True muscle compartments may be subject to elevated pressures, either because of direct injection of venom with intracompartmental edema, from passage of venom into a compartment via direct spread or lymphatics, or as a result of extrinsic pressure on a compartment secondary to subcutaneous edema. Lower extremity bites may damage venous valves and produce long-term dependent edema. Decreased mobility and mobilization after a bite may predispose to deep venous thrombosis or other morbidities.

Age and Health of the Victim

Those at greatest risk of morbidity and mortality include patients with long delays to treatment, those with significant comorbid conditions, and those at the extremes of age. Because of smaller body mass, children receive a relatively greater dose of venom. As with native envenomations, some private collectors may be under the influence of alcohol at the time of envenomation, which may affect their ability to avoid envenomation, predispose to multiple bites, and delay seeking care.

Symptoms and Manifestations

Since snakes can, to some extent, control whether and how much venom to deliver, and as other factors may affect the quantity and specific components available and delivered, it is difficult to make an a priori determination of the clinical potential of the envenomation. The manifestations of snake envenomations can be divided into local and systemic effects.

Local Effects. Snake venom that produces local effects causes pain and edema at the bite site, erythema, ecchymosis, and occasional bleb formation. Later, the increased membrane permeability and cellular destruction produced by proteases result in spreading edema both distally and proximally, and may cause tissue necrosis. If the bite is on an extremity, elevated tissue pressures may compromise vascular supply or result in elevated compartmental pressures. Periodically marking the extent over time of proximal spread of edema directly on the skin is useful in documenting the progression of local venom effects and response to treatment. The leading edge is usually palpable as a sharply demarcated ridge and differs from later redistribution of tissue edema, which more gradually transits to normal tissue. Edema may spread from an extremity onto the trunk or involve the head and neck, compromising the airway (62,63). Pain, possibly requiring opioid-level management, is common and cannot be used to diagnose compartment syndrome. Because of the similarity of findings with compartment syndrome, if there is concern for elevated tissue or compartmental pressures, they should be measured directly (Stryker Intra-Compartmental Pressure Monitor System, Stryker United Kingdom; COACH Transducer, MIPM GmbH, Muennefeld, Germany). Local venom effects will respond to adequate amounts of antivenom with cessation of progression of proximal edema and reduced tissue pressures. Recurrence of progression of local effects may occur, particularly with Fab antivenoms, which have a larger volume of distribution and, thus, its circulating concentrations fall more quickly than Fab(3) or IgG antivenoms. Locally acting venom components are usually exhausted by 24 to 36 hours, although the resulting tissue injury may continue to develop over days to weeks. Starting on the second day post envenomation, the clinical appearance of the bitten extremity, with increased heat and inflammation of the lymphatics, may be difficult to distinguish from an infective process. Overall, the incidence of infection is
low, but will vary depending on the snake, the host, and factors such as the development of necrosis and wound manipulation. Potentially life-threatening infections such as necrotizing fasciitis and disseminated osteomyelitis, have been reported following snakebites (64–66).

Hematologic Effects. Coagulation alterations result from pro-teases acting on various parts of the coagulation cascade and may occur singly or in any combination. Fibrinogenolysis may occur, resulting in decreased levels of fibrinogen and increased levels of fibrin degradation products (60,66–69). Platelet inhibition, aggregation, or consumption may occur with abnormal function and/or decreased platelet counts (60,70). Intravascular hemolysis has also been reported with some snake venoms (71). The coagulation defects may result in local or systemic bleeding, including life-threatening hemorrhage (71–76). Laboratory tests, including a complete blood count (CBC) with platelet count, PTT, international normalized ratio (INR), PT, fibrinogen, and fibrin degradation products (or d-dimers), should be obtained on arrival and periodically reassessed. Most patients who will develop hematologic abnormalities will demonstrate them within 1 to 2 hours, although early use of antivenom may mask this finding; normal hematologic values at 6 hours suggest an absence of such effects. If abnormalities are present, the use of antivenom may halt (e.g., fibrinogenolysis) or reverse (e.g., platelet aggregation) venom effects. The timing of repeat labs is based on the use of antivenom, clinical findings, and laboratory trends. Unneutralized venom components responsible for hematologic effects may remain active in the body for up to 3 weeks, resulting in delayed, persistent, or recurrent hematologic abnormalities (29,77,78).

Neurologic Effects. These may result from Atractaspis, Elapid, Helodermid, Hydrophiid, or Viperid envenomations. Clinical effects can include sweating, numbness, paresthesias, convulsions, coma, muscle fasciculation, muscle weakness, and respiratory arrest. Respiratory muscle paralysis is the primary cause of death with most Elapid and Hydrophiid venoms. Viperid snakes rarely cause clinically significant respiratory compromise. Coma may be secondary to hypovolemia or to a direct effect of the toxin (68). Neurologic effects may develop rapidly, with respiratory arrest occurring within 15 to 30 minutes, but also may be delayed by many hours (79,80). Measures such as the application of a pressure immobilization bandage (PIB) may also delay the onset of neurotoxicity (81). Even with delayed onset, once neurologic effects occur, they may progress very rapidly. Patients should be observed for a sufficient period of time, and preparations to manage the airway should be readily available. It should be kept in mind that some Elapid produce little or no local effects, and therefore, their absence cannot be relied upon to confirm nonenvenomation. Once muscle weakness or paralysis has occurred, it may be difficult to reverse, although both antivenom and cholinergic agonists will generally stop the progression of effects and have been reported to result in either dramatic or more rapid improvement than would otherwise be expected (82–86). Exclusion criteria are based on standard tests of respiratory sufficiency.

Nonhematologic Systemic Effects. These include effects on the cardiovascular, respiratory, and neurologic systems. In general, snakes from any family may produce any of these effects, although certain effects predominate within families. Type I hypersensitivity reactions to venom (IgE or non-IgE mediated) with or without hypotension may occur. The incidence is believed to be approximately 1% (85). Type II hypersensitivity reactions are characterized by wheal and flare, urticaria, lymphocutaneous edema, and/or hypotension. Airway compromise from laryngeal edema may also occur, and direct myocardial depression, irri-tation, or dysthyemic effects of venom have been reported (85–90). The clinical picture may be complicated by possible adverse reactions to antivenom. The incidence of type I hypersensitivity reactions to antivenoms varies from less than 5% to 25%. Other systemic findings common in snakebites are nausea, vomiting, diarrhea, and pulmonary edema, especially in more severe cases. These usually resolve in response to antivenom and rarely persist beyond the immediate postbite period. Adverse reactions to antivenoms can complicate care. Type III hypersensitivity reactions—"serum sickness"—may occur in any patient who has received antivenom and are the result of circulating immune complexes. The frequency of occurrence is dependent on the amount of antivenom received as well as the type (e.g., source animal, immunoglobulin fragment). Type III reactions usually occur between 5 and 21 days after receiving antivenom and vary widely in incidence by antivenom utilized, from less than 5% to 100% (91–95). Symptoms and signs usually consist of muscle and joint aches, low-grade fever, and/or a urticarial rash; severe cases may have severe symptoms, including renal insufficiency.

Diagnosis

The diagnosis of snakebite may be a clinical one and should be suspected in any unknown presentation with any of the above clinical manifestations. Although immunoassays and bioassays have been used to identify various snake venoms in tissue within endemic areas, such tests are not available in the United States (96,97). In the United States, envenomations are likely to occur in zoo, academic, and private collector settings (47). Snake identification may be inaccurate in noninstitutional settings, yet obtaining an accurate identification of the snake is of utmost importance in order to select the appropriate antivenom. When dealing with private collectors, consideration should be given to independently verifying the snake species. A local zoo or aquarium may be of assistance in identifying the snake.

Management

The management of clinically significant snake envenomation can be divided into first aid, specific antivenin therapy, and supportive therapy (Table 68.6).

Online Antivenom Index. Initiation of efforts to obtain the appropriate antivenom should not wait until symptoms or signs develop; rather, this should be done immediately following the bite. The Online Antivenom Index is a resource for determining the appropriate antivenom(s) for any given snake and maintains a continuously updated listing of zoo antivenom stocks and contact information. It is accessible by regional poison centers (1-800-222-1222), which can assist in the identification and acquisition of an appropriate antivenom and in the clinical management of a snake envenomation.

First Aid. In general, the patient should get away from the snake and the snake should be secured by a qualified individual. Pre-existing medical information, information regarding the biting species, and any available antivenom should be transported with the patient. The bitten body part should be splinted...
Opioid analgesics are best deferred until after administration of antivenom, the bitten area should be kept at or slightly below the level of the heart. A dependent position may be used if rapid, severe systemic effects are occurring. These may include (b) local tissue injury and (c) hematologic abnormalities. Type I hypersensitivity reactions (anaphylaxis) may occur to venom or antivenom. Anaphylaxis, cardiotoxicity, or fluid loss may produce hypotension. Local tissue injury may result in severe swelling, pain, and elevated tissue and/or compartmental pressures. Functional impairment, necrosis, and tissue loss may occur. Hematologic effects include impairment or consumption of platelets, fibrinogenolysis, hypofibrinogenemia, prolongation of PT/PTT, procoagulant effects, and other abnormalities, either singly or in combination; also, significant bleeding may occur. Neurologic effects include diplopia, ptosis, fasciculations, and respiratory muscle paralysis, and arrest. Viperids may cause significant bleeding, but usually not respiratory compromise. Other venom effects include tachycardia, nausea, vomiting, diaphoresis, and anxiety. Wound infection is uncommon, documented in less than 5% of cases. Local effects may continue or recur for the first 24–36 h, and hematologic effects may continue or recur for up to 3 wk.

**TABLE 68.6**

<table>
<thead>
<tr>
<th>DIAGNOSTIC PEARLS</th>
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<tbody>
<tr>
<td>Up to 30% of Viperid and 50% of Elapid bites do not result in envenomation.</td>
</tr>
<tr>
<td>Signs and symptoms of envenomation may be delayed by many hours.</td>
</tr>
<tr>
<td>Identification of the snake to the species level is required for antivenom selection.</td>
</tr>
<tr>
<td>Viperid venoms usually produce (a) local tissue injury and (b) hematologic abnormalities, and may also include (c) cardiovascular effects and (d) neurologic effects.</td>
</tr>
<tr>
<td>Elapid venoms usually produce (a) neurologic toxicity, progressing to respiratory muscle paralysis, and may also include (b) local tissue injury and (c) hematologic abnormalities.</td>
</tr>
<tr>
<td>Type I hypersensitivity reactions (anaphylaxis) may occur to venom or antivenom.</td>
</tr>
<tr>
<td>Anaphylaxis, cardiotoxicity, or fluid loss may produce hypotension.</td>
</tr>
<tr>
<td>Local tissue injury may result in severe swelling, pain, and elevated tissue and/or compartmental pressures. Functional impairment, necrosis, and tissue loss may occur.</td>
</tr>
<tr>
<td>Hematologic effects include impairment or consumption of platelets, fibrinogenolysis, hypofibrinogenemia, prolongation of PT/PTT, procoagulant effects, and other abnormalities, either singly or in combination; also, significant bleeding may occur.</td>
</tr>
<tr>
<td>Neurologic effects include diplopia, ptosis, fasciculations, and respiratory muscle paralysis, and arrest. Viperids may cause weakness, but usually not respiratory compromise.</td>
</tr>
<tr>
<td>Other venom effects include tachycardia, nausea, vomiting, diaphoresis, and anxiety.</td>
</tr>
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<td>Wound infection is uncommon, documented in less than 5% of cases.</td>
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<tr>
<td>Local effects may continue or recur for the first 24–36 h, and hematologic effects may continue or recur for up to 3 wk.</td>
</tr>
</tbody>
</table>

**TABLE 68.7**

<table>
<thead>
<tr>
<th>PREHOSPITAL MANAGEMENT</th>
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<tbody>
<tr>
<td>A pressure immobilization bandage (PIB), a crepe bandage wrapped at lymphatic pressure tension from the distal to the proximal aspects of an extremity (or lymphatic constriction band [LCB; i.e., a blood pressure cuff inflated to 15–25 mm Hg]) will retard progression of venom into the general circulation.</td>
</tr>
<tr>
<td>To avoid prehospital with Vipers, in Viperids with early, severe, systemic effects; and possibly when there are long transport times</td>
</tr>
<tr>
<td>The bitten body part should otherwise be kept gently splinted, slightly below heart level. It may be lowered further if systemic effects are seen, and elevated for excessive swelling.</td>
</tr>
<tr>
<td>At least one large-bore IV should be initiated.</td>
</tr>
<tr>
<td>Venoms other than Vipers should be identified to the species level, if possible.</td>
</tr>
<tr>
<td>If available, antivenom should accompany the patient.</td>
</tr>
<tr>
<td>The victim should be rapidly transported by emergency medical services to a health care facility.</td>
</tr>
<tr>
<td>CONTRAINDICATED MANagements</td>
</tr>
<tr>
<td>Arterial or venous tourniquets</td>
</tr>
<tr>
<td>Incision, excision, heat, cold, electricity, or other local wound manipulations</td>
</tr>
<tr>
<td>Suction devices are not effective and should not delay transport to definitive care.</td>
</tr>
</tbody>
</table>

PT, prothrombin time; PTT, partial thromboplastin time.

to slow the passage of venom into circulation (98). With envenomations from known neurotoxic snakes, generally the Elapids and sea snakes, the application of a PIB (a wide crepe bandage wrapping the entire extremity from distal to proximal at lymphatic compression pressures) or a lymphatic constriction band (LCB; i.e., a blood pressure cuff inflated to 15–25 mm Hg) has been shown to slow central compartment spread of venom and reduce the risk of out-of-hospital respiratory arrest, and thus should be routinely employed (99,100). With Viperid envenomations, the risk of rapidly developing life-threatening systemic effects is generally less. Although the use of a PIB prolonged survival in an animal model, it also resulted in increased tissue pressure; thus, the potential benefits must be weighed against the risk of increased local injury in Viperid envenomations (101). Hypotension, airway compromise, or other signs of a severe type I hypersensitivity reaction would be examples of appropriate indications for the use of a PIB or LCB in a Viperid bite. In general, prior to arrival at a hospital and administration of antivenom, the bitten area should be kept at or slightly below the level of the heart. A dependent position may be used if rapid, severe systemic effects are occurring. These measures can be instituted on arrival at the hospital if they have not been done previously. Transport to a health care facility should be by paramedic ambulance. The initiation of two, large-bore intravenous lines is a sensible precaution. The PIB or LCB should not be removed until antivenom has been obtained and is infusing, if nonvenenomation appears to be the case, or a decision has been made to observe the patient without specific treatment (Table 68.7).

Hospital Care. At the hospital, basic wound care should be provided, including updating the tetanus status, if needed. If, after a sufficient period of observation, which varies from 8 to 24 hours depending on the species of the snake, the victim demonstrates no signs or symptoms of envenomation, the person can be released from the hospital (Tables 68.8 through 68.10).

Pain Control. Opioid analgesics are best deferred until after hospital evaluation because of the risk of potentiating respiratory depression. An ice pack applied to the bite site, with customary precautions, may provide some pain relief without risking additional tissue injury (98,102). Opioid-level analgesia, however, may be required and its judicious use can be considered.

Antibiotics. Most authors recommend against routine prophylactic antibiotics. Antibiotics are suggested only for those with necrosis or clinical or laboratory evidence of infection (103).

Antivenom. Antivenom is composed of antibodies raised in an animal such as a sheep or horse to the venom of one or more species of snakes. A single snake’s venom may be used to produce a monovalent antivenom, effective only against that snake or other snakes with the same or a subset of venom components. Since, in their endemic areas, it may not always be possible to identify the biting species, many antivenoms
Antivenoms for non-native snakes are imported into the United States under Investigational New Drug (IND) application. As such, their use carries additional Food and Drug Administration (FDA) and institutional review board (IRB) reporting requirements. For indeterminate species, zoos and other institutions may ship antivenoms for non-native species, such as antivenoms are generally acquired by zoos and other institutions against the species they have in their collection for use in the event of one of their worker's being envenomed. Zoos have traditionally made their antivenoms available to physicians on a compassionate basis. Since an IND antivenom will usually be brought into a hospital from an outside, nonhospital source, questions may be raised by the pharmacy regarding storage conditions, expiration dates, and other issues relating to its administration. If the potential for a non-native envenomation can be anticipated, such as a known zoo or university collection, it is prudent to have a pre-existing protocol as well as having obtained prior IRB approval (104).

Antivenom is considered the definitive treatment for all clinical effects of snake venom, although for a variety of reasons, such as incorrect snake identification, geographic variation of venom components, irreversible or time-dependent toxicity, and so forth, it may have limited to no observable efficacy against any particular venom effect (103–108). In addition, there are rarely prospective, controlled clinical trials to document appropriate indications, efficacy, and safety or to

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**TABLE 68.8**

<table>
<thead>
<tr>
<th>HOSPITAL BITE SITE AND WOUND MANAGEMENT</th>
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</thead>
<tbody>
<tr>
<td>- If previously applied, a pressure immobilization bandage (PIB) or lymphatic constriction band (LCB) should not be removed until antivenom is being administered or a decision has been made to observe without antivenom.</td>
</tr>
<tr>
<td>- Wash the bite site, apply antibiotic ointment, leave it otherwise uncovered, and provide tetanus immunization updating as needed.</td>
</tr>
<tr>
<td>- Once antivenom has been initiated, or a decision has been made not to administer a life- or limb-threatening envenomation with periodic assessment of edema (and tissue pressures if indicated), and monitor for development or progression of systemic symptoms.</td>
</tr>
<tr>
<td>- Management of progressive tissue edema and elevated tissue or compartmental pressures is by adequate amounts of antivenom and elevation, if tolerated.</td>
</tr>
<tr>
<td>- Frankly necrotic tissue should be debrided.</td>
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<tr>
<td>- There is little to no role for dermotomy or fasciotomy.</td>
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**TABLE 68.10**

<table>
<thead>
<tr>
<th>HOSPITAL SYMPTOMATIC MANAGEMENT</th>
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<tbody>
<tr>
<td>- Hypotension</td>
</tr>
<tr>
<td>- May be due to type I hypersensitivity reaction to venom or to antivenom, cardiotoxins, or fluid loss.</td>
</tr>
<tr>
<td>- Management is with Trendelenburg positioning, crystalloid fluid expansion, pressors, anaphylaxis treatments (epinephrine, H1, and H2 blockers), and antivenom (if believed to be secondary to venom).</td>
</tr>
<tr>
<td>- Neurologic effects</td>
</tr>
<tr>
<td>- Should be managed with antivenom and mechanical airway support as needed.</td>
</tr>
<tr>
<td>- Cholinergic agonists, such as neostigmine, may be used as adjunctive or substitute managements of muscle weakness in some Elapid envenomations.</td>
</tr>
<tr>
<td>- Hematologic effects</td>
</tr>
<tr>
<td>- Severe or multicomponent abnormalities are managed primarily with antivenom.</td>
</tr>
<tr>
<td>- Blood products are reserved for clinically significant hemorrhage, and given with additional antivenom if needed.</td>
</tr>
<tr>
<td>- Some effects (e.g., platelet aggregation) may be readily reversed, while other processes (e.g., fibrinogenolysis) may be stopped, with components returning to normal levels by their natural replenishment.</td>
</tr>
<tr>
<td>- Other systemic effects are managed with symptomatic and supportive care.</td>
</tr>
<tr>
<td>- Parenteral opioids may be required for pain.</td>
</tr>
<tr>
<td>- Recurrence of local and/or hematologic venom effects may occur.</td>
</tr>
<tr>
<td>- Patients at high risk should be closely monitored, especially postdischarge.</td>
</tr>
<tr>
<td>- Additional antivenom should be considered for recurrent local effects in the first 24 h or recurrent severe or multicomponent hematologic abnormalities.</td>
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</tbody>
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Antivenoms range from those that are relatively unpurified—whole IgG immunoglobulins, containing other proteins and immunoglobulin fractions—to highly purified specific IgG, Fab, or Fab immunoglobulin fragments. In general, horse serum-based products are more immunogenic than sheep-based antivenoms. IgG has a smaller volume of distribution, longer half-life, and higher rates of allergic reactions, while Fab antivenoms have the largest volume of distribution, shorter half-lives, and lowest rates of allergic reactions. There is both considerable overlap and considerable variation of venom components within genera and species. When possible, species-specific antivenom that claims efficacy for the particular snake should be used. Antivenoms effective against other snakes in the same genus may be tried if species-specific antivenom is not available.

Antivenoms are polyvalent; that is, they are designed to provide neutralizing efficacy for a number of different snake species. Venoms range from those that are relatively unpurified—whole IgG immunoglobulins, containing other proteins and immunoglobulin fractions—to highly purified specific IgG, Fab, or Fab immunoglobulin fragments. In general, horse serum-based products are more immunogenic than sheep-based antivenoms. IgG has a smaller volume of distribution, longer half-life, and higher rates of allergic reactions, while Fab antivenoms have the largest volume of distribution, shorter half-lives, and lowest rates of allergic reactions. There is both considerable overlap and considerable variation of venom components within genera and species. When possible, species-specific antivenom that claims efficacy for the particular snake should be used. Antivenoms effective against other snakes in the same genus may be tried if species-specific antivenom is not available.

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**TABLE 68.9**

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<tbody>
<tr>
<td>- Antivenom is the definitive management of snake envenomation, when it is available.</td>
</tr>
<tr>
<td>- Antivenom for an exotic species can be located via the Online Antivenom Index: Poison centers (1-800-222-1222) can assist.</td>
</tr>
<tr>
<td>- When available, species-specific antivenom should be used.</td>
</tr>
<tr>
<td>- Skin testing is indicated if recommended by the manufacturer.</td>
</tr>
<tr>
<td>- Skin tests are neither sensitive nor specific to predict hypersensitivity reactions.</td>
</tr>
<tr>
<td>- A positive reaction does not preclude antivenom administration.</td>
</tr>
<tr>
<td>- Skin testing should not delay administration of antivenom in a life- or limb-threatening envenomation.</td>
</tr>
<tr>
<td>- Exotic antivenoms are imported under Investigational New Drugs license and if used, appropriate reports need to be made to the hospital’s institutional review board (IRB) and the Food and Drug Administration (FDA).</td>
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</tbody>
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**TABLE 68.11**

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</tr>
</tbody>
</table>
establish optimal dose and dosing regimens. Since antivenoms carry a risk of allergic reactions, potential benefits must be weighed against the risks of administration. Skin tests are neither sensitive nor specific enough to predict type I hypersensitivity reactions, but if recommended by the manufacturer, they should be administered. Their result, however, should not serve as a contraindication to administration when indicated, and preparations to manage an allergic reaction should always be immediately available. Regardless, skin testing should not delay administration of antivenom in a life-threatening envenomation.

Treatment with antivenom alters venom component distribution pharmacokinetics. Venom components bound to antibody become inaccessible to target tissues and are thus neutralized. Therefore, the dose of antivenom should be great enough to theoretically bind/neuralize the entire venom dose injected by the snake. These doses have been determined by knowledge of typical snake venom loads, neutralization properties of antivenoms in animal studies, and clinical studies. In most cases, it would be best to give doses of antivenom to ensure adequate venom neutralization on the assumption of a severe envenomation, since the degree of envenomation is difficult to appreciate early in the course. Such neutralization, however, occurs predominantly in the vascular compartment, and there may be unneutralized venom components remaining in the tissues. Venom may thus redistribute from target tissues and continue to produce toxicity if the antivenom dose is inadequate or if unbound antivenom has been eliminated. These pharmacokinetic relationships illustrate why antivenom administration as soon as possible following envenomation is beneficial and why the use of shorter-acting antivenoms may result in recurrent hematologic effects. Also, because of difficulty reaching damaged tissue and despite the use of antivenom early in the course of a severe envenomation, there may still be limitations as to the effectiveness of antivenom in preventing worsening of local tissue damage, and it will not benefit already devitalized tissue.

Indications, timing, and doses of antivenom will vary and expert guidance should be sought. Since the required dose of antivenom is that needed to neutralize a given amount of venom in the body, it is not dosed by patient weight, and children may require larger doses than adults. Over a 10-year period in the United States, antivenom was only used in 26% of non-native snake envenomations, possibly because of difficulties in determining, locating, and obtaining appropriate antivenom in a timely manner (47,104). Antivenom is most effective in preventing or ameliorating local venom effects when given early in the course. Since most local reactions have progressed within 24 to 36 hours, giving an initial dose of antivenom after this time frame is not likely to be of any benefit. Antivenom is also most effective at preventing or reversing hematologic effects when given early, but may still be beneficial for weeks after envenomation if there are still circulating venom components (67,77,109). Clinically significant hemorrhage is most effective at preventing or reversing hematologic effects. Also, because of difficulty reaching damaged tissue and despite the use of antivenom early in the course of a severe envenomation, there may still be limitations as to the effectiveness of antivenom in preventing worsening of local tissue damage, and it will not benefit already devitalized tissue.

Finally, zoos may only have or choose to send expired antivenoms in animal studies, and clinical studies. In most cases, it would be best to give doses of antivenom to ensure adequate venom neutralization on the assumption of a severe envenomation, since the degree of envenomation is difficult to appreciate early in the course. Such neutralization, however, occurs predominantly in the vascular compartment, and there may be unneutralized venom components remaining in the tissues. Venom may thus redistribute from target tissues and continue to produce toxicity if the antivenom dose is inadequate or if unbound antivenom has been eliminated. These pharmacokinetic relationships illustrate why antivenom administration as soon as possible following envenomation is beneficial and why the use of shorter-acting antivenoms may result in recurrent hematologic effects. Also, because of difficulty reaching damaged tissue and despite the use of antivenom early in the course of a severe envenomation, there may still be limitations as to the effectiveness of antivenom in preventing worsening of local tissue damage, and it will not benefit already devitalized tissue.

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Close follow-up is necessary for at least 2 to 4 d to detect latrodectism. Type III hypersensitivity reactions ("serum sickness") are described. Bites from the widow spiders can produce systemic symptoms known as "target" effect (126). Local injection of venom is not believed to cause necrotic wounds and, while superinfection is possible, it is uncommon.

Pathophysiology. The primary component of widow spider venom that causes human clinical effects is α-latrotoxin. It binds to neuronal tissue and causes neurotransmitter release in at least two ways: (a) it binds to and helps form ion channels, which allow calcium and other ions to leak, causing a calcium-dependent release of neurotransmitter; and (b) it binds to the latrophilin receptor on neuronal tissue, and causes a calcium-independent release of synaptic vesicles (125). This neurotransmitter release, either through calcium-dependent or -independent means, is believed to cause the clinical symptoms seen after widow spider envenomation.

Diagnosis. Diagnosis is primarily clinical and historical, as there are no laboratory tests to confirm envenomation. Typically, bite victims will recall a painful pin-prick-like bite, but the bite can be painless. Bites can occur in dark, outdoor places such as leaf litter or woodpiles and, historically, are associated with onehanded dressing or putting on shoes, especially if they are left outside, or even while in bed (126).

Clinical Effects: Local. Bites from the widow spiders can produce mild local irritation. The bite is classically described as two small punctures with a small area of erythema surrounding a minimally blanched area centrally, producing a "halo" or "target" effect (126). Local injection of venom is not believed to cause necrotic wounds and, while superinfection is possible, it is uncommon.

Clinical Effects: Systemic. The more medically significant effects following widow envenomation are the constellation of systemic symptoms known as latrotoxism. Typically, symptoms begin within an hour after the bite. What may begin as local muscle cramps can progress to involve larger muscle groups, spreading continuously from the site of the bite. Abdominal muscles can be involved, leading to abdominal rigidity that can imitate the peritoneal signs of a perforated viscus and which may result in an incorrect diagnosis in the young child or uncommunicative adult. Priapism (127), compartment syndrome (128), elevations in creatine kinase (126), and

### Spiders

Spiders are medically significant. They are classified as medically important spiders, and representatives are found almost worldwide. In the United States, the widow spiders are found throughout most of the country but are most common in the southeast, with the black widow (Latrodectus mactans) believed to cause most envenomations. The female black widow, more harmful to humans than the male, has a shiny black round abdomen and a characteristic bright red hourglass marking on her underside (123). Other species of widow spiders can also be found in the United States. Widow spiders are considered shy spiders and can be found in dark, secluded areas such as under leaf litter (124). All widow spiders worldwide are believed to have similar venom characteristics and similar clinical symptoms.
myocarditis (129) have been reported as associated with a Latrodectus bite. Though no reported cases of spontaneous abortion have been reported in pregnant patients (130), concern exists for prematurity delivery given the intense muscle cramping and hypertension that can occur following a widow spider envenomation. Hypertension has been reported (126) and could be life threatening in susceptible populations.

Management. While the Latrodectus venom is very potent, the volume of venom is miniscule. There is no rule for tourniquets, incision, or excision at the venom injection site. Initial control of pain and muscle contraction should be accomplished through administration of opiates and benzodiazepines. Benzodiazepines are preferred as muscle relaxants, given their wider therapeutic window and minimal hemodynamic and cardiac side effects when compared to agents such as cyclobenzaprine or methocarbamol. Intravenous calcium has not been shown to provide significant benefit (123,126) and is no longer considered a first-line agent.

An antivenom specific to L. mactans is available ([L. mactans] Black Widow Spider Antivenin, Equine Origin, Merck & Co., Inc.). As with administration of other IgG antivenoms, there is a risk of hypersensitivity reactions, including anaphylaxis (126) and serum sickness (131). While skin testing is recommended by the manufacturer, it is insufficiently sensitive or specific to either predict or exclude the likelihood of a type I hypersensitivity reaction (123). Type III hypersensitivity reactions (“serum sickness”) have been reported, (131) though they are believed to be a rare complication given the small volume of antivenom necessary to neutralize the injected venom. The use of antivenom is controversial. Most would agree that when dealing with patients in the extremes of age, pregnant patients, or those with intractable muscle cramping and pain, the use of antivenom should be strongly considered. For those with mild to moderate envenomations, clinicians can attempt a trial of benzodiazepine and opioid therapy. Moss and Binder (131) found that most bite effects were self-limited and needed only minimal pharmacologic intervention, while others found that antivenom was associated with minimal adverse events and rapid resolution of symptoms, and should therefore be considered early in the course after moderate to severe envenomations (123,126,132). The clinician at the bedside must weigh the small risk of hypersensitivity reactions to the possible benefit from reversal of the venom’s effects. If administered, the antivenom should be administered in a controlled, monitored environment, with treatments for acute reactions available such as steroids, histamine blockers, and epinephrine immediately available. There is no evidence that pretreatment with any of these agents is efficacious in preventing a reaction, and caution should be used before administering antivenom to anyone with risk factors for immediate hypersensitivity reactions (126). The dose for adults or children is the contents of one restored vial (2.5 mL) of antivenom. It can be given as an intramuscular injection (133) but is typically administered as a slow intravenous infusion (134). It can be redosed if needed, but one vial of antivenom is usually sufficient (133).

There is evidence for cross-reactivity of antivenoms produced to various Latrodectus species, including a purified Fab′ of antivenin produced in Australia to the red-backed spider (Latrodectus hasselti) by CSL Limited and which possesses an improved safety profile compared with the U.S. product (135). As this antivenom is not currently approved for use in the United States, consultation with a regional poison center (1-800-222-1222) can be beneficial.

Follow-up. Unless antivenom is administered, in which case monitoring for serum sickness should be arranged, there are no long-term sequelae expected from a widow spider envenomation (131). Local wound care should be satisfactory for the bite site, and prophylactic antibiotics are not warranted. Standard recommendations for any secondary sequelae such as rhabdomyolysis are appropriate.

Brown Spiders (Loxosceles Genus)

Loxosceles spiders are found primarily in the southern half of the United States. While at least 50 species of Loxosceles can be found on several continents, the Loxosceles reclusa species (“brown recluse”) is the most common and medically important in the United States (123,136). As their name implies, these are considered shy spiders, hiding in woodpiles and dark corners, only biting when threatened. Bites are more common in warmer months and are often presumed to occur when a spider is caught next to skin by clothing or linens (136). True epidemiology is difficult, as necrotic wounds, which can occur because of Loxosceles envenomations, are often inaccurately attributed to spider bites when other insect bites, skin infections, or other dermatologic conditions are truly responsible.

Pathophysiology. Venom from Loxosceles spiders is a complex mixture of cytotoxic components that indirectly cause impressive, delayed local symptoms and have the potential for causing human systemic toxicity. Hyaluronidase in the venom causes significant tissue destruction, allowing spread of other venom components in the soft tissues following an envenomation (137). Sphingomyelinase D in Loxosceles venom is believed responsible for the delayed reaction seen after bites (138). Venom injected in the skin starts a cascade of cellular reactions including neutrophil migration and degranulation, which leads to potentially severe local tissue injury (139).

Diagnosis. Because the bite is usually painless and thus unnoticed at the time, unless a Loxosceles bite is witnessed and positive identification of the spider occurs, the diagnosis is typically a historical and clinical one. The necrotic wounds found with Loxosceles spider bites can mimic numerous other common cutaneous conditions, such as bites by other spiders or other insects, soft tissue bacterial infections, or a vasculitis. A broad differential, including these, as well as conditions such as erythema nodosum, pyoderma gangrenosum, procarcinomatous granuloma, and herpetic infections, should be reviewed before a necrotic wound is attributed to a Loxosceles spider in the absence of a known bite (140). Cases of necrotic wounds have been linked to other U.S. spiders such as the hobo spider (141), though clear and well-accepted causation between these spiders and dermonecrotic wounds is not established (135,142). Positive laboratory identification by enzyme-linked immunosorbent assay (ELISA) or hemagglutination is possible to confirm Loxosceles envenomation in research settings (143), but is not at this time clinically useful. Results are not available in a clinically relevant time frame, and specific therapeutic interventions are not available.

Clinical Effects: Local. Unlike the widow spiders, the majority of clinical effects seen from Loxosceles spiders are a result of
local tissue injury. The characteristic necrotic wounds are described as having a “red, white, and blue” appearance, though clearly demarcated color rings are rare and not needed to make a diagnosis. Local tissue inflammation occurs over the first day after envenomation, causing skin erythema. In the center of this reddened skin, a small necrotic or “blue” area develops that is surrounded by a halo of blanched tissue appearing gray or “white.” Often the wound is not noted until it begins to cause significant pain or the necrotic area becomes prominent.

Clinical Effects: Systemic. Rarely, a Loxosceles spider bite can lead to a clinical syndrome known as systemic loxoscelism. Children are at a higher risk than adults, and in young children, systemic loxoscelism can present as a potentially life-threatening illness characterized by hypotension and shock (136,144,145). Systemic loxoscelism should be in the differential of unexplained hemolysis associated with shock (145).

Management. Many pharmacologic and surgical treatments have been proposed in the management of the necrotic dermal wounds associated with Loxosceles spiders, but none has been proven to have significant effects in preventing or reversing damage. These include hyperbaric oxygen (146,147), steroids (148), dopamine (146–150), nitroglycerin (151), and early surgical debridement, and are not recommended. The venom spreads rapidly after a bite, and early attempts to “core” out affected areas to prevent venom spread result in poor wound healing and worsened scarring (149). If significant cosmetic defects occur as a result of the necrotic wound, surgical intervention, including skin grafting, should be delayed at least 4 to 12 weeks (152).

Systemic loxoscelism should be treated with symptomatic and supportive care. Successful treatment of proven loxoscelism cases has included aggressive fluid resuscitation, blood product transfusion, and vasopressor use. While there is no antivenom available in the United States for Loxosceles bites, antivenoms to Loxosceles spiders exist in South America. Although Loxosceles venoms of a variety of species share many antigenic components (153), cross-reactivity data are lacking, and it is unknown whether such antivenoms would confer any benefit in a U.S. Loxosceles envenomation.

Non-native Spiders

The funnel web spiders (Hadronyche and Atrax spp.), native to Australia, and the banana spiders (Phoneutria spp.), native to South America, are considered far more dangerous than the native Loxosceles and Loxosceles spiders. In the United States, these can be found through collectors or as accidental stowaways in goods transported internationally. The funnel web spider venom contains a potent neurotoxin that can cause fasciculations, weakness, and autonomic instability, with coma and pulmonary edema complicating the clinical course. An antivenom available in Australia has been successfully used in severe envenomations (154).

The South American spiders belonging to the genus Phoneutria are a neurotoxic venom that can cause pain and neurologic and gastrointestinal symptoms, as well as shock and pulmonary edema in severe cases (155). An equine antivenom is available in South America. These antivenoms may be located in the United States through the Online Antivenom Index, with the assistance of a regional poison center (1-800-222-1222).

Scorpions

In the United States, there is only one medically significant species of scorpion, Centruroides exilicauda (formerly Centruroides sculpturatus). Found in the southwestern United States, primarily in southern Arizona, it is commonly known as the bark scorpion. Stings occur by the tail, with the venom containing neurotoxins and other components. Pediatric patients are at greatest risk of having clinically significant symptoms associated with such a scorpion sting. Symptoms can be minor with only some local paresthesias, but, for some, symptoms can be severe, including cardiac manifestations such as tachycardia and hypertension, neurologic manifestations such as roving eye movements and agitation, and respiratory manifestations, including tachypnea and stridor (156,157). Cholinergic symptoms such as hypersalivation have also been reported (158).

Treatment options in the past have included a goat-derived antivenom, limited to use within the state of Arizona. This antivenom is no longer produced, however, and existing supplies are rapidly dwindling. A Fab1γ antivenom is currently in clinical trials. A continuous midazolam infusion, ventilatory support, and otherwise supportive and symptomatic care are current mainstays of treatment (159,160). Atropine for excessive cholinergic signs has been recommended (158).

MARINE ANIMALS

This review will cover marine envenomations. Organisms that are poisonous when ingested will not be covered. Marine envenomations can occur from interaction with both vertebrate and invertebrate organisms. In the vertebrate category are stingrays, sea snakes, catfish, scorpionfish and leatherjacks, among others. Invertebrates encompass a much larger group- ing, including coelenterates, echinoderms, annelid worms, and mollusks.

Stingray

Eleven different species of stingray are found in U.S. waters, seven of which are found in the Atlantic Ocean (161). These animals have long, sharp, serrated barbs along the dorsal surface of their tails, which can cause significant tissue damage and death, even without envenomation (162). They often will bury themselves in the sandy bottom of temperate shallow waters where they may be inadvertently stepped on or otherwise startled to lash out with their tail. The tail barbs are covered in an integumentary sheath that covers two ventrolateral venom glands. Their venom is a complex mixture that includes phosphodiesterase, nucleosidases, and serotonin (161,163).

Clinical Effects

Burning pain at the wound site typically intensifies with time, and local symptoms may last up to 48 hours (162). Venom can cause initial vasodilation and edema at the bite site, then
vasoconstriction with hemorrhagic necrosis of tissue and inflammatory infiltrate (163,164). Cardiac conduction abnormalities ranging from bradycardia to atrioventricular nodal blocks with dysrhythmias and cardiac arrest from asystole have been reported. Venom effects also include nausea/vomiting, diarrhea and abdominal pain, as well as ataxia, seizure, coma, hypotension, and respiratory distress (161,163).

**Treatment**

Treatment is symptomatic and supportive. Radiographic imaging as well as local wound exploration is necessary to evaluate for retained foreign body in the wound. Tetanus prophylaxis should be administered if needed. Prophylactic antibiotics to cover marine microorganisms should be considered, as secondary bacterial infections are common (161,165). Pain control with narcotic analgesia is often required, and immersion of the limb in hot water (110°F, 43°C) may aid in pain relief (162,166,167). Care should be taken to not produce thermal injury. Consider an observation period of at least 4 hours to ensure that symptoms do not progress to systemic effects.

### Scorpaeoidea

This group is composed of a number of venomous fish, and is the most common marine source of human envenomation, both in the wild and in home aquaria. They are found in the warm waters of the Gulf of Mexico and Florida Keys, as well as the Pacific, including around Hawaii, and the Indian Ocean. Fish in this group include lionfish (Pterois), zebrafish (Dougias), scorpionfish (Scorpaena), and stonefish (Synanceja) among many others. Venom apparatus is a collection of spines along the body of the fish, each composed of paired venom glands covered by an integumentary sheath. The dorsal spines are typically the most numerous and can inject the most venom (163). The venom of the fish in this phylum is a complex mixture, and most contain significant amounts of inflammatory mediators such as thromboxane and prostaglandins (161,163). The chemical makeup and potency of venom varies by species within this group, and clinical effects range from very severe (stonefish) to mild (lionfish). The stonefish is by far the deadliest of this group; however, outside of zoos, educational institutions, and private aquaria, it is not likely to be encountered in the United States. It lives in the temperate and warm waters of the Australian and Indo-Pacific and east African coast. There is the potential for envenomation by stonefish in private collections. Of more relevance in this group are the lionfish, zebrafish, and scorpionfish since, although not found wild in U.S. coastal waters, they are a favorite of exotic fish collectors, and stings can result from pets although not found wild in the United States. It lives in the warm waters of the Indo-West Pacific. None are found in the Atlantic Ocean or Caribbean Sea. Envenomations are likely the result of such stings being kept in zoos or academic institutions or kept by private collectors. Their venom is similar to Elapid venom, with neurotoxicity—and potentially respiratory arrest—as the primary clinical effect. See the section on non-native snake envenomations for management considerations.

### Invertebrates

There are over 10,000 species in the phylum Cnidaria (formerly Coelenterata), and several hundred are dangerous to humans. This grouping includes jellyfish (class Scyphozoa), the Portuguese man-of-war and other sea hydrions (class Hydrozoa), and the sea anemones and fire corals (class Anthozoa). All possess envenoming apparatus in the form of nematocysts (161,163,177).

In jellyfish and hydrions, nematocysts are primarily on the tentacles, and each tentacle can contain thousands. Each nematocyst is a spiral-coiled dart-like structure within venom sacs. Venon is injected when the barb penetrates the flesh of its prey. Nematocysts that have become detached from the tentacle, tentacles of dead jellyfish, or detached tentacles can all still cause envenomation upon contact. The popularity of scuba diving and snorkeling has increased the chances of contact with the nematocysts of sessile Cnidaria, such as sea anemones and soft and true corals (178). The Portuguese man-of-war (Physalia physalis) is found in the Atlantic waters off the southern coast of the United States, especially from July through September, and is actually a complex colony of multiple hydrions (179). The body is pale blue and bell or bottle shaped and the tentacles may grow to more than 100 feet in length. The venom is especially complex and also contains neurotoxins.

The severity of the sting depends on the organism, the number of successful discharges, and the composition of the venom. Like the majority of venoms, Cnidaria venoms are complex mixtures of many substances. Commonly found chemicals...
include histamine, serotonin, alkaline and acid phosphatases, proteases, hyaluronidase, nucleosides, hemolysins, and inflammatory mediators (187,188).

Clinical Effects
Most organisms in this grouping, with the exception of the Portuguese man-of-war, cause only mild local effects in humans. These local effects consist of burning pain at the site of the sting, which may be severe, with swelling, erythema, and possible vesicle formation and ulceration of the area (181,182). Regional lymphadenopathy may be seen, and secondary infection and scarring are common. Anaphylactoid reactions can occur as well. Systemic effects, if any, are mild, but immune reactions such as erythema nodosum and reactive arthritis have been reported (183-185). Irukandji syndrome is a constellation of both local and systemic symptoms that occur in a delayed fashion after envenomation by an Australian jellyfish (Carukia barnesi). There have been reports of a similar syndrome occurring in swimmers and divers off the coast of southern Florida, likely after exposure to another organism in the same genus, although the responsible organism has not yet been identified (185).

With envenomation by the Portuguese man-of-war, there is immediate intense local pain at the sting site, with development of large, linear, erythematous welts where tentacles have contacted the skin. These welts often leave significant scarring. Systemic effects include nausea and vomiting, headache, and myalgias, and may progress to muscle weakness, respiratory distress, and cardiovascular collapse in severe envenomations (161,167,186). The intense pain and occasional paralysis caused by many stings from this jellyfish can result in drowning. Multiple stings can be fatal.

Fire coral (Millepora) is not a true coral, rather a relative of fresh water hydra, but has nematocysts to envenomate its prey. The stings cause local burning pain, urticaria, and intense pruritus (179). These wheals may take weeks to heal completely and may leave hyperpigmented scars.

The Scyphozoa contain the “true” jellyfish, including the deadly box jellyfish (Chironex fleckeri or sea wasp), which is not found in U.S. waters, and is present here in zoos, institutional, and possibly private collections only. It is usually found in tropical climates of the Indian and Pacific Oceans, including the coastal waters of Australia. The box jellyfish is so named because of its four translucent panels that roughly form a box. The sting of the box jellyfish is painful and can cause death within minutes, and the mortality rate in native settings is 15% to 20% (161,187,188). An antivenom is available and should be stocked by the institutions that house these creatures; an anaphylactic reaction may be life-threatening. Papain meat tenderizer has been reported to improve symptoms and may be used with caution (167). Alcohol or fresh water may cause the remaining nematocysts to fire and should not be used. A few species’ nematocysts will fire in the setting of acetic acid, including the American sea nettle, the little maure stinger jellyfish, and the hazy or lion’s mane jellyfish. For these few, a slurry of baking soda should be applied for at least 10 minutes over the affected area. If tentacles remain attached to the skin, a vinegar or baking soda slurry should be applied, then shaving cream and scraping as for nematocysts to remove the tentacles. Many components of the venoms of these organisms are heat-labile, and immersion of the affected area in nonscaling hot water (110°F, 43°C) may aid in pain relief (162,166,167,169,189,190).

Tetanus prophylaxis should be given as needed and a third-generation cephalosporin used for secondary infection. Pain should be treated with both NSAIDs and opioids as needed. Persistent pruritus and swelling should be treated with antihistamines. Systemic steroids have not been shown to be of any benefit.

Sea Lice (Seabather’s Eruption)
The prolific time period for the appearance of sea lice is March through June on the southeast coast of Florida. A contact dermatitis can develop with exposure to the larvae of sea lice (Linchole spiculata). The larvae attach to the fibers in bathing suits and can cause a rash in the distribution of the swimwear, thus “seabather’s eruption.” The rash is pruritic, erythematous, and maculopapular, and typically resolves spontaneously in hours to days without sequelae (178,191-193). Topical treatment with antihistamines and calamine lotion may give relief.

Sponges
Some sponges contain spicules composed of calcium carbonate and silica, which can cause local irritation and itching of skin upon contact. This is also known as “skin diver’s” or “sponge fisherman’s” disease. The fire, red, and bunsponges also have toxins in their coatings that can cause local irritation, which may be painful and pruritic and produce erythema (178,194). Pain and paresthesias after contact may persist for weeks (161,194).

Treatment
Remove spicules with adhesive tape or the edge of a dull knife attached to the skin, a vinegar or baking soda slurry should be applied, then shaving cream and scraping as for nematocysts to remove the tentacles. Many components of the venoms of these organisms are heat-labile, and immersion of the affected area in nonscaling hot water (110°F, 43°C) may aid in pain relief (162,166,167,169,189,190).

Tetanus prophylaxis should be given as needed and a third-generation cephalosporin used for secondary infection. Pain should be treated with both NSAIDs and opioids as needed. Persistent pruritus and swelling should be treated with antihistamines. Systemic steroids have not been shown to be of any benefit.

Mollusca
Conus Snails
Cone shell snails have an ejectable tooth at the end of a long flexible proboscis, and envenomate their prey by sinking this
Clinical Effects. Clinical effects include local burning pain, numbness, and paresthesia, as well as systemic effects of peripheral neuropathy, cranial nerve palsies, coma, respiratory muscle paralysis, and cardiovascular collapse (161). Although the majority of human envenomations are mild and limited to local effects, at least 15 deaths have been reported (194).

Treatment. Treatment is primarily symptomatic and supportive.

Toxic Octopi

Other marine animals may cause serious, and at times fatal, envenomations. The bite of the blue-ringed octopus introduces tetrodotoxin, a potent neurotoxin also found in the puffer fish, as well as several other neurotoxins, including maculotoxin (167,179). This organism is of importance, as it may be found in zoo aquariums and the home aquarium of private collectors in the United States. The giant monster octopus should not be of concern in the United States.

Clinical Effects

Clinical effects include local pain, numbness, and paresthesia, which may also involve distant sites such as the lips and tongue. Cranial nerve palsies can be seen and, in severe envenomations, muscle weakness progressing to respiratory paralysis and cardiovascular collapse occurs (163,167,196).

Treatment

Treatment is primarily symptomatic and supportive care. Respiratory and cardiovascular support may be required. No antivenom is available.

Echinodermata

Crown of thorns (Acanthaster planci) is found primarily in the Indo-Pacific Oceans and should be of little concern in the United States except when encountered in zoo, academic institutions, and private collector aquaria. Sharp, rigid spines over the dorsum of the organism can cause deep puncture wounds, even through gloves, and the venom delivered is a complex mixture of inflammatory mediators, histamine, and others including toxic saponins, with hemolytic and anticoagulant effects (163,194,197).

Clinical Effects

Local effects predominate, such as burning pain and local hemodynamic injury. Secondary infection and retained foreign body from broken spines are not uncommon. Systemic effects are rarely reported but may include nausea, vomiting, and fever. Immersion of the limb in non-scalding hot water (110°F, 43°C) may aid in pain relief, as the venom components are heat-labile (162,166,167,169,197).

Sea Urchins

Many sea urchins have long, sharp spines composed of calcium carbonate that cause local injury, but most are not venomous. Deep tissue injury and extension of spines into organs and joint spaces may cause tissue destruction and morbidity from secondary infection. If it is a venom-containing species, the gland is located at the end of the spines and in their pedicellaria (the mouthlike apparatus at the end of a stalk used to gather food). Venom is composed of a mixture of steroid glycosides, serotoxin, proteases, and others (198).

Clinical Effects

Local pain, erythema, and edema are typically self-limited. Partial paralysis of the envenomated limb has been reported with exposure to some species (194,197). Rare systemic symptoms are noted in the literature.

Treatment

The affected area should be immersed in non-scalding hot water (110°F, 43°C), with oral analgesics and local wound care, and removal of any embedded spines as needed. Care is otherwise symptomatic and supportive.

Annelid Worms

The common bristle worm, found in Floridian and Caribbean waters, causes intense local inflammation with edema, erythema, and urticaria (163). No systemic reactions have been reported, and the toxin is unknown. Removal of any bristles adherent to the skin and otherwise simple symptomatic and supportive care are the mainstays of treatment.

References


Chapter 68: Envenomation


Section VII: Pharmacology, Nutrition, Toxicology, and the Environment