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Toxicology in the ICU

Part 3: Natural Toxins

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This is the third article of a three-part series that reviews the care of poisoned patients in the ICU. This article focuses on natural toxins, such as heavy metals and those produced by plants, mushrooms, arthropods, and snakes. The first article discussed the general approach to the patient, including laboratory testing; the second article focused on specific toxic agents, grouped into categories. ***CHEST 2011; 140(5):1357–1370***

Abbreviations: FEP = free erythrocytic protoporphyrin; ZPP = zinc protoporphyrin

This is the final article of a three-part series in *CHEST* that reviews the generalized care of poisoned patients in the ICU. This article focuses on natural toxins.

Plants

Although plant exposures are very common, fatalities are rare.[1,2] A list of plants associated with toxicity is found in Table 1. In general, all parts of the plants are poisonous, although roots or seeds may contain higher concentrations of the toxin.

Anticholinergic Species

Various plants contain anticholinergic alkaloids such as hyoscyamine and atropine. Such plants include jimsonweed, angel's trumpet, deadly nightshade, mandrake, and black henbane.[3-10] Anticholinergic symptoms generally begin within 1 h of ingestion and may continue for days. Severe toxicity results in agitation, hallucinations, hyperthermia, tachycardia, rhabdomyolysis, renal failure, and death.[4,11-13] Without aggressive supportive care, death can result from rhabdomyolysis-induced renal failure, disseminated intravascular coagulation, dysrhythmias, or uncontrolled seizures. Sedation with benzodiazepines may be required to control hyperthermia and rhabdomyolysis. In the absence of contraindications (eg, history of seizures or the presence of intraventricular conduction delay, bronchospasm, or impaired atrioventricular nodal conduction), physostigmine can be used. It should be noted that duration of the anticholinergic effects can outlast the effects of the physostigmine, making redosing occasionally necessary.

Nicotine Alkaloids

Nicotine alkaloids that activate and then block acetylcholine nicotinic receptors are found in tobacco species, betel nut, and poison hemlock.[14-16] Patients commonly experience paresthesias, nausea, and vomiting. More severe cases progress to generalized seizures, autonomic instability, salivation, bronchospasm, and bronchorrhea.[17-22] Symptoms typically commence 15 to 60 min postexposure. Seizures are best treated with benzodiazepines, whereas symptomatic bradycardia, bronchospasm, or bronchorrhea are treated with atropine.[23]

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Hallucinogens

Indole compounds capable of producing hallucinations through activation of 5-HT_2 receptors are found in morning glory and Hawaiian baby woodrose.[24,25] Nutmeg[26] and peyote contain compounds that structurally resemble amphetamines yet also interact with serotonin receptors.[27] Illness usually begins with vomiting followed by hallucinations. Profound mydriasis is common and agitation, tachycardia, and rhabdomyolysis can also occur. Agitation is best treated with benzodiazepines. The differential diagnosis for poisoning by these plants includes poisoning by anticholinergic botanicals, with axillary anhydrosis suggesting anticholinergic toxicity.

Water Hemlocks/Dropworts

Plants of the genera *Cicuta* and *Oenanthe* contain complex alcohols (eg, cicutoxin) that antagonize γ aminobutyric acid-A (GABA-A) receptors.[23,28] These plants grow near water and can be mistaken for wild parsley or carrots. Ingestion is associated with a high mortality rate[26] and can produce sudden onset of vomiting and seizure.[23] Seizures should be treated with benzodiazepines or barbiturates. Rhabdomyolysis is also possible.

Strychnine

Strychnine toxicity can occur from consuming contents of the strychnine tree. However, in North America, toxicity is most likely encountered following exposure to strychnine-containing rodenticides or following use of strychnine-contaminated heroin. Strychnine's antagonism of the glycine receptors in the CNS produces hyperreflexia, rigidity, and opisthotonus.[29] Minimal stimulation can elicit muscle contraction and rigidity, but true seizures are not typically encountered. The diffuse excessive motor activity, often mistaken for seizures, occurs in patients with a clear sensorium. Prolonged muscular contractions can lead to rhabdomyolysis, renal failure, respiratory failure, and death.[30] In patients refractory to benzodiazepines, nondepolarizing neuromuscular blockade and mechanical ventilation may be required.[29]

Cardiac Glycosides

Cardiac glycosides are found in several species, including foxglove, common oleander, yellow oleander, and lily of the valley.[31,32] The illness resulting from ingestion of these plants is identical to that of acute digoxin poisoning. Vomiting, bradycardia and/or atrioventricular blocks, and increased automaticity can occur. The degree of hyperkalemia correlates with mortality.[33,34] Serum digoxin levels measured by immunoassays may be elevated from cross-reaction with various glycosides similar to digoxin,[33,35] although the reported serum digoxin concentration will not necessarily correlate with toxicity. Digoxin-immune Fab fragments should be administered for the same indications as digoxin poisoning, namely life-threatening dysrhythmias or hyperkalemia.[36] Higher doses may be required for treatment of botanical-induced cardiac glycoside toxicity.[37]

Sodium Channel Openers

Aconitine from monkshood, veratrum alkaloids from hellebores, and grayanotoxins from rhododendrons open voltage-gated sodium channels or prevent sodium channel inactivation.[38-42] The resultant rise in intracellular sodium concentration produces increased vagal tone and automaticity, which resembles cardiac glycoside toxicity, but without hyperkalemia. Veratrum alkaloids and grayanotoxins mainly produce sinus bradycardia and heart blocks with resultant hypotension and syncope.[43,44] Paresthesias and vomiting are also possible. Atropine is usually successful in restoring normal heart rhythm and BP.

In contrast, aconitine poisoning carries the highest mortality and is more likely to produce tachydysrhythmias, including torsade de pointes.[45] Various antidysrhythmic drugs have anecdotally been reported in treatment of aconite-induced ventricular dysrhythmias, including amiodarone and magnesium.

Sodium Channel Antagonists

Taxines, as found in the yew, are alkaloids that inhibit sodium and calcium transport across cell membranes. Following ingestion, intraventricular conduction delays, hypotension, and ventricular dysrhythmias may result.[46] Primary treatment is supportive care. Animal data failed to demonstrate benefit from hypertonic sodium bicarbonate,[47] although a single case report described narrowing of the QRS complex with sodium bicarbonate.[48]

Pyrrolizidine Alkaloids

Various species contain a collection of hepatotoxic pyrrolizidine alkaloids, including groundsel and comfrey.[49] These botanicals are often ingested as herbal preparations, commonly in the form of tea. The alkaloids undergo hepatic metabolism to pyrroles that serve as alkylating compounds.[50] Acute ingestions produce acute liver failure with centrilobular necrosis. In contrast, hepatotoxicity from chronic ingestion is characterized by hepatic microvenoocclusive disease with hepatomegaly, ascites, and jaundice.[49,50] N-acetylcysteine may be beneficial if administered early.[51]

Cyanide Glycosides

Numerous plants contain cyanide glycosides, such as amygdalin, that following ingestion are cleaved by glucosidases to release hydrogen cyanide.[52] Toxicity can result from ingestion of pits from apricots or peaches or from amygdalin purchased as a nutritional supplement.[52-54] After a latency period of minutes to hours, the clinical findings and management are identical to cyanide toxicity due to other causes.[52] The reader is referred to the second part of this series for a discussion on cyanide toxicity.[36]

Antimitotic Agents

Colchicine and podophyllotoxin affect microtubule formation to interfere with cellular function and division. Ingestions produce gastroenteritis and abdominal pain followed by multiple organ system failure and death over hours to days.[55,56] An initial leukocytosis is followed by leukopenia or pancytopenia. Podophyllotoxin is more likely to produce neurotoxicity early, but both groups of toxins can cause coma. Furthermore, rhabdomyolysis, cardiomyopathy, and alopecia can occur with both. Death, if it occurs, is due to either cardiovascular collapse or sepsis, with the latter typically occurring several days later, as a result of pancytopenia from bone marrow suppression. Treatment is supportive and may include granulocyte colony-stimulating factor once pancytopenia develops.[57]

Ackee Poisoning

The unripe ackee fruit contains the toxin hypoglycin A which inhibits β oxidation of fatty acids.[58,59] Ingestion of unripe fruit leads to hepatic microvesicular steatosis, hyperammonemia, metabolic acidosis, hypoglycemia, and secondary carnitine depletion.[58] Vomiting, abdominal pain, hypotonia, seizures, and coma are observed.[58,60,61] In addition to supportive care and correction of hypoglycemia, therapy focuses on providing adequate calories in the form of carbohydrates and possibly the administration of levocarnitine.

Mushrooms

Mushroom poisoning frequently occurs following misidentification of toxic mushrooms as edible species and is responsible for numerous fatalities annually worldwide.[62,63] Table 2[64-77] summarizes the major syndromes. The following discussion emphasizes those most likely to result in admission to an ICU in North America. In general, if the onset of gastrointestinal symptoms occurs > 6 h postingestion the concern for ingestion of hepatotoxic or seizurogenic mushrooms rises. Early vomiting makes systemic toxicity unlikely, with the exception of allenic norleucine-containing mushrooms.[62,63] Ingestion of more than one type of mushroom makes the above rule unreliable.

Cyclopeptides

Amanita phalloides, *Lepiota* species, and *Galerina* species contain amatoxin, which inhibits protein synthesis.[63,78] An asymptomatic latency of > 6 h usually precedes gastroenteritis. Hepatic failure develops within several days. Encephalopathy and convulsions are common in severe cases.[62,63] Histologically, fatty degeneration and centrilobular hepatic necrosis are observed.[79] Despite recommendations for various therapies, none have been examined in well-designed trials. Enterohepatic recirculation of amatoxin might be reduced by the use of a dose of activated charcoal.[64] The early administration of high-dose IV penicillin (1,000,000 units/kg) may be protective, although data are conflicting.[65,66] IV N-acetylcysteine is often administered without consistent evidence.[63,78,79] Silibinin from the milk thistle plant is commonly used in Europe but has been ineffective in at least some animal studies.[63,65,78,80] Liver transplantation may ultimately be required.[81,82]

Gyromitrin

Ingestion of *Gyromitra* species (false morels) results in gastroenteritis beginning several hours postingestion.[83] Monomethylhydrazine inhibits pyridoxal kinase in a manner similar to isoniazid to produce generalized seizures that respond to IV pyridoxine (5 g IV for an adult).[68] Hemolytic anemia and methemoglobinemia may also develop.[63]

Muscimol/Ibotenic Acid

Amanita muscaria (fly agaric), *Amanita pantherina* (panther), and other mushrooms contain muscimol, an agonist at γ aminobutyric acid-A receptors, and ibotenic acid, an agonist of glutamate receptors.[63,67] Ibotenic acid also undergoes decarboxylation to muscimol. Symptoms typically develop shortly after ingestion and include nausea and vomiting and CNS depression or stimulation, depending on the concentrations of ibotenic acid and muscimol. Seizures, ataxia, hallucinations, or somnolence can occur.[63,67,84,85] Treatment is supportive.

Nephrotoxins

Orellanine is a nephrotoxic compound found in *Cortinarius orellanus* and several other species.[63,65,68] Following a latency period of up to 3 weeks, patients

Table 1—*Common Toxic Plants*

System Involved	Syndrome	Common Name	Genus	Signs and Symptoms
CNS[a]	Anticholinergic[b]	Jimsonweed	*Datura*	CNS excitation
		Angel's trumpet	*Brugmansia*	CNS depression
		Deadly nightshade	*Atropa*	Mydriasis
		Black henbane	*Hyoscyamus*	Mumbling speech
		Mandrake	*Mandragora*	Picking behavior
				Dry skin
				Tachycardia
				Urinary retention
	Nicotinic[b]	Tobacco	*Nicotiana*	Hypertension or hypotension
		Poison hemlock	*Conium*	Tachycardia or bradycardia
		Betel nut	*Areca*	Vomiting/diarrhea
		Blue cohosh	*Caulophyllum*	Muscle fasciculations
		Golden chain tree	*Laburnum*	Seizures
		Kentucky coffee tree	*Gymnocladus*	Paralysis
		Mescal bean bush	*Sophora*	Coma
	Hallucinogenic[b]	Morning glory	*Ipomoea*	Hallucinations
		Nutmeg	*Myristica*	
		Marijuana	*Cannabis*	
		Peyote	*Lophophora*	
		Ibogaine	*Tabernanthe iboga*	
		Khat	*Cathus*	
	Sedating[a]	Poppy	*Papaver*	Sedation
	Paralyzing[c]	Yellow jessamine	*Gelsemium*	Weakness
	Epileptogenic[b,d]	Strychnine	*Strychnos*	Twitching
		Water hemlock	*Cicuta*	Seizures
		Wild wisteria	*Securidaca*	Hyperreflexia
		Myrtle-leaved coriaria	*Coriaria*	GI distress
				Altered mental status
Cardiovascular[a]	Na^+,K^+ ATPase inhibitors	Foxglove	*Digitalis*	GI distress
		Common oleander	*Nerium*	Visual changes
		Yellow oleander	*Thevetia*	Altered mental status
		Squill	*Urginea*	Dysrhythmias
		Sea mango	*Cerbera*	Hypotension
		Lily of the valley	*Convallaria*	Hyperkalemia
		Ouabain	*Strophanthus*	
		King's crown	*Calotropis*	
	Sodium channel openers[c]	Monkshood	*Aconitum*	GI distress
		Hellebore	*Veratrum*	Visual disturbances
		Death camas	*Zigadenus*	Paresthesias
		Rhododendron	*Rhododendron*	Altered mental status
		Azaleas	*Rhododendron*	Weakness/paralysis
				Dysrhythmias
				Hypotension
	Na^+ and Ca^+ transport inhibitors	Yew	*Taxus*	GI distress
				Altered mental status
				Dysrhythmias
				Widening of QRS
				Hypotension
Oral and GI[e]	Oral irritants	Philodendron	*Philodendron*	Hypersalivation
		Dumb cane	*Dieffenbachia*	Oropharyngeal edema
		Peace lily	*Spathiphyllum*	Vesicles
		Elephant's ear	*Colocasia*	Dysphagia
		Giant elephant's ear	*Alocasia*	Aphonia
				Airway compromise
	GI irritants	Chinaberry tree	*Melia*	GI distress
		Nightshade	*Solanum*	Neurologic symptoms
		Pokeweed[f]	*Phytolacca*	Vomiting
				Foamy diarrhea
				Dehydration

(Continued)

Table 1—*Continued*

System Involved	Syndrome	Common Name	Genus	Signs and Symptoms
				Altered mental status
				Plasmablasts
				Proplasmacytes
	Protein synthesis inhibitors	Castor bean	*Ricinus*	GI distress
		Rosary pea	*Abrus*	Dehydration
		Purging nut	*Jatropha*	Elevated liver enzymes
		Black locust	*Robinia*	multiorgan failure
	Hepatotoxins	Groundsel	*Senecio*	Venoocclusive disease
		Gordolobo	*Senecio*	Hepatomegaly
		Tansy ragwort	*Senecio*	Jaundice
		Comfrey	*Symphytum*	
		Mate	*Ilex*	
		Rattlebox	*Crotalaria*	
Renal	Oxalates	Rhubarb	*Rheum*	Hypokalemia
		Sorrel	*Rumex*	Tetany
				Renal failure
	Other	Aloe	*Aloe*	Renal insufficiency
		Birthwort	*Aristolochia*	Renal failure
		Djenkol bean	*Pithecolobium*	
		Oduvan	*Cleistanthus*	
Hematopoietic	Anticoagulating	Yellow sweet clover	*Melilotus*	Bleeding
		Tonka bean	*Coumarouna*	
		Woodruff	*Galium*	
	Bone marrow inhibitors	Autumn crocus	*Colchicum*	GI distress
		Christmas bells	*Sandersonia*	Dehydration
		Glory lily	*Gloriosa*	Pancytopenia
		Podophyllum	*Podophyllum*	Weakness
	Hemolytic	Fava bean	*Vicia*	Hemolysis
				Hemoglobinuria
				Anemia
				Jaundice
Endocrine and metabolic	Hypoglycemia inducers[d]	Ackee fruit	*Blighia*	Vomiting
		Wild yams	*Dioscorea*	Seizures
		Cocklebur	*Xanthium*	Hypoglycemia
		Bird-lime	*Atractylis*	Metabolic acidosis
		Ox-eye daisy	*Callilepis*	Liver disease
	Mineralocorticoid inducers	Licorice	*Glycyrrhiza*	Hypertension
				Edema
				Weakness
				Rhabdomyolysis
				Hypokalemia
	Cyanogenic	Apple seed	*Malus*	GI distress
		Cherry pits	*Prunus*	Bitter almond breath
		Peach pits	*Prunus*	Agitation/seizures
		Plum pits	*Prunus*	Coma
		Apricot pits	*Prunus*	Metabolic acidosis
				Dysrhythmias

[a] Many plants that affect the CNS and cardiovascular system can result in sedation and seizures.
[b] Anticholinergic and nicotinic plants can be hallucinogenic and epileptic.
[c] Cardiovascular agents that open sodium channels may also produce weakness or paralysis.
[d] Hypoglycemic agents are also epileptic.
[e] The majority of toxic plants cause some GI distress.
[f] Also a hematopoietic poison.

develop interstitial nephritis with tubular necrosis.[65,68] Treatment may require hemodialysis, with almost half of those requiring early dialysis developing chronic renal failure.[63]

In the northwestern United States, ingestion of *Amanita smithiana* or *Amanita abrupta*, which contain allenic norleucine, has produced early gastrointestinal symptoms followed by renal failure several days later.[63] Hemodialysis is often required. The potential for early-onset gastroenteritis is an important exception to the general rule that more serious mushroom poisoning results in delayed GI symptoms.

Table 2—*Mushroom Toxicity Classification*

Toxin or Syndrome (Mushroom Species Examples)	Characteristic Toxicity	GI Distress	Symptom Onset	Potential Severity	Treatment
Cyclopeptides (*Amanita*, *Galerina*, and *Lepiota* species)	Hepatic failure, renal failure, encephalopathy, seizures	Can be severe, but delayed (occasionally bloody)	5-24 h	++++	Reportedly used: activated charcoal; high-dose penicillin G; N-acetylcysteine, Silibinin; liver transplantation
Nephrotoxins (*Cortinarius* species)	Nephrotoxicity	Generally mild; may be absent	1-20 d	+++	Hemodialysis, kidney transplantation
(*Amanita smithiana*)	Nephrotoxicity	Mild to moderate	0.5-12 h	+++	Hemodialysis
Gyromitrin (*Gyromitra esculenta* and other species)	Seizures, ataxia, coma, mild to moderate hepatotoxicity, hemolysis, methemoglobinemia	Occasionally bloody	5-12 h when eaten; as soon as 2 h if inhaling steam from cooking	+++	Pyridoxine for seizures; methylene blue for methemoglobinemia
Muscarine (*Inocybe*, *Clitocybe*, *Boletus*, and *Robinoboletus* species)	Cholinergic syndrome	Present	15 min to 5 h	+++	Atropine for moderate to severe illness
Muscimol/Ibotenic acid (*Amanita muscaria*, *Amanita pantherina*)	CNS excitation or depression; hallucinations	May occur	30 min to 3 h	++	Supportive care
GI (*Chlorophyllum molybdites*, *Omphalotus illudens*, and others)	Nausea, vomiting, abdominal pain, diarrhea	Mild to marked (occasionally bloody)	30 min to 3 h	++	Supportive care
Disulfiramlike reactions (*Coprinus* species)	Ethanol intolerance	Flushing, tachycardia, nausea/vomiting after ethanol ingestion	15-30 min after ethanol ingestion	++	Supportive care
Hemolytic anemia (*Paxillus involutus*)	Hemolytic anemia, followed by acute renal failure or multiple organ dysfunction	Present	30 min to 3 h	+++	Plasma exchange, hemodialysis
Rhabdomyolysis (*Tricholoma* species)	Rhabdomyolysis with involvement of myocardium; secondary renal failure	Sometimes	24-72 h after last mushroom meal	++++	Supportive care

Data from References 64-77.

Miscellaneous

Hallucinogenic mushrooms, including *Psilocybe* species, contain an indole hallucinogen. The illness is rarely life threatening and treatment is supportive.[86]

Coprinus (inky caps) and *Boletus* species contain a toxin that inhibits acetaldehyde dehydrogenase. Although co-ingestion of alcohol with the mushrooms usually is tolerated without problems, the ingestion of alcohol hours to days later results in disulfiram-like reactions, with flushing, diaphoresis, vomiting, headache, and tachycardia. The illness is usually mild and treatment is supportive.[87]

Metals

Lead

Although the overall prevalence of lead toxicity is declining, this condition remains an important health concern throughout the United States and worldwide. Most cases of lead toxicity result from chronic toxicity, rather than single acute ingestion. Single, acute toxic lead ingestions are rare, but can result in diarrhea, hemolysis, hepatic necrosis, encephalopathy, and renal failure.[88]

More commonly, patients present with relatively acute onset of signs and symptoms from previously unrecognized chronic lead poisoning.[89] For example, the ingestion of elemental lead objects (eg, curtain weights), can cause delayed, life-threatening poisoning.[88] Chronic poisoning can produce anemia, abdominal pain, malaise, renal failure, and encephalopathy.[90-94] Radiographs in children may demonstrate "lead lines" in bones, which represent areas of increased calcium density, not lead deposition. Retained bullets do not produce lead poisoning unless fragments are in prolonged contact with synovial fluid, pleural fluid, or cerebrospinal fluid.[95-98]

When evaluating patients for lead toxicity, a capillary blood concentration can be used only for screening but is notoriously inaccurate and should not be used for treatment decisions. Only whole blood lead concentrations should be used when deciding on a management strategy. In situations in which chronicity is not able to be established, free erythrocytic protoporphyrin (FEP) and zinc protoporphyrin (ZPP) concentrations can be helpful. Chronic toxicity will have elevated FEP and ZPP, whereas acute toxicity will have normal FEP and ZPP.[99]

The ideal therapy involves interpreting the patient's whole blood lead concentration in context with the patient's age and clinical symptoms. The Centers for Disease Control and Prevention publishes guidelines to assist in deciding appropriate treatment of these patients. In asymptomatic patients with only moderately elevated lead concentration, chelation is not necessarily recommended. For cases in which chelation is recommended, however, 2, 3-mesodimercaptosuccinic acid (succimer), or dimercaprol and calcium disodium ethylene diamine tetraacetic acid may be used.[93,100]

Treatment of Lead Encephalopathy: In addition to supportive care (eg, benzodiazepines or barbiturates for convulsions, treatment of intracranial hypertension), chelation therapy is usually begun with dimercaprol 75 mg/m^2 deep intramuscular injection every 4 h for 5 days. At least 4 h following administration of dimercaprol, calcium disodium ethylene diamine tetraacetic acid 1,500 mg/m^2 IV per day (continuous infusion or over two to four divided doses) should be commenced, and continued for at least 5 days.[96] Nephrotoxicity can occur as a result of the chelators.[101]

Iron

Although packaging laws have reduced the incidence of accidental ingestions of iron in children,[102] acute iron toxicity remains a common problem in both adults and children.[1] Iron exists in many formulations, with ferrous fumarate, sulfate, and gluconate being three of the most common preparations. These ferrous salts contain 33%, 20%, and 12% elemental iron, respectively. The risk for acute toxicity of iron correlates with the amount of elemental iron ingested. Significant, life-threatening toxicity is unlikely with ingestions < 60 mg/kg,[103] but histories of amounts ingested are commonly inaccurate.

Following acute ingestion, iron absorption occurs via receptor-dependent and receptor-independent processes.[104] Toxicity is classically described as occurring in four stages. The first stage occurs within 6 h of ingestion and is characterized by vomiting, diarrhea, and abdominal pain.[105] Stage II is classically described as a quiescent period due to resolution of gastrointestinal illness, although metabolic acidosis can progress. Stage III is characterized by multisystem organ failure.[105] Patients who survive stage III may develop bowel obstructions or gastric outlet obstruction (stage IV).[104]

The decision to start therapy should be based on the clinical and metabolic findings and not strictly based on the serum iron concentration.[105] Patients should first undergo aggressive crystalloid fluid resuscitation. Patients with significant symptoms, including repeated vomiting or diarrhea, CNS depression, metabolic acidosis, or hypotension should undergo chelation with IV deferoxamine mesylate. Although outcome data on whole bowel irrigation are lacking, its use can be considered in significant iron ingestions.[106]

North American Arthropods

Bark Scorpion (Centruroides sculpturatus)

In North America, *Centruroides sculpturatus* is the only species that produces systemic human toxicity.[107] The venom consists of neurotoxins that prevent sodium channel inactivation leading to repetitive axonal firing.[107,108] The clinical effects of cholinergic, adrenergic, and neuromuscular findings are graded on a scale (Table 3).[107,109]

Following envenomation, immediate onset of painful burning and paresthesias in the affected area is common.[109] Severe cases advance to cranial nerve dysfunctions, including opsoclonus, tongue fasciculations, hypersalivation, thrashing, and loss of pharyngeal muscle control.[107,109] Emesis is typically self-limited, but aspiration and difficulties with oral secretions are possible.

Supportive care is the cornerstone of treatment. Most patients with low-grade envenomations respond to analgesics alone. Those patients with high-grade envenomations may benefit from short-acting parenteral opioids (eg, fentanyl 1-2 μg/kg) and sedative hypnotics (eg, midazolam 0.01-0.05 mg/kg).[107,108] Atropine can be used to help control significant hypersalivation.[110,111] However, the hypersalivation that is observed is typically transient; repeated doses of atropine are unlikely to be beneficial and have the potential to cause anticholinergic toxicity. Deaths rarely occur because of advancements in supportive care. However, they may result from respiratory failure. Loss of airway protection is particularly problematic in children who manifest hypersalivation and pharyngeal motor dysfunction. Endotracheal intubation may be required. A polyvalent $F(ab')_2$ antivenom is currently used successfully in both the United States and Mexico.[112] Without antivenom, severe symptoms may persist for 24 h.

Spiders

Although there are nearly 42,000 spider species worldwide,[113] the vast majority of envenomations in the United States are benign because of short fang length, insufficient venom volume, or lack of physiologic human effect. Definitive diagnosis of envenomation typically requires both a witnessed bite and a properly identified species known to cause the observed syndrome.[114]

Table 3—*Grading of Bark Scorpion* (Centruroides sculpturatus) *Envenomation*

Grade one	Pain and/or paresthesias local to sting site
Grade two	Pain and/or paresthesias remote from sting site
Grade three	Either cranial nerve or somatic skeletal neuromuscular dysfunction
Grade four	Both cranial nerve and somatic skeletal neuromuscular dysfunction

Each grade may involve any or all lower grade findings. (Data from Curry et al.[107])

Brown Recluse (Loxosceles reclusa)*: Loxosceles reclusa* is a small brown spider that is generally active at night and only bites defensively.[108,115,116] Figure 1[117] demonstrates a geographical distribution of spiders in the *Loxosceles* genus. Hyaluronidase and sphingomyelinase D are primary components of the venom. These result in prostaglandin release, activation of complement, platelet aggregation, and enhanced neutrophil chemotaxis.[108,114-116] Enzyme-linked immunosorbent assays of wound toxin have been studied but are not readily available.[115,118]

Most envenomations are self-limited, but clinical effects range from local erythema to large ulcerative lesions.[114] Sharp, burning pain begins within several hours. Dermal lesions progresses over days to form a central, hemorrhagic area that degrades to necrosis and ulceration.[108,114,115] The resulting eschar may dehisce and take several weeks to heal. Early surgical interventions following the formation of necrosis are unlikely to affect outcome.[116] Viscerocutaneous loxoscelism occurs in $<1\%$ of cases and is characterized by arthralgias, fever, vomiting and diarrhea, rhabdomyolysis, and hemolysis.[114,116] Although rare, fatalities are usually related to cardiovascular collapse and hemolysis.[115]

Although treatment is conservative, it is imperative to not misdiagnose an alternative condition (eg, skin infection, granulomatous disease, autoimmune skin lesion, and so forth) as *Loxosceles* envenomation. Furthermore, it is important to realize that not all necrotic skin lesions, including those associated with an arthropod envenomation, are caused by the brown recluse. Other arthropod species can cause dermonecrotic lesions.[114,116] In addition, many necrotic skin lesions are incorrectly attributed to arthropods. One such example involves the hobo spider (*Tegenaria agrestis*) in the Pacific Northwest.[118,119]

Treatment is largely supportive. Early surgical excision is contraindicated, but delayed debridement or grafting may be required depending on cosmetic outcome.[108,114,116] Close outpatient follow-up for wound progression is recommended.[108] Dapsone, corticosteroids, prophylactic antibiotics, hyperbaric oxygen, vasodilators, colchicine, and antihistamines lack supporting data and are not indicated.

Black Widow (Latrodectus mactans)*:* Of the many widow spiders species worldwide, *Latrodectus mactans* is the most clinically significant in North America.[120] α-Latrotoxin results in diffuse neurotransmitter release, including acetylcholine and norepinephrine.[114,120,121]

FIGURE 1. US geographic distribution of verified widespread populations of six native *Loxosceles* species. (Reprinted with permission from Swanson and Vetter[117]).

The initial bite is usually painful, and presence of a "target lesion" is a fairly reliable indicator of widow envenomation.[121] This lesion is characterized by a central area of pallor surrounded by erythematous rings, resembling a target. Twenty-five percent of envenomations progress to a systemic syndrome of latrodectism within 2 h. Latrodectism consists of severe pain and muscle spasms involving the back, abdomen, and chest, which may wax and wane. Hypertension, tachycardia, and diaphoresis are commonly seen. The muscle spasms and diaphoresis can be diffuse or localized to the site of the bite.[114,121] Other effects include fever, priapism, paresthesias, fasciculations, and agitation.[114,121] Acute cardiomyopathy complicated by pulmonary edema has been reported.[122] No *Latrodectus*-related deaths have been reported to US poison centers in several decades.[123]

Treatment consists of supportive care, with titration of opioids and benzodiazepines.[114,121] Calcium gluconate is not beneficial and is not recommended.[121] A whole IgG antivenom is available but can lead to immediate or delayed (serum sickness) allergic reactions.[118] Discussion with a medical toxicologist is recommended prior to using antivenom.

Bees and Wasps (Order Hymenoptera)

Honeybee and wasp stings may cause severe allergic reaction, but toxicity is generally limited to massive envenomations involving hundreds of stings. Envenomation preferentially occurs about the head and neck, with intraoral stings being common.[124] Honey bees have a barbed stinger that remains in tissue leading to evisceration after a single sting, whereas wasps are capable of stinging repeatedly. Both species contain similar toxins with similar clinical syndromes. Melittin and phospholipase A_2 are the primary venom toxins, with phospholipase A_2 being the major allergen.[124,125]

Excluding an immediate anaphylactic reaction, most envenomations are limited to local cutaneous reactions with erythema, pruritus, edema, and pain. Systemic reactions after massive envenomation may include emesis, diarrhea, fever, and myalgias. Significant third-spacing edema with hypotension or shock can occur. Coagulopathy, transaminitis, rhabdomyolysis, and hemolysis may develop within hours.[124,126] Clinically, the symptoms observed with massive envenomation may resemble an IgE-mediated anaphylactic event. However, unlike a patient with an anaphylactic event, the patient with a massive envenomation may develop delayed toxicity over the first 24 h.

Treatment is supportive with IV fluids, systemic steroids, antihistamines, and analgesics. Retained stings may be removed but should not be the focus of initial management as the timing of removal does not change outcome.[127] All patients with evidence of systemic envenomation, significant comorbidities, >50 stings (adult), or more than two stings per kilogram (children) should be evaluated for admission. Serial laboratory studies, including creatinine kinase, electrolytes, renal function, coagulation studies, and electrocardiograms, should be followed during the first 24 h. Cardiac enzymes should be obtained in critically ill individuals. Patients with evidence of systemic toxicity should receive parenteral antihistamines and steroids.

NORTH AMERICAN SNAKES

Nearly 5,000 patients present to EDs each year with venomous snake bites; many of these patients are admitted to ICUs.[128] Although the diagnosis is more common in southern and rural areas, bites may occur in any city or state, partly due to the practice of keeping venomous snakes as pets.

Most envenomations in the United States follow encounters with pit vipers, which include rattlesnakes, copperheads, and cottonmouths. Rattlesnakes account for roughly one-half of reported pit viper envenomations and are responsible for the greatest morbidity and mortality due to native snake envenomation. Coral snakes and a variety of nonnative venomous snake species cause <5% of envenomations.[1]

Approximately 25% of pit viper bites result in no venom deposition. In the remainder, venom is usually deposited subcutaneously, resulting in a wide spectrum of clinical severity ranging from mild local effects, which resolve quickly, to immediate systemic toxicity and death. Where one falls on the spectrum is largely influenced by venom load and potency.[129] Venom contains proteins that may possess cytotoxic, hemotoxic, neurotoxic, and/or myotoxic properties.[130,131] Clinically important components in native venoms are

those that destroy tissue, produce capillary permeability and edema, inhibit platelets and fibrinogen, and produce anaphylactoid reactions and neurotoxicity.

Following envenomation, edema and pain typically develop within minutes to a few hours, although onset may be delayed, particularly in lower extremity bites. Puncture wounds are visible and hemorrhagic bullae may develop within hours and progress for days. As venom is absorbed via lymphatics, edema increases and tenderness of proximal lymph nodes develops. Tachycardia, vomiting, paresthesias, fasciculations, diarrhea, and hypotension may occur. Although some symptoms may be related to anxiety, early systemic symptoms should alert the clinician to the possibility of a severe envenomation, which may progress quickly or herald an anaphylactoid response to venom, with pending oropharyngeal angioedema or shock. True anaphylaxis may also occur in patients with preformed IgE antibodies against venom proteins. When neurotoxic effects occur, they often include only fasciculations or paresthesias, but some patients bitten by Mojave rattlesnakes may develop ptosis, weakness, and respiratory failure. Although very uncommon, patients may develop life-threatening bleeding. Rarely, true disseminated intravascular coagulation has occurred and has been associated with direct intravascular injection of venom.[129,132]

Any patient presenting with signs of envenomation should be admitted to the hospital. Patients without swelling should be observed at least 8 h, since even swelling that is delayed in onset may become significant. Some experts opt to admit all children with leg bites for overnight observation regardless of presence of swelling. Constrictive dressings are not recommended, and if placed in the field, should be removed immediately. Prophylactic antibiotics are not indicated. The bitten extremity may be immobilized with a posterior splint and placed in near full extension to avoid increased edema and pain at the joint flexure. The extremity should be elevated as much as possible to avoid dependent edema, and the circumference monitored frequently (at least every 30-60 min) to determine if swelling is progressing.

All patients should receive IV fluid boluses and have their tetanus vaccine updated, if warranted based on the vaccination history. Hemoconcentration and intravascular hypovolemia are common because of venom-induced capillary permeability. Treatment of hypotension may require many boluses of crystalloid. If blood pressure does not respond rapidly, an epinephrine infusion should be initiated. Patients with anaphylactoid reactions resulting in angioedema or those with bites to the head or neck should be intubated at the first sign of facial, tongue, or airway swelling. Hypersensitivity reactions are treated with steroids, antihistamines, and epinephrine.

Hematotoxicity is most common following rattlesnake envenomation, but may occur with any native pit viper envenomation. Initial laboratory studies should include a complete blood count, fibrinogen, and prothrombin time. Unstable patients should also have electrolytes, renal function, and creatine kinase measured. Thrombocytopenia, hypofibrinogenemia, and coagulopathy may develop quickly, but even when severe, rarely represent disseminated intravascular coagulation, as incomplete degradation of fibrinogen by thrombinlike enzymes in venom leads to a poorly formed fibrin clot and coagulation does not occur.[130,133] If initial studies and physical examination are normal, the patient may have a "dry bite," in which the patient is bitten, but no venom is injected. In such cases, the laboratory studies should be repeated in 6 h, while observation for swelling continues. Patients with mild swelling without other findings should be observed 12 to 24 h to monitor for progression.

Unstable patients should be treated with antivenom. In a stable patient, the decision to treat with antivenom is based on presence of swelling that is progressing, hematotoxicity, or systemic toxicity. Crotalidae Polyvalent Immune Fab (ovine) (CroFab) is the only available antivenom approved for treatment of pit viper envenomation in the United States. When indicated, CroFab should be administered as soon as possible, as it can stop progression of swelling and reverse hematotoxicity. Dosing can be complex and is beyond the scope of this review, but a treatment algorithm is available.[134] In general, an initial dose of four to six vials in stable patients or eight to 12 vials in unstable patients is appropriate. No pediatric dose adjustments are needed. Pregnant women appear to be at increased risk of death following snake bite, and the abortion rate is high,[135] so CroFab should not be withheld due to its class C categorization. It is important to monitor for acute hypersensitivity reactions to CroFab, which are reported in 5.4% of patients.[136] Most reactions are rate-related, and after treatment with antihistamines and resolution of symptoms, CroFab infusion can often be completed at a slower rate.

Patients with severe venom-induced thrombocytopenia and coagulopathy may exhibit minor bleeding from puncture wounds. These laboratory abnormalities do not require administration of blood products. If blood products are given to treat severe hemorrhage, it is critical that antivenom also be administered. Critical platelet, fibrinogen, or prothrombin values alone are not indications for blood products in the setting of pit viper envenomation.

Extremity edema can be impossible to distinguish clinically from compartment syndrome, due to exquisite pain and tenderness, paresthesias and decreased

sensation in tense digits, and pulses that are difficult to palpate. Nonetheless, true compartment syndrome following North American pit viper envenomation remains very rare. Fasciotomy should not be performed without first measuring and confirming elevated compartment pressures. Even if pressures moderately exceed 30 mm Hg, some authorities advocate management with further antivenom, elevation, and reassessment in a few hours. If pressures fail to decrease within several hours, fasciotomy may be required.[137] The authors recommend consulting an envenomation specialist if deciding whether to perform fasciotomy.

In the days following the bite, hemorrhagic bullae often expand. Debridement should be performed as it allows for pain relief and evaluation of underlying tissue. If significant necrosis is evident, consultation with a surgeon is recommended as further debridement in the operating room, eventual skin grafting, or even amputation may be necessary. It is important to inform patients from the outset that early antivenom administration does not prevent tissue necrosis or the possibility of loss of a digit.

Another important subacute problem is that of recurrence. In the first 36 h following CroFab administration, patients may develop increased extremity swelling. This is expected when the extremity is dependent, but if swelling increases despite elevation, additional antivenom may be needed. Late hematotoxicity (in which patients may develop severe thrombocytopenia or coagulopathy days after treatment, even if these were not present during the initial treatment) is common and potentially serious. For this reason, all patients treated with CroFab should have platelets and fibrinogen assessed 2 to 4 days and again 5 to 7 days after antivenom.[138] Discharge instructions should advise to monitor for bleeding; avoid aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), or antiplatelet and anticoagulant drugs; and avoid surgical or dental procedures for at least 2 weeks following the bite. Management of late or recurrent hematotoxicity should be discussed with an envenomation expert, as retreatment decisions are based on many factors. Patients should also be advised that serum sickness may develop up to 3 weeks following antivenom and is treated with steroids and antihistamines.

Coral snake envenomations differ from those inflicted by pit vipers in that they produce isolated neurotoxicity. Since the venom does not possess cytotoxic or hemotoxic components, local effects do not occur and hematologic studies are normal. Any patient reporting a coral snake bite (except from the Sonoran coral snake) should be observed for 24 h, as puncture wounds are not always visible and neurotoxic effects, including paresthesias, ptosis, weakness, and respiratory failure, may be delayed. Care is supportive, with intubation and mechanical ventilation should symptoms of neurotoxicity, such as diplopia or dysarthria, develop. Rhabdomyolysis should be ruled out. North American Coral Snake Antivenom (Pfizer; New York, New York) is no longer produced, and remaining supplies are limited. If available, patients should be treated with a starting dose of four vials at the first sign of envenomation, to prevent progression of symptoms.[139,140]

Decisions regarding management of snake envenomation are affected by a variety of factors, including species, specific venom effects, and availability of appropriate antivenom. Clinicians are advised to contact the poison center (in the United States, 1-800-222-1222) to discuss all cases of snake bite with a specialist.

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References

1. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. *Clin Toxicol (Phila)*. 2009;47(10):911-1084.
2. Lin TJ, Nelson LS, Tsai JL, et al. Common toxidromes of plant poisonings in Taiwan. *Clin Toxicol (Phila)*. 2009;47(2):161-168.
3. Caksen H, Odaba D, Akbayram S, et al. Deadly nightshade (Atropa belladonna) intoxication: an analysis of 49 children. *Hum Exp Toxicol*. 2003;22(12):665-668.
4. Greene GS, Patterson SG, Warner E. Ingestion of angel's trumpet: an increasingly common source of toxicity. *South Med J*. 1996;89(4):365-369.
5. Isbister GK, Oakley P, Dawson AH, Whyte IM. Presumed Angel's trumpet (Brugmansia) poisoning: clinical effects and epidemiology. *Emerg Med (Fremantle)*. 2003;15(4):376-382.
6. Pekdemir M, Yanturali S, Akay S, Alagoz G. Acute anticholinergic syndrome due to Datura innoxia Miller mixed with lime tea leaves. *Vet Hum Toxicol*. 2004;46(4):176-177.
7. Piccillo GA, Mondati EG, Moro PA. Six clinical cases of Mandragora autumnalis poisoning: diagnosis and treatment. *Eur J Emerg Med*. 2002;9(4):342-347.
8. Schneider F, Lutun P, Kintz P, Astruc D, Flesch F, Tempé JD. Plasma and urine concentrations of atropine after the ingestion of cooked deadly nightshade berries. *J Toxicol Clin Toxicol*. 1996;34(1):113-117.
9. Southgate HJ, Egerton M, Dauncey EA. Lessons to be learned: a case study approach. Unseasonal severe poisoning of two adults by deadly nightside *(Atropa belladonna)*. *J R Soc Promot Health*. 2000;120(2):127-130.
10. Krenzelok EP. Aspects of Datura poisoning and treatment. *Clin Toxicol (Phila)*. 2010;48(2):104-110.
11. Centers for Disease Control and Prevention (CDC). Jimson weed poisoning—Texas, New York, and California, 1994. *MMWR Morb Mortal Wkly Rep*. 1995;44(3):41-44.

12. Ertekin V, Selimoğlu MA, Altinkaynak S. A combination of unusual presentations of Datura stramonium intoxication in a child: rhabdomyolysis and fulminant hepatitius. *J Emerg Med*. 2005;28(2):227-228.
13. DeFrates LJ, Hoehns JD, Sakornbut EL, Glascock DG, Tew AR. Antimuscarinic intoxication resulting from the ingestion of moonflower seeds. *Ann Pharmacother*. 2005; 39(1):173-176.
14. Biberci E, Altuntas Y, Cobanoglu A, Alpinar A. Acute respiratory arrest following hemlock (Conium maculatum) intoxication. *J Toxicol Clin Toxicol*. 2002;40(4):517-518.
15. Schep LJ, Slaughter RJ, Beasley DM. Nicotinic plant poisoning. *Clin Toxicol (Phila)*. 2009;47(8):771-781.
16. West PL, Horowitz BZ, Montanaro MT, Lindsay JN. Poison hemlock-induced respiratory failure in a toddler. *Pediatr Emerg Care*. 2009;25(11):761-763.
17. Boucher BJ, Mannan N. Metabolic effects of the consumption of Areca catechu. *Addict Biol*. 2002;7(1):103-110.
18. Chiang WT, Yang CC, Deng JF, Bullard M. Cardiac arrhythmia and betel nut chewing—is there a causal effect? *Vet Hum Toxicol*. 1998;40(5):287-289.
19. Deng JF, Ger J, Tsai WJ, Kao WF, Yang CC. Acute toxicities of betel nut: rare but probably overlooked events. *J Toxicol Clin Toxicol*. 2001;39(4):355-360.
20. Huang Z, Xiao B, Wang X, Li Y, Deng H. Betel nut indulgence as a cause of epilepsy. *Seizure*. 2003;12(6):406-408.
21. Lin SH, Lin YF, Cheema-Dhadli S, Davids MR, Halperin ML. Hypercalcaemia and metabolic alkalosis with betel nut chewing: emphasis on its integrative pathophysiology. *Nephrol Dial Transplant*. 2002;17(5):708-714.
22. Nelson BS, Heischober B. Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Ann Emerg Med*. 1999;34(2):238-243.
23. Schep LJ, Slaughter RJ, Becket G, Beasley DM. Poisoning due to water hemlock. *Clin Toxicol (Phila)*. 2009;47(4):270-278.
24. Graeme KA, Kunkel DB. Psychoactive plants and mushrooms. *Top Emerg Med*. 1997;19(4):64.
25. Furbee RB, Curry SC, Kunkel DB. Ingestion of Argyreia nervosa (Hawaiian baby woodrose) seeds. *Vet Hum Toxicol*. 1991;33(4):370.
26. Sjöholm A, Lindberg A, Personne M. Acute nutmeg intoxication. *J Intern Med*. 1998;243(4):329-331.
27. González-Maeso J, Weisstaub NV, Zhou M, et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron*. 2007;53(3):439-452.
28. Centers for Disease Control and Prevention (CDC). Water hemlock poisoning—Maine, 1992. *MMWR Morb Mortal Wkly Rep*. 1994;43(13):229-231.
29. Philippe G, Angenot L, Tits M, Frédérich M. About the toxicity of some Strychnos species and their alkaloids. *Toxicon*. 2004;44(4):405-416.
30. Burn DJ, Tomson CR, Seviour J, Dale G. Strychnine poisoning as an unusual cause of convulsions. *Postgrad Med J*. 1989;65(766):563-564.
31. Newman LS, Feinberg MW, LeWine HE. Clinical problem-solving. A bitter tale. *N Engl J Med*. 2004;351(6):594-599.
32. Bandara V, Weinstein SA, White J, Eddleston M. A review of the natural history, toxinology, diagnosis and clinical management of Nerium oleander (common oleander) and Thevetia peruviana (yellow oleander) poisoning. *Toxicon*. 2010;56(3):273-281.
33. Eddleston M, Ariaratnam CA, Sjöström L, et al. Acute yellow oleander (Thevetia peruviana) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. *Heart*. 2000;83(3):301-306.
34. Eddleston M, Ariaratnam CA, Meyer WP, et al. Epidemic of self-poisoning with seeds of the yellow oleander tree (Thevetia peruviana) in northern Sri Lanka. *Trop Med Int Health*. 1999;4(4):266-273.
35. Dasgupta A, Risin SA, Reyes M, Actor JK. Rapid detection of oleander poisoning by Digoxin III, a new Digoxin assay: impact on serum Digoxin measurement. *Am J Clin Pathol*. 2008;129(4):548-553.
36. Brooks DE, Levine M, O'Connor AD, French RNE, Curry SC. Toxicology in the ICU: part 2: specific toxins. *Chest*. 2011;140(4):1072-1085.
37. Eddleston M, Rajapakse S, Rajakanthan K, et al. Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. *Lancet*. 2000;355(9208):967-972.
38. Chan TY. Aconite poisoning. *Clin Toxicol (Phila)*. 2009; 47(4):279-285.
39. Schep LJ, Schmierer DM, Fountain JS. Veratrum poisoning. *Toxicol Rev*. 2006;25(2):73-78.
40. Rauber-Luthy C, Halbsguth U, Kupferschmidt H, et al. Low-dose exposure to Veratrum albumin in children causes mild effects: a case series. *Clin Toxicol*. 2010;48(3):234-237.
41. West P, Horowitz BZ. Zigadenus poisoning treated with atropine and dopamine. *J Med Toxicol*. 2009;5(4):214-217.
42. Gunduz A, Turedi S, Russell RM, Ayaz FA. Clinical review of grayanotoxin/mad honey poisoning past and present. *Clin Toxicol (Phila)*. 2008;46(5):437-442.
43. Yilmaz O, Eser M, Sahiner A, Altintop L, Yesildag O. Hypotension, bradycardia and syncope caused by honey poisoning. *Resuscitation*. 2006;68(3):405-408.
44. Carlier P, Efthymiou ML, Garnier R, Hoffelt J, Fournier E. Poisoning with Veratrum-containing sneezing powders. *Hum Toxicol*. 1983;2(2):321-325.
45. Leichter D, Danilo P Jr, Boyden P, Rosen TS, Rosen MR. A canine model of torsades de pointes. *Pacing Clin Electrophysiol*. 1988;11(12):2235-2245.
46. Pietsch J, Schulz K, Schmidt U, Andresen H, Schwarze B, Dressler J. A comparative study of five fatal cases of Taxus poisoning. *Int J Legal Med*. 2007;121(5):417-422.
47. Ruha AM, Tanen DA, Graeme KA, et al. Hypertonic sodium bicarbonate for Taxus media-induced cardiac toxicity in swine. *Acad Emerg Med*. 2002;9(3):179-185.
48. Pierog J, Kane B, Kane K, Donovan JW. Management of isolated yew berry toxicity with sodium bicarbonate: a case report in treatment efficacy. *J Med Toxicol*. 2009;5(2): 84-89.
49. Chen Z, Huo JR. Hepatic veno-occlusive disease associated with toxicity of pyrrolizidine alkaloids in herbal preparations. *Neth J Med*. 2010;68(6):252-260.
50. Fu PP, Xia Q, Lin G, Chou MW. Pyrrolizidine alkaloids—genotoxicity, metabolism enzymes, metabolic activation, and mechanisms. *Drug Metab Rev*. 2004;36(1):1-55.
51. Ji L, Liu T, Chen Y, Wang Z. Protective mechanisms of N-acetyl-cysteine against pyrrolizidine alkaloid clivorine-induced hepatotoxicity. *J Cell Biochem*. 2009;108(2):424-432.
52. Barceloux DG. Cyanogenic foods (cassava, fruit kernels, and cycad seeds). *Dis Mon*. 2009;55(6):336-352.
53. Unproven methods of cancer management. Laetrile. *CA Cancer J Clin*. 1991;41(3):187-192.
54. Herbert V. Laetrile: the cult of cyanide. Promoting poison for profit. *Am J Clin Nutr*. 1979;32(5):1121-1158.
55. Brvar M, Kozelj G, Mozina M, Bunc M. Acute poisoning with autumn crocus (Colchicum autumnale L.). *Wien Klin Wochenschr*. 2004;116(5-6):205-208.
56. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol (Phila)*. 2010;48(5):407-414.

57. Critchley JA, Critchley LA, Yeung EA, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol*. 1997;16(4):229-232.
58. Barceloux DG. Akee fruit and Jamaican vomiting sickness (Blighia sapida Köenig). *Dis Mon*. 2009;55(6):318-326.
59. McTague JA, Forney R Jr. Jamaican vomiting sickness in Toledo, Ohio. *Ann Emerg Med*. 1994;23(5):1116-1118.
60. Meda HA, Diallo B, Buchet JP, et al. Epidemic of fatal encephalopathy in preschool children in Burkina Faso and consumption of unripe ackee (Blighia sapida) fruit. *Lancet*. 1999;353(9152):536-540.
61. Joskow R, Belson M, Vesper H, Backer L, Rubin C. Ackee fruit poisoning: an outbreak investigation in Haiti 2000-2001, and review of the literature. *Clin Toxicol (Phila)*. 2006;44(3):267-273.
62. Erguven M, Yilmaz O, Deveci M, et al. Mushroom poisoning. *Indian J Pediatr*. 2007;74(9):847-852.
63. Diaz JH. Syndromic diagnosis and management of confirmed mushroom poisonings. *Crit Care Med*. 2005;33(2):427-436.
64. Berger KJ, Guss DA. Mycotoxins revisited: part I. *J Emerg Med*. 2005;28(1):53-62.
65. Karlson-Stiber C, Persson H. Cytotoxic fungi—an overview. *Toxicon*. 2003;42(4):339-349.
66. Poucheret P, Fons F, Doré JC, Michelot D, Rapior S. Amatoxin poisoning treatment decision-making: pharmacotherapeutic clinical strategy assessment using multidimensional multivariate statistic analysis. *Toxicon*. 2010;55(7):1338-1345.
67. Michelot D, Melendez-Howell LM. Amanita muscaria: chemistry, biology, toxicology, and ethnomycology. *Mycol Res*. 2003;107(pt 2):131-146.
68. Frank H, Zilker T, Kirchmair M, et al. Acute renal failure by ingestion of *Cortinarius* species confounded with psychoactive mushrooms: a case series and literature survey. *Clin Nephrol*. 2009;71(5):557-562.
69. Ferenc T, Lukasiewicz B, Ciećwierz J, Kowalczyk E. Poisonings with Amanita phalloides [in Polish]. *Med Pr*. 2009;60(5):415-426.
70. Ganzert M, Felgenhauer N, Schuster T, Eyer F, Gourdin C, Zilker T. *Amanita* poisoning—comparison of silibinin with a combination of silibinin and penicillin [in German]. *Dtsch Med Wochenschr*. 2008;133(44):2261-2267.
71. Köppel C. Clinical symptomatology and management of mushroom poisoning. *Toxicon*. 1993;31(12):1513-1540.
72. Leathem AM, Dorran TJ. Poisoning due to raw *Gyromitra esculenta* (false morels) west of the Rockies. *CJEM*. 2007;9(2):127-130.
73. Lehmann PF, Khazan U. Mushroom poisoning by *Chlorophyllum molybdites* in the Midwest United States. Cases and a review of the syndrome. *Mycopathologia*. 1992;118(1):3-13.
74. Lurie Y, Wasser SP, Taha M, et al. Mushroom poisoning from species of genus *Inocybe* (fiber head mushroom): a case series with exact species identification. *Clin Toxicol (Phila)*. 2009;47(6):562-565.
75. Michelot D, Toth B. Poisoning by *Gyromitra esculenta*—a review. *J Appl Toxicol*. 1991;11(4):235-243.
76. Musselius SG, Ryk AA, Lebedev AG, et al. Toxicity of mushrooms Paxillus involutus and Paxillus atrotomentosus [in Russian]. *Anesteziol Reanimatol*. 2002;2(2):30-35.
77. Winkelmann M, Stangel W, Schedel I, Grabensee B. Severe hemolysis caused by antibodies against the mushroom *Paxillus involutus* and its therapy by plasma exchange. *Klin Wochenschr*. 1986;64(19):935-938.
78. Enjalbert F, Rapior S, Nouguier-Soulé J, Guillon S, Amouroux N, Cabot C. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40(6):715-757.
79. Pond SM, Olson KR, Woo OF, et al. Amatoxin poisoning in northern California, 1982-1983. *West J Med*. 1986;145(2):204-209.
80. Giannini L, Vannacci A, Missanelli A, et al. Amatoxin poisoning: a 15-year retrospective analysis and follow-up evaluation of 105 patients. *Clin Toxicol (Phila)*. 2007;45(5):539-542.
81. Yildiz BD, Abbasoglu O, Saglam A, Sökmensüer C. Urgent liver transplantation for Amanita phalloides poisoning. *Pediatr Transplant*. 2008;12(1):105-108.
82. Escudié L, Francoz C, Vinel JP, et al. Amanita phalloides poisoning: reassessment of prognostic factors and indications for emergency liver transplantation. *J Hepatol*. 2007;46(3):466-473.
83. Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med*. 2005;12(2):78-85.
84. Benjamin DR. Mushroom poisoning in infants and children: the *Amanita pantherina/muscaria* group. *J Toxicol Clin Toxicol*. 1992;30(1):13-22.
85. Satora L, Pach D, Butryn B, Hydzik P, Balicka-Slusarczyk B. Fly agaric (Amanita muscaria) poisoning, case report and review. *Toxicon*. 2005;45(7):941-943.
86. Beck O, Helander A, Karlson-Stiber C, Stephansson N. Presence of phenylethylamine in hallucinogenic Psilocybe mushroom: possible role in adverse reactions. *J Anal Toxicol*. 1998;22(1):45-49.
87. Michelot D. Poisoning by Coprinus atramentarius. *Nat Toxins*. 1992;1(2):73-80.
88. Vance MV, Curry SC, Bradley JM, Kunkel DB, Gerkin RD, Bond GR. Acute lead poisoning in nursing home and psychiatric patients from the ingestion of lead-based ceramic glazes. *Arch Intern Med*. 1990;150(10):2085-2092.
89. Paglicua A, Mufti GJ. Lead poisoning: an age old problem. *BMJ*. 1990;300(6728):830.
90. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P. Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol*. 2005;99(4):105-110.
91. Cullen MR, Robins JM, Eskenazi B. Adult inorganic lead intoxication: presentation of 31 new cases and a review of recent advances in the literature. *Medicine (Baltimore)*. 1983;62(4):221-247.
92. Papanikolaou NC, Hatzidaki EG, Belivanis S, Tzanakakis GN, Tsatsakis AM. Lead toxicity update. A brief review. *Med Sci Monit*. 2005;11(10):RA329-RA336.
93. Gracia RC, Snodgrass WR. Lead toxicity and chelation therapy. *Am J Health Syst Pharm*. 2007;64(1):45-53.
94. Woolf AD, Goldman R, Bellinger DC. Update on the clinical management of childhood lead poisoning. *Pediatr Clin North Am*. 2007;54(2):271-294., viii.
95. Scuderi GJ, Vaccaro AR, Fitzhenry LN, Greenberg S, Eismont F. Long-term clinical manifestations of retained bullet fragments within the intervertebral disk space. *J Spinal Disord Tech*. 2004;17(2):108-111.
96. Madureira PR, De Capitani EM, Vieira RJ, Sakuma AM, Toledo AS, Mello SM. Lead poisoning due to gunshot bullet in contact with cerebrospinal fluid: case report. *Sao Paulo Med J*. 2009;127(1):52-54.
97. Fernandes JL, Rocha AA, Soares MV, Viana SL. Lead arthropathy: radiographic, CT and MRI findings. *Skeletal Radiol*. 2007;36(7):647-657.
98. Meggs WJ, Gerr F, Aly MH, et al. The treatment of lead poisoning from gunshot wounds with succimer (DMSA). *J Toxicol Clin Toxicol*. 1994;32(4):377-385.
99. Lerner S, Gartside P, Roy B. Free erythrocyte protoporphyrin, zinc protoporphyrin and blood lead in newly

re-exposed smelter workers: a prospective study. *Am Ind Hyg Assoc J*. 1982;43(7):516-519.
100. Lin JL, Ho HH, Yu CC. Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency. A randomized, controlled trial. *Ann Intern Med*. 1999;130(1):7-13.
101. Moel DI, Kumar K. Reversible nephrotoxic reactions to a combined 2,3-dimercapto-1-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics*. 1982;70(2):259-262.
102. Tenenbein M. Unit-dose packaging of iron supplements and reduction of iron poisoning in young children. *Arch Pediatr Adolesc Med*. 2005;159(6):557-560.
103. Dean BS, Krenzelok EP. Multiple vitamins and vitamins with iron: accidental poisoning in children. *Vet Hum Toxicol*. 1988;30(1):23-25.
104. Tenenbein M. Toxicokinetics and toxicodynamics of iron poisoning. *Toxicol Lett*. 1998;102-103:653-656.
105. Mills KC, Curry SC. Acute iron poisoning. *Emerg Med Clin North Am*. 1994;12(2):397-413.
106. Position paper: whole bowel irrigation [published correction appears in *J Toxicol Clin Toxicol*. 2004;42(7)1000]. *J Toxicol Clin Toxicol*. 2004;42(6):843-854.
107. Curry SC, Vance MV, Ryan PJ, Kunkel DB, Northey WT. Envenomation by the scorpion Centruroides sculpturatus. *J Toxicol Clin Toxicol*. 1983-1984;21(4-5):417-449.
108. Walter FG, Bilden EF, Gibly RL. Envenomations. *Crit Care Clin*. 1999;15(2):353-386.
109. LoVecchio F, McBride C. Scorpion envenomations in young children in central Arizona. *J Toxicol Clin Toxicol*. 2003;41(7):937-940.
110. Seifert SA. Atropine use in *Centruroides* scorpion enveonomation–contraindicated or not? *J Toxicol Clin Toxicol*. 2001;39(6):599.
111. Suchard JR, Hilder R. Atropine use in *Centruroides* scorpion envenomation. *J Toxicol Clin Toxicol*. 2001;39(6):595-598.
112. Boyer LV, Theodorou AA, Berg RA, et al. Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med*. 2009;360(20):2090-2098.
113. Platnick NI. The World Spider Catalog, v12.0. American Museum of Natural History Web site. http://research.amnh.org/iz/spiders/catalog/COUNTS.html. Updated June 21, 2011. Accessed September 6, 2011.
114. Vetter RS, Isbister GK. Medical aspects of spider bites. *Annu Rev Entomol*. 2008;53:409-429.
115. Furbee RB, Kao LW, Ibrahim D. Brown recluse spider envenomation. *Clin Lab Med*. 2006;26(1):211-226.
116. Hogan CJ, Barbaro KC, Winkel K. Loxoscelism: old obstacles, new directions. *Ann Emerg Med*. 2004;44(6):608-624.
117. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med*. 2005;352(7):700-707.
118. Saucier JR. Arachnid envenomation. *Emerg Med Clin North Am*. 2004;22(2):405-422.
119. Vetter RS, Isbister GK. Do hobo spider bites cause dermonecrotic injuries? *Ann Emerg Med*. 2004;44(6):605-607.
120. Jelinek GA. Widow spider envenomation (latrodectism): a worldwide problem. *Wilderness Environ Med*. 1997;8(4):226-231.
121. Clark RF, Wethern-Kestner S, Vance MV, Gerkin R. Clinical presentation and treatment of black widow spider envenomation: a review of 163 cases. *Ann Emerg Med*. 1992;21(7):782-787.
122. Levine M, Canning J, Chase R, Ruha AM. Cardiomyopathy following latrodectus envenomation. *West J Emerg Med*. 2010;11(5):521-523.
123. Bush SP. Why no antivenom? *Ann Emerg Med*. 2003;42(3):431-432.
124. Vetter RS, Visscher PK, Camazine S. Mass envenomations by honey bees and wasps. *West J Med*. 1999;170(4):223-227.
125. Banks BEC, Shipolini RA. Chemistry and pharmacology of honey-bee venom. In: Piek T, ed. *Venoms of the Hymenoptera: Biochemical, Pharmacological and Behavioural Aspects*. Orlando, FL: Academic Press; 1986:329-416.
126. Bousquet J, Huchard G, Michel FB. Toxic reactions induced by hymenoptera venom. *Ann Allergy*. 1984;52(5):371-374.
127. Visscher PK, Vetter RS, Camazine S. Removing bee stings. *Lancet*. 1996;348(9023):301-302.
128. Seifert SA, Boyer LV, Benson BE, Rogers JJ. AAPCC database characterization of native U.S. venous snake exposures, 2001-2005. *Clin Toxicol*. 2009;47(4):327-335.
129. Gold BS, Barish RA, Dart RC. North American snake envenomation: diagnosis, treatment, and management. *Emerg Med Clin North Am*. 2004;22(2):423-443.
130. Kini RM. Anticoagulant proteins from snake venoms: structure, function and mechanism. *Biochem J*. 2006;397(3):377-387.
131. Lewis RL, Gutmann L. Snake venoms and the neuromuscular junction. *Semin Neurol*. 2004;24(2):175-179.
132. Curry SC, Kunkel DB. Toxicology rounds. Death from a rattlesnake bite. *Am J Emerg Med*. 1985;3(3):227-235.
133. Kitchens CS. Hemostatic aspects of envenomation by North American snakes. *Hematol Oncol Clin North Am*. 1992;6(5):1189-1195.
134. Lavonas EJ, Ruha AM, Banner W, et al; Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med*. 2011;11:2.
135. Dunnihoo DR, Rush BM, Wise RB, Brooks GG, Otterson WN. Snake bite poisoning in pregnancy. A review of the literature. *J Reprod Med*. 1992;37(7):653-658.
136. Cannon R, Ruha AM, Kashani J. Acute hypersensitivity reactions associated with administration of crotalidae polyvalent immune Fab antivenom. *Ann Emerg Med*. 2008;51(4):407-411.
137. Gold BS, Dart RC, Barish RA. Bites of venomous snakes. *N Engl J Med*. 2002;347(5):347-356.
138. Ruha AM, Curry SC, Albrecht C, Riley B, Pizon A. Late hematologic toxicity following treatment of rattlesnake envenomation with crotalidae polyvalent immune Fab antivenom. *Toxicon*. 2011;57(1):53-59.
139. Kitchens CS, Van Mierop LH. Envenomation by the Eastern coral snake (Micrurus fulvius fulvius). A study of 39 victims. *JAMA*. 1987;258(12):1615-1618.
140. Sánchez EE, Lopez-Johnston JC, Rodríguez-Acosta A, Pérez JC. Neutralization of two North American coral snake venoms with United States and Mexican antivenoms. *Toxicon*. 2008;51(2):297-303.