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 various substances mild to serious, or even be fatal, and the treatment can range from supportive to the administration of various substances.

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 brought a variety of exotic poisonous snakes. As complex and varied as these are, one can deduce that there is no clear “standard of care.”

88. Kolar H. The pharmacology and toxicology of “ecstasy” (MDMA) and related drugs. CMAJ. 2001;164:977.
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.

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. 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.

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and dwindling supplies available, present statements and future predictions on how to treat envenomation by coral snake are most difficult. If antivenin can be procured, and if symptoms are deemed either imminent or present, usually three to five vials of the antivenom are given intravenously about every 8 to 12 hours until symptoms stop progress. Typically, a single treatment is sufficient. If symptoms develop an hour or more before antivenin administration, it is notoriously difficult to reverse the neurologic blockade, and repeated administration of antivenom is not only futile, but in this time of extremely limited supplies, is probably unwise for society in general. Skin testing has been suggested prior to intravenous administration of the antivenom, but is imperfect in predicting safety or reaction to this antivenom, and should not delay administration in life-threatening situations in any case.

With the impending collapse of the supply of coral snake antivenom presently in the United States, it is unclear what course of action to recommend. It appears that antivenom prepared for South American members of the Micrurus family is not very effective for the Micrurus species in the northern hemisphere (3). A coral snake antivenom, prepared in Mexico (Coralmyn, Biodron), is available in emergencies. Presently, it is recommended to call your regional poison center (1-800-222-1222) to assist in acquisition, as most of the Mexican product in the United States is held by zoos. See the section on Snakes Non-native to the United States for further information.

**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 the two largest snakes, namely the eastern diamondback rattlesnake (*Crotalus adamanteus*) and the western diamondback rattlesnake (*Crotalus atrox*). Some special comments will also be made about specific effects of the venoms of the canebrake rattlesnake (*Crotalus horridus atricaudatus*) and the Mojave rattlesnake (*Crotalus scutulatus*). The remaining rattlesnakes tend to be smaller and located mostly in the desert southwest and California.

2. *Sistrurus*: Two other species of rattlesnakes are in the second genus, *Sistrurus*. *Sistrurus catenatus* (also known as the massasauga) is mostly encountered in the upper Midwest 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 (4–6). We use antivenin 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. Neither species of *Agkistrodon* 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 antivenin 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 proteinaceous 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 nonenzymatic 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] [FabW]), 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 scutu- latus*, or *Agkistrodon piscivorus*. The Fab fragments from all four preparations are then mixed together to produce a polyclonal 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. Thís no doubt explains, in part, the variability of the response of some envenomation
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, hyaluronidase, proteases, 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 bitten extremity and hemorrhage only rarely occurs systemically 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 after the bite) 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 systemically with total defibrinogenation, resulting in plasma extravasation end point (visible fibrin clot) of routine coagulation tests, fibrinogen levels less than 50 mg/dL. Therefore, the coagulation abnormalities seen with envenomation by the smallest of eastern diamondbacks may be associated with total defibrinogenation, resulting in plasma fibrinogen levels less than 50 mg/dL. Therefore, the coagulation abnormalities seen with envenomation by the smallest of eastern diamondback snakes are by far most pronounced within the Crotalus genus and rarely encountered in the Agkistrodon genus (9, 10) and rarely, if ever, in the Sistrurus genera (10).

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 genus (9, 10) and rarely, if ever, in the Sistrurus genera (10).

Laboratory coagulation abnormalities that have been described as being caused by envenomation by 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 a-subunit as does thrombin but, unlike thrombin, does not complete fibrinogen cleavage as it neither cleaves the non clotting component C-peptide from the a-subunit nor activates factors V, VIII, or XIII. This partially clotting fibrinogen forms a loose gel that is exquisitely sensitive to any proteolytic activity, as visible thromboembolic or organ manifestations of systemic thrombosis 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-croslinked, partially formed clot that produces massive quantities of circulating fibrin degradation products (FDPs). As a result of 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 defect 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 bleeding 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 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 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, 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. Odeleye 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 Saint-Martins et al. (35) regarding the South American cascadel (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. (36) 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 is a result not of frank hemorrhage, but of the direct effect of the venom 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 constriction 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. Confirm 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

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<th>Table 68.1</th>
<th>INITIAL EVALUATION AND DIAGNOSTIC POINTS</th>
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<tr>
<td><strong>CONFIRM</strong></td>
<td>Patient was bitten by a venomous snake; determine snake species if possible.</td>
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<tr>
<td><strong>CONFIRM</strong></td>
<td>Evaluate for local signs of envenomation:</td>
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<td>Pain</td>
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<td><strong>CONFIRM</strong></td>
<td>Evaluate for systemic signs of envenomation:</td>
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<td>Alterations in vital signs, nausea, vomiting, diarrhea</td>
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<td>Fasciculations</td>
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<td>Coagulation abnormalities</td>
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<td>Altered mental status</td>
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forward, replacing one another with time. Similarly, a single puncture wound may be present on a smaller part of the body (such as a finger) with the other fang missing the target altogether. Some victims may have three or even four puncture wounds per bite. The vast majority of patients will have the prompt triad of pain, swelling, and discoloration confined to the bite site almost within minutes of the event, but up to 2 hours later in unusual cases. If a patient does have puncture wounds consistent with pit viper envenomation, and does not have pain, swelling, and discoloration, or any systemic symptoms such as hypotension, nausea, vomiting, diarrhea, constipation, mental status changes, fasciculations, or diaphoresis, one may strongly consider that the patient has been bitten yet not envenomated. A caveat for this pronouncement is that many children, when anxious, frequently vomit, which may be a misleading sign. An alarming number of victims of snakebites are not at their normal mental status, given the frequency of concomitant inebriation from alcohol or other substances. This impedes obtaining a detailed history and the patient’s full cooperation. In many locales, a minority of bites are accidents in the true sense of the word.

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, are available to assist identification.

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.

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 diaphoresis, 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. 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.

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.

### Table 68.2

<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><em>Crotalus adamanteus</em></td>
<td>Southeastern United States</td>
<td>+</td>
<td>Prolonged PT/PTT; minimal thrombocytopenia</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Canebrake</td>
<td><em>Crotalus horridus</em></td>
<td>Eastern United States</td>
<td>nil</td>
<td>nil</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Mojave</td>
<td><em>Crotalus atrox</em></td>
<td>Desert southwest United States</td>
<td>+++</td>
<td>nil</td>
<td>+ + + +</td>
</tr>
<tr>
<td>Timber</td>
<td><em>Crotalus horridus</em></td>
<td>Eastern United States</td>
<td>nil</td>
<td>Prolonged PT/PTT; moderate to severe thrombocytopenia</td>
<td>+ + + +</td>
</tr>
</tbody>
</table>

PT, prothrombin time; PTT, partial thromboplastin time.

+ + = usually minimally present; + ++ = usually moderately present; +++ = usually extensively present; ++++ = always present.
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 (7–9) 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 (15%) 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 $30,000.

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 exsanguination 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 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</td>
<td>0</td>
</tr>
<tr>
<td>Minimal envenomation</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 envenomation</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 envenomation</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
- Obtain IV access and administer crystalloid as indicated.
- 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.**

**FabAV, fragment antigen-binding fragment of antibody.**
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, fasciotomy 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-2. 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 redistribution and shorter half-life than IgG, periodic readministration during the initial treatment period is important. Reassurance of the patient is more important than the initial administration during the initial treatment period is important. Re- search and development of a Fab(ab)2 antivenom is currently under way. Fab(ab)2 has a smaller volume of distribution and a longer circulating half-life, and thus may decrease the recurrence syndrome.

Another 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 coagulopathy or in the management of recurrence.

We hold that the debrinogenation 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 debrinogenation 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, noncritical coagulation abnormalities without bleeding do not in and of themselves, in our opinion, demand antivenom treatment (10).

Some species of snakes, particularly the timber rattlesnake (Crotalus bororudus bororudus), 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 paradoxic 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 required 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 infection, which would allow for the possibility of inadequate 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).
loss of tissue, including fingers or limbs, is very rare, and often occurs with the injudicious prehospital use of ice or tourniquets or, perhaps, very delayed care. Unfortunately, patients who are bitten by snakes tend to continue their risky behavior, resulting in the finding that re-envenomation is not rare.

**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, aquaria, 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 approximately 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 involved 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 Elapids. Naja naja, Naja mossambica, and Ophiophagus hanah 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 adamanteus, Bothrops asper, Bitis gabonica, and Lachesis mutus are the most commonly encountered viperid species (47).

*Compared with other etiologies of critical illness, venomous snake bites account for few ICU admissions per year. Nevertheless, almost one third of non-native envenomations develop major to moderate symptoms and signs of disease, and are admitted to an ICU. The case fatality rate of approximately 1% is significantly greater than in native snakebites. Males are involved in 84% of bites, a similar percentage to that in native bites. Almost 15% are aged 17 years or less, and approximately 7% are aged 5 years or younger, most likely as a result of private collections in home settings (47). Identification of the snake in non-native bites is usually not difficult, as zoos, aquaria, and academic institutions will know their collections. However, the bitten individual with a private collection may not be capable of communication, and potential penalties for possession of venomous animals in some jurisdictions may result in the withholding of critical information (48). A qualified herpetologist should be consulted for the identification of non-native snakes that are otherwise unidentified. The presence of a puncture and typical appearance of the site, progression of findings, and consistent laboratory abnormalities of a snakebite, indicate the possibility even when the history is not available.*

**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 venoms 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, fibrinogenation, prothrombin action, collagenase-like activity, and other effects (58–60). Elapid venoms vary widely among species but contain more neurotransins and cardioxotoxins (51), resulting in various expressions of nerve and cardiac toxicity. Sea snakes have venom similar to elapid.
Snake venom that produces local effects causes hemolysis; may potentiate neurotoxins; myonecrosis; tissue destruction; hematologic effects. It catalyzes hydrolysis of acetylcholine, producing flaccid paralysis and muscle fasciculation. Determination of the clinical significance of these effects may be under the influence of alcohol at the time of envenomation. As with native envenomations, some private collectors may be under the influence of alcohol at the time of envenomation. Some private collectors may be at greater risk of morbidity and mortality. Larger snakes contain and deliver more venom, but fatal envenomations may result from juvenile snakes. Toxins of the venom will depend on the species and other factors that affect venom production. The quantity injected as many as 30% of Crotalid bites and 50% of Elapid bites may result in no envenomation. 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 poor penetration of the fang or recent previous feedings. Bite location. Tissues and anatomic areas with a low capacity for swelling, or which are functionally important, such as 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. 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. 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 as 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 co-morbid 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 transitions 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, Mainneim, 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 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

### TABLE 68.5

<table>
<thead>
<tr>
<th>Component</th>
<th>Viperid</th>
<th>Elapid</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteases</td>
<td>++++</td>
<td>+</td>
<td>Tissue destruction; hematologic effects</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>+</td>
<td>++++</td>
<td>Hydrolyzes connective tissue stroma; promotes spread</td>
</tr>
<tr>
<td>Cholinesterase</td>
<td>+</td>
<td>++++</td>
<td>Catalyzes hydrolysis of acetylcholine</td>
</tr>
<tr>
<td>Phospholipase A₂</td>
<td>+</td>
<td>++++</td>
<td>Hemolysis; may potentiate neurotoxins, myonecrosis</td>
</tr>
<tr>
<td>Phosphodiesterase</td>
<td>+</td>
<td>++++</td>
<td>Unknown</td>
</tr>
<tr>
<td>Neurotoxins</td>
<td>+</td>
<td>++++</td>
<td>Placed paralysis; muscle fasciculation</td>
</tr>
<tr>
<td>Cardiotoxins</td>
<td>+</td>
<td>++++</td>
<td>Depolarizing/depresorhythms disturbances</td>
</tr>
</tbody>
</table>

+ = usually minimally present; ++ = usually moderately present; +++ = usually extensively present.
low, but will vary depending on the snake, the host, and fac-
tors such as the development of necrosis and wound manipula-
tion. Potentially life-threatening infections such as necrotizing
fasciitis and disseminated osteomyelitis, have been reported fol-
lowing snakebites (64–66).

Hematologic Effects. Coagulation alterations result from pro-
teases acting on various parts of the coagulation cascade and
day 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 inhi-
bition, aggregation, or consumption may occur with ab-
normal function and/or decreased platelet counts (60,70). In-
travascular 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),
PTT, 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 suggests an absence of such effects. If abnormalities
are present, the use of antivenom may halt (e.g., fibrinogolen-
ysis) 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 compo-
nents 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 Atractaspid, Elapid,
Helodermid, Hydrophiid, or Viperid envenomations. Clinical
effects can include sweating, numbness, paresthesias, convul-
sions, coma, muscle fasciculation, muscle weakness, and respi-
ratory arrest. Respiratory muscle paralysis is the primary cause
of death with most Elapid and Hydrophiid venoms. Viperid
snakes rarely cause clinically significant respiratory compro-
mise. Coma may be secondary to hypovolemia or to a direct
effect of the toxin (88). 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 de-
layed onset, once neurologic effects occur, they may progress
very rapidly. Patients should be observed for a sufficient pe-
riod of time, and preparations to manage the airway should be
readily available. It should be kept in mind that some Elapids
produce little to no local effects, and therefore, there absence
cannot be relied upon to confirm nonenvenomation. Once mus-
cle 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 (82–84). 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, al-
though certain effects predominate within families. Type I hy-
persensitivity reactions to venom (IgE or non-IgE mediated)
with or without hypotension may occur. The incidence is be-
lieved to be approximately 1% (85). Type I hypersensitivity
reactions are characterized by wheal, urticaria, laryngeal
edema, and/or hypotension. Airway compromise from laryn-
geal edema may also occur, and direct myocardial depression,
irritation 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 set-
tings, yet obtaining an accurate identification of the snake is
of utmost importance in order to select the appropriate an-
tivenom. 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 ap-
propriate 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 main-
tains 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 identifica-
tion 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 individu-
al. Pre-existing medical information, information regarding
the biting species, and any available antivenom should be trans-
ported with the patient. The bitten body part should be splinted
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 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 be possible to identify the biting species, many antivenoms

tility 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 nonenvenomation 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

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**DISCLAIMER**: The information provided is for educational purposes only and should not be used as a substitute for professional medical advice. Individual medical decisions should be made in consultation with a qualified healthcare provider.
Cholinergic agonists, such as neostigmine, may be used. Management of progressive tissue edema and elevated systemic symptoms may be assisted by keeping the bitten extremity elevated. A positive reaction does not preclude antivenom administration. Recurrence of local and/or hematologic venom effects may be managed with antivenom and mechanical immobilization. Skin testing should not delay administration of antivenom and elevation, if tolerated. There is little to no role for dementia or fasciitis. 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'2, 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 type I and type III hypersensitivity 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.

### Table 68.8: HOSPITAL BITE SITE AND WOUND MANAGEMENT

- 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.
- Wash the bite site, apply antibiotic ointment, leave it otherwise uncovered, and provide tetanus immunization updating as needed.
- Once antivenom has been initiated, or a decision has been made not to administer a life-threatening envenomation elevated with periodic assessment of edema (and tissue pressures if indicated), and monitor for development or progression of systemic symptoms.
- Management of progressive tissue edema and elevated tissue or compartmental pressures is by adequate amounts of antivenom and elevation, if tolerated.
- Frankly necrotic tissue should be debrided.
- There is little to no role for debridement or fasciectomy.

### Table 68.9: HOSPITAL ANTIVENOM MANAGEMENT

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

### Table 68.10: HOSPITAL SYMPTOMATIC MANAGEMENT

- Hypotension
  - May be due to a type I hypersensitivity reaction to venom or to antivenom, cardiotoxicity, or fluid loss.
  - Management is with Trendelenburg positioning, crystalloid fluid expansion, pressures, anaphylaxis treatments (epinephrine, H1, and H2 blockers), and antivenom (if believed to be secondary to venom).
- Neurologic effects
  - Should be managed with antivenom and mechanical airway support as needed.
  - Cholinergic agonists, such as neostigmine, may be used as adjunctive or substitute management of muscle weakness in some Elapid envenomations.
- Hematologic effects
  - Severe or multicomponent abnormalities are managed primarily with antivenom.
  - Blood products are reserved for clinically significant hemorrhage, and given with additional antivenom if needed.
  - 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.
- Other systemic effects are managed with symptomatic and supportive care.
  - Parenteral opioids may be required for pain.
  - Recurrence of local and/or hematologic venom effects may occur.
  - Patients at high risk should be closely monitored, especially postdischarge.
  - Additional antivenom should be considered for recurrent local effects in the first 24 h or recurrent severe or multicomponent hematologic abnormalities.

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. As no U.S. hospital routinely stocks antivenoms for non-native species, such 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 workers 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...
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/neutralize 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 hematomic effects. Also, because of difficulty reaching damaged tissue and despite the use of antivenom early in the course of a snake 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 stopped progressing 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 managed with additional antivenom as well as blood component components (67,77,109). Clinically significant hemorrhage is managed with additional antivenom as well as blood component components (67,77,109). Mannitol and hyperbaric oxygen have also been used in conjunction with antivenom (116). Noninvasive vascular studies may identify patients at risk for ischemia (117).

Other Supportive Therapies. These include basic wound care and updating tetanus status. Blood products should be reserved for significant hemorrhage or hemolysis and administered with additional antivenom. Ventilatory support and hemodialysis may be necessary for pulmonary and renal complications of severe envenomation. Corticosteroids may be used for hyperemic reactions to venom or antivenom. Antibiotics are indicated for documented infection or in the presence of frank necrosis.

Hypersensitivity Reactions. If a type I hypersensitivity reaction develops, the antivenom infusion should be stopped. Anaphylactoid reactions are primarily related to rate of infusion, and stopping the infusion often results in rapid improvement. Anaphylactic reactions (i.e., those IgE mediated) are often dramatic and continue to progress after the infusion has been stopped. There is, as one might expect, considerable clinical overlap between the reactions (118). Standard managements should be used. If symptoms persist, the patient should be treated with H̄2 (e.g., diphenhydramine, 50 mg IV) and H̄3 (e.g., ranitidine, 50 mg IV) blockers. Wheezing may respond to β-adrenergics by nebulizer (e.g., albuterol). If there is hypotension or laryngeal edema, epinephrine, either subcutaneously or intravenously, should be considered (119). Antivenom should be withheld until the reaction has subsided and then a determination made whether to restart it. If restarted, the patient should receive pretreatment with H̄2 and H̄3 blockers and the infusion begun more slowly.

Type III reactions are usually managed with nonsteroidal anti-inflammatory drugs (NSAIDs) and H̄2 and H̄3 blockers. More severe cases may require opioid-level pain relief, as well as corticosteroids. All patients receiving antivenom should be
POSTDISCHARGE MANAGEMENT

1. Physical therapy may be helpful in minimizing the extent and duration of functional impairment.
2. Type III hypersensitivity reactions ("serum sickness"): 
   a. They usually develop between 3 and 14 d following antivenom administration.
   b. The incidence varies from less than 5% to greater than 80% of cases depending on the antivenom, host, and other factors.
   c. Neutrophilic anti-inflammatory drug analgesics and antihistamines are usually sufficient for symptomatic care.
   d. Severe reactions may have renal involvement and require steroids and, in rare cases, rehospitalization.
3. Patients with significant hematologic abnormalities, especially those treated with Fab antivenoms, may be at risk of recurrent effects postdischarge.
4. Close follow-up is necessary for at least 2 to 4 d to detect recurrence.
5. Consider readministration of antivenom for clinical bleeding or multicomponent or severe hematologic abnormalities, especially with comorbid conditions.

Post discharge Considerations. It is desirable to see patients at least once post discharge in order to monitor for persistent or recurrent hematologic effects if indicated or tissue injury and which may result in an incorrect diagnosis. Patients should also be cautioned regarding the possibility of a type III reaction occurring after discharge.

Treatments Not Recommended

1. There is no evidence for efficacy, and there is potential for additional injury with arterial or venous tourniquets, incision or excision of the wound, or the application of heat, cold, or electricity.
2. Suction apparatuses remove only a small amount of venom, have not been shown to improve outcome, and may only serve to delay transport and definitive care (120,121).
3. Although some snake venoms also contain procoagulant factors, and the overall clinical picture is DIC-like, the conditions are not identical, so heparinization and other treatments for DIC are not applicable in snakebites.
4. In the absence of necrosis, prophylactic antibiotics also are of no proven value.
5. Corticosteroids are of no proven value for acute venom effects.

TABLE 68.11

<table>
<thead>
<tr>
<th>POSTDISCHARGE MANAGEMENT</th>
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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.

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 superficial infection is possible, it is uncommon.

Clinical Effects: Systemic. The more medically significant effects following widow envenomation are the constellation of systemic symptoms known as latrotoxin. 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
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 premature 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 minuscule. There is no role 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 benzodiazipines. Benzodiazipines are preferred as muscle relaxants, given their wide 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 benzodiazipine 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 antivenom is 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(γ) 2 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 dermal inflammation 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, proderma gangrenosum, pyogenic granuloma, and herpes 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 still 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. Cases of envenomation in children, begin as low-grade febrile illness with arthralgias and other nonspecific symptoms (144). Within 24 to 48 hours after the bite, these symptoms can progress to a potentially life-threatening illness characterized by hemolysis 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), dapsone (146–150), nitroglycerin (151), and early surgical debridement, and are not recommended. The venom spreads rapidly after a bite, and early attempts to "core" the wound without appropriate medical care can cause significant systemic effects. Early medical attention is necessary.

Systemic loxoscelism should be treated with symptomatic and supportive care. Successful treatment of proven loxoscelism cases has included aggressive fluid reuscitation, 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 (*Hadrurus* and *Atrax* spp.), native to Australia, and the banana spiders (*Phormetria* spp.), native to South America, are considered far more dangerous than the native *Lattrodectus* 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 fasculations, 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 *Phormetria* 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 *Cen- truroides 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 hyperactivation 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 F(ab’)_2 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).

**MAREAN 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, 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 inguinal 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 vasodilatation 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/diabetes 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.

Scorpaenidae
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 (Danio), 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 for management considerations. See the section on non-native snake envenomations for management considerations.

Sea Snakes
There are approximately 50 species of sea snakes in several subfamilies. They are found primarily in the warm tropical waters of the Indo-West Pacific. None are found in the Atlantic Ocean or Caribbean Sea. Envenomations are likely the result of such snakes 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
Five phyla—Cnidaria, Porifera (sponges), Echinodermata (sea urchins, starfish), Mollusca (octopi and cone snails), and Annelida (bristle worms)—constitute the venomous 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 hydroids (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 hydroids, nematocysts are primarily on the tentacles, and each tentacle can contain thousands. Each nematocyst is a spiral-coiled dart-like structure within venom sacs. Venom 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 southwestern coast of the United States, especially from July through September, and is actually a complex colony of multiple hydroids (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 proteins and polypeptides, some of which have potent local and systemic effects. These include proteins involved in coagulation and fibrinolysis, as well as proteins that are involved in inflammation.
include histamine, serotonin, alkaline and acid phosphatases, proteases, hyaluronidase, nucleosidases, hemolysins, and inflammatory mediators, among others (167,180).

Clinical Effects
Most organisms in this group, 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). Ikukandji 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 webs where tentacles have contacted the skin. These wefts 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 scarring.

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 given by the institutions that house these creatures; an antivenom is available and 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 (Lynceus seminulceatus). The larvae attach to the fibres in bathing suits and 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 bun sponges 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 sponges with adhesive tape or the edge of a dull knife. Washing the area with 5% acetic acid may aid in the shaving process. 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 bun sponges 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).

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
tooth deep into the flesh (194). The venom contains primarily neurotoxins that act by ion channel effects (167,195).

Clinical Effects. Clinical effects include local burning pain, numbness, and parasthesia, as well as systemic effects of peripheral paralysis, cranial nerve palsy, 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 aquaria 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 parasthesia, 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. 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 institution, 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 symptoms 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, serotonin, proteases, and others (198).

Treatment

The affected area should be immersed in nonscalding 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.

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