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More Snakebites and Less Antivenom

Prescribing Burdens for Venomous Envenoming

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When you see a snake, never mind where he came from![1]

Snake envenoming is responsible for premature death and disability on every continent. Locations for venomous snakes vary as a function of ecological, geographic, and environmental factors. Worldwide, there are 5.8 million persons at significant risk, with approximately 7400 persons bitten each day. An estimated 2.7 million cases a year result in 81 000 to 138 000 deaths, with an estimated 400 000 persons experiencing permanent disability that includes blindness, amputation, contractures, and posttraumatic stress disorder. Typical victims are poor, from rural communities in tropical and subtropical areas across the world. Children are the most likely to be bitten, become disabled, or die. Right now, the world needs at least 3 million antivenom treatments a year that are safe, affordable, and effective.[2,3]

Envenomation describes the process by which venom is injected via a bite or sting of a venomous animal. Not every snake bite results in envenomation—so use of antivenom is not always necessary.[3] However, in many parts of the world, for those who do require antivenom, this product is not available or accessible.[2] Antivenom is only 1 part of managing envenomation because antivenom cannot reverse damage to organs or tissues nor reach toxins inside cells. Thus, treatment often includes hemodynamic and respiratory support, fluid resuscitation, dialysis, wound debridement, surgery, and rehabilitation, as well as support for posttraumatic stress disorder and depression.[2]

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VENOMOUS SNAKES IN NORTH AMERICA

Snakes are found in every state of the United States except Alaska, Maine, and Hawaii.[4] There are approximately 20 types of venomous snakes in North America, including pit vipers (family *Viperidae*) and subfamily *Crotalidae*, which includes rattlesnake, copperhead, and cotton mouth (water moccasin). In addition, there are 3 coral snake species in the United States; the Eastern coral snake (*Micrurus fulvius*) in the family of *Elapidae* is found in southeast to Florida and as far west as Louisiana and southern Texas, with the Texas coral snake (*Micrurus tener*), and the Sonoran coral snake (*Micruroides euryxanthus*).[5] Worldwide, there are 3000 species of snakes, except in Antarctica, Iceland, Ireland, Greenland, and New Zealand, of which about 600 are venomous and only 200 can kill or significantly wound a human.[6] Snakebites are more common from April to October, when weather is warmer with more human activity outside.[7]

EMERGENCY CARE

Venom is a complex natural poison composed of proteins and enzymes, with cytotoxins, neurotoxins, hemotoxins, and cardiotoxins. The amount, composition, and strength of the venom are a function of the snake type, age, geographic location, time of year, and diet.[4] Treatment is not just receiving antivenom, which neutralizes available venom elements.[2] Treatment also requires monitoring, vigilance, and support. Table 1 describes the physiological responses to snake venom, and Table 2 describes the primary nursing care interventions after envenomation.[4,8]

Not every snake bite results in envenomation, so use of antivenom is not necessary.[3] Patients with "dry bites" or bites without venom will have no evidence of a local or systemic reaction.[3,4] However, patients should be observed for a least 8 hours to detect hidden envenomation in subcutaneous, adipose, or muscle tissues that manifests symptoms later. Patients should be instructed to monitor and report any signs or symptoms described in Table 1 for up to 2 weeks after the bite.

Table 1. Physiological Responses to Snake Venom[4,8]

Neurotoxic Effects	Cardiovascular Effects	Hematological Effects	Soft Tissue/Organ Effects
Drooping eyelids	↑Capillary permeability	Thrombocytopenia	Inflammation
Sleepiness	Hypovolemia	Hypofibrinogenemia	Necrosis
Paresthesia	Hypotension	↑Prothrombin time	Renal failure
Respiratory distress r/t flaccid paralysis	Nausea and vomiting	↑International normalized ratio	↑ Risk rhabdomyolysis
Lack of coordination	Angioedema	Fibrinogen degradation	Burning pain
Muscle weakness	Anaphylaxis	Platelet aggregation	Edema
Blurred vision	Tachycardia		
Muscle fasciculations	Diaphoresis		
Numbness at bite site	Cardiac arrest		
Metallic taste			

Rattlesnake envenomation—more likely to manifest abnormal coagulation parameters, platelet counts, and bleeding risks.[8]
Coral snake envenomation—does not result in coagulopathy activity; restriction from medications that increase bleeding risk does not apply.[8]

Persons seeking emergency care usually present with great anxiety and panic, all of which are normal responses to a snakebite. Pain is common, and explaining to the patient that pain does not mean harm may reduce some anxiety. Physical activity should be minimized, and remove rings, jewelry, and tight-fitting clothing. Do not overwhelm the patient with information, medical language, or speculation. Most symptoms will begin to develop 30 to 60 minutes after envenoming. Consider administering tetanus vaccination if indicated because clostridium tetani infections have been reported after a snake bite.[3]

Finally, never handle a snake brought to the emergency department, dead or alive, because cases of venom exposure have been reported when handling the snake.[3,7] Most helpful is having a formal relationship with a herpetologist at a local zoo to assist with snake identification when needed.[7] Bite wound infections are rare, but possible. However, use of prophylactic antibiotics is not recommended.[4]

For humans and animals, snake venom can precipitate multiorgan and multisystem disease. Table 3 describes the most serious responses.[2] First aid interventions such as wound cutting, tourniquets, electric shock, ice therapy, alcohol, and herbal remedies, as well as fasciotomy, are not evidence-based interventions and harmful. The most effective interventions are hemodynamic support and antivenom for symptoms.[9] If symptoms continue to progress after initial

Table 2. The Top 10 List: Nursing Care After Envenomation[4]

1. Emergency equipment with diphenhydramine and epinephrine must be readily available.
2. Tetanus vaccination if tetanus is not current.
3. Assess for allergy to sheep serum, papaya or latex.
4. Monitor and *measure* swelling and tenderness, marking leading edges with a permanent marker with date/time. Circumferential measures are *not* recommended.
5. Elevate the extremity above the heart to reduce risk for compartment syndrome.
6. Keep limb in a neutral position. *No* ice.
7. Minimize patient activity.
8. Treat pain with intravenous opioids; *No* nonsteroidal anti-inflammatory drugs.
9. Careful intravenous fluid therapy to reduce risk for rhabdomyolysis.
10. For patients arriving with a tourniquet, and antivenom is required, *do not* remove until first dose of antivenom is infused. If circulation is impaired, loosen the tourniquet without removing. Be prepared for anaphylaxis when the tourniquet is removed and possible movement of venom.
11. Assess indications for antivenom treatment: progressive tissue swelling, elevated prothrombin time, declining platelet and/or fibrinogen, hypotension, fasciculations, excessive bleeding, or airway compromise.

Table 3. Possible Multiorgan and Multisystem Disease Expression Precipitated by Snake Venom[2]

• Conjunctivitis, corneal ulceration, infection, or blindness from spat venom
• Toxin effects on pituitary gland tissues
• Blocked neuromuscular transmission resulting in paralysis/apnea
• Myocardial ischemia
• Liver dysfunction
• Acute and chronic kidney injury
• Placenta dysfunction in pregnancy
• Platelet degradation
• Consumption of clotting factors
• Tissue damage/death; swelling, necrosis, loss of blood supply
• Leaking capillaries syndrome from toxins
• Hyponatremia

antivenom dose, and/or coagulation status does not demonstrate improvement, consider additional antivenom doses.

ANTIVENOM

Venom is a complex natural poison composed of proteins, enzymes, with cytotoxins, neurotoxins, hemotoxins, and cardiotoxins. The amount, composition, and strength of the venom are a function of the snake type, age, geographic location, time of year, and diet.[4] In the presence of coagulation deficit, bleeding, neurotoxicity or myotoxicity, renal failure, hypotension, or shock antivenom is indicated. Symptoms generally improve quickly after anti-venom is given.[3] Adrenalin should always be readily available for anaphylactic reaction to antivenom. Patients who receive antivenom will also require follow up related to risk for serum sickness, which manifests as fever, joint pain, rash, and malaise. Patients should be instructed to contact their care provider immediately if these symptoms occur. Oral prednisolone until the signs and symptoms of serum sickness are alleviated may be indicated.[3]

ANTIVENOM CONSIDERATIONS FOR NORTH AMERICAN VIPERIDAE AND CROTALIDAE ENVENOMATION

Two antivenoms specific for North American crotalidae envenomation are available: crotalidae polyvalent immune FAB (OVINE) or CroFab, "Fab," available since 2007 and the recently approved crotalidae equine immune F(ab')2 or Anavip. CroFab has had widespread use and experience because it was the only commercially available treatment for crotalid envenomation until 2015. This antivenom binds and neutralizes venom and helps to redistribute venom from target tissues and facilitates venom elimination from the body. Although effective, late coagulopathy after hospital discharge and antivenom clearance was a problem for some patients, with risk lasting for up to 2 weeks with serious and sometimes with fatal bleeding complications. Anavip has demonstrated a longer half-life in clinical trials and a reduced risk of subacute coagulopathy and bleeding after treatment of envenomation.[10] Prescribing considerations for both agents are described in Table 4.[11–15]

ANTIVENOM CONSIDERATIONS FOR CORAL SNAKE (EASTERN, TEXAS, AND SONORAN) ENVENOMATION

Rather than swelling, pain, or coagulopathy, coral snake bites are associated with respiratory failure and paralysis occurring hours after envenomation.[5] Antivenin (*M. fulvius*) (trade name North American Coral Snake Antivenin; Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc, Philadelphia, Pennsylvania) is indicated for the treatment of envenomation by North American coral snakes. This horse-derived antivenom was approved in 1967 for adults and children and binds to coral snake venom. Persons sensitive to horse serum are at risk for developing anaphylaxis with dosing, so emergency care must be readily available and patients should also be monitored for serum sickness post treatment. Despite decades of use, risk for fetal harm or reproduction capacity is unknown, and this agent should be given to a pregnant woman only if clearly indicated.[16,17]

Limited antivenom supply and no other licensed alternative product in the United States for coral snake envenomation have resulted in the Food and Drug Administration extending expiration dates on current lots based on evaluations of drug stability, with Wyeth Pharmaceuticals carefully managing the remaining inventory.[18,19] Because Pfizer/Wyeth stopped manufacturing coral snake antivenom, when the present inventory is exhausted, there will be no Food and Drug Administration–approved antidote for coral snake bites.[20]

Only 25 to 50 of the estimated 9000 snake bites each year in the United States are caused by coral snakes because unlike pit vipers, coral snakes are elusive and usually retreat rather than attack. Although neurotoxicity of the venom can be life threatening, death is rare. However, patients need to be carefully monitored for at least 24 hours for respiratory insufficiency and failure, as well as for swallowing and muscle strength. If the patient develops neurotoxicity or respiratory failure and antivenom is not available, possible treatment options include a trial dose of an anticholinesterase, such as neostigmine to increasing acetylcholine in the neuromuscular junction to counter postsynaptic blockade. Consider also pretreatment with atropine or glycopyrrolate to prevent possible excessive cholinergic effects of neostigmine. The best course of action

Table 4. Prescribing Considerations for 2 Agents to Treat North American Viperidae and Crotalidae Envenomation in Adults and Children[11–13]

Prescribing considerations	CROFAB contains purified immunoglobulin fragments (IgG) from the blood of sheep immunized with US snake venoms approved to treat all North American pit viper and crotalidae envenomations in adults and children. Controls local, systemic, and hematological effects for 10 clinically important crotalid snakes in the United States.	ANAVIP contains venom-specific antigen binding F(ab')2 fragments of IgG derived from equine hyperimmune plasma. Fragments bind to venom to prevent/reverse local and systemic effects of rattlesnake envenomation. Indicated for the management of adult and pediatric patients with North American rattlesnake envenomation.
Prescribing Information	BTG International Inc, West Conshohocken, PA 19428.	Rare Disease Therapeutics Inc, Franklin, TN 37067.
Allergy risk	Known hypersensitivity to papaya or papain.	Known hypersensitivity to horse proteins or cresol
Coagulopathy characterized by ↓fibrinogen, ↓platelets, ↑prothrombin time	Coagulopathy recurrence after successful treatment with antivenom is a risk. The optimal dose to prevent recurrent coagulopathy is unknown. CROFAB has a shorter persistence in the blood than snake venoms that can leak from deposit sites over prolonged periods of time. Repeat dosing to prevent or treat such recurrence may be necessary.	ANAVIP is made from equine horse plasma; risk for transmission of disease, for example, virus. Cresol (trace amounts) from manufacturing process is present and may result in generalized myalgias and/or local reaction. Monitor for at least 18 hours after control of S/S and provide additional doses as directed for reemerging S/S (including coagulopathies).
Hypersensitivity	Discontinue the infusion and begin emergency treatment in anaphylaxis and anaphylactoid reactions.	Discontinue the infusion and begin emergency treatment in anaphylaxis and anaphylactoid reactions.
Pregnancy	Unknown whether CROFAB can cause fetal harm or affect reproduction capacity. CROFAB should be given to a pregnant woman only if clearly indicated.	Unknown whether ANAVIP can cause fetal harm or affect reproduction capacity. ANAVIP should be given to a pregnant woman only if clearly indicated.
Patient teaching	Call immediately for unusual bruising or bleeding; nosebleeds, ↑gum bleeding, blood in stools or urine, ↑menstrual bleeding, petechiae, ↑bruising, persistent oozing from superficial injury	The antivenom has a longer half-life to minimize risk of reemergent venom effects (↓platelets, ↑bleeding times), which require additional doses of antivenom. Patients still require instruction to report any S/S of bleeding.

is to contact poison control and obtain a toxicologist consultation to guide treatment.[21]

FUTURE OF SNAKES, HUMANS, AND ANTIVENOM

The World Health Organization current goal is to reduce mortality and disability from snake envenoming by 50% before 2030. Strategies include teaching vigilance, understanding risk, first aid, and rehabilitation.[2] The current situation in sub-Saharan Africa is worrisome. Antivenom production for Africa and the Middle East has significantly declined from 1980 to 1990, and in 2015, a primary manufacturer of antivenoms stopped production. With a similar situation emerging in Asia, a public health crisis is imminent.[2,8] In these areas, treatment and follow-up care make the poor poorer, with some experiencing financial losses equal to 3.6 years of income or selling land worth 14 years of income. Most of the antivenoms outside North America have not been tested and evidence for safety and effectiveness is weak at best.[2,8] Increasing numbers of poor worldwide with inferior housing conditions have enabled more human contact with snakes. Warmer climates have extended the geographic borders for snake activity. Tropical storms that displace snakes to human communities via flooding are increasing as well.[8] Somehow, the number of companies producing high-quality antivenom must be increased.[2,8]

Surprisingly, snake venom may also provide life. Snake venom is already part of the formulary; consider Captopril, the first angiotensin-converting enzyme inhibitor that was designed based on the structure of a peptide from snake venom.[22] Since the 1930s, researchers have been studying the possible effects of snake venom in the treatment of cancer. Recent proposed therapy models suggest conjugation with monoclonal antibodies that recognize and bind to malignant cancer cells and combining snake venom with silica nanoparticles to inhibit cellular proliferation and induce apoptosis without effecting normal tissue. The future is promising for use of snake venom as a path for cancer drug development.[22,23]

For now, a warmer planet, rising rodent populations, and poor waste management are ever increasing the contact between humans and snakes. Simple interventions such as wearing boots and gloves and exercising vigilance and caution in rural and at-risk areas can begin to make a huge difference in avoiding envenomation.[24]

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