

Myths and Facts: **Venomous Snakebites**

Although venomous snakebites are rare in the U.S. compared to other countries, they are still medical emergencies that need to be treated with today's safe and effective methods.

By Ronale Tucker Rhodes, MS



Globally, at least 421,000 venomous snakebites, known as envenomings, occur each year.¹ In the U.S., that number is considerably lower — between 7,000 and 8,000, which equates to fewer than one in 37,500 people² — due to fewer venomous snakes inhabiting this country. In fact, out of more than 3,000 species of snakes in the world, approximately 600 are venomous and only slightly more than 200 are considered to be medically important.³ Of the latter, only two types are indigenous to the U.S.: pit vipers (rattlesnakes, copperheads, cottonmouths/water moccasins), which are also known as crotalids, and coral snakes, which are also known as elapids.⁴ Nonetheless, when these uncommon bites occur, they are medical emergencies. Consequently, it's extremely important to dispel the many misconceptions about snakebites and how they should be treated.¹

Separating Myth from Fact

MYTH: Venomous snakebites aren't that dangerous.

FACT: Most venomous snakebites can cause significant pain and disability. And, this is especially true for children who are at higher risk of serious complications because of their small body size.⁵ When an individual is injected with venom from a snake, it can cause paralysis, blindness and death.⁶

MYTH: All venomous snakebites are the same.

FACT: According to Spencer Greene, MD, MS, FACEP, FACMT, director of the medical toxicology consultation services at Ben Taub General Hospital and Texas Children's Hospital, and a consulting toxicologist for the Southeast Texas Poison Center, "There are dozens of components in snake venom. Pit vipers have enzymes, metals and other antigens that can cause a variety of toxicity, from tissue damage to abnormal blood clotting (i.e., too little or too much), airway swelling and



other signs and symptoms. Some pit vipers also have neurotoxins that can decrease muscle strength and lead to paralysis, including respiratory paralysis. Coral snakes, the other group of venomous snakes found in the U.S., are not vipers.

They're elapids, and their toxicity is primarily neurotoxic. There is some local swelling but you don't see the tissue destruction common in pit viper bites."

MYTH: The symptoms of venomous snakebites occur immediately.

FACT: This is true for some venomous snakebites, but not for all. So, regardless of symptoms presenting immediately, medical treatment should be sought.

Symptoms depend on the type of toxin(s) secreted into the bite and on how much toxin is present in the tissue. Types of symptoms are attributed to four toxin categories: cardiotoxins (affecting the heart tissue), neurotoxins (affecting the nervous system tissue), cytotoxins (affecting the site of the bite or the tissue that absorbs the toxin) and hemotoxins (affecting the blood coagulation system).⁶ As a result, symptoms can include bleeding, breathing difficulty, blurred vision, convulsions, eyelid droop, low blood pressure, nausea and vomiting, numbness, pain at the site of the bite, paralysis, rapid pulse, shock, skin color changes, stomach and abdominal pain, swelling, tingling, tissue damage, thirst, tiredness, weakness

and weak pulse.⁵ Other complications include vision damage, compartment syndrome, infection, limb loss, gangrene, sepsis, internal bleeding, cardiac damage and respiratory compromise.⁶

While pit viper bites are typically painful and result in symptoms that occur right away, symptoms from coral snakebites often don't develop for hours.⁵ And, if left untreated, a concentrated snakebite will leave an individual paralyzed, blind⁷ and, potentially, dead from cardiac and renal failure.⁸

MYTH: Venomous snakes always deliver venom when they bite.

FACT: Snakes voluntarily deliver venom, so not all bites are venomous. Nonvenomous bites are known as dry bites. According to estimates, 20 percent to 25 percent of pit viper bites and 50 percent of coral snakebites are dry bites.² In addition, some snakes only deliver a specific amount of venom.⁹

Symptoms depend on the type of toxin(s) secreted into the bite and on how much toxin is present in the tissue.

Accretion of venom in snakes occurs in the mandibular gland that contains large alveoli (sacks made out of various types of tissues), which can contract or expand. The full venom solution sits inside the alveoli until it is used. When attacking, a snake will pull out its fangs to bite the victim, during which time it can contract the gland to release venom into a duct that carries the venom from the gland to its fangs, which release it into the victim's bloodstream.⁷ However, snakes aren't known to attack prey larger than themselves unless they strike in self-defense. And, a defensive bite is more likely to be a dry bite. However, if a snake has already been injured, has been harassed or is in pain, it is more likely to deliver a fully envenomating bite.¹⁰



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Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care

All hospitals that provide emergency care should stock CroFab® appropriately⁵:

- ▼ 12 to 18 vials—enough antidote to treat one patient for 8 to 24 hours

Indication

CroFab® Crotalidae Polyvalent Immune Fab (Ovine) is indicated for the management of patients with North American crotalid envenomation. The term crotalid is used to describe the Crotalinae subfamily (formerly known as Crotalidae) of venomous snakes that includes rattlesnakes, copperheads, and cottonmouths/water moccasins. Early use of CroFab® (within 6 hours of snakebite) is advised to prevent clinical deterioration and the occurrence of systemic coagulation abnormalities.

Important Safety Information

The most common adverse events reported in clinical studies were mild or moderate reactions involving the skin and appendages (primarily urticaria, rash, or pruritus), which occurred in 14 out of 42 patients. Three patients experienced a serious adverse event. Two patients had a severe allergic reaction (severe hives and a severe rash and pruritus) following treatment. One patient had a recurrent coagulopathy due to envenomation, which required rehospitalization and additional antivenin administration. In clinical trials, recurrent coagulopathy (the return of a coagulation abnormality after it has been successfully treated with antivenin), characterized by decreased fibrinogen, decreased platelets, and elevated prothrombin time, occurred in approximately half of the patients studied. Recurrent coagulopathy may persist for 1 to 2 weeks or more. One patient discontinued CroFab® therapy due to an allergic reaction. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also be at risk for an allergic reaction to CroFab®.

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Because a snake's glands are "spongy," it is nearly impossible for it to expel all of its venom. After a bite, it takes between 15 days and 20 days for the secretory tissue to refill the glands. Nevertheless, venomous snakes may possess dangerous quantities of venom within a day or two of its expulsion.⁹

Snakes voluntarily deliver venom, so not all bites are venomous.

MYTH: A baby venomous snake is more venomous than an adult venomous snake.

FACT: Actually, the opposite is true. An adult's venom is much more deadly than the venom in a baby snake. Not only do studies show that the "activity level of some venom enzymes tends to increase with the size and age of the snake," but an adult snake can deliver a lot larger venom dose than a smaller one. For example, a baby eastern diamondback rattlesnake can typically deliver less than 70 milligrams of venom, whereas an adult can deliver between 492 and 666 milligrams; 848 milligrams is the maximum dose that can be delivered in a single bite. A lethal dose in an adult human is about 100 milligrams.¹¹

MYTH: When bitten by a venomous snake, individuals should try to extract the venom.

FACT: After failing to obtain medical attention, tourniquets and electrotherapy, the next most dangerous myth pertaining to venomous snakebites is trying to extract the venom by sucking it out or slashing the wound. Extraction is one of many home remedies (including applying ice, immersing the wound in water and drinking alcohol or caffeine) that worsen the effects of the snakebite.

Without a doubt, attempting to extract the venom delays getting medical attention, and because the venom spreads very quickly into the blood system, time is critical. Attempting to suck the poison out of the wound can cause the poison to spread to the mouth and even into the lymphatics through any cuts in the lips or gums. Using suction cups contained in snakebite kits to remove venom from a bite is also inadequate because the venom progresses into the lymphatics much faster than it can be extracted. And, finally, cutting the wound will cause more tissue damage and more blood loss that will only weaken the body's immune system.⁶

MYTH: All individuals bitten by a venomous snake are treated the same.

FACT: Treatment depends on the severity of the envenomation. Because the signs and symptoms can vary greatly, which can result in severe complications, a panel of experts developed a unified treatment algorithm in 2011 for the management of pit viper snakebites (the predominant form of snakebite) in the U.S. in hopes of reducing variation in care and possibly improving clinical outcomes.¹² The step-by-step algorithm consists of 15 actions that include assessing the patient, checking for signs of envenomation, checking for indications for antivenom, administering antivenom, determining if initial control of envenomation has been achieved, monitoring the patient, determining if the patient meets discharge criteria and post-discharge planning. In addition, there are steps to follow if envenomation is not present, if envenomation is minor, if initial control of envenomation is not achieved, as well as when to call a physician expert, when to administer maintenance antivenom therapy, post-discharge planning and treatments to avoid in pit viper snakebite.

Medscape also provides a list of "approach considerations" for pit viper snakebites that is divided into fields of care and hospital management. Fields of care consist of pulmonary, cardiovascular, local wound, gastrointestinal, hematological and central nervous system, each of which contains a scale of symptoms from none to moderate or severe that physicians can use to calculate a severity score to determine whether antivenom therapy is required.¹³

MYTH: There is a shortage of antivenom to treat venomous snakebites.

FACT: Today, chances of dying from a venomous snakebite are very low because there is antivenom to reverse its effects. "In areas where snakebites are common, many, if not most, hospitals carry CroFab, which is used to treat pit viper bites. Pit vipers account for approximately 98 percent of bites from venomous snakes in the U.S., so it's important to have access to it," says Dr. Greene. "Coral snakes account for approximately 2 percent of venomous bites. There are three species of coral snakes in the U.S. Toxicity is unheard of from Arizona coral snakes. Significant toxicity is rare from Texas coral snakes. It's only Florida coral snakes that typically cause serious neurotoxicity, so it's important to have antivenom available in areas where these bites are common."

Snakebite antivenom is divided into two types: monovalent, which is useful against only one type of species, and polyvalent, which treats several types of venomous snakebites.¹⁴

In the U.S., there is only one polyvalent antivenom, which treats pit viper bites. CroFab (crotalidae polyvalent immune fab, ovine), manufactured by BTG International and approved by the U.S. Food and Drug Administration (FDA) in 2000, is produced by milking the venom from four species of snakes in Utah that is shipped to Wales for processing and then injected into sheep in Australia. Once the sheep create antibodies to the

venom, blood samples from the sheep are sent back to Wales to manufacture the antivenom. According to BTG, a typical dose involves four to six vials of CroFab given intravenously over an hour.¹⁵

Previously, Wyeth's USA Polyvalent was also available to treat pit viper bites. But, after CroFab was determined to be more specific against rattlesnake venom and less allergenic, manufacturing of the Wyeth product was discontinued.¹⁶ Looking ahead, a competitor to CroFab will become available in 2018, which could help to lower the price of treatment. The new product is a result of a settlement of an infringement complaint filed by BTG against Instituto Bioclon of Mexico and Rare Disease Therapeutics of Nashville, Tenn., for the "unlawful and unauthorized importation and sale into the U.S. of certain crotalid antivenom pharmaceutical compositions that infringe one or more claims of BTG's U.S. Patent No. 8,048,414 (the '414 patent')." The agreement will allow Bioclon to sell its crotalid antivenom product relying on BTG's 414 patent beginning October 2018, with BTG receiving a royalty on sales until the patent's exclusivity period ends in 2028.¹⁷

There is also only one monovalent antivenom in the U.S., available since the 1960s, to treat coral snakebites (endemic to the southeastern U.S.). However, in 2003, Pfizer/Wyeth stopped producing the antivenom known as Micrurus fulvius, which is developed using horses as hosts to create antibodies to the venom. In response to the dwindling supply, FDA has extended the use-by dates on existing antivenom in frozen storage several times after testing samples for efficacy and safety. In addition, three Florida hospitals, which treat between 75 and 80 coral snakebites a year, are now participating in an end-phase clinical trial of experimental antivenom. Patients being treated for a coral snakebite are given the option of receiving the existing antivenom product or participating in the trial of the newer drug, which is funded by an FDA grant.¹⁸

If necessary, antivenom from other countries can be used. For instance, antivenoms are produced in Brazil and Costa Rica for non-North American coral snakes. And, Mexico produces antivenom that is likely effective for coral snakebites in the United States.¹⁹

Guidelines for stocking antidotes at hospitals that provide emergency care were established in 2009 by an expert panel and are expected to be updated in mid-2016. The guidelines were established because it was documented that important antidotes such as antivenom were not stocked at all or were stocked in an insufficient amount. The panel identified 24 antidotes for stocking, 12 of which they recommend be available for immediate administration on patient arrival; another nine, which included CroFab, that they recommend be available to administer within one hour of the patient's arrival, allowing the antidote to be stocked in the hospital pharmacy if the hospital has a mechanism for prompt delivery

of antidotes; and three more that they recommend be stocked by the hospital but are not usually needed within the first hour of treatment.²⁰

Florida has its own antivenom bank. Administered by the Miami-Dade Fire Rescue Department, the bank was started as a private project, and after years of development, it was able to dispatch the first antivenom in 1996. The bank sends the appropriate venom whenever it is notified by emergency departments, hospitals and poison centers that someone has been bitten by a venomous snake. Antivenom is available to facilities not only in Florida, but also to other states in the U.S. and areas outside the U.S. in North America, via an arrangement with American Airlines, which takes the antivenom on the first available flight to be met with a rescue official at its destination.¹⁴

MYTH: Antivenom isn't always effective.

FACT: According to the World Health Organization, "Antivenoms can prevent or reverse most of the snakebite envenomings effects, and play a crucial role in minimizing mortality and morbidity."²¹ Antivenom consists of antibodies that bind to the venom and chemically change it to something that cannot interact with the body, thus neutralizing its effects and halting further damage. "Think about your immune system," says Dr. Greene. "One of the ways a body fights a foreign substance is by making antibodies that specifically bind to those antigens and keep them from binding elsewhere and causing damage. Antivenom is essentially purified/modified antibodies made in an animal host that can bind to various snake venom antigens, keeping them from exerting toxicity until they are removed from the body."

Today, chances of dying from a venomous snakebite are very low because there is antivenom to reverse its effects.

Of course, the right type of antivenom must be given. And, it is recommended to be given early as it cannot reverse damage already done. Antivenom "is recommended to be used in the first six hours, but [patients] should see a benefit even afterward if there is still circulating venom for it to bind," says Dr. Greene. "That being said, there's a minimum amount of damage that is determined shortly after the bite that antivenom cannot reverse or prevent. Antivenom won't work if it's given incorrectly or given for the wrong species. For example, CroFab

won't work for coral snake envenomations because the antigens are completely different and toxicity manifests differently."

While CroFab is FDA indicated for the treatment of pit viper envenomations, there is currently a study being conducted to evaluate the recovery from copperhead snakebites in patients with mild or moderate venom effect who are treated with CroFab.²² "Copperheads are pit vipers, but they were not included in the original research on CroFab, so there's no proof that it works on copperhead bites," says Dr. Greene. "And there are some people who minimize the potential significance of copperhead bites, so they don't want to use antivenom if it's not going to confer a benefit. I think people inappropriately minimize the significance of copperhead bites. People can have significant morbidity and, occasionally, mortality from these envenomations."

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The study, which enrolled 76 patients and was conducted by emergency physicians, toxicologists and surgeons at hospitals in regions where copperhead bites are common, compared recovery with antivenom versus placebo as measured by the Patient Specific Functional Scale 14 days after treatment. "The study has just concluded, and the data are being analyzed, but in my experience, people tend to improve faster when they get antivenom than when they don't," adds Dr. Greene. "Hopefully, the study [for which he was principal investigator at two sites: Ben Taub General Hospital and Texas Children's Hospital] was powered sufficiently to show a difference. I would hate for people to not use antivenom because the study wasn't large enough to show the difference."

Dispelling the Myths Now

With so few cases of venomous snakebites, the myths about proper treatment continue to subsist, not just among the general public, but among medical professionals as well. Treatment shortcomings often arise when physicians who were trained years ago to treat venomous snakebites with

outdated methods continue these dangerous practices today. "Most of the hospital interventions such as prophylactic antibiotics and surgery that were previously recommended are ineffective and detrimental," says Dr. Greene. Today, the only effective treatment is "antivenom combined with supportive care." Until doctors are educated about the current treatment processes, which include the recommended guidelines and published algorithms, Dr. Greene urges that patients be attended by physicians experienced in treating snakebites. ❖

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RONALE TUCKER RHODES, MS, is the editor of BioSupply Trends Quarterly.