Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/the-3-critical-aspects-of-snake-bite-management/11389/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The 3 Critical Aspects of Snake Bite Management

Announcer:

You're listening to ReachMD.

This medical industry feature, titled "Snake Bite Management: 3 Critical Aspects" is sponsored by BTG Specialty Pharmaceuticals.

To view the images references, please visit ReachMD.com/SnakeVenom to view the video. Please stay tuned for Important Safety Information at the end of this episode and see the full prescribing information at crofab.com

Here's your guest, Dr. Bill Banner.

Dr. Banner:
Hello, I'm Dr. Bill Banner. I'm a pediatric critical care attending and a medical toxicologist with the University of Oklahoma Poison Center. I'm here to speak to you about the management of North American pit viper envenomation. Just so we differentiate what species we have here in North America, we have Crotalinae pit vipers, which is what we're talking about today. And then we have also a group of Elapidae, which is the coral snake in the United States. The coral snake is down in the Gulf region, and there's some species in the Southwestern desert that are fairly rare. We are talking about what 98% of the snake bites are due to: the rattlesnakes, the copperheads, and the moccasins, which is also called a cottonmouth; it's the same snake. We see a variety of pit vipers in the United States, and according to Poison Center data, there are approximately 5,000 to 9,000 bites a year that present to the emergency department. Copperheads are the most common snake bites coming in at about 50% of all bites, followed by unknown pit vipers. This means the patient couldn't identify the type of snake that bit them, but they knew it was a pit viper based on location or the types of snakes in the area. Now, in the United States, the reporting of snake bites is increasing. We know that since 1999, Poison Control Centers have been involved almost two and a half times more commonly. As you might expect, it is predominantly a male problem, as they seem to be interacting with snakes more and out more in the environment. And it's a summertime phenomenon, particularly in the states where the temperatures drop more in the wintertime. So we see this epidemiology. The picture here gives you some idea of the typical appearance of these envenomations. Once you've seen a few snake bites, it's not much question that you've got something going on that's a problem. So I think what we need to think of as kind of a hand-and-foot kind of phenomenon, or at least lower extremity-upper extremity. It's rare to have a torso bit or a head bite, but they do occur, and they are always very serious. The characteristics of the pit viper are very unique, and have developed over time to make them a very efficient hunter. To start, they have a triangular-shaped head, as you see here. This can be seen without having to get close to the snake. Pit vipers also have elliptical pupils, which is a unique characteristic in North America. They are called pit vipers because they have a unique organ that is situated between the eye and the nose, just below it. That's an infrared hunting device. The reason that the Navy named its heat-seeking missile the "Sidewinder" was after the sidewinder rattlesnake, because it's also a heat-seeker. They also have a very unique feature, which is anterior fangs. They have a retractable mechanism that is actually connected by a tubular tooth or fang to their upper jaw where they have a gland that actually manufactures their venom. And when they squeeze that gland, it injects. So it's a two-step process, where the snake strikes and puts a fang through the superficial layers of the skin, and then contracts and injects. But the snake doesn't always inject venom with every bite. The classic presentation is two fang marks, but there may only be one fang mark, and at other times there may only be scratches. With CroFab, it isn't necessary to identify the type of snake, as long as we know it's a pit viper. I don't recommend you handle the snake dead or alive. Even a dead snake can cause an envenomation. If you're able to take a picture without putting yourself at risk, that's fine, but please don't bring the snake into the emergency department. The next thing we're going to talk a little bit about is how antivenoms have developed around the world and, in particular, the United States. Antivenom, as we know it today, is a relatively recent development. Research began on using antibodies for treatment of envenomations in the late

1800s. As more experience was gained and the benefit of using antibodies to manage envenomations was seen, the process became more developed, allowing for some degree of specificity and efficacy. In the 1950s, the first commercial pit viper antivenom for humans was developed and released by Wyeth. This was a game changer, but unfortunately it was known to cause a high degree of significant allergic reactions, including fatalities. Due to concerns over time with this antivenom and the high risk of allergic reactions, a group of physicians and toxicologists came together to develop an antivenom that used different technology; FAB versus a full IgG antibody and using snakes that are entirely native to the United States. This went through a purification process that would eliminate antibodies not specific to the snake bite, and hopefully improve safety. As a result, CroFab was developed and approved in the early 2000s, and has radically changed how snake bites are managed. Due to the improved safety profile and efficacy, CroFab was able to decrease the number of fasciotomies performed on patients and also allowed for a greater number of snake bites to be treated that previously would not have been treated due to concerns of antivenom safety. One of the reasons CroFab is very appealing to us is that it is comprehensive in its species coverage and focused on snakes that we see here in the United States. The Western diamondback, the Eastern diamondback are two big vectors of rattlesnakes, although there are more than 20, and closer to 30 different types of rattlesnakes and subspecies. It is also made with the venom of a water moccasin, which provides coverage for the Agkistrodons, which include the copperheads. Those two seem to go hand-in-hand a little bit in their venom toxicity. The fourth snake that they use is a particularly toxic snake that exists mostly in the Southwestern desert and that is the Mojave rattlesnake. And even though it's named after the Mojave Desert, it's very common in Southern Arizona and on into New Mexico, and even into that part of Texas that borders on New Mexico. So having the Eastern and Western diamondback of Mojave and the water moccasin to manufacture CroFab gives it a good specific North American antivenom profile. Why treat these envenomations? Well, I think once you've seen a few bites from pit vipers, you can understand the need for treating them. Certainly, pain and disfigurement damage to tissue is part of it, but these can also be a very life-threatening envenomations. So let's go more into what's going on when you get injection. What you need to realize is that there's a purpose to these venoms. It's a very complex mixture. People often ask why don't we make a monoclonal antibody. And the reason is that there's no single antibody that would cover the mixture of these toxins because they're so far flung. You have to have something that's sort of a shotgun approach in order to neutralize all the different proteins present. Here's a list of some of the pit viper venom components, but venom can contain over 40 different venom enzymes and proteins. There are things that can cause worsening coagulation and anticoagulation; neurotoxins, cytotoxins, hemotoxins, metalloproteinases. There are all kinds of studies that have been done on the chromatography of these venoms. It's fascinating scientific stuff. Since snakes cannot chew their prey, they have to start digesting them before they eat them; that's the role of venom. The venom components work together to improve the ability of the snake to defend itself, but more importantly to feed. Here's a little pop quiz. I'm sure you've been thinking about this. What is the purpose of a snake's venom? Well, first, you have to realize that the snake cannot outrun some of its prey. So it wants to keep them very close to them after the envenomation occurs, particularly in the dark. The second thing is that snakes ingest their prey as a whole organism. And because they eat their prey whole, they have to start the digestive process from the inside out in order to facilitate that process. So the answer to our question is the primary purpose is to immobilize and digest the prey that they're trying to eat. Defense, as I said, is a secondary consideration for them. As you can see here, the consequences of envenomation can be quite disfiguring, and also life-threatening. There's a high risk for long-term morbidity, as well, with snake bites. There's the potential for irreversible local and systemic damage. As you can see here, the snake bite can cause a lot of blistering, particularly in places where you've got a need or function like your fingertips or your whole hand. You can see compromise where you lose digits. You may lose function. You may also have sensory loss. In this instance, the child actually picked up a small snake. And even though we think copperheads are not very toxic, this child did not have the wherewithal to let go of the snake, and so it envenomated the child multiple times on that hand. Neutralizing the venom was critically important or he might have had a lot more damage. So he received CroFab and did quite well. So we know that there are a lot of local effects, but we're also going to talk about some systemic effects. You've got to know that with any snake in our pit viper family, you can have death as a possibility. It's important not to overgeneralize pit viper bites since there are so many factors that go into whether or not the snake envenomates and how much venom, if at all, is injected. Here are some examples of signs and symptoms that you might expect to see. We try to divide these into three different categories for you to think about, and that's local, hematologic, and the systemic. Local is what we think when you think most often about because you can take pictures. You got the swelling, the pain is way out of proportion to what it looks like, and that's also cytokine release with an inflammatory cascade. They get erythema, they get blisters, they get bruising, a lot of soft tissue damage. The reason we see a lot of hand bites is because people are putting their hands near the snake, either intentionally or accidentally reaching behind a rock or working in the garden. According to data from the North American Snake Bite Registry, 100% of patients experienced local tissue damage and swelling; whereas, about 20% of patients will experience thrombocytopenia or hypofibrinogenemia. The other common thing that we see are these hematologic effects. Venoms by different species of snake and different families of snake will produce different effects on the coagulation system. The big Western diamondbacks can cause fibrinogen to drop very quickly, and you may get a call that the lab can't even measure it. You may see pro-times go up, and platelet counts may drop rather precipitously in the 20,000 to 10,000 range. I've seen them as low as 3,000 to 4,000 very quickly after an envenomation. Some snakes, like our pygmy rattlesnake, tends to drop platelet count, but spare

fibrinogen and INR. I don't know why, but people have studied these venoms and found different particular proteins that may cause these different effects. This may rapidly lead to effects like hypotension. Also, the ability of the venoms to degranulate mast cells, and thereby release histamine and other inflammatory mediators may also contribute. Plus, there's components of the venom that can drop your blood pressure directly. One of the things that the venoms do very quickly is to try to cause you to vasodilate and cause you to leak fluid out of the blood vessels, particularly into your GI tract. And that also drops your blood pressure. That's all part of the immobilization process. Vomiting and diarrhea are fairly unique findings in that they may indicate a more severe envenomation. The angioedema, as we mentioned, can have – from histamine release, and so you can have a patient whose lips become swollen, or who has more traditional itching type reaction. It can fool some people, but it's not an allergy per se; it is simply angioedema. And last, but not least, and most people think of Asian snakes as having this neurotoxicity, but we have two particular species in North America; the Mojave rattlesnake and, to a lesser extent, the timber rattlesnake that can affect cranial nerves and cause neurotoxicity. The type of neurotoxicity associated with these two snakes is sort of a top-down, head-to-toe rather than toe-to-head. So it's very different from Guillain-Barre, and it's more like botulism. You see cranial nerve functions change and patients will complain of double vision. It's not very common in the timber rattlesnake, but it's fairly common in Mojave envenomation, and it's fairly characteristic to see somebody that can't open their eyes or can't move their eyes about very well. I've seen this progress to where they were completely areflexic and on a ventilator, particularly in children. That is a very ominous finding. So, how much you get, where you get it; all of these things will contribute overall to these effects. I will tell you, the only caveat out of these is that if you're bitten on the head or the neck, or on the torso, you are going to have systemic effects that can be very life-threatening. So, you have to treat any snake bite as a critical situation until you've got it under control. The takeaway from this slide, in my experience, is that all pit viper bites can affect three main body systems: local, hematologic, and systemic. Why are these effects concerning? The consequences of these things may be very obvious, but local effects may cause you to lose a digit. And back in the day when we were afraid to use the antivenom, we saw patients refuse treatment and have a lot more damage and local manifestations that reduced function on their extremities, particularly on the hands. Obviously, they're cosmetic and they're never going to look right, but they may, even with the picture we have here, end up with a reasonably good cosmetic result. It can heal and granulate and look fairly functional. And with good intervention, you can prevent the loss of function. And I think that's the most important thing to remember, is that the deeper the effects, the more quickly you treat them and intervene, you can start to avoid particularly those damages to the extremities. In terms of the hematologic effects, they can have a very low percentage of bleeding, surprisingly. But you can see some laboratory values that will make you go crazy. And again, before the evolution of CroFab back prior to 2000, we would see patients that literally had oozing and loss of capillary integrity throughout large portions of their body when they refused antivenom treatment. Their hemoglobin would drop and they would not so much have an acute bleeding episode, as they would just kind of ooze. The laboratory values, particularly fibrinogen, may be undetectable. Platelet counts may be below 1,000, and INR may be as high as something like 13. Again, this is about 20% of the time that you're going to get into these problems. The last thing is obviously the systemic effects. You can die from this. Every year, we have some patients that don't seek treatment or have some unusual presentation. There can be irreversible induced damage and they may need to be intubated. We had a person who was recently bitten by a timber rattlesnake that had to be intubated for respiratory failure. They can go into shock very quickly as a result of fluid loss. All of the kinins and vasoactive substances that are released during these events contribute to mortality. And last, if you think about the function of the snake venom, it's to induce the digestive process. If you don't neutralize the venom successfully, it will start to break down muscle. The most striking case I saw had a CK of 234,000; that's a six-digit number. The patient had fatal rhabdomyolysis and was literally digested at autopsy. So that's something to keep in mind as something to aggressively pursue treatment. The first, and more important principle that we need to talk about in terms of management of these snakes is something that we call initial control. I don't like the term loading dose, because that implies there's a dose and you give that loading dose and you're done. No. Initial control means that you have successfully achieved certain endpoints. The patient comes in and they're having progressing local effects, swelling, pain moving up the extremity, obvious tissue damage, and you want to get that to stop. Usually if you run your hand along the patient's extremity from proximal to distal, you'll hit a point where all of a sudden, you realize you're causing them some discomfort. Obviously, we don't go any further, particularly in children. That is a distinct finding and that will give you an indication of whether the venom is progressing by the lymphatic drainage. So it's a fairly slow process. They may skip a little bit where they get local lymph nodes in their groin or their axilla that are painful, but the rest of the venom is progressing slowly up the extremity. We'll talk a little bit more about distribution edema, but you can see that that initial process of stopping local progression is incredibly important. Secondarily, you want to make sure that the patient's systemic symptoms are resolved. Getting them out of shock and any kind of neurotoxic involvement is neutralizing the venom. Although there may be a slower improvement, it should start to trend in the right direction. And third, you need to reverse the coagulation. In certain types of shock situations like sepsis, you're giving them platelets, it's taking a long time to correct the process, even after antibiotics, not so with antivenom. When you start antivenom, you will see over the course of an hour and a half all of a sudden their platelet count's improving, fibrinogen may go back up into the normal range. So it's a very rapid process of reverse in coagulopathy and halting the damage that's being done to the coagulation cascade. Another way to understand initial control is that you're giving enough venom antibodies to the patient to neutralize

a sufficient unknown quantity of venom toxins to halt the progression and prevent it from getting worse. That's why it's so important to give an adequate dose up front; otherwise, you're just kicking the can down the street. The last point in want to emphasize is that, regardless of species, time is tissue. According to the North American Snake Bite Registry, all envenomated patients reported local tissue effects. CroFab can prevent the worsening of tissue damage, but antivenom will not reverse damage that has occurred prior to treatment. Clinicians should treat with a sense of urgency in order to reduce the potential of long-term morbidity. That includes loss of a digit or loss of function that may impact the patient for a lifetime. I think the biggest mistake people make is they see a rattlesnake envenomation, and it's pretty easy to say, 'Oh my gosh, we've got to do something right away.' The less aggressive snake venoms like the copperheads, people tend to say, 'Well, we've got some time.' But you don't. Damage is occurring just like with any other snake that you could see. You're going to have swelling and ecchymosis in a large percentage of those, even when we say that there are less directly toxic venoms. So, remember the key take-home point is time is tissue, and CroFab should be administered as soon as possible in patients with North American pit viper envenomations.

Announcer:
Let's now hear the indication and important safety information for CroFab®.

INDICATION

CroFab® Crotalidae Polyvalent Immune Fab (Ovine) is a sheep-derived antivenin indicated for the management of adult and pediatric patients with North American crotalid envenomation. The term crotalid is used to describe the Crotalinae subfamily (formerly known as Crotalidae) of venomous snakes which includes rattlesnakes, copperheads and cottonmouths/water moccasins.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Do not administer CroFab® to patients with a known history of hypersensitivity to any of its components, or to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is readily available.

WARNINGS AND PRECAUTIONS

Coagulopathy: 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; one patient required re-hospitalization and additional antivenin administration. Recurrent coagulopathy may persist for 1 to 2 weeks or more. Patients who experience coagulopathy due to snakebite should be monitored for recurrent coagulopathy for up to 1 week or longer. During this period, the physician should carefully assess the need for re-treatment with CroFab® and use of any type of anticoagulant or anti-platelet drug.

Hypersensitivity Reactions: Severe hypersensitivity reactions may occur with CroFab®. In case of acute hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, discontinue infusion and institute appropriate emergency treatment. Patients allergic to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also have an allergic reaction to CroFab®. Follow-up all patients for signs and symptoms of delayed allergic reactions or serum sickness (e.g., rash, fever, myalgia, arthralgia).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% of subjects) reported in the clinical studies were urticaria, rash, nausea, pruritus and back pain. Adverse reactions involving the skin and appendages (primarily rash, urticaria, and pruritus) were reported in 12 of the 42 patients. Two patients had a severe allergic reaction (severe hives and a severe rash and pruritus) following treatment and one patient discontinued CroFab® due to an allergic reaction. Recurrent coagulopathy due to envenomation and requiring additional treatment may occur.

To view the full prescribing information visit Crofab.com.

This program was sponsored by BTG Specialty Pharmaceuticals. If you missed any part of this discussion or to find others in this series, visit ReachMD.com/SnakeVenom. This is ReachMD. Be part of the knowledge.