NEWS FROM THE PIT

Arizona Poison and Drug Information Center

Rattlesnake Venom Variation
What is it and why does it matter?

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The vast majority of the 8,000 or so venomous snakebites in the United States each year are inflicted by rattlesnakes. And, if you are like most ED clinicians, you were never trained on snakebites and have likely never treated one. And you've probably heard a lot of stories about which rattlesnakes are most deadly, baby rattlesnakes being more dangerous than adults, new hybrids, etc. So, what should you expect when a patient shows up in your ED with a rattlesnake bite?

In this News from The Pit, we'll concentrate on rattlesnake venoms and how they can vary from bite to bite. First, lets start by clarifying the terminology: "venom" is a cocktail of toxins produced by an organism with an accompanying delivery mechanism, like the fangs of a snake or spider, or the sting of a wasp, ant, or scorpion. And, in the case of rattlesnakes, this cocktail contains several kinds of toxins, the combination and proportions of which will shape the clinical effects in your patient.

NEWSLETTER HIGHLIGHTS

Venom yield, composition and variation

Image 1: Adult male Western Diamond-backed Rattlesnake

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Let's start with the simplest part of the equation: how much venom was injected into your patient? That's the simple part because the answer is easiest – you don't know. At least not right away. It may take a few minutes to a few hours for visible signs and symptoms of a significant envenomation to appear. But there are some bits of information you can elicit quickly from your patient and other witnesses that may be informative. Was there more than one bite? How long did the snake hang on? How large was the snake? Multiple bites, a snake that hangs on for longer than a moment (most bites are a brief stab), and larger snakes, all argue for the likelihood of a relatively larger venom dose. To be sure, some rattlesnake bites are "dry," that is, the snake does not inject enough venom to produce clinical effects. But the percentage of "dry bites" varies between studies and we believe true dry bites are quite uncommon. In any event, the amount of venom delivered is highly variable and snake size is probably the most misunderstood factor. Baby snakes are not more dangerous than adults, contrary to the common belief. Venom yield increases exponentially with snake length and baby rattlesnakes are the size of pencils, so they have a tiny fraction of the venom available in adult rattlesnakes. Big rattlesnakes sometimes deliver a small venom dose, but a baby is not capable of delivering anything close to the volume an adult can deliver. That said, bites by baby rattlesnakes are often clinically significant, just not as potentially devastating as a serious bite by a large rattler.

Image 2: Fresh venom samples from an adult Rock Rattlesnake (R) and a much larger adult Black-tailed Rattlesnake (L); yielding about 0.08 and 0.35 mL of venom, respectively. The yellow color is caused by L-amino acid oxidase, a common venom constituent.

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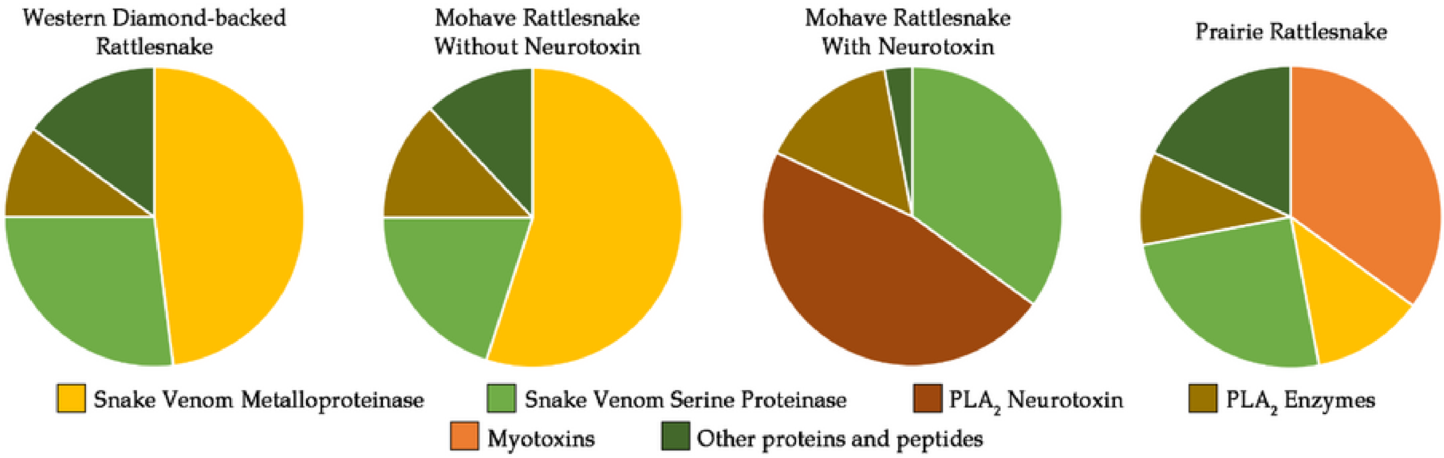
What about venom composition? And what effect does it have on my patient? Steve Mackessy, who studies venomous snakes and the biochemistry of their venoms at the University of Northern Colorado, divides rattlesnake venoms generally into two dichotomous groups he calls "toxicity vs. tenderizers." The highly toxic venoms cause paralysis and death, at least in lab animals, and they are commonly found in juvenile rattlesnakes where they are hypothesized to subdue ectothermic ("cold-blooded") prey like lizards more efficiently. But not to worry; the difference in toxicity is only significant to creatures weighing a few grams, like frogs and lizards. In humans, venom volume is easily the most important factor clinically. Tenderizing venoms are less lethal to lab animals and their major constituents are enzymatic, primarily causing tissue injury and bleeding. And we know that the proportion of tenderizing vs. highly toxic components varies not only between rattlesnake species, but geographically between populations within a species, and ontogenetically within individuals as they age.

A great example of venom variation within a species is the Mohave rattlesnake (*Crotalus scutulatus*), one of a few species in which adults retain venom that is highly toxic in adulthood without the tenderizing properties. Found from southern California, southeastward to the Big Bend region of Texas and deep into Mexico, Mohaves have long been known for their ability to kill lab mice with very little venom. But, in the 1970s, a large area was discovered in southcentral Arizona where the same species produces tenderizing venom without paralysis, which is much less lethal to lab animals. Moreover, recent research indicates that the two populations are constantly exchanging DNA in the intergrade zone and neither venom type seems to be spreading into the other population. The evolutionary pressures causing this phenomenon are unknown but remain the focus of continuous study. And human mortality from either population is extraordinarily rare.



Examples of the distribution and proportions of some of the dominant protein families in the venom of adult rattlesnakes from three of the most common Arizona species. Other toxin combinations and proportions exist in various geographic subgroups. (Adapted from Mackessy 2021)

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We should note here that, while fear of extreme lethality due to respiratory paralysis caused by Mohave rattlesnake bites arose from all those benchtop studies, the history of human cases has been quite different. Fatalities appear to be no more common than from bites by other rattlesnakes and respiratory failure/paralysis has proven to be extraordinarily rare following rattlesnake bites, including by Mohaves. In fact, there are only about five or so fatalities from venomous snakebites each year in the U.S, or less than 0.1% of bites.

So, what do we know about why venom constituents vary? A good place to start is the "arms race" between venomous snakes and their prey. Multiple examples of coevolution have been documented, wherein prey animals continually develop physiological resistance to local snake venoms while the snakes develop novel toxins that elude the prey's evolving immunity. Thus, prey selection and foraging strategies are believed to affect venom components, with animals in different habitats feeding on different prey, and baby rattlesnakes eating different prey than adults. Most of our large common rattlesnake species feed primarily on rodents as adults, and rattlesnake venom is believed to have evolved to subdue prey, rather than for defense. In fact, their venom does not work quickly enough to save the snake from an antagonist (contrast with Gila monsters, who do not need venom for the eggs and nestling animals they eat but who's venom produces immediate severe pain).

Social media is awash with sensational stories about rampant hybridization between rattlesnake species, venom toxicity changing over just a few decades, and mythical animals like the "Mohave green" – all of which scientists know to be untrue but which persist anyway. While we haven't unraveled all the answers about rattlesnakes and their venoms, we have a pretty good understanding of the big story. And we're working hard on the fine details!

Image 3: Venom extraction from an adult Mohave Rattlesnake

Image 4: Adult male Mohave Rattlesnake

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The bottom line is this: rattlesnake venom – and what it does to your patients – is variable due to multiple factors, only some of which we understand. And there are occasional outliers; rattlesnakes with random mutations of genes that either control toxin properties or that regulate the expression of certain toxins. Thus, clinicians must be alert and prepared for anything to happen following a rattlesnake bite, regardless of the suspected species, while being guided by what has been occurring with rattlesnake exposures in the surrounding region. Of course, current and regionally specific clinical expertise is usually available with a call to your nearest poison control center.

Image 5: The authors, Mike (left) and Dan, collecting venom from a freshly-caught Black-tailed Rattlesnake (in the tube) for research being conducted at the Arizona Poison and Drug Information Center.