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Review Article

An Historical and Medical Review of the North American Timber Rattlesnake (*Crotalus horridus*)

Christopher J. Nash[1] and Timothy B. Erickson[2]*

[1]*Harvard-Affiliated Emergency Medicine Residency Training Program, Massachusetts General Hospital / Brigham and Women's Hospital, USA*

[2]*Department of Emergency Medicine, Brigham & Women's Hospital, Harvard Medical School, Harvard Humanitarian Initiative, USA*

***Corresponding author**

Timothy B. Erickson, Department of Emergency Medicine, Brigham & Women's Hospital, Harvard Medical School, Harvard Humanitarian Initiative, USA, Email: TERICKSON@BWH.HARVARD.EDU

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Abstract

The timber rattlesnake (*Crotalus horridus*), also known as the canebrake rattlesnake or banded rattlesnake, is native to eastern regions of North America. Classified as pit vipers, these snakes can deliver enough venom in one bite to be life-threatening, although they uncommonly victimize humans and even more rarely cause death. This review describes an historical and medical perspective of this once plentiful, and now endangered species of snake. Several factors explain the timber rattlesnake's endangered status including, low reproductive rates, late maturing age, long generational time, disease, and potentially its sensitivity to certain climactic conditions such as temperature and altitude. In addition, human activities which encroach on the snake's natural habitat have vastly reduced the timber rattlesnake populations contributing to their demise. The venom of the timber rattlesnake is multifaceted with some species containing both neurotoxic and hemorrhagic/proteolytic properties. When indicated, administration of the ovine-derived antivenom Crotalidae Polyvalent Immune Fab (FabAV), rapidly reverses coagulopathy and can be life-saving. Continued investigation is needed to characterize the nature and changing geographic distribution of the timber rattlesnake, its toxicological effects, and ultimately its preservation.

INTRODUCTION

Approximately 2700 species of snakes inhabit the planet, of which 375 (14%) are considered venomous. Rattlesnakes (Crotalus sp) comprise 36 of these species. Christened after their namesake row of beads forming the rattle atop their tails, they are all native to the North and South America [1]. The timber rattlesnake (*Crotalus horridus*), also known as the canebrake rattlesnake or banded rattlesnake, is endemic to eastern regions of North America. Classified as pit vipers, they are equipped with long fangs that can deliver enough venom in one bite to be poisonous to humans. In this review, we offer an historical and medical perspective of this once plentiful, and now endangered species of snake.

ANATOMY

The timber rattlesnake is a heavy-bodied serpent that varies widely in outward appearance with some common motifs. Rattlesnakes as a species have some features almost entirely in common - as with all pit vipers, they possess the heat sensitive pits on either side of their face that allow them to locate prey and predators from which the term "pit vipers" is derived. The timber rattlesnake also has vertical pupils in their large eyes as well as a rattle, which produces a characteristic high-pitched buzzing sound. The skin is composed of keeled scales that have a central ridge in contrast to smooth scales. The snake may have one of many different primary colorations-black, gray, brown, or yellow with V or M -shaped cross-bands along their backs as a particular distinguishing feature, typically culminating in a solid black tail preceding the rattle [2] (Figure 1). Their triangular heads are so-shaped due to the presence of venom glands on both sides of the head. The snakes can vary in length, typically between 36 and 60 inches long, though have been reported to be as long as 72 inches [3], with an expected lifespan in the wild of 16-22 years [4]. Their long fangs are retractable and are replaced constantly throughout the life of the snake, meaning defanged rattlesnakes will still remain capable of a venomous strike [1].

DISTRIBUTION

Geographic location alone is generally enough to identify these snakes, which are distributed in southern New England through-out the Appalachian Mountains into Georgia and northern Florida, west to parts of Illinois, Wisconsin and northeastern Texas (Figure 2). Unlike other types of rattlesnakes, they are rarely encountered west of the central United States [5].

HISTORICAL PERSPECTIVE

At the time of the arrival of colonists to North America in the 17th and 18th centuries, the canebrake rattlesnake had a much larger footprint than it does today. At its most vigorous time, it existed in most of New England, even extending to Wisconsin and Minnesota around the Mississippi River valley [6]. For example,

in Massachusetts, the timber rattler was previously "abundant in Essex, Middlesex, Worcester, Suffolk, Norfolk, Franklin, Hampshire, Hampden, and Berkshire Counties until the last-19th centuries [7]". Over time, the snake's population has been dwindling. These days, the animal carries endangered status in the state of Massachusetts [3], and there are believed to be as few as 200 individuals remaining within its borders [8].This trend persists across North America.

The timber rattlesnake, akin to the bald eagle, plays an interesting and important role in the history of the United States of America. Referring to this snake, a writer under the nom de plume American Guesser (believed to be Benjamin Franklin), noted that "the Rattle-Snake is found in no other quarter of the world besides America" and "She never begins an attack, nor, when once engaged, ever surrenders;" it is perhaps no surprise that the colonists found these qualities appealing when displaying its image on the yellow Gadsden flag, known for its coiled rattlesnake on a plain yellow background adorned with the phrase, "Don't Tread on Me."[9] (Figure 3) A recent book published by Levin entitled,

America's Snake: The Rise and Fall of the Timber Rattlesnake,

Figure 1 Timber Rattlesnake (Crotalus horridus) Tony Alter, Newport News, USA, Wikimedia commons.

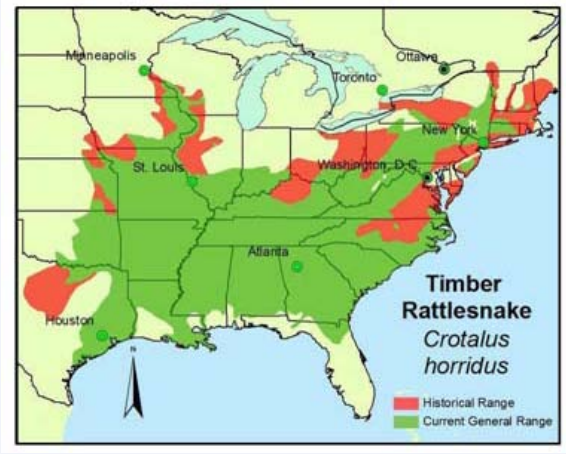

Figure 2 Current and historic range of the Timber Rattlesnake. Venomous Serpents by toddkonitzer (permission granted by the Orianne Society: http://www.orianne.org).

Figure 3 Gadsden Flag of the U.S. Colonies, 1775.

details the tale of the Timber Rattler and its connection to the history of the United States [10].

ENDANGERED SPECIES STATUS

Several factors explain the Timber Rattlesnakes endangered status. Among them is its low reproductive rate, late maturing age, long generational time, disease, and potentially its sensitivity to certain climactic conditions such as temperature and altitude [6,11,12]. Nevertheless, these features are not alone the reason for its decline. Human activities have vastly reduced the Timber Rattlesnake's livelihood. In the 17th and 18th centuries, there were numerous efforts to round-up Timber Rattlesnakes and kill them, devastating large portions of the population [10]. In more modern times, climate change at large [6,12] as well as specific activities such as the construction of roads [13-15] have been hypothesized to be contributing to their demise. Nevertheless, the timber rattlesnake may still be occasionally encountered on hiking trails and in the forests across the eastern United States.

VENOM

There was a time that the venom produced by timber rattlesnakes was believed to be universally weak and less potent than other venomous snakes. It was not until 1967 that Minton discovered that the species could produce a very toxic form of venom. Over time, more research has better characterized the nature of the timber rattler's venom. The venom of the timber rattlesnake varies substantially within the species, with venom types first definitively categorized into four groups in 1992 by Glenn, et al [16]: Type A, Type B, Type A + B, and Type C.

Type A venom, also known as the canebrake toxin or Crotoxin, is a beta-neurotoxin (functions presynaptically) [17] that is active at the neuromuscular junction. The canebrake toxin contains two subunits, one basic and one acidic. Crotapotin is the acidic component which thought to be itself inactive but serves to increase the lethality of the basic subunit (phospholipase A_2) by chauffeuring it to its site of action, increasing its activity by an order of magnitude [18]. The inhibition of ACh release is due to the breakdown of the cell membrane of the presynaptic neuron by phospholipase A_2, diminishing the ability of the neuron to release neurotransmitters [19,20].

Type B venom contains hemorrhagic and proteolytic activity [21]. This venom contains a zinc-dependent metalloproteinase

that works by direct destruction of the basement membranes of capillary blood vessels as well as the nearby extracellular matrix observed microscopically, causing hemorrhage [22]. Additionally, this molecule cleaves the fibrinogen molecule which inactivates it, thereby rendering it incapable of participation in the coagulation cascade, decreasing the body's ability to create the clots that would help halt the bleeding induced by the capillary breakdown [23].

Type C venom is also described in some timber rattlesnakes and is comparatively weak venom. The toxins within are tame in comparison to A and B, and this venom lacks neurotoxic or hemorrhagic properties. Some snakes have venom with both neurotoxic and hemorrhagic/proteolytic properties, though this combination venom is actually less lethal than canebrake toxin alone-in order, the lethality of the venoms are A > A + B > B > C [24]. Additionally, there are small basic peptides (crotamine) that have also been identified in the timber rattlesnake venom with myotoxic effects [25]. A platelet-activating protein known as crotalocytin has also been isolated from timber rattlesnake venom [26,27]. It was shown in the 1960s that the venom of timber rattlesnake (of unknown locale or venom type) measured to be between 0.29 to 0.52 mg/kg via intraperitoneal routes of administration in animal models [16,17,28] and may be as low as 0.006 mg/kg via the intramuscular route [29], among the most potent of all snakebites [30].

Like many types of rattlesnakes, the timber rattlesnake has considerable venom variation geographically [16], and has been described since the 1930s [31,32]. Broadly speaking, the canebrake toxin (Toxin A) is found in two separate areas, one region in the states of Louisiana, Arkansas, and Oklahoma and another region resting in southeastern South Carolina through eastern Georgia and northern Florida [16]; timber rattlesnakes outside of these regions are less likely to have the neurotoxic canebrake toxin in their venom. The underlying reasons behind this are not yet fully understood.

EMERGENCY MANAGEMENT

When bitten by a timber rattlesnake, immediate and correct intervention is of the utmost importance. Immediately after being bitten, it is recommended that the patient be removed from the vicinity of the snake and transported to an emergency department for further treatment. Although it is important to remove all constrictive clothing (such as watches or rings), it is no longer recommended to tourniquet the affected limb or attempt to "suck out" or extract the venom of the snake. Treatment in the emergency department consists of assessment of airway, breathing, and circulation; serial examination of the bite site; laboratory studies including a complete blood count, electrolyte panel, and coagulation profile studies. If indicated, an antivenom should be administered in consultation with a medical toxicologist unless contraindicated (allergy to prior administration of antivenoms or known allergy to papaya or papain [53]). The patient should be monitored in an emergency or intensive care setting. [1]

ANTIVENOM

Historically snake bite treatments were ineffective and varied wildly, ranging from whiskey, strychnine, enemas, electric shocks, and direct incision of the bite (ancient Egyptian priests cut open the bite site in order to "let the evil spirits out"[33]), and application of split chick to the site [34]. Modern antivenoms were first conceived in the 1800s and was improved during the 1900s. Modern antivenoms are derived from antibodies, created by the immunization of animals against venom and collection of the antibodies from plasma after sufficient time has passed for the animal to create the antibodies [34]. Currently, there are three antivenoms that have been developed for the treatment of crotalid bites, and the creation of antivenom compounds (likely in conjunction with improved overall delivery of healthcare) has drastically improved outcomes. Of note, all data here mentioned for these antivenoms includes all crotalid bites and does not distinguish among species. Estimates of mortality from crotalid bites during the 1800s are on the order of 25% -- in more modern times, estimates are that mortality from a timber rattlesnake bite rapidly transported and treated in comprehensive medical facilities is less than 0.1% [33]. In 1954, the first antivenom made available was the Antivenin (Crotalidae) Polyvalent (ACP). This medication was derived from horse serum and was successful at treating crotalid bites at the cost of a number of side effects. Acute type I hypersensitivity reactions occurred in up to a quarter of administrations of this drug, including reports of death by anaphylaxis. Additionally, type III reactions (such as serum sickness) are also common following its administration, as high as 75% incidence [35,36]. In 2000, a newer ovine-derived antivenom called the Crotalidae Polyvalent Immune Fab (FabAV) was made available and is associated with lower incidence of acute adverse reactions, although both acute hypersensitivity and delayed hypersensitivity reactions due still occur with an overall incidence of 5-14% for acute reactions and 16% for serum sickness [33,35,37]. Pretreatment with antihistamines, bronchodilators, or epinephrine may be indicated [38]. Due to superior safety profile of the FabAV, ACP antivenom has not been distributed in the US since 2002 and has not been available since 2007 [38]. FabAV controls symptoms in 82% of patients with envenomation, though more severe bites or those who had thrombocytopenia, bleeding, or neurological events were less well-controlled [39]. Given the incidence of adverse reactions, the potential benefits of administration of antivenoms must be carefully weighed against its risks. Notably, the use of FabAV is expensive, as control of symptoms often requires the administration of ten to fifteen or more vials [1], leading to attempts to develop administration protocols that reduce unnecessary administration and optimize the ratio of cost to benefit [40,41]. Current guidelines suggest administration of the antivenom only if moderate to severe toxicity or significant possibility of airway obstruction [38]. One drawback of the FabAV is the human body's ability to clear the antivenom, leading to the need for maintenance dosing in order to avoid recurrence phenomena – in the near future, a longer half-life formulation, known as F(ab')2 will be available commercially [42].

MORBIDITY AND MORTALITY

Despite the lethality of rattlesnake bites (especially the timber rattler), according to the CDC of the approximately 8000 venomous snakebites each year, only five die on average annually [5] – it is not reported how many are due to the timber rattlesnake itself. Reports of lethal timber rattlesnake bites in

rare, and although this may be due to underreporting, the snake has been well-documented to be calm and docile unless provoked [10,43,44]. There are occasional reports of a definitive lethal timber rattlesnake bite in the media, most recently in 2015 in Pennsylvania where the victim suffered"allergic reaction" to the snake's venom [45]. On the whole, these cases are uncommon—for example, the last fatal timber rattlesnake bite in the state of Massachusetts was in 1791 although, unfortunately, no further descriptions of this case are readily available [46].

It also is interesting to note who is most likely to be the victim of a rattlesnake bite. The most common demographic for all rattlesnake bite victims (not exclusively timber rattlesnakes) is men between ages of 17 and 27, with alcohol intoxication commonly implicated. There is also an increased risk of being bitten if holding a snake in captivity or as a pet [47]. Most studies that examine rattlesnake bites unfortunately do not differentiate the species of the snake involved, but data presented is still likely generalizable. A recent study in *Pediatrics* reported on over 18,000 child victims of snakebites, half of those were venomous (either copperheads or rattlesnakes). Twenty percent of the victims were ultimately admitted to an intensive care unit, but only four victims died [48]. A study in *Clinical Toxicology* described almost 24,000 snakebites as reported to the American Association of Poison Control Centers, finding that most victims were adult males and only 12% were under the age of 10. Approximately half of those victims were admitted to the hospital, with more severe outcomes such as edema, prolonged prothrombin time, and low blood pressure more commonly resulting from rattlesnake and copperhead bites, but an overall fatality rate of only 0.06% [49].

Descriptions of confirmed timber rattlesnakes in the medical literature are rare but interesting. One report from 2001 highlights a case of airway obstruction after a timber rattlesnake bite postulated to be due to the mucosal absorption of venom after the patient, who was intoxicated, had sucked the venom out of the bite inflicted by his pet snake – he ultimately was treated with antivenom (ACP) and was intubated fiberoptically, ultimately extubated 28 hours later and discharged on the third hospital day [50]. Possibly due to the platelet-active and fibrinogen targeting components of the timber rattlesnake venom, disseminated intravascular coagulation (DIC)-like syndromes have also been reported in the literature (DIC-like because, unlike true DIC, thrombin formation was not involved) [51]. Although there is a medical literature base of reviews of snake bites at large and rattlesnake bites as a collective, larger scale reviews of timber rattlesnake bites specifically are scarce. One retrospective multicenter investigation reviewed 18 cases of timber rattlesnake envenomation at two institutions. In all cases, the antivenom rapidly reversed coagulopathy and all patients survived. Suggesting that current medical management of timber rattlesnake bites is effective. Of uncertain clinical significance, however, thrombocytopenia did not resolve in most patients prior to discharge [52], suggesting that current medical management of timber rattlesnake bites is effective. Larger scale studies would be indicated in the future, although the rarity of confirmed timber rattlesnake bites may render this difficult.

CONCLUSION

The timber rattlesnake (*Crotalus horridus*), is native to North America with a rich history and a poisonous bite that uncommonly victimizes humans and even more rarely causes death. Its venom is multifaceted and diverse, ranging in mechanism of action and virulence, and as the understanding of its function has evolved, so too has our ability to treat its effects. Continued research over time will further characterize the nature of the timber rattlesnake, its toxicological effects, and ultimately its preservation.

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