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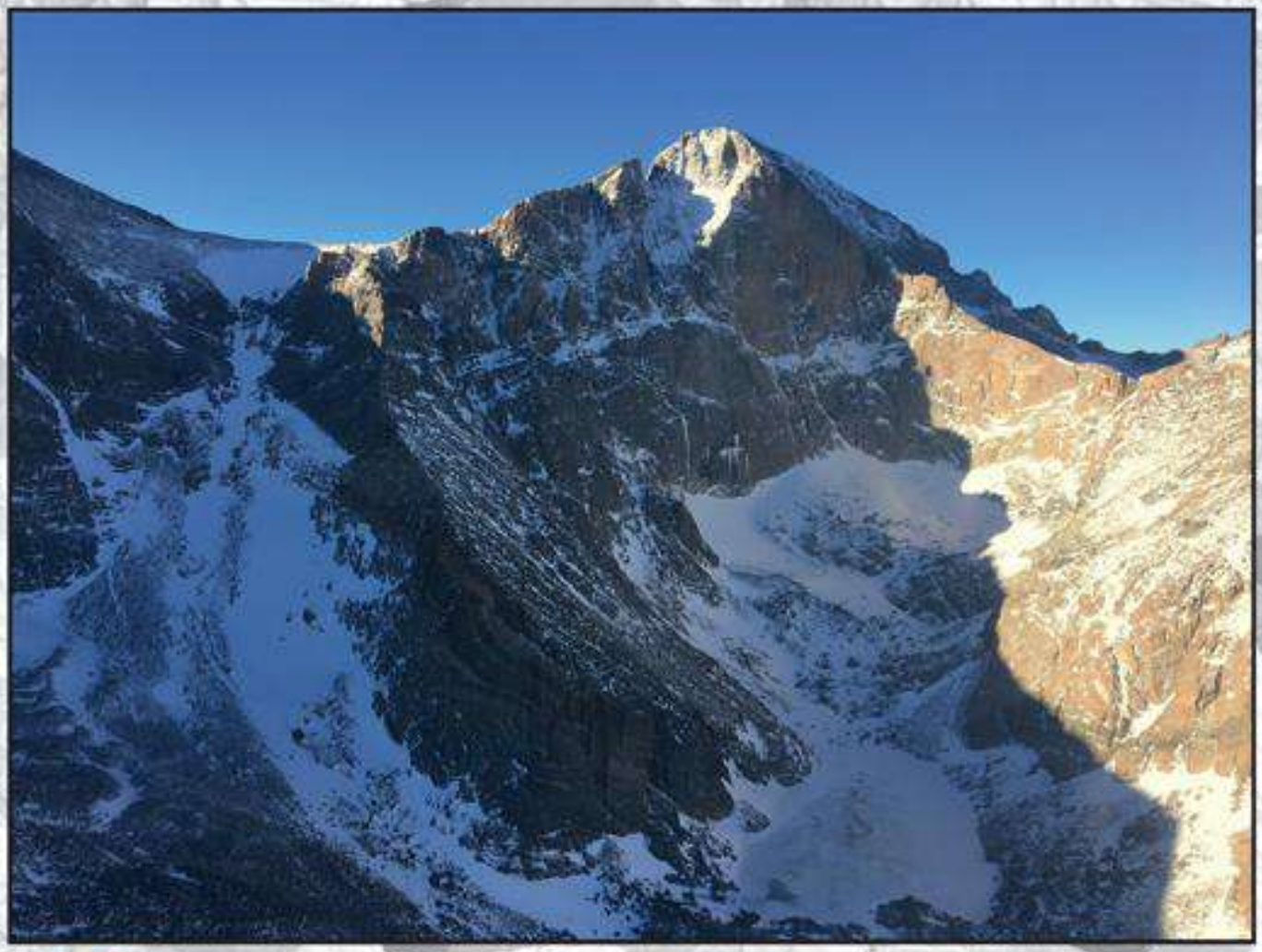

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CLINICAL IMAGE

A Shocking Experience

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Clinical Presentation

A healthy 33-y-old man was hiking with 2 friends in the Spanish Pyrenees during the summer. In the early afternoon, he reached the high point of the hike (2400 m). Suddenly, he heard a boom and felt something hit his left shoulder. He was unconscious for a few seconds. When he awoke, he was rolling down a slope. He seemed to be paralyzed. He stopped at a flat spot about 15 m below the high point. A few seconds later, he smelled burnt clothing. He was then able to make limited movements and called for help. His left arm was blue for a few minutes. His friends found him and notified emergency services. A rescue helicopter extricated him, with some difficulty because of the weather, and transferred him to an air ambulance. Vital signs were respiratory rate $16 \cdot min^{-1}$, heart rate 86 beats$\cdot min^{-1}$, blood pressure 164/76 mm Hg, and oxygen saturation by pulse oximeter (SpO_2) 99%. He still had weakness of the legs during extrication that resolved before he reached the hospital.

When the patient arrived at the hospital, he said that something had exploded at his side, knocking him down the mountain. He reported back pain and bruises from the rocks over which he had rolled. On examination he was alert, in no respiratory distress, and able to converse normally. His Glasgow Coma Score was 15. He was diaphoretic. Vital signs were respiratory rate $14 \cdot min^{-1}$, heart rate 78 beats$\cdot min^{-1}$, blood pressure 130/77 mm Hg, and SpO_2 100% on room air. Peripheral pulses were full and regular. Capillary refill time was <2 s. The chest was nontender without deformity, the abdomen was soft and nontender, and the pelvis was stable. The patient had full range of motion of all extremities. There were no apparent extremity injuries other than contusions. Motor and sensory examination was normal, without weakness or sensory deficits. An electrocardiogram showed normal sinus rhythm without ectopy or ischemic changes.

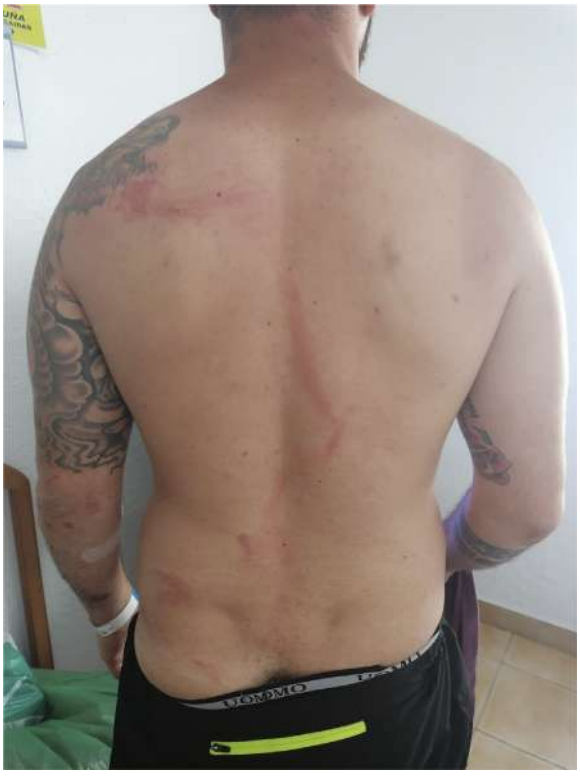

Figure 1. The victim after the event.

A peripheral line was placed and fentanyl 150 µg was administered intravenously. The secondary survey revealed erythematous discoloration of the skin, extending from the superior left scapula along a paraspinal course to the right leg and foot, and abrasions of the lower back and left buttock (Figure 1). There were also abrasions where the pants and right shoe were torn. He was transferred to the burn unit for further management.

What is the diagnosis? How would you manage this condition?

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Diagnosis

Lightning injury with keraunoparalysis.

Discussion

On admission to the burn unit, the patient was diagnosed with lightning injury, rhabdomyolysis (creatinine kinase 3497 $IU \cdot L^{-1}$), and keraunoparalysis (which had resolved). He was discharged, completely recovered, the next day. He did not require further treatment, except for dressing changes for the burn on his back and right leg. Six months later, the patient was seen in follow-up, was still fully recovered, and had resumed an active lifestyle. The only sequelae were scarring of the back and right leg.

Lightning injuries can be fatal, but the vast majority of people struck by lightning survive. Although data are incomplete, lightning causes about 24,000 deaths worldwide every year, with about 250,000 injuries.[1] Long-term medical and psychiatric sequelae are common.

Lightning does not usually cause burns. Most burns from lightning are superficial, caused by vaporization of sweat on the skin and in clothing. Unusual types of burns caused by lightning include punctate and linear burns. Lightning can also produce transient feathering patterns on the skin (Lichtenberg figures) that are not burns. Feathering is pathognomonic for lightning injury but is not always seen.[2]

Figure 1 shows a linear burn that took about 10 d to heal. The burn tracked from the area of the left scapula to the right foot, affecting areas that were damp from sweat. The right leg of the pants was destroyed, with burnt areas. The patient recalled that he felt "a kind of electricity" in the left shoulder that went down the back then to the right foot. There was no entrance or exit wound. Entrance and exit wounds are rare in lightning injury because the duration of current is too brief (10–100 ms) to overcome the resistance of the skin. Lightning usually travels over the surface of the skin, a phenomenon known as flashover.[1]

The patient explained that he was paralyzed initially and then gradually recovered full movement. Transient neurologic symptoms, including weakness or paralysis, can begin immediately after a lightning strike. Transient paralysis can be caused by keraunoparalysis (lightning paralysis), in which paralysis of 1 or more, usually lower, extremities is associated with intense vaspospasm. If there has been trauma with the possibility of spinal injury, spinal motion restriction should be instituted. This should be maintained if paralysis persists after pallor or pulselessness of the extremity has resolved.[1] Keraunoparalysis generally lasts from 1 to a few hours before resolving spontaneously and completely.

Men are 5 times more likely than women to sustain a lightning injury. Lightning injuries in temperate climates are most frequent during summer months, especially on weekends and during outdoor recreational activities.[3] Most lightning injuries are avoidable.[4] Education on how to prevent lightning injuries has the potential to decrease the numbers of injuries and deaths.

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LESSONS FROM HISTORY

Historical Features Regarding the Neuropathic Outbreaks in Brazilian Troops in the Paraguayan War

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During the Paraguayan War, Brazilian army and navy officers attributed outbreaks of combatant limb weakness with particular features such as tingling to palustrian causes. A dietary basis was not fully suspected at the time, and the popular name beriberi had not been coined. During wartime, there was a shortage in the food supply in addition to poor environmental conditions and diarrheal diseases, and many reports of "palustrian cachexia" were made. There are also reports of the use of native flora to feed troops, as well as alcoholism. There are also accounts of the death of horses with symptoms similar to those of combatants. It was reported that black soldiers were more resistant to "palustrian cachexia." This article presents the disease ecology and clinical manifestations of beriberi at wartime, linked to starvation and consumption of pickled food and native flora. These military explorations and operations in the Paraguayan War happened more than 150 y ago and present some aspects of wilderness medicine in the past.

Keywords: beriberi, polyneuropathy, thiamine, thiaminase

Introduction

The Paraguayan War, which lasted from November 13, 1864, to March 1, 1870, and was initially between Paraguay and Brazil but soon against the Triple Alliance of Brazil, Argentina, and Uruguay, was a regional conflict that became the bloodiest confrontation in Latin America. This long war troubled 4 nations and all soldiers, but mainly the Paraguayan population, which suffered incalculable losses and deprivation.[1]

The Franco-Prussian War (July 19, 1870 to January 28, 1871) started at the end of the Paraguayan War and had some similarities and significant differences. The first hit the center of the country, Paris. In Brazil, the distant and isolated southwest province of Mato Grosso was the hardest hit by the war conflicts; however, to fight against Paraguayan forces, the imperial government located in Rio de Janeiro summoned fighters from all over continental Brazil.[2] In both wars, the starving population and the combatants were all subjected to lethal infectious diseases. In addition, the logistics of health care were disorganized, especially in the remote Brazilian regions of the battlefield; moreover, anesthesia and antiseptic surgery were in their beginnings.[3] The distance from the wealthier centers made the feeding and medical care of the troops even more challenging.[2,4]

In times of war, there is an opportunity for the development of new techniques, and further questions arise about diseases that affect combatants. During World War I, for instance, Georges Guillain (1876–1961), Alexandre Barré (1880–1967), and André Strohl (1887–1977) witnessed (1916) 2 cases of soldiers with similar symptoms and signs that are known today as Guillain-Barré syndrome.[5]

In this article, outbreaks of peculiar symptoms of neuropathy in Brazilian soldiers in the Paraguayan War are studied. The original reports and contemporary science did not have the critical clinical elements needed to reach a diagnosis at the time.[6-13]

Vitamin B1 (thiamine) deficiency is called beriberi, and descriptions of the term's origins vary, with some claiming that it means weak movement or "an awful sickness" in the language of natives of what is now Sri Lanka. Currently, the causes and consequences of thiamine deficiency are widely studied and known.[14-21] Silva Lima[13] meticulously described the clinical picture of beriberi, establishing the differential diagnosis with pellagra, and recorded anatomopathological data of necropsy. He classified

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beriberi into 3 clinical forms: polyneuritic, edematous, and mixed. Later, the medical literature subdivided it into dry and wet, based on the amount of fluid that accumulates in the body. Many systems aside from the nervous and cardiovascular systems are affected by severe thiamine deficiency, including the gastrointestinal tract.[15] Several of the cases reported by the primary referred authors[7,8,10-12] of this article are suggestive of thiamine deficiency, which can represent dry or wet beriberi. The former occurs when the nervous system is involved and features impaired reflexes and symmetrical motor and sensory deficits in the extremities. Another variation of dry beriberi is Gayet-Wernicke's encephalopathy (GWE). Wet beriberi occurs when the cardiovascular system is stricken with heart failure, with or without neuropathy.[16]

Although beriberi was known for millennia in Asia, it became more common in the late 1800s with the increased processing of rice. It was accurately described for the first time in 1629 by the Leiden physician, Jacobus de Bondt, also called Bontius. He reported progressive sensorimotor polyneuropathy.[14,17,18] Factors postulated at the time to contribute to beriberi comprised poor hygiene, poor sanitation, overcrowding, and high ambient temperatures, all coincident with the Paraguayan War battlefield.

From 1878 to 1882, a large percentage of Japanese naval personnel experienced beriberi. Kanehiro Takaki, a Japanese surgeon, hypothesized that beriberi was linked to a protein-deficient diet; after changing the rice-based diet, the incidence of beriberi in the navy fell dramatically.[18] Consequently, the nutritional impact difference of beriberi was more marked throughout the Sino-Japanese War (1894–1895) with sustained barley supplementation in the Japanese navy, but not in the army. The same happened during the Russo-Japanese War (1904–1905).[18] Another Dutch physician, Christiaan Eijkman, in Java, serendipitously recognized dietary factors as a significant cause of "chicken polyneuritis." In this way, he demonstrated that beriberi is the result of a meager diet. His findings led to the discovery of antineuritic vitamins, "anti-beriberi factor" (1897), and "Together with the biochemist Frederick Hopkins who identified certain 'accessory factors' (1906), Eijkman received the Nobel Prize for Physiology or Medicine (1929) for the discovery of vitamins."

In this article, to establish a retrospective diagnosis, several scenarios describing neuropathic outbreaks affecting Brazilian troops are retrieved and scrutinized.

Study Methodology and the Chief Information Collected

This project was carried out by a physician aiming to make a retrospective diagnosis of the epidemic experienced by Brazilian troops on the front of the Paraguayan War. This was done mainly by reviewing compelling observations made by Brazilian scholar officers and observers at the time, in addition to academic studies originating from the Escola Tropicalista Baiana (Figure 1). The first testimony came from Alfredo Maria Adriano d'Escragnolle Taunay (1843–1899) (Figure 2), an aristocrat, writer, military officer, and politician of the Brazilian empire, who was a member of the Commission of Engineers of the Expeditionary Corps that went to the province of Mato Grosso.[2,6]

Another officer, Carlos Frederico dos Santos Xavier Azevedo, made reports that are important because they come from a physician versed in the medical literature of the time; his reports address the privations of sailors,[7] to be compared with Taunay's reports on infantry fighters.[8-11] Regarding the Tropicalista School, José Francisco da Silva Lima, a Brazilian born in Portugal, published communications on beriberi in the pages of *Gazeta Médica da Bahia*, under the title "Contribution to the history of a disease that currently reigns in Bahia, in epidemic form, characterized by paralysis, edema, and general weakness."[12,13] In 1872, these communications were published as a book entitled *Essay on Beriberi in Brazil*,[13] but this study was carried out far from the war front.

Here, the most considerable interest is in the 21st issue published in 1867, which gathers some officers' depositions published in newspapers about what occurred at the front regarding a disease similar to that Silva Lima had been studying.[12]

Scenarios

The first struggle the Brazilian military force faced was precarious sanitary conditions and hygiene, in addition to hunger. All predisposed the combatants to smallpox, "typhoid fever, and cholera, as well as other mysterious diseases, such as those which affected the nervous system, including 'tetanus which developed in large numbers in the army's wounded' as quoted by Azevedo."[7] Based on the reports of these situations, their probable diagnoses are estimated in the next section.

To begin, it is realized that sailors and soldiers were frequently weak and unwell even before battles. The same author[7] reiterates the precarious conditions experienced by the combatants:

> for the most part, on the insufficiency and low quality of food, on the bad water, on the action of humidity, heatstroke, lack of air renewal, conservation of wet clothes, applied to the body, and lack of cleanliness, ... resulting in illnesses, which significantly abate the forces, and exhaust the

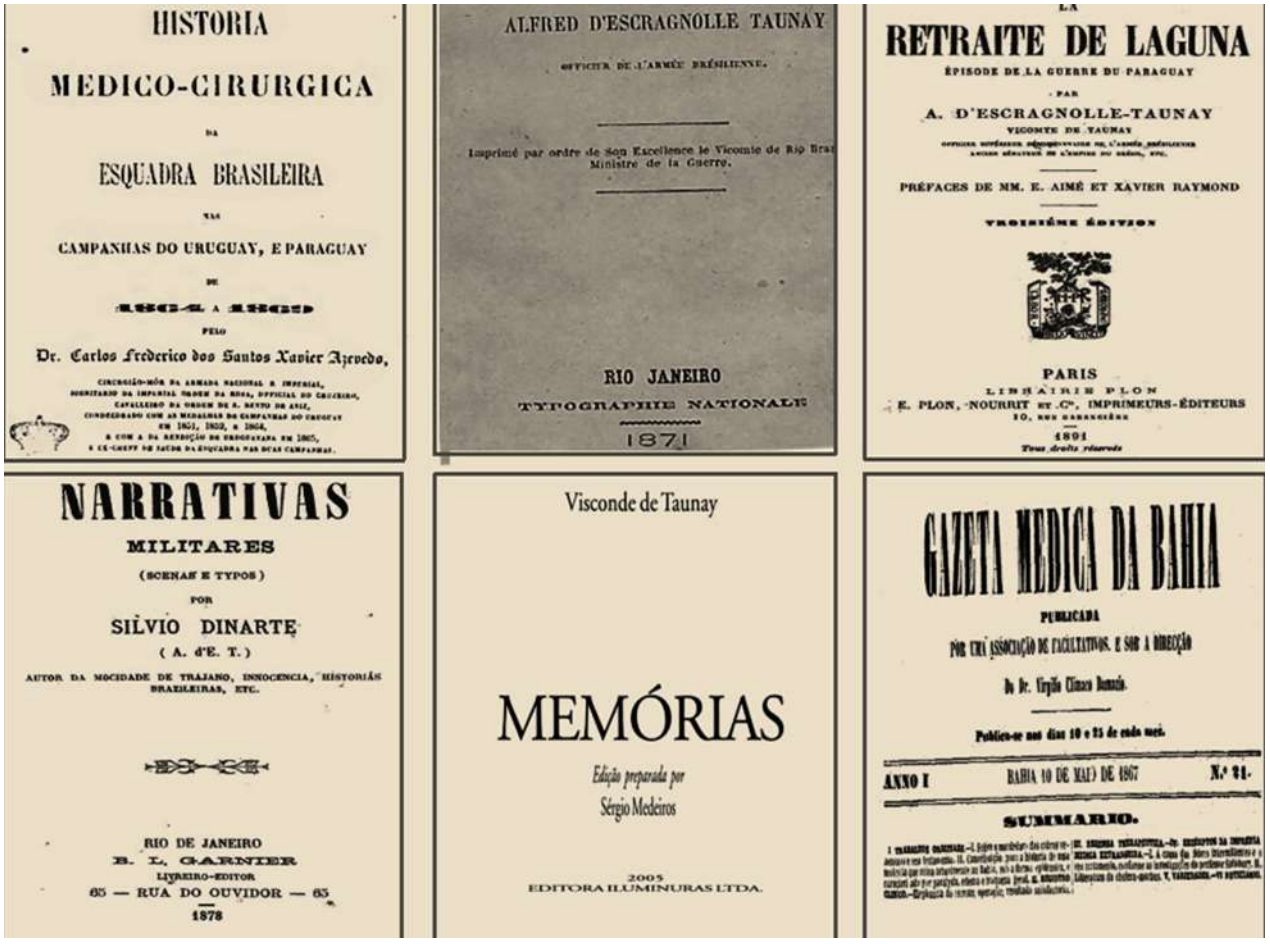

Figure 1. Primary sources of consultation on episodes of muscle weakness and paraesthesia experienced by Brazilian combatants. Carlos Frederico dos Santos Xavier Azevedo published (1870) the book *Medical-Surgical History of the Brazilian Police in the Campaigns in Uruguay and Paraguay from 1864 to 1869*.[7] Taunay published several accounts about the war; the most expressive, regarding medical aspects, are presented here, which include *La Retraite de Laguna* (1871),[10] *Military Narratives: Scenes and Types* (1878),[8] and *Memórias do Visconde de Taunay*[11] (posthumous). José Francisco da Silva Lima and his publications in the *Gazeta Médica da Bahia* about beriberi (issue published in 1867).[12]

> individual, who, continually exposed to the action of the same causes, it acquires a remarkable predisposition for scurvy.

The use of pickled food was very common in the navy, but in its absence, combatants were forced to eat native foods; this was more common among terrestrial combatants.[7] When the fighters lacked food, they had to eat what they found available in the region, and frequently the water was not drinkable; as a result, soldiers were not only in need of food but also of water supply, as is reported in Azevedo's book. Taunay[11] also notes the report of resource shortages: "Such a shortage of food, and such a desperate state had arrived, that the general diet was almost exclusive of forest fruits, especially jatobá, whose abundance had taken providential visions." The same author, in his other book published in 1878,[8] emphasized that

> Jatobá pods and coconuts were the exclusive food of almost 3,000 people for eight tremendous and endless days... Two more engineers, Ghichorro and Fragoso, threw themselves ... to seek a way out of such a horrible situation and were unable to achieve anything. They fell back; both attacked with beriberi, one never to get up, another healthier having to seek two months later on prompt withdrawal the only way to escape death.

The troops were astonished by the new ailments, as reported by Silva Lima,[12] "a new obstacle, and perhaps invincible, before them it is faced. An epidemic was entirely unknown in Brazil. More daring and reckless

Figure 2. Alfredo d'Escragnolle Taunay (1843–1899) is on the left side of Prince Gastão de Orleans (1842–1922), son-in-law of Emperor Pedro II and General in Chief of the Brazilian Armies (with his hand at his waist), and other Brazilian officers and authorities who participated in the Paraguayan War. Credit: Biblioteca Digital da Fundação Biblioteca Nacional.

than morbus cholera, it blows up like a destructive volcano in the middle of the camp."

The Expeditionary Force did not recognize the new clinical manifestations that affected the combatants during wartime, which were collectively called "Symptoms of palustrial cachexia."[7] The author of the Retraite Lagune[9] calls this strange disease the "Climacteric epidemic of a new species, reflex paralysis." These symptoms were also called gaiters, as reported by the same author in another book, *Memorias*[11]: "the gaiter epidemic worsened [popular name the soldiers used to describe beriberi, for the characteristic hardness of the legs, excluding the calves, at the beginning of the disease]."

Soon, however, the troops recognized the syndrome that Taunay[11] described in such terms:

> Then an evil of origin began to appear and marches until then unknown. It attacked in different ways, but always severe if not deadly, sometimes perfidiously and slowly, sometimes with sudden and more terrifying and cruel symptoms, bringing more or less generalized paralysis.

More particularly, the author of *Memorias*[11] describes the hallmark polyneuropathy: "he saw Carvalho that had dawned with his feet and legs very swollen, trapped and numb, as well as painful tingling in his hands."

Taunay, in his memoir[11] published decades after the war, referred to the term beriberi several times but mostly related to the climate: "how not to catch beriberi in such conditions?"; "There the unfortunate column was subjected to the devastation of beriberi"; "In this case, beriberi took the simply paralytic form without any swelling"; "In Coxim, the terrible epidemic began - the plague of chairs - nothing more, nothing less than the beriberi of the mules"; "the beriberi that had not yet been spoken of in all of Brazil and which has become so well known today, without losing, however, the character of gravity that distinguishes it."

Such symptoms were also described by many other writers to newspapers in such terms as "They start by swelling their feet, their legs have weakened, and death follows soon. Some officers walk on a crutch" and "Many officers had left sick, and some had died on the way. As soon as swelling in the legs appears, it is a rarity to escape. The people who resist the most are those of color," as reproduced by Silva Lima.[12] Silva Lima continued to present these reports: "the famous paralysis that until the last date had already caused 30 victims among the officers ... who had marched from Coxim." Furthermore, in *Memorias*,[11] concerning the association of symptoms and the evolution of the disease, the author affirms that

> Sometimes the patient would accuse tingling in the soles of his feet and difficulty in walking, feeling that these signs worsen during the day; to which oppressions, dyspnea, after

> all, the agony and death came; others, it all ran over, and soon passed away who, just before, had been strong and healthy.

Taunay[11] also differentiated the forms of this neuropathy: "it took the simply paralytic form without any swelling, on the contrary drying out day by day, so that it looked like a hinged doll." He emphasized the lethality of the disease and the importance of environment: "However, the mortality from the leg was still high, and as the doctors had finally concluded that the change of air became the only means to shorten the march of such a singular disease."

Taunay[11] also highlighted the ignorance the doctors of the time about the nature of this clinical picture: "We certainly found our colleague very badly, almost hampered by any movement due to paralysis. They treated him disorderly, with no plan made, nor logical medication." Again, he[11] reiterates the doctors' perplexity at the time about this clinical configuration and its treatment: "The doctors, quite ignorant, by the way, were astonished and dared not decide anything, prescribing erratically and with inconsistency and lack of logic worthy of regret."

Reports by the navy doctor[7] indicate that the navy did not have more knowledge than the ground forces. They too included cases of probable peripheral neuropathy as palustrial cachexia and scurvy:

> The symptoms of palustrial cachexia and rheumatism are all diverse, as can easily be seen, and we agree with our distinguished colleague that scurvy may manifest itself in different ways, simulating this or that disease, we cannot, however, admit that these diseases were not accompanied by scurvy symptoms, which they never observed in the cases, which presented themselves. Having studied the malarial fevers, which we are concerned with, we see that palustrial cachexia is a consequence of these complex pyrexias, having different characters, and which are so common in swampy countries, in filthy rivers, in different climates.

The same navy doctor[7] also associated malaria with palustrial cachexia, as a multifactorial result:

> The continuous attacks of fevers were followed by palustrial cachexia, which was characterized by other accidents, such as anemia, edema of the face, and lower limbs, neuralgic pain of the limbs, and trunk increased volume of the spleen, and liver, difficulty in respiratory function, chest and abdominal spills, vomiting, delirium in some cases, and finally death when cachexia had already made significant progress. After the autopsy of the serviceman, who succumbed to palustrial cachexia, the following changes were noted: congestion of the spleen and liver, serous effusions, distending the pericardium, lung edema, abdominal effusion, and injection of the meninges.

Evaluation of the Diagnostic Etiological Hypothesis

The clinical picture repeatedly described by Taunay and Silva Lima was one of tingling, paralysis, and edema, mainly of the lower limbs. However, it was poorly defined by Azevedo and was generally reported as "Symptoms of palustrial cachexia" and as mixed with scurvy symptoms.[7] Only in the reissue of *Retraite de Laguna*[9] did Taunay recognize the manifestations as those of beriberi, although he still related them to malaria: "This malaria-related disease is known in Brazil under the name beriberi."[9]

Interestingly, Taunay[9,10] related the manifestations to those seen in horses: "we no longer had horses: they had all been removed, in the district of Miranda, by an epizootic of the kind of reflex paralysis which had so cruelly tested us ourselves." Indeed, thiamine deficiency is uncommon in the horse but can occur when the animal eats bracken fern that contains a compound that inhibits the activity of thiamine.[17]

As for genetic predisposition, Silva Lima[12] notes that "The people who resist the most are those of color," black or indigenous. Notably, black soldiers belonged to a lineage of human trafficking survivors from Africa or may have had some personal food strategy; it is less likely that the selectivity of involvement was due to genetic factors—that is, due to rare pathogenic mutations in genes that encode enzymes and transporters involved in thiamine metabolism.[15] The latter is less convincing owing to the heterogeneous ethnicity of the Brazilian population.

There are also many accounts that Brazilian combatants, as a result of the shortage of supplies, made use of native vegetables and fruits. Taunay[8] reported that jatobá pods and coconuts were the exclusive food of almost 3000 people for 8 vast and endless days. It should be noted that the jatobá tree (*Hymenaea courbaril* L.) is used extensively for its hardwood and its seed pods for food. It can be eaten raw or roasted.[22] However, consumption of other toxic native food cannot be ruled out, and some can promote thiamine deficiency. An example is the disastrous trans-Australian Burke-Willis exploratory expedition of 1860–1861. This is an example of an endogenously induced thiamine deficiency and consequent beriberi experienced by the explorers, who were desperate with hunger. They started to eat nardoo, a flour prepared from

the sporocarp of the nardoo fern (*Marsilaea drummandi*); this plant contains a large amount of thiaminase I, even more than the fronds of bracken fern, which cause the "staggers" in horses and sheep. Thiaminase, in large quantities, soon depletes the thiamine in the body.[17]

It is essential to emphasize the extensive use of cassava in Brazil. Cassava can be harmful if underprocessed, which may have happened among Brazilian troops in times of food limitation. Furthermore, a diet with polished rice or cassava as a staple may induce thiamine deficiency.[20] Concerning cassava, Arlindo de Assis, the first Brazilian to publish experimental studies of beriberi, "obtained polyneuritis with the cassava flour commonly used in Brazil," *apud* Rodrigues Figueiredo.[23] A century later, in an endemic area of Nigeria, Osuntokun defined the occurrence of ataxic polyneuropathy that has been attributed to exposure to cyanide from cassava foods.[24]

In addition, pickled food was frequently used in the navy, according to Azevedo. This raises the suspicion of the presence of sulfites added to foods, usually as a preservative.[19] Azevedo also talks about the ample use of alcohol by the combatants, in medicines as well as by ingestion. Likewise, he claims that "drunkenness, producing serious illnesses, maximum in hot countries, compromised nutrition."[7] Moreover, there is a record that "a large quantity of hooch (aguardente) circulated in the camps," as recorded by Dourado.[4] The nervous system may be damaged by alcohol, either through its direct action or its derivatives. Vitamin deficiencies associated with alcoholism and other causes are eventually connected to the failure of vital organs, such as the liver. Notably, the mechanisms hypothesized for GWE and ethyl polyneuropathy are both direct alcohol toxicity and a deficiency, in particular of thiamine.[25]

Bruyn et al[7] reinforce the idea that beriberi has rarely been reported in Latin America, one of the few exceptions being the report by Silva Lima of an outbreak of beriberi in 1866–1868.[13] In the face of so many uncertainties, it is easy to understand why Taunay and his translators insisted on an infectious etiology of beriberi instead of nutritional deficiency during wartime. This error persisted in the Brazilian historical records regarding the Paraguayan War. At the beginning of the 20th century, cases of beriberi in Mato Grosso and Amazon were considered by the locals as a "quinine-resisting form of paludism," as quoted by Lindsay.[26]

It is possible to affirm that the patients described by Taunay and the officers' letters published in newspapers, with ideas reproduced by Silva Lima, resembled those studied by Silva Lima in Bahia, Brazil, far from the war front.[12]

Now, we may conclude that the main etiological suspicion of the frequently reported polyneuropathy was caused by thiamine. Thiamine deficiency typically presents with peripheral or central neurological symptoms, the latter commonly known as GWE.

Conclusions

We reach a diagnosis of beriberi, both dry and wet types, during the Paraguayan War as the cause of the epidemics of sensorimotor polyneuropathy presenting with symptoms and signs of dysesthesia, limb weakness, and edema. The multifactorial risk factors, mainly related to thiamine deficiency, include food with low thiamine levels or meals containing thiaminase or thiamine antagonists, in addition to alcoholism.

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LESSONS FROM HISTORY

The Wind-Chill Index

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This Lessons from History article about the wind-chill index (WCI) explores the historical polar and meteorologic literature relevant to the topic and presents unpublished work from 1939. Geographer Paul Siple (1908–1968) was a 6-time Antarctic explorer and scientist who invented and named the WCI in his doctoral dissertation at Clark University. Siple and Charles Passel (1915–2002) performed studies in Antarctica in 1940 that led to publication in 1945. This paper is often credited as the beginning of the WCI. Through years of critiques and revisions by others, these efforts evolved into the wind-chill equivalent temperatures (WCTs) used today. This essay explores the history, the science, and the overlooked originality, simplicity, and details of Siple's unpublished work. The remarkable similarity of the original chart to a current chart is shown by adapting and overlaying the 1939 WCI onto a current WCT chart with its times-to-frostbite data. The writings of Siple, Passel, and others provide an evocative supporting narrative to illustrate some of the problems of living in cold environmental conditions.

Keywords: Siple, Antarctica, weather, cold, frostbite, bioclimatology

Wind chill is a phenomenon caused by the effect of wind on heat loss from bare human skin, with a resultant increased rate of cooling and increased sensation of cold. Wind-chill indices and other tools are used in wilderness and nonwilderness weather reporting to warn people of cold weather hazards, particularly frostbite.[1] American geographer Paul Siple (1908–1968) invented the wind-chill index (WCI) in 1939. It was briefly adopted for polar and military purposes and is referred to here as the 1939 WCI. It is an index because it is a scale or chart that correlates clinical manifestations of cold with the environmental parameters of wind and temperature. In 1940, on another trip to Antarctica, Siple and Charles Passel (1915–2002) performed studies of the effects of wind and air temperature on humans. Their study was published in 1945.[2] This paper is the one usually cited for the creation of the WCI. This Lessons from History article explores the chronicle of the WCIs and related wind-chill equivalent temperatures (WCETs or simply WCTs). It examines the overlooked originality, simplicity, and details of the unpublished 1939 WCI and presents a remarkable comparison of the original and current charts.

Wind-chill terminology can be confusing. Wind chill is often used interchangeably with, or as an abbreviation for, any of several terms. SP 1945 WCI is used in this article to denote the heat loss rate measurements or the WCI of Siple and Passel. The SP 1945 WCI was employed and criticized for decades until it evolved into the WCTs. WCT may refer to an individual figure but, depending on context, may mean the whole structure of physics, calculations, and charted figures. When "the WCT" is presented on a chart that relates grades of danger, the term WCT index (WCTI) is correct but not always used. The term "old WCT" refers to any WCT or WCTI based on the SP 1945 WCI. The 2001 "new WCT" uses updated biophysical models. It predicts the risk of frostbite, so formally it is the "new WCTI" as described in the official report.[1] Despite this distinction, terms such as "new WCT," "2001 WCT," and "current WCT" are commonly used.

The convective cooling power of the wind has long been studied. A compilation of 89 early physics-laden references for experiments and calculations between 1912 and 1941 included terms such as comfort index, cooling power, cooling temperature, sensation scales, effective temperature index, and equivalent comfort conditions.[3] These were in the realm of mathematicians and other scientists. The emerging field that studied the interaction of human body temperature with the environment included leaders such as American biophysicist A. Pharo Gagge (1908–1993). In 1941, he proposed new units so that varying specialists could have a common system of communicating about thermal exchanges.[4] In an individual sitting/resting comfortably indoors at 21°C

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(70°F) and less than 50% humidity, 1 clo was the insulation value of everyday clothing and 1 metabolic equivalent of task (MET) was the metabolic rate of an average-size person at rest. Today's related MET is a ratio of the rate at which a person expends energy relative to the mass of that person while performing some specific activity compared to sitting/resting. Gagge et al. produced brief tables suggesting optimal temperatures and clothing requirements for comfort in indoor or outdoor conditions.[4] Siple and Passel cited the work of Gagge and the other forerunners.[2] The original MET and clo definitions were restated in 1966 with commonly used engineering terms and other changes at the US Army Research Institute of Environmental Medicine (USARIEM), whose mission statement includes the enhancement of health and performance through medical research.[5] Similarly, in 1966, the first institutional standards for comfortable temperature and airflow in the indoor thermal environment were published by the American Society of Heating, Refrigerating and Air-Conditioning Engineers, last revised in 2020.[6] The early studies laid some of the groundwork for a WCI, but a polar venue, a more memorable term, and popularization awaited.

Siple was a 6-time Antarctic explorer and scientist. At age 19, he was an American Eagle Scout selected from a national contest to accompany Richard E. Byrd, Jr (1888–1957) on his first expedition to Antarctica in 1928 to 1930.[7,8] Siple recorded that "the day we felt the cold most was one when the temperature was down fifty-five degrees [F] below zero [-48°C] and there was a wind of twenty miles an hour [32 km·h^{-1}]. One could remain out of doors for only a few minutes."[7] These words were an inkling of his future career. On the second Byrd expedition (1933–1935), a member of the ice party keenly portrayed cold conditions as "the real agony of cold comes from the wind" and, more sharply, "like a knife drawn across the face."[9] Siple deemed it radically different from his previous trip to now be a supply officer and group leader, participate in biology experiments, head a 77-d exploration studying geology, glaciology, and biology, and have findings published in his name.[8,10,11] Afterward, he earned a doctorate in geography. Siple's naming of the "wind-chill index" and the rudimentary first formula is found in his unpublished dissertation of 1939.[12] It was only occasionally cited, and few details were published even by Siple himself.[2] The 1939 WCI was produced by simply multiplying the temperature in degrees below zero Celsius by wind speed (in m·s^{-1}) and correlating the resultant product with the risks of cold outdoor travel. The results were chosen to be unitless, and the formula would never be so plain again. There had not been a known request for the dissertation until the time of this writing, according to the resource sharing librarian of Clark University Goddard Library (K Stebbins, October, 2020; personal communication). More features of Siple's early work are provided here. Near the conclusion of this paper is an adaptation of Siple's original work that shows a remarkable comparison of the 1939 WCI to a current WCT chart with its times-to-frostbite data.

Charles Passel (1915–2002) was a sedimentary paleontologist on the US Antarctic Expedition of 1939 to 1941, on which Siple was West Base leader. Passel went south to look for fossils in particular during 87 d of exploring by dogsled to map mountains. His contemporaneous diary *An Antarctic Journal* initially was limited to 200 personal copies and was not published until 1995 as the book *Ice*.[13] Siple's *90° South* is not a diary but an autobiographical memoir emphasizing his later trips to Antarctica.[8] Passel recalled in an interview that expedition meteorologist Arnold Court was occupied with collecting radiosonde data, so Passel was asked to help with a new experiment.[14] Passel attributed to Siple "the wind chill index and the background for his interest in the subject."[13,14] Returning home in 1941, Passel used his own Antarctic material for a master's degree in geology and served in the US Marine Corps.

Siple and Passel's experiments in Antarctica in 1940 made correlations "between atmospheric cooling rates and states of human comfort."[2] Final publication of their landmark 1945 paper was much delayed by the events of December 1941. During World War II, Captain Siple evaluated cold-weather clothing and later joined the US Army Office of Research and Development as a civilian scientist.[8,15] Siple devoted 26 pages in his dissertation to the Antarctic clothing of his era and in 1945 published an extensive paper on selection of winter clothing and gear that was supplementary to the WCI paper.[12,15] Modern materials have solved some of the problems of the older clothing. Siple's last trip to Antarctica began in 1956 at the US Amundsen-Scott South Pole Station as the inaugural science leader of the International Geophysical Year (IGY) 1957–1958. The history of the WCIs and WCTs continues forward from the 1940s with a return to Siple's 1939 WCI after that.

Leading up to the 1940/1945 study, Siple was aware of thermogenesis, insulation values of subcutaneous tissues, vasoconstriction, individual variability, and more, but early in his career he added a disclaimer that physiology textbooks should be consulted. He recognized that his original qualitative 1939 WCI represented "a real factor of climatic sensible temperatures to a certain extent, although it may not indicate the exact proportion of cooling effect. To calculate or measure the true cooling effect would entail a cumbersome process and would probably not give a much better picture of true wind-chill."[12] This would

prove to be a substantial understatement. He wrote that any scale needed to limit complicating factors such as humidity and solar gain. These were conveniently avoided in the dark and dry dead of Antarctic winter. Siple noted that the effects of insensible losses and clothing could be addressed in later corrections.[2] With knowledge of chamber experiments by the John B. Pierce Hygiene Laboratories and others, he and Passel proceeded in 1940 to quantitatively perform the carefully described "measurement of dry atmospheric cooling in subfreezing temperatures."[2] They would opine that, with a limited library in Antarctica, their methodology was not biased by knowledge of all previous studies.[2]

Siple set aside his elementary 1939 WCI in part because it did not actually measure heat loss.[2,8] Instead, in 1940 he constructed a "relative comfort thermometer" on a 10-m pole, stating that "I set up an experiment to try to measure the rate in time it took a small cylinder of water to freeze. Charlie Passel helped me measure accurately the exact length of time that the cylinder remained at the freezing point while it was letting up its heat of crystallization under nearly 100 different combinations of wind velocity and temperature."[8] An anemometer recorded wind speed.

Rather than a thermometer, a thermohm measured water and ice temperature by changes in electrical resistance through a platinum wire in the cylinder. A separate naked thermohm measured ambient air temperature. From observational "runs" at different temperatures and wind speeds made in the dark Antarctic winter in the absence of insolation (solar radiation) and ignoring any effects of evaporation or other factors, the data were recorded.[2] Siple and Passel measured the cooling rate of water freezing into ice in the cylinder, with attention to the time water remained at 0°C while freezing and giving up its heat of fusion. By knowing this property, time, the mass of water, and surface area, they calculated the SP 1945 WCI in units of $kcal \cdot m^{-2} \cdot h^{-1}$.[2]

The typically 3- or 4-digit WCI figure was neither a temperature nor did it resemble a temperature like the later WCTs. It needed a clinical relationship to have practical use. The inanimate test cylinder had no feelings, so the physics-based values correlated the cold sensations or manifestations of field parties with various wind and temperature combinations. For example, the SP 1945 WCI paper's Table 5 includes times elapsed to sudden pain and blanching of the cheek, known as frostnip.[16] Table 7 has a column of WCI numbers indexed with clinical descriptors in a second column. Table 7 is not titled as a wind-chill chart but as "stages of relative human comfort and environmental effects of atmospheric cooling."[2] The SP 1945 WCI values range from 0 to 100 ("nude sun-bathing possible") to 2600, including 2300 where "exposed areas of face will freeze within less than 1/2 minute."[2] A later reading of 3290 at the South Pole by Siple during the IGY in 1957 indicates "little chance for lengthy survival."[8]

Another example from the SP 1945 WCI Table 7 is a reading of 2000, signifying that "travel and living in temporary shelter becomes dangerous."[2] That closely echoes the words in Siple's different scale of 1939, where 500 indicates "conditions dangerous for travel or temporary shelter." As of 1945, there were 2 indices. One was the uncomplicated practical scale of 1939 still popular with the Antarctic services.[2,8] The other was the physics-based SP 1945 WCI.[2] The preliminary 1940 table of results made its way into polar, military, and climatology usage and publications.[14,17] The final form was published in 1945 and used for decades. Pragmatic rules of thumb were also commonplace. For example, military personnel in Alaska in 1964 were taught the "rule of 30s." At -30°F (-34°C) with a wind speed of 30 mph (13 $m \cdot s^{-1}$), there was risk of frostbite in 30 s according to a former US Army Specialist 4 (I. Coddington, December, 2020; personal communication).

In 1948, the aforementioned meteorologist Court focused on wind chill, stating that "no precise explanation or critical discussion of it and its method of computation has heretofore appeared."[17] Despite working with Siple in Antarctica in 1940, Court cited only the 1939 WCI but did not mention the graphs and tables. Instead, he focused on the physics-based SP 1945 WCI work, disagreed with the units, and rightly noted that the method did not consider the complex ways the human body exchanged heat with its surroundings. Court did compliment the study as the first performed at such low temperatures.[17] In a discussion section accompanying a 1951 report of 35 indoor workers' subjective sensations of the outdoors of Saskatchewan, Court audaciously declared that an objective numerical indicator would someday make such subjectivity unnecessary.[18]

In 1960, as displeasure with the SP 1945 WCI units continued, Siple recommended that the index be used "just as numbers," perhaps harkening back to what his 1939 WCI plainly did.[19,20] He continued defensively: "looking back, we perhaps made a rather too naive approach, and we may have made assumptions which were a little careless. From the practical standpoint, I think we evolved a schema that has been of some use."[19] It was useful, but modifications would come. The portrayal of the cooling effect of the wind would eventually be changed from the WCI to a different type of index that was more intuitively understood by regular users as a "feels like" temperature. Equivalent temperatures have been used for years to express various environmental conditions, but in the context here, WCTs are mathematically computed colder

temperature-like figures at which the cooling effect of the wind and cold on the exposed dry face is the same as if wind is not present.[1,20,21]

The US Department of Defense has long been interested in developing operational thermal indices.[1] In 1961, the US Army Armored Medical Research Laboratory (AMRL) at Fort Knox, Kentucky, consolidated with other laboratories into what is now USARIEM at Natick, Massachusetts. The AMRL's WCT chart of 1961 was based on the SP 1945 WCI and, despite its unrealistically cold results and awkward design, the AMRL chart was included in a 1963 textbook.[22] In 1967, the site of the US Air Force Arctic Aeromedical Laboratory at Ladd AFB, Alaska, became the Arctic Medical Research Lab, a subsidiary of USARIEM, at US Army Garrison Alaska, Fort Wainwright. A 1965 US Air Force Arctic Aeromedical Laboratory paper by Canadian biophysicist Charles Eagan identified problems with the AMRL WCT chart.[23] His WCT chart, while still based on SP 1945 WCI, had warmer WCTs than the AMRL version. It was much easier to use and, being indexed to degrees of danger, it was a WCTI. The source or formula of the chart in Eagan's paper was not stated. The US Army printed WCT charts on pocket cards.[23] Eagan would be recognized for his explanation that natural convection around the body produces a "wind" of 0.9 $m{\cdot}s^{-1}$ (2 $mi{\cdot}h^{-1}$) and that people in the cold outdoors do not stand still but move themselves or their limbs at about 1.8 $m{\cdot}s^{-1}$ (4 $mi{\cdot}h^{-1}$). Baseline wind velocity necessitated Eagan's correction of earlier WCTs.[23,24] The definition of walking speed was decreased to 1.3 $m{\cdot}s^{-1}$ (3 $mi{\cdot}h^{-1}$) in the 2001 WCT revision.[1]

In the 1970s, the use of WCTs began to supplant the SP 1945 WCI.[1,25] US National Weather Service (NWS) meteorologists began using WCTs in 1973 to describe comfort levels and contribute to forecasts and safety warnings according to a 2003 report by the US Office of the Federal Coordinator of Meteorological Service and Support Research (OFCM).[1] The history is obscure. It is likely that the NWS used both the SP 1945 WCI and the WCTs derived from it. The date and usage could not be fully corroborated so the term old WCT is used. Some weather sources still show the old WCT chart for comparison to the new one. The formula printed on the old WCT chart is the same as the one listed in a 1992 NWS operation manual so it must have been in use then.[21] It seems likely to have been in use before that because the old WCT values match those from Eagan's WCT tables II and III of 1965.[23] In the late 1970s Canada began using the SP 1945 WCI converted from $kcal{\cdot}m^{-2}{\cdot}h^{-1}$ to SI units of $W{\cdot}m^{-2}$ but some regions reported old WCT because WCTs resembled "regular" temperatures that were preferred over the WCI in user surveys.[1,25,26]

In the 1990s the SP 1945 WCI computation, and its continued heat flux basis of the old WCT, was once again under scrutiny for its seemingly impromptu initiation, lack of sound theoretical basis, and dubious experimentation.[20] Some of the many criticisms were that body heat production and transfer should have been considered; skin temperature was not constant as they assumed but fell when exposed, although vasodilatation could offset some of that; wind speed on a 10-m pole did not reflect the level of the face; a plastic water cylinder wall did not transmit heat like bare or clothed human skin and subcutaneous tissues or have proper surface area; wind speeds tested were limited or their cooling effects exaggerated; there was wide scatter or omission of some data points and inappropriate extension of parabola fit; the units were wrong; and more.[20,21,25,27] As additional scientists piled on, it was wondered if it was "time to bury the wind chill index rather than to praise it."[20]

That quip was from environmental physicist Randall Osczevski of Defence Research and Development Canada (DRDC), who measured heat loss from a head manikin in a wind tunnel to develop a mathematical model for new WCTs rather than the old WCTs based on the SP 1945 WCI data.[20,25] American biomechanical engineer Maurice Bluestein from the Purdue School of Engineering and Technology used an enclosed hollow cylinder to approximate a head. By using modern heat transfer principles, he found a numerical solution for a facial cooling model.[24,25,27] Despite the criticism of SP 1945 WCI, Osczevski in 1994 sympathetically wrote that "All the technical objections, valid as they may be, miss the point. Siple and Passel were not seeking a formula to calculate the heat loss of a clothed or a nude human body, or some small part of one. They were looking for and found a mathematical way to combine wind and temperature to create a scale that they could calibrate to consistently reflect how cold different combinations of those factors would feel."[20] A somewhat similar sentiment had been stated by a critic of a 1932 study: "too much mathematics and not enough experiment."[3] More pithy was a proverb offered by the anti-science, cold-ocean sailor and mountaineer H.W. Tilman (1898-1977): "Science is madness if common sense does not cure it."[28]

In 1999 a cold snap over Ontario made headlines with a dangerous WCI of nearly 1800 $W{\cdot}m^{-2}$. This was the WCI and unit of heat flux still used in some of Canada in 1999, rather than the WCT method.[1,25] It was just one event, along with many other concerns over the years, that led to a goal of making a new WCT chart that was more understandable, more recognizable, and more accurate than prior SP 1945 WCI-based WCT charts and that involved human studies to determine thresholds for the risk of frostbite.[1] The latter requirement made it a WCTI and better able to suggest the

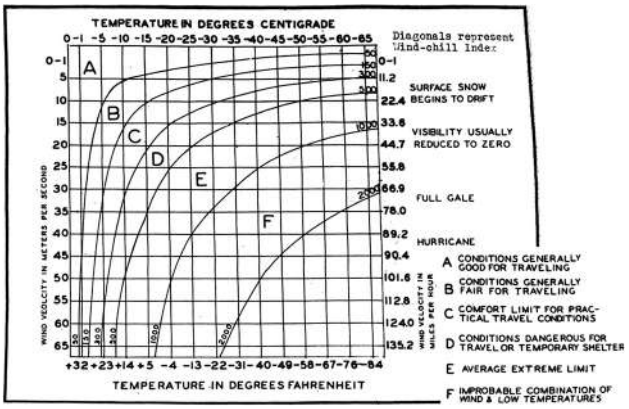

Figure 1. Original wind-chill index (WCI) chart from Figure 69 of Paul Siple's 1939 unpublished dissertation. Permission to reproduce this chart was granted by Clark University Goddard Library. The 1939 WCI was a 2- to 4-digit unitless number and not a temperature-like wind-chill equivalent temperatures number. Constant WCI values were displayed as curved lines (isopleths) across the figure and were correlated with observed or inferred temperatures and wind speeds. Between the WCI isopleths were bands of clinical risks, described in the legend, rating the suitability of being outdoors in the cold of Antarctica.

level of danger. The US Office of the Federal Coordinator of Meteorological Service and Support Research formed the Joint Action Group on Temperature Indices (JAG/TI) but primarily focused on cold to develop a new WCT. Participants included the Meteorological Service of Canada, DRDC, NWS, military, and other organizations and individuals. Multiple experimental models were examined, but ultimately the new 2001 WCT relied on the modeling of Osczevski and Bluestein. The site of cooling, chill sensation, and risk of frostbite was not the clothed whole body but the exposed dry face. The new 2001 WCT charts were implemented in the winter of 2001 to 2002.[1] The effects of humidity, evaporation, wet clothing, or solar gain were purposefully not included, although JAG/TI began a commission to study these issues in a universal thermal climate index.[1] Many such multivariable indices have been described and compared.[29,30]

The 2001 WCT numbers are not large heat flux numbers as used in the older WCI method and, except for extraordinary conditions, are only 2-digit calculated equivalent temperatures similar in appearance to ordinary air temperature readings. WCTs are not real temperatures. Although derived from units of temperature and wind, WCTs are expressed on charts only as degrees Celsius or Fahrenheit. Shaded areas on the charts indicate zones of frostbite risk limited to the exposed dry face.[1,31] WCT's popularity with the public was, and still is, a major part of its success and longevity as a weather tool, but the weather services of the United States and Canada began issuing extreme cold or other named watches, warnings, and advisories for some locations even in the absence of wind. There are various temperature and time thresholds for these depending on local or regional setting, populations at risk, suddenness or duration of hazard, and more. According to the NWS winter program coordinator, a future consolidation of watches, warnings, and advisories and other weather advice into one nationwide "seamless product suite" is intended for late 2022 (M. Muccilli, November, 2020; personal communication).

A return to 1939 and a closer examination of the past reveals many new details. Siple's 1939 dissertation was seldom cited by Court or others, and few or no specifics from the reference were given. It is not known how or if Siple's 525 pages, 16 tables, 156 maps, sketches, and photos, and 223 sources may have been communicated since signed by his advisors, the eminent geographers Samuel Van Valkenberg and T. Griffith Taylor.[12] Figure 69 from the 1939 dissertation is published here as Figure 1 possibly for the first time, or at least for the first time in many decades, with a new analysis.

On page 166 to 168 of his dissertation, Siple felt that "With so many factors to consider, no practical solution to the problem for quick computation and simple form will likely ever be invented… it seems therefore advantageous to use the simplest system."[12] The original 1939 WCI was described in 4 steps, beginning with Step 1 that identified the simple formula "C° x V = W-C," where he multiplied "temperatures in degrees of minus Centigrade [°C below zero] by wind speed in meters per second [$m \cdot s^{-1}$], the product of which I shall call the wind-chill index."[12] He chose to report the product as unitless. Step 2 was Siple's Table 12, not shown here, which did not list observations but only convenient round numbers for temperatures and wind speeds to perform the multiplication and develop a table. The multiplication product—the 1939 WCI—was applied to Steps 3 and 4, where it became meaningful.

Step 3 is shown in Figure 1 (Siple's figure 69). Along the axes are the same temperatures and wind speeds as in Siple's Table 12. Observed data points are plotted but not shown. Instead, curved lines of constant WCI values are drawn smoothly through the data points on the chart in a presumably best-fit manner, either by visual inspection or by an unrevealed method. Some, especially at higher wind speeds, were estimated by extrapolation.

Curved lines of constant values are called diagonals by Siple but are isopleths. For example, an isopleth for temperature is an isotherm and an isopleth for wind speed is an isotach. An isopleth for Siple's combination of temperature and wind speed is his 1939 WCI.

In Step 4, shown in Figure 1, Siple correlated his WCI with the level of discomfort and danger. Between the WCI isopleths he defined bands of risk that were a

surrogate for heat loss and the sensation of cold. In his Figure 69 legend, he rated the suitability of outdoor travel on foot or by dogsled in Antarctica:

- A: Conditions good for traveling (WCI 0–50)
- B: Conditions fair for traveling (WCI 50–150)
- C: Comfort limit for practical travel (WCI 150–300)
- D: Conditions dangerous for travel or temporary shelter (WCI 300–500)
- E: Average extreme limit (WCI 500–1000)
- F: Improbable combination of wind and low temperature (WCI 1000–2000)

This was not founded solely on his own experience. His personal WCI record while traveling was just over 400, but he amassed WCI values based on instantaneous, daily, seasonal or yearly past or contemporaneous meteorologic readings from 21 Antarctic stations, sledging parties, camps, or icebound ships.[12] The primary data were there, but he organized it into something new—the WCI.

Produced in Figure 2 are middle-range 1939 WCI isopleths plotted as an overlay onto a 2001 WCT chart adapted from the NWS and Meteorological Service of Canada.[1,31] The chart coordinates are in degrees Celsius, but the 1939 wind speeds had to be converted by the authors from $m \cdot s^{-1}$ to $km \cdot h^{-1}$. The underlying 2001 WCT chart's plotted digits are equivalent temperatures. Some further direction is needed to interpret what Figure 2 reveals because the overlay of the 2 charts visually presents 2 methods with different (but related) outcomes obtained using different approaches.

In Figure 2, the underlying 2001 WCT chart's shaded areas warn of the thermodynamically predicted 30-, 10-, and 5-min times-to-frostbite estimated separately from the WCTs.[1,31] To confirm these mathematical predictions, a small number of human volunteers had skin temperatures monitored for facial frostbite in an environmentally controlled wind tunnel, yielding a table of times whose large increments had a staircase appearance.[1] These uneven results were smoothed for the stylized 2001 WCT chart to display shaded zones of frostbite times.[1,31] It is these zones, not the WCTs, that are most useful for the chart overlay comparison.

The overlying 1939 WCI isopleths of green, yellow, and red lines in Figure 2 do not offer times-to-frostbite but are derived from a wealth of experientially obtained ratings of the safety of Antarctic travel or temporary shelter. The rating is fair (WCI 150), practical comfort limit (WCI 300), or dangerous (WCI 500). For example, the red 500 isopleth of 1939, although reflecting a different outcome (dangerous travel with frostbite or worse), offers a reasonable approximation of the perilous 5-min frostbite border of the 2001 WCT chart. The overlay shown in Figure 2 does not compare the 1939 WCI to the SP 1945

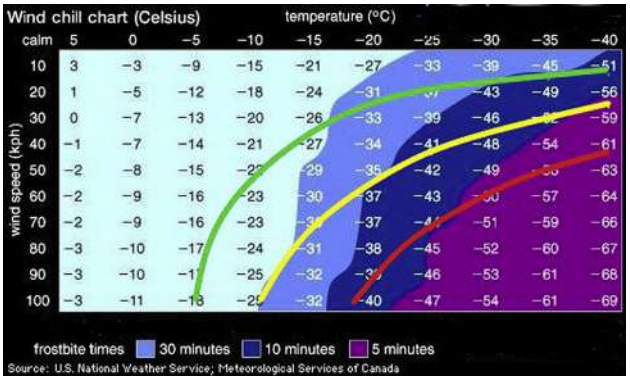

Figure 2. The middle range of Siple's 1939 wind-chill index chart isopleths has been placed as an overlay on a currently used 2001 wind-chill chart, adapted with permission from the US National Weather Service. The coordinates on the chart are temperatures and wind speeds. The digits are not temperatures but wind-chill equivalent temperatures. Shaded areas represent 30-, 10-, and 5-min frostbite warning zones. The overlying colored lines are 1939 wind-chill index isopleths of 150, 300, and 500 indicating the suitability of outdoor travel or temporary shelter as fair (green), comfort limit (yellow), or dangerous (red).

WCI or the old WCT chart but to a more accurate 2001 WCT chart currently in use. What is most remarkable about the overlay is that the middle range of Siple's original 1939 method, despite the obvious simplicity and limitations, closely parallels what is seen over 80 y later on the frostbite zones of the current WCT chart.

It does not take Antarctic-grade cold to feel or to be dangerously cold. Mountaineer-writer Frank Smythe advised with wit on the Himalayan peak Kangchenjunga: "In order to experience a really unpleasant form of cold, it is unnecessary to leave Great Britain."[32] Closer to sea level, British physiologist Griffith Pugh analyzed reports of hill-walkers who perished in hazardous conditions of wind, wetness, fatigue, and air temperatures as high as +10°C (+50°F).[33] Some of today's WCT charts start at that above-freezing ambient temperature where there is no frostbite but where wetness greatly contributes to heat loss and the risk of other cold injury and hypothermia.[1]

Siple's original 1939 WCI used below-freezing ambient temperatures and was a valuable guide in the dry cold and wind of Antarctica and elsewhere. The SP 1945 WCI was used for decades. There are other indices of thermal stress, such as the universal thermal climate index, that incorporate more parameters, but the WCI evolved into the 2001 WCT and continues as a commonly used cold weather guide that is popular with the public.[1,29,30] There are still concerns. For example, the more thermodynamically comprehensive 2001 WCT chart suggests the time for unprotected mid-cheek skin temperature to fall to a steady state with resultant risk of frostbite for the most

susceptible individuals.[1] Most people take less time than that to discern how cold it feels, but JAG/TI desired an objective endpoint in the 2001 WCT. Siple's modest original 1939 WCI did not give an immediate answer to the subjective question "How does it feel?" Instead, it gave valuable functional advice in a different way about the objective question "Is it safe to be outside?"

Conclusions

This Lessons from History article has explored the environmental topic of the WCI first described by Paul Siple in his unpublished 1939 doctoral dissertation. Details of Siple's original WCI reveal his early insights and practical approach. Despite the obscurity, simplicity, or even naiveté of the 1939 work, an overlay of charts suggests that the 1939 WCI provides, in at least some of the range of conditions, a reasonably close approximation of the frostbite guidance of a current WCT chart. Siple's original idea has evolved and lives on as the 2001 WCT chart, but we think that in his own way and time, he may have been on the right track in the beginning.

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WILDERNESS & ENVIRONMENTAL MEDICINE 2021; 32(3): 400–6

WILDERNESS ESSAY

Expected and Unexpected Risks for Canoe Travel in Flood Conditions

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Flood conditions present dangers for canoe camping, with the highest risk for injury or death related to water submersion of paddlers. Other hazards can exist at high water stages as well. This essay discusses preparation for risks associated with canoe travel during record flood conditions in Alabama's Mobile-Tensaw River Delta. It examines the unique aspects of paddling through submerged forests, route detours necessitated by flooding, potential encounters with dangerous wildlife, and the case of a stinging ant attack on a paddler who unexpectedly comes in contact with a displaced ant colony.

Keywords: fire ants, Hymenoptera, floods, *Sus scrofa,* Solenopsis, cottonmouth

Introduction

The Mobile-Tensaw Delta is the second largest delta in the contiguous United States. Located entirely in southwest Alabama and encompassing 777 km^2 (300 mi^2) (Figure 1), it is a 64 km (40 mi) long serpentine tangle of crisscrossed rivers, bayous, and creeks, with land masses accessible primarily by boat. The Delta has long been a fascination of E.O. Wilson, famed biologist and University Research Professor Emeritus at Harvard, whose childhood was spent in nearby Mobile, Alabama. Wilson articulated similarities between the Amazon and the Mobile-Tensaw Delta: "The Amazon to me is the Delta writ large. It is a miniature wilderness, exotic, mysterious and had the reputation of being impenetrable."[1] Wilson's description may explain why, despite its juxtaposition to a large metropolitan area, few but the most accomplished outdoor enthusiasts enter the Delta. Biting insects, alligators, water moccasins, black bears, and feral swine are all possible wilderness encounters. This lack of human intrusion creates a pristine and convenient wilderness located along the highly populated US Gulf Coast. Indeed, Wilson said it is one of "the few places where you can leave the city and head into the wilderness in less than an hour."[1] For the last 19 y, I have regularly camped, canoed, and explored the Delta. In 2020, a wilderness medicine senior elective expedition presented unprecedented challenges.

The Mobile-Tensaw Delta serves as a classroom for Alabama medical students completing their elective. Our February 2020 class faced a river system in flood stage. According to the United States Geological Survey (USGS) national water information system (February 2020), we were soon to experience one of the highest water levels in 40 y. In good water conditions, a lack of land-based campsites presents difficulties for Delta camping. However, flooding of this magnitude exacerbates the problem, covering the forest floor with 3 to 6 m of water (Figure 2), diminishing options, and consolidating wildlife such as feral swine (*Sus scrofa*) in high-ground spaces near the Mobile-Tensaw Delta (Figure 3). We were made acutely aware of this danger by campsite owner Luke Adams, who repeatedly warned of "wild hogs" on his property. An additional hazard of navigating the Delta at flood stage includes unavoidable routes bringing paddlers in close proximity to the tree canopy, which during high water may harbor stinging insects and snakes (Figure 4). Although the majority of the latter are nonpoisonous, cottonmouth water moccasins (*Agkistrodon piscivorus*) often bask in the branches of dead trees overhanging the water[2] and can drop into boats when startled.

Preparations and decision-making for canoe travel during flood conditions will be discussed, as well as feral

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Figure 1. Partial aerial view, Mobile Tensaw Delta. Photo courtesy of Google Earth Pro.

swine as an invasive species and fire ant rafts that occur during flooding. I hope this information will help others prepare for high water canoe travel in comparable ecosystems.

Preparation

In preparing for this course, we screen all students for medical issues. We assess their ability to swim and then require personal flotation devices as conditions warrant. Before the expedition, we have students spend 2 weekends camping, where instruction includes basic outdoor skills, map and compass use, paddling techniques, and a 20-h wilderness first aid training course. This time allows instructors to assess student boating skills and outdoor abilities.

Our curriculum included lectures on moving-water safety excerpted from the American Red Cross Small Craft Safety Program.[3] Flooding of any river from winter rains increases the risk of drowning due to the formation of strainers and potential immersion in cold water.[4] We taught avoidance of strainers and foot entrapment and practiced victim rescue techniques and how to right a capsized canoe. Canoe maneuvering in a current was simulated by racing through an obstacle course in a man-made lake. Boating partners were assigned to ensure at least 1 paddler in each craft is proficient, with the experienced canoeist assigned to the stern for the first 2 d of travel. Canoe convoy spacing, the importance of maintaining visual contact between boats, and paddle signal communication for river directions and warnings were all drilled in the weekends before departure.

The Expedition

The 2020 flood provided multiple challenges for our crew of 12 students and 2 instructors. In the weeks leading up to the expedition, we monitored the USGS Alabama River levels daily to determine whether the water would fall below 9.1 m (30 ft) (Figure 5). In the event levels remained high, we visited various put-in points to ascertain unpredictable currents, obscured landmarks, and the extent of submersion of several strategic campsites (Figure 6).

The instructors conferred regularly about whether to cancel the expedition. In the Delta, rapids are rare when rivers and creeks overflow their banks. Venturi effects are diminished when the constricting effects of riverbanks are eliminated by submersion. Although we could experience Class II white water[3] in the main river channels,

Figure 2. Forest in flood. Photo courtesy of Lynn Yonge.

Figure 4. Snake in tree. Photo courtesy of Cori Yonge.

we would more commonly travel in the safer zones of water moving slowly through heavily wooded forests.

Years of well-maintained river notes and reconnaissance told us our first river island campsite was under 6.1 m (20 ft) of water, which forced us to cleave approximately 24 km (15 mi) from our 80.5 km (50 mi) itinerary. Choosing to launch at a downriver access point, our team paddled over a submerged roadbed until we found the bridge marking entry to a body of water known as Globe Creek, an established Delta starting point. During flood conditions, the natural banks of small creeks feeding the larger Delta rivers overflow, making it difficult to recognize their normal course. Thus, it was necessary to rely on multiple methods of navigation to negotiate the high water. The most basic method involved following the current downstream until we located a recognizable landmark. Global positioning system navigation devices are standard on student river expeditions, but the United States Geological Survey topographic maps are preferred because their larger size is superior to the receiver's small screen. The tools are often combined, with the global positioning system generated track superimposed on the topographic map to determine a location.

Ant Encounter

Delta flooding provides opportunities to paddle directly through submerged forests, allowing shortcuts between waterways. This can be advantageous when trying to avoid wind or waves in wide bodies of water but can create other risks. On day 2, we paddled overland through a tract of woods laden with small-diameter saplings that were 4.6 to 6.1 m (15–20 ft) tall. We spotted 2 cottonmouth water moccasins suspended and intertwined in branches 46 cm (18 in) above the water. Moments later,

Figure 3. Game camera photo of feral swine in vicinity of training campsite. Photo courtesy of Larry Yonge.

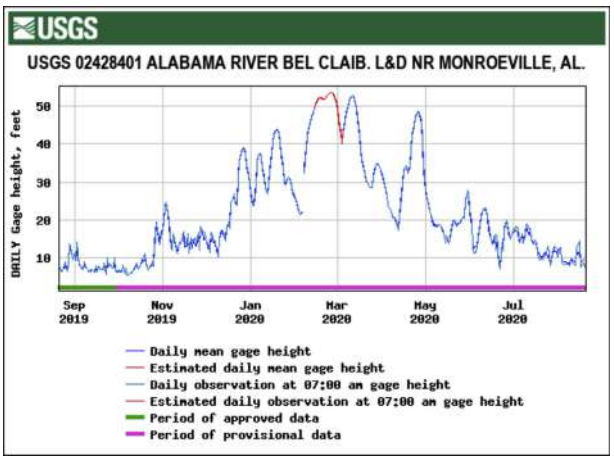

Figure 5. US Geological Survey water levels rising during February 2020. Graph courtesy of US Geological Survey.

Figure 6. Flooded campsite. Photo courtesy of Lynn Yonge.

an ant colony fell from a small tree, enveloping a medical student. The student initially described seeing hundreds of ants on her left arm. Peeling off winter outer layers, the student discovered more ants underneath her clothing. She called for help when the ants began biting her neck, upper back, and scalp. With the assistance of 2 other canoes to stabilize the boat, the student stripped down to her underwear, rinsed the ants from her body, and then redressed. Once settled, she administered Benadryl and hydrocortisone cream from her personal first aid kit and ate caffeinated jellybeans to counteract the sedative effect of the antihistamine.

After collision with the tree, the canoe partner in the stern described the ants as small, black, and definitely in a single big mass. She provided a photo similar to what was observed (Figure 7) and pointed out they had to have fallen from or been shaken out of the branches of the small tree we were working our way past.

The chaos associated with a paddler standing and disrobing in a canoe to rid herself of stinging ants made accurate identification of the species an afterthought. On further reflection, I realized this incident exemplified a danger for which other expeditions in similar ecosystems

Figure 7. Floating fire ant colony. Photo courtesy of Ben Raines.

should prepare. In this environment, students are routinely reminded to look up in trees to spot poisonous snakes or hornet nests, but before this event they were never warned about ants.

I contacted Dr. John McCreadie, medical entomologist at the University of South Alabama in nearby Mobile, to provide detailed information regarding the behavior of the ants and the location of the encounter. He shared this information with medical entomologists at the University of Georgia and Clemson University. In written correspondence (August 2020), all 3 agreed that the offending species is most certainly a type of fire ant. All believe the fire ants formed a raft and drifted to the tree, where the student made contact. *Fire ant* is a general term used to describe ants that deliver a painful sting and is the common name for several species of ants in the genus *Solenopsis*. There are 16 members of the Solenopsidini ant tribe in Alabama.[5] Although no sample of the ants was collected, the clearly dark color (Figure 8) of the offending insects narrowed the species list further. It is believed the offending ants could be one of several *Solenopsis* species or a hybrid imported fire ant listed as one of the common pest ants regularly encountered by humans: *Solenopsis invicta x richteri*.[6] From a wilderness medicine perspective, one should remember that *Solenopsis invicta* occupies much of the southern United States and is responsible for 95% of North American clinical cases.[7] Wilson is credited with discovering the first imported fire ant colony in the continental United States, in Mobile, in 1942.[8]

Although we cannot be sure of the genus and species of the offending ants, I believe it is worth knowing more about the behavior of the most likely suspect. The area of the ant attack was flooded with winter rains at record levels. During flooding, an entire fire ant colony can emerge from its nest and form a free-floating, amoeba-like ball (Figure 7). Research at the Georgia Institute of Technology in 2011 established this mechanism of ant

Figure 8. Fire ant raft climbing tree during flood. Photo courtesy of SciencePhotoLibrary.

survival.[9] In floods, fire ants build a waterproof, flexible fabric of ants (called ant rafts) by clamping their mandibles and claws onto one another. Ant bodies are moderately hydrophobic, and this cooperative action traps air in the lower levels of the ant mat to provide oxygen to the colony. The ants systematically trade places to keep the queen alive and afloat until the colony is safe. Although we can find no documentation of any similar incidents of ants dropping from trees, the scientists consulted theorize the ants were living in the tree until the flood receded. According to Wilson, ant rafts will float until they come into contact with any stationary object above flood level, including a tree branch.[8] They will stay in place until a mound can be re-established in the soil.

The behavior and toxicity of fire ants in flood conditions is also of interest to healthcare workers involved with disaster relief after floods and hurricanes. Dr. Linda Bui, an entomologist at Louisiana State University, was impressed by bands of unexplained rashes on the legs and abdomens of victims who waded through floodwaters during Hurricane Katrina. Bui described seeing "literally fire ant stings on top of fire ant stings." Victims presented with classic wheal and flare response[10] to ant venom from hundreds of stinging ants. Bui later coauthored an article documenting that fire ants develop larger venom sacs in flood conditions, a finding that could explain why fire ants deliver more venom during flooding.[11] In fact, fire ants deliver 87% more venom during flood conditions compared to normal conditions.[12] They are also able to sting their victims repeatedly by anchoring themselves with their jaws while they sting. This allows them to remove their stinger, rotate, and sting again. A single ant can sting multiple times in a few moments.[12] Because the ants are anchored, the best way to dislodge them is to rub them off,[13] as submerged ants will hold onto their target.

Ant venom is a protein of alkaloid nature that generally causes the formation of the fluid-filled vesicles characteristic of fire ant stings.[14] Fire ants are included in the order Hymenoptera[15] and their stings have been known to occasionally cause anaphylactic reactions. Fire ant venom is unique with the exception of 1 protein that shows limited cross-reactivity with a vespid allergen.[14] The Vespidae family includes yellow jackets, hornets, and wasps. Individuals who are allergic to vespids should be cautious about exposure to fire ants. This danger can be amplified by their tendency to sting en masse and become more defensive during flood conditions.[12]

Our student experienced the classic hymenoptera sting symptoms of instant pain, wheal and flare reaction, and variable edema.[15] Allergy is the most serious aspect of hymenoptera stings. Anaphylaxis and related syndromes from this source are relatively common outdoor wilderness emergencies.[15] An estimated 0.4% of the US population shows some degree of clinical allergy to insect venoms, and 40 to 50 deaths are reported annually.[15] Fatal anaphylaxis to fire ant stings has been reported,[15] including the 2016 case of an Alabama woman who died from anaphylaxis secondary to multiple fire ant stings.[16] Considering the number of stings our student received, we were fortunate she did not have hymenoptera allergy and develop symptoms of a systemic allergic reaction.

The student's self-administered postencounter therapy of oral antihistamines likely lessened itching.[15] Topical steroids were of doubtful value. Oral corticosteroid therapy is most effective in reducing inflammation and swelling after ant stings.[14] Had her condition worsened, both oral prednisone and epinephrine for anaphylactic reactions were available in the instructor first aid kit.[15] Large local reactions to insect stings can be mistaken for cellulitis. These reactions are characterized by severe swelling (20–25 cm), developing over 24 to 48 h.

Antibiotic therapy is not needed for local reactions.[14] Breaking fire ant blisters should be avoided[15] because skin infections are fairly common after ant bites. Topical and oral antibiotics should be available in the event of secondary cellulitis.

Feral Swine

We planned to camp the next 2 nights in areas with well-documented herds (sounders) of feral swine (Figure 3). Feral swine are an invasive species known to decimate natural areas, pollute streams and water sources,[16] and compete with native species for food. Their diet consists of small mammals as well as turkey, quail, and reptile eggs. The hazard feral swine impose on the Delta ecosystem is so large there are neither bag limits nor a designated hunting season for them. The Alabama Department of Conservation and Natural Resources quotes studies suggesting 80% of a population must be removed just to keep the populations from continuing to grow.[17] The Alabama Department of Conservation and Natural Resources encourages a multifaceted approach to control swine sounders, including carrying a firearm on private property in the event there is an opportunity to remove one.[17] Lethal methods are often the most practical and widely used for feral swine control.[18] The owner of the property on which we camped our second night routinely traps and harvests feral swine to reduce damage to his sensitive natural ecosystem. This hunting minimized our exposure because feral swine learn to avoid hunting pressure.[18] Feral swine will attack humans without provocation[19] and are the animal I fear most in the southern forest. In preparation for the expedition, we coached students to keep food in locked containers and out of their tents and to back away slowly and climb a tree[20] if they encountered a feral hog. Injuries from wild boar attacks generally involve soft tissue lacerations to lower extremities from sharp canine incisor tusks (Figure 9).

Potentially lethal lacerations can occur on other parts of the body if the victim falls while trying to escape. Feral swine are known to attack ferociously and repeatedly with their sharp tusks.[19] Although rare, fatalities from wild boar attacks have been known to occur.[21] Although we saw signs of feral swine at our campsites, no sightings occurred during the trip.

Railroad Bridge Obstruction

Our last significant challenge was perhaps one of the most serious I have encountered while canoeing. With flooding at a 40-y high, we were unaware there was not enough vertical clearance to paddle beneath the CSX railroad bridge crossing the Tensaw River (Figure 10). Had we not left the main river currents north of the bridge and sought safe passage via a forest route, flood currents would have swept us under the structure, capsizing our canoes. As we approached the bridge, I scouted the area, gauged the space below the bridge as inadequate for canoe passage, and communicated the danger by radio to other crew members. We turned west, paddled along the mounded track, and found an unmarked underpass deep in the forest. From there, we paddled underneath the track and were able to rejoin the Tensaw River channel moving south. Portaging canoes across an active railroad was not considered. By using this alternate route for downriver passage, we avoided reversing course in flood currents and ending our trip prematurely.

Figure 9. Feral swine tusks. Photo courtesy of Luke Adams.

Figure 10. CSX Railroad crossing Tensaw River. Photo courtesy of Amy Karras, Unnamedadventures.com.

Conclusions

Canoe camping expeditions have inherent outdoor risks no matter the ecosystem. Instructor experience, moving-water safety training, radios for communication, and attention to native and invasive animal and insect species are vital to ensuring group welfare. Flood conditions do not necessitate postponing an expedition, but care in advance of departure should be taken to avoid obstacles. Despite our best efforts to gather information about the Mobile-Tensaw Delta in flood, we did not foresee 2 of the dangers we encountered: fire ants in trees and a railroad trestle with inadequate vertical clearance. These unknown perils could have placed any expedition and its members in jeopardy. Therefore, it is imperative not only to be trained for expected hazards but also to carry a well-equipped first aid kit for the unexpected and to possess the confidence to pause, reassess, and search for alternative, safer routes.

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Letters to the Editor

Optic Nerve Ultrasound Evaluation in Acute High Altitude Illness

To the Editor:

We read with great consideration the valuable and interesting case report by Wipplinger et al concerning the use of ultrasound as a diagnostic tool to identify acute high altitude illness.[1] Particularly, we focused on the optic nerve sheath diameter (ONSD) ultrasound evaluation, and we would like to point out some considerations on this helpful method.

The authors used B-scan ultrasonography to assess the ONSD increase between Day 7 and Day 8, as shown in Figures 3 and 4 of their paper.[1] However, these 2 figures seem not to be comparable with each other. Regardless of a small methodological bias related to the difference of 0.01 cm in the ONSD measurement distance between the 2 figures,[1] which would not significantly alter the ONSD results, the optic nerve sections evaluated and depicted in the 2 figures are not the same. Figure 4 seems to show the optic nerve insertion, but the same could not be said for Figure 3, where some scleral tissue appears to be present between the optic nerve and the retinal margin. This is due to the nonperpendicularity of the ultrasound beam to the optic nerve head in this scan, which could provide misleading data.

Furthermore, in this kind of measurement, to provide information regarding the gain used, the probe positioning on the eye and the echographic plane are required for repeatable and reliable results. Unfortunately, this information is missing from the presented case. Moreover, trustworthy and precise caliper positioning in ONSD measurements with B-scan ultrasonography is very difficult because it has been widely demonstrated that this technique is affected by the "blooming" effect, which makes such measurements inaccurate and unreliable.[2-5]

For all the aforesaid limitations, it is advisable to use the standardized A-scan technique proposed in the 1970s,[6] which is able to provide more objective measurements. This technique is free of the "blooming" effect to allow more precise optic nerve identification and evaluation through the visualization of easily discernible high reflective spikes from the interface between arachnoid and subarachnoidal fluid.[7,8] Another important advantage of this ultrasound technique is the ability to perform the "30 degrees" test, a very useful test to discriminate between an ONSD increase related to raised intracranial pressure and an ONSD increase due to a solid thickening of the optic nerve.[9,10]

In conclusion, we would like to suggest the use of the standardized A-scan technique, instead of B-scan ultrasonography, to obtain a more complete, accurate, and reliable optic nerve evaluation.

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In reply to Vitiello, De Bernardo, Capasso, and Rosa

To the Editor:

We have received and read with interest the letter from Vitiello et al[1] regarding our article entitled "Point-of-care ultrasound diagnosis of acute high altitude illness: a case report," recently published in *Wilderness & Environmental Medicine*.[2]

In their letter, the authors raised 2 issues with our use of B-scan ultrasonography to demonstrate an increase in optic nerve sheath diameter (ONSD) in a patient with suspected high altitude cerebral edema (HACE). They argued that the images used to evaluate the patient's condition were not comparable and could have provided misleading information. They also proposed the use of A-scan ultrasonography as a more objective method for ONSD measurement.[1]

The use of the A-scan technique for the diagnosis of ONSD enlargement in a patient with suspected HACE is an interesting suggestion. In eye ultrasonography, the A-scan is routinely used by ophthalmologists to determine eye biometrics in common sight disorders. The A-scan can also be used as an adjunct to the B-scan for the diagnosis of specific intraocular pathologies, such retinal detachments or uveal tumors.[3] In the literature, we found a number of similar letters written by the same group of authors in response to other publications using B-scan ultrasonography for ONSD measurements to detect raised intracranial pressure. To our knowledge, however, there is no recent original research regarding the use of the A-scan for this particular indication. In contrast, the B-scan has been accepted as a useful method for the detection of ONSD enlargement and raised intracranial pressure in critical care medicine.[4,5] The B-scan has also been used reliably with portable ultrasound devices in high altitude environments.[6-8]

In high altitude and expedition medicine, we consider B-scan ultrasonography to be the most evidence-based and practical method for ONSD measurement. B-scan ultrasonography is used in many other protocols for point-of-care ultrasound that can be useful in remote, high altitude settings. One example is lung ultrasound for the differential diagnosis of acute dyspnea.[9] Other potential uses include cardiac, abdominal, and trauma protocols. Most physicians are familiar with B-scan techniques but have never been trained in the use of A-scan techniques. Additionally, A-scan probes are usually not included on standard devices used for point-of-care ultrasound, which means that a secondary device would have to be taken into the field. Furthermore, the A-scan technique relies on direct contact between the ultrasound probe and the cornea or sclera, which requires application of topical anesthetic. Although topical anesthetics have been used successfully in high altitude research, the participants in this study stayed in the protective environment of a mountain hut during the entire study.[10] In the ever-changing environment of remote, high altitude expeditions, the use of topical anesthetics for repeated ONSD examinations can pose logistical problems and safety concerns.

We agree that B-scan measurement of ONSD can be subject to methodologic bias. In hospital environments, ONSD measurements are often performed on sedated patients, which minimizes spontaneous eye movement. In our experience, performing precise measurements on awake patients in remote, high altitude areas can be more difficult, especially if severe acute mountain sickness or HACE is present. Obtaining perfectly comparable images can also be technically challenging owing to unfavorable surroundings and varying clinical situations. To limit bias, ONSD measurements in high altitude environments for research purposes have in the past been based on the mean ONSD calculated from multiple measurements per patient.[6-8]

For practical reasons, we used a completely handheld device because we were on a trekking expedition and moved to a different location every day. The ONSD measurements were made using a linear high-frequency probe, which provided high-quality images and allowed for accurate measurements. On this particular device, the electronic measurement calipers needed to be positioned using the touchscreen of the device. This accounts for the small imprecision of 0.01 cm when comparing the provided images. As Vitiello et al noted, this should not have significantly altered the ONSD results.[1] Considering our working environment, we believe that the possibility of methodologic bias was sufficiently limited and that our interpretations were correct.

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In our opinion, point-of-care ultrasound diagnosis of HACE should not be based on single-point ONSD values but rather on serial measurements over time. Practitioners should be aware of the limitations of B-scan ultrasonography and always correlate the obtained images with the available clinical information. Owing to the lack of evidence and the practical limitations of the A-scan, we currently recommend the use of the B-scan for the evaluation of patients with a clinical suspicion of HACE. A comparison of A-scan and B-scan techniques for the detection of HACE could be an interesting topic for future research.

In conclusion, we believe that serial ONSD measurement using B-scan ultrasonography can be a valuable tool to assist in the diagnosis of patients with HACE in remote, high altitude environments.

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Suggested Addition to Wilderness Medical Society Snow Burial Guidelines

To the Editor:

There is no denying that early death from snow burial is often due to asphyxia, as is death from drowning. However, we would like to highlight that the Wilderness Medical Society (WMS) clinical practice guidelines pertaining to these situations differ.[1,2] Although the guidelines discourage hands-only cardiopulmonary resuscitation (CPR) and emphasize ventilation during standard CPR in drowning, this is not a recommendation in the snow burial guidelines.

WMS guidelines reflect the excellent work performed over the past few decades to determine the survivability of snow burial. One of the most significant factors is the cut-off time for survivability for victims of snow burial without an air pocket. Prognosis for survival is dismal if burial is prolonged, but with improved training, awareness, and technology, many snow burial victims are dug out quickly. For these patients, the WMS guidelines put little emphasis on the basic life support (BLS) resuscitation of a victim in cardiac arrest rescued within 60 min. Identifying an

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WMS guidelines reflect the excellent work performed over the past few decades to determine the survivability of snow burial. One of the most significant factors is the cut-off time for survivability for victims of snow burial without an air pocket. Prognosis for survival is dismal if burial is prolonged, but with improved training, awareness, and technology, many snow burial victims are dug out quickly. For these patients, the WMS guidelines put little emphasis on the basic life support (BLS) resuscitation of a victim in cardiac arrest rescued within 60 min. Identifying an

ice-plug or lack of air pocket does prompt rescuers to identify and, hopefully, clear the obstruction, but this is a subtlety that could be missed by nonmedical or companion rescuers. What is notably missing from the snow burial guidelines is the emphasis on ventilation during CPR. The WMS drowning guidelines, on the other hand, specifically state that BLS care must include ventilation. Why not add the same recommendations for snow burial victims without an air pocket who are in cardiac arrest and rescued within the first few minutes of burial?

The International Liaison Committee on Resuscitation CPR guidelines changed its recommendations regarding CPR in 2010.[3] During the last decade, priority has been on circulation, and then on airway and breathing, as the focus of BLS training. Hands-only CPR has also been promoted with the hope that chest compression-only CPR is better than no CPR. The American Heart Association (AHA) 2020 guidelines recommended that emergency call takers providing telecommunicator CPR instruct callers to perform hands-only CPR.[4] Providing hands-only CPR is obviously not ideal in special resuscitation situations involving asphyxia. The 2010 AHA guideline highlights did address this and indicated that CPR for drowning patients must include artificial respiration.[3] However, by 2020 those recommendations were no longer highlighted but buried in section 3 part 9.5.[5]

Shortly after the 2010 AHA guidelines were published, the International Commission for Alpine Rescue Medical Committee considered hands-only CPR not appropriate and recommended ventilation during CPR for the resuscitation of avalanche victims.[6]

The influence of the WMS guidelines is significant, as can be seen in the 2020 AHA recommendations, which specifically mention the WMS drowning guidelines as a supplemental reference.[5] Suggestions from the WMS that include specific wording regarding snow burial victims could foreseeably be included in the AHA recommendations also. The WMS should emphasize CPR with ventilation in snow burial victims in cardiac arrest and work with organizations such as the Canadian and American Avalanche Associations to highlight this among their target groups. We need to guide the companion rescuer because it will be the on-scene bystander who must conduct the immediate rescue sequence and resuscitation.

As our colleague and coauthor of the drowning guidelines Dr. Sempsrott pointed out, drowning victims are still drowning after they are rescued from the water. The drowning process has not stopped until adequate ventilation has begun. If this is true for drowning, why then should it not apply to asphyxia related to snow burial?

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Rhabdomyolysis After Consumption of Freshwater Fish (*Neolissochilus soroides*)

To the Editor:

Exercise and nutrition are essential to good health. However, exercise combined with the consumption of risky food or drugs can cause serious illness.

A 41-y-old man who had been receiving simvastatin therapy (40 $mg \cdot d^{-1}$) for dyslipidemia for a few years presented to the emergency department of Maharaj-

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Figure 1. The cooked fish meal that was consumed by the patient during a trekking trip on a mountain in southern Thailand. Image used with permission from the patient.

Nakhornsrithammaraj Hospital because of a 2-d history of generalized myalgia and weakness. The patient had been on a mountain trek with 3 companions for 1 d and had ingested freshwater fish that they had caught for dinner (Figure 1 and 2). The patient had eaten the largest portion and developed nausea in 30 min and shortness of breath, muscle pain, and weakness approximately 5 h after the meal. The next morning, the patient was unable to walk and had little urine, which was dark brown in color. The 3 companions who shared the dinner also had nausea and vomiting in 30 min and myalgia approximately 5 to 6 h after the meal; however, their symptoms were self-limited and resolved the following morning.

The patient's companions required 2 d to carry him down the mountain using a bamboo stretcher, which also constituted vigorous exercise. The patient denied fever, new medications, recreational drug use, recent illness, trauma, or other vigorous exercise. He was conscious, fatigued, and tachypnic on arrival. His temperature was 36.7°C; heart rate was 100 beats·min^{-1}, blood pressure was 127/70 mm Hg, respiratory rate was 36 beats·min^{-1}, and oxygen saturation was 98% on room air. Physical examination revealed tenderness in both thighs and the shoulder area and generalized weakness. Electrocardiography revealed sinus tachycardia with tall peak T waves. Laboratory results demonstrated hyperkalemia and elevated creatinine, urea, and creatine phosphokinase levels (Table 1). Urine myoglobin analysis was unavailable. The patient's companions also had elevated creatine phosphokinase levels of 1235, 1728, and 490 U·L^{-1} (normal range, 24–195 U·L^{-1}).

Figure 2. *Neolissochilus soroides,* a freshwater fish, which is called Rangaea in the local language. Image used with permission from the patient.

The patient was diagnosed as having rhabdomyolysis, acute kidney injury, and hyperkalemia. He received intravenous fluid and standard treatment for hyperkalemia. However, he remained oliguric despite adequate fluid replacement, and his renal function declined. On hospital Day 3, he developed severe dyspnea owing to volume overload. He was intubated and underwent hemodialysis. He improved clinically and was extubated on Day 7. The patient required intermittent hemodialysis for 3 wk and was discharged uneventfully on Day 34. He had no further symptoms during the 2-wk post-discharge follow-up, at which time his serum creatinine level was 1.8 mg·dL^{-1}.

The primary cause of the rhabdomyolysis was considered to be fish ingestion, a condition often known as Haff disease, which in this case was potentially precipitated by vigorous exercise (mountain trekking) and simvastatin ingestion. He was thus diagnosed on the basis of following rationale. First, all his companions, who ingested the same fish meal, also had clinical and

Table 1. Laboratory parameters and volume status during hospitalization

Hospital day	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*12*	*23*	*34*
BUN ($mg \cdot dL^{-1}$)	41	61	85	61	52	53	95	95	50	
Cr ($mg \cdot dL^{-1}$)	4.2	6.7	9.0	8.4	7.7	6.8	12.1	10.0	6.4	2.2
Sodium ($mmol \cdot L^{-1}$)	139	136	137	140	140		142	144	144	
Potassium ($mmol \cdot L^{-1}$)	6.1	4.4	3.2	3.0	4.1		4.0	5.3	5.2	
Chloride ($mmol \cdot L^{-1}$)	101	94	100	102	99		100	107	104	
Bicarbonate ($mmol \cdot L^{-1}$)	21	20	15	17	25		27	22	24	
Creatinine phosphokinase ($U \cdot L^{-1}$)	25,240		12,420		16,253	2723	895			
Fluid intake/ output (mL)	3432/ 500	2275/ 510	2111/ 1530	1660/ 2170	2140/ 2250	1790/ 140	893/ 200	2441/ 500	1343/ 4200	3290/ 4950

elevated creatine phosphokinase levels of 1235, 1728, and 490 $U \cdot L^{-1}$. Second, a temporal relationship exists between the fish ingestion and the illness experienced by all who had eaten the fish because gastrointestinal symptoms occurred within 30 min and myalgia developed in approximately 5 h. Finally, the biological plausibility of the soro brook carp, *Neolissochilus soroides* (family Cyprinidae) (Figure 2), causing rhabdomyolysis, as previously reported after consumption of other cyprinids, was also considered.[1] Statin-induced rhabdomyolysis is more common than Haff disease. The reported incidence of statin-associated muscle symptoms varies greatly, ranging from 5 to 29%, with milder symptoms being common and more serious symptoms being rarer. However, rhabdomyolysis is far rarer, with an incidence of approximately 1 in 10,000 population.[2] Elevated risk of statin-related muscle adverse events can be attributed to various genetic backgrounds.[3] Therefore, the patient may have had higher risk of statin-induced rhabdomyolysis owing to his Asian ethnicity and excessive exercise.[4] However, he had used the same dose of simvastatin and previously trekked to the same extent without developing rhabdomyolysis. In addition, a detailed history review found that the patient and his companions had no underlying diseases for which trekking is considered a serious predisposing risk factor.[5] We hypothesized that compared with his companions, the patient had severe rhabdomyolysis due to consuming the most fish and taking simvastatin.

Haff disease, named after the Königsberg Haff, which lies along the Baltic coast, was first reported in 1924 and recurred in periodic clusters.[6] Comparison of features of confirmed cases of the disease in the United States and China during the reporting period, 1997 to 2014, revealed that the median incubation period was 8 h for the United States, ranging from 3 to 21 h, and 7 h for China, ranging from 0.1 to 41 h. The major symptoms are muscle pain and stiffness. Other symptoms are nausea or vomiting, stomachache, diarrhea, headache, chest pain, shortness of breath, sweating, and pain to light touch.[7] Haff disease is associated with various types of fish, such as carp, crayfish, pomfret, freshwater eel, and marine boxfish. No information has been reported about which part of the fish contains more toxins than others. The toxins are heat stable and cannot be recognized by smell or taste. Currently, the toxin and etiology of the disease have not been identified.[8] Treatment is mainly supportive and standard care for rhabdomyolysis and its complications.[9]

Haff disease is not widely recognized, so it is understandably underreported. A high index of suspicion and exclusion of other causes are important parts of the diagnosis. Trekkers should not consume fish from mountain waterfalls because they can cause Haff disease. In addition, foraging wildlife has a negative impact on the ecosystem.

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Exposure to Bat Droppings Among Tourists Visiting Caves in the Brazilian Amazon: A Risk for Disease Transmission

To the Editor:

Bats harbor diverse pathogens and are considered as a source of zoonotic diseases, in particular those caused by viruses. Large-scale epidemics that have occurred since the end of the 20th century have been associated with viruses of bat origin, such as Hendra virus, Nipah virus, and SARS-CoV virus. The etiology of the coronavirus disease 2019 pandemic is a betacoronavirus of probable bat origin.[1] The reason why these mammals carry numerous viruses is under debate, with strong evidence suggesting unique immunologic features. In several animal species including bats, pathogens are shed via saliva, feces, and urine. Infections from these secretions can occur via direct contact or indirectly through contaminated soil, water, food, and aerosols. Thus, places with high concentrations of excreta, such as caves, mines, tunnels, and bridges, may be the origin of zoonotic infections.

Tourists Highly Exposed to Bat Droppings in Amazon Caves—The facts presented refer to 2 d of field observations carried out in July 2018 in Presidente Figueiredo (PF), a small tourist town in Amazonas state, Brazil. PF has approximately 36,000 inhabitants and is 128 km away from the Manaus urban center. The city is located

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Tourists Highly Exposed to Bat Droppings in Amazon Caves—The facts presented refer to 2 d of field observations carried out in July 2018 in Presidente Figueiredo (PF), a small tourist town in Amazonas state, Brazil. PF has approximately 36,000 inhabitants and is 128 km away from the Manaus urban center. The city is located

Figure 1. Interior of Maroaga cave, Presidente Figueiredo, Amazonas state, Brazil (July 2018). A thick, brownish layer of bat droppings can be observed covering the ground surface, except for the middle path of the cave where a small stream runs toward the exterior. The image was captured approximately 50 m inside the cave, where tourists access frequently.

Figure 2. Onça cave, Presidente Figueiredo, Amazonas state, Brazil (July 2018). Large amounts of bat droppings were present in the areas accessed by tourists, with various spots featuring a reddish color due to ingestion of açaí (*Euterpe oleracea*), a purple fruit highly consumed by insectivorous bats (numerous seeds of açaí discarded by bats were present over their excreta).

within the dense Amazon rainforest in a region with low deforestation levels. The Maroaga and Onça caves (2°3'3.31"S 59°58'14.61"W and 1°59'13.94"S 60°3'35.30", respectively) are among the most visited tourist destinations of Amazonas state. Both of these caves lacked safety measures to support tourist activities, such as handrails, stairs, signposts, and artificial lighting. In Maroaga, approximately 50 m after the cave entrance, there were copious amounts of bat excreta covering extensive areas of the ground (Figure 1), and it was virtually impossible to avoid stepping on it. Most of the tourists present on that occasion had their feet unprotected and inevitably stepped in soil moistened with droppings or stepped into the small stream that started inside the cave. Few bats were observed, but most presumably inhabited the deeper interior of the cave, where tourist access was prohibited. The tour guide reported that the cave was visited daily by several tourists, who had free access regardless of the guide's presence. She mentioned having no concern regarding the risks of exposure to bat feces.

The geologic structure of the Onça cave was relatively small and more open than Maroaga. It featured abundant bat droppings in areas accessed by tourists (Figure 2). Numerous bats were observed, and it was possible to be in close proximity owing to the low height of the cave. The tour guide here also declared no concerns about the exposure to bats and their droppings and was constantly encouraging tourists to get close to these mammals to observe them and take pictures. The events witnessed in PF presumably reflect daily tourist activities in Maroaga and Onça caves.

Evidences of Zoonoses Transmitted Through Bat Droppings—Although various pathogens originate from bats, information on the transmission pathways to humans need further studies. Nonetheless, exposure to droppings has been demonstrated or proposed as an important source of zoonoses. Histoplasmosis, caused by the fungus *Histoplasma capsulatum*, is one of the most frequently observed diseases associated with bat excreta and is commonly referred to as "cave disease." Although the majority of infected people present either no symptoms or mild illness, some individuals develop more severe clinical symptoms leading to mortality, such as acute pulmonary histoplasmosis, granulomatous mediastinitis, and disseminated histoplasmosis.[2] Transmission to humans occurs mainly via inhalation of fungal spores from the feces of bats and birds; thus, places with high concentrations of excreta from these animals may be the origin of histoplasmosis outbreaks.[3,4]

Nipah virus is a highly virulent bat-borne paramyxovirus that emerged in Malaysia in 1998, causing outbreaks with high fatality rates in Asian countries. Infection occurs through contact with the secretions of infected pigs and via person-to-person transmission. Nipah virus infection in humans is likely to occur via consumption of date palm sap contaminated with bat excreta.[5] The sap is traditionally collected in open pots placed at the top of palm trees, a procedure that enables

bats to access the harvested sap to consume it and may allow contamination by bat excreta.

Empirical evidence on the transmission routes from bats to humans for certain bat-transmitted diseases needs to be confirmed; however, available data suggest that high exposure to droppings is the most likely source of infection, as observed in the case of Marburg hemorrhagic fever (MHF). Since 1975, outbreaks of MHF have been associated with visits to caves and mines,[6] and the Egyptian fruit bat *Rousettus aegyptiacus* was later identified as the prime reservoir host for Marburg virus. Unprotected contact with infected bat feces or aerosols is considered to be the source of MHF infection,[7] as successfully demonstrated via experimental respiratory infections in animal models.[8] Other human pathogens found in bats may be transmitted via exposure to bat droppings, such as *Leptospira* spp and *Hantavirus*, both of which are primarily transmitted to humans through rodent excreta.

Final Considerations—The high level of exposure to bat droppings in PF needs greater attention from the public health perspective. Histoplasmosis is the most likely zoonosis to emerge from this scenario. Furthermore, exposure to bat droppings should be recognized as a risk for spillover events, with new and undiscovered pathogens (mainly viruses) emerging in human populations. Such risk is possibly enhanced by the proximity of PF to the city of Manaus and to the high biodiversity of the Amazon biome, as the emergence of zoonotic pathogens of wildlife origin correlates strongly with both human density and wildlife biodiversity, respectively.[9] The development and operation of new strategies to mitigate the risks of disease transmission inside Maroaga and Onça caves are warranted. Briefly, such strategies should include specific protocols for personal protection (eg, the use of appropriate clothing, footwear, safety helmets, and safety instructions), professionalization of tour guides, and studies to characterize the risks of disease transmission during speleological tourism.

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Cardiac Arrest by Aconite Poisoning

To the Editor:

At the end of 2020, the European Resuscitation Council published its draft guidelines on cardiac arrest management.[1] Cardiac arrest in special circumstances can be challenging for clinicians who are not accustomed to dealing with these uncommon clinical situations. We present a case of cardiac arrest as a result of aconite poisoning.

A 67-y-old male with no known allergies and no relevant medical history was walking in the forest. Two hours later, once at home, he experienced rapid onset of diarrhea and vomiting, perioral numbness, diaphoresis, and progressive decrease in level of consciousness. When first responders arrived, he reported accidental ingestion of a plant he found in the forest. Given this information, the initial differential diagnosis included an allergic reaction or plant-based intoxication. He was transferred by ambulance to the closest hospital and was administered methylprednisolone 125 mg, metoclopramide 10 mg, dexchlorpheniramine 5 mg, and 1250 mL crystalloids. Once at

bats to access the harvested sap to consume it and may allow contamination by bat excreta.

Empirical evidence on the transmission routes from bats to humans for certain bat-transmitted diseases needs to be confirmed; however, available data suggest that high exposure to droppings is the most likely source of infection, as observed in the case of Marburg hemorrhagic fever (MHF). Since 1975, outbreaks of MHF have been associated with visits to caves and mines,[6] and the Egyptian fruit bat *Rousettus aegyptiacus* was later identified as the prime reservoir host for Marburg virus. Unprotected contact with infected bat feces or aerosols is considered to be the source of MHF infection,[7] as successfully demonstrated via experimental respiratory infections in animal models.[8] Other human pathogens found in bats may be transmitted via exposure to bat droppings, such as *Leptospira* spp and *Hantavirus*, both of which are primarily transmitted to humans through rodent excreta.

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the emergency department, he continued to experience nausea, vomiting, diarrhea, and decreased responsiveness to stimuli. Examination revealed sinus tachycardia of 175 beats·min^{-1}, hypotension (90/60 mm Hg), reduced consciousness, and bilateral mydriasis. Given his neurologic clinical status impairment, his airway was secured by tracheal intubation. A standard preoxygenation was performed during 2 min with facial mask and 0.15 mg of fentanyl; 20 mg of etomidate and 100 mg of succinylcholine were administered in bolus intravenously in a rapid sequence intubation. Anesthesia maintenance was obtained with midazolam and fentanyl perfusion. While awaiting transfer, the patient experienced cardiac arrest. Advanced cardiopulmonary resuscitation maneuvers were initiated, and the first rhythm detected by electrocardiography monitoring was ventricular tachycardia that quickly progressed to ventricular fibrillation and then torsades de pointes. A total of 3 defibrillations (200 J), 3 g of magnesium sulfate, and 300 mg of amiodarone were administered, with recovery of spontaneous circulation after 12 min of resuscitation. The patient was admitted to an intensive care unit with the initial diagnosis of plant intoxication and was transferred by helicopter under mechanical ventilation.

On arrival, noradrenaline infusion was required to maintain hemodynamic stability, and constant changes in electrical rhythm and QRS morphology were observed (alternating left bundle branch block, bigeminy, frequent ventricular extrasystoles, sinus rhythm, atrial fibrillation, and nodal rhythm). Lidocaine was administered, 100 mg intravenously in bolus, and 1.5 μg·kg·min^{-1}. Transthoracic echocardiography was performed with no relevant findings. Therapeutic hypothermia was not pursued owing to the arrhythmogenic risk involved. Potassium and magnesium levels were checked regularly and remained within normal range.

After 3 h of treatment in the intensive care unit, electrocardiography showed short periods of sinus bradycardia alternating with atrial fibrillation. Within the first 24 h, the patient was successfully extubated with no neurologic damage observed (cerebral performance category 1). Seventy-two hours after cardiac arrest, he was discharged to a regional hospital.

Plant intoxication is a rare condition but can often be catastrophic. *Aconitum napellus* is a plant commonly found in the moderate altitude of European mountains. It contains several alkaloids with potent cardiac and neurologic toxicity. Aconite intoxication is a life-threatening situation owing to its manifestations in overexcitable tissues. Aconitine is an alkaloid (representing 30% of the alkaloids in this plant) with a high affinity for voltage-dependent sodium channels. The toxin causes these sodium channels to remain in an active state of continuous depolarization, giving rise to many severe clinical effects.[2] A lethal dose is estimated to be between 1 and 2 mg of aconitine for an 80-kg individual. In the case we report, the patient believed that the plant ingested was *Molopospermum peloponnesiacum* rather than *Aconitum napellus*, a very dangerous confusion.

Clinical manifestations are variable and depend on the toxicity of the alkaloids. The earliest symptoms are usually numbness and burning in the perioral area. Neurologic complications are also frequent and can include diaphoresis, obnubilation, blurred vision, color distortion, weakness, tingling, incoordination of extremities, and muscular paralysis that can result in respiratory arrest. Gastrointestinal symptoms include vomiting, diarrhea, and nausea. At a cardiovascular level, ventricular disturbances can quickly progress to cardiac arrest.[3] No antidote for aconitine poisoning has been discovered.[4] Treatment consists of supportive care and treatment of complications. Some drugs (amiodarone, flecainide, procainamide, mexiletine, lidocaine, magnesium sulfate) and electrical cardioversion have been tested with varying results.[5] Amiodarone and flecainide are the recommended first-line treatment.[6] The half-life of aconitine is about 3 h; therefore, resuscitation using extracorporeal life support to restore and maintain hemodynamics is recommended if necessary. A small number of cases successfully using extracorporeal life support have been described.[7]

Aconitium napellus intoxication is a rare condition that can lead to catastrophic outcomes, including cardiac arrest. Early recognition of rare clinical conditions can be life-saving. Training clinicians in the resuscitation of patients in cardiac arrest in special circumstances and implementing educational information in mountain areas regarding potential dangers for mountaineers are strategies that should be promoted.

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Book Review

Australia's Dangerous Snakes—Identification, Biology, and Envenoming
Peter Mirtschin, Arne R. Rasmussen, Scott A. Weinstein
Clayton South, Australia: CSIRO Publishing, 2017
424 pages; hardcover $86 USD

Australia is famous for its unique and often dangerous animal life, and especially its venomous snakes. *Australia's Dangerous Snakes* provides an in-depth look into the lives of this iconic group of animals.

More than 100 terrestrial and 30 marine species of venomous snakes inhabit this island continent and the waters surrounding it; these include some of the world's most deadly serpents. The book reviews the biology, natural history, behavior, and health risks of Australian snake species that are dangerous to humans, including the production, actions, and uses of their venoms and the clinical management of their bites. Something not usually seen in books about venomous snakes and a particular strength of this book is its discussion of the essential roles these animals play in their ecosystems.

After a short introduction, Chapter 2 discusses the public health significance and relative danger of snakes and snakebites. Chapters 3 through 5 then cover in much detail the morphology, identification, and distribution of the species most dangerous to humans. These 3 chapters constitute 40% of the book. Chapter 6 reviews the declining numbers of snakes and conservation efforts to combat the many existential threats facing some of these species. Chapters 7 and 8 will likely be of most interest to medically oriented readers insofar as they discuss envenomation and the various snake venoms, as well as the first response to, clinical management of, and complications of bites from these species. Although the discussion of snakebite medical management is substantive, many clinicians will want to have ready access to other clinical references when managing bites from these species, especially when managing their diverse complications. The body of the book concludes with a chapter on snake-human interactions. This is followed by an appendix on Australian antivenoms and snake handling, a glossary, a 45-page bibliography, and an index. I was disappointed that the many references are not linked to the content of the chapters, precluding the ability to easily access references supporting individual statements or data cited in the text.

Australia's Dangerous Snakes is a substantive, fact-filled, and easy-to-read book. The clear and straightforward text is robustly augmented by photographs, species distribution maps, tables, and other illustrations. The book will be equally at home on a herpetologist's laboratory bookshelf or an outdoor adventurer's living room coffee table. The book may be of particularly keen interest to herpetologists and other snake aficionados, but physicians, toxicologists, and other healthcare professionals who have an interest in snakebites—as well as zoo personnel, outdoor enthusiasts exploring Australia, and anyone else wanting detailed information about Australia's dangerous snakes—will find the book to be a rich resource.

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Book Review

Advanced Environmental Exercise Physiology, 2nd edition
Stephen S. Cheung, PhD, Philip N. Ainslie, PhD
Champaign, IL: Human Kinetics, 2022
296 pages; paperback $119 USD; e-book $90 USD

Advanced Environmental Exercise Physiology was developed as a concise survey of the field of environmental physiology appropriate for those entering the research arena. The first edition was authored by Cheung alone in 2010. The second edition, released in 2021 in both e-book and print versions, is coauthored by Cheung and Ainslie, with the contributions from several other individuals acknowledged.

The textbook contains 16 chapters covering classic topics in environmental physiology: fundamentals of temperature regulation, heat stress, heat adaptation and heat therapy, hydration strategies for exercise, cold air exposure, cold water immersion, breath-hold diving, diving and hyperbaric physiology, physiologic adjustments to acute hypoxia, high altitude physiology, altitude training and performance, microgravity and spaceflight, exercise in polluted environments, chronobiology, cross-adaptation, and individual variability.

Each chapter begins with a list of objectives and closes with a short list of review questions. The content delivers a mix of fairly standard descriptive text, select research findings, and personal or practical perspectives. The depth of coverage varies across chapters, and this is reflected in the referencing. The use of tables and figures is appropriate to summarize or illustrate concepts. Text citations use author names, and these, along with research focus box descriptions, provide a sense of connection to the research community. There is sufficient detail to satisfy interested nonspecialists, and the switch in tone between dispassionate and conversational provides a welcome balance for those less interested in reading straight technical content.

The appendix provides a helpful list of relevant societies, agencies, organizations, and books, with a strong North American bias. The reference list provides a sampling of the literature, with a mix of classic and less frequently cited works. The index is quite detailed, with embedded hyperlinks in the e-book version to quickly take readers to sections of interest.

The e-book is offered in most standard formats, protected from unauthorized redistribution but available for offline reading. It can be accessed by course instructors through HK*Propel*, but ancillary material for instructors was not found in preparing this review. The e-book explored on the HK*Propel* platform was readable with some lack of polish. Examples of the latter include inconsistencies in font and text sizing, some small images with often smaller text, and minor editorial errors.

Subject matter experts will certainly find areas of greater and lesser strength. This is not surprising for a book covering a broad field of inter- and multi-disciplinary research. Ultimately, though, the book is successful in positioning itself as an advanced introductory text. It will be of value to keen upper-level undergraduates, early phase graduate students, and residents or other medical readers looking for a highly digestible overview of environmental physiology. It will not be appropriate for those interested in comprehensive coverage of individual topics and the related literature.

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WILDERNESS & ENVIRONMENTAL MEDICINE 2021; 32(3): 420

WILDERNESS IMAGE

Sierra Skies

Marc Cassone, DO, FAWM[1]; Christopher Winstead-Derlega, MD, MPH[2]

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White Mountain (37.3803°N, 118.1520°W) is the third tallest peak in California, sitting at 4344 m (14,252 ft). These photos were taken by members of the 2018 SEAWARD altitude research study[1] on their way to Barcroft Station, a research laboratory built in 1951 on a lower saddle of the peak at 3798 m (12,470 ft). Barcroft Station is part of University of California Los Angeles' White Mountain research station and is host to facilities and laboratories for various types of research. It hosted Nobel laureate George Smoot during his research on cosmic background radiation and still serves as the site for current studies on altitude's effect on human physiology. The round-trip hike from Barcroft Station to the summit is approximately 24 km (15 mi) with 1051 m (3448 ft) elevation gain and stunning views along the way. On the drive up, peakbaggers and altitude enthusiasts should consider stopping at the Patriarch Grove, home to some of the highest—and largest—bristlecone pines in the world. Even the drive up the unpaved road to the trailhead can reveal the impressive vistas of the Sierras.

Led by Dr. Grant Lipman, the 2018 SEAWARD study investigated day of ascent dosing of acetazolamide for the prevention of acute mountain sickness (AMS). The double-blind, randomized, controlled trial brought participants to Barcroft Station and compared the incidence of AMS in participants initiating acetazolamide on the day of ascent and those who took the initial dose the night prior. One hundred four participants were included in the analysis. Day-of-ascent acetazolamide yielded a 9% greater incidence of AMS (48% vs 39%, 95% CI 12–30) compared to acetazolamide initiated the night prior to ascent.[1]

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EDITOR'S NOTE

Referencing in Scientific Writing

Referencing in scientific writing has long been viewed as arcane to the uninitiated. The confusion in the pre-internet era was largely due to highly specific format requirements that differ between types of articles and between publications. The new reality is much worse.

The ever-increasing array of online resources has many people able to access a tremendous wealth of content with ease from almost any location. It is possible to find what can seem to be relevant material on any topic with a remarkably small number of keystrokes. The rapidity in finding information can promote the sense of a limitless trove of knowledge, but in this is a major hazard.

The ease of access to information does not confirm validity, let alone authority. Critical thinking remains essential to weigh the value of any piece of information. The established structure in traditional literature aids in the assessment. The greatest academic weight is generally given to well-designed primary research reports published in respected, peer-reviewed journals. This work is most likely reviewed by subject matter experts who help authors overcome or acknowledge any perceived shortcomings.

Review papers are useful as syntheses, but they tend to have lower academic weight because they rely on the selective interpretation of other original work. Brief reports can offer good insights, but their authority is generally limited by small sample sizes. Case reports provide the most extreme example of limited sample size, with a concomitant lack of authority. Gray literature, such as proceedings papers, is often published with little or no meaningful peer review. Although these works can be insightful, they are rarely accepted as authority. The final traditional literature class is textbooks, which are effectively thirdhand summaries with selective content that can fall anywhere on the continuum between compelling and misleading.

The internet confounds the classic hierarchy of published material. It can, in some cases, be used to access top-ranked peer-reviewed original and formally published research, but it can also place such items next to unreviewed "preprints" or informally published commentaries that may or may not be well founded. There is no standard for internet content, generally no checks on content quality, and almost never any promise of content stability or archival access. It is left to the reader to evaluate and use the material appropriately.

The first step in evaluating any content is consideration of validity. Finding something that agrees with a position or that could reinforce an argument may be attractive, but these things do not ensure validity. Assuming that validity can be satisfactorily established, it needs to be determined whether the material is appropriately referenceable.

Content stability and archival access are priority concerns in referencing in scientific articles. There is an expectation that references cited in a paper will be not only valid but accessible for the foreseeable future in the form used to generate the citation. This provides an important guide for reference selection.

The only content that can be considered unquestionably suitable for inclusion in the reference list is formally published material. The fact that something was written on some web page at some point or that it was found in a portable document format (PDF file) does not justify inclusion in a reference list. Formal publication requires, at a minimum, a publication or version date, a listed author and/or publisher, and a stable form that can reasonably be expected to be available in the future.

The other end of the extreme is easier to describe. Items that are definitely disqualified from reference lists are general web pages (eg, "landing pages") and dynamic pages. Landing pages generally do not contain the specific information relevant to the discussion. They have no value as references. Dynamic pages that are continually updated will, by their nature, be inconstant and inappropriate to reference: They could tell similar, stronger, or completely different stories at any point in the future. The descriptive term for the weakness associated with dynamic pages is "reference rot." Effectively, the pages may appear to be the same, but the content could be substantially different.

The debate over using informal or unpublished reports available online is more challenging. The content may be compelling—there may be a version date, author, and even a publisher listed, and preservation may be assumed—but caution is required. Organizations can change hosts or reorganize, reduce, or replace content. The lack of formal publication makes any such material less likely

to survive. The term "link rot" applies to addresses no longer accessing the expected content. The problem is huge, particularly given the dearth of rules regarding website archiving. The scientific literature is intended to stand as a record of scientific endeavor, and it is important to incorporate elements most likely to endure.

There can be frustration among those comfortable with internet content to learn that some is disqualified from reference lists, but it is important to understand that this does not eliminate the presentation of relevant sites. There is a tiered approach to referencing. Formal publications are those most appropriate for reference lists. Material with lesser provenance can still be included, but as text citations, completely independent of the reference list. For example, the landing page of an organization could be listed parenthetically after the organization name. This is a generic text reference, with no promise of specific content. Similarly, text citation is possible for a dynamic web page collecting data relevant to the topic under discussion. There needs to be more explanation in the text, and no reliance on a formal reference, but the existence of the relevant site and cautious use of its content can be reasonable.

Text citations are the equivalent to personal communications, where material held in written form can be cited within the text. The caveat here is that steps should be taken to capture and preserve the content at the point of writing. It should be kept available in a form that can be reviewed upon demand.

Complicating the current discussion is the fact that referencing standards will vary between journals. Some might rely on author discretion, whereas others more actively promote the tiered approach to mandate preservation of the traditional standards for reference lists. *Wilderness & Environmental Medicine* operates in the latter form, generally accepting only formally published material in the reference list. As is the case with almost all journal guidelines, the argument that similar content was allowed elsewhere or previously holds no weight.

Neal W. Pollock, PhD
Editor-in-Chief

WILDERNESS & ENVIRONMENTAL MEDICINE 2021; 32(3): 271–7

ORIGINAL RESEARCH

Prehospital Cross-Sectional Study of Drowning Patients Across the United States

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Introduction—Every year drowning is responsible for 7% of injury-related deaths worldwide, making it the third leading cause of unintentional injury-related death. However, in the United States, little is known regarding the prehospital presentation and management of these patients. The purpose of this study was to describe the drowning population in the United States, with a focus on prehospital time intervals, transport, and cardiac arrest frequency.

Methods—A retrospective cross-sectional study was performed querying records from emergency medical services encounters across the United States over 30 mo (January 2016 to July 2018) using the ESO (Austin, TX) national emergency medical services data registry. Patients with a dispatch or chief complaint of drowning were included. Descriptive statistics, binomial proportion tests, and general linear and logistic regression models were used.

Results—There were 1859 encounters that met the study criteria. Median age was 18 y (n=1855, LQ-UQ 4–46). Pediatric patients accounted for 50% (n=919, 95% CI 47–52). Cardiac arrest occurred in 29% (n=537, 95% CI 27–31), and return of spontaneous circulation occurred in 37% (n=186, 95% CI 32–41). Times were 8±5, 19±17, and 15±10 min (mean±SD) for arrival, on-scene, and transport times, respectively.

Conclusions—This national prehospital drowning study demonstrated that despite an 18% fatality rate in drowning encounters, patients were more likely to have return of spontaneous circulation when compared to the overall prehospital national average, with rates higher in pediatric patients. Future studies with outcomes data should focus on identifying factors that improve cardiopulmonary resuscitation success rates.

Keywords: emergency medical services, pediatric, cardiac arrest, return of spontaneous circulation

Introduction

Drowning is responsible for approximately 7% of all injury-related deaths worldwide each year according to the World Health Organization, making it the third leading cause of unintentional injury-related death. In the United States, drowning is the second leading cause of injury-related death among children 1 to 4 y of age.[1] The Centers for Disease Control report that 1 in 5 people who die from drowning are children aged 14 y and younger, with many additional pediatric patients requiring treatment and hospitalization for nonfatal submersion injuries. For every fatal drowning reported, it is estimated that another 5 persons seek emergency care for nonfatal drownings.[2] This could indicate a severe underreporting and misrepresentation of the burden of drowning.

Drowning is a sudden or progressive respiratory impairment from submersion or immersion in liquid.[3] Aspiration impairs oxygen exchange, which results in hypoxia.[4] Hypoxia leads to cardiac rhythm abnormalities, typically tachycardia followed by bradycardia, pulseless electrical activity, and, ultimately, asystole.[4-6] The whole drowning process, from submersion to cardiac arrest, typically occurs in seconds to minutes.[7] Exceptions can

Preliminary data were presented at the Society of Academic Emergency Medicine's southeast regional meeting in 2020 in Greenville, North Carolina, and national meeting in 2020 in Denver, Colorado.

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prolong this process, particularly with extremes in environmental temperature.[7] Because of the rapid deterioration in drowning patients, early response and recognition by prehospital care providers is imperative for positive outcomes.

Emergency medical services (EMS) play an important role in patient outcomes, but a critical evidence gap exists regarding the prehospital presentation and management of drowning patients. Patients present with logistic and environmental challenges not seen in typical prehospital encounters, and an understanding of patient presentation and time intervals is imperative in developing treatment and risk reduction protocols for this population. The purpose of this study was to describe drowning patients in the United States, with a focus on prehospital time intervals, transport, and cardiac arrest frequency.

Methods

A national retrospective cross-sectional study of drowning patients from across the United States was performed by querying patient care reports from 1314 EMS agencies collected over 30 mo (January 2016 to July 2018) using a de-identified research database maintained by ESO, Inc. (Austin, TX). All agencies that use the ESO system were included. Prehospital providers manually enter data into the ESO electronic health record (EHR) to approximate the care they provide for each patient. Records with a dispatch or chief complaint of "drowning" were included in the study. The ESO prehospital EHR software facilitates the collection of comprehensive clinical information, including event dispatch data, patient demographic characteristics, clinical presentation and course, interventions and treatments, and outcome at the transfer of care. Data elements collected within the ESO database are compliant with the National EMS Information System standard, which increases the standardization of collected data across EMS systems. Data fidelity was ensured by direct population of the ESO research database from the ESO EHR. The institutional review board at Wake Forest University Health Sciences approved this investigation and waived the requirement for informed consent. The strengthening the reporting of observational studies in epidemiology guidelines helped direct the research and article development processes.[8]

All EMS encounters with a dispatch or chief complaint or impression of "drowning" were included in the analysis. Patients were excluded if they were declared dead in the field with no resuscitation attempted. Interfacility transport patients were not included. Patients were categorized by age, sex, race, and transport decision. Age was categorized as adult or pediatric, with pediatric defined as <18 y old. Race was categorized into White, African American, Latino, and Other. Race categories were determined by predefined ESO user input options.

Patient data were categorized based on inputs into the EHR system, defined in Table 1. Prehospital times included response time, on-scene time, and transport time. These were defined as the difference between dispatch time and arrival time, arrival time and scene

Table 1. Defined variables with ESO category chosen by prehospital provider

Variable	*ESO category*
Level of service	Level of service
Basic life support	Basic life support
Advanced life support	Advanced life support
	Advanced life support 2
	Basic life support, upgraded
	Critical care
Transport decision, urgency	Disposition
Transported, emergent	Transported lights/siren
	Transported no lights/siren upgraded
Transported, nonemergent	Transported no lights/siren
	Patient treated, transferred care to another EMS professional
	Patient dead on scene, resuscitation attempted (with transport)
Not transported	Assist
	Dead on scene
	No treatment, no transport
	Patient care transferred
	Patient treated, no transport
	Personnel aiding in transport
	Treated, transported by private vehicle
	Treatment, no transport
Cardiac arrest	Cardiac arrest
Cardiac arrest	Yes, after EMS arrival
	Yes, before EMS arrival
No cardiac arrest	No
Return of spontaneous circulation	ROSC occurred
ROSC	After ALS
	After bystander CPR only
	After bystander defibrillation shock
	After EMS CPR only
	After EMS defibrillation shock
	Return of spontaneous circulation (in discontinuation reason)
No ROSC	Never
	Unknown

ALS, advanced life support; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.

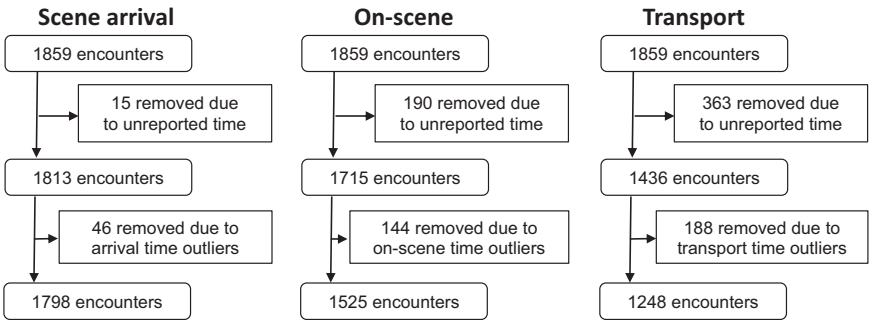

Figure 1. Case selection flow diagram for prehospital time intervals.

departure time, and scene departure time and destination arrival time, respectively. Only those transported were included in the transport interval analysis. Advanced life support was defined as services provided exceeding the capabilities of a basic emergency medical technician. Cardiac arrest and return of spontaneous circulation (ROSC) occurrence were assessed by the prehospital provider as the absence or return of a pulse.

Descriptive statistics were used to characterize the sample. Age was presented as median and interquartile range. Mean times were presented with SD. Encounters were excluded from the time interval calculations if there was an unreported value for the specified time interval. Zero-minute and negative time intervals were also excluded. Certain events, such as failure to regain ROSC after cardiac arrest, produced scenarios with time intervals that did not represent the typical prehospital drowning patient encounter and were thus excluded. Extreme rightward limits were defined as time values greater than 3 SD above the mean, resulting in upper limits of 25, 115, and 53 min for response time, on-scene, and transport intervals, respectively (Figure 1). Values exceeding these limits suggest failed or withheld resuscitation attempts or improper data entry, none of which accurately represent time standards of a patient transported by EMS, and were thus excluded.

Binomial proportion tests were used to determine the significance of the categorical variables when compared to the theoretically expected value. General linear models were used to compare the effects of age, sex, race, and cardiac arrest on EMS time intervals. A logistic regression with odds ratios (ORs) was used to compare the same predictors for cardiac arrest and ROSC occurrence. Age was treated as a categorical variable owing to the effect age-based EMS protocols could have on the linear and logistic models. Statistical significance was determined with 95% CIs of measured proportions between categories with an a priori alpha level of 0.05. Post hoc analysis of 1859 encounters revealed that the statistical power for this study exceeded 0.99 for measuring effect size. Values compared with previous studies were deemed significant with comparison to the confidence interval for difference between proportions (CIDP). SAS 9.4 (SAS Institute Inc., Cary, NC) was used to conduct statistical analyses.

Results

There were 1859 drowning encounters (Table 2). Binomial proportion tests are reported in Table 3. The median age was 18 y (n=1855, LQ-UQ 4–46). Pediatric encounters accounted for 50% (n=919, 95% CI 47–52) of the sample. Males accounted for 65% (n=1200, 95% CI 63–67) of the sample, and white patients accounted for 69% (n=1231, 95% CI 67–72).

Overall response time was 8±5 min. Overall on-scene time was 19±17 min. Overall transport time was 15±10 min. A general linear model for EMS response times that accounts for age, sex, race, and cardiac arrest presentation is presented in Table 4. On-scene time was shorter for younger patients (β=−0.9, 95% CI −10.4 to −7.9) and longer for cardiac arrest patients (β=3.4, 95% CI 2.1–4.8); transport time was shorter for African American patients (β=−2.6, 95% CI −4.0 to −1.2) and cardiac arrest patients (β=−3.4, 95% CI −4.7 to −2.2). Associations between pediatric cardiac arrests and time intervals were nonsignificant.

Advanced life support treatment was provided to 79% (n=874, 95% CI 64–70) of the sample. Encounters transported by EMS accounted for 67% (n=1248, 95% CI 65–69) of the sample, with the remaining encounters providing alternative means of hospital transport or refusing medical treatment. Of those encounters transported, 62% (n=774, 95% CI 59–65) were transported as

Table 2. Descriptive statistics for the study population

Variable	*Statistics*
Continuous variable	
Age (n=1855), median (LQ-UQ), y	18 (4–46)
Time interval, mean±SD, min	
Response (n=1798)	8±5
On-scene (n=1525)	19±17
Transport (n=1278)	15±10
Categorical variable, n (%)	
Age	1855
Pediatric[a]	919 (50)
Adult	936 (50)
Sex	1845
Male	1200 (65)
Female	645 (35)
Race	1774
White	1231 (69)
African American	310 (18)
Latino	95 (5)
Other	138 (8)
Level of service	1114
Basic life support	240 (22)
Advanced life support	874 (79)
Transport decision	1859
Transported	1248 (67)
Not transported	611 (33)
Transport urgency	1248
Emergent[b]	774 (62)
Nonemergent	474 (38)
Cardiac arrest	1859
Cardiac arrest	537 (29)
No cardiac arrest	1322 (71)
ROSC[c]	196 (37)
No ROSC	341 (64)

LQ, lower quartile; ROSC, return of spontaneous circulation; UQ, upper quartile.

[a]Defined as age less than 18 y.

[b]Of those transported.

[c]Of those with cardiac arrest.

emergency traffic with activated lights and sirens, with the remaining encounters transported as routine traffic without lights and sirens.

Cardiac arrest was reported in 29% (n=537, 95% CI 27–31) of encounters. ROSC was reported in 37% (n=196, 95% CI 32–41) of those presenting in cardiac arrest. A logistic regression model was performed for cardiac arrest and ROSC occurrence that accounted for age, sex, and race (Table 5). Cardiac arrest was reported less often for pediatric patients (OR=0.7, 95% CI 0.6–0.8) than adult patients. ROSC was reported more often in pediatric patients (OR=1.6, 95% CI 1.1–2.3). This study showed a total prehospital fatality rate of 18% (n=341, 95% CI 17–20).

Discussion

This study analyzed 1859 prehospital drowning encounters in the nationwide ESO database to determine population effects on prehospital time intervals and cardiac arrest frequency. Cardiac arrest occurrence was notably high; however, rates of successful cardiopulmonary resuscitation after drownings were higher than in general prehospital cardiac arrest encounters.[9,10] Although adult patients presented with cardiac arrest more frequently, pediatric patients had higher rates of ROSC. Time intervals were found to be shorter in both pediatric and African American patients.

This study demonstrated a ROSC rate of 37% (95% CI 32–41) for drowning patients. This is notably higher than the 11% (95% CIDP 24–28) and 10% (95% CIDP 24–28) prehospital ROSC rates after nondrowning cardiac arrest of unspecified origin.[9,10] A study also examining survival rates after cardiac arrest due to drowning showed a similar ROSC rate of 34% (95% CIDP −0.02 to 0.07).[11] Adults were found to present with cardiac arrest more frequently than their pediatric counterparts. This is most likely due to a higher prevalence of substance involvement and pre-existing conditions. In contrast, pediatric patients were found to have higher ROSC rates, possibly due to limited pre-existing conditions and closer attention by bystanders. Further studies examining these factors are warranted. It is important to note that although ROSC was more common in pediatric patients, both groups still demonstrated higher rates of ROSC than traditional cardiac arrest patients. In-hospital complications after ROSC in drowning patients increase mortality in the drowning population. This suggests that the long-term survivability of the patient population was lower than reported in this prehospital-focused study. These complications include aspiration pneumonia and poor neurologic outcome resulting from hypoxic brain injury.[12,13] Another study suggested that only 8% of drowning patients who experience ROSC in the prehospital setting survive to hospital discharge.[14] Although long-term survival could not be determined with these data, similar drowning studies suggest that worse outcomes were associated with male sex and the presence of specific chronic conditions.[15,16]

This study is consistent with the results of demographic disparities addressed in several other observational studies. White patients constituted the majority of drowning encounters in multiple studies.[17-19] Males have been shown to have a higher frequency of drownings.[18,20-22] Differences in sex have been attributed to increased time spent in water-related activities and risk-taking behaviors among males.[18,19] The effects of race remain unclear.[18,19] This study

Table 3. Binomial proportion tests for categorical variables

Variable	*Male % (95% CI)*	*Female % (95% CI)*	*Total % (95% CI)*
Age			
Pediatric[a]	47 (44–50)	54 (50–58)	50 (47–52)
Adult	53 (50–56)	46 (42–50)	50 (48–53)
Race			
White	69 (66–71)	71 (68–75)	69 (67–72)
African American	18 (16–20)	15 (13–19)	18 (16–19)
Latino	5 (4–7)	6 (4–8)	5 (4–6)
Other	8 (6–9)	8 (6–10)	8 (7–9)
Level of service			
Basic life support	20 (17–23)	24 (20–29)	22 (19–24)
Advanced life support	80 (77–83)	76 (71–80)	78 (76–81)
Transport decision			
Transported	67 (64–70)	68 (64–72)	67 (65–69)
Not transported	33 (30–36)	32 (28–36)	33 (31–35)
Transport urgency			
Emergent[b]	65 (61–68)	58 (53–62)	62 (59–65)
Nonemergent	35 (32–39)	42 (38–47)	38 (35–41)
Cardiac arrest			
Cardiac arrest	31 (28–34)	25 (22–29)	29 (27–31)
No cardiac arrest	69 (66–72)	75 (71–78)	71 (69–73)
ROSC[c]	35 (30–40)	40 (33–48)	37 (32–41)
No ROSC	65 (60–70)	60 (52–67)	63 (59–68)

CI, confidence interval; ROSC, return of spontaneous circulation.
[a]Defined as age less than 18 y.
[b]Of those transported.
[c]Of those with cardiac arrest.

demonstrated a frequency of drownings that was slightly higher in the adult population (51%). However, according to the United States Census Bureau, pediatric patients represent 22% of the United States population, suggesting a greater impact of drownings on the pediatric population. Regardless, deaths from drowning occur at younger ages relative to many other causes of death, resulting in a substantial loss of productive life years.[17] Further research should attempt to address the cause of these disparities.

This study examined EMS time interval data for drowning patients. The average response time was 8±5 min. This is consistent with the overall EMS mean response time of 8 min,[23] suggesting no notable differences caused by drowning etiology. Response time was shorter for African American and pediatric patients, suggesting an inherent urgency with pediatric patients. Although the reasons for a faster response with African American patients are unclear, this could be because African American populations tend to concentrate around urban centers, which have higher concentrations of EMS bases and proximity to hospitals.[24,25] On-scene time was 19±17 min, longer than the target 10 min on-scene time adopted by most EMS systems. This reflects a possibly prolonged extrication requirement and on-scene resuscitation attempt. On-scene times were shorter for younger patients and longer for cardiac arrest patients. This is most likely due to the generally preferred expedited transport of pediatric patients by most prehospital providers and attempts to regain spontaneous circulation in cardiac arrest patients before transport. Comparison with transport time is difficult due to variance in scene location and destination distance. Times were shorter for African American patients owing to the increased concentration of hospitals in urban populations, and for cardiac arrest patients owing to their critical nature. This study showed an EMS transport frequency of 67%, which was comparable to the overall national transport average of 71% (95% CIDP −0.06 to −0.02),[23] suggesting that drowning patients are similarly transported. Research with outcomes data should be completed to determine the clinical effect of these time discrepancies.

LIMITATIONS

This cross-sectional study retrospectively analyzed a single electronic medical record provider database of patients from EMS systems that have agreed to share their de-identified data for the purposes of research and benchmarking. These data are also observational.

Table 4. General linear model for emergency medical services times

Predictor	*Response β (95% CI)*	*On-scene β (95% CI)*	*Transport β (95% CI)*
Pediatric[a]	−1.5 (−2.0 to −1.1)	−9.1 (−10.4 to −7.9)	0.2 (−0.9 to 1.4)
Cardiac arrest	−0.2 (−0.7 to 0.3)	3.4 (2.1−4.8)	−3.4 (−4.7 to −2.2)
Sex			
Female	ref	ref	ref
Male	0.2 (−0.4 to 0.7)	0.6 (−0.7 to 1.9)	0.4 (−0.8 to 1.6)
Race			
White	ref	ref	ref
African American	−1.1 (−1.7 to −0.5)	−1.3 (−2.9 to 0.3)	−2.6 (−4.0 to −1.2)
Hispanic or Latino	−0.5 (−1.5 to 0.5)	−1.3 (−4.2 to 1.6)	−1.0 (−3.6 to 1.6)
Other	0.7 (−0.2 to 1.5)	1.1 (−1.3 to 3.5)	0.6 (−1.6 to 2.8)

CI, confidence interval; ref, reference category of comparison for other categories.
[a]Defined as age less than 18 y.

Therefore, inferences of causality are limited. This convenience sample is composed of a large number of encounters from the southern United States. Therefore, our results may not be generalizable to drowning patients in all EMS systems. Although demographics and cardiac arrest occurrences were significant, their clinical significance is unclear. Characteristic of retrospective prehospital research, the EMS dataset was limited and could not be linked with outcomes data and did not include any prehospital interventions. This study only addresses ROSC in the prehospital setting and does not provide any indication of improved resuscitation with neurologic recovery. Specific EMS agencies included were unknown, as were the urbanicity or rurality of where the encounters occurred. The definition of drowning is also historically challenging, with the possibility of documentation of "drowning" events varying from region to region or provider to provider. This could lead to the inclusion or exclusion of misreported encounters in the dataset. With these limitations, drawing definitive conclusions regarding out-of-hospital time and mortality is impossible. Because of the current process of prehospital data collection and relative outliers, a substantial number of patients were excluded from certain calculations, which could lead to unintended selection bias. Manual data input or bias of prehospital providers could lead to unintended data collection errors.

Table 5. Logistic regression model for cardiac arrest and return of spontaneous circulation occurrence

Predictor	*Cardiac arrest odds ratio (95% CI)*	*ROSC[a] odds ratio (95% CI)*
Pediatric[b]	0.7 (0.6−0.8)	1.6 (1.1−2.3)
Sex		
Female	ref	ref
Male	1.2 (0.9−1.5)	0.8 (0.5−1.2)
Race		
White	ref	ref
African American	1.1 (0.8−1.4)	1.3 (0.8−2.1)
Hispanic or Latino	0.6 (0.4−1.1)	0.9 (0.3−2.3)
Other	1.0 (0.7−1.6)	1.3 (0.7−2.6)

CI, confidence interval; ROSC, return of spontaneous circulation; ref, reference category of comparison for other categories.
[a]Of those encounters presenting with cardiac arrest.
[b]Defined as age less than 18 y.

Conclusions

This national prehospital drowning study demonstrates that despite an 18% fatality rate in drowning encounters, patients were more likely to have ROSC when compared to the overall prehospital national average, with rates higher in pediatric patients. Response times were shorter for pediatric and African American patients. On-scene times were shorter for pediatric patients and longer for cardiac arrest patients. Transport times were shorter for cardiac arrest and African American patients. Future studies with outcomes data should focus on identifying factors that improve cardiopulmonary resuscitation success rates.

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ORIGINAL RESEARCH

Evaluation of High Altitude Interstitial Pulmonary Edema in Healthy Participants Using Rapid 4-View Lung Ultrasound Protocol During Staged Ascent to Everest Base Camp

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Introduction—Prior research identified possible interstitial pulmonary fluid, concerning for early high altitude pulmonary edema (HAPE), in a large percentage of trekkers above 3000 m using a comprehensive 28-view pulmonary ultrasound protocol. These trekkers had no clinical symptoms of HAPE despite these ultrasound findings. The more common 4-view lung ultrasound protocol (LUP) is accurate in rapidly detecting interstitial edema during resource-rich care. The objective of this study was to evaluate whether the 4-view LUP detects interstitial fluid in trekkers ascending to Everest Base Camp.

Methods—Serial 4-view LUP was performed on 15 healthy trekkers during a 9-d ascent from Kathmandu to Everest Base Camp. Ascent protocols complied with Wilderness Medical Society guidelines for staged ascent. A 4-view LUP was performed in accordance with the published 2012 international consensus protocols on lung ultrasound. Symptom assessment and 4-view LUP were obtained at 6 waypoints along the staged ascent. A 4-view LUP was positive for interstitial edema if ≥3 B-lines were detected in 2 ultrasound windows.

Results—A single participant had evidence of interstitial lung fluid at 5380 m as defined by the 4-view LUP. There was no evidence of interstitial fluid in any participant below 5380 m. One participant was evacuated for acute altitude sickness at 4000 m but showed no preceding sonographic evidence of interstitial fluid.

Conclusions—In this small study, sonographic detection of interstitial fluid, suggestive of early HAPE, was not identified by the 4-view LUP protocol.

Keywords: altitude sickness, acute mountain sickness, wilderness medicine, mountaineering, austere medicine, lung comets

Introduction

High altitude pulmonary edema (HAPE) is noncardiogenic interstitial edema associated with ascent above 2500 m.[1,2] HAPE is more common at higher altitudes, with an incidence of 0.6 to 6% above 4500 m and 2 to 15% above 5500 m.[3] Mild cases include cough or exertional dyspnea. Severe cases are associated with high morbidity and mortality and require costly evacuation to lower altitudes.[4,5] Although chest radiograph is commonly used to assess for HAPE in high-resource settings, few imaging modalities that can be used to assist in the diagnosis of HAPE are available in austere situations.[6] High-resolution, point-of-care ultrasound units have emerged as useful diagnostic adjuncts to assess many pulmonary conditions, including pneumothorax and interstitial fluid, in critical and emergency care.[7,8] The characteristic sonographic lung findings of interstitial fluid are termed sonographic B-lines or B-pattern.[8,9] B-lines are comet tail-like reverberation artifacts that represent increased interstitial fluid within the lung parenchyma. In most situations, the number of B-lines generally correlates to the degree of interstitial fluid and has been shown to be useful in determining the severity

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and clinical course of several conditions with increased interstitial fluid content, among which pulmonary edema and congestive heart failure are well described.[10] More recently, ultrasound has shown clinical utility in detecting the interstitial fluid associated with HAPE.[11,12]

The 2012 international pulmonary ultrasound guidelines adopted 2 primary technical protocols.[13] The first is a 28-view, comprehensive protocol that provides a detailed view of both lung fields and cardiac windows. This technique also employs a semiquantitative scoring system to assess changes between examinations. The second technique is a 4-view (8-zone) lung ultrasound protocol (LUP). This protocol uses 4 views of each lung in the anterolateral plane. This technique is well described in the literature and is generally considered the preferred technique for most emergency and critical care situations; it is faster and more practical because the patient can remain supine or recumbent during the entire examination.

A previous study suggested that trekkers at altitude may have detectable B-lines on comprehensive 28-view lung ultrasound in the absence of frank pulmonary symptoms or changes on pulmonary auscultation.[14] This suggested that participants may have underlying interstitial pulmonary edema but did not meet classic definitions of HAPE. We evaluated whether the more common 4-view LUP examination would detect similar findings on recreational trekkers traveling to Everest Base Camp (EBC).

Methods

PARTICIPANT ENROLLMENT

This was an observational cohort study conducted during April and May 2015. Participants were selected from a professionally guided, recreational trek to EBC from Kathmandu, Nepal. The study was approved by the University of California at Davis Institutional Review Board. Participants were recruited for participation in the study during the pretrek orientation in the United States. Written informed consent was obtained.

Study exclusion criteria included history of pulmonary or cardiovascular disease, history of hypertension (defined as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg), history of HAPE, recent trek or prolonged exposure (>1 wk) to high altitude (>2000 m) in the 30 d before study involvement, and those who were native Nepalese Sherpa or porters. No participants were excluded from participation based on these criteria. All received physician clearance for participation in high altitude activity independent of participation in this study.

ASCENT

Wilderness Medical Society guidelines for staged ascent were followed during the trek.[15] Above 3000 m, daily elevations in sleeping altitude were not increased by greater than approximately 500 m. A rest day was included with each increase in altitude of 1000 m above 3000 m, which equaled every third or fourth day. Approximate trek altitudes and locations can be seen in Figure 1. During each day of altitude gain, participants ascended an additional 100 to 200 m before descent to sleeping altitudes to aid in acclimatization. All participants were prophylactically given 125 mg acetazolamide orally twice daily throughout the study in accordance with Wilderness Medical Society recommendations. The first dose was taken 1 d before commencing activity.

DATA COLLECTION

Participants had study-related events measured 6 times throughout the course of the ascending phase of the trek. Baseline measurements were obtained in Kathmandu (altitude 1400 m) and the subsequent 5 measurements during various portions of the ascent phase. Measurements were obtained each evening immediately after the evening meal during rest periods on predetermined stops along the ascent. Vital signs included blood pressure, heart rate, and pulse oximetry using a portable pulse oximeter (Nellcor portable pulse oximeter PM10, Medtronic Minneapolis, MN). Participants completed the modified Borg dyspnea scale (MBDS) and the Lake Louise acute mountain sickness score (LLS) before each LUP for a subjective evaluation of clinical symptoms associated with high altitude exposure. Participants could rate perceived dyspnea with an MBDS between 0 (no dyspnea, asymptomatic) and 10 (maximal work of breathing, severe dyspnea) for their current work of breathing. Participants provided an LLS between 0 (asymptomatic) and 3 (severe, incapacitating) for each of the following categories: headache, gastrointestinal symptoms, fatigue, lightheadedness, and difficulty sleeping. The LLS protocol was used because this study was performed before the 2018 update, which removed sleep disturbance as a component. Although acute mountain sickness (AMS) and HAPE are independent clinical events with differing pathophysiology, it is common to include AMS symptoms when evaluating for maladaptive acclimatization conditions.

Pulmonary ultrasound was performed using the previously described 4-window LUP.[16] This protocol uses 2 anterior views, upper and lower, at the midclavicular line and 2 lateral views, upper and lower, at the midaxillary line. These are done bilaterally for a total of 8 zones of the pulmonary fields. All examinations were performed

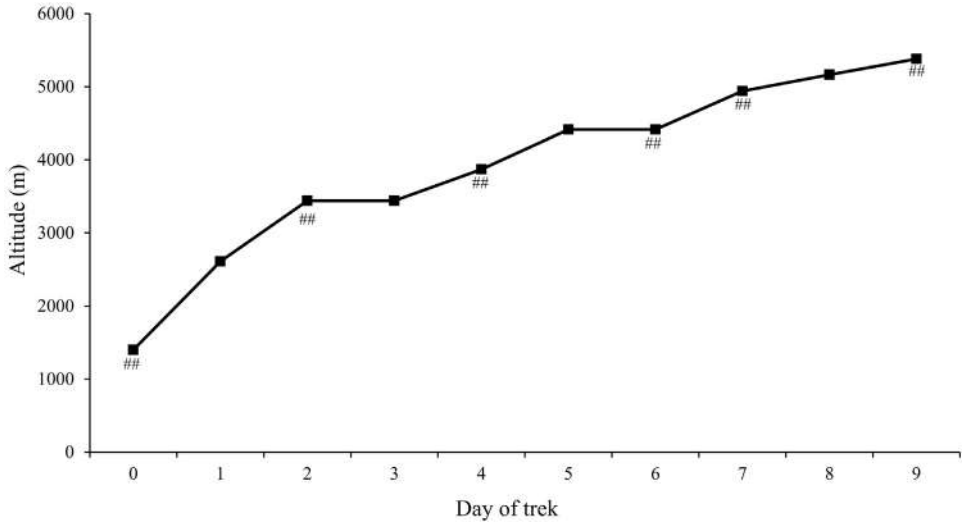

Figure 1. Approximate daily trek altitudes and locations. Day on which 4-view lung ultrasound protocol were performed are marked with ##. Location by day: 0 – Kathmandu, 1 – Phakding, 2 – Namche Bazaar, 3 – Namche Bazaar, 4 – Tengboche, 5 – Dingboche, 6 – Dingboche, 7 – Lobuche, 8 – Gorak Shep, 9 – Everest Base Camp.

using a portable ultrasound unit (MicroMaxx Ultrasound System; FUJIFILM SonoSite, Bothell, WA). Examinations were performed using a 1 to 5 MHz phased array ultrasound transducer at 14 cm depth (P17 Phased Array, FUJIFILM SonoSite). Examinations were performed with the patient in a recumbent or supine position and after no exertional activity had been performed for at least 30 min. A single, board-certified emergency medicine physician performed the ultrasonography during this study using the same ultrasound unit, transducer, and examinatino settings. The sonographer/physician (JSR) had extensive clinical and research experience with emergency ultrasound. Images were labeled using a unique participant identifier and a corresponding lung location. Video recordings of 5 s in length were archived until completion of the study. The ultrasound batteries were recharged daily using portable solar panels.

ANALYSIS

On return, the archived ultrasound video recordings were independently reviewed by 2 board-certified emergency medicine physicians (KMK, DHC) with fellowship training in emergency ultrasonography and clinical experience with the 4-view LUP. The reviewers were blinded to the participant number, reported symptoms, chest location, and altitude associated with each recording. Ultrasonography B-lines were predefined as long, wide echogenic artifacts that originate from the pleural line and cross the ultrasound screen. Each recording was reviewed and the number of B-lines was documented. Reviewers classified each recording as having 0, 1 to 2, or 3 or more B-lines. A 4-view LUP was considered positive if any 2 of the patient's 4 ultrasound recordings contained 3 or more B-lines in a longitudinal plane between 2 ribs, in compliance with the international definition of interstitial edema in previous ultrasound literature.[9,13,17] Any discrepancies between the 2 reviewers were reassessed by both physicians and consensus was reached.

Continuous variables are presented as mean±SD. Discrete variables are presented as median (interquartile range). Interrater reliability was assessed using Cohen's kappa coefficient. Statistical analysis was performed using commercial software (STATA version 14.0; Stata Corp., College Station, TX).

Results

Fifteen participants were recruited: 11 male and 4 female. The median age of participants was 42 (IQR 34–52) y. Vital signs, oxygen saturation, LLS, and MBDS are presented by altitude in Table 1. As expected, participants' subjective report of acute altitude-related symptoms increased with the change in altitude. Two-thirds (10 of 15) of participants were asymptomatic (LLS of 0) during baseline collection at 1400 m. However, all participants were mildly symptomatic on arrival at EBC at 5380 m with a median LLS of 3 (IQR 2–4). All 15 respondents reported an MBDS of 0 during baseline collection. Four participants reported an MBDS of 1 at 5380 m. Participants had a progressive decrease in

Table 1. Participant vital signs, subjective modified Borg dyspnea scale, Lake Louise acute mountain sickness score, and participant ultrasounds

	Kathmandu 1400 m	*Namche Bazaar 3440 m*	*Tengboche 3870 m*	*Dingboche 4415 m*	*Lobuche 4940 m*	*Everest Base Camp 5380 m*
Participants, n	15	15	15	14	14	14
Lake Louise score	0 (0–1)	1 (0–1)	1 (1–1)	1.5 (1– 2)	2.5 (2–3)	3 (2–4)
Modified Borg score	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.75)
Systolic blood pressure (mm Hg)	133±12	134±14	136±18	133±12	131±10	130±10
Diastolic blood pressure (mm Hg)	77±22	77±11	74±8	76±7	77±8	73±6
Heart rate (beats·min^{-1})	76±14	93±14	79±12	79±12	83±13	91±16
Respiratory rate (breaths·min^{-1})	18±1	16±2	18±4	18±5	21±4	22±3
Oxygen saturation (%)	97±2	94±2	91±5	86±6	82±6	77±6
Positive 4-view ultrasound protocol	0	0	0	0	0	1
No B-lines detected	14	14	14	10	9	12

Continuous variables are presented as mean±SD. Discrete variables are presented as median (interquartile range). A positive 4-window lung ultrasound protocol was defined by any examination with >3 B-lines on 2 or more video recordings. A study was considered to have no B-lines detected when 0 B-lines were identified after review of all video images.

oxygen saturation and increase in respiratory rate, consistent with altitude exposure.

The results of ultrasound examinations are shown in Table 1. The video views obtained were satisfactory for assessment by both reviewers. A Cohen kappa coefficient of 0.72 was measured between the 2 reviewers. There was no evidence of interstitial edema in any participant below 5380 m. At 5380 m, a single patient met the 4-window LUP definition of positive for interstitial edema but reported no significant pulmonary symptoms. B-lines were detected in the bilateral lower pulmonary windows. This patient had no evidence of B-lines on any ultrasound below 5380 m. At the time of the positive finding, this participant reported an MBDS of 0 but an LLS of 6, consistent with mild altitude sickness. In the majority of patients at each altitude, 0 B-lines were detected during all ultrasounds.

One female trekker was medically evacuated by helicopter at approximately 4000 m for worsening AMS (headache, nausea, and fatigue) and inability to continue because of symptoms. This participant's ultrasound examinations at 1400, 3440, and 3870 m showed no evidence of B-lines. It is unclear whether this participant was answering the symptom instruments honestly given an underlying reluctance to terminate her trek. Owing to her medical evacuation, the data presented for subsequent altitudes contain the remaining 14 participants.

Discussion

We sought to evaluate whether the commonly used 4-view LUP examination would detect pulmonary fluid in healthy recreational trekkers traveling to EBC from Kathmandu. We were unable to detect evidence of interstitial pulmonary fluid using the 4-view LUP. A single participant had a positive 4-window LUP examination consistent with interstitial fluid while at EBC at 5380 m but reported no pulmonary symptoms.

The 28-view, comprehensive lung ultrasound is considered the most inclusive protocol for lung ultrasound by international guidelines.[13] The original protocol involves a pulmonary and cardiac examination with ultrasonographic assessment of 28 chest locations.[18] The total number of B-lines identified in each field are summed to obtain a comet tail score. Using the 28-view, comprehensive lung ultrasound, previous research reported that nearly all trekkers at altitudes of >3000 m develop interstitial edema on portable ultrasonography despite no reported dyspnea or change in lung auscultation, possibly suggesting early HAPE.[14] It was noted that a large majority of participants (15 of 18 at 3340 m; 18 of 18 at 4790 m) had a comet tail score of >5 detected during the pulmonary examination at altitude.[14] However, the authors did not report the more commonly accepted criteria for a positive examination, which is 3 or more B-lines in 2 or more windows.[13,16]

We chose to evaluate the 4-view LUP given that, in emergency situations in austere environments, it would likely be the preferred technique because it is faster, the patient can be supine or recumbent, and many emergency and critical care providers are familiar with the technique. Additionally, the examination requires less battery power, which is ideal in austere environments. In clinical practice, it has been found to be accurate in the detection

of interstitial lung fluid and pulmonary edema in both ambulatory[19,20] and hospitalized[21-23] patients with congestive heart failure. Furthermore, the 4-view LUP is advocated in emergency and critical care situations.[13,16,17]

Although we expected fewer B-lines would be detected by the 4-view LUP compared to the 28-view comprehensive protocol given the reduced number of windows, we detected far fewer total B-lines at altitude than expected. Prior research detected the presence of B-lines in 100% of trekkers at an altitude of 5130 m using the 28-view protocol.[14] However, at a similar altitude, our study detected B-lines in only 2 of the 14 participants, of whom only 1 case met the international consensus definition of a B-pattern consistent with interstitial fluid. By contrast, no B-lines were detected in any of the other 12 trekkers at EBC. Although we performed fewer total ultrasounds, this does not fully explain the discrepancy between the studies. It remains unknown whether the cohorts had different rates of interstitial edema, whether findings are related to the method of detection, or if findings were influenced by other factors (eg, acclimatization protocol, speed of ascent, vascular remodeling).

LIMITATIONS

There are many known and unknown confounding variables when attempting research in austere environments, and this study had several limitations. First, the sonographer was not blinded to the hypothesis while performing the ultrasounds, which could inadvertently affect ultrasound quality and B-line detection. Second, interstitial fluid associated with HAPE may have distribution characteristics that limit its detection by the 4-view LUP until more fluid is present. The maximum altitude achieved during this study was 5380 m. We cannot draw conclusions about the development or detection of HAPE at higher altitudes. Furthermore, the risk factors for the development of HAPE remain poorly understood. It is believed that genetics play a substantial role in determining HAPE risk.[24] Given our small sample size of 15 participants, it is possible that a cohort with a different genetic risk would have developed interstitial edema at a different rate.

Finally, a notable limitation to this study is the lack of prior, prospective comparisons between the 4-view LUP and 28-view comprehensive protocol. Although the 4-view LUP is commonly used by providers, we know of no study that has directly compared and quantified differential B-line detection between the 2 protocols. We were unable to perform both the 4-view and 28-view protocols during our study owing to limitations on ultrasound battery life. Additional research will be required to further quantify the difference between these techniques in austere conditions and further explore the presence of possible interstitial edema in the absence of frank pulmonary symptoms.

Conclusions

In this small study, sonographic evidence of interstitial lung fluid was not detected by the 4-view LUP examination in healthy participants during a trek to an altitude of 5380 m.

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ORIGINAL RESEARCH

The Usefulness of Platelet Distribution Width and Platelet Distribution Width to Lymphocyte Ratio in Predicting Severity and Outcomes in Patients with Snakebite

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Introduction—Tissue damage, inflammatory response, and hematologic abnormalities may occur in snakebite envenomation. This study aimed to evaluate the predictive ability of platelet distribution width (PDW) and platelet distribution width to lymphocyte ratio (PDWLR) in the severity and outcome of envenomation in patients with snakebites in the emergency department (ED).

Methods—All adult patients admitted to the ED after a snakebite were retrospectively evaluated. Patients were classified according to the severity of envenomation. The relationship between the PDW and PDWLR and envenomation severity and patient outcomes was analyzed. Multivariate logistic regression analysis was performed to determine the predictors of severe envenomation. Results were presented as 95% CIs with odds ratios. Statistical significance was accepted at $P<0.05$.

Results—Envenomation was classified as none/minimal in 42 patients and moderate/severe in 29. PDW and PDWLR were significantly higher in the moderate/severe group ($P=0.016$ and $P<0.001$, respectively). Cut-off values of 16.5 for PDW and 6.15 for PDWLR were related to more severe envenomation (area under the curve 0.67, 95% CI 0.55–0.78 and area under the curve 0.85, 95% CI: 0.74–0.92, respectively). Blood product replacement, thrombocytopenia, hematologic abnormality, advanced local findings, compartment syndrome/fasciotomy, antivenom dosing, and moderate/severe envenomation were associated with PDWLR >6.15 ($P<0.05$). In multivariate analysis, PDWLR (odds ratio 1.19 [95% CI 1–1.4]; $P=0.04$) was an independent predictor of severe envenomation.

Conclusions—Higher PDW and PDWLR were associated with severe envenomation in patients with snakebites in the ED. PDWLR may be used as a predictor of severe envenomation and adverse outcomes.

Keywords: envenomation, hematotoxicity effect, platelet indices, emergency medicine

Introduction

Envenomation from snakebite is a significant health problem worldwide. Approximately 40 to 41 snake species have been reported in Turkey. Of those, 13 to 15 are venomous. Most venomous species are reported to be from the Viperidae family.[1-5] The venom of such snakes usually causes local toxicity and hematotoxicity, whereas neurotoxic effects are relatively rare.

Snakebites may cause regional tissue damage, inflammation through cytokine release, and deterioration in hematologic parameters owing to hematotoxic effects.[6] Hematologic features may include thrombocytopenia, increased prothrombin time (PT), hypofibrinogenemia, and anemia.[7] Treatment of venomous snakebites usually aims to correct severe local findings (necrosis, compartment syndrome), hematologic problems, and clotting abnormalities.[8]

Early diagnosis and management are essential in patients with severe envenomation to prevent adverse

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outcomes. In this regard, there is a need for fast and readily accessible aids to guide physicians in such cases. A complete blood count (CBC) is a practical and relatively inexpensive tool to diagnose and monitor systemic envenomation, guide supportive care, and control the antivenom dose.[9] Platelet count (PLT) is an important parameter in determining the systemic envenomation and severity of snakebites, making PLT and platelet indices of particular value in routine CBC. Recent studies on platelet indices (platelet distribution width [PDW] and mean platelet volume [MPV]) have demonstrated a relationship between platelets and inflammation.[10] Platelet indices (PDW and MPV) are considered markers of platelet activation, and increased PDW levels have been shown in several conditions.[11,12] Similar to PLT, platelet indices (MPV, PDW, and the PDW to lymphocyte ratio [PDWLR]) may be indicative for severe envenomation and may therefore be useful for detecting severe envenomation and adverse outcomes. To our knowledge, the significance of these platelet parameters in patients with snakebites has not been reported in the literature.

This study aimed to evaluate the benefit of PDW and PDWLR in predicting the severity of envenomation and clinical outcomes in patients with snakebite in the emergency department (ED).

Methods

PATIENTS AND SETTING

This study was approved by the Mersin University faculty of medicine Ethics Committee (01/04/2020; approval no. 2020/249).

All patients aged ≥17 y who presented to the ED of Mersin University Hospital with snakebite between January 2011 and November 2019 were evaluated for eligibility in the study. Patients meeting all of the following criteria were included:

1) Patients admitted to the ED with International Classification of Diseases (ICD) codes of T63.0-9, W57, and W59 recorded with the terms "bite, sting, toxic, poisonous" or "envenomation" in the electronic medical record (EMR). Considering the possibility of ICD coding errors, all bites and stings were screened from the ED admission form, and patients with snakebite were included.
2) Patients with a history of exposure to snakebite or patients diagnosed with snakebite who had related local or systemic findings.[7]
3) Patients who had laboratory tests (CBC, biochemistry, and coagulation tests).

Exclusion criteria included (Figure 1) absence of bite marks; lack of an ED patient file, observation form, or clinical information about the clinical course in the EMR; lack of laboratory test results (CBC, biochemistry, and coagulation tests); presence of underlying conditions likely to cause bleeding disorders or affect leukocyte and platelet counts; and erroneous ICD coding of snakebite.

SEVERITY OF ENVENOMATION

Envenomation was categorized using a 4-grade standard snakebite severity classification system.[7] The grades were defined as follows: 0: site of the bite alone, without local or systemic sign and symptoms (no envenomation); 1: minimal tissue swelling and normal laboratory results without systemic symptoms (minimal envenomation); 2: progressive swelling, mild systemic symptoms with pain, and/or ecchymosis in addition to certain laboratory abnormalities (increased PT and PT-international normalized ratio [INR] and/or thrombocytopenia) (moderate envenomation); and 3: advanced swelling, severe pain, serious systemic symptoms with ecchymosis, necrosis and bullous lesions, coagulopathy, and organ failure (severe envenomation). Envenomations classified as grade 0 or 1 were assigned to the none/minimal group, and those classified as grade 2 or 3 were the moderate/severe group. The staging from grade 0 to grade 3 depended on the severity of the envenomation and was determined based on the literature in the study planning.[7] A number of the stages were decided by the clinician while caring for the patient in the ED and recorded in the EMR. However, the majority of grading was carried out retrospectively by the researchers. Grading was conducted considering both clinical (local and systemic signs/symptoms) and laboratory values. Cases were separated into 2 groups to aid statistical analysis because of the small sample size. Because the severity of envenomation was not static, to define the cases, laboratory results, clinical findings (local and systemic findings), and treatment/interventions at the time of admission and during follow-up were all evaluated for classification and included in the study. The highest severity score during the patient's treatment was used.

LABORATORY ANALYSIS

Trends in laboratory values during the follow-up period were recorded. The specific laboratory values were defined before the screening of data. These included white blood cell (WBC) count, neutrophil count, lymphocyte count, hemoglobin, and PLT. Platelet parameters PLT, MPV, PDW, and PDWLR (calculated as PDW divided by the lymphocyte count) were also recorded. Biochemical tests recorded for the study

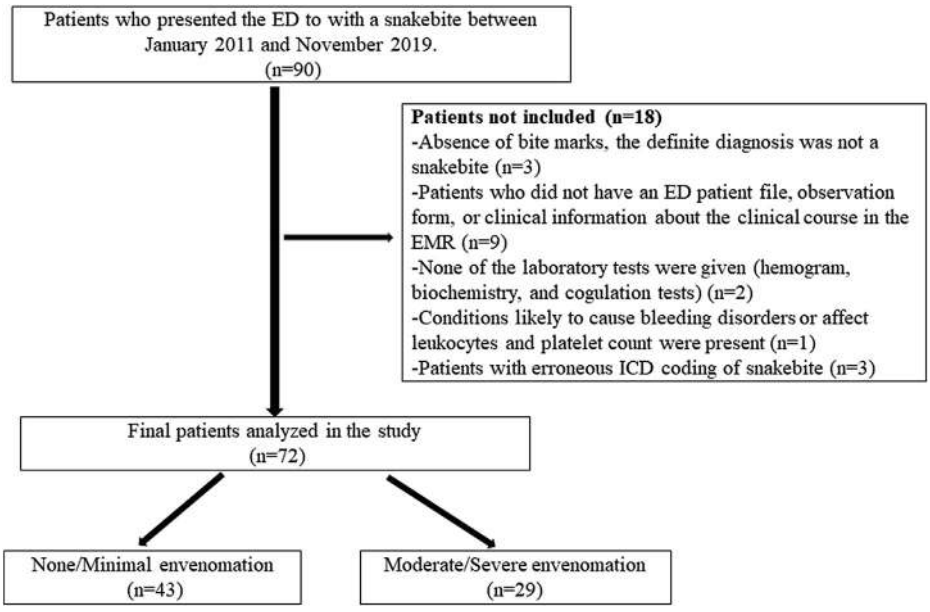

Figure 1. Flow chart of the study population. ED, emergency department; ICD, international classification of diseases; EMR, electronic medical records.

included glucose, sodium, creatinine, C-reactive protein (CRP), and coagulation tests (PT, PTT, PT-INR). Normal reference values for the parameters measured in the study were as follows: leukocyte count ($4.5–10.0 \times 103 \cdot L^{-1}$), platelet count ($150–400 \times 103 \cdot L^{-1}$), MPV (7.4–10.4 fL), PDW (9–17 fL), CRP ($0–5$ mg$\cdot$dL^{-1}), and hemoglobin ($11.7–16$ g$\cdot$dL^{-1}). Patients were stratified according to PDWLR cutoff values.

ADVERSE OUTCOMES

Adverse outcomes were defined as hospitalization, severe local findings, compartment syndrome/amputation, antivenom use, moderate/severe toxicity, the need for any blood product replacement, or any hematologic abnormality.

Hematologic abnormalities were defined as anemia, thrombocytopenia, increased PT, increased PT-INR, and any sign of bleeding. Abnormalities in laboratory values were defined based on the lower or upper limit of reference values. Thrombocytopenia was defined as a platelet count $<150 \times 109 \cdot L^{-1}$. Severe local findings were defined as progressive swelling and/or necrosis. Blood product replacement was defined as the transfusion of any blood product, mainly fresh frozen plasma. Systemic envenomation was defined as nausea/vomiting, abnormal vital signs, metallic taste in the mouth, weakness, abnormal laboratory test results (anemia, thrombocytopenia, increased PT, increased PT-INR, renal dysfunction), and local or systemic bleeding.

STATISTICS

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality of distribution. Normally distributed variables were presented as mean±SD. Non-normally distributed variables were expressed as median (25th–75th percentile). Categorical variables were expressed in numbers (percentages). Continuous variables were compared by Student's *t*-test or Mann-Whitney U test as appropriate. A χ^2 test was used to evaluate the associations between categorical groups. The area under the curve (AUC) was determined using receiver operating characteristic (ROC) curves to evaluate the predictive ability of PDW/PDWLR in classifying envenomation severity. The ROC curves and AUC values (95% CIs) were compared. The DeLong method was used to compare the paired AUC. Optimal cut-off values of the variables were estimated using ROC curves and the Youden index. Analysis of one variable at a time was used to describe the strength of the unadjusted association in our data. Significant variables on univariate analysis were analyzed in multiple logistic regression analysis to identify predictors of severe envenomation. Results were presented as a 95% CIs with odds ratios (ORs). A P value <0.05 was considered statistically significant.

Table 1. Clinical characteristics and laboratory findings of patients with snakebite

Variables	*All (n=72)*	*None/Minimal envenomation (n=43 [60%])*	*Moderate/Severe envenomation (n=29, [40%])*	P *value*
Clinical characteristics				
Age (y)	45±14	44±14	47±15	0.265
Male sex, n (%)	43 (60)	29 (67)	14 (48)	0.104
Comorbidities, n (%)	27 (38)	14 (33)	13 (46)	0.239
Diabetes, n (%)	15 (21)	7 (16)	8 (29)	0.215
Cardiovascular disease, n (%)	10 (14)	8 (19)	2 (7)	0.158
Site of the bite, n (%)				
Upper extremity	46 (65)	29 (68)	17 (62)	0.833
Lower extremity	23 (32)	13 (30)	10 (36)	
Trunk and other	2 (3)	1 (2)	1 (4)	
Estimated time to presentation to ED (h)[a]	1.5 (1.0–4.5)	1 (1.0–2.3)	2.5 (1.0–9.0)	**0.019**
Systolic blood pressure (mmHg)	128±19	130±15	125±25	0.394
Heart rate (beats·min^{-1})	82±14	78±11	88±17	**0.015**
Laboratory findings				
WBC count (×10^3·L^{-1})	10.6±4.9	8.4±2.2	13.8±5.9	**<0.001**
Lymphocyte count (× 10^3·L^{-1})	2.0±1.1	2.5±0.1	1.2±0.8	**<0.001**
Hemoglobin (g·dL^{-1})	13.6±1.8	13.6±1.7	13.5±2.1	0.866
Platelet count (× 10^3·L^{-1})	201.8±83.4	234.4±58	153.5±92.3	**<0.001**
MPV (fL)	10.6±1.1	10.4±0.9	10.7±1.4	0.334
PDW (fL)	13.4±2.7	12.7±2.17	14.5±3.2	**0.016**
PDWLR[a]	6.4 (4.8–12.8)	5.4 (3.8–7.4)	12.8 (7.2–23.6)	**<0.001**
CRP[a] (mg·dL^{-1})	2 (0.8–6.8)	1 (0.6–2.8)	5.2 (1.6–13.3)	**<0.001**
Glucose (mg·dL^{-1})	141.5±57.7	132.4±60	155.2±52.3	0.105
Creatinine (mg·dL^{-1})	0.7±0.1	0.7±0.1	0.7±0.1	0.053
Sodium (mEq·L^{-1})	139.2±2.8	139.1±2.7	139.5±2.9	0.524
PT (s)	14.1±2.2	13.5±1.6	14.9±2.8	**0.021**
PT INR	1.1±0.2	1.0±0.1	1.2±0.2	**0.001**
PTT (s)	26.5±4.3	26.4±6.1	25.5±3.9	0.143
Outcomes				
Serious local finding, n (%)	21 (29)	0 (0)	21 (72)	**<0.001**
Compartment syndrome, n (%)	4 (6)	0 (0)	4 (14)	**0.006**
Thrombocytopenia, n (%)	15 (21)	0 (0)	15 (52)	**<0.001**
Hematologic abnormality, n (%)	15 (21)	0 (0)	15 (52)	**<0.001**
Antivenom dose (vial)[a]	1 (0–4)	0 (0–0)	4 (2–4)	**<0.001**
Analgesics, n (%)	43 (60)	15 (35)	28 (97)	**<0.001**
Antibiotics, n (%)	34 (47)	10 (23)	24 (83)	**<0.001**
Blood replacement, n (%)	6 (8.3)	0 (0)	6 (21)	**0.001**
Hospitalization, n (%)	33 (46)	7 (16)	26 (90)	**<0.001**
Estimated length of stay (h)[a]	55.2±66.3	15.0±15.8	114.7±68.0	**<0.001**

CRP, C-reactive protein; ED, emergency medicine; MPV, mean platelet volume; PTT, partial thromboplastin time; PDW, platelet distribution width; PDWLR, platelet distribution width to lymphocyte ratio; PT, prothrombin time.

[a]Data are expressed as mean±SD or numbers (percentage) or median (25th–75th percentile).

Results

After excluding 18 patients, a total of 72 patients with snakebite were included in the study. Of these, 43 had no/minimal envenomation and 29 had moderate/severe envenomation. The time from snakebite to ED was longer (P=0.019) and heart rate was higher (P=0.015) in patients with moderate/severe envenomation. PDW (P=0.016) and PDWLR (P<0.001) were associated with snakebite severity. Analysis of laboratory parameters showed that WBC, CRP, PT, and PT-INR values were significantly higher in the moderate/severe envenomation group (P<0.05). The mean lymphocyte and PLT counts were significantly lower in patients with moderate/severe

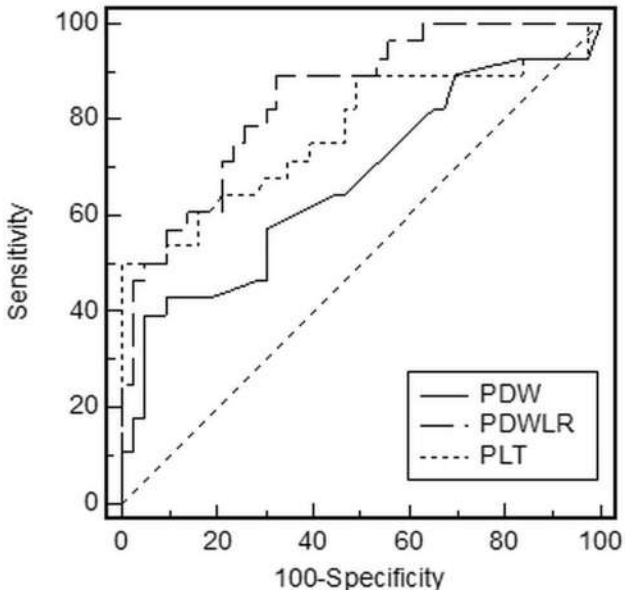

Figure 2. Comparison of ROC curves of PDW, PDWLR, and PLT for the prediction of severe envenomation in patients with snakebite. The dotted line represents the diagonal reference line. ROC, receiver operating characteristic; PDW, platelet distribution width; PDWLR, platelet distribution width to lymphocyte ratio, PLT: platelet.

envenomation (P<0.001). Compartment syndrome (P=0.006), serious local findings, hematologic abnormalities, thrombocytopenia, antivenom dose, analgesic use, antibiotic use, need for blood products, and hospitalization rate and length of stay were higher in patients with moderate/severe envenomation (P<0.001; Table 1).

The cutoff values of PDW, PDWLR, and PLT, which predicted moderate/severe envenomation, were obtained from the ROC analysis. In our data, a PDW cutoff of >16.5 and a PDWLR cutoff of >6.15 were the best fit. The PDWLR cutoff of >6.15 had the greatest power to predict more severe envenomation. The AUCs for predicting more severe envenomation using PDW, PDWLR, and PLT counts were 0.67 (95% CI 0.55–0.78), 0.85 (95% CI 0.74–0.92), and 0.77 (95% Cl 0.66–0.86), respectively. A comparison of the ROC curves of these parameters revealed that the AUC of PDWLR was more relevant in differentiating minimal and severe envenomation (Figure 2; Table 2).

Table 2. Receiver operating characteristic analysis of variables for the prediction of severe snakebite envenomation

	PDW	*PDWLR*	*PLT*
Cut-off	>16.5	>6.15	≤134
AUC	0.67	0.85	0.77
95% CI	0.55–0.78	0.74–0.92	0.66–0.86
P	0.012	<0.001	<0.001

AUC, area under the curve; 95% CI, 95% confidence intervals; PLT, platelet; PDW, platelet distribution width; PDWLR, Platelet distribution width to lymphocyte ratio.

There was a significant relationship between PDW and PDWLR cutoff values and severity of envenomation (P<0.001). The moderate/severe envenomation rate was 85% in patients with a PDW of >16.5 and 29% in those with a PDW of <16.5. The moderate/severe envenomation rate was 64% in patients with a PDWLR of >6.15, but it was only 9% in those with a PDWLR of <6.15.

Univariate and multivariate logistic regression analysis was performed to examine the relationship between PDW and PDWLR cutoff values and envenomation severity. Initially, only PDW and PDWLR were included in the multivariate logistic regression analysis. In the univariable analysis, PDW (P=0.002) and PDWLR (P<0.001) were associated with severity of envenomation. The rate of severe envenomation in patients with a PDW >16.5 was 13.26 (95% CI 2.65–66.31, P= 0.002) times higher than in those with a PDW <16.5. The rate of severe envenomation in patients with a PDWLR >6.15 was 17.26 (95% CI 4.44–67.04, P<0.001) times higher than in those with a PDWLR <6.15. Multivariable analysis revealed that a PDWLR of >6.15 was significantly associated with the severity of envenomation (OR 11.28; 95% CI 2.73–46.51; P=0.001).

Patients with snakebite who had a higher PDWLR value were associated with older age and longer transfer duration (P<0.05). The analysis of laboratory parameters

Table 3. Relationship between PDWLR cut-off value and clinical parameters

Variables	*PDWLR <6.15 (n=32)*	*PDWLR >6.15 (n=39)*	P *value*
Clinical characteristics			
Age (y)	41±13	49±15	0.037
Male sex, n (%)	22 (69)	21 (54)	0.201
Comorbidities, n (%)	10 (31)	17 (45)	0.248
Diabetes, n (%)	5 (16)	10 (26)	0.278
Cardiovascular disease n (%)	4 (12)	6 (16)	0.694
Site of the bite, n (%)			
Upper extremity	22 (69)	23 (60)	0.740
Lower extremity	9 (28)	14 (37)	
Trunk and other	1 (3)	1 (3)	
Estimated time to presentation to ED (h)[a]	1 (1–2)	2 (1–8)	**0.009**
Systolic blood pressure (mm Hg)	131±14	127±22	0.359
Heart rate (beats·min^{-1})	80±12	84±16	0.205
Laboratory findings			
WBC count (× 10^3·L^{-1})	8.5±2.1	12.2±5.9	**0.001**
Lymphocyte count (× 10^3·L^{-1})	2.9±0.8	1.3±0.8	**<0.001**
Hemoglobin (g·dL^{-1})	13.6±1.7	13.6±1.7	0.992
Platelet count (× 10^3·L^{-1})	239.1±66.1	175.7±82.2	**0.001**
MPV (fL)	10.4±0.8	10.7±1.4	0.239
CRP (mg·dL^{-1})	1.0 (0.6–3.3)	2.2 (1.2–8.8)	**0.022**
Glucose (mg·dL^{-1})	128.8±49.8	152.2±62.8	0.096
Creatinine (mg·dL^{-1})	0.7±0.1	0.7±0.2	0.799
Sodium (mEq·L^{-1})	139.7±2.7	138.9±2.8	0.279
PT (s)	13.9±1.6	14.2±2.5	0.571
PT-INR	1.0±0.1	1.1±0.2	**0.030**
PTT (s)	27.6±4	25.7±4.4	0.066
Outcomes			
Hospitalization, n (%)	6 (19)	26 (67)	**<0.001**
Estimated length of stay (h)[a]	10.0 (6.0–21.5)	48 (14–120)	**<0.001**
Need for blood replacement, n (%)	0 (0)	5 (13)	**0.012**
Hematologic abnormality, n (%)	2 (6)	12 (31)	**0.010**
Thrombocytopenia, n (%)	2 (6)	12 (31)	**0.010**
Compartment syndrome/fasciotomy, n (%)	0 (0)	4 (10)	**0.026**
Serious local finding, n (%)	3 (9)	17 (44)	**0.001**
Antivenom dose (vial)[a]	0 (0–1)	2 (0–4)	**0.001**
Analgesics, n (%)	13 (41)	29 (74)	**0.004**
Antibiotics, n (%)	10 (31)	23 (59)	**0.020**
Moderate/Severe envenomation, n (%)	3 (9)	25 (64)	**<0.001**

CRP, C-reactive protein; ED, emergency medicine; INR, international normalized ratio; MPV, mean platelet volume; PTT, partial thromboplastin time; PDW, Platelet distribution width; PDWLR, Platelet distribution width to lymphocyte ratio; PT, prothrombin time.

[a]Data are expressed as mean±SD or numbers (percentage) or median (25th–75th percentiles).

revealed higher CRP levels (P=0.022), WBC count (P=0.001), and PT-INR time (P=0.03) in patients with a PDWLR of >6.15. Lower lymphocyte (P<0.001) and PLT (P=0.001) counts were detected in patients with a PDWLR of >6.15. Patients with snakebite who had a PDWLR of >6.15 were associated with a higher hospitalization rate (P<0.001), a longer length of stay (P<0.001), use of blood product replacement (P=0.012), hematologic abnormalities (thrombocytopenia in particular) (P=0.010), serious local findings (P=0.001), compartment syndrome/fasciotomy (P=0.026), higher antivenom dose (P=0.001), analgesic use (P=0.004), and antibiotic use (P=0.020) (Table 3).

In multiple logistic regression analysis, PDWLR (OR 1.19; 95% CI 1–1.4; P=0.04) was found to be more significant in evaluating the severity of envenomation in patients with snakebites (Table 4).

No mortality or complications related to antivenom use was recorded. Finger amputation was recorded in 2 patients.

Table 4. Predictors of severe envenomation in patients with snakebite on multivariate logistic regression analysis

Variables	*Odds ratio (95% CI)*	P *value*
Heart rate	1.04 (0.97–1.12)	0.27
PLT	0.99 (0.97–1.03)	0.06
PT	1.39 (0.86–2.23)	0.17
WBC	1.33 (0.95–1.84)	0.09
CRP	1.11 (0.99–1.25)	0.08
PDWLR	1.19 (1–1.40)	**0.04**
PDW	1.09 (0.73–1.62)	0.66

CI, confidence interval; CRP, C-reactive protein; ED, emergency medicine; MPV, mean platelet volume; PTT, partial thromboplastin time; PDW, platelet distribution width; PDWLR, platelet distribution width to lymphocyte ratio; PT, prothrombin time; PLT, platelet count; WBC, white blood cell.

Discussion

Snake venom induces enzymatic activities such as metalloproteinase and procoagulant activities (especially in viper and crotalid snakes). These enzymes cause edema, muscle necrosis, hematotoxicity, vascular endothelial lesions, local tissue damage, and inflammatory response.[1,8,13-15] Additionally, these enzymes may affect the hemostasis cascade, leading to clotting, platelet dysfunction, and thrombocytopenia.[14,16] In the circulatory system, snake venom not only affects the vascular wall and platelets, but also targets blood cells. White blood cells are highly sensitive and involved in the inflammatory and oxidative response to damage.[17] Significant rates of leukocytosis, neutrophilia, and lymphopenia have been reported in patients with snake envenomation.[3,9,18-20] In this study, there was a significant increase in WBC count and a significant decrease in lymphocyte count in the group with moderate/severe envenomation.

Apart from white blood cells and their subgroups, platelets are the dominant cellular elements in the process of thromboinflammation.[21] Thrombocytopenia is known to be an indicator of the severity of various conditions. At the time of admission, thrombocytopenia directly correlated with the development of systemic bleeding and the severity of snake envenomation.[9] In critical patients, platelet count and morphology of platelets also change, causing alterations in platelet indices.[22,23] Increased PDW levels have been observed in several conditions.[11,12,24] In a retrospective study, low platelet count, high MPV value, and high PDW value were shown to be associated with more severe disease and a higher risk of mortality.[25] Another study on platelet indices could not find a relationship between MPV, platelet to lymphocyte ratio, and the severity of snakebites.[26] Another study demonstrated that platelet count and MPV were significantly lower in envenomated blood samples compared to the healthy group.[27] To the best of our knowledge, there have been no previous studies evaluating PDW and PDWLR in snakebite envenomation.

In this study, PDW and PDWLR were found to be higher in patients with severe envenomation. In particular, PDWLR values >6.15 have been associated with adverse outcomes. Although predictability studies based on laboratory value cut-off points were reported previously, different cut-off values were demonstrated. For parameters including CRP, RDW, MPV, and PDW, different cut-off or predictive values have been defined in studies performed on a variety of disorders. Again, although these values were within the normal reference range for MPV, PDW, PLT, CRP, and WBC, many studies have showed that differences in mortality, severity, and adverse outcomes could be seen in various illnesses.[22,28-33] The cut-off values that were determined in this study were also associated with the severity of envenomation. The sensitivity of PDW was found to be low in ROC analysis; however, PDWLR seems to be more relevant to severity. We also found that PDWLR is superior to PDW in multivariable logistic regression. In addition, we determined that PDWLR is more significant than other routine parameters, such as platelet count, in multivariable logistic regression. Platelet count is a known parameter used in the diagnosis of snakebite severity and patient follow-up in the literature. We suggest that platelet indices such as PDW and PDWLR (especially PDWLR) can be used in addition to clinical and known laboratory parameters (eg, platelet count, fibrinogen, D-Dimer, PT, and PT-INR).

LIMITATIONS

The primary limitations of this single-center study are the small number of patients and retrospective use of cut-offs that emerged from the data to test the predictive value. This may have reduced the potential statistical power and possibly caused bias. The results of the analysis of these data cannot be generalized to a broader population. A prospective multicenter study involving a large number of patients should be conducted, where cut-off values can be varied. The fact that the species responsible for the snakebite could not be precisely determined confers another limitation. Additionally, other coagulopathic parameters such as D-dimer and fibrinogen levels were not routinely investigated in this population.

Conclusions

We found a potential relationship between higher PDW and PDWLR values and severe toxicity in patients who presented to the ED with snakebite. We conclude that

PDW and PDWLR are associated with the severity of envenomation, in addition to the clinical and diagnostic factors previously described in the literature. A PDWLR of >6.15 is associated with the need for blood product replacement, hematologic abnormalities, thrombocytopenia, serious local findings, compartment syndrome/fasciotomy, higher antivenom doses, and longer length of hospital stay. Our data suggest that PDWLR in particular may be used as a predictor of serious envenomation and adverse outcomes. PDWLR is a fast, readily accessible, and inexpensive measure that may be useful to evaluate the severity and guide the management of snakebite. Further studies are needed to evaluate severe envenomation and mortality in a larger patient population and to address the aforementioned limitations.

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ORIGINAL RESEARCH

Independent Risk Factors Predicting Gradual Onset Injury in 2824 Trail Running Race Entrants: SAFER XVIII Study

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Introduction—Trail running is characterized by elevation changes, with uneven and varying running surfaces. Risk factors that may predict gradual-onset running-related injuries (GORRIs) in short-distance trail running have not been explored. The objective was to determine risk factors that predict GORRIs in trail running race entrants who entered mass community-based trail running events.

Methods—In this descriptive cross-sectional study, data were collected prospectively from a prerace medical screening questionnaire over 4 trail run events held annually. Using a Poisson regression model, runner demographics, race distance, running training/racing variables, history of chronic diseases (number of chronic diseases reported as a cumulative "chronic disease composite score"), and allergies were investigated to determine factors predicting self-reported GORRI history in the previous 12 mo.

Results—This study included 2824 race entrants (80% of entrants). The retrospective annual incidence for GORRIs was 13%. Independent risk factors predicting GORRIs were longer race distance ($P<0.0001$), increasing chronic disease composite score ($P=0.0012$), and a history of allergies ($P=0.0056$). The lower limb (94%) was the main anatomic region of GORRIs, and soft tissue injuries accounted for most (83%) GORRIs. Common specific GORRIs were iliotibial band syndrome (22%), Achilles tendon injury (10%), and hamstring injury (9%).

Conclusions—Independent risk factors predicting GORRIs among trail running entrants included longer race distance, a higher chronic disease composite score, and a history of allergies. This study has highlighted trail running race entrants at risk for sustaining GORRIs who could be targeted for future injury prevention interventions.

Keywords: chronic disease, running related injuries, incidence, epidemiology, off-road running, prerace medical screening

Introduction

Physical activity is associated with a reduced risk for developing chronic disease and premature all-cause mortality.[1] Evidence further suggests that participating in outdoor physical activity improves mental well-being.[2] Trail running involves running on off-road terrains in outdoor environments and is characterized by large elevation changes.[3] Although running has numerous proven physical and mental health benefits, it is still associated with a high risk for injury.[4]

The most common injuries described in the running literature involve gradual-onset running-related injuries (GORRIs)[4,5] as a result of low kinetic energy transfer over

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time causing tissue damage.[6] Most studies only focus on marathon and ultramarathon running distances,[7-14] with limited information on GORRIs among trail runners participating in shorter-distance trail run events.

In one study among ultradistance trail runners, injury risk factors among elite runners included more experience in running and physical labor occupations. However, the authors did not investigate the medical history of participants.[13] The prevalence of certain chronic diseases among endurance runners is up to 13%,[15] and chronic diseases are also associated with an increased risk for gradual-onset injuries.[16-20] Additionally, some medications used in the treatment of chronic diseases are associated with an increased risk for injury.[21-27] The relationship between chronic diseases and risk of GORRIs has not been explored in trail runners.

The importance of investigating injury profiles and determining associated injury risk factors for GORRIs in this population is emphasized by the challenges faced during medical coverage at some trail running events.[28] These events can span large geographical regions in remote settings where medical staff and runners are exposed to environmental hazards that include extreme weather, water crossings, insect-borne infections, and wildlife.[28,29] In these settings, injured runners often receive delayed medical care owing to the logistical challenges of providing emergency medical care in remote regions.[28,29] A history of injury is a known injury risk factor among runners[30,31]; therefore, an attempt should be made to prevent injury in the training period before race participation. For specific injury prevention strategies for short-distance trail runners in the training period before race participation, we need an improved understanding of the injury profiles and associated injury risk factors for GORRIs in this population.

The main aim of this study was to determine risk factors that predict a history of GORRIs in trail running race entrants who entered mass community-based trail running events. A secondary aim was to report the epidemiology and clinical characteristics of self-reported GORRIs among trail running race entrants.

Methods

STUDY DESIGN

This is a descriptive cross-sectional analysis of data collected prospectively at 4 annual trail running events.

PARTICIPANTS AND DATA COLLECTION

The research ethics committee of the University of Cape Town (REC 009/2011 and REC 030/2013) approved the protocol, and the research ethics committee of the University of Pretoria (REC 433/2015) approved the ongoing data collection and subsequent analysis of the data.

This study forms part of the strategies to reduce adverse medical events for the exerciser (SAFER) studies—SAFER XVIII. Participants in this study were race entrants from the Two Oceans trail runs, a mass community-based trail running event in South Africa that is composed of a 10-km and a 22-km race. No qualification was required for either of the events. Entrants were defined as any runner registering for the races (registration typically opens 3–5 mo before the races) held annually over 4 y (2012–2015).

ONLINE PRERACE MEDICAL SCREENING

In this 4-y study period, a compulsory prerace medical screening questionnaire was implemented for all race entrants. The prerace medical screening questionnaire was based on the European Association for Cardiovascular Prevention and Rehabilitation recommendations[32] and consisted of the following main categories: history of cardiovascular disease (CVD), symptoms of CVD, risk factors for CVD, other chronic diseases, general prescription medication use, medication use during racing, injury, and a history of collapse during racing. The full details of this online medical screening and implementation thereof have been described in previous studies.[15,33] Entrants completing the screening were given the opportunity to consent to their data being used for research purposes.

In the prerace medical screening, entrants were asked the following specific question related to gradual-onset injuries: "*Do you or did you suffer from any symptoms of a chronic (no accident) running injury (muscles, tendons, bones, ligaments or joints) in the past 12 months or currently?*" We defined these injuries as GORRIs, as recommended by the 2020 International Olympic Committee consensus statement.[6] For inclusion, an injury was defined as "*An injury that is/was severe enough to interfere with running or require treatment, eg, use medication or require you to seek medical advice from a health professional.*" If the response to the previous question was "yes," entrants were required to complete additional questions related to the gradual-onset running injury, including where it is a past or current injury, anatomic region, body area, type of anatomic structure, severity, and whether the injury was one of the more commonly known GORRIs.

PRIMARY OUTCOME

The primary outcome of this study was a history of GORRIs in the past 12 mo among trail running race

entrants. The following 3 categories of independent variables of interest as factors predicting GORRIs were explored: 1) demographics (sex and age groups) and race distance; 2) running training/racing variables (years as a recreational runner, average weekly training/running frequency in the last 12 mo, average weekly training/running distance in the past 12 mo, average training speed, race vs average training speed ratio); and 3) history of chronic disease (any risk factors for CVD, history of existing CVD, symptoms of CVD, endocrine disease, respiratory disease, gastrointestinal disease, nervous system/psychiatric disease, kidney/bladder disease, hematological/immune system disease, and cancer) and any allergies. We calculated a further variable, a chronic disease composite score (out of 10), which is a continuous variable of the sum of an individual's answer to 10 questions related to the aforementioned history of chronic disease.

In reporting on the outcomes in this manuscript, we use the terminology "prediction" instead of "association," based on recently published guidelines regarding clear goal setting in sports injury research.[34] In addition, we report the retrospective annual incidence (percentage of runners: 95% CI) and frequency of injury characteristics (percentage of injuries) for anatomic region, body area, tissue type, and common specific GORRIs. Injury severity was recorded as frequency (percent) of less severe (Grade I—only experience symptoms after exercise; and Grade II—experience symptoms during exercise but they do not interfere with exercise) and more severe (Grade III—experience symptoms during exercise that may interfere with training/competition; and Grade IV—may not be able to train/compete due to pain) injuries.[35] More severe injuries were classified as those that interfered with the runner's ability to continue with training or racing.

STATISTICAL ANALYSIS

All race entrants' data were entered into Microsoft Excel and then transferred into SPSS statistical software (version 25) and SAS (V.9.4) statistical analysis system. The binary-scaled dependent variable in the model was the response to the question related to GORRI. Entrants were coded as having a GORRI if they reported 1) a GORRI in the past 12 mo or 2) a current GORRI. Entrants could report more than 1 injury. Frequency analysis was performed for the descriptive data (percentage of all entrants; 95% CIs). For the risk factors, 2 groups were used (injured group, n=338; control group, n=2486), a Poisson distribution with a log link function was used, and the *P*-values for a Type 3 GEE analysis were reported. All possible factors were first explored in a univariate analysis. Using highly significant factors ($P<0.001$, owing to the small sample size) from the univariate model, a multiple regression model was performed. Prevalence ratios (PR; 95% CIs) were reported, and a final significance level of <0.05 was accepted.

Table 1. Characteristics of all trail run race entrants and study participants

Characteristics	*All trail run entrants (n=3547)*	*Study participants (n=2824)*	P *value*[b]
	%[a] (n)	%[a] (n)	
Sex			
Male	57 (2003)	57 (1597)	0.9485
Female	44 (1544)	43 (1227)	
Age groups (y)			
≤30	30 (1073)	30 (857)	0.9124
31–40	37 (1312)	36 (1022)	
41–50	23 (816)	24 (666)	
>50	10 (346)	10 (279)	
Race distance (km)			
10	41 (1463)	40 (1131)	0.3342
22	59 (2084)	60 (1693)	

[a]Percentage of the total.
[b]*P* value—all trail run entrants vs entrants consenting as study participants.

Results

Over the 4 annual events, 3547 runners entered and 2824 entrants (80%) gave consent for their data to be analyzed (10 km [n=1131] and 22 km [n=1693]). There were no significant differences between entrants who consented to study participation and all race entrants by sex, age group, or race distance (Table 1).

ANNUAL INCIDENCE OF GORRIS

In the previous 12 mo, 338 trail running race entrants reported a total of 349 GORRIs. Eleven (3%) of the 338 participants reported a second injury (total injuries, n=349) and 82 (24%) of the 338 participants had a "current" injury at the time of completing the prerace screening questionnaire at race registration. The retrospective annual incidence of injuries in this study population was 13% (95% CI: 11–14).

CHARACTERISTICS OF GORRIS AMONG TRAIL RUNNING RACE ENTRANTS

The main anatomic region affected by GORRIs was the lower limb (94%: n=328), followed by the trunk (5%: n=16) and the upper limb (1%: n=2). The most common

Table 2. Anatomic region and specific body area of gradual-onset running-related injuries among trail running race entrants (n=349)

Anatomic region	*Body area*	*% (n)*
Head and neck	Head	0 (1)
Upper limb	Shoulder	0 (1)
	Wrist	0 (1)
Trunk		5 (16)
Lower limb	Hip/Groin/Pelvis	5 (18)
	Thigh	11 (38)
	Knee	35 (123)
	Achilles tendon	11 (37)
	Shin/Lower leg/Calf	16 (55)
	Ankle	6 (21)
	Foot	10 (36)
Unspecified		1 (2)
Total		100 (349)

body areas affected by GORRIs were the knee (35%: n=123), followed by the shin/lower leg/calf (16%: n=55) and the thigh (11%: n=38) (Table 2).

The most common specific GORRI was iliotibial band syndrome (ITBS) (22%: n=78), followed by Achilles tendon injury (10%: n=35), hamstring injury (9%: n=30), calf muscle injury (7%: n=23), and foot/heel pain (5%: n=19) (Table 3).

The frequency of Grade IV injuries (not able to train or compete due to injury) was 18% (n=63). The frequency of Grade III injuries was 33% (n=114), followed by Grade II (26%: n=90) and Grade I (23%: n=79). Slightly more severe GORRIs were reported among 51% (n=177) compared to less severe injuries among 48% (n=169).

RISK FACTORS PREDICTING A HISTORY OF GRADUAL-ONSET INJURIES IN TRAIL RUNNING RACE ENTRANTS (UNIVARIATE ANALYSIS)

Runner demographics (sex, age group) and race distance

The overall prevalence of GORRIs (n=338) among trail running race entrants was 12% (95% CI: 11–14). The prevalence of GORRIs was not significantly different between males and females (PR=1.0, P=0.7722) or across age groups (P=0.1246). There was a higher prevalence of GORRIs among trail running race entrants participating in the longer-distance race (PR=1.8, P<0.0001) (Table 4).

RUNNING TRAINING/RACING HISTORY

The number of years of recreational running (PR=1.1 per 5-unit increase; P=0.0014) and an increased average weekly training/running distance in the last 12 mo (PR=1.0 per 5-unit increase; P=0.0061) were associated with an increased PR for GORRIs (Table 5).

HISTORY OF CHRONIC DISEASE AND ALLERGIES

The results of trail running race entrants with a GORRI by history of chronic disease and allergies is shown in Table 6.

A higher chronic disease composite score was associated with a higher prevalence of GORRIs among trail running race entrants (PR=1.7; P=0.0004) in a "dose-dependent" fashion (Figure 1). For every 2 additional chronic diseases, the prevalence of GORRIs increased 1.7 times. Notably, the confidence intervals widened as the score increased, owing to the number of entrants with higher composite scores decreasing. A history of any allergies (PR=1.7, P=0.0008) was associated with a higher PR for GORRIs among trail running race entrants.

INDEPENDENT RISK FACTORS PREDICTING A HISTORY OF GORRIS IN TRAIL RUNNING RACE ENTRANTS (MULTIPLE REGRESSION ANALYSIS)

Independent risk factors predicting a history of GORRIs in trail running entrants were longer race distance (PR=1.9, P<0.0001), a higher chronic disease composite score (PR=1.6, P=0.0012), and a history of any allergies (PR=1.6, P=0.0056) (Table 7).

Discussion

In our study, runners entering for the longer trail run had a higher prevalence of self-reported GORRIs. Runners

Table 3. Frequency of common specific gradual-onset running-related injuries (12 mo prior to race entry) among trail running race entrants (n=349)

Common specific gradual-onset running-related injuries	*% (n)*
Knee-iliotibial band syndrome	22 (78)
Achilles tendon injury	10 (35)
Hamstring injury	9 (30)
Calf muscle injury	7 (23)
Foot or heel pain	5 (19)
Anterior knee pain/Patellofemoral pain	5 (16)
Lower back pain	4 (15)
Plantar fasciitis	4 (14)
Hip muscle injury (including gluteus/buttock muscles)	3 (12)
Shin splints (muscle/tendon)	3 (10)
Shin splints (bone)	2 (8)
Quadriceps muscle injury	1 (3)
Lower leg compartment syndrome	1 (2)
Other	24 (84)
Total	100 (349)

Table 4. Number, prevalence, and PR of trail running race entrants with a history of GORRI by race distance, sex, and age group

Characteristics	*Study participants (n=2824)*	*Study participants with a GORRI (n=338)*		*PR (95% CI)*	P *value*
	n	*n*	*Prevalence (%; (95% CI)*		
Overall	*2824*	*338*	*13 (11–14)*		
Runner demographics					
Sex					
Male	1568	184	12 (10–14)	1.0 (0.8–1.3)	0.7722
Female	1210	154	12 (11–14)		
Age groups (y)					
≤30	840	86	10 (8–13)		0.1246
31–40	1002	128	13 (11–15)	1.3 (1.0–1.7)	
41–50	663	92	14 (11–17)	1.4 (1.0–1.8)	
>50	273	32	11 (8–16)	1.1 (0.7–1.6)	
Race distance (km)					
10	1113	93	8 (7–10)	1.8 (1.4–2.3)	<0.0001[a]
22	1665	245	15 (13–17)		

GORRI, gradual-onset running-related injury; PR, prevalence ratio.
Missing data in 46 entrants.
[a]Statistically significant.

entering longer-distance races are usually more experienced and train at higher weekly running distances in comparison to entrants of shorter-distance races. Among Greek trail runners, increased running experience was associated with a higher risk of injury.[13] We found similar results in our univariate analysis, indicating that increased years of running were associated with a higher PR of a GORRI. Our univariate analysis also indicated that an increased average weekly running distance was associated with a higher prevalence of a GORRI. Future

Table 5. Prevalence and PR of trail running race entrants with a GORRI by training/racing history (unadjusted)

Running training/ racing history	*Points in the continuous variable*[a]	*Trail run race entrants with a GORRI (n=338): prevalence (%; 95% CI)*	*PR (95% CI)*	P *value*
Time as a recreational runner (y)	3	11 (9–12)	5-unit increase	0.0014[a]
	6	11 (10–13)	1.1 (1.0–1.2)	
	13	13 (12–14)		
Average weekly training/ running frequency in the last 12 mo (times·wk^{-1})	2	11 (9–13)	2-unit increase	0.0610
	3	12 (11–13)	1.1 (1.0–1.3)	
	4	13 (11–14)		
Average weekly training/running distance in the past 12 mo (km)	15	11 (10–12)	5-unit increase	0.0061[a]
	25	12 (11–13)	1.0 (1.0–1.1)	
	40	13 (12–15)		
Average training speed (km·h^{-1})	9	12 (10–13)	1-unit increase	0.5046
	11	12 (11–14)	1.0 (1.0–1.1)	
	13	13 (11–14)		
Race vs training speed ratio (RS/TS[b])	0.5	14 (12–17)	0.5-unit increase	0.0590
	1.0	11 (9–13)	1.0 (0.9–1.1)	
	1.5	8 (5–13)		

GORRI, gradual-onset running-related injury; PR, prevalence ratio.
[a]Statistically significant.
[b]Race speed (km·h^{-1}) vs training speed (km·h^{-1}) ratio = race speed/training speed; a value >1 is a faster average race speed compared to average training speed, and a value <1 is a slower average race speed compared to average training speed.

Table 6. Number, prevalence, and PR of trail running race entrants with a GORRI by history of chronic disease and allergies (unadjusted)

Characteristics	*Study participants (n=2824)*	*Race entrants with a GORRI (n=338)*		*PR (95% CI)*	P *value*
	n	*n*	*Prevalence (%; 95% CI)*		
History of chronic disease					
Chronic disease composite score (0–10)[a]					
0	–	–	11 (10–12)	2-unit increase	0.0004[b]
2	–	–	19 (15–23)	1.7 (1.4–2.2)	
4	–	–	32 (21–49)		
History of allergies					
Any allergies					
Yes	322	65	19 (15–24)	1.7 (1.3–2.2)	0.0008[b]
No	2455	273	11 (10–13)		
Missing	47	0			

GORRI, gradual-onset running-related injury; PR, prevalence ratio.
[a]The composite number of 10 chronic diseases for an individual (continuous variable, therefore no number of participants in the groups).
[b]Statistically significant.

studies using larger sample sizes may identify running experience and weekly running distance as independent risk factors predicting a history of GORRIs.

We showed that a higher chronic disease composite score predicted a history of GORRIs. Specifically, for every 2 additional chronic diseases present, the prevalence of GORRIs increased 1.6 times in a "dose-dependent" fashion. This is an intriguing finding. The prevalence of chronic disease among endurance runners has been reported at 2 to 13%, and 16% of runners have at least 1 risk factor for CVD.[15] Studies confirm that a variety of chronic diseases, which affect various organ systems, are associated with an increased risk for gradual-onset injuries.[16-20] For example, diabetes mellitus, hypercholesteremia, and obesity are associated with a higher risk of tendinopathy,[16-18] and chronic obstructive pulmonary disease is associated with an increased risk for bone stress injuries.[19,20]

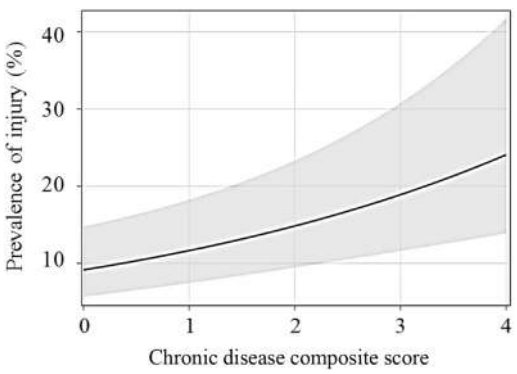

Figure 1. The relationship between the prevalence of gradual-onset running-related injuries and the number of chronic diseases (chronic disease composite score) (shaded area is 95% CI). Wide confidence intervals are indicative of the small sample size at that score.

Another consideration is that the medications used in the treatment of chronic diseases may be associated with an increased risk for injury.[21-27] There are reports that drug-induced tendinopathy is associated with the use of fluoroquinolones,[24] statins,[22,25] corticosteroids,[21] aromatase inhibitors,[27] and isotretinoin.[23] A higher risk for tendon ruptures[21] and osteoporosis[26] has been reported with the use of corticosteroids, and isotretinoin use increased the risk for developing enthesopathy.[23] The relationship between the medication dosage and adverse effects is not well quantified in the use of corticosteroids,[26] but the adverse effects of statins appear to be dose-dependent. Finally, certain medication interactions are associated with increased tendon toxicity,[36] and combinations of medications are a further risk factor for developing toxic tendinopathy.[37]

The cross-sectional nature of our study limits our ability to establish a cause-effect relationship between the chronic disease composite score and injury risk. These findings do suggest that not only the presence of chronic disease but also the choice of medication used in treatment, medication dosage, and medication interactions need to be explored as risk factors for GORRIs in future studies.

We also showed that a history of allergies predicted a history of GORRIs. Trail runners participate in various

Table 7. Independent risk factors that predict a history of GORRIs in the past 12 mo (multiple regression analysis)

	Runners with a GORRI % (95% CI)	*PR (95% CI)*	P *value*
Race distance (km)			
10	9 (7–11)	1.9 (1.5–2.4)	<0.0001[a]
22	17 (15–20)		
History of chronic disease			
Chronic disease composite score[b]			
0	12 (10–14)	2-unit increase:	0.0012[a]
2	19 (15–23)	1.6 (1.3–2.1)	
4	30 (20–46)		
History of allergies			
Any allergies			
Yes	18 (14–22)	1.6 (1.2–2.0)	0.0056[a]
No	11 (10–13)		

Adjusted for age and sex.

GORRI, gradual-onset running-related injury; PR, prevalence ratio.

[a]Statistically significant.

[b]The composite number of 10 chronic diseases for an individual (continuous variable).

outdoor settings where they are exposed to a variety of potential allergens. Trail running is an endurance sport, and it is well established that a history of allergies is common in endurance athletes.[15,38] We can only speculate on the possible reasons for the association between allergies and GORRI. Again, both the allergy itself and the medication used to treat it may be mechanisms responsible for the increased risk of injury. Antihistamines are commonly used to treat allergies but have side effects such as fatigue and drowsiness.[39] If this medication is used during training and racing, acute fatigue can alter lower extremity muscle strength, postural control, and ankle joint position sense, which may increase injury risk.[40] Future research should explore the relationship between allergies, the medication used to treat allergies, and GORRIs.

This is the only study to report the annual incidence (13%) of GORRIs among short-distance trail running race entrants; therefore, we could not compare our results to any current literature. Our results show that the lower limb (94%) is the most commonly injured anatomic region, and this finding is similar to that previously reported among longer-distance trail runners.[8,9,11,13,14,41] In our study, the knee was the most common body area for GORRIs (35%), at a rate that is much higher compared to Dutch trail runners (18%).[41] In downhill running, the knee is exposed to increased flexion angles during load absorption and redistribution, and this may contribute to the higher prevalence of knee injuries.[42] The lower frequency of knee injuries reported among Dutch trail runners[41] may be related to a difference in the trail running landscape in the Netherlands, with minimal elevation changes.

Our results indicated that soft tissue accounted for 82% of all injured tissue types. The specific tissues involved were muscle (33%), followed by tendon (30%) and ligament (18%), and these findings are similar to those reported in Dutch trail runners (muscle=28%, tendon=24%, ligament=7%).[41] In ultradistance trail runners, similar injured tissue types were found (tendon: 36%; ligament: 43%; and muscle: 21%).[11] However, we note that in the Italian trail running study, acute injuries were included, specifically a high number of ankle sprains. Therefore, we cannot strictly compare our data to that study.[11]

Finally, we show that 51% of GORRIs are severe enough to interfere with training or competition (Grade III and IV). Although Grade IV injuries were the least frequently reported (18%), they are of concern if a trail runner cannot continue with running owing to pain, especially during training/racing in remote regions where medical evacuation is challenging.[28] We cannot compare this finding to other studies because there is substantial variation in the definition of injury severity in the trail running literature,[8,41] which restricts our ability to compare results.

LIMITATIONS

This study has several limitations. We cannot determine a cause-effect relationship between any of the identified risk factors because of the cross-sectional nature of the study. All injury and training data are self-reported and could have been affected by recall bias. Owing to recall bias, we could not accurately determine the study participants' actual running exposure on trails. The diagnosis of injuries could not be verified. Lastly, we acknowledge

that many other factors (eg, elevation change, running surface, individuals' level of conditioning, intrinsic lower limb biomechanics, footwear) may also be associated with the risk for developing GORRIs, but these could not be explored in our study. Future studies are needed to explore the causal relationship between the risk factors and GORRIs among short-distance trail running race entrants.

Conclusions

Independent risk factors that predict a history of GORRIs among short-distance trail running entrants include longer race distance, a higher chronic disease composite score, and history of any allergies. Specifically, for every 2 additional chronic diseases present, the prevalence of GORRIs increased by 1.6 times in a "dose-dependent" fashion. Our results highlight trail running race entrants at risk for sustaining GORRIs who could be targeted for future injury prevention interventions.

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ORIGINAL RESEARCH

Comparison of Radiographic, Ultrasound, and Magnetic Resonance Imaging for the Detection of Retained Stingray Barb: A Cadaveric Study

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Introduction—Stingray envenomations are a common marine animal injury for which it is important to identify and remove retained barbs to prevent secondary infection. The optimal imaging modality in stingray foreign body detection is not well characterized in the existing literature. In this study, we compared the accuracy of plain radiography, ultrasound, and magnetic resonance imaging (MRI) in detecting stingray barbs in the human foot and ankle.

Methods—This cadaveric study included a 1:1 randomization to the presence or absence of barbs in 24 sample injuries of human cadaveric foot and ankle specimens. Physicians trained in emergency medicine and radiology performed ultrasound examinations on each specimen and interpreted the presence or absence of a barb. Participants also interpreted x-ray images in the same manner. MRI scans were separately interpreted by a musculoskeletal radiology attending. Data were analyzed using McNemar's test.

Results—The 19 participants included 14 (74%) trained in emergency medicine and 5 (26%) trained in radiology. Forty-seven percent were residents, 42% faculty, and 11% fellows. X-ray was associated with the highest sensitivity of 94% for the identification of a retained barb, followed by MRI (83%) and ultrasound (70%). MRI was associated with the highest specificity of 100%, followed by x-ray (98%) and ultrasound (73%).

Conclusions—Retained stingray barbs can lead to secondary infection after envenomation. In human cadaveric specimens, x-ray demonstrated the highest sensitivity, MRI demonstrated the highest specificity, and ultrasound demonstrated lower sensitivity and specificity.

Keywords: envenomation, x-ray, ultrasonography, foreign body, spine, ray

Introduction

With over 150 different species existing in both seawater and freshwater, the stingray is often sought out as an underwater attraction for snorkelers and scuba divers.[1] However, armed with 1 to 4 retroserrated barbs with associated venom glands on its tail, the stingray is prepared to attack when threatened.[2] Anywhere from 750 to 2000 stingray injuries are reported in the United States each year,[3,4] making them a commonly reported marine animal to cause human envenomation. The wound inflicted is typically a combination of a puncture wound and laceration and occurs most commonly on the lower extremity.[5] As the barbed tail contacts the swimmer's skin, the integumentary sheath that covers the barb is torn, releasing venom into the wound, and fragments of both the sheath and the barb may be retained at the site of injury.[1] Although most injuries do not jeopardize the life of a patient, the released venom causes immediate pain and vasoconstriction, and some patients may develop systemic symptoms including but not limited to nausea, vomiting, diarrhea, muscle cramps, hypotension, and cardiac dysrhythmias.[1,5] Retention of stingray barbs has

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the potential to lead to secondary infection, which in some rare cases has progressed to life-threatening necrotizing fasciitis.[6,7] For this reason, it is important to identify and remove any retained foreign bodies from a stingray injury.[1,8]

Though literature on management of stingray envenomation is limited, hot water immersion is the mainstay of treatment.[6] Antibiotics and pain medications may also be used. Many individuals have adequate control of symptoms after hot water immersion[9-11] on the beach or at home and require no further evaluation or treatment. Those stingray injuries that require further medical attention are typically evaluated in an emergency department, urgent care, or other primary care setting where x-ray imaging and bedside ultrasound may be available; however, magnetic resonance imaging (MRI) may not be accessible. It is generally recommended that if a retained foreign body is suspected, wounds should be explored and debrided to ensure all remnants of the barb and sheath are removed to prevent delayed healing and infection.[12] The utility of radiographs, ultrasound, and MRI to aid in this endeavor has yet to be well characterized in the literature.[4] The value of radiographs, specifically, has been a long debated topic in the management of these injuries, as some sources suggest that stingray barbs may not be radiopaque whereas other case reports indicate successful visualization with x-rays.[4,13] To our knowledge, the use of ultrasound and MRI as potential imaging modalities in detecting retained barbs has not been studied. The aim of our study was to compare the accuracy of plain radiography, ultrasound, and MRI in detecting retained stingray barbs in the human foot and ankle.

Methods

This study was submitted to the University of California San Diego institutional review board and deemed exempt. It was approved by the Birch Aquarium at Scripps animal care use committee.

In this cadaveric study, we randomized the presence or absence of stingray barbs in predetermined locations of 12 human fresh frozen cadaver foot and ankle specimens. The foot and lower ankle were chosen as the anatomic sites for this study because they are the most common locations of injury. Round stingray (*Urobatis halleri*) barbs were collected over a 6-mo period when trimming was performed by Birch Aquarium staff as part of their routine animal management protocols.

We obtained 12 fresh frozen cadaveric specimens and used 2 sites (foot and ankle) per specimen to mimic the stingray injury, providing a total of 24 samples for interpretation. There were 4 samples for each of the 6 anatomic sites: the medial arch, lateral arch, and heel on the foot and the medial malleolus, lateral malleolus, and posterior calf on the ankle. We replicated a small skin defect for each simulated injury, mimicking the common clinical presentation of a stingray puncture wound. We made a 5-mm incision at a 30° angle using an 11-blade scalpel and then inserted and opened a hemostat to 20° to provide the same tissue distortion for each sample site. The injury sites were randomized in a 1:1 fashion for the presence or absence of a retained barb. In those sites randomized to include the presence of a barb, a standard 3-mm by 15-mm piece of stingray barb was inserted into the simulated wound defect using a hemostat until the barb was no longer visualized at the wound defect or palpable. The fragment was the same width as and approximately half the length of the round stingray barbs collected. This fragment size was chosen because it was believed to be similar in dimension to other retained organic materials, such as cactus spines or large wooden splinters.

Radiographs were performed and recorded by trained technicians for each cadaveric specimen. A radiopaque marker was placed over the skin defect, and anteroposterior and lateral radiographs of the foot and the ankle were obtained using the Siemens Ysio Max machine. These images were de-identified and randomized in order. The radiopaque markers were removed, and the site of injury on each specimen was marked with a skin marker before the ultrasound and MRI portions of the study. Specimens were again de-identified and randomized for the ultrasound and MRI interpretation.

Emergency medicine (EM) and radiology physician trainees and attendings were recruited to participate as evaluators in the study. Participants filled in a written questionnaire for demographic data, including medical specialty, training level, and any additional pertinent training or certification in ultrasound or musculoskeletal imaging. Participants were blinded to which extremity sites actually had a retained foreign body. EM physicians attended a 20-min didactic session in which principles of soft tissue ultrasound and foreign body location were discussed, including proper scanning technique and methods of visualization. In addition, all EM resident physicians at the study location had baseline ultrasound training that included over 20 h of didactic and hands-on scanning during the postgraduate year (PGY)-1, which included soft tissue applications. After the ultrasound didactic presentation, all EM and radiology physicians used a high frequency linear (HFL50x) transducer on the Sonosite Edge II ultrasound system to review the cadaveric specimens and record whether a foreign body was present. Participants worked independently and

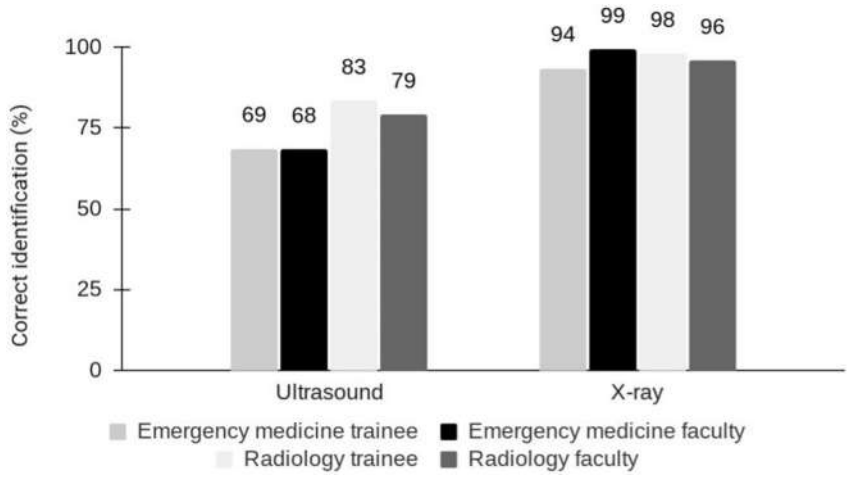

Figure 1. Identification of retained stingray barb by imaging modality, level of training, and specialty.

without a time limit. Commercial ultrasound gel and gel-filled gloves, used as a standoff pad, were provided for the ultrasound scanning portion. The x-rays of the same specimens were then reviewed by the same physicians, who were blinded as to which extremities had a retained foreign body. The reviewers recorded whether a foreign body was detected.

Standard MRI sequences were acquired in routine imaging planes, again randomized in order and then reviewed by 1 board certified musculoskeletal attending radiologist, who was blinded as to which extremities had a retained foreign body. The reviewer recorded whether a foreign body was detected on MRI.

STATISTICS

For each imaging technique (x-ray, ultrasound, and MRI), we calculated the overall detection sensitivity, specificity, false positive rate, and false negative rate along with individual reviewers' sensitivity and specificity. The test characteristics were compared among imaging modalities using McNemar's test. Interobserver reliability was compared using the Fleiss kappa test. Comparing sensitivity and specificity of the various imaging methods, with alpha set at 0.05 and a sample size of over 430 (24 specimen "injuries" × 18 participants), the study had an 80% power to detect an effect size of 15%.

Results

The 19 reviewers included 14 (74%) emergency physicians and 5 (26%) radiologists. The emergency physicians included 9 (64%) resident physicians and 5 (36%) attending physicians. The EM resident physician PGY breakdown was 3 (33%) PGY-1, 5 (56%) PGY-2, and 1 (11%) PGY-4. Among the EM attending physicians, 1 (20%) was a registered diagnostic medical sonographer, 2 (40%) had completed ultrasound fellowships, and 3 (60%) were ultrasound credentialed within the EM department. All EM attendings were board certified in EM. The breakdown of radiologists included 2 (40%) musculoskeletal fellow physicians and 3 (60%) attending physicians board certified in radiology.

X-ray was associated with the highest sensitivity of 94% for the identification of a retained barb, followed by MRI (83%) and ultrasound (70%). MRI was associated with the highest specificity of 100%, followed by x-ray (98%) and ultrasound (73%).

There was no difference in correctly identifying the presence or absence of a retained barb on ultrasound or x-ray based on the reviewer's level of training (P=0.13 and P=0.85, respectively) (Figure 1). There was no difference observed amongst PGY training for the EM resident physicians. For x-ray, success rates ranged from 94 to 99%. There was no difference in the accuracy of identification of a stingray barb on x-ray between the EM physicians and the radiology physicians (P=0.68). For ultrasound, success rates ranged from 68 to 83% with radiology faculty and fellows performing better than their EM colleagues (P=0.03).

Foreign body identification accuracy was also evaluated based on the anatomic location of injury by imaging modality (Figure 2). The easiest location for identification was the heel, at 87% sensitivity for ultrasound and 100% sensitivity for both x-ray and MRI. The medial arch proved most challenging for x-ray (82% sensitivity), whereas the medial and lateral malleoli were the most challenging for MRI (75% sensitivity). The remainder of

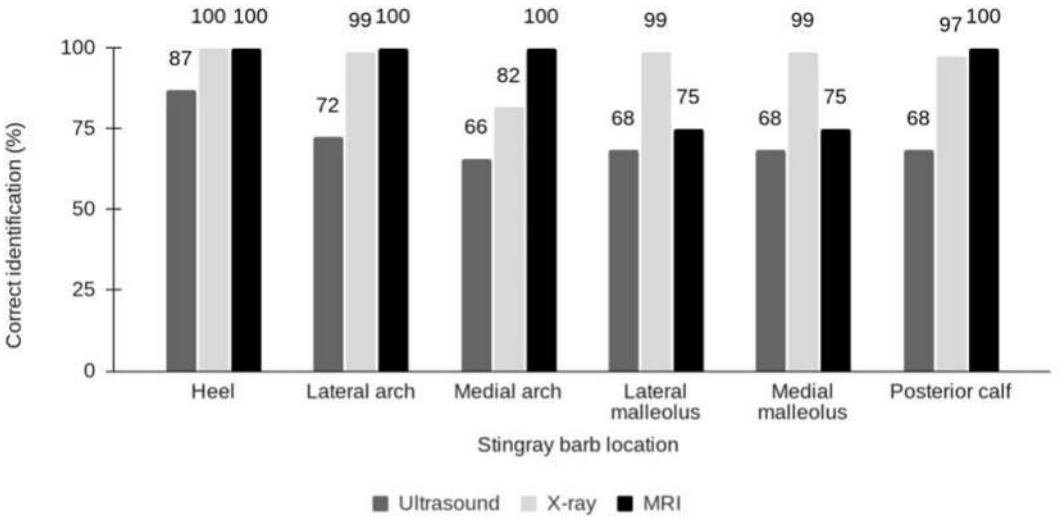

Figure 2. Identification of retained stingray barb by anatomic location and imaging modality.

locations did not show a difference in accuracy in regard to ultrasound imaging.

Discussion

This cadaveric study found that plain radiography was associated with the highest sensitivity for detection of retained stingray barb after injury and that MRI was associated with the highest specificity. Ultrasound was associated with the lowest sensitivity and specificity of the 3 modalities studied.

Radiology physicians performed better than EM physicians in identifying retained barbs on ultrasound. One of the radiology faculty and both radiology fellows had special training in musculoskeletal imaging, which may have contributed to their better performance on ultrasound identification of barb retention. Overall, variations in performance across different levels of training and specialties speak to user discrepancy in interpreting both ultrasound and x-ray images. Furthermore, when using ultrasound, it is important to consider variability in user proficiency in obtaining adequate images, in addition to their ability to interpret those images.

The heel was the anatomic site associated with the highest rate of accuracy across all 3 imaging modalities (Figure 3). For MRI, injuries that were simulated at the medial malleolus and lateral malleolus had the lowest percentage of correctly identified images. We suspect this observation is related to the type of surrounding tissue at each site. The heel contains a subcutaneous fat pad that assists in providing contrast for stingray barb identification, whereas the malleoli are bony structures with less surrounding subcutaneous tissue and therefore provide less contrast for barb identification.

LIMITATIONS

This study has limitations that are inherent to a cadaveric study. The use of cadaveric specimens and simulated injury does not provide the exact environment that would be encountered in the clinical setting. Soft tissue swelling is often present in stingray injuries, and fluid collections may be seen when a deep space infection has developed. These associated findings may enhance visualization via ultrasound or MRI, which use variations in tissue density to identify structures.

Frequently a water bath is used in the clinical setting to enhance ultrasound images when searching for retained foreign bodies. We decided not to include a water bath as an option, given the potential risk of water dissecting down into the simulated wounds and distorting images for subsequent evaluators. Additionally, there was concern for loss of integrity of the cadaveric specimens if they were submerged in water repeatedly. Gel-filled gloves, to be used as standoff pads, were offered as an alternative to commercial ultrasound gel; however, the gloves were infrequently used by the participants. Using water baths may have increased the accuracy of ultrasound identification.[14]

It is notable that we had clinician-sonographers, including PGY-1 physicians, obtaining and interpreting the ultrasound images, whereas the MRI scans were obtained by MRI technologists and interpreted by a board-certified musculoskeletal radiologist. Given the vast difference in training and expertise of our

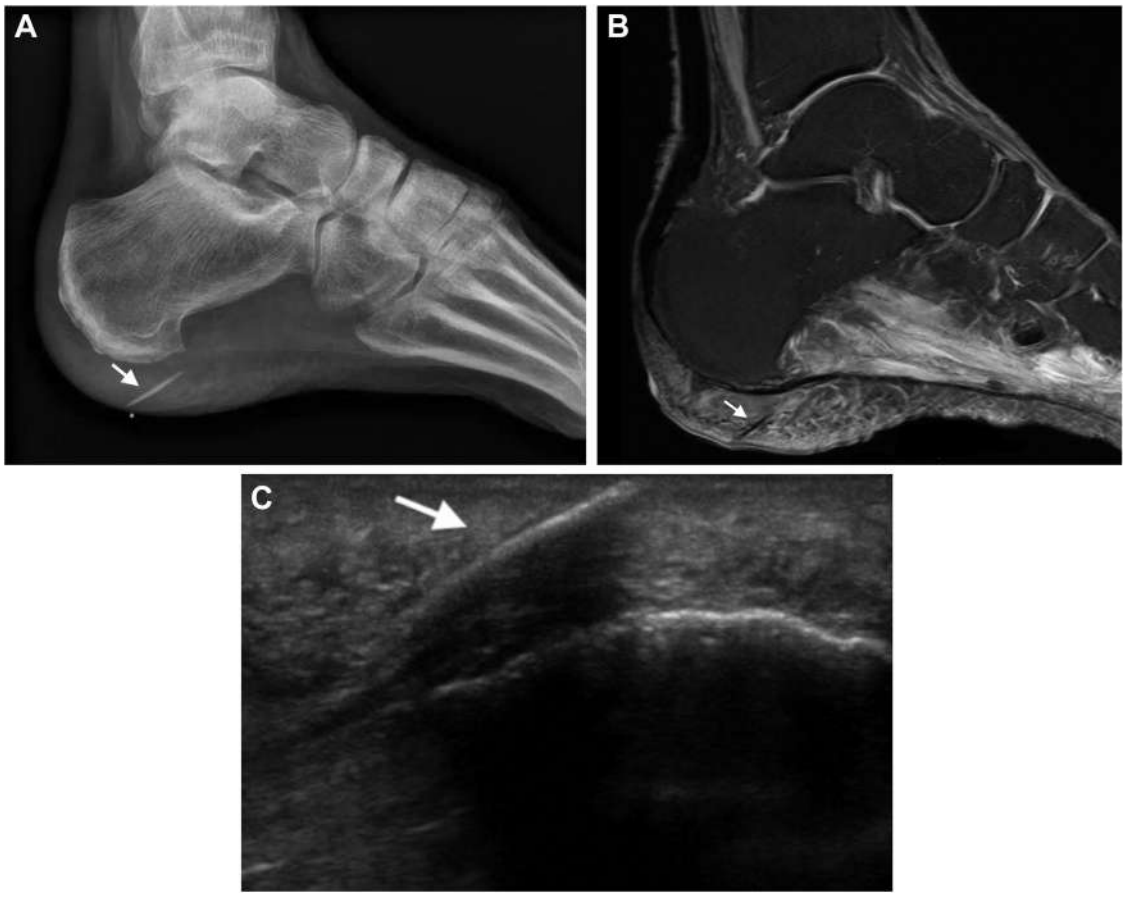

Figure 3. The heel was the anatomic site associated with the highest rate of accuracy across all 3 imaging modalities. A, Lateral view x-ray demonstrating stingray barb (arrow). B, Sagittal cut of magnetic resonance imaging demonstrating stingray barb (arrow). C, Ultrasound demonstrating stingray barb (arrow) in the longitudinal axis.

physician participants, our results do not provide a head-to-head comparison of ultrasonography and MRI in the detection of stingray barbs in human feet and ankles. The possibility of user error in ultrasound image acquisition and interpretation presents a challenge in determining whether ultrasonography is truly inferior. Rather, our study sought to assess the relative merits of provider-performed ultrasound (point-of-care ultrasound) compared with radiology-performed imaging modalities. In our urban, academic emergency department setting, it is commonplace for providers to perform such focused ultrasound examinations at the bedside. However, given that this may not be the norm in other practice settings, our results are less generalizable.

The small number of participants from different specialties and training levels also limits any conclusions regarding the optimal physician background in performing these imaging studies. Moreover, there was only a single MRI reviewer, compared to multiple reviewers for ultrasound and plain radiography.

Finally, our study used stingray barbs that had been stored and no longer had an integumentary sheath, which typically encases the barb in live animals. In some clinical cases, fragments of the integumentary sheath may be left in the wound without any barb fragments, and this organic material can also be a nidus of infection, leading to antibiotic use or potential foreign body removal. We did not use freshly trimmed barbs in this investigation because it took several months to collect an adequate number of barbs to complete the study. Our study instead focused exclusively on the comparison of imaging modalities in identifying barb fragments rather than retained portions of the integumentary sheath. If feasible, future investigations of the integumentary sheath alone or using freshly trimmed barbs could yield different results than the current study. This research used barbs from round stingrays. It is unknown whether the species of stingray affects how barbs

are visualized using different imaging modalities. Studies using other stingray species may have different results.

Conclusions

Retention of stingray barbs has the potential to turn a low-risk injury into a life-threatening infection. In human cadaveric specimens, x-ray demonstrated the highest sensitivity, MRI demonstrated the highest specificity, and clinician-performed ultrasound demonstrated the lowest sensitivity and specificity in detecting retained stingray barbs. In this study, EM physicians had the same accuracy in identifying stingray barbs on plain radiographs as radiology physicians. Given that plain radiography demonstrated higher sensitivity than MRI in our study, and that MRI is more time-consuming and costly, we would recommend considering the use of plain radiography as the initial imaging modality to look for retained barb fragments after a stingray injury.

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Author Contributions: Study concept and design (CHC, TD, KVH, SMS, AM, CBC); acquisition of the data (TD, LA, KVH, AM, SMS, CBC, CHC); analysis and interpretation of the data (LA, TD, CHC); drafting of the manuscript (TD, CHC, LA); critical revision of the manuscript (CHC, KVH, AM, SMS, CBC). All authors approved the final manuscript.

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ORIGINAL RESEARCH

Epidemiology of Eastern Massasauga (*Sistrurus catenatus*) Snakebites in the Great Lakes States, 1800–2015

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Introduction—The eastern massasauga rattlesnake (*Sistrurus catenatus*) has the northernmost distribution of any venomous snake in the United States and presents a potential, but little-studied, risk to humans.

Methods—We quantified the reported incidence of massasauga bites to humans in the Great Lakes states by searching historic and contemporary media reports between 1800 and 2015.

Results—We identified 848 reported massasauga bites across the region, most of which were concentrated along the border of Indiana and Michigan. The number of bites per decade increased into the late 1800s as human population increased; it then declined sharply in the 1900s, likely owing to declining massasauga population and habitat. The majority of bites were to adult males. There was no relationship between victim sex and age or activity when bitten. Most bites resulted from snakes the victims were unaware of, usually when individuals accidentally put their hands or feet near an unseen snake. Many bites, however, resulted from people intentionally interacting with a massasauga, such as attempting to capture or kill it. Fatality rates were lower among men than among women and were lower in adolescents than older or younger victims. No fatalities from massasaugas were reported after 1935.

Conclusions—Fatality rates from massasauga bites reported herein should be interpreted with caution owing to the nature of the data we collected. In the modern era, massasauga bites are generally considered neither common nor life-threatening, although our findings suggest that historically they may have been both more frequent and potentially more dangerous.

Keywords: rattlesnakes, pit vipers, envenomation, media reporting

Introduction

Snakebite represents a substantial risk to human health worldwide, with an estimated 1 to 5 million bites occurring annually.[1] Although risk of snakebite is much lower in the United States than in other parts of the world, approximately 8000 bites still occur each year in the United States.[2] The majority of these are bites from rattlesnakes (*Crotalus* and *Sistrurus* spp) but also from copperheads, cottonmouths, and coral snakes (*Agkistrodon* and *Micrurus* spp) and thus are concentrated in southern and western states where these snakes are most abundant.[3] The eastern massasauga rattlesnake (*Sistrurus catenatus*) has the northernmost distribution of all venomous snakes in North America, ranging into the midwestern United States and southern Canada, regions where snakebite may not always be thought of as a serious threat.

Eastern massasaugas are found predominantly east of the Mississippi River across the Great Lakes region (Illinois, Indiana, Michigan, Ohio, Wisconsin, and southern Ontario), with some occurrence along the western edge of Iowa and small pockets extending into western New York and Pennsylvania. It was historically found in western Missouri and Minnesota but is now considered extirpated in both states. The species is in decline across its range, likely owing to a combination of habitat loss and fragmentation, road mortality, and direct persecution by humans.[4] Deliberate, widespread killing of massasaugas was once common,[5] but currently *S catenatus* is legally protected as a species of "special concern" in Michigan and as endangered in every other state in which it occurs. *Sistrurus catenatus* was formerly classified as 1

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Figure 1. Eastern massasauga rattlesnake, *Sistrurus catenatus*. Photograph by Bruce Kingsbury, used with permission.

of 3 massasauga subspecies, but it is now generally considered to be distinct from the western and desert massasauga (*S tergeminus tergeminus* and *S t edwardsii*),[6,7] which are found from Nebraska and Missouri southwest into Arizona and northern Mexico.

Sistrurus catenatus is a moderately sized (55−80 cm mean adult total length)[8] and cryptically colored pit viper, generally similar to the larger and more familiar *Crotalus* rattlesnakes. Its color pattern is a drab tan or gray base with darker blotches along the sides and back (Figure 1). It is sometimes colloquially known as the swamp rattlesnake owing to its strong association with wet, marshy habitats.[9] When approached by humans, eastern massasaugas most often either rely on camouflage to remain unseen or quietly retreat; less frequently they may rattle in warning. They rarely attempt to bite unless restrained or physically disturbed.[10] Owing to their rarity in many locations, their reclusive nature, their wetland habitat preference, and the difficulty of detecting individuals,[11] human interactions with massasaugas are more limited than with many rattlesnake species. However, unintentional contact between humans and massasaugas (eg, stepping on or putting hands near an unseen snake) may elicit a defensive strike. Defensive bites from massasaugas present a low venom yield, but *S catenatus* venom is more potent than some larger *Crotalus* rattlesnakes and these bites can be medically significant.[12-14]

Many analyses of US snakebites rely on data collected from medical entities such as emergency departments and poison control centers.[15-17] Although highly valuable, these sources provide only contemporary accounts and often only clinical data. Popular media such as newspapers represent a useful supplement—albeit one with limitations—to these traditional data sources because they chronicle incidence before the existence of such medical entities and often contain additional details surrounding the actual bite occurrence.[3]

To gain broader historical insight into human envenomations by the eastern massasauga, we assessed both contemporary and historical accounts of snakebites reported in popular media. Here, we document media-reported bites to humans by eastern massasaugas, focusing on the core of their range in the Great Lakes region of the United States (Illinois, Indiana, Michigan, and Ohio) from 1800 to 2015. Specifically, we identified the geographic locations of bites, the temporal distribution of bites both over the study period and seasonally, the activity of victims while bitten, the demography of bite victims, and the reported fatality rate of massasauga bites.

Methods

Institutional review board evaluation was not sought for this study because it did not involve research on human or animal subjects.

DATA COLLECTION

From 2002 to 2017, regular searches were conducted on the digitized newspaper databases www.newspaperarchive.com and www.newspapers.com. Additional databases, including the United States Library of Congress "Chronicling America" collection (mostly for historic accounts) were also periodically searched, and area-specific searches were conducted at regional sources such as Central Michigan University's Clarke Library and city libraries across each study state. In some cases, older reports had information missing from digitized versions, so these were double-checked by microfilm.

Searches were constrained to the word "rattlesnake." Additional search terms (eg, "rattle snake" and colloquial names) did not return appreciable additional results. Search results were then manually sorted to include only cases that contained an actual snakebite report and to screen out duplicate reports of the same case. Species identification was usually confirmed by the use of the common name "massasauga" or by geographic location. In some cases from areas in which massasauga and timber rattlesnake (*Crotalus horridus*) populations may overlap currently or historically (eg, southern Ohio or western Illinois), it was not possible to definitively ascertain the species responsible, so these cases were excluded. For each case of massasauga bite, we recorded (when possible) the date and time of the bite, county and township where the incident occurred, sex and age of the victim, whether the bite was fatal, and what the victim was doing when bitten, including whether they seemed

Table 1. The number of human bites by massasaugas identified from popular media reports from 1800–2015

State	*Bites (n)*	*Fatalities (n)*	*Fatality rate (%)*
IL	70	25	36
IN	304	38	13
MI	416	46	11
OH	58	9	16
Total	848	118	14

aware of the snake's presence. Where actual victim age was not available, we attempted to infer general age classes of child (aged 12 y or under), adolescent (12–17 y) or adult (18 y or over).

ANALYSIS

To assess the geographic distribution of massasauga bites, the location of each bite report was determined to the county level where possible. For each state, we then determined both the overall number of snakebites and the number of fatal bites reported during all years collectively. To assess long-term temporal patterns of snakebite, we determined the number of overall bites and number of fatal bites reported during each decade of the study, collectively across all 4 states. The seasonality of bites was addressed by determining the number of bites that occurred during each month, collectively across all states and years.

Victim demography (sex, age class) and activity when bitten were analyzed across all states and years collectively. Possible association between victim sex and age class or between victim sex and activity when bitten was analyzed using χ^2 tests. Possible associations between fatality rate and state, victim sex, and victim age class were also analyzed using χ^2 tests. For all tests we used $P \leq 0.05$ as an indicator of statistical significance.

Maps were created in Adobe Photoshop CS5 (Adobe Systems Inc, San Jose, CA). Statistical analyses were performed in Systat 12.0 (Systat Software Inc., Chicago, IL). Figures were created in Excel 2019 (Microsoft, Redmond, WA). Estimated human population during the study period was obtained from United States Census Bureau data (www.census.gov).

Results

We identified a total of 848 individual reports of snakebites in humans that could be reliably classified as massasauga bites (Table 1). Searches also identified an additional 152 bites to animals (most often horses, dogs, or cows), 836 reports of snakes being deliberately killed, 252 reports in which snakes were observed but not disturbed, and 535 cases in which snakes were collected (eg, for museum specimens, pets, relocation, or for unreported reasons), and 208 additional anecdotes regarding massasaugas, but all of these are excluded from the current analysis. Bites were located across the study region within massasaugas' reported range, with the greatest concentration along the border of Indiana and Michigan near Lake Michigan (Figure 2).

Michigan had the greatest number of reported bites at 416 and Ohio the fewest at 58 (Table 1). Across all states collectively, the number of bites initially increased with growing human population with a peak in the late 1800s and then declined dramatically into the 1900s (Figure 3). The number of reported fatalities was generally low relative to number of bites, although 36% of 70 bites in Illinois were fatal. The highest number of fatal bites occurred in the 1880s, with 25 fatal bites during the decade. No human fatalities from massasauga bites were reported after 1935.

Seasonality of bites strongly coincided with the warmer months, when snakes in temperate regions are more active (Figure 4). The few bites that were reported in colder winter months were from snakes that were inside buildings or were apparently disturbed while hibernating.

Most victims were bitten when they accidentally touched or placed their hands near a snake (42%), followed by stepping on or near an unseen snake (41%) (Figure 5). Victims who were aware of the snake were more often bitten while intentionally handling or attempting to kill it. However, we determined activity and awareness separately because they were not universally related—for example, there were reports of individuals being bitten while stepping over a snake they knew was present or intentionally grabbing a snake they had accidentally misidentified as an inanimate object.

Most cases (98%) reported the victim's sex, but only 316 (37%) specified the victim's exact age. An additional 106 cases directly implied age class (eg, "a little girl," "a middle aged man"). For the remainder, we attempted to infer age class based on context (eg, a "man" bitten while at work, the victim referred to as "Mrs."). Cases in which victim sex or age could not be reliably determined (n=49) were excluded from analysis. Our review found there were more bites to males than females across all age classes (Figure 6) but that there was no significant association between sex and age class (χ^2=0.158, P=0.92) or sex and activity when bitten (χ^2=5.85, P=0.12).

Of all massasauga bites, 122 (15%) were reported as being fatal, 447 (53%) were explicitly reported as nonfatal, and the eventual outcome was not included for

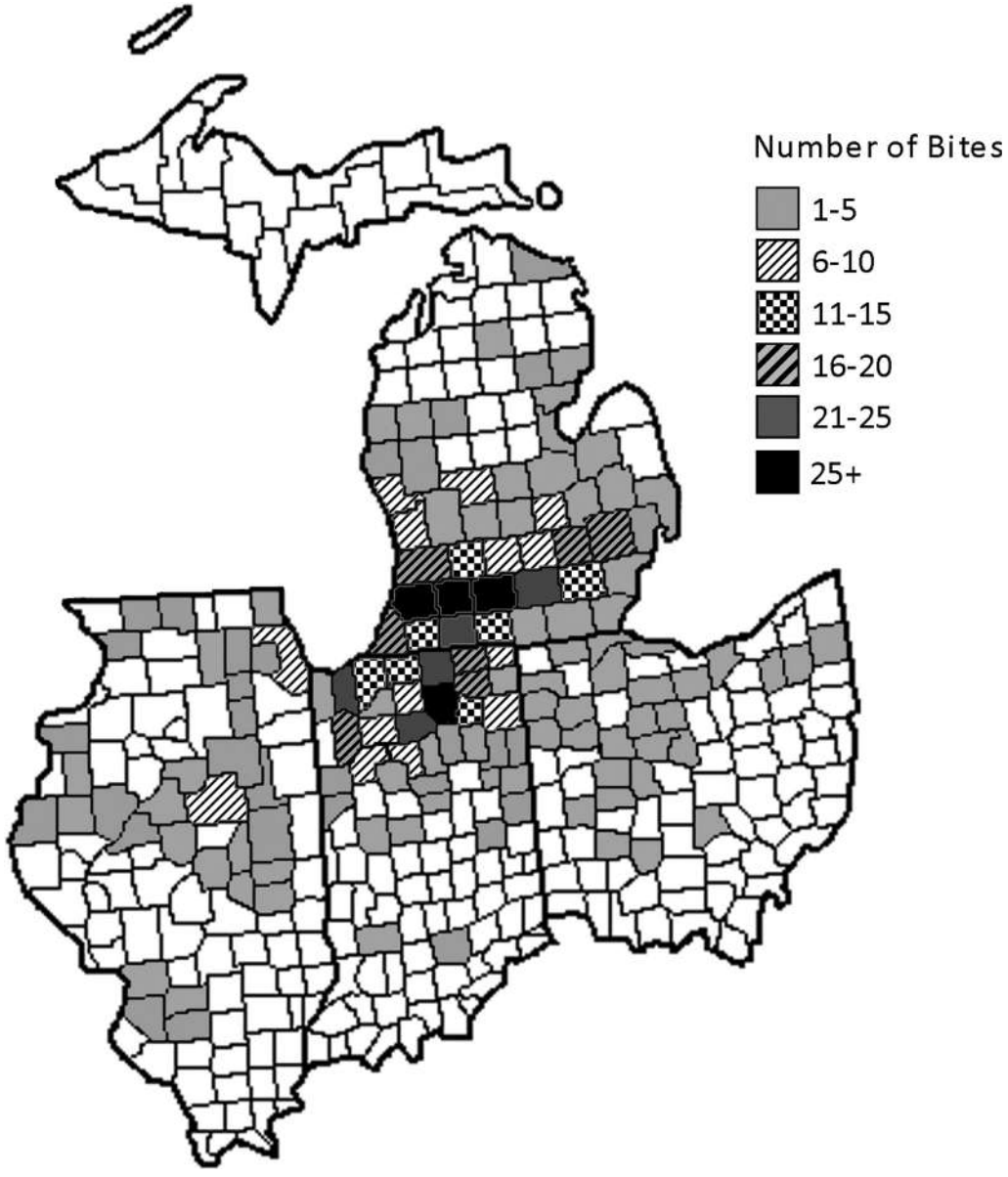

Figure 2. Map of all massasauga bite reports that could be identified to the county level (n=847).

279 (33%). In assessing fatality rates, we assumed that bite victims survived unless specifically stated otherwise. Fatality rate was significantly associated with state (χ^2=33.21, P<0.01). Illinois had relatively few bites at 70, but had 25 fatalities, nearly triple the rate of other states. Fatality rates were significantly higher for women than for men (20 and 11%, respectively; χ^2=14.58, P<0.01). Fatality rate was also significantly associated with age class (χ^2=6.07, P=0.047), with a lower fatality rate among adolescents (10%) than among children (20%) or adults (29%).

Discussion

Media searches revealed a surprisingly large number of massasauga bites considering the current perception that massasaugas are both uncommon and reluctant to bite. Owing to the nature of our media-reported data, our results will be influenced by both the actual number of snakebites that occurred and by the availability, trends, and biases of media reporting over the study period. Therefore, our results should not necessarily be considered a direct measure of the actual number of snakebites

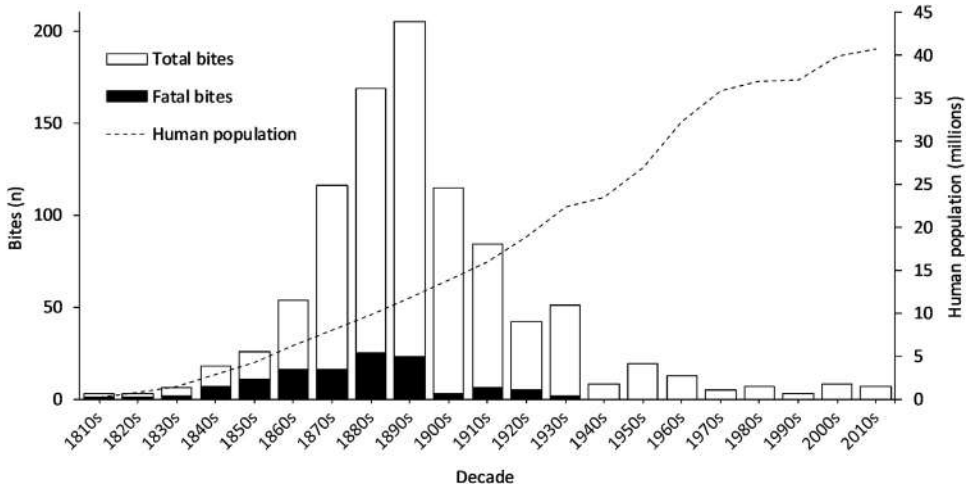

Figure 3. The number of total massasauga bites to humans, number of fatal bites, and estimated human population reported during each decade. Data are collective for all 4 study states (Illinois, Indiana, Michigan, and Ohio).

that occurred. They can, however, reveal spatiotemporal trends and human factors associated with massasauga bites.

Bites were distributed widely across the study area, but a very strong cluster was found around the border of northern Indiana and southwestern Michigan. The counties in this region are in the center of massasaugas' geographic range, and many saw a rapidly increasing human population in the late 1800s. These 2 states also had a much higher number of bites overall than Illinois and Ohio. We identified no bites from the upper peninsula of Michigan, which is predominantly rural and sparsely populated by humans even at the current time. There were also no bites identified from the southernmost counties across the entire region, a boundary that largely coincides with the reported southern limit of the massasauga's range.

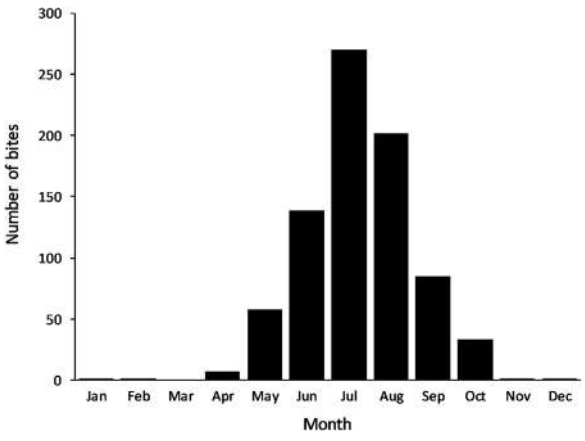

Figure 4. The total number of massasauga bites to humans reported in each month, collectively across all years and states, for cases in which month could be determined (n=797).

Seasonally, bites predominantly occurred during the warmest summer months. This is not surprising for an ectothermic species in a northern, strongly temperate region and is characteristic of venomous snakebites across much of the United States.[18] Although some bites were reported during colder months, these typically resulted from humans disturbing a sheltered snake (eg, "ran into a nest of rattlers" while plowing) or rarely from a snake that had apparently wandered into a building, possibly for warmth (eg, several reports of a snake being found in one's bed).

The number of bites reported was extremely low from 1800 through the 1830s, with fewer than 5 bites identified in each decade. This may be due to the low human population during this period (less than 5 million across all 4 states) or the low availability of media outlets to report snakebites in developing rural areas. The number of bites increased in each decade to a peak of 182 bites in the 1890s and then decreased sharply to no more than 5 bites per decade since the 1940s. This pattern could be explained initially by increasing human population and development across the region (which continues to the current day) leading to increased encounters with massasaugas, and the later decrease in bite occurrence could be explained by declining snake population as a result of that development.

The majority of bite victims (77%) were unaware of the snake when they were bitten, with the most frequent activities associated with snakebite being accidentally stepping on or near a snake or accidentally grabbing or putting hands near a snake. Only 16% of victims were reportedly aware of the snake before they were bitten.

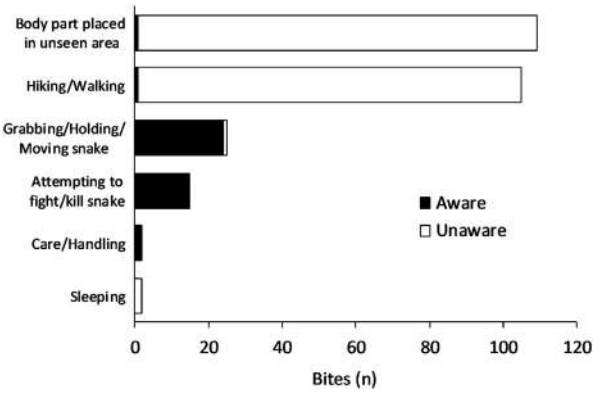

Figure 5. Victim's activity when bitten and awareness of the massasauga's presence before being bitten, for cases in which such information could be determined (n=258).

These bites almost always resulted from the person deliberately interacting with the snake, such as attempting to move, capture, or kill it. Although some studies have reported that most human snakebites occur from such intentional interactions,[19,20] our data concur with other media-based studies finding that most bites are accidental.[3] The reason for this discrepancy is unclear, although it could partially be explained by the information victims are willing to provide to medical personnel in a confidential setting (the data on which many snakebite studies are based), versus that provided to public media outlets. Few data available to address this idea.

There were more massasauga bites to male than female victims across all age classes, and the majority of bites were to adults. Age data proved difficult to definitively quantify; in many cases we had to infer the victim's age as adult, so some cases may have been miscategorized (child vs adolescent, adolescent vs adult). However, these results are consistent with reviews finding that most snakebites in the United States are to young men.[15,20]

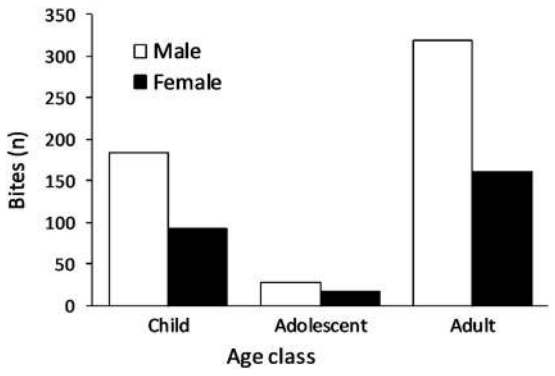

Figure 6. Age class and sex of massasauga bite victims for cases in which both could be determined (n=799).

We found no association between sex and either age class or activity when bitten. This indicates that neither sex was more likely than the other to be bitten at a given age or during any particular activity, in contrast to a previous study.[3] The limited details provided by historical data hindered rigorous demographic analysis. We also cannot discount the possibility of reporting bias, with bites considered more newsworthy if they occurred to certain groups (eg, children) or under unusual or dramatic circumstances (eg, several individuals bitten while in bed or while "killing" a "nest" of massasaugas). It is also possible that changes in cultural or social norms between the early 1800s and early 2000s affected the exposure of different age classes and sexes to the risk of snakebite. For example, it is clear from the reports that people of both sexes and all ages spent a great deal of time outdoors in the early 1800s.

Trends in fatal massasauga bites largely followed the patterns of snakebites overall, with a similar increase into the late 1800s as human population increased and a dramatic decrease into the 1900s. No fatalities due to massasaugas were reported after the 1930s. This decline in fatalities likely coincides with the increasing availability of medical care over that time period and the commercial production of crotaline antivenom beginning in 1927. Adolescents had the lowest fatality rate, which corresponds to a greater susceptibility of very young and old victims.[15,16]

LIMITATIONS

The data on which this study is based were drawn from a wide variety of informal news outlets across more than 2 centuries, often from rural and sparsely populated areas. Many bites likely went unreported to any media outlet, and there was little uniformity in the information included for cases that were reported. For example, we were able to reasonably infer a general age class for most (94%) bite victims, but victim age was only explicitly stated for about a third of cases.

Although many of the trends in massasauga envenomations illustrated here seem reasonable compared to other published snakebite studies,[3,15] fatality data in particular should be interpreted with caution. Reporting bias may again play a role because fatal snakebites will likely always be considered more notable than nonfatal bites. Additionally, a third of all reports did not include the eventual fate of the victim. Even assuming that all of these victims survived, calculated fatality rates from massasaugas in some states were substantially higher than those reported from other developing areas of the world that feature highly venomous species such as mambas, cobras, and vipers and where immediate

medical care was similarly unavailable.[21,22] Fatality rates were also far higher than those from the modern United States, with more robust media reporting.[3] The fatality data presented in this paper are therefore useful for assessing general temporal, geographic, and demographic trends, but specific individual mortality figures (eg, a reported 36% fatality rate in Illinois) should be viewed with caution.

Conclusions

Currently, massasauga snakebites are considered dangerous but are rarely life-threatening or ultimately fatal.[23] Historically, however, massasauga snakebites appear to have been much more common and potentially much more dangerous owing to the unavailability of rapid medical care. Specifically, we found that the number of massasauga bites and bite fatalities increased to a peak in the late 1800s with rising human population and subsequently decreased dramatically into the 1900s. The data herein should be interpreted with caution owing to the nature of popular media reporting and are best used to consider trends rather than quantify actual snakebite statistics. Overall, our results concur with studies finding that most snakebite victims are adult males and that most snakebites are the result of accidental rather than deliberate interaction with a snake.

Author Contributions: Study concept and design (TFB); acquisition of the data (TFB); analysis of the data (DKW, SGB); drafting of the manuscript (DKW); critical revision of the manuscript (DKW, SGB); approval of final manuscript (DKW, SGB, TFB).

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ORIGINAL RESEARCH

No Change in the Use of Antivenom in Copperhead Snakebites in Ohio

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Introduction—Historically, copperhead snake (*Agkistrodon contortrix*) envenomations were not treated with antivenom owing to related adverse events and little benefit. However, recent studies have shown improved outcomes with antivenom use. We hypothesized that the frequency of antivenom use for copperhead envenomation in Ohio has increased as benefits of administration became more widely known.

Methods—All copperhead snakebites reported to the Ohio poison control centers from 2006 through 2016 were compiled. Antivenom use, bite severity, and disposition were abstracted. A nonparametric test for trend was used to evaluate changes over time for the number of patients treated with antivenom and patient disposition. Logistic regression was used to assess the odds of admission vs discharge with antivenom administration, bite severity, age, and sex as independent variables.

Results—Ninety-eight patients reported copperhead snakebites to the poison control centers. The test of trend showed no change in the proportion of patients treated with antivenom by year (P=0.42). There was no difference in the proportion of patients discharged home (P=0.38) per year. Logistic regression showed antivenom use was associated with an odds ratio for admission of 46.7 (95% CI: 7.3–296.4).

Conclusions—The frequency of antivenom use for copperhead bites did not significantly increase between 2006 and 2016. Administration of antivenom was associated with a large increase in the odds of admission to the hospital, even when controlling for bite severity. Further education regarding the benefits and safety of antivenom may increase its use for copperhead snakebites, but may lead to an increase in hospital admissions.

Keywords: toxicology, wilderness medicine, emergency medicine

Introduction

Approximately 5000 to 9000 people in the United States present to an emergency department (ED) each year with snakebites.[1] Copperhead (*Agkistrodon contortrix*) snakes, a member of the family Crotalidae, are one of the more common, resulting in approximately 2000 ED visits in the United States per year.[2] As shown by NatureServe and the International Union for Conservation of Nature from 2007, their range extends throughout Mexico and much of the United States, including the Midwest, Southeast, and Mid-Atlantic (Figure 1). However, despite the frequency of copperhead envenomation, management of these bites remains controversial.[3-8]

Severe crotalid envenomations can result in local tissue destruction, coagulopathy, shock, and death.[9-11] In instances of severe envenomation, the decision to use antivenom is fairly straightforward.[12] However, copperhead snake envenomations rarely cause severe symptoms and are almost never fatal.[10,13,14] Most copperhead envenomations result in only local pain, swelling, and ecchymosis, with rare nausea or paresthesias.[10,13,14] Coagulopathy is often the most concerning symptom of pit viper envenomations.[10,13] However, it is a minor concern with copperheads, because most coagulopathy is not associated with significant

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Figure 1. Distribution map of copperhead snakes (*Agkistrodon contortrix*), courtesy of NatureServe and International Union for Conservation of Nature, 2007.

bleeding.[10,13] Approximately 7% of copperhead bites in patients who present to the ED are dry bites.[15] As a result, copperhead snakebites were not historically treated with antivenom, because the risks of adverse events were thought to be too high.[5,16,17] This was especially true before the release of Crotalidae Polyvalent Immune Fab-Ovine (CroFab, BTG, UK) in 2000.[18] CroFab is a much smaller polyvalent antibody fragment (Fab), with a much lower incidence of allergic reactions and serum sickness than the previously available horse-derived IgG antibody.[19] It is typically dosed from 4 to 6 vials as an initial dose, with repeat doses of 2 vials given every 6 h for 18 h.[20] Vials contain a lyophilized powder with standard minimum mouse LD50 neutralizing units per vial for 4 common pit vipers found in the United States.[20] The powder is first reconstituted and then diluted in normal saline and infused intravenously over 60 min.[20] Hospital admission is often required when administering antivenom for repeat dosing.[20]

Despite the historical reluctance to use antivenom for copperhead bites, recent studies and case reports have shown improved outcomes in copperhead envenomations treated with antivenom, including less morbidity, quicker return to work, and less opiate pain medication use.[21,22] Thus, anecdotally, toxicologists and poison controls centers have become more aggressive with the use of antivenom for copperhead bites.

As part of this change, it has been suggested that bite severity is being inadequately gauged in copperhead bites.[8,23] Bite severity has traditionally been measured with a traditional snakebite severity score, which focuses on systemic symptoms and laboratory analysis to determine the need for antivenom.[23] Bites are graded 0 to 4, with grades of 2 to 4 requiring involvement of systemic symptoms.[23] Given this requirement, some have postulated that traditional snakebite severity scores minimize the symptoms associated with copperhead envenomations, leading to undertreatment.[8] Instead, they have recommended focusing on local effects with a local severity score to better determine the need for antivenom.[8] In this score, bites are graded from 0 to 4, but pain, swelling, ecchymosis, and time of progression determine the grade, with no weight put on systemic effects.[8]

We hypothesized that use of antivenom for copperhead envenomations would increase over time. We also hypothesized that antivenom administration would increase the odds of admission to the hospital when controlling for bite severity.

The primary objective of this study was to describe the use of antivenom for copperhead envenomations over a

Table 1. Clinical and demographic characteristics of patients with copperhead snakebite reported to Ohio poison control centers from 2006 through 2016, stratified by patient disposition from the emergency department

Characteristic		*ED disposition, n=96 (2 missing)*		
	All cases n=98	*Admitted or transferred n=50*	*Home or left AMA n=46*	P-*value (admit vs home)*
Male sex, n (%)	70 (71)	35 (70)	34 (74)	0.42[a]
Age (y), mean±SD	34±20	35±19	32±19	0.43[b]
Antivenom used to treat snakebite patient, n (%)	44 (45)	40 (80)	2 (4)	<0.001*[a]
Antivenom vials per treated patient, mean±SD	n=44 8±5	n=40 8±5	n=2 7±4	0.78[b]
Bite severity (traditional scale), n (%)	n=97	n=50	n=46	<0.001*[a]
None	22 (23)	0 (0)	22 (48)	
Mild	43 (44)	20 (40)	23 (50)	
Moderate	31 (32)	29 (58)	1 (2)	
Life threatening	1 (1)	1 (2)	0 (0)	
Bite severity (local scale), n (%)	n=97	n=50	n=46	<0.001*[a]
Absent/Mild	23 (24)	1 (2)	22 (48)	
Moderate	33 (34)	14 (28)	18 (39)	
Severe/Very severe	41 (42)	35 (70)	6 (13)	
Bite severity (PCC), n (%)	n=89	n=43	n=45	<0.001*[a]
No exposure/No effect	6 (7)	0 (0)	6 (13)	
Minor effect	28 (32)	3 (7)	25 (56)	
Moderate/Major effect	55 (62)	40 (93)	14 (31)	
Disposition from ED, n (%)	n=96	–	–	
Home/AMA	46 (48)	–	–	
Admitted/Transferred	50 (52)	–	–	

AMA, against medical advice.
[a]Fisher exact test.
[b]Student's t-test.
*Denotes significant P values < 0.05.

10-y time frame (2006–2016) in the state of Ohio. Secondary objectives included assessing temporal patterns for the amount of antivenom used per treated bite, changes in disposition over time, bite severity, and contributing factors to disposition from the ED.

Methods

This study was approved by the institutional review board of the University of Cincinnati. The requirement for informed consent was waived by the institutional review board. This study is a retrospective chart review of all copperhead snakebites reported to the Ohio poison control centers (PCCs) from January 1, 2006, through December 31, 2016, for which records were readily available. Patients who were bitten by a snake, with the bite reported to the PCC by the patient, the patient's family, or a medical facility, were identified by searching the PCC medical record. Cases were included if the snake was positively identified as or suspected to be a copperhead snake. Cases were excluded if the snake could not be identified at all or if it was confirmed or suspected to be another species. Paper copies of the PCC medical record were printed, and data were extracted and entered directly into an electronic research database (REDCap).[24]

The primary study outcome was the number of patients who had a copperhead envenomation treated with antivenom per year over the study period. CroFab was the only antivenom used. Secondary outcomes were the amount of antivenom used per treated snakebite, disposition from the ED, bite severity as estimated by the PCC practitioner, and bite severity estimated using both a traditional snakebite severity scale and the local snakebite severity scale.[8,23]

Fisher exact test was used to compare categorical data and Student's t-test to compare continuous variables in bivariate comparisons. A nonparametric test of trend was used to assess the change in the proportion of patients treated with antivenom, the proportion of patients

Table 2. Number of snakebite patients, proportion of patients treated with antivenom, proportion of patients with a disposition home from the emergency department, amount of antivenom per treated patient by year, and bite severity by year

Year	*No. of patients*	*Patients treated with antivenom, n/N (%)*	*Disposition home, n/N (%)*	*Vials of antivenom per treated patient, median (IQR)*	*Severity of bites (local scale), median (IQR)*
2006	11	4/11 (36)	6/10 (60)	10 (7–11)	2 (2–3)
2007	6	2/6 (33)	3/6 (50)	10 (4–16)	2 (1–2)
2008	6	3/6 (50)	2/6 (33)	4 (1–10)	3 (2–3)
2009	10	5/10 (50)	5/9 (56)	7 (4–9)	2 (1–2)
2010	8	5/8 (63)	2/8 (25)	6 (4–14)	3 (2–3)
2011	8	0/8 (0)	7/8 (88)	–	2 (1–2)
2012	17	9/17 (53)	5/17 (29)	6 (4–10)	3 (2–3)
2013	7	2/7 (29)	3/7 (43)	8 (8–8)	2 (1–3)
2014	4	3/4 (75)	0/4 (0)	8 (2–10)	3 (2–3)
2015	11	6/11 (55)	5/11 (45)	6 (4–10)	3 (1–3)
2016	10	5/10 (50)	5/10 (50)	10 (8–10)	3 (2–3)
Test for trend, *P*-value	0.76[a]	0.42[b]	0.38[b]	0.52[c]	0.30[b]

IQR, interquartile range.
[a]Linear regression.
[b]Nonparametric test for trend across ordered group.
[c]Negative binomial regression.

dispositioned home over time, and bite severity over time. Negative binomial regression was used to compare the total amount of antivenom per patient over time, and linear regression was used to examine the number of patients with snakebite reported over time. Multivariable logistic regression was used to identify risk factors associated with ED disposition after snakebite treatment. Model fit (Hosmer-Lemeshow goodness-of-fit test) and calibration (area under the receiver operating characteristic curve) were used to assess the quality of the final model. Data are presented as mean±SD. A *P*-value of ≤0.05 was considered statistically significant. Statistical analyses were conducted using Stata v15.2 (Stata Corp LLC, College Station, TX).

Results

Ninety-eight patients were included in this analysis. Seventy (71%) patients were male, and the age was 34±20 y. Forty-four (45%) patients were treated with antivenom, with 8±5 vials of antivenom used per patient treated. Fifty (52%) patients were admitted to the hospital. Bite severity and additional demographics are described in Table 1.

The proportion of patients treated with antivenom, amount of antivenom used per patient treated, and disposition from the ED did not significantly vary over time (Table 2). There was no change in bite severity over time (Table 2). Admission to the hospital was significantly associated with use of antivenom, as well as increased severity graded by a traditional bite severity scale, a local bite severity scale, and the severity as estimated by PCC (Table 1). Logistic regression revealed that patients treated with antivenom had an adjusted odds ratio for admission of 46.7 (95% CI 7.3–296.4) compared with those not treated. Bite severity as measured by local bite severity scale also increased the odds of admission, with each point increase in bite severity associated with an adjusted odds ratio of admission of 4.6 (95% CI 1.7–12.6; Table 3).

Discussion

Management of copperhead envenomations remains controversial. Historically, providers were concerned

Table 3. Logistic regression for hospital admission as outcome

Outcome=admission (vs disposition home)	*Odds ratio (95% CI)*	
	Crude	*Adjusted*[a]
Characteristics		
Use of antivenom (vs no use)	88.0 (18.1–426.1)	46.7 (7.3–296.4)
Local severity scale (per 1-point increase)	8.1 (3.5–18.9)	4.6 (1.7–12.6)
Age (per y)	1.0 (0.99–1.03)	0.98 (0.94–1.02)
Male (vs female) sex	0.8 (0.3–2.0)	1.5 (0.3–7.2)

[a]Adjusted for all variables listed; Hosmer-Lemeshow goodness of fit: *P*=0.25; area under the receiver operating characteristic curve: 0.951.

about the negative effects of antivenom in the setting of mild envenomation symptoms.[13,17,25] However, recent studies have shown improved outcomes with the use of antivenom. [6,7,13,17,26-29] Despite new evidence showing the benefits of antivenom therapy, the use of antivenom for copperhead snake envenomations did not change in Ohio between 2006 and 2016. There was no increased use of antivenom for all reported patients bitten by copperhead snakes. There was no change in the severity of bites that were discussed with the PCC over the study period, so it is unlikely that patients with less severe envenomation were treated with antivenom over time. Additionally, there was no change in the amount of antivenom used per snakebite treated with antivenom.

Unfortunately, reasoning for the decision of whether to administer antivenom was not available; only information from the PCC was available. Staff and toxicologists at PCCs act in an advisory role, and the final decision rests with providers managing the patients in person. The lack of change over time may reflect the controversial nature of the use of antivenom for copperhead snakebites, or it may reflect a lack of dissemination or integration of newer research. The majority of studies and guidelines promoting or describing aggressive use of antivenom in copperhead bites have been published from 2010 onward, and there have been studies showing lack of benefit in that time frame as well.[3,7,16,21,22,30] Before 2010, most published reports of successful use of antivenom for copperhead envenomations were case reports.[9,31,32] Increased provider education may lead to increased use of antivenom for copperhead bites, which may lead to decreased use of narcotic pain medication and improved return of limb function.

There was no change in ED disposition for patients presenting with copperhead bites, with similar proportions being admitted and discharged year to year. There was no association between disposition and sex, despite some evidence that males have demonstrated better recovery than females from copperhead bites.[33] Both bite severity (by all 3 scales) and use of antivenom were significantly associated with increased odds of hospital. Use of antivenom had the strongest association (ie, higher odds ratio) with admission in the multivariable model that included bite severity. This likely corresponds with the underlying concern about adverse events, such as anaphylaxis, which may require intervention, or the need for additional doses of antivenom should symptoms recrudesce. It is also possible that the severity of the bite does not capture the anticipated clinical course and need for antivenom, as the severity of bite did not have as strong an association with admission to the hospital as use of antivenom. If less severe bites are treated with antivenom, this may lead to an increase in hospital admission and possibly increased cost for these patients.[34] This is relevant in the setting of increasing concerns about healthcare costs and emergency department boarding.[35,36]

Future studies should evaluate antivenom use across the United States as more studies are published and the current studies become more disseminated into standard emergency medicine and toxicology practice.

LIMITATIONS

The data collected represent a 10-y period that ended in December 2016, and more studies recommending the use of antivenom for copperhead bites have been published since. These data represent a single state and may not reflect nationwide practice patterns. Grading for severity of bites was performed by staff at PCCs, and no standard grading system was used for the grading. Outcomes other than ED disposition were not available. Potential dry bites were not excluded because it was impossible to definitively determine which bites were dry. However, these were included across all years and are thus unlikely to introduce systemic bias. Suspected copperhead bites were included because definitive identification by a provider significantly limited the number of envenomations. However, these suspected copperhead envenomations were managed by PCCs and providers as if they were confirmed copperhead bites. It was also believed that including suspected bites would accurately reflect clinical practice, where definitive identification of a snake is usually unavailable. Additionally, the only other venomous snakes in Ohio are rattlesnakes, which are unlikely to be confused with copperheads.[37] Finally, this is a retrospective study that cannot establish cause and effect, and we cannot rule out the effect of unknown or unstudied confounders or sources of bias.

Conclusions

We did not detect any significant changes in the proportion of copperhead snakebites treated with antivenom or amount of antivenom used in the state of Ohio over the years 2006 through 2016. Use of antivenom was associated with increased odds of hospital admission after treatment in the ED. Increased provider education may lead to increased use of antivenom for copperhead bites, which may lead to an increase in hospital admission.

The work described in this manuscript was presented as a lightning oral abstract presentation at the virtual Society of Academic Emergency Medicine annual meeting, May 12–15, 2020 (meeting was scheduled to be in Denver, CO, but transitioned to virtual format due to COVID-19).

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ORIGINAL RESEARCH

Survey of Musculoskeletal Injuries, Prehike Conditioning, and On-Trail Injury Prevention Strategies Self-Reported by Long-Distance Hikers on the Appalachian Trail

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Introduction—Studies show that 40 to 60% of long-distance hikers on the Appalachian Trail experience musculoskeletal (MSK) injuries, but these studies are over a decade old. The increasing popularity of hiking and injury prevention advances warrant re-evaluation of injury patterns. We sought to determine the frequency of self-reported MSK injuries in long-distance hikers on the Appalachian Trail and associations with prehike conditioning and on-trail injury prevention strategies.

Methods—The Appalachian Trail Conservancy surveys registered hikers annually. Our orthopedic team added 10 questions specific to MSK injury, training, and equipment to the 2018 to 2019 electronic, cross-sectional Appalachian Trail Conservancy survey. Descriptive statistics and frequencies were calculated. Categorical variables were compared using χ^2 analysis. Correlations were performed for associations between training and gear and MSK injury. Logistic regression assessed the effect of training on MSK injury. Statistical significance was set at $P<0.05$.

Results—Of 1295 respondents (52% response rate), 61% (n=791) reported MSK complaints; 28% (n=363) reported overuse/chronic MSK injuries, and 18% (n=238) reported acute injuries. MSK complaints resulted in 11% (n=147) stopping their hike. Respondents who did not train (13%, n=168) were significantly more likely to report an MSK injury (odds ratio 2.82; 95% CI 1.92–4.24; $P<0.001$). Strength training, stretch/yoga, and endurance training were associated with less injury (all $P<0.001$). Stabilizing footwear and poles/sticks were associated with fewer MSK complaints (all $P<0.001$).

Conclusions—Prehike training and hiking gear correlate with fewer injuries. Further research is warranted to elucidate whether promoting injury prevention strategies can reduce MSK injuries among long-distance hikers.

Keywords: endurance activity, backpacking, mountaineering, hiking, overuse injuries, training, gear

Introduction

Musculoskeletal (MSK) conditions affect 20 to 30% of people worldwide and are the main contributors to disability.[1] In the United States, MSK injuries account for more than 1.7 million hospitalizations, 23 million emergency or outpatient visits, and 40 million physician office visits per year.[2] Identifying injury patterns and prevention strategies in recreational activities with high MSK injury rates provides background data for the creation of injury prevention programs.

Hiking is the fourth most popular outdoor activity in the United States.[3] The activity is increasing in popularity, with 45 million people participating in hiking in 2017, up from 32 million in 2008.[3,4] MSK injuries are common among long-distance hikers, a subset of the hiking population. An example of a long-distance hike is attempting to complete the Appalachian Trail (AT), which runs from Georgia to Maine, covering approximately 3540 km (2200 mi) with a total elevation gain/loss of over 141,580 m (464,500 ft). To complete the trail in 1 season, an average AT hiker will backpack 13 to 32 km (8–20 mi) per day over 5 to 7 mo.

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Table 1. Survey questions from the ATC annual survey with absolute count and relative frequency of cases (%) using respondents per question as denominator

Questions	*Absolute count* (*n*)	*Relative frequency* (%)
"How would you describe your 2018 AT hike?" (n=1259)		
Northbound starting in Georgia	815	65
Southbound starting in Maine	114	9
Flip-flop starting in Harpers Ferry	93	7
Flip-flop starting in Georgia	59	5
Other	178	14
"When did you start your 2018 AT hike?" (n=1154)		
January	11	1
February	135	12
March	435	38
April	311	27
May	99	9
June	82	7
July	41	4
August	22	2
September	11	1
October	5	<1
November	2	<1
December	0	0
"Did you complete your 2018 AT hike?" (n=1188)		
Yes	724	61
No	464	39
"How many zero days did you take during your 2018 AT hike?" (n=449)		
0	35	8
1–5	141	31
6–10	93	21
11–15	73	16
16–20	39	9
21–25	22	5
26–30	21	5
31–35	4	1
36 or more	21	5
"Would you be willing to answer 9 additional questions about injuries during your AT hike?" (n=1033)		
Yes	949	92
No	84	8
"Did you have any of the following specific illnesses/injuries while on the AT?" (n=923)		
Cuts/Scrapes	560	61
Blisters	541	59
Knee injury/pain	421	46
Foot pain including plantar fasciitis	373	40
Dehydration	178	19
Diarrhea/Vomiting	154	17
Ankle sprain	133	14
Achilles tendon pain	122	13

(continued on next page)

Table 1 *(continued)*

Questions	*Absolute count*	*Relative frequency*
	(n)	*(%)*
Shin splints	115	12
Iliotibial band syndrome	86	9
Hypothermia/Hyperthermia	62	7
Muscle tear	53	6
Stress fracture, lower extremity	35	4
Concussion/Head injury	23	3
Lyme disease	23	3
Broken bone, lower extremity	20	2
Broken bone, upper extremity	7	1
Stress fracture, upper extremity	2	<1
Other	249	27
"If you did not complete your 2018 AT hike, what was the main reason?" (n=404)		
Injury	114	28
Family concerns	45	11
Mental fatigue/Lost interest	34	8
Illness	22	5
Weather	21	5
Time	17	4
Ran out of money	11	3
Partner couldn't finish	7	2
Loneliness	5	1
Too difficult	2	<1
Other (please specify)	126	31
"Is there one body part injury or illness that was a deciding factor for you stopping during your 2018 AT hike?" (n=682)		
No, I did not stop due to an injury	456	67
Knee	53	8
Foot	44	6
Ankle	27	4
Back	11	2
Lower leg (calf/shin)	9	1
Hip/Thigh	9	1
Shoulder	7	1
Head	2	0
Neck	1	0
Wrist/Hand	1	0
Face	0	0
Elbow	0	0
Other (please specify)	62	9
"How long did it take you to seek treatment for your injury or illness?" (n=838)		
1 d	88	11
2–3 d	135	16
5–7 d	63	8
1–2 wk	48	6
1 mo	22	3
>1 mo	28	3
I did not seek treatment	395	47
Other (please specify)	59	7

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Table 1 *(continued)*

Questions	*Absolute count* (*n*)	*Relative frequency* (%)
"How much time did you take off from your AT hike due to the injury or illness?" (n=882)		
1 d	88	10
2–3 d	171	19
5–7 d	100	11
1–2 wk	69	8
1 mo	24	3
>1 mo	51	6
I did not take any time off from my AT hike	283	32
Other (please specify)	96	11
"How long did it take your 2018 AT injury or illness to heal?" (n=825)		
1 d	35	4
2–3 d	131	16
5–7 d	105	13
1–2 wk	127	15
1 mo	87	11
>1 mo	171	21
It did not heal	59	7
Other (please specify)	119	13
"What's the longest distance on your 2018 AT hike you completed before the injury?" (n=784)		
0–16 km (0–10 mi)	28	4
17–80 km (11–50 mi)	139	18
81–160 km (51–100 mi)	97	12
162–804 km (101–500 mi)	196	25
>805 km (>501 mi)	324	41
"How did you train prior to starting your 2018 AT hike?" (n=934)		
I walked/hiked regularly near my home	461	49
I walked/hiked regularly near my home with a pack weight similar to what I carried on the AT	361	39
I did strength training	300	32
I did endurance training	296	32
I did stretch/yoga exercises	247	26
I hiked 40–160 km (25–100 mi) in 1 backpacking trip	213	23
I did not train for my AT hike	150	16
I never hiked more than 16 km (10 mi) at a time	87	9
I've completed trails that were more than 804 km (500 mi) long	48	5
Other (please specify)	105	11
"Please check what type of stability equipment you used on your AT hike" (n=936)		
Trekking poles or walking stick	843	90
Running or trail shoes	699	75
Hiking boots	310	33
Knee brace	261	28
Ankle brace	51	5
Traction system (for ice, etc.)	30	3
Other type of footwear or stability equipment (please specify)	77	8

AT, Appalachian Trail; ATC, Appalachian Trail Conservancy.

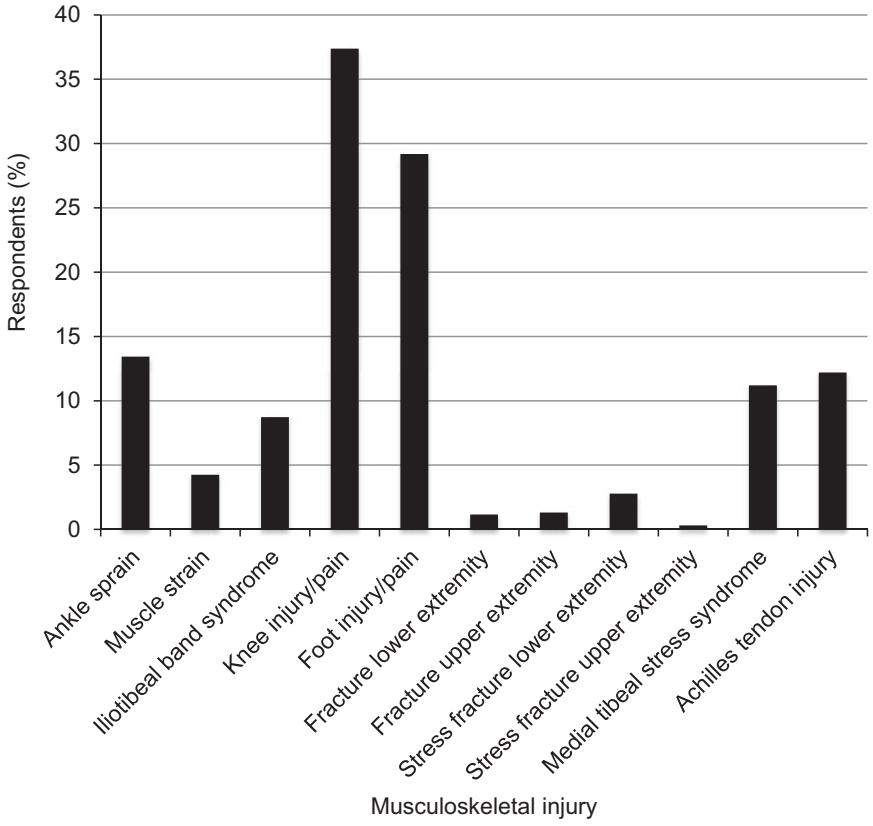

Figure 1. Musculoskeletal complaints reported by respondents.

Previous studies have attempted to evaluate injuries in this population. A survey of 180 long-distance hikers during the 1987 to 1988 AT hiking season found 62% of hikers reported extremity or joint pain.[5] Another study surveyed 280 participants who hiked along the AT for at least 7 d (duration of hike: 140±60 [mean±SD] d) in 1997.[6] Among these hikers, acute and overuse MSK complaints were reported by 43% and were the most common cause for discontinuing the hike. In 2006, a survey evaluated the effects of ultralight backpacking and less rigid footwear in 128 long-distance hikers, hypothesizing that improvement in hiking gear may have decreased MSK injury rates over the years.[7] MSK complaints were reported in 42% of participants.

Although these studies show a pattern of MSK injuries in long-distance hikers, the studies are over than a decade old and have limited sample sizes. Given advances in hiking gear and training knowledge, as well as a large increase in the numbers of hikers, recent MSK injury patterns may differ from those previously reported. The goal of this study was to determine the frequency of self-reported types of MSK injury among long-distance hikers on the AT and their association with prehike conditioning, stabilization gear, and recovery days. In addition, we assessed on-trail strategies such as hiking patterns—some hikers consider a northbound route on the AT a strategy for on-trail training by hiking flat lands before reaching higher elevations. As an exploratory survey, the objective was to ascertain a more current picture of MSK injuries and injury prevention strategies reported by AT long-distance hikers.

Methods

This was a cross-sectional electronic survey of AT long-distance hikers in the 2018 to 2019 season. Long-distance hikers on the AT have a choice to voluntarily register with the Appalachian Trail Conservancy (ATC) at the beginning of the hiking season. At the end of every season, the ATC emails a survey using SurveyMonkey Inc. to all registered hikers. The yearly survey created by the ATC includes questions about trail specifics such as hiking patterns, amenities, security, and trail crowding.

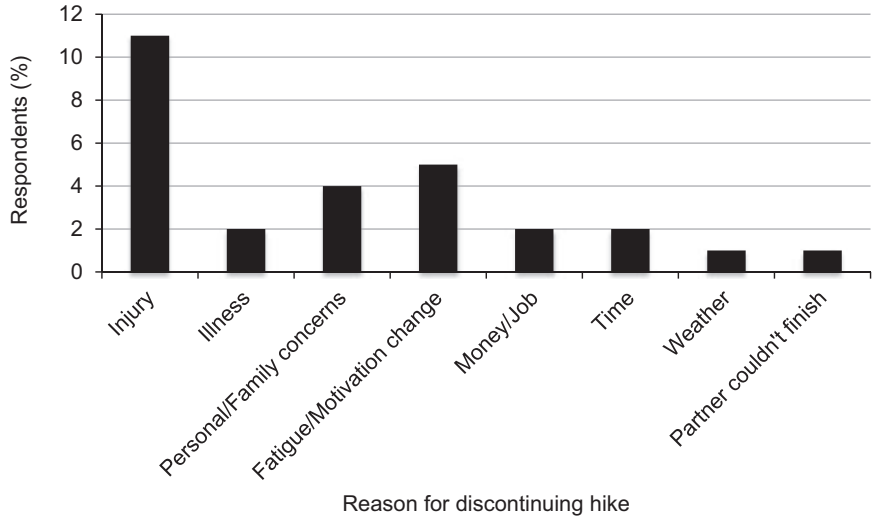

Figure 2. Top reasons reported by respondents for discontinuing the hike early among those surveyed who did not complete their planned hike.

Our orthopedic team added 10 questions specific to training and injury to the ATC yearly survey. We did not have input on the rest of the yearly survey. Participants answered a total of 57 questions. From the final survey, 15 questions were analyzed for this study (10 that were added and 5 that were part of the original ATC survey). The added questions can be found in Table 1. The remaining 42 questions were specific to trail conditions and amenities rather than hikers and were not used for this research. This study was deemed exempt by the Thomas Jefferson University institutional review board.

The nonvalidated survey included structured and semistructured questions. Questions were not pretested. All registered long-distance hikers during the 2018 to 2019 AT hiking season were included in the study and contacted by the ATC through email for possible participation in the survey. Our research team did not have direct access to the hikers per the agreement with the ATC for the intent of preserving hiker confidentiality. Long-distance hikers on the AT who did not register with the ATC were excluded from the study. The survey invitation was sent once by email using the registered account information. There were no reminders or follow-up contact. The surveys were distributed electronically by the ATC in January 2019, coinciding with the ending of the hiking season. Survey results were collected by the ATC through the end of April to allow adequate time for response. Upon completion of the collection period, the ATC forwarded deidentified data to our orthopedic team for the purpose of analysis. No data were provided on the nonresponse group. Basic demographic information, such as age, sex, and body mass index, was not included.

Descriptive statistics and measures of frequencies are reported. Percentages were calculated from the number of the research cohort. All responses that were listed under "other, please specify" were reviewed by an orthopedic provider to determine MSK category. Those injuries that

Table 2. Descriptive table comparing those who reported prehike training to those who reported not doing any prehike training

	Prehike training	*No prehike training*	*P value*[a]
	n=1127	*n=168*	
	n (%)	*n (%)*	
Direction			0.553
Northbound	785 (73)	124 (75)	
Southbound	121 (11)	21 (13)	
Alternating	169 (16)	21 (13)	
Any MSK injury	657 (58)	134 (80)	<0.001
No. of MSK injuries			<0.001
None	470 (42)	34 (20)	
1	276 (25)	54 (32)	
2	209 (19)	37 (22)	
3	116 (10)	25 (15)	
4	36 (3)	12 (7)	
5	13 (1)	4 (2)	
6	7 (0.6)	2 (1)	
Overuse/Chronic injury	293 (26)	70 (42)	<0.001
Traumatic/Acute injury	198 (18)	40 (24)	0.066

MSK, musculoskeletal.
[a]Significant at $P<0.05$.

Table 3. Musculoskeletal injuries associated with having to discontinue the hike

Variable	*P value*[a]
Prehike training	
Previous hiking experience	<0.001
Strength training	<0.001
Stretch/Yoga	<0.001
Endurance training	<0.001
Hiking gear	
Running/Trail shoes	<0.001
Trekking poles/Hiking stick	<0.001
Traction system	0.007
Hiking boots	<0.001

[a]Significant at $P<0.05$.

did not fall under MSK injury (eg, vitreous detachment) were not used for calculations. Pearson χ^2 analysis was used to compare categorical variables. Simple logistic regression was performed to determine the effect of prehike training on having an MSK injury. Statistical significance was set at $P<0.05$. All statistical analyses were done using R Studio (Version 3.6.3, Vienna, Austria).

Results

A total of 2507 people registered as long-distance hikers on the AT in the 2018 to 2019 hiking season and were emailed an invitation to participate in the survey. Of those contacted, 1295 respondents completed the survey (52% response rate).

The majority of respondent start times coincided with the traditional start of the hiking season for the AT, which is February, March, and April. More respondents (70%, n=909) hiked a northbound route than hiked a southbound route (11%, n=142). Some backpacked different parts of the trail out of sequence, traveling both northbound and southbound during their hike (15%, n=190). There was no between-group difference in injury rate based on direction of hike ($P=0.580$).

When asked about what experience they had with hiking, 89% (n=1148) reported they had never attempted or completed a trip of similar length or duration, 6% (n=71) reported they had never hiked more than 16 km (10 mi) at a time, 13% (n=170) reported they had hiked 40 to 161 km (25–100 mi) in 1 backpacking trip, and 2% (n=28) reported they had completed a trail that was more than 805 km (500 mi) long before this hike.

In response to questions about training regimen, 13% (n=168) reported they did not train before starting the hike. Less than one-third of participants reported doing strength training (26%, n=338), stretch/yoga (19%, n=249), or endurance training (26%, n=338).

During a long-distance hike, backpackers can use "zero days" for recovery; they do not log any mileage on those days. When asked how many zero days each hiker took, 10% (n=123) reported none, 13% (n=173) reported 1 to 5 d, 15%, (n=192) reported 6 to 15 d, 2% (n=19) reported 16 to 30 d, and 3% (n=33) reported more than 30 d.

When asked about the type of stability equipment they used on the hike, 58% (n=749) had running or trail shoes, 24% (n=305) had hiking boots, 70% (n=902) had trekking poles or a walking stick, 20% (n=263) had a knee brace, 7% (n=90) had an ankle brace, and 3% (n=34) had a traction system for ice or other difficult terrain.

Knee injury/pain was reported by 37% (n=483) of respondents, and foot injury/pain was reported by 29% (n=374). Among other specific self-reported MSK injuries were ankle sprains (13%, n=174), medial tibial stress syndrome (11%, n=145), Achilles tendon injury/pain (12%, n=156), and IT band syndrome (9%, n=114) (Figure 1).

When asked if they completed their planned hike, 55% (n=708) were successful and 42% (n=546) had to stop before completion. Injury was listed as the primary reason for discontinuing the hike for 11% (n=147) of participants (Figure 2).

When asked how long they took to seek treatment, 33% (n=430) did not seek treatment, 22% (n=289) sought treatment within 1 wk of the injury, 4% (n=53) sought treatment within 2 to 4 wk of the injury, 4% (n=53) sought treatment within 2 to 4 mo of the injury, and <1% (n=1) sought treatment after waiting more than 4 mo. When asked how long the injury took to heal from the onset of symptoms, 20% (n=263) reported less than 1 wk, 9% (n=118) reported 2 to 4 wk, 23% (n=294) reported greater than 1 mo, and 8% (n=109) reported it had not healed at the time of the survey. There were 26% (n=337) of respondents who reported they did not take any time off from hiking on the trail for an injury.

Table 4. Musculoskeletal injuries associated with having to discontinue the hike

Variable	*P value*[a]
Achilles tendon injury/pain	0.02
Ankle sprain	0.01
Foot injury/pain	<0.001
Iliotibial band syndrome	0.049
Knee injury/pain	<0.001
Shin splints	0.03

[a]Significant at $P<0.05$.

Hikers were asked to determine the longest total distance they completed before experiencing an injury. Of those surveyed, 3% (n=44) reported an injury in the first 0 to 16 km (0−10 mi), 13% (n=174) reported 18 to 80 km (11−50 mi), 6% (n=81) reported 82 to 161 km (51−100 mi), 16% (n=210) reported 163 to 805 km (101−500 mi), and 24% (n=312) reported completing greater than 805 km (>500 mi) before the injury.

Respondents who stated they did not train before the hike were more likely to report an MSK injury (80% vs 58%, $P<0.001$), an overuse/chronic injury (42% vs 26%, $P<0.001$), medial tibial stress syndrome (17 vs 10%, $P=0.011$), a lower extremity stress fracture (5 vs 2, $P=0.036$), or Achilles tendon pain/injury (18 vs 11%, $P=0.019$) (Table 2). They were more likely to report knee injury/pain (51 vs 35%, $P<0.001$) and foot injury/pain (38 vs 28, $P=0.006$). They were also more likely to report multiple injuries ($P<0.001$) (Table 2). Regression showed that respondents who did not train had greater odds of an MSK injury (odds ratio 2.82, 95% CI 1.92−4.24) that reached statistical significance ($P<0.001$).

Correlations revealed that strength, stretch/yoga, and endurance training were associated with avoiding injury (all $P<0.001$). Stabilizing gear such as running shoes/trail shoes/hiking boots and trekking poles/hiking sticks were associated with less injury (all $P<0.002$) (Table 3). Specific injury types were correlated with a respondent discontinuing a hike early, including Achilles tendon injury/pain ($P=0.02$), ankle sprains ($P=0.01$), IT band syndrome ($P=0.049$), and medial tibial stress syndrome ($P=0.03$) (Table 4).

Questions used for the survey with response rates, absolute, and relative frequency using respondents per question as the denominator can be found in Table 1. Final calculations were completed after "other, please specify" categories were screened.

Discussion

Our research provided current data on self-reported MSK injuries in long-distance hikers on the AT and found an inverse relationship between prehike training and MSK injury. Identifying injury patterns and prevention strategies in recreational activities helps in the development of injury prevention programs, and this survey served as an initial step in that process.

In our study, knee injury/pain was reported by over one-third of respondents and was the most commonly reported site of MSK pain. Although earlier studies did not isolate complaints related to the knee, 1 study found that 43% of hikers reported acute joint pain, and another found 44% of long-distance hikers reported knee/ankle pain.[5,6] Research evaluating lower limb kinematics and kinetic changes in participants carrying loads for prolonged periods of time found fatigue in the quadriceps muscles.[8] The fatigued muscles then were unable to effectively absorb impact forces, leaving the participants at increased risk of knee injury. This finding may explain the high rate of knee pain in long-distance hikers and could present an opportunity for injury prevention training in the form of muscle strengthening. Because of the way the survey question was worded, we were unable to decipher whether the knee pain was due to acute injury, overuse injury, or exacerbation of a chronic condition, such as pre-existing osteoarthritis. Future work should delineate the causes of the reported knee pain to help determine possible prevention strategies.

When participants reported specific MSK injuries rather than generic joint pain, overuse MSK complaints represented the largest category, with 28% (n=363) of participants reporting medial tibial stress syndrome, Achilles tendonitis, iliotibial band syndrome, or stress fractures. Overuse MSK injuries result from repetitive microtraumas resulting in breakdown in tendons and bone.[9] During tendon healing, fatigued tendons under repetitive stress lose the ability to repair, resulting in weakened collagen cross-linking and disruption of tendon vasculature.[10] Similarly, if microdamage accumulates faster than bone remodeling can occur, bone stress and eventual fracture results. Both intrinsic and extrinsic factors have been linked to MSK overuse injuries. Intrinsic factors include muscle weakness, malalignments, and inflexibility.[9] Extrinsic factors include "training errors" such as large changes in activity duration or frequency.[9,11] Walking more than 32 km (20 mi) per week has also been found to be a strong predictor of MSK overuse injuries, placing long-distance hikers at risk.[12] Acute injuries were less commonly reported than overuse injuries, with 18% (n=238) of respondents noting ankle sprains, muscle tears, or a traumatic fracture. These results suggest overuse MSK injuries of the lower extremity may be an appropriate target for injury prevention programs and could include muscle strengthening, flexibility training, and graduated activity development.

Previous studies did not find a correlation between prehike conditioning and injury rates in long-distance hikers, which contradicts our results.[5,13,14] This difference may be a result of construct definition. For example, in 1 study, prehike conditioning was defined as performing hard physical activity for 4 $h \cdot wk^{-1}$.[13] Defining this construct differently in terms of hours of training or types of training may yield different results. Our survey asked participants about previous hiking distances and cross-training history. We chose these definitions because building stamina and using multimodal approaches to

fitness are linked to MSK injury prevention in other recreational activities. Few of our respondents had hiked over 805 km (>500 mi) in 1 trip before this attempt, and less than one-third had added strength, stretch, or endurance into their training regimen. Each of these types of prehike training was associated with lower MSK injury, suggesting that further research needs to explore both how to define prehike conditioning as well as how different prehike training regimens affect MSK injuries. Although we were unable to assess optimal prehike training regimens, we were able to find a correlation between prehike training and reduced MSK injury.

Recovery days may also be useful to prevent or lessen the impact of overuse MSK injuries such as tendinopathies and bone-stress reactions. Once acquired, excessive loading and insufficient recovery can lead to a failed healing response in these injuries. Currently, there is no clear consensus in the literature on the optimal quantity or frequency of recovery days in long-distance hiking or their ability to prevent overuse injuries in hikers. However, relative rest is a treatment strategy and therefore an important concept in MSK injury prevention and treatment programs.[9] We attempted to assess how long-distance hikers use recovery days. However, we had a high item nonresponse rate (58%, n=755) to the question about zero days, making it difficult to assess their use in our study population. It is possible the terminology "zero days" was not as widely accepted as believed at the start of the study, and therefore the question will need to be reassessed before future surveys.

Specialized gear may play a role in injury prevention. Studies on the effectiveness of footwear choice to decrease MSK injuries among long-distance hikers have been inconclusive, but use of hiking boots or trail shoes correlated with lower MSK injury when compared to participants who did not report using either of these shoe types (ie, those who reported wearing sandals) in our study.[7] Trekking poles have been shown to improve balance while carrying a load and to reduce muscle activity around the lower extremity joint on downhill grades.[15,16] They were widely carried by the respondents and were associated with lower MSK injury in our study, which agrees with previously reported results. Previous studies did not address joint braces for stability. About 27% of our study population carried a knee or ankle brace, suggesting the possibility of pre-existing medical conditions in the joints. We had not anticipated that possibility. An additional survey question will need to be added to future studies to help decipher pre-existing conditions when long-distance hikers are surveyed for this purpose. We will also need to expand the medical conditions lists to include such MSK complaints as osteoarthritis because it may have accounted for otherwise unspecified joint pain found in this population.

Less than 25% of participants sought medical treatment within 7 d of an injury. It is unclear whether the injuries were not substantial enough to warrant treatment, whether medical care was not available, or whether the hikers chose not to seek treatment despite the level of injury. However, 8% of those injured on the trail reported that the injury had not healed at the time of the survey, suggesting some injuries occurring on the trail result in MSK complaints that transition to chronic in definition.

LIMITATIONS

This study has several limitations. Only using long-distance hikers who registered with the ATC may have introduced selection bias. For example, more experienced hikers who were not interested in being recognized or less experienced hikers who were not aware of the registration process may have been excluded. The limited response rate (52%) may have created bias because those who responded may not adequately reflect the target population.

Another limitation is the use of self-reported injuries. Although diagnosis by a medical provider may have provided information that is more accurate, the hikers determined that not all of the injuries required medical attention or they chose not to seek care. Relying on hikers to self-report injuries provided insight into their MSK injuries, but it created the potential for inaccurate reporting. Recall bias may have also influenced results because participants were given the questionnaire at the end of the hiking season.

In addition, the questions in the survey were untested. They may not have collected the information as intended or they may have introduced surrogate information bias (forcing respondents to choose from a list of options). By adding "other, please specify," we attempted to decrease this bias and give participants an opportunity to generate their own answers. Item nonresponse was an issue and may have led to biased estimates. It may have partly been a result of question design, such as in the example of using the terminology "zero days", which may not have been as widely used by hikers as believed during study design. Unmeasured confounding may have also influenced results, including creating a barrier to determine how basic demographics such as age, sex, and body mass index influenced outcomes. We were unable to establish optimal descriptive statistics and correlations across data owing to limited, untested questions and lack of demographic information.

Conclusions

Among multiple MSK injuries reported, overuse/chronic injuries were reported more frequently than acute MSK injuries in long-distance hikers who responded to this survey. Although prehike training strategies, utilization of stabilization gear, and use of recovery days varied among respondents, those who reported that they did not train before the hike were more likely to have an MSK injury, whereas those who used stabilizing footwear and aids were less likely to do so. Further research is needed to understand whether prehike conditioning and on-trail strategies can decrease MSK injuries in the AT long-distance hiking population.

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ORIGINAL RESEARCH

Differentiating Sources of Fecal Contamination to Wilderness Waters Using Droplet Digital PCR and Fecal Indicator Bacteria Methods

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Introduction—Human activity in wilderness areas has the potential to affect aquatic ecosystems, including through the introduction of microorganisms associated with fecal contamination. We examined fecal microorganism contamination in water sources (lake outlets, snowmelt streams) in the popular Absaroka Beartooth Wilderness in the United States. Although the region is remote, increasing human visitation has the potential to negatively affect water quality, with particular concern about human-derived microorganism fecal contaminants.

Methods—We used standard fecal indicator bacterial assays that quantified total coliform bacteria and *Escherichia coli* concentrations, together with more specific polymerase chain reaction-based microbial assays that identified possible human sources of fecal microorganisms in these waters.

Results—Total coliforms were detected at all lake outlets (21 of 21 sites), and *E coli* was detected at 11 of 21 sites. Droplet digital polymerase chain reaction assays revealed the presence of human feces-derived microorganisms, albeit at abundances below the limit of detection (<10 gene copies per milliliter of water) at all but 1 of the sampling sites.

Conclusions—Our results suggest low prevalence of water-borne pathogens (specifically *E coli* and human-derived *Bacteroides*) in this popular wilderness area. However, widespread detection of total coliforms, *Bacteroides*, and *E coli* highlight the importance of purifying water sources in wilderness areas before consumption. Specific sources of total coliforms and *E coli* in these waters remain unknown but could derive from wild or domesticated animals that inhabit or visit the Absaroka Beartooth Wilderness. Hence, although contamination by human fecal microorganisms appears minimal, human visitation could indirectly influence fecal contamination through domesticated animals.

Keywords: microbial source tracking, water quality, Absaroka Beartooth Wilderness, visitor impacts, environmental management, wilderness character

Introduction

Designated wilderness areas in the United States are unique in that there are restrictions on permanent facilities to manage visitor impacts and human waste.[1] However, human visitation to these areas continues to increase,[2] creating challenges for managers seeking to minimize impacts of human activities on wilderness natural resources.[2-4] In particular, fecal contamination of wilderness water sources presents a growing problem, requiring managers to identify areas of potential contamination to protect public health.[5] Outbreaks of illnesses associated with fecal bacteria (eg, diarrhea) have been documented in congested recreational sites in wilderness areas,[6,7] with possible sources of fecal contaminants including livestock, dogs, wild animals, and humans.

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Fecal indicator bacteria (FIB) assays are often used to identify the presence of total coliform bacteria, fecal coliforms, and *Escherichia coli* in aquatic ecosystems.[8] Coliform bacteria can be introduced from various sources, and although the occurrence of *E coli* is frequently attributed to fecal contamination, many strains of *E coli* are not pathogenic and are not associated with feces.[8] Moreover, standard FIB tests do not discriminate among the potential sources (eg, wildlife or human) of these microorganisms. Therefore, increasingly, DNA and polymerase chain reaction (PCR)-based methods are used to aid microbial source tracking (MST), linking microbial pathogens to specific host sources.[9-12]

Bacteria belonging to the phylum Bacteroidetes are often used as targets in MST assays because of source specificity to mammalian guts and feces.[12-15] Members of *Bacteroides* can comprise upwards of 26 to 36% of the gut microbiota,[16,17] and several *Bacteroides* genetic markers have been developed and successfully applied in PCR assays targeting humans, cattle, pigs, and horses.[9,10,12,13,18-20]

Our study focused on potential fecal contamination of waters in the Absaroka Beartooth Wilderness (ABW) in south central Montana. The ABW is a mountainous wilderness area northeast of Yellowstone National Park. The region ranges in elevation from approximately 1.6 km to over 4.1 km and contains a network of subalpine forests and alpine tundra. With over 1100 km of trails, the area receives high recreational use, including backpacking and stock packing, but no livestock grazing. Most human visitation is concentrated around lakes and at water sources near popular summits. Backcountry campsites are required to be >60 m from lakeshores, and popular campsite locations have been cataloged in a geospatial database maintained by the US Forest Service for over 20 y. We sought to examine the occurrence of total coliform and *E coli* in ABW water sources adjacent to backcountry camping areas and use MST methods to quantify members of *Bacteroides* derived from human feces.

Methods

STUDY AREA AND SAMPLING SITES

We selected a total of 23 sampling locations within the ABW (21 remote alpine lake outlets and 2 snowmelt streams) using geospatial information on campsite condition and popular recreational sites. Sampling sites were identified using ArcMap (version 10.5.1), overlaying campsite point locations with a wilderness-wide opportunity class layer representing 3 zones of recreational use: 1) pristine, 2) primitive, and 3) transition zones. Pristine zones were those with negligible anthropogenic influence, primitive zones were those with measurable anthropogenic influence, and transition zones were those where human impacts were moderate to substantial. All of our sampling was done within the transition zone, between 4.5 and 24 km from main trailheads (Figure 1).

WATER SAMPLING, FIB DETECTION, AND DNA EXTRACTION

Water samples from 21 different alpine lake outlets and 2 snowmelt streams were collected in triplicate over 13 d in July and August 2018 (Table 1). Water samples were placed into sterilized 250-mL polypropylene bottles and transported to the laboratory in the dark and on ice. In the laboratory, samples were stored at 4°C until processing (within 48 h of sample collection). Two 100-mL aliquots of sample water from each of the triplicate 250-mL sample bottles were vacuum filtered onto separate 47-mm diameter, 0.45-µm pore size (mixed cellulous ester) gridded, pre-sterilized filters (Millipore Sigma**,** Burlington, MA). One of these filters was used for total coliforms and *E coli* analyses, and the other filter was used for subsequent extraction of DNA. No filter was processed for DNA from Sylvan Lake, and only filters for subsequent extraction of DNA were collected from the 2 snowmelt streams.

Filters for FIB analyses were placed in M-ColiBlue24 broth petri dishes and incubated at 35°C for 24 h (Millipore Sigma). Colony-forming units (CFUs) were quantified by counting and recording the number of red (non-*E coli* coliforms) and blue (*E coli* coliforms) plate-forming colonies. Total coliforms were calculated as the sum of red and blue colonies.

DNA was extracted from filters using the MasterPure DNA Purification kit (Lucigen Corporation, Middleton, WI). Triplicate blank filters (ie, no sample filtered onto them) were processed alongside samples. Filters were transferred from 15-mL centrifuge tubes to 2-mL microcentrifuge tubes containing 600 µL of a cell lysis solution and 100 µL of 0.1-mm and 100 µL of 0.5-mm glass beads. The tubes containing filters were frozen at -80°C, thawed, and placed into a mechanical bead beater for 2 min, followed by the addition of proteinase-K (50 $\mu g \cdot \mu L^{-1}$ final concentration). Samples were incubated at 65°C for 15 min and placed on ice for 3 to 5 min, and DNA was extracted following the MasterPure DNA Purification kit protocols. DNA was resuspended in 100 µL of nuclease-free water and stored at -80°C.

DROPLET DIGITAL PCR FOR DETECTION OF UNIVERSAL AND HUMAN-SPECIFIC BACTEROIDES GENE MARKERS

We used 2 different droplet digital PCR (ddPCR) assays: one targeting bacteria belonging to the genus *Bacteroides*

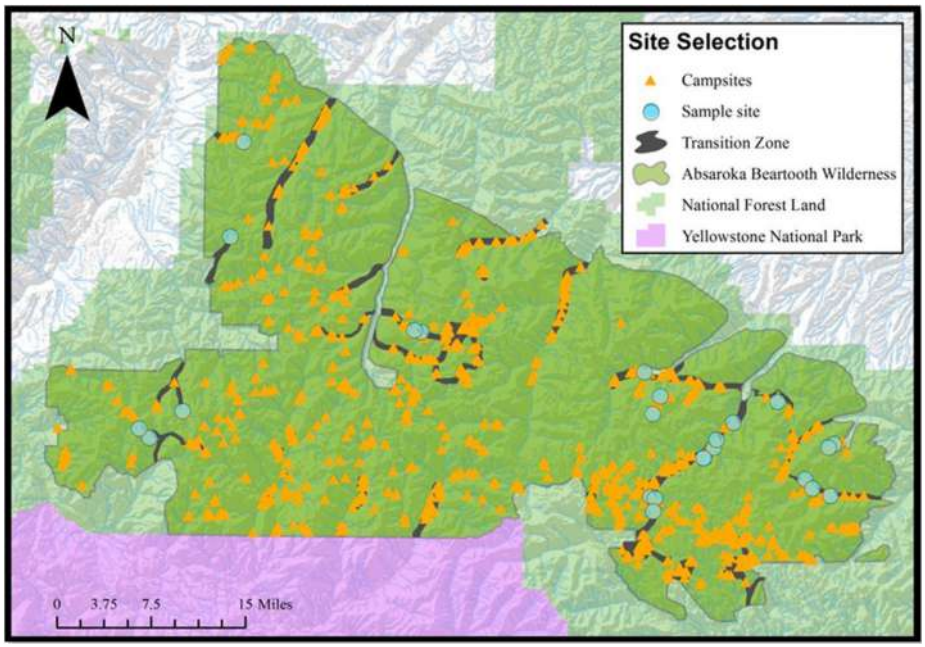

Figure 1. Sampling sites in the Absaroka Beartooth Wilderness. Backcountry campsites are indicated with orange triangles, and sampling sites for this study are indicated with blue circles.

and another specific to members of *Bacteroides* known to be associated with human feces. Both assays relied on previously published MST PCR methods.[9,18] Two different pairs of PCR primers were used for each assay (Table 2): The AllBac primer pair was designed to amplify 16S rRNA genes of members of *Bacteroides*, inclusive of those previously recovered from mammalian feces,[13,18] and the BacH primer pair targets 16S rRNA genes from the HF183 cluster of human feces-associated *Bacteroides*.[9,10,14,21,22] ddPCR assays were applied to sites where *E coli* was detected using the FIB assays (excluding Sylvan Lake). We also used both ddPCR assays on samples collected from 3 lake outlets (Diamond, Rainbow, September Morn) where no *E coli* was detected but total coliform abundances were relatively high. Finally, both ddPCR assays were used on the samples collected from the 2 snowmelt streams.

Triplicate filter extracts from the lake outlets and snowmelt streams were analyzed by ddPCR using a QX200 Droplet Digital PCR System (Bio-Rad Laboratories, Hercules, CA). Each ddPCR reaction (20 µL total) contained EvaGreen Supermix (Bio-Rad Laboratories), nuclease-free water, DNA extract, and 0.18 µM (final concentration) of each primer. Triplicate controls (with no added DNA) were included as negative controls. Filter blank DNA extracts were also analyzed in triplicate to estimate the detection limits associated with both ddPCR assays (see description in Statistics subsection). PCR reaction mixes were combined with droplet generation oil specific for EvaGreen, and droplets were generated using the droplet generator (Bio-Rad Laboratories). Droplets (40 µL total, including PCR reaction mix and oil) were transferred by multichannel pipettor into 0.2-mL 96-well PCR plates. Plates were heat sealed and placed in a Bio-Rad C1000 thermal cycler.

Amplification conditions were as follows: 95°C for 6 min, followed by 40 cycles of 95°C for 30 s, 61°C for 30 s, and 72°C for 45 s.[13] A QX200 Droplet Reader (Bio-Rad) was used to quantify droplet specific fluorescence. The fluorescence amplitude threshold was manually adjusted to distinguish positive droplets from those that demonstrated no amplification (negative droplets). We excluded reactions with <10,000 accepted droplets from subsequent analyses (n=3). Gene abundances (copies per milliliter of sample water) were quantified for each sample using the manufacturer's software (QuantaSoft, Bio-Rad Laboratories).

STATISTICS

The method detection limit (MDL) of the ddPCR assays was defined as the lowest number of genes that could be

Table 1. Elevation, distance to trailhead, number of campsites, groundcover, and types of use for all sites surveyed in this study

Sampling site	*Date sampled (2018)*	*Elevation (m)*	*Distance to trailhead (km)*	*No. of established campsites*[a]	*Ground cover*[b]	*Use type*[c]
Bald Knob	Jul 22	2871	12	11	Rock	Foot, stock
Diamond	Aug 12	2982	13	1	Alpine tundra	Foot, stock
Elbow	Jul 17	2664	11.2	5	Open forest	Foot, stock
Elk	Jul 29	2071	5	16	Open forest	Foot, stock
Fish	Jul 23	2732	8	2	Forest, meadow	Foot, stock
Horseshoe	Aug 14	2922	11.2	8	Alpine tundra	Foot
Keyser Brown	Aug 4	2650	11.2	9	Open forest	Foot, stock
Knox	Jul 23	2584	5.6	9	Open forest	Foot, stock
Lake at Falls	Jul 29	2499	14.5	5	Open forest	Foot, stock
Lake Gertrude	Aug 3	2924	7	4	Forest, meadow	Foot, stock
Lost	Aug 4	2583	8	18	Open forest	Foot, stock
Mystic	Jul 18	2337	5	44	Open forest	Foot, stock
Ouzel	Jul 22	2870	11.6	7	Rock	Foot, stock
Pine Creek	Jul 11	2801	8	14	Forest, meadow	Foot
Rainbow	Jul 29	2376	13.6	23	Open forest	Foot, stock
Rimrock	Jul 29	2317	9.6	5	Rock	Foot
Russell	Jul 22	2667	9.6	9	Open forest	Foot, stock
September Morn	Aug 4	3005	11.2	13	Open forest	Foot, stock
Sylvan	Jul 28	2799	9.6	3	Forest, meadow	Foot, stock
Thompson	Jul 12	2447	9.6	16	Open forest	Foot, stock
Timberline	Aug 3	2985	8	14	Forest, meadow	Foot, stock
Snowmelt stream 1	Aug 22	3547	11.2	5	Alpine tundra	Foot
Snowmelt stream 2	Aug 22	3642	16	3	Alpine tundra	Foot

[a]The US Forest Service does not designate campsites in this area, but it monitors well-established but illegal camping sites.
[b]Ground cover designations defined by US Forest Service monitoring.
[c]Use-type: Foot refers to human foot traffic; foot and stock refers to both human and stock animal traffic.

distinguished based on replicate (n=4) amplification of the filter blank DNA extracts. We estimated the MDL for each assay as

$$MDL = Mean_{blank} + 3 \times SD_{blank}$$

We defined the target gene as "present" if 1 or more of the triplicate ddPCR reactions amplified above the detection limits after 40 cycles. We quantified gene abundances only for those samples for which all triplicate ddPCR reactions amplified above the detection limits. Data are presented as mean±SD with range.

Least-squares linear regression analyses of square root transformed count data were used to examine relationships between CFUs of coliform and *E coli* and between CFUs and site-specific characteristics (eg, elevation, distance from trailhead). Given the large number of 0 values (for the FIB assays) or values below the MDL (for ddPCR assays), data were square root transformed as

$$y_t = (y + 0.5)^{1/2}$$

where y_t is the transformed variable, y is the measured property (eg, CFUs, gene abundances), and 0.5 is a constant. For those sites with gene abundances below the MDL, we assumed y=0 before transforming; for those sites where total coliform CFUs were above the upper threshold for accurate quantification (>200 CFUs), we assumed y=200 before transformation.

Results

TOTAL COLIFORM AND *E COLI* OCCURRENCES

Total coliforms were found in all 21 of the lake outlets sampled, and *E coli* was found in approximately half (11 of 21) of the sampled sites. Total coliform CFUs ranged from 27 to >200 CFUs per 100 mL of water, whereas *E coli* ranged from undetectable to 23 CFUs per 100 mL of lake outlet water (Figure 2, Table 3). Total coliform levels of >100 CFUs per 100 mL of lake water were found in 14 of the 21 (67%) lake outlet sites sampled (Table 3). Total coliform and *E coli* CFUs were correlated across the various sampling sites (least-squares linear regression, R^2=0.26, P=0.018); however, neither total coliform nor *E coli* CFUs were correlated with site-specific properties such as elevation, distance from trailhead, or number of established campsites (least-squares linear regressions, P>0.05).

Table 2. Polymerase chain reaction primers used for microbial source tracking analyses

Target	*Primer*	*Sequence*	*Amplicon size (bp)*	*Ref.*
Universal *Bacteroides*	AllBac 296f	5′- GAGAGGAAGGTCCCCCAC -3′	116	17
	AllBac 412r	5′- CGCTACTTGGCTGGTTCAG -3′		
Human *Bacteroides*	BacH_f	5′- CTTGGCCAGCCTTCTGAAAG -3′	93	18
	BacH_r	5′-CCCCATCGTCTACCGAAAATAC-3′		

UNIVERSAL AND HOST-SPECIFIC *BACTEROIDES* MST

The amplitudes of fluorescence (in relative fluorescence units [RFUs]) for droplets binned as positive for the AllBac and BacH assays were 1.7- and 1.6-fold greater, respectively, than fluorescence amplitudes of the negative droplets. The amplitude of fluorescence for positive droplets in the AllBac assay was 15,571±1195 (11,628−17,579) RFUs, whereas the fluorescence amplitude of negative droplets was 9247±773 (8044−11,026) RFUs. The fluorescence amplitude of the positive droplets for the BacH assay was somewhat lower at 9206±2849 (6270−19,885) RFUs, with negative droplets at 5799±1030 (4129−9971) RFUs. The number of accepted droplets for both assays was 15,043±1877 (10,404−18,558). The MDL for the BacH ddPCR assay was 18 copies per ddPCR reaction, equivalent to 9 copies per milliliter of lake water, whereas the MDL for the AllBac ddPCR assay was 42 copies per reaction, equivalent to approximately 21 copies per milliliter of lake water.

AllBac genes were present in all of the sites examined by ddPCR, with gene abundances quantifiable in 11 of 15 sites (Table 3). For those sites where gene abundances were quantifiable, AllBac gene abundances ranged from 5×10^3 to 131×10^3 genes per 100 mL of sampled water, with peak abundances observed in the same 2 lakes where *E coli* abundances were greatest (Lost and Keyser Brown lakes; Table 3). One of the snowmelt streams sampled near the base of Granite Peak also contained high abundances of the AllBac gene targets, with AllBac gene targets below the limit of detection in the other snowmelt stream sampled (Table 3).

Human-associated *Bacteroides* were found in very low abundances at all sites tested. BacH genes targets were present, but not quantifiable, at 52% (7 of 15 sites) of the sites examined. Only 1 of the sampled sites (Elk Lake) had quantifiable but relatively low BacH gene abundance (Table 3). Elk Lake was notable as the site closest (4.8 km) to the main trailhead into the ABW and hence likely receives the most visitation of any of the sites sampled. All sites that tested positive for the presence of BacH gene targets also tested positive for the presence of AllBac gene targets. Neither of the snowmelt streams sampled contained quantifiable abundances of BacH gene targets (Table 3).

Based on least-squares linear regressions of the square root transformed data, total coliform CFUs and the AllBac gene abundances were correlated (R^2=0.57, P=0.004); however, there were no significant relationships between the AllBac and BacH gene abundances or between AllBac abundances and any of the site-specific environmental properties (ie, elevation, distance from trailhead, number of established campsites; least-squares linear regressions; P>0.05).

Discussion

By leveraging culture-based FIB assays and culture-independent MST assays, we evaluated the spatial distribution and potential sources of fecal bacteria in selected ABW waters. Total coliforms were present in all of the lake outlets sampled, with positive occurrence of *E coli* at 52% of these sites. The highest *E coli* CFUs were found in lake outlets that are popular recreational water sources and accessible to stock animals and human foot traffic. Total coliform and *E coli* counts were positively related, suggesting that for these waters, the occurrence of elevated *E coli* covaries with abundances of total coliforms. Use of both FIB and PCR-based assays to examine fecal contamination of ABW waters revealed that in some cases, despite testing positive for the presence of *E coli*, human-derived *Bacteroides* were not present. These results point to other possible sources of fecal contaminants, including animals (wild or domesticated).

Our study highlights the utility of combining FIB and MST methods for discerning possible sources of feces-associated microorganism contaminants. For example, we did observe a weak but significant positive relationship between the FIB-derived total coliform CFUs and AllBac gene abundances, suggesting the presence of mammalian *Bacteroides* may be related to increased prevalence of total coliform bacteria. However, there were no clear patterns linking those lakes with high CFUs or *Bacteroides* gene abundances to

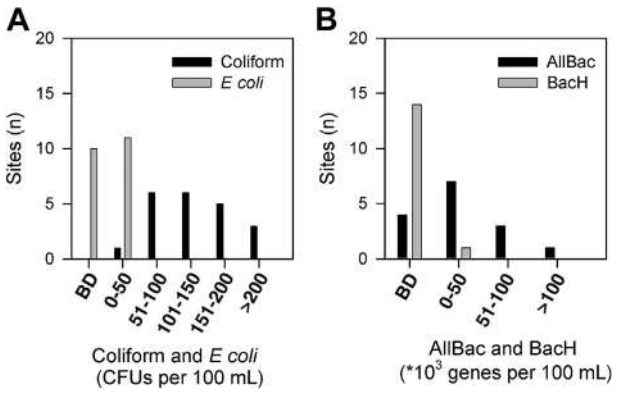

Figure 2. Histograms of colony-forming units (per 100 mL of water) for total coliforms and *E coli* (panel A) and ddPCR quantification of *Bacteroides* gene abundances for AllBac and BacH gene targets (panel B). BD = below limits of detection.

their surrounding environment or use types. Moreover, there were no apparent relationships between *Bacteroides* gene abundances or coliform CFUs and landscape types (eg, open forest, meadow, alpine tundra), elevation, or distance to trailhead. The extent to which variations in the local environment or watershed influenced the resulting microorganism distributions remains unclear; however, pack or domesticated animals may have contributed to the presence of coliform bacteria and *Bacteroides*.

Use of the AllBac ddPCR assay revealed widespread occurrence of members of *Bacteroides*. These microorganisms can be dominant members of ruminant, human, and waterfowl gut microbiomes[14,21,23]; thus, the occurrence of these microorganisms could indicate fecal contamination from various sources. We detected the presence of human feces-associated *Bacteroides* at 7 of the 15 of the sampling sites, but in all but 1 of these sites (Elk Lake) abundances were too low to quantify. Elk Lake was the lowest elevation site sampled, the closest to the trailhead (4.8 km), and it lies downstream of lakes that also tested positive for the presence of human-derived *Bacteroides* using the ddPCR assay. Thus, although most lakes in the ABW had very low human feces contamination, we did observe the presence of human-derived microorganisms in waters from highly trafficked areas.

We also sampled 2 snowmelt streams near Granite Peak, Montana's highest point and a popular summit within the ABW. The scarcity of water around Granite Peak creates congested basecamp areas that place disproportionate pressures on adjacent water resources. Prior studies on wilderness waters noted that both total coliform and *E coli* counts correlated with periods of peak human visitation.[24-26] Both of the snowmelt streams tested positive for the presence of enteric members of *Bacteroides*, and human feces-associated *Bacteroides* were found in 1 of these streams. We attribute these findings to fecal contamination from various sources, including wildlife and human fecal bacteria. The detection of human-derived fecal bacteria in 1 of the 2 snowmelt streams emphasizes that future studies should include sampling of running waters in this region.

Although use of culture-based FIB- and PCR-based MST methods revealed that several lakes in the ABW appear to be influenced by fecal microorganism contaminants, for most lakes we were unable to identify sources of these potential contaminants. The human-specific fecal indicator MST assay indicated that most of these lakes received little fecal input from humans. These results highlight the utility of combining more traditional FIB assays with emerging MST methods for information on both the occurrence and specific sources of microorganism contaminants to aquatic systems.

LIMITATIONS

A limitation in this study was the relatively high MDLs estimated for both ddPCR assays. Detection limits for both assays were somewhat higher than has been previously reported for quantitative PCR-based MST methods[27]; the detection limits for the ddPCR assay derive from any amplification in the blanks, together with the volume of water filtered to concentrate microorganism biomass. We processed relatively small volumes of water for subsequent extraction of DNA, constrained in part by the remote locations and the need to transport water back to the laboratory. We also did not include PCR inhibition controls as part of our ddPCR analyses; hence, we do not have information on the extent to which the presence of inhibitors may have resulted in underestimation of the target gene abundances. In addition, our sampling was restricted to a single summer season; hence, we do not have information on how seasonal- to episodic-scale changes in the local environment (eg, rainfall, snowfall) might affect the introduction of fecal contaminants to these waters.

Conclusions

Our results suggest relatively low prevalence of waterborne pathogens (specifically *E coli* and human-derived *Bacteroides*) in this popular wilderness area. The sources of total coliforms and *E coli* to these waters are unknown but could derive from wild or domesticated animals that inhabit or visit the ABW. Hence, increased human

Table 3. Occurrence of total coliform and *E coli* CFUs and detectable occurrences of AllBac and BacH gene markers in lake outlets and snowmelt streams sampled in the Absaroka Beartooth Wilderness

Sampling site (lake outlets and streams)	*Total coliform (CFUs per 100 mL)*	*E coli (CFUs per 100 mL)*	*AllBac gene abundances (× 10^3 copies per 100 mL)*	*AllBac present?*	*BacH gene abundances (× 10^3 copies per 100 mL)*	*BacH present?*
Bald Knob	89	0	NA	NA	NA	NA
Diamond	144	0	5.0±0.7	Yes	BD	No
Elbow	93	0	NA	NA	NA	NA
Elk	152	2	33±19	Yes	3.3±2.2	Yes
Fish	>200	0	NA	NA	NA	NA
Horseshoe	>200	1	15±19	Yes	BD	No
Keyser Brown	>200	5	96±56	Yes	BD	No
Knox	73	1	78±29	Yes	BD	No
Lake at Falls	142	1	29±2.2	Yes	BD	Yes
Lake Gertrude	174	1	20±11	Yes	BD	No
Lost	192	23	92±48	Yes	BD	Yes
Mystic	85	0	NA	NA	NA	NA
Ouzel	62	0	NA	NA	NA	NA
Pine Creek	27	0	NA	NA	NA	NA
Rainbow	82	0	BD	Yes	BD	Yes
Rimrock	124	1	BD	Yes	BD	Yes
Russell	127	1	14±4.3	Yes	BD	No
September Morn	162	0	15±3.2	Yes	BD	No
Sylvan	180	4	NA	NA	NA	NA
Thompson	129	0	NA	NA	NA	NA
Timberline	149	2	BD	Yes	BD	Yes
Stream 1	NA	NA	BD	Yes	BD	Yes
Stream 2	NA	NA	131±11	Yes	BD	No

Presence of target gene indicates detectable but not quantifiable genes (ie, at least 1 sample from the triplicate ddPCR reactions amplified; "No" indicates none of the triplicate polymerase chain reaction reactions amplified above the lower limit of detection). Mean±SD of triplicate analyses from each lake outlet or snowmelt stream. BD indicates gene abundances below detection (<900 gene copies per 100 mL of lake water for BacH and <2100 gene copies per 100 mL of lake water for AllBac). NA indicates sample not analyzed.

visitation to the ABW could have indirect impacts on water quality via fecal contamination attributable to domesticated animals. Furthermore, widespread occurrence of total coliforms, *Bacteroides*, and *E coli* highlights the importance of purifying water sources in wilderness areas before consumption.

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CASE REPORT

A Rare Case of Micro-Angiopathic Hemolytic Anemia Due to Envenoming by Giant Asian Honey Bee (*Apis dorsata*)

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Giant Asian honey bee sting envenoming is a recognized cause of morbidity and mortality in rural Sri Lanka. Mass envenoming causes clinical effects, either as allergic and anaphylactic reactions or bee sting toxin-induced multiorgan damage. We report a patient who had mass envenoming from more than 1000 stingers who subsequently developed hematologic features suggestive of thrombotic microangiopathy-related hemolytic anemia. The transient acute kidney injury and acute hepatic failure seen in the patient were also considered to be secondary to thrombotic microangiopathy. A normal clotting profile and a high proportion of schistocytes in blood film ruled out disseminated intravascular coagulation as the underlying cause of the microangiopathic hemolytic anemia. The normal platelet count raised the possibility of a "partial" thrombotic microangiopathy, as has previously been reported in association with Shiga toxin-related hemolytic uremic syndrome and hump-nosed pit viper envenoming. Venom-induced direct toxicity on red cells was another possible explanation for the hemolysis, but the high proportion of schistocytes made it less likely. The place of therapeutic plasma exchange for venom-associated thrombotic microangiopathy is controversial. The patient recovered with symptomatic treatment and meticulous fluid management, without needing therapeutic plasma exchange as an adjunct treatment.

Keywords: hymenopterans, *apis dorsata*, thrombotic microangiopathy, microangiopathic hemolytic anemia, kidney injury

Introduction

The order Hymenoptera includes both bees and wasps. Most bees and wasps live solitarily and are not predisposed to stinging humans. The greatest threat to health of humans is posed by a few species of social bees (eg, different types of honey bees) and social wasps (eg, hornets, yellow jackets, and paper wasps), which produce large numbers of sterile workers.[1] The domesticated Asian honey bee (*Apis cerana*—Mee messa in the vernacular), the feral giant Asian honey bee (*Apis dorsata*—Bambara in Sinhalese and Karunge kulavi in Tamil), the feral dwarf honey bee (*Apis florae*—Danduwel mee), and the stingless bee (*Tetragonula iridipennis*—Kaneyya messa) are honey bees frequently encountered both in rural and urban landscapes of Sri Lanka.[2] Giant Asian honey bees are the largest, measuring 17 to 20 mm in length, and they make large hives in open areas. The hives hang from branches of large trees, roofs, rock caves, and other similar areas. Thousands of colony members leave the nest and attack humans in defense when they are disturbed.[3] Female hymenopterans have a modified ovipositor called stinger, associated with venom glands located at the tip of the abdomen. After honey bees sting, the stingers are deeply embedded in the victim's skin, detach from the insect, and continue to deliver the venom,[4] including melittin, mast-cell degranulating peptides, phospholipase A2, hyaluronidase, acid phosphatase, and histamine.[1]

Most clinically important incidents and fatalities due to Hymenoptera venom occur as a result of anaphylactic shock.[1] However, mass envenoming from hundreds of Hymenoptera stings causes life-threatening complications due to multiorgan damage. Rhabdomyalysis, acute kidney injury, noncardiogenic pulmonary edema, acute

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Figure 1. A giant Asian honey bee (*Apis dorsata*) found at the site where the hive was burnt by villagers after the incident.

Figure 2. The patient with swelling and small ulcers over the stinging sites.

myocardial infarction, bowel gangrene, and multiorgan failure have all been reported.[1,4,5] We report a rare case of giant Asian honey bee mass envenoming in which the hematologic investigations were suggestive of a hitherto unreported complication, microangiopathic hemolytic anemia, in a Sri Lankan patient.

Case Report

A previously healthy 86-y-old male was admitted to the emergency unit of a regional hospital 30 min after a mass envenoming by giant Asian honey bees (*A dorsata*). He was stung by bees while walking outdoors. The beehive was found on a nearby Kitul (*Caryota urens*) tree. Apart from infrequent episodes of bronchial asthma, he had no hematologic, renal, or hepatic diseases in the past, no previous exposure to Hymenoptera stings, and no food or drug allergies (Figures 1 and 2).

On admission, the patient was anxious and in pain with large numbers of stingers embedded in the skin over the head, neck, and hands. His body was swollen and his skin was erythematous. His pulse rate was 112 beats·min^{-1} and blood pressure was 150/90 mm Hg. All stingers, numbering more than a 1000, were removed with utmost care. Hematologic and biochemical investigations performed on admission were unremarkable except for an elevated white blood cell count. He was treated with intravenous hydrocortisone, normal saline infusion, oral chlorpheniramine, cefuroxime, paracetamol, and tetanus toxoid. He passed normal amounts of urine, and the color of the urine was normal.

On Day 2, he reported feeling dizzy and lifeless, and investigations were repeated. The white blood cell count was further elevated (29×10^9 L^{-1} [normal $4–11\times10^9$]) with neutrophils comprising 90% of cells. Hemoglobin had decreased (9.1 g·dL^{-1} [normal 13–17]), but platelet count remained within the normal range. Total bilirubin was elevated (3.9 g·dL^{-1} [normal 0.2–1.0]), and the predominant rise was in the indirect fraction (Table 1). The blood picture examination revealed polychromatic cells, ovalocytes, and schistocytes. The schistocytes constituted approximately 5% of the red cell population. White cells appeared increased with a left shift of the neutrophils. The hematologist concluded that the blood picture was suggestive of microangiopathic hemolytic anemia. A normal direct antiglobulin test ruled out immune hemolysis. Because the clotting profile was normal, disseminated intravascular coagulation was considered unlikely and a thrombotic microangiopathy was considered the most likely cause of hemolysis. Renal impairment was present with a serum creatinine of 1.9 mg·dL^{-1} (normal 0.8–1.3) on Day 2. Urinalysis was normal with no hemoglobinuria. Hepatic function impairment was also noted by Day 2, with elevated alanine transaminase (91 U·L^{-1} [normal 5–30]) and a marginally increased direct bilirubin fraction.

A diagnosis of thrombotic microangiopathy associated with hemolysis, acute kidney injury, and acute liver injury as a result of giant Asian honey bee envenoming was made. The patient recovered by Day 5 with antihistamines for symptomatic alleviation, antibiotics for prevention of skin sepsis, and meticulous fluid management. He did not require renal dialysis for renal impairment or therapeutic plasma exchange for microangiopathic hemolytic anemia (Table 1).

Table 1. Investigations results on admission, Day 2, and discharge

	On admission	*Day 2*	*On discharge*
White blood cells (normal 4–11 L^{-1})	20.8×10^9	29.0×10^9	11.4×10^9
Hemoglobin (normal 12–16 $g\cdot dL^{-1}$)	12.4	9.1	11.1
Platelet count (normal 150–450×10^3 μL^{-1})	332×10^3	259×10^3	264×10^3
Serum bilirubin (normal 0.2–1.0 $mg\cdot dL^{-1}$)	1.1	3.9	1.0
Alanine transaminase ($U\cdot L^{-1}$)	56	91	44
Serum creatinine ($mg\cdot dL^{-1}$)	1.2	1.9	1.3
PT/INR (s)	Not done	13/1.1	12/1.0
aPTT (s)	Not done	32	32
D-dimer (normal <500 $ng\cdot mL^{-1}$)	Not done	256	250

PT, prothrombin time; INR, international normalized ratio; aPPT, activated partial thromboplastin time.

Discussion

The feral giant Asian honey bee sting is an environmental hazard in rural Sri Lanka. In an observational study of 322 patients admitted to a rural hospital after Hymenoptera sting, 292 were instances of giant Asian honey bee stings.[3]

In this case report, the hematologic investigations were suggestive of the occurrence of a rare complication, microangiopathic hemolytic anemia. Microangiopathic hemolytic anemia is caused by the destruction of red cells as they squeeze through capillaries that have damaged endothelial linings covered by fibrin clots. The fragmented cells appear as schistocytes in a blood picture. The causes of microangiopathic hemolytic anemia are either a thrombotic microangiopathy or disseminated intravascular coagulation. These 2 conditions are differentiated based on the clotting profile. If disseminated intravascular coagulation is the cause of microangiopathic hemolytic anemia, the clotting profile is abnormal with prolonged prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), and high D-dimer levels. In contrast, in thrombotic microangiopathy, the clotting profile is normal. The patient's normal clotting profile was suggestive of hemolysis being part of a thrombotic microangiopathy. The other useful distinguishing feature is the proportion of schistocytes in blood picture. In a normal person, it is <0.5%. A person with disseminated intravascular coagulation will have a higher proportion of schistocytes, but it will be less than 1%. If the cause of the schistocyte formation is thrombotic microangiopathy, the proportion will be higher than 1%.[6] In this patient, the proportion of schistocytes was approximately 5%, providing further evidence to support thrombotic microangiopathy as the probable etiology of hemolysis.

In a thrombotic microangiopathy, it is usual to see thrombocytopenia in the blood counts and the blood picture. This occurs due to platelet adherence to the damaged vascular endothelium. The patient described had normal platelet counts. There are 2 possible explanations for this finding. Thrombotic microangiopathy related to Shiga toxin–induced hemolytic uremic syndrome has been shown to occur in some instances with normal platelet counts. This entity is described as "partial HUS."[7] Thrombotic microangiopathy sans thrombocytopenia has also been described after envenoming by hump-nosed pit vipers.[8,9] A similar "partial" thrombotic microangiopathy could explain the giant Asian honey bee–induced hemolytic anemia without thrombocytopenia. The second possible explanation is direct toxicity on the red cells by the toxin, thus leaving platelet counts unaffected. Although such direct toxicity has not been demonstrated after bee sting envenoming, there is evidence for toxin-induced hemolysis after viper bites.[10-12] Although direct venom-induced hemolysis needs to be considered, the presence of a high proportion of schistocytes favors a microangiopathic genesis for the hemolysis. Further research into mechanisms of hematotoxicity of bee venom is needed in the future.

Vascular injury associated with thrombotic microangiopathy causes organ failure. The patient's transiently elevated serum creatinine was suggestive of damage to renal vasculature. Liver enzyme alanine transaminase elevation and the direct fraction of bilirubin elevation were suggestive of injury to hepatic vasculature. The mixed picture of indirect and direct bilirubin rise is consistent with thrombotic microangiopathy-associated hemolysis and acute liver injury.

The standard management for microangiopathic hemoytic anemia secondary to primary thrombotic microangiopathic syndromes such as thrombotic thrombocytopenic purpura is therapeutic plasma exchange.[13] In venom-associated thrombotic microangiopathy, however, the value of therapeutic plasma exchange is controversial. There are a few case reports suggesting a useful role as an adjunct treatment.[14] More robust evidence is awaited. There is presently a systematic review of the literature being conducted, and its results are likely to give us more evidence-based guidance.[15] We were spared the dilemma

of whether to perform therapeutic plasma exchange in this patient because he recovered from the hemolysis and renal and hepatic injuries with symptomatic treatment, meticulous fluid management, and antibiotic therapy.

Conclusions

This case report highlights the need to add microangiopathic hemolytic anemia to the growing list of probable life-threatening complications associated with mass envenoming due to giant Asian honey bee sting. Thrombotic microangiopathy being the underlying cause of microangiopathic hemolytic anemia provides a pathophysiological explanation for the transient renal and hepatic failure that occurred in the patient.

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CASE REPORT

Hyperendogenous Heparinization Suggests a Guideline for the Management of Massive Wasp Stings in Two Victims

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Bees and wasps (order Hymenoptera) are commonly encountered worldwide and often deliver defensive stings when in contact with humans. Massive envenomation resulting from >50 stings causes a toxic reaction and life-threatening complications that typically result in rhabdomyolysis and disseminated intravascular coagulation. Two male patients who were stung over 80 times by wasps experienced severe coagulation abnormality. Consecutive examination by thromboelastography (TEG) guided by heparinase treatment during their hospitalization evidenced heparin-like coagulation dysfunction despite no clinical use of heparin-like substances. Numerous tests were also conducted to confirm whether the coagulation abnormalities could be attributed to hyperendogenous heparinization and allergic reaction, rhabdomyolysis, and vascular endothelial cell injury without apparent disseminated intravascular coagulation, which might all be affected by the production of endogenous heparin. The reduced coagulation potential caused by hyperendogenous heparinization was associated with the binding of antithrombin and the activation of fibrinolysis. In addition, TEG-identified coagulopathy was moderated using protamine for heparin neutralization. The massively envenomed patients survived and were discharged after completion of medical care. We also review clinical manifestations from other published case reports, including topical treatment. Our study provides clinical evidence and guidance for diagnosis via TEG and appropriate intervention with protamine for patients with massive wasp envenomation.

Keywords: massive envenomation, coagulopathy, endogenous heparin-like, protamine, resuscitation, transfusion

Introduction

The most common injury caused by an animal is a wasp, hornet, or bee sting, with an incidence as high as 49%.[1] Stings cause local reactions and generalized symptoms, such as vomiting, diarrhea, dyspnea, redness and swelling, acute renal failure, and hypotension.[2] One reported case of massive wasp stings presented with disseminated intravascular coagulation (DIC), stroke, and acute renal failure.[3] Patients experiencing insect sting-related anaphylactic shock have also exhibited clinical and laboratory features of a severe acute generalized fibrinolytic state, but not DIC.[4] The distinctive manifestation of coagulopathy in patients stung by wasps (*Vespa affinis,* common species in Xiamen, Fujian, China), with severe coagulation abnormalities, has been observed (case collections from our hospital).

Two male workers (weed-whackers for cutting grass fields in Xiamen) accidentally disturbed a wasp hive and were subsequently attacked. The physical examination identified numerous stings in both. They were immediately brought to the outpatient clinic for a dermatology assessment and were given dexamethasone 10 mg intramuscularly. One day after the wasp stings, they presented to the clinical nephrology department. In this case report, we present biochemical and physical examination findings, treatment regimens, and the progress of

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Table 1. The biochemical measurements of 2 wasp sting victims

Measure	*AST (IU·L^{-1})*	*ALT (IU·L^{-1})*	*LDH (IU·L^{-1})*	*TBIL (IU·L^{-1})*	*BN (IU·L^{-1})*	*BUN (mmol·L^{-1})*	*Cr (μmol·L^{-1})*	*Creatine kinase isoenzyme (U·L^{-1})*	*CKMB (IU·L^{-1})*
Normal value	*15–40*	*9–50*	*100–240*	*3–25*	*0–20*	*2.9–8.2*	*59–104*	*30–270*	*0–24*
Case 1									
21 h	5089		3092					64,628	5874
24 h	5240	961	2995	324	108			70,786	7383
48 h	987	284	1112	118	35	7.9	56	25,207	4798
72 h	973	354	1171	84	26	7.0	55	15,096	1930
96 h	641	340	1184	63	21	7.3	52	8421	527
Case 2									
21 h	3400		1879					40,855	1636
24 h	2740		1692	26	15	10.8		53,400	1420
48 h	1511	873	1383	18	12	6.3		40,593	1389
72 h	987		1032					27,404	4194
96 h	328		829			5.8	76	6344	291

ALT, alanine aminotransferase; AST, aminotransferase; BN, indirect bilirubin; BUN, urea nitrogen; CKMB, creatine kinase myocardial band; Cr, creatinine; LDH, lactate dehydrogenase; TBIL, total bilirubin.

envenomations. Both patients provided written consent allowing the case to be published.

Case Reports

CASE 1

A 58-y-old man presented to the nephrology department with dark brown urine and muscle soreness. He became jaundiced around 6 h after the initial clinic visit. He was conscious with normal vital signs, including a blood pressure of 133/96 mm Hg, heart rate of 72 beats·min^{-1}, and a respiratory rate of 18 breaths·min^{-1}. He was admitted to the nephrology inpatient department 15 h later. On physical examination, 121 wasp sting wounds with pus were found on his back and shoulders. He had a normal abdominal palpation examination, without renal percussive pain. The results of laboratory investigations are shown in Table 1 and Figure 1. Urine analysis showed protein 1.0 g·L^{-1}, occult blood 300 Ery·μL^{-1}, white blood cell 35.6 p·μL^{-1}, and glucose 28 mmol·L^{-1}. Urine culture was negative. Routine blood examination showed a white blood cell count of 14.1×10^{9}·L^{-1} and neutrophil count of 12.8×10^{9}·L^{-1}.

The patient was diagnosed with greater than 120 wasp stings, rhabdomyolysis, and liver function failure. Owing to his poor clinical presentation, he was admitted as an inpatient 24 h after the initial wasp stings. Multiple organ dysfunction, including liver and kidney failure and abnormal coagulation, was confirmed, and he was transferred to the intensive care unit immediately and treated with methylprednisolone 30 mg intravenously (IV), vitamin C 3.0 g IVgtt (intravenously guttae), sodium bicarbonate 1.2 thrice daily orally (po), and fluid infusion of 1600 mL IV gtt. Emergent hemoperfusion and plasma exchange were completed within 4 h after consultation with a doctor in the hematology and infectious diseases department (sodium citrate was used as an anticoagulant during plasma exchange). He was again treated with methylprednisolone 40 mg IV gtt, ademetionine 1.0 g, reduced glutathione 1.2 g, ornithine aspartate 7.5 g, loratadine 10 mg 4 times daily po, antihistamines, and fluid infusion therapy.

Deteriorated coagulation function was observed on the second day of admission, and previous venipuncture sites exhibited bleeding. Cryoprecipitated antihemophilic factor (10 units) and platelets (2 units) were infused, following reports of critical platelet values (18×10^{9}·L^{-1}). Compromised hemostasis was also shown by the following: A hematoma about 5 cm in size was observed at the puncture site of the left femoral artery; thrombin time (TT) results exceeded the maximal detection, D-dimer was 550 ng·mL^{-1} DDU, and fibrin degradation product was 6.4 ug·mL^{-1} (Figure 1).

Unexpectedly, without evident use of heparin-like substances in clinical practice, all thromboelastography (TEG) and routine coagulation examined values showed the evidence of heparin-like activity, with R time 15 min, K 6.8 min, Angle (α) 25.5°, MA 39.3 mm, activated partial thromboplastin time (APTT) 190 s, and prothrombin time 11.7 s at 24 h after the wasp stings. The clinician confirmed that no heparin-like drugs were used in the patient. On sample neutralization with heparinase, TEG values were improved, with R time 5.2 min, α 59.6°, and MA 43.8 mm (Figure 2A). When symptoms of overreactive heparinization occurred, provision of 40 mg

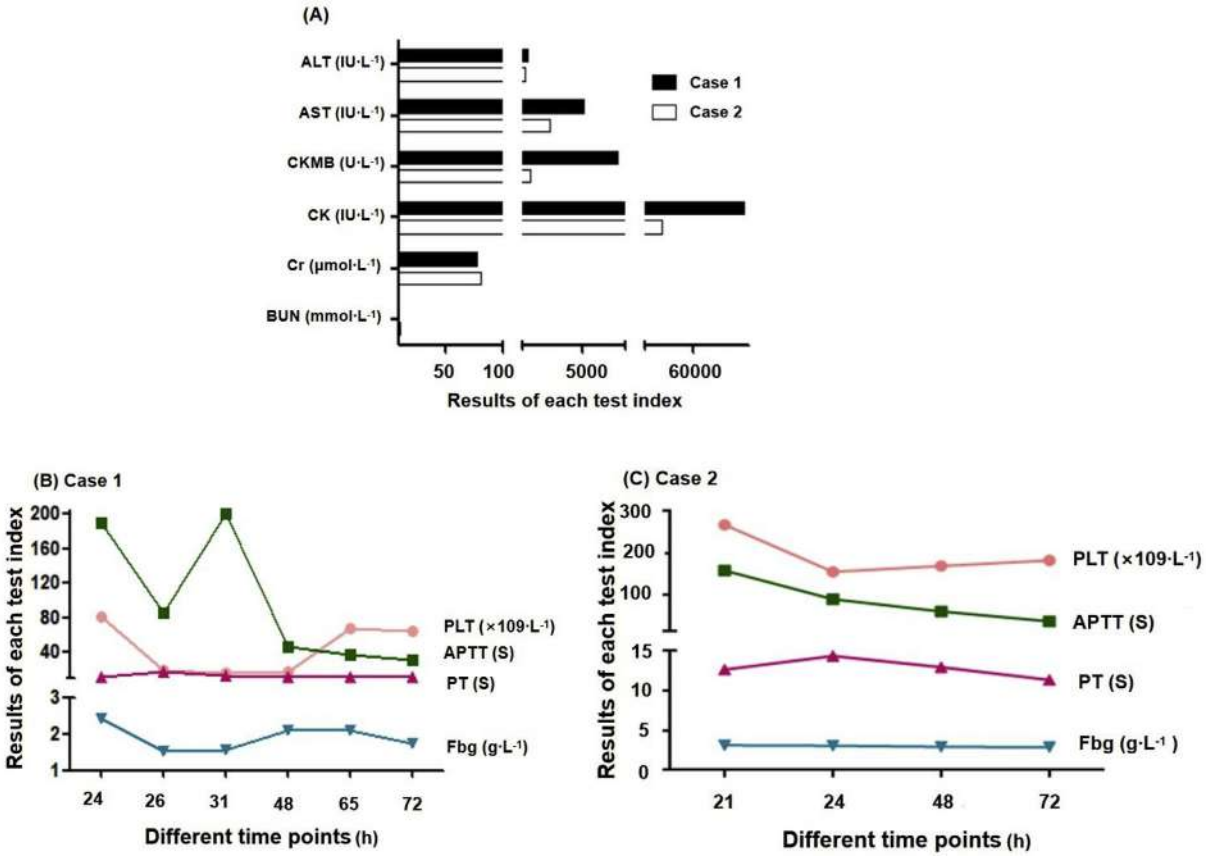


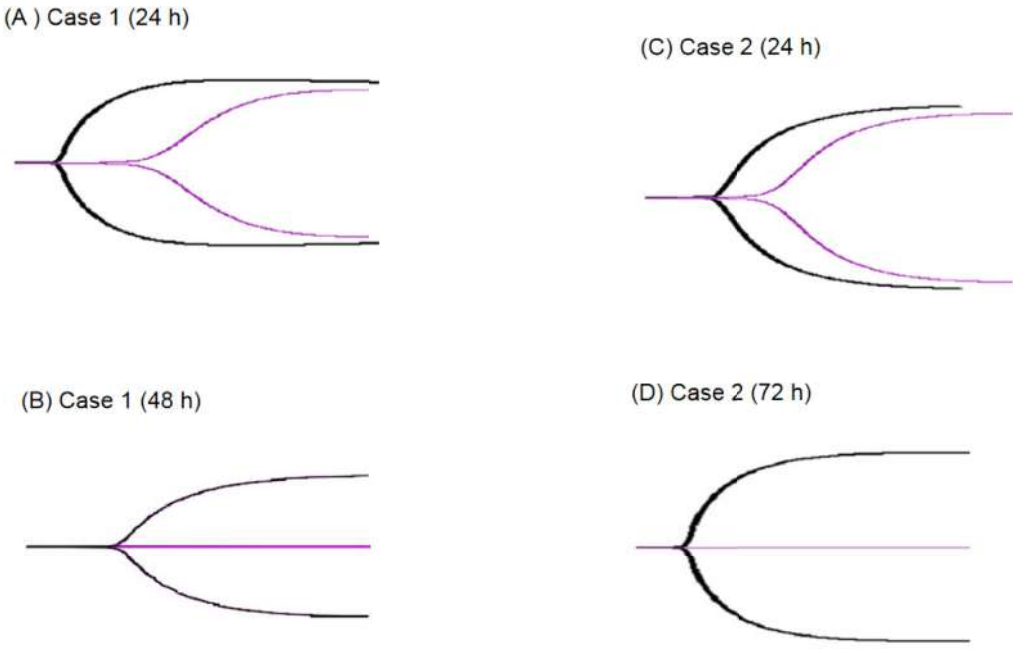
Figure 1. The laboratory examinations of the wasp stings patients in various time period. (A) 2 cases at hospital visit time; (B) case 1; (C) case 2. Aspartate aminotransferase (AST); alanine aminotransferase (ALT); creatine kinase (CK), creatine kinase isoenzyme (CKMB); creatinine (Cr); urea nitrogen (BUN); activated partial thromboplastin time (APTT); prothrombin time (PT); fibrinogen (Fbg); platelet (PLT).

protamine IV resulted in pronounced improvement in coagulation function (R time 8 min, α 47.6°, MA 41.0 mm) at 0.5 h posttreatment. At 48 h after the wasp stings, however, TEG and coagulation values were deranged again, with R time >60 min, APTT >200 s, and prothrombin time 13.8 s. After sample neutralization by heparinase, all TEG values were improved, with R time 11.9 min, α 33.4°, and MA 32.7 mm (Figure 2B). After a second injection of 40 mg protamine IV, coagulation function also showed improvement (R time 7 min, α 49.1°, MA 45.0 mm) at 0.5 h posttreatment. Platelet count progressively decreased from $81\times10^{9}\cdot L^{-1}$ at 24 h after the initial wasp stings to $17\times10^{9}\cdot L^{-1}$ at 48 h. After infusion of platelets with 2 therapeutic doses at 48 h after the wasp stings, platelet counts gradually increased and recovered to normal level on the fourth day. After the wasp stings, fibrinogen was decreased from 2.4 $g\cdot L^{-1}$ (at 24 h) to 1.5 $g\cdot L^{-1}$ (at 48 h).

Other key results were as follows: increased plasmin-a2-inhibitor complex (PIC) at 2.1 $\mu g\cdot mL^{-1}$ (<0.8 $\mu g\cdot mL^{-1}$), decreased antithrombin (AT) at 41% (82–121%), tissue plasminogen activator inhibitor 1 complex (tPAI-C) at 34.7 $ng\cdot mL^{-1}$ (<10.5 $ng\cdot mL^{-1}$), and IgE at up to 295.6 $KIU\cdot L^{-1}$ at 24 h after the wasp stings (Figure 3). The percentage of B lymphocytes increased from 5% (at 24 h) to 8% (at 48 h), and the absolute count increased from 1.2 to $2.9\times10^{11}\cdot L^{-1}$. On the fourth day, wet rales were auscultated throughout the lungs, and cefazolin 2.0 g 4 times daily IV gtt was given as a precaution against infection. At 72 h after the wasp stings, blood coagulation function recovered. In total, the endogenous heparinization lasted for 36 h. When the patient's condition improved and became stable, he was transferred out of the intensive care unit and into the infection nursing unit. Liver, renal, and coagulation functions all gradually returned to within normal limits, and the patient was discharged on day 10.

CASE 2

A second 42-y-old man presented to the nephrology clinic. The patient stated his urine had turned dark brown 12 h before the clinic visit. The patient was



	24 h		48 h		72 h		Reference
	CK	CKH	CK	CKH	CK	CKH	
R	1.5	5.2	>30	11.9	8.3	Nd	4-8 min
K	6.8	2.3		6	2.1	Nd	1-3 min
α	25.5	59.6		33.4	58.1	Nd	53-72 deg
MA	39.3	43.8		32.7	49.6	Nd	50-70 mm

	24 h		48 h		72 h		Reference
	CK	CKH	CK	CKH	CK	CKH	
R	12.2	7.6	10.9	Nd	>30	5	4-8 min
K	4.5	2.5	3	Nd		1.2	1-3 min
α	37.6	55.3	48.2	Nd		66	53-72 deg
MA	52.2	56.8	51.4	Nd		61.9	50-70 mm

Figure 2. The profiles of thromboelastography (TEG) in the wasp stings patients. (A) case 1 (24 h), (B) case 1 (48 h), (C) case 2 (24 h), and (D) case 2 (72 h). Note: X-axis: the readout of each index. Y-axis: various test index. The purple curve is the result of control and the black curve is the result of heparinase coating. The curve with a short R time is the image after neutralization with heparinase. Normal range: R time: 8−10 min, α: 53−72°, K: 1−3 min, and MA: 50−70 mm. CK: standard; CKH: neutralization with heparinase. Nd: non-detection.

conscious with normal vital signs, including a blood pressure of 123/85 mm Hg and respiratory rate of 18 breaths·min^{-1}. He was admitted to the nephrology inpatient unit. On physical examination, 86 red and swollen wasp sting wounds with pus were found on his chest, back, and upper and lower limbs. His heart rate was 98 beats·min^{-1}, and abdominal palpation was normal, without renal percussive pain. Platelets decreased from 221×10^{9}·L^{-1} to 156×10^{9}·L^{-1}. Coagulation recovered gradually at 48 h after the wasp stings. Clinical manifestations of organ dysfunction, including some abnormalities in liver and kidney function (Table 1) along with abnormal coagulation, were observed, similar to Case 1.

He was treated with methylprednisolone 30 mg IV, vitamin C 3.0 g IV drip (IV gtt), sodium bicarbonate 1.0 3 times daily po, and a fluid infusion of 1600 mL IV gtt. Without using heparin-like substances in clinical practice, at 24 h after the wasp stings, all examined values were suggestive of heparin, with R time 12 min, α 37.6°, MA 52.2 mm, APTT 159.2 s, and TT results exceeding the maximal detection. After sample neutralization with heparinase, TEG values were improved, with R time 7.6 min, α 55.3°, and MA 56.8 mm (Figure 2C). This again confirmed a heparin-like effect. At 0.5 h after injection of 40 mg protamine IV, the patient's coagulation function on TEG manifested improved (R time 8 min, α 50.4°, MA 50.0 mm). PIC was increased to 1.9 (<0.8 μg·mL^{-1}), AT was decreased to 68% (82−121%), and tPAI-C was 10.8 (<10.5 ng·mL^{-1}) (Figure 3). The percentage of B lymphocytes increased from 9% (at 24 h) to 11% (at 48 h after wasp sting). The absolute count increased from 5.3 to 12.0×10^{11}·L^{-1}, and IgE was 241.6 KIU·L^{-1} at 24 h after the wasp stings. After active rehydration, liver protection, antioxidation, antiallergy, inflammatory

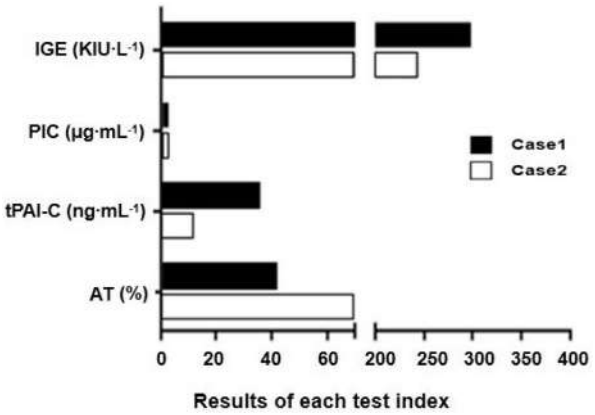


Figure 3. Coagulation tests of the wasp sting patients. PIC: Plasmin-a2-inhibitor complex (normal range: 0-0.85 μg·mL^{-1}); tPAI-C: tissue plasminogen activator inhibitor 1 complex (normal range: 0-17 μg·mL^{-1}); AT: antithrombin (normal range: 82−121%); IGE: Ig E.

reaction reduction, and other treatments, the myozyme was significantly decreased, and the patient was discharged 3 d later.

Discussion

Insect venom-induced allergic reactions are potentially life-threatening. Clinically, insect stings can cause severe anaphylaxis and lead to cardiovascular collapse and death. The mortality rate is estimated to be 1 to 5% in different countries.[5] Ordinarily, injuries caused by mild stings can be corrected by routine antiallergy and anti-infection therapies. Recently, a transient deranged coagulation profile (transient coagulopathy) with a normal platelet count resulting from wasp venom anaphylaxis was reported.[6] Moreover, a previous report on massive bee envenomation observed the occurrence of DIC due to delayed toxic reaction.[7] In severe cases, patients may die of DIC after severe wasp stings.[8]

Case 1 presented to nephrology with dark brown urine and muscle soreness. Wasp stings lead to necrosis of myocytes, and myoglobin and other contents are released into the blood circulation, subsequently causing biochemical disorders and organ function damage. Because the half-life of myoglobin (partly depending on the formation of oxidized adducts and individual elimination kinetics) in serum may be up to 6 h,[9] and low levels of myoglobin in blood circulation can be phagocytosed and cleared via mononuclear macrophage. Once muscle damage occurs, a large amount of myoglobin released in the blood exceeds the binding capability of globin. Therefore, free serum myoglobin causes myoglobinemia that results in the appearance of reddish-brown blood or dark brown urine. A rapidly implemented regimen with correct diagnosis is critical for a successful treatment strategy.

Coagulopathy featuring DIC is predominant in many published cases of mass bee sting envenomation; however, the etiology of coagulation dysfunction has rarely been comprehensively investigated. Interestingly, our cases showed dysfunctional coagulation owing to hyperendogenous heparinization, as evidenced by TEG guidance. TEG guidance more typically aids in resuscitation and blood product transfusion.[10,11] In Case 1, the patient did not evolve to DIC because of timely neutralization of endogenous heparin after administration of protamine and plasma exchange. The timely identification and targeted treatment of hyperendogenous heparinization was an important and effective strategy that reversed the coagulopathy. Protamine is currently the most widely used drug for the reversal of heparin anticoagulation and is used to treat bleeding after injection of excessive heparin-like substances. In this report, 2 patients were effectively treated with protamine without other substitutes to neutralize the endogenous heparin-like substances. We found that endogenous heparinization plays an important role in coagulation dysfunction in patients with wasp sting, owing to similar symptoms caused by venom.[12] Of note, autoheparinization has been previously found in a few studies, including drowning-related asphyxia and acute traumatic coagulopathy.[13-16] The mechanistic actions of acute traumatic coagulopathy have demonstrated protein C activation, endothelial glycocalyx disruption, depletion of fibrinogen, and platelet dysfunction, indicating that the injury of vascular endothelial cells causes the release of endogenous heparin-like substances, which is consistent with a previous report.[16] These multifactorial processes lead to hypoperfusion, decreased clot strength, autoheparinization, and hyperfibrinolysis.[14,16]

Heparin is an acid mucopolysaccharide that is mainly produced by mast cells and basophils and is widely found in human vascular endothelial cells, liver, intestine, and muscle tissues. Once mast cells and basophils are activated in allergic reactions, the production and release of heparin or heparin-like substances may be an important source for hyperendogenous heparinization. Hyperendogenous heparinization is not directly caused by toxic or allergic events. Mostly, it is triggered by the release of toxic substances such as bee venom peptide PLA_2 in the body from allergic reactions and poisoning. PLA_2 can destroy the integrity of the lipid bilayer by hydrolyzing membrane phospholipids, resulting in vascular endothelial damage.[17] In the presence of melittin, PLA_2 also has a strong prohemolytic effect and is a potential factor in rhabdomyolysis in wasp sting victims. After vascular endothelial injury and rhabdomyolysis, a large amount of

endogenous heparin-like substances will be released and cause deranged coagulation. Moreover, when rhabdomyolysis and liver failure occur, a large amount of heparin and heparin-like substances are released from injured muscle tissues and hepatic vascular endothelial cells.[8] The main manifestation in our cases was that, without use of heparin-like substances, the clinical R time was significantly prolonged and the α (fibrin polymerization function) was considerably decreased in TEG analysis. In addition, APTT was significantly increased 2- to 4-fold, and TT was also abnormal.

In general, heparin plays an indirect anticoagulative role, mainly enhancing the activity of AT, and the inactivation rate of serine protease by AT is dependent on heparin. We found the AT was decreased in both cases. This may be ascribed to the consumption of AT after anticoagulation with endogenous heparin. One study has demonstrated that heparin-like substances could cause excessive consumption of platelets and concurrent bleeding.[18] In the present report, we found a progressive decrease in platelets with the persistent production of endogenous heparin. Furthermore, 1 study also confirmed the antifibrinolytic effects of heparin-like substances.[19]

In our report, fibrinogen was decreased in the 2 patients when hyperendogenous heparinization occurred. The measurements of PIC and tPAI-C, which represented the activation of the fibrinolytic system as well as vascular endothelial cell injury, increased. Vascular endothelial cell injury may cause the production of endogenous heparin, the activation of PIC, and a decrease in fibrinogen, indicating increased fibrinolysis. Moreover, these changes reversed when heparinization disappeared.

The patients' symptoms varied significantly, perhaps related to the number of wasp stings. The levels of cPAIC and PIC were significantly higher in Case 1 than in Case 2, suggesting that a higher number of stings may cause more serious conditions, such as liver damage, rhabdomyolysis, and vascular endothelial injury, as well as more significant fibrinolysis. The present report also found coagulation abnormalities reported in previous observations,[20] and our observations and those of other investigators suggest that coagulopathy after mass hymenopteran stings is probably due to activated mast cells that release mediators such as heparin and tryptase.[21-23] Although the mechanisms of heparinization and hyperfibrinogenolysis via phospholipase A_2 have been described in vitro and in vivo in animal trials and a human clinical setting,[24,25] some reports still maintain that the occurrences of these abnormalities excluded heparin use and bleeding that caused the prolonged clotting times and the low fibrinogen level.[4,26] Recurrent coagulopathy may have occurred because of sequestration of a large amount of venom in the integument. Hyperendogenous heparinization was solely observed in the 2 patients in our report and has not been previously reported in the literature.

Conclusion

We found distinctive coagulation abnormalities in 2 cases of massive wasp stings and further demonstrated that this unique phenomenon could be the cause of hyperendogenous heparinization. Our observations have shown that TEG guidance and coagulation tests are imperative for the management of mass wasp stings. When hyperendogenous heparinization is identified, protamine is the main intervention of choice to achieve maximal recovery.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.wem.2021.02.009.

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CASE REPORT

Visual Hallucinations After a Russell's Viper Bite

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Visual hallucinations (VHs) are extremely rare in snakebites. We report a case of Russell's viper bite in an otherwise healthy 55-y-old woman who presented to a hospital in south India with established clinical features of systemic and local envenomation, including coagulation failure, without any neurologic manifestations on admission. She reported simple VH on the third day, which abruptly stopped on the fifth day without any specific medications. Clinical, laboratory, imaging, and electrophysiological studies did not reveal any neuropsychiatric disorders. Including this case, only 5 cases of VH are documented in the literature, 2 following cobra and viper bites and 1 after a sea snake bite. Two cases were reported from Australia and 1 each from the United States, Iran, and India.

Keywords: snakebite, delayed manifestation, mechanisms, illusion, psychological processes

Introduction

Hallucinations are defined as "the perception of an object or event (in any of the 5 senses) in the absence of an external stimulus; experienced by patients with various conditions that span several fields (eg, neurology, ophthalmology and psychiatry)."[1] Although visual hallucinations (VHs) have numerous etiologies, they are not a pathognomonic feature of a primary psychiatric illness.

Snakebite is a neglected tropical disease contributing to significant morbidity and mortality. It is relatively more common among the poor rural population living in south Asia, southeast Asia, and sub-Saharan Africa. Various neurologic manifestations have been documented in snakebite cases.[2-4] VHs have been cited as a presenting feature of snakebite in some medical textbooks; however, the mechanisms behind this presentation remain unclear. A MEDLINE search revealed only 3 published reports[5-7] on VHs in snakebite victims, and a fourth was found via query of a search engine ("Bryan's life of pain: 26 snake bites, acid trips" by *The Queensland Times* in 2017).

We present the case of a 55-y-old woman who developed VHs after a Russell's viper bite. Our purpose is to highlight a rare manifestation of the Russell's viper bite and to review and summarize the literature regarding possible mechanisms that underlie this manifestation.

Case Report

A 55-y-old female patient with no known comorbidities was brought to the emergency room of a hospital in South India 2 h after she was bitten by a Russell's viper (*Daboia russelii*) on the right foot while working in a paddy field. The snake was identified as a Russell's viper by a local herpetologist.

On arrival, she was conscious, well oriented, afebrile, and hemodynamically stable, with adequate oxygen saturation in room air. Her 20-min whole blood clotting test was positive (no clot formation after 30 min), and this result was reinforced with the abnormal international normalized ratio (5.8) detected in the instrumented laboratory results (Table 1). The other hematologic, metabolic, and biochemical parameters (eg, complete blood

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count; blood urea; serum creatinine and electrolytes; glucose; liver transaminases and alkaline phosphatase; total protein, albumin, globulin, and albumin:globulin ratio; total, direct, and indirect bilirubin and uric acid) were within normal limits. Owing to her deranged coagulation profile (ie, prolonged prothrombin time with international normalized ratio and activated partial thromboplastin time), she was administered 100 mL of polyvalent antivenom from Bharat Serums and Vaccines Limited, as per protocol. The manufacturer indicates an experimental neutralizing capacity of the antivenom for the following snake venoms (mg neutralized·mL antivenom^{-1}): Indian cobra (*Naja naja*), 0.6 mg·mL^{-1}; Indian krait (*Bangarus caeruleus*), 0.45 mg·mL^{-1}; Russell's viper (*Daboia russelii*) 0.6 mg·mL^{-1}; and saw scaled viper (*Echis carinatus*), 0.45 mg·mL^{-1}. The patient did not have any adverse reactions to antivenom upon observation. Table 1 shows basic laboratory results.

The patient received another 8 vials of antivenom to normalize her coagulation profile over the next 24 h owing to persistence of coagulopathy. She was comfortable on the second day, and local inflammatory changes were not alarming. There was no pain and minimal tenderness, redness, and swelling around the bite. There was no increase in bruising, bleeding, or blistering. On the third day, the patient reported sudden-onset VHs, consisting of seeing ropes dangling in the air and bright colors and lights with geometric shapes (eg, red, blue, and yellow in rectangles and circles), which lasted for 20 s. These recurred 25 to 30 times on the third and fourth day and reduced to 15 to 20 times on the fifth day. The VHs did not have any diurnal variation or any identifiable configuration and stopped abruptly on the fifth day. There were no VHs from the morning of the sixth day of admission, and they did not recur during her follow-up visit 12 mo later. She did not have any other neurologic symptoms or signs such as headache, seizures, drop attacks, delirium, encephalopathy, or loss of consciousness. Since admission, she had reported no delusions and denied any auditory hallucinations. She was fully oriented to time, place, and person. Her speech was well organized, and her memory was intact. Her insight was preserved through her hospital stay, and she was able to distinguish the hallucinations from reality. Her sleep cycle was normal without any medications. She was not experiencing depersonalization-derealization illness, and she remained alert during her hospital stay. Her brain magnetic resonance imaging scan and electroencephalogram were normal on the fourth day after the bite.

She was examined by an ophthalmologist and was found to have normal visual acuity. Other ophthalmologic assessments such as color vision, extraocular motility, and intraocular pressures were within normal limits. Slit-lamp examination and fundoscopic examination did not reveal any abnormalities. She had no medical history of head injury, migraine, epilepsy, possessive attacks, or any other psychiatric illnesses, and there was no family history of psychiatric illness. She had not previously experienced VHs. Her pregnancies and postpartum periods were uneventful. Her thyroid profile and calcium, magnesium, and copper levels were within normal limits. Blood examinations excluded sepsis or any metabolic abnormalities. She was free from substance abuse. Her sleep pattern was the same as before the onset of VHs. She was assessed by a psychiatrist and neurologist both during the hospital stay and during follow-up and was found to be free from neuropsychiatric disorders. Post-traumatic stress disorder was ruled out by the psychiatrist during the follow-up period. VHs did not recur during a follow-up of 12 mo.

Discussion

Snakebite is a neglected tropical disease. Snake venom contains a complex mixture of toxins. Studies on neurotoxins highlight neuromuscular transmission and receptor functions, categorized into fasciculins (toxins that attack cholinergic neurons, destroying acetylcholinesterase), dendrotoxins (inhibiting neurotransmission), and alpha-neurotoxins (attacking nicotinic acetylcholine receptors, blocking acetylcholine flow). Various neurologic manifestations of snakebite have been extensively reviewed,[2] and there was no mention of VHs. The wide range of neurologic presentations after snakebite is attributable to patient-related factors and snake venom–related factors. Important patient-related factors include interindividual variations in envenomation, physiologic status, and the body's response to the venom. Venom composition can vary from snake to snake, even among the same species. Furthermore, venom composition is also known to have seasonal, diurnal, and geographical variations.

Assessment of reported cases of post-snakebite VHs suggests that such hallucinations usually occur soon after the bite and can occur with any species of snake. Furthermore, a possible role of antivenom cannot be ruled out in our case, as the onset of VHs was seen after administration. Our case had isolated simple VHs without any underlying neuropsychiatric illnesses. In the 5 reported cases in the medical literature, patients with post-snakebite VHs were adults in 3 cases, a preschool child in 1 case, and a teenager in 1 case. Three of these patients were male, and 2 were female. The nature of VHs was simple in 4 cases; however, the details of VHs were not described in 1. Two cases were recorded from Australia and 1 each from the United States, Iran, and India. The details of each case are provided in Table 2.

Table 1. Basic laboratory examination results

Investigation	*Results*	*Unit*	*Normal range*
Hemoglobin	12.1	g%	13.0–16.0
Total RBC count	4.31	million·μL^{-1}	4.00–5.00
HCT	44.3	%	41.0–50.0
MCV	90.1	fL	81.1–96.0
MCH	31.2	pg	27.2–33.2
MCHC	34.2	g·dL^{-1}	32–36
Total WBC count	10.6	$\times 10^3$ cells·μL^{-1}	4.0–11.0
Neutrophils	6.13	$\times 10^3$ cells·mu;L^{-1}	2.0–7.0
Lymphocytes	2.17	$\times 10^3$ cells·μL^{-1}	1.0–3.0
Monocytes	1.09	$\times 10^3$ cells·μL^{-1}	0.1–08
Eosinophils	0.15	$\times 10^3$ cells·μL^{-1}	0.02–0.5
Basophils	0.05	$\times 10^3$ cells·μL^{-1}	0.02–0.1
Platelet count	309	$\times 10^3$ cells·μL^{-1}	150–450
MPV	9.5	fL	6.5–12.0
PDW	11.2	fL	9.0–13.0
PT	45	s	11.5–14.5
INR	5.8		0.8–1.1
aPTT	89	s	30–40

HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; RBC, red blood cell; WBC, white blood cell; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

VHs can be the result of interplay among disturbances of brain anatomy (psycho-physiologic), brain chemistry (psycho-biochemical), and prior experiences (psychodynamic).[8] A common pathway may be involved if there is similarity of VHs in apparently diverse conditions. VHs can be classified as simple elementary and complex; this is attributed to irritation of the primary visual cortex (Brodmann's area 17) and visual association cortices (Brodmann's areas 18 and 19), respectively, with the support of electroencephalogram and direct stimulation experiments.[9]

Because VHs are rarely encountered in snake envenomation, there is limited knowledge regarding their exact mechanism, which may involve any combination of the aforementioned pathways. The venom or antivenom might have induced transient vasculitis or caused deafferentation of the visual system, leading to the cortical release phenomenon[10] and thus leading to VHs. The other possibility is that venom-induced deafferented neurons can undergo specific biochemical and molecular changes and contribute to an overall increase in excitability, leading to VH. Reticular activation system and brainstem (as in peduncular hallucinosis) involvement contributing to VH were ruled out by clinical, neurophysiologic, and imaging studies in our case. Lack of sleep as a contributing factor for VH was ruled out because the patient slept well without any sedatives and her sleep cycle was normal. Intensive care delirium as a contributory factor was ruled out clinically. The occurrence of VH at presentation, as documented in earlier cases, may be related to the psychedelic effects of the venom. However, nondocumentation of VH at presentation with snake envenomation may be attributed to the dominant symptoms of local pain, fear of death, and other clinical manifestations.

Although follow-up studies in cases of snake envenomation have revealed various psychiatric morbidities, there has been no report of VH on follow-up.[11,12]

Table 2. Analysis of visual hallucinations in snakebite

No.	*Age/Sex/Country*	*Snake*	*Description of hallucination and recovery*	*Year*	*Reference/ Source*
1	2/female/Australia	*Astrotia stokasii* (Sea snake)	Visual hallucination while recovering and after spasmodic generalized tonic movements. Recovered.	1981	5
2	30/male/United States	*Ophiophagus hannah* (King cobra)	Brightly colored visual hallucination at presentation. Recovered.	1989	6
3	19/male/Iran	*Vipera berus* (Adder)	Visual hallucinations (seeing objects around him in colored droplets) immediately after snakebite. Recovered.	2018	7
4	46/male/Australia	*Crotalus horridus* (Timber rattlesnake)	Hallucination at presentation. Details not available.	2017	*The Queensland Times*, 2017
5	55/female/India	*Daboia russelii* (Russell's viper)	Appearance of seeing ropes dangling in air and bright colors and lights with geometric shapes. Recovered.	2021	Present case

Other causes of VH, such as cognitive dysfunction, drug interaction, adverse drug events, metabolic disorders, sepsis, intensive care psychosis, or underlying psychiatric conditions, have to be kept in mind and ruled out when handling such cases. One must also consider critical illness neuropathy and myopathy in such cases. In our case, follow-up over a period of 1 y with the support of a physician, psychiatrist, and neurologist did not reveal any abnormalities.

Interestingly, venom-induced hallucinations have been observed with the venom of fish,[13] spiders,[14] toads,[15] and wasps.[16] Some cases of VHs may not be mentioned by the patient, and physicians must remember to elicit relevant history. Because patients with envenomation experience greater pain and local symptomatology, VH may not receive due attention. Thorough bedside clinical history and examination are the most vital elements of a workup for VHs. Associated symptoms and characteristics of VH may direct the diagnosis. Before attributing VH to envenomation, the physician must rule out psychosis, inattention, Parkinsonism, disorders of cognitive dysfunction, sleep disorders, impaired vision, and headache. It appears that patients experiencing VHs do well with reassurance, as noted in our case and other published ones.

Mental health conditions after snakebite envenomation are not uncommon, with post-traumatic stress disorder being the most common mental health condition reported. Depression, psychosocial impairment, organic delusional (schizophrenia-like) disorder, and hysteria have also been a focus in some studies.[17] Hysteria, currently classified in ICD-10 as unspecified dissociative and conversion disorder, has been reported in 2 case reports: 1 from Bangladesh in 1948[18] and another from Nigeria in 1992.[19] Both of these patients were female, and both cases manifested in the acute setting with hysterical paralysis after snakebite envenoming. More research is needed to understand this neglected aspect of snakebite morbidity, especially in countries with a high burden.

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REVIEW ARTICLE

Urological Emergencies and Diseases in Wilderness Expeditions

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When considering medical emergencies that might affect an expedition, urologic emergencies are typically not included. However, the reality is that manageable and prevalent urologic disease processes can pose significant challenges for the wilderness medicine physician and warrant consideration. The purpose of this review is to identify and discuss the most commonly encountered urologic emergencies and diseases in the wilderness setting and to prepare the expedition medicine physician for management of these urgent conditions. A PubMed and Internet search for urologic emergencies and diseases in wilderness conditions was conducted. We also searched bibliographies for useful supplemental literature and material from leading mountain medicine and wilderness medicine societies as well as population-based studies for common urologic diseases. Urologic emergencies and diseases on expeditions and in wilderness conditions have been reported primarily with retrospective case series and case reports. The most commonly reported urologic emergencies in this setting include urologic trauma, renal calculi, and urinary retention. Parasitic infections in the urinary tract also have been reported to cause urinary symptoms and urinary retention in wilderness conditions. Although urologic diseases in such conditions are uncommon, significant morbidity and even potentially life-threatening sequelae to urologic emergencies were found to occur. Major genitourinary emergencies in expedition medicine are uncommon but involve both potentially manageable urgent conditions and serious life-threatening conditions best treated with urgent stabilization and occasionally medical evacuation. The opportunity exists for increased awareness for management strategies for urologic conditions in the often remote or extreme environments of an expedition.

Keywords: genitourinary, renal calculi, urinary retention, urologic trauma, remote, ultrasonography

Introduction

Explorer Sir Ranulph Fiennes' attempt to become the first person to trek across Antarctica alone in 1996 was abruptly cut short after nearly 48 h of constant pain from renal calculi.[1] Similarly, many other diseases processes such as urinary retention, traumatic injuries, and parasitic organisms can pose significant urologic challenges in remote settings.

Management of emergencies in remote settings is very similar to that in traditional settings with a few exceptions where resource limitations and equipment are factors. The standard ABCDE algorithm (airway, breathing, circulation, disability, and environment) can be modified in wilderness medicine to MARCH (massive hemorrhage, airway, respirations, circulation, hypo-/hyperthermia, and hike vs helicopter). These steps are imperative for prevention of further deterioration of any wilderness expedition patient's condition. Urologic function also should be considered upon stabilization of these factors because maintaining adequate renal function via the urologic tract is essential for any expedition participant's normal health in the wilderness. A genitourinary (GU) emergency in a remote setting is considered any medical or traumatic event that places an expedition participant at risk of loss of life or at risk for significant impairment of normal urologic or renal function. The challenge for an expedition physician is to prepare for and have adequate provisions for GU emergencies when they arise without

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overburdening the supplies included on the expedition. Our aim is to identify and discuss the most commonly encountered urologic emergencies and diseases in the expedition setting to prepare the expedition medicine physician for management of these conditions in remote settings.

SEARCH STRATEGY

A PubMed search for GU emergencies in wilderness and expedition conditions was conducted. A Medline search using the PubMed database was conducted using the following keyword combinations: (genitourinary and wilderness) OR (renal calculi and wilderness) OR (urinary retention and wilderness) OR (urologic emergency and wilderness) OR (urologic ultrasonography and wilderness) OR (genitourinary and expedition) OR (renal calculi and expedition) OR (urologic emergency and expedition) OR (urologic ultrasonography and expedition) OR (testis torsion and expedition) OR (testis and wilderness) OR (genitourinary trauma and expedition) OR (genitourinary and wilderness) OR (candiru and expedition) OR (candiru and wilderness) OR (leeches and genitourinary and expedition) OR (leeches and genitourinary and wilderness) OR (candiru and genitourinary) OR (leeches and genitourinary).

Further information was gathered from the previously stated Internet word combination searches using the Google search engine. We also searched bibliographies of relevant articles identified for useful supplemental literature as well as population-based studies for common urologic diseases.

REVIEW

A total of 255 records were identified and reviewed to identify articles relevant to the aims of the study. All relevant articles were reviewed and included in this study. Germane references identified in the aforementioned reviews were included in this analysis.

GU diseases and emergencies on expeditions and in wilderness conditions have been reported with small retrospective case series, case reports, and 1 prospective analysis. GU injuries and diseases are generally not common relative to other problems encountered on wilderness expeditions, and the incidence of true GU emergencies is likely to be even less common than that of minor urologic diseases encountered on an expedition. Two maritime expedition reviews reported that GU disorders occur in 0.9 and 9% of patients treated, respectively.[2,3] The first review detailed medical logs from 11 voyages to Antarctica over a 2-y period, and the second review investigated medical contacts made by shipboard caregivers to US emergency medicine physicians on 90 US-based vessels over a 4-y period. Although neither reference describes the specific diagnoses or incidence of GU emergencies, the latter outlined common urologic symptoms such as dysuria, hematuria, and scrotal/testicular pain as examples of GU problems encountered.

In general, the GU emergencies most commonly identified in this setting by this review included passage of renal calculi, urinary retention, and urologic trauma. Testis torsion and parasitic invasion of the GU tract also have been observed to cause GU emergencies in wilderness conditions. Although GU emergencies in expedition medicine are very uncommon, significant morbidity and even life-threatening sequelae were found to occur.

RENAL CALCULI

Renal calculi typically present with symptoms of intermittent, severe, debilitating abdominal and flank pain. Often this flank pain is accompanied by hematuria, nausea or vomiting, and malaise. Patients also may experience fever and chills. The protocol for diagnosis, management, and treatment of patients with suspected kidney stones in a traditional medical setting has been well described (Figure 1).[4] Management includes hydration, use of nonsteroidal anti-inflammatory drugs or narcotics for pain relief, alpha blockers to allow ureteral smooth muscle dilation (for medical expulsion of ureteral calculi), antiemetics to manage nausea/vomiting, and referral to urology for intractable pain, vomiting, or fever. Unfortunately, many of these traditional resources are not available for expeditioners while in a remote setting. Making a diagnosis of renal calculus passage will likely be limited to patient history and physical examination findings.

Management and treatment of renal calculi is slightly different in the remote setting as well. Inclusion of nonsteroidal anti-inflammatory drugs, narcotics, antiemetics, and perhaps tamsulosin in one's expedition kit in the event of presumed renal calculus would be beneficial to patients in need of care while in a remote setting. Although diagnostic tools are often unavailable for diagnosis of renal calculi, one such tool that may be available is a handheld ultrasonography device. Point-of-care ultrasound has demonstrated 70% sensitivity and 75% specificity in the identification of renal calculi.[5] There are no surgical options for renal drainage in a remote setting. Consequently, if the patient develops high fever owing to pyelonephritis, intractable vomiting with dehydration, or recalcitrant pain, emergency medical evacuation must be initiated. Body temperature ≥38°C or ≤36°C, tachycardia ≥90 beats·min^{-1}, or tachypnea ≥20 breaths·min^{-1} are typical inflammatory responses for

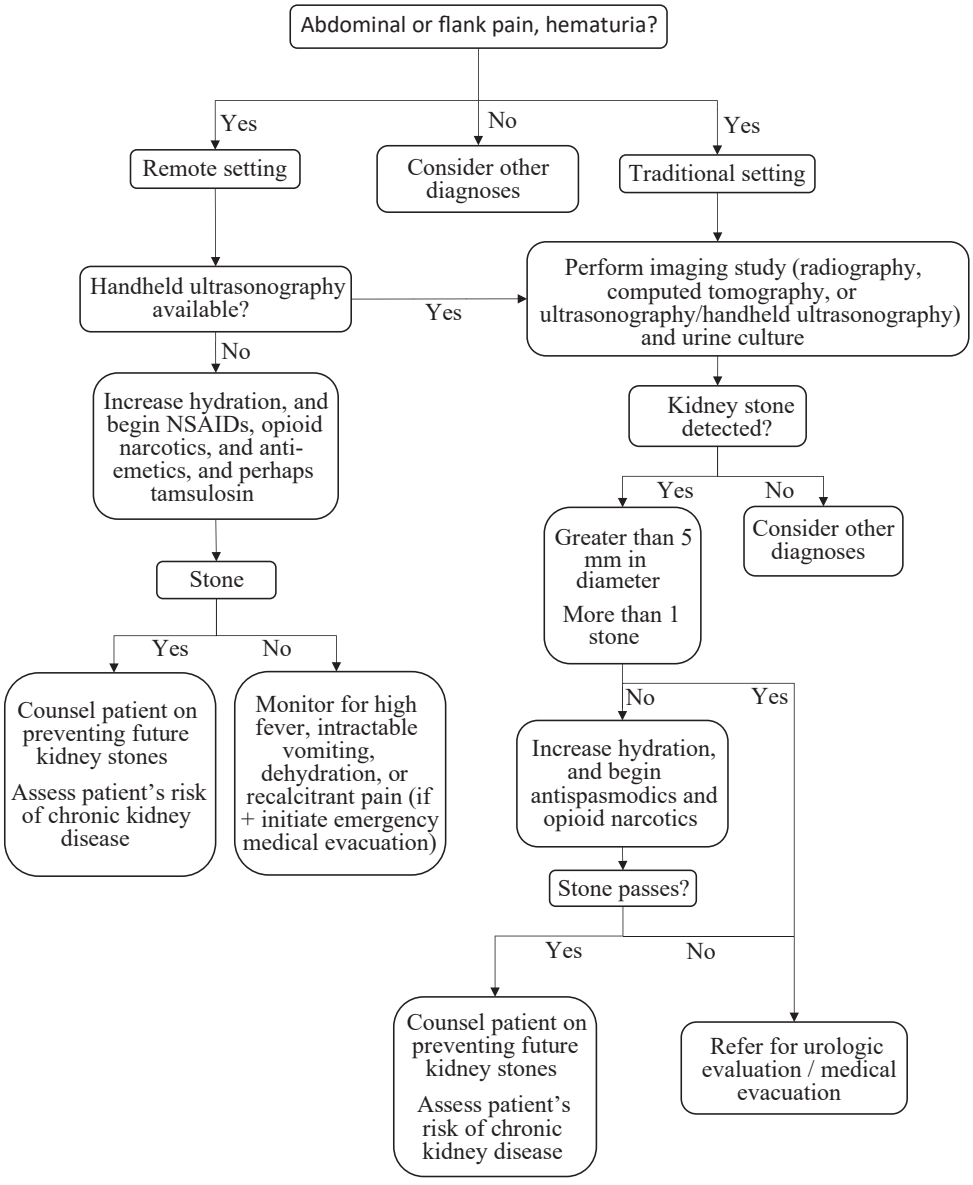

Figure 1. Diagnosis and management of acute kidney stones. Algorithm for the diagnosis and management of acute kidney stones.[4] (Adapted with permission from American Family Physicians from Frassetto et al [citation #: 3855].)

urosepsis. These findings in conjunction with renal colic should prompt medical evacuation to ensure adequate urinary tract drainage and intravenous antibiotic therapy for management of such an infection.[6]

The risk of developing renal calculi varies across settings. The annual incidence of stone occurrence in the United States is less than 1% but appears to be increasing.[7] Little prevalence data for stone occurrence in wilderness conditions have been reported. However, 1 review of Japanese Antarctic expeditions conducted over a 50-y period and involving 1734 total expedition members reported 13 episodes of renal calculi passage, consistent with incidence of less than 1%.[8]

Another consideration is that the conditions encountered in the expedition setting are widely varied, potentially affecting the incidence of stone occurrence. In many remote settings involving heat and tropical weather, the likelihood of renal calculi formation will presumably be greater owing to water conservation by the kidneys and increased urinary concentration. Dehydration caused by the immediate impact of high altitude expeditions also might increase the risk of calculus

formation.[9] The paucity of clean water in many expedition settings can further compound the dehydration encountered in such environments and further increases the likelihood of renal calculus formation. Consideration of these climate-related concerns should be given by any physician planning an expedition.

URINARY RETENTION

Acute urinary retention due to benign prostatic hypertrophy (BPH) has previously resulted in discontinuation of a Mount Everest ascent. The dehydrating effects of altitude stimulates increased fluid intake to keep up with the body's demands.[9] Increased hydration also may exacerbate urinary retention, although no data are available on the incidence of urinary retention in high altitude settings. This complete or partial inability to urinate over a prolonged period of time can even be associated with acute renal failure. Acute urinary retention includes difficulty initiating urination with a weak stream accompanied by severe suprapubic and genital pain. The causes of acute urinary retention vary, but some medical conditions increase the likelihood of acute urinary retention. In a population-based study of 1192 men 50 y and older with BPH, the acute urinary retention rates were 8.5 per 1000 man-years with a 95% CI of 6.4 to 11.2.[10] One example for an expedition setting in which this issue relevant is Mount Everest, where approximately 1000 people ascend each year, with 54% of Everest climbers from 2006 to 2019 being ≥40 y old and 85% being male.[11] Considering these demographics, there is a reasonable likelihood that a few climbers per year experience acute urinary retention related to BPH as they attempt to summit the peak.

Other potential causes of acute urinary retention include neurologic abnormalities. Spinal cord injuries are known to occur in wilderness expeditions, with 1 study of mountaineering in Scotland describing 21 patients sustaining spinal injuries between 1992 and 2001.[12] The frequency of these types of injuries has even prompted guidelines for protection of the spine from such injuries in wilderness medicine.[13] Similarly, the urinary tract is also acutely affected, with spinal cord injuries manifesting with urinary retention owing to spinal shock.[14] Placement of an indwelling urethral catheter after acute spinal cord injury and before medical evacuation also is recommended. Furthermore, wilderness physicians may encounter the need to oversee intermittent catheterization of the bladder for management of patients with chronic neurologic disease because such patients do participate in wilderness expeditions.[15] Although chronic management of urinary retention from neurologic disease has not been well documented, one such patient with Friedrich's ataxia summited Mount Kilimanjaro while maintaining intermittent catheterization during the expedition.[16] Failure to adequately maintain bladder management for these conditions also would increase the risk of renal failure. Consequently, understanding the timing, technique, and supplies required for intermittent catheterization is important for a wilderness physician when overseeing an expedition with patients who have neurologic disease.

Acute urinary retention can be related to the usage of alpha agonists as well.[17] The use of alpha agonists for nasal congestion is common in individuals at altitude, with 29% of individuals having reported nasal congestion after ascent to a mountain clinic at 3450 m in one study.[18] When taken systemically, alpha agonists can cause contraction of the internal urethral sphincter, leading to increased resistance to urinary flow.[19] Although no data have been published on the incidence of acute urinary retention related to alpha agonist usage in wilderness settings, the potential for common usage of nasal decongestants in settings such as high altitude may further increase the likelihood of this problem for men older than 40 y owing to potential underlying BPH. Consideration of these factors for an expedition physician is recommended as well.

Although the prevalence of acute urinary retention in the wilderness setting is not known, reports have demonstrated this to be a potential problem for expedition medicine. During a Japanese Antarctic expedition, one such patient in acute renal failure owing to urinary retention underwent formation of a vesicostomy, a surgically reconstructed incontinent urinary diversion in which an opening to the bladder is created in the suprapubic region. The surgery was performed with use of local anesthesia.[8] With examples like this being reported and with known high prevalence rates for urinary retention from diseases such as BPH, inclusion of supplies for intervention in urinary retention in an expedition medicine kit is warranted. An 18F coudé catheter is large and rigid enough to push through an enlarged and edematous prostatic urethra for a man with BPH (Figure 2).[20] Alternatively, if a urethral catheter is unavailable in an expedition medical kit, a needle and syringe and local anesthetic would be adequate for temporary management of acute urinary retention via suprapubic aspiration (Figure 3).

The same Japanese expedition group also prospectively analyzed the presence of urinary symptoms in the polar Antarctic environment.[21] In this analysis, 12 members of an Antarctic polar expedition completed various urinary and sleep surveys and kept daily voiding dairies for 3 d consecutively every 2 mo during their voyage. No worsening of urinary symptoms was reported in this cohort exposed to high altitude in Antarctica.

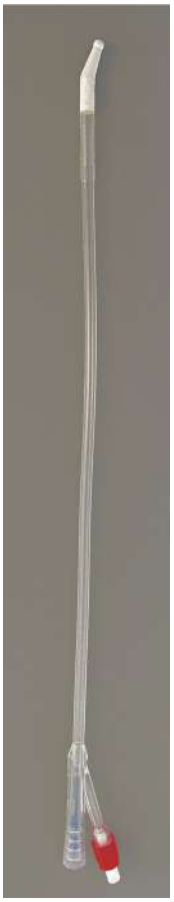

Figure 2. Coudé catheter (46 cm). Coudé "elbow" catheter is preferred for catheterization of patients with benign prostatic hypertrophy to allow easier traversal of the proximal urethral opening.

However, it is worth noting that the median age was 38 y (range 26–52) with only a small number of patients evaluated (12), one of whom was a woman. Because of the low median age range of the population studied, the likelihood of lower urinary tract symptoms caused by BPH in this population was very low.

TRAUMA

One retrospective study evaluated the epidemiologic findings for multiple India to Antarctic expeditions between 1993 to 2011 comprising a total of 1989 medical evaluations for 235 men and 2 women.[22] The group identified trauma as the most common medical condition for expeditions on Antarctica, although they did not subcategorize the incidence of specific body systems involved with these injuries, nor were urologic injuries specified in this study. In the Japanese Antarctic expeditions between 1956 and 2016, there were 6837 cases

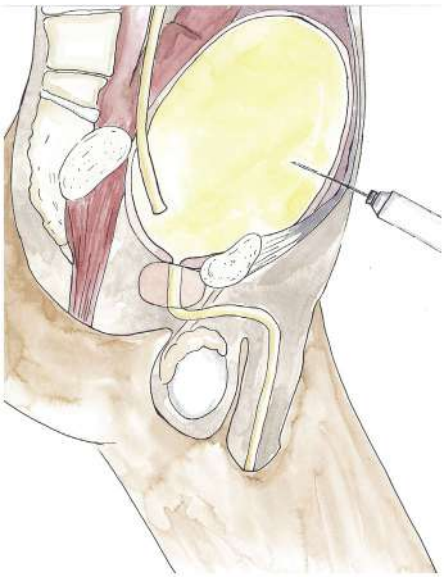

Figure 3. Suprapubic aspiration technique. Technique for performing a suprapubic aspiration of bladder fluid: Full bladder should be palpated, 2 cm above the pubic symphysis, with the needle perpendicular to abdomen; insert needle and allow urine to drain until urine stops flowing. (Artwork courtesy of Lauren Kinder.)

involving medical evaluations, with urologic cases accounting for 30 of the total (0.4%).[8] One specific urologic trauma case involved a pelvic fracture and urethral injury caused by a snow vehicle that required hospitalization for 3 mo at the Antarctic base, Syowa Station.

From the upper to the lower urinary tract, both blunt and penetrating trauma can cause injury to varying degrees. Signs of renal injury from blunt or penetrating trauma include hematuria, flank ecchymoses, and hypotension.[23] The challenges for treatment of significant renal trauma will likely exceed equipment that is available remotely, underscoring the importance of stabilization, fluid resuscitation, and medical evacuation in the initial management of these types of injuries. With suspected renal injuries, the ability to use a point-of-care ultrasound study for renal trauma has been reported in the literature, although its sensitivity and specificity have not been described (Figure 4).[24,25] The ability to use a portable ultrasonography device for a focused assessment with sonography in trauma examination for identification of intra-abdominal fluid has allowed for efficient triage of conditions even in a remote setting.[23,24] Identification of a renal injury on point-of-care ultrasound may theoretically influence medical evacuation, although clinical suspicion based on history, physical examination findings, and mechanism of injury is fundamental in a wilderness physician's management and decision-making in determining the need for medical evacuation.

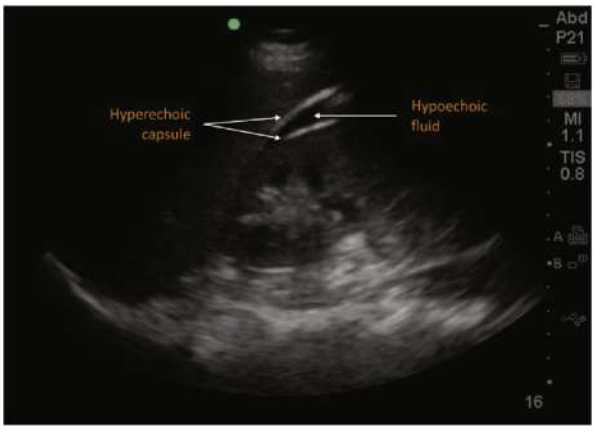

Figure 4. Point-of-care ultrasound of subcapsular hematoma. Hypoechoic fluid deep to renal capsule, consistent with subcapsular hematoma.[26] (Open Access CC-BY 3.0 unrestricted reuse and reproduction, curtesy of Cureus.)

Isolated ureteral injuries are rare and would likely occur in the situation of multiple system injuries. Ureteral injury would therefore be managed via medivac owing to the likely critical status of a patient with such injuries.[26] Bladder injuries can occur through significant blunt abdominal trauma. Most bladder injuries are associated with pelvic fractures and gross hematuria.[27] Diagnosis of bladder injuries in a remote setting would include a clinical history and physical examination, with management consisting of urinary diversion with a Foley catheter and subsequent medical evacuation.

External genitalia injuries can be significant as well. Expedition medicine management of genital trauma requires irrigation of the wound site and an antibiotic regimen. Additionally, assessment of the urethral injury would be achieved based on the injury mechanism and blood at the urethral meatus, which is consistent with initial traditional assessment. Management, however, would differ from traditional practice by initially attempting urinary diversion with a Foley catheter if the patient presents with urinary retention. Unsuccessful initial Foley catheter placement would prompt medical evacuation and possibly suprapubic bladder aspiration if medical evacuation is prolonged. Acute testicular injury will be evident based on the mechanism and physical

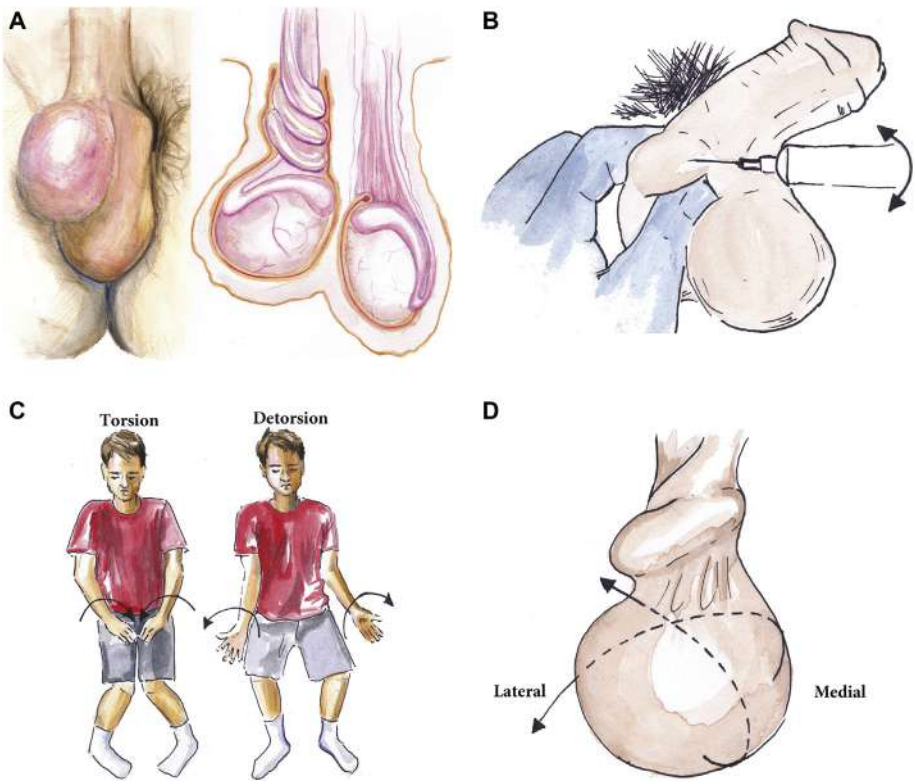

Figure 5. Manual testicular detorsion. Algorithm for management of acute testis torsion in a nonsurgical urgent setting by manual detorsion. (A) Presentation and anatomy of testicular torsion. (B) Perform a spermatic cord block to provide anesthesia to the testicle and epididymis with the use of a local anesthetic. (C) Torsion directionality: General directionality of torsion and detorsion procedure. (D) Detorsion maneuver: simultaneous rotation in the medial to lateral and caudal to cranial direction.)[34] (This figure was published in Roberts and Hedges' Clinical Procedures in Emergency Medicine and Acute Care, 7th edition, James Roberts, Urologic Procedures, Page 1143, Copyright Elsevier [2018]). (Adapted with permission courtesy of Elsevier.) (Artwork courtesy of Lauren Kinder.)

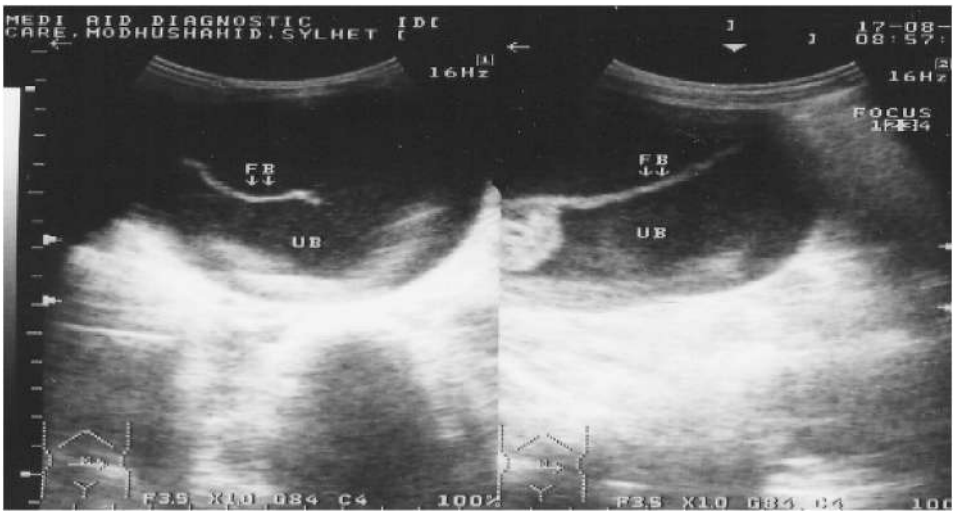

Figure 6. Bladder leech ultrasonography. Ultrasonography showing an intravesical mobile foreign body.[37] (Reprint permission courtesy of Elsevier, license number 4794950384097.)

examination, with acute testicular tenderness and scrotal laceration or dramatic echymoses present.[28] As is the case with all traumatic injuries, medical evacuation is vital if the patient is unstable or septic.

TESTIS TORSION

A time-sensitive trauma situation of high importance is testes torsion. Testis torsion presents as acute onset of testis pain and/or vomiting accompanied by a high-riding testis, acute scrotal edema, and significant tenderness (Figure 5A). Importantly, there will be no dysuria or voiding symptoms present. Diagnoses of testis torsion is achieved by examination and ultrasonography if available. The triad of nausea/vomiting, scrotal skin changes, and absence of the cremasteric reflex has been shown to enable diagnosis of torsion without a scrotal ultrasound, with a high specificity and a positive predictive value of 1.0 and 1.0 but a low sensitivity of 0.25 for all 3 findings to be present for a given patient.[29] In a case report of 2 separate episodes of testicular torsion, time from diagnosis to surgical treatment was shortened by 2 to 3 h with the assistance of point-of-care ultrasonography performed by emergency physicians, demonstrating the potential utility of ultrasound in confirming a diagnosis of torsion.[30] Patients not treated with manual detorsion or scrotal exploration with detorsion within 6 h will typically experience testicular infarction.[31] In a remote setting, urology consultation likely will be unavailable. Thus, management of torsion will include narcotics and antiemetics to manage the pain and nausea and spermatic cord block for anesthesia to enable attempted detorsion (Figure 5).[23,32] Ultrasonography imaging should be used if available with comparison of the affected testicle to the normal contralateral testicle being critical for proper assessment of torsion. Although no data for testis torsion on wilderness expeditions exist, testicular torsion is fairly common, with 1 in 4000 males affected.[33] The authors are aware of such an occurrence from a unpublished, direct report of a wilderness physician who previously assisted in the evacuation of a young male 3 mi out of a park during an endurance hike in Maryland. Depending on the demographics of the expedition team, awareness and preparedness for management of this problem by a wilderness physician may be beneficial.

FRESH WATER UROLOGIC PARASITIC INVASION

In light of the potential communication between the urinary tract and the local water source with prolonged exposure from swimming or bathing, urinary tract invasion by endemic parasites is another scenario to consider.

The candiru, a parasitic toothpick-like fish that feeds on blood from the gills of its host fish, is indigenous to the Amazon River. The candiru has been of unfounded concern since 19th century explorers such as Carl Frederick Phillip von Martius traveled to the Amazon region and described local accounts of the fish and its affinity for the male urethra.[34] The work of Von Martius and other early explorers greatly contributed to the narrative of the candiru in popular culture, despite the lack of evidence in the medical literature. However, these fears appear to be unwarranted because there is a lack of objectively confirmed cases of candiru of the bladder to date.[34]

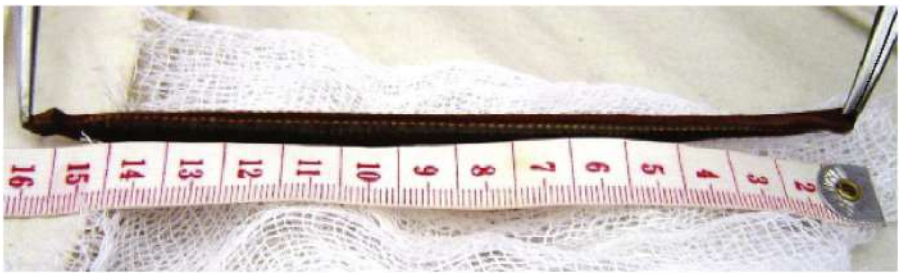

Figure 7. Bladder leech, gross appearance. Whole leech showing anterior and posterior suckers. Leech length shown in centimeters, with length reaching 16 cm.[37] (Reprint permission courtesy of Elsevier, license number 4794950384097.)

Conversely, invasion of the urinary tract by another parasite—leeches—has been supported in the literature but may not be as widely recognized in expedition medicine. There are about 300 species of leeches known to be found in temperate/tropical climates, the most common aquatic species encountered being *H granulose, H viridis, H javanica,* and *H manilensis*.[35] Leeches in the urinary tract typically present with hematuria and suprapubic pain, although cases of urinary retention and even hypovolemic shock associated with vaginal leeches have been reported.[36,37] Two large studies have been conducted in Bangladesh, with the most recent study in 2012.[35,38] One such study demonstrates that visualization of intravesical leeches is possible with ultrasound, which could be used if available on an expedition (Figure 6).[35] In the retrospective series conducted, 117 patients were treated with catheter and saline irrigation (50 mL of saline instilled with Foley clamped for 3 h), with 57 patients having successful spontaneous expulsion and the remaining 60 requiring cystoscopic removal (Figure 7).[35,38] Therefore, inclusion of a Foley catheter and saline in an expedition medical kit when there is concern about indigenous leeches is recommended.

One nonemergent consideration when venturing into indigenous tropical freshwater is schistosomiasis. Schistosomes, macroscopically visible flatworms, are found in Africa, South America, and South/East Asia.[39] Schistosomiasis invasion can lead to acute or long-term health complications. A common initial presentation of schistosomiasis is itching accompanied by a rash and later flu-like symptoms that result from allergic reaction in the weeks after primary infection.[39] *Schistosome haematobium*, endemic to Africa, specifically migrates to the bladder, where it can cause chronic inflammation that has been shown to lead to squamous cell carcinoma of the bladder. Beause this diagnosis is typically confirmed by microscopic evaluation, an expedition physician will likely only be able to rely on clinical history and examination to make the diagnosis of schistosomiasis. Recommended treatment for this infection consists of 1 to 2 d of praziquantel by mouth.[40] As compared to the other parasitic infections discussed, the overall incidence of urinary invasion for areas endemic to schiostosomiasis is very high, with approximately 290 million people treated in 2018 alone. In light of both the acute symptoms and the significant potential long-term complications, inclusion of praziquantel when traveling to Africa or other areas endemic to schistosomiasis is recommended.

LIMITATIONS

Although data exist in the literature pertaining to urologic emergencies and urologic diseases in wilderness settings, the majority of the published literature consists of case reports and retrospective reviews with inherent potential underlying bias present. Furthermore, for the Google search component of the literature review, the authors' search history was not cleared before execution of the searches outlined. Future prospective and potentially multi-institutional or multinational studies are needed to better understand the full impact of urologic emergencies and urologic diseases in wilderness expeditions.

Conclusions

Major GU emergencies are very uncommon but involve serious life-threatening conditions that should be addressed with urgent stabilization and medical evacuation. GU problems such as renal calculi passage, urinary retention, GU trauma, and testis torsion are more common and typically can be managed effectively during a wilderness expedition. Parasitic infections in the urinary tract also have been reported to cause urinary symptoms and urinary retention in wilderness conditions and should be considered in preparation for an expedition. An effective medical kit should be prepared accordingly for patients with a history of such urologic conditions or predisposing factors to better manage these problems remotely.

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REVIEW ARTICLE

Regional Rodent-Borne Infectious Diseases in North America: What Wilderness Medicine Providers Need to Know

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Rodents can transmit infectious diseases directly to humans and other animals via bites and exposure to infectious salivary aerosols and excreta. Arthropods infected while blood-feeding on rodents can also transmit rodent-borne pathogens indirectly to humans and animals. Environmental events, such as wet winters, cooler summers, heavy rains, and flooding, have precipitated regional rodent-borne infectious disease outbreaks; these outbreaks are now increasing with climate change. The objectives of this review are to inform wilderness medicine providers about the environmental conditions that can precipitate rodent-borne infectious disease outbreaks; to describe the regional geographic distributions of rodent-borne infectious diseases in North America; and to recommend prophylactic treatments and effective prevention and control strategies for rodent-borne infectious diseases. To meet these objectives, Internet search engines were queried with keywords to identify scientific articles on outbreaks of the most common regional rodent-borne infectious diseases in North America. Wilderness medicine providers should maintain high levels of suspicion for regional rodent-borne diseases in patients who develop febrile illnesses after exposure to contaminated freshwater after heavy rains or floods and after swimming, rafting, or paddling in endemic areas. Public health education strategies should encourage limiting human contact with rodents; avoiding contact with or safely disposing of rodent excreta; avoiding contact with contaminated floodwaters, especially contact with open wounds; securely containing outdoor food stores; and modifying wilderness cabins and campsites to deter rodent colonization.

Keywords: climate change, Hantaviruses, leptospirosis, plague, *Yersinia pestis*

Introduction

Rodents can transmit several bacterial and viral infectious diseases directly to humans and other animals via bites and exposure to infectious salivary aerosols and excreta (Table 1). Arthropod vectors, such as mites, ticks, and fleas, can also indirectly transmit pathogens from infected rodent hosts to humans and animals by their bites (Table 1). Rodents are both reservoirs and vectors of several pathogens that can cause infection without clinical disease. Environmental events, such wet winters followed by cooler summers, heavy rains, and flooding, have precipitated regional rodent-borne infectious disease outbreaks by forcing rodents from their burrows near food and freshwater sources into developed environments and closer to humans.[1-9]

The objectives of this review are to inform wilderness medicine providers of the environmental conditions that can precipitate outbreaks of rodent-borne infectious diseases; to describe the geographic distributions of rodent-borne infectious diseases in North America; to describe the epidemiologic features and presenting clinical manifestations and outcomes of the most common rodent-borne infectious diseases; and to recommend prophylactic therapies and effective prevention and control strategies for rodent-borne infectious disease outbreaks.

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Table 1. Infectious diseases directly transmitted by rodents and indirectly transmitted by arthropod vectors feeding on rodents

Direct transmission[a]	*Indirect transmission*[b]	*Arthropod vectors*
Hantavirus cardiopulmonary syndrome	Anaplasmosis	*Dermacentor* ticks
Hantavirus hemorrhagic fever with renal syndrome	Babesiosis	*Ixodes* ticks
Lassa fever	Colorado tick fever	*Dermacentor* ticks
Leptospirosis	Cutaneous (sylvatic) leishmaniasis	*Lutzomyia* sandflies (Americas) *Phlebotomus* sandflies (Old World)
Lymphocytic choriomeningitis	Epidemic typhus	*Pediculus corporis* (body louse)
Omsk hemorrhagic fever	La Crosse encephalitis	*Aedes* mosquitoes
Plague	Lyme disease	*Ixodes* ticks
Rat-bite fever	Murine typhus	Fleas
Salmonellosis	Omsk hemorrhagic fever	*Dermacentor* ticks
South American Andes virus[c]	Powassan virus	*Ixodes* ticks
South American Arenaviruses	Scrub typhus	*Leptotrombidium* mites
Argentine hemorrhagic fever		
Bolivian hemorrhagic fever		
Sabiá-associated hemorrhagic fever		
Venezuelan hemorrhagic fever		
Tularemia	Relapsing fever	*Ornithodorus* ticks
	Rocky Mountain spotted fever	*Dermacentor* ticks
	Salmonellosis	Flies
	Tularemia	Fleas, flies, midges, and ticks
	West Nile virus	*Culex* mosquitoes

Source: CDC Fact sheet about Andes virus. Available at: https://www.cdc.gov/hantavirus/resources/andes-virus.html#::text=Andes%20virus%20is%20a%20type.

Partial source: Available at http://www.cdc.gov/rodents/diseases

[a]Direct transmission: Diseases transmitted directly by rodent bites; by ingestion of rodent excreta-contaminated food or water; or by inhalation of or transmucosal exposures to infectious aerosols of rodent saliva or excreta.

[b]Indirect transmission: Diseases transmitted indirectly by bites from infected arthropod vectors feeding on infected rodent hosts or their excreta, or by bites from infected arthropod vectors exposed to infectious rodent aerosols or excreta.

[c]Andes virus is a South American Hantavirus found in rodents primarily in Argentina and Chile that can cause an initial influenza-like illness and progress to a cardiopulmonary syndrome 4 d to 6 wk after exposure to infected rodents or their aerosols or excreta. Andes virus is the only Hantavirus known to be transmitted from person to person by direct contact with a symptomatic person for a prolonged period (>1 h) or by contact with infectious bodily fluids. Nosocomial transmission has occurred.

Methods

To meet the study's objectives, Internet search engines, including Google, Google Scholar, PubMed, Medline, and Ovid, were queried to examine peer-reviewed scientific articles on the most common regional rodent-borne infectious disease outbreaks in North America. The keywords included climate change, Hantaviruses, leptospirosis (LS), plague, and *Yersinia pestis*. The study period was defined as 1970 to 2020. The articles reviewed included microbiological articles, meteorological/climate change studies, disease surveillance studies, review articles, case reports and series, and disease outbreak investigations (Table 2). Articles reviewed but excluded as references included

Table 2. Scientific articles reviewed, referenced, and stratified by subtypes

Methods	*Stratification by subtype*						*Totals*
	Microbiological articles	*Disease surveillance studies*	*Outbreak investigations*	*Meteorologic/ Climate change articles*	*Case reports and series*	*Review articles*	
Reviewed and stratified	5	10	4	14	15	10	58
Referenced	4	8	2	7	6	8	35

Figure 1. A North American deer mouse, *Peromyscus maniculatus*, which serves as the rodent reservoir and transmitter of the *Sin Nombre* Hantavirus in Western Canada, California, and the Southwest United States. Source: United States Centers for Disease Control and Prevention. Public domain. Available at: https://phil.cdc.gov/Details.aspx?pid=8358. Photo credit: James Gathany, CDC.

letters to the editor, dispatches, opinion-editorial articles, clinical-pathological case conferences, and abstracts of posters and presentations at conferences and scientific meetings. This methodology met all recommended criteria for narrative reviews, including use of several keywords, 2 or more Internet search engines, a defined study period, and article inclusion and exclusion criteria.[10] Institutional review board approval was not required for this review of peer-reviewed scientific publications.

Results

THE IMPACT OF CLIMATIC PATTERNS ON REGIONAL RODENT-BORNE INFECTIOUS DISEASES

Unanticipated regional outbreaks of Hantavirus cardiopulmonary syndrome (HCPS) have occurred after periods of relative drought followed by heavy rainfall in the United States.[1,3,4] During the spring of 1993, the first New World Hantavirus to be identified in the United States, later named *Sin Nombre* virus, caused a cluster outbreak of severe pneumonia with cardiopulmonary failure in 24 young, healthy patients, 18 of whom died.[11,12] All 18 cases were clustered in the Four Corners region of the southwestern United States where the borders of 4 states (Arizona, Colorado, New Mexico, and Utah) meet.[11,12] Subsequent investigations by mammologists from the United States Centers for Disease Control and Prevention (CDC) confirmed that the increased precipitation and moisture from an *El Niño* winter spawned abundant vegetation with a seed crop that provided shelter and food for the regional rodent population of deer mice (*Peromyscus maniculatus*) (Figure 1).[13] Subsequent explosive growth in the deer mouse population increased the likelihood of human exposure to the infectious secretions of rodent vectors, setting the stage for the first Hantavirus outbreak in the United States.[12,13]

During the summer of 2012, after a rainy winter and spring, 10 cases of *Sin Nombre* Hantavirus infections

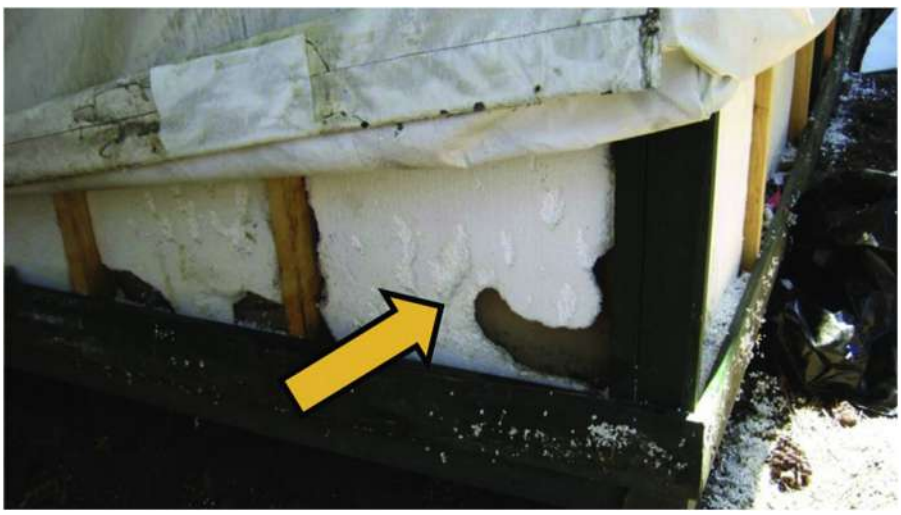

Figure 2. Damage (yellow arrow) from deer mice tunneling in the foam insulation of a signature tent cabin in Yosemite National Park, California, the site of a *Sin Nombre* Hantavirus outbreak during the summer of 2012. Source: United States Centers for Disease Control and Prevention. Public domain. Reference: Nuñez et al.[15] Available at: https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=3944872_13-1581-F4.jpg.

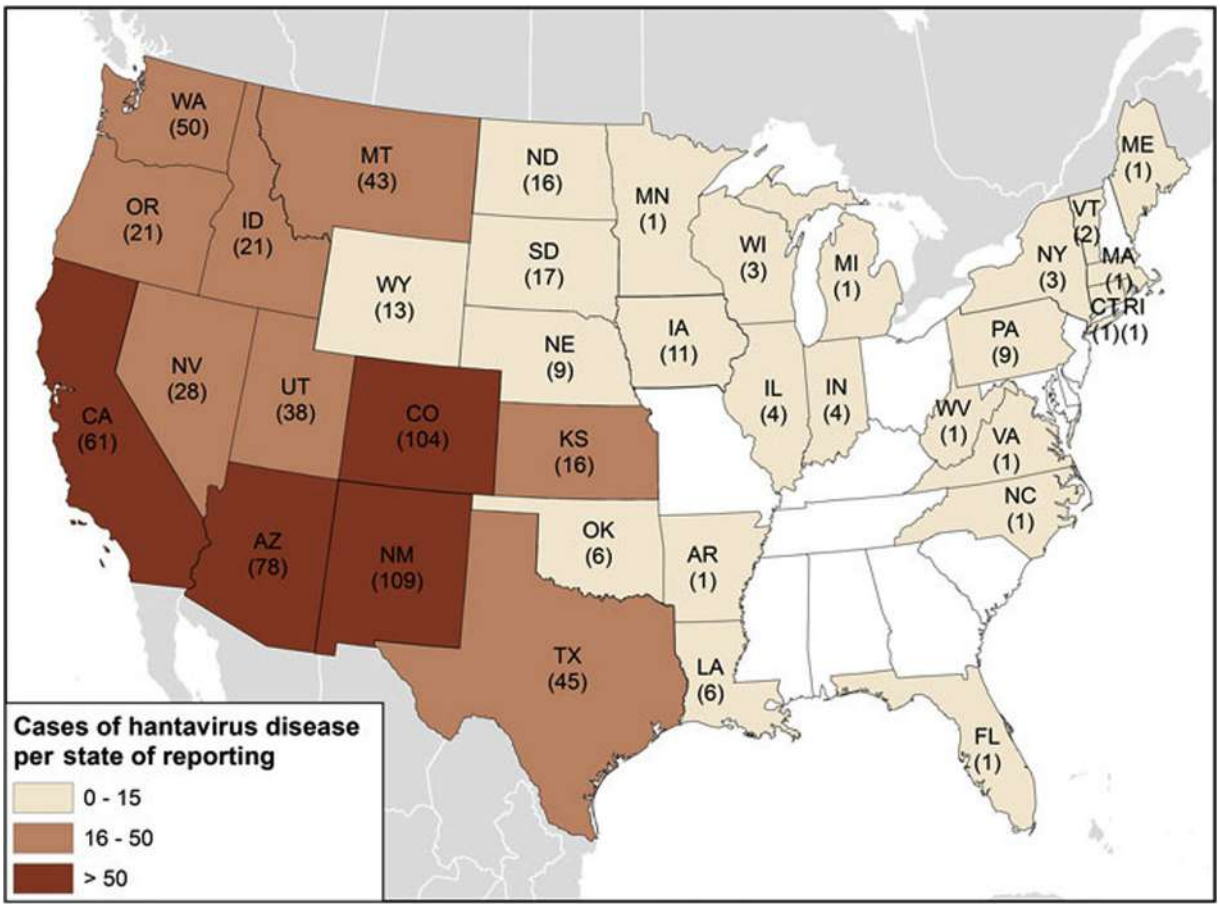

Figure 3. Geographic distribution of total cases of Hantavirus diseases (n=728) since 1993 by states of reporting as of 2017, continental United States. Source: United States Centers for Disease Control and Prevention. Public domain. Available at: https://www.cdc.gov/hantavirus/surveillance/reporting-state.html.

occurred in overnight visitors to California's Yosemite National Park, 9 of whom stayed in panel-walled, canvas-covered (or signature-level) tent cabins (Figure 2).[14,15] Eight patients developed HCPS, 5 required mechanical ventilation for respiratory failure in intensive care, and 3 patients died.[14,15] Staying overnight in a signature tent cabin in the park was significantly associated ($P<0.001$) with the risk of becoming infected with Hantavirus.[15] Rodent tunnels and nesting sites were identified in the foam insulation of the tent cabins (Figure 2).[15] CDC mammologists later detected antibodies to *Sin Nombre* Hantavirus in 10 of 73 (14%) locally captured deer mice.[15] The case fatality rate for HCPS caused by the *Sin Nombre* virus in the Yosemite outbreak was 33%, which was consistent with the current North American case fatality rate for HCPS of 30 to 35%.[16]

The *Sin Nombre* virus is transmitted to humans by infective secretions from deer mice and remains the most common cause of HCPS in the United States and Canada (Figure 1). Most cases are regionally confined to California and the Four Corners region in the United States and to the western provinces in Canada, especially Alberta (Figures 3 and 4).[12,17] Heavy winter and spring precipitation followed by cooler summers have preceded *Sin Nombre* Hantavirus outbreaks in the infected deer-mouse–endemic regions of the United States and Canada.[12,17]

LS is a rodent zoonosis that, like Hantavirus, causes infection without clinical disease in rodents. Transmission to humans occurs through exposure to floodwater and sediment contaminated with the urine of infected rodents. Regional LS outbreaks have occurred after flooding in Hawaii and Europe, typhoons in Asia, and tropical storms and hurricanes in the southeastern United States.[2,5-8]

In a 2013 descriptive epidemiologic analysis of hospitalized patients with LS after a typhoon in the Philippines, investigators reported 259 laboratory-confirmed cases out

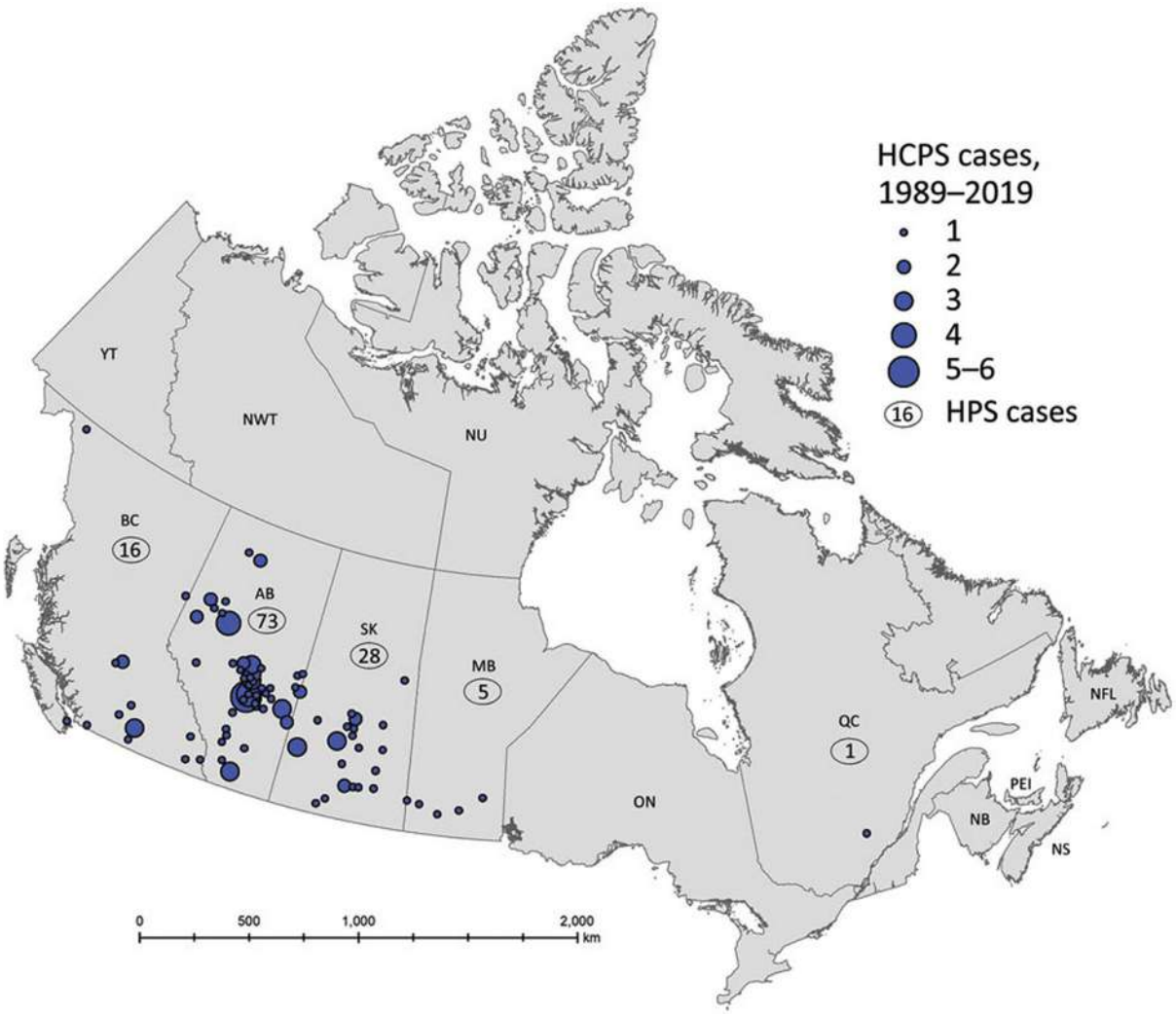

Figure 4. Geographic distribution of total cases of Hantavirus cardiopulmonary syndrome (n=143) caused by the *Sin Nombre* Hantavirus by reporting Canadian provinces, 1989–2019. Source: United States Centers for Disease Control and Prevention. Public domain. Reference: Warner et al.[17] Available at: https://wwwnc.cdc.gov/eid/article/26/12/20-2808-f1.

of 670 possible cases.[7] Of the confirmed cases, the mean patient age was 39 y, and most were males (82%) who had waded in floodwaters (98%).[7] Fever was the most common presenting symptom (99%), followed by myalgia (78%), malaise (75%), conjunctival suffusion (59%), oliguria (57%), diarrhea (39%), and jaundice (38%).[7] Complications included renal failure, pulmonary hemorrhage, meningitis, and myocarditis.[7] The mortality rate was 5%, primarily owing to pulmonary hemorrhage.[7] The investigators recommended that clinicians maintain a high index of suspicion for LS during monsoon seasons when heavy rains and typhoons could lead to flooding.[7]

Although plague is often considered a rodent-borne disease, rodents are only the animal reservoirs of the plague bacterium and not the vectors of *Yersinia pestis*, which is transmitted via the bite of plague-infected rodent fleas. In a 1999 descriptive epidemiologic analysis of human plague cases in New Mexico, investigators reported that cases occurred more frequently after periods of above-average winter and spring precipitation.[9] Like cases of *Sin Nombre* Hantavirus, most cases of plague occur in the Southwest, mostly in California and the Four Corners region.

In summary, rodent-borne infectious disease outbreaks of HCPS, LS, and plague spawned by favorable weather patterns have been increasing in endemic regions across North America, especially in the Four Corners area and subtropical and tropical regions in the United States and in western Canada.

Table 3. North American Hantaviruses capable of causing the Hantavirus cardiopulmonary syndrome

North American Hantavirus species	*Rodent reservoirs (common names)*	*Rodent reservoirs (Latin names)*	*Geographic distributions (North America)*
Bayou	Marsh rice rat	*Oryzomys palustris*	Louisiana, Texas
Black Creek Canal	Cotton rat	*Sigmodon hispidus spadicipygus*	Southeast United States, Florida
Bloodland Lake[a]	Prairie vole	*Microtus ochrogaster*	Missouri
El Moro Canyon	Western harvest mouse	*Reithrodontomys megalotis*	Canada, western United States
Isla vista[a]	California vole	*Microtus californicus*	Pacific Northwest United States, California
Limestone Canyon[a]	Brush mouse	*Peromyscus boylii*	Southwest United States
Monongahela	Deer mouse	*Peromyscus maniculatus*	Pennsylvania, West Virginia
Muleshoe	Cotton rat	*Sigmodon hispidus texianus*	Southeast United States, Florida, Texas
New York	White-footed mouse	*Peromyscus leucopus*	Canada, New England States
Prospect Hill[a]	Meadow vole	*Microtus pennsylvanicus*	Canada, throughout United States
Sin Nombre	Deer mouse	*Peromyscus maniculatus*	Canada, western United States

[a]Human diseases caused by these North American Hantaviruses have not been reported to date. All other Hantaviruses listed have caused the Hantavirus cardiopulmonary syndrome in North America.

HANTAVIRUS IN THE UNITED STATES AND CANADA

The Hantaviruses are a single genus of enveloped, single-stranded RNA bunyaviruses that cause infection without disease in rodents and insectivores, such as shrews and voles. There are about 40 species of Hantaviruses, which are divided into 2 strains based on their geographic distribution and clinical manifestations. The New World Hantaviruses target the lungs and cause pulmonary edema and effusions with respiratory failure and cardiovascular depression, whereas the Old World Hantaviruses target the vascular system and the kidneys, causing hemorrhagic shock and renal failure (Table 3).

Since the Four Corners outbreak in 1993, the CDC has maintained a registry of all Hantavirus cases in the United States. From 1993 to 2009, there were 510 confirmed cases of HCPS, with case counts ranging from 11 to 48 per year and case fatality rates averaging 35%.[18] During this period, cases were reported from 30 states, but most cases occurred in the southwestern United States.[18] From 1993 to 2013, there were 624 confirmed cases of HCPS, with most cases caused by *Sin Nombre* virus in states west of the Mississippi River.[19] In addition, 12 Hantavirus cases were reported from the eastern United States and were caused by other New World Hantaviruses, including Bayou, Black Creek Canal, New York, and Monongahela Hantaviruses (Figure 3).[19] From 1993 to 2015, a descriptive analysis of the exposure characteristics of 662 confirmed cases of HCPS identified Native Americans in the southwestern United States as accounting for 18% of cases, with higher case-fatality rates (46%) than whites (33%).[20] Seventeen percent of case-patients reported rodent exposure, with 71% of rodent exposures occurring in homes, 32% at work, and 24% in recreational settings such as parks and riversides.[20]

From 1993 to January 1, 2020, the Public Health Agency of Canada reported 143 confirmed cases of HCPS for an average of 4 to 5 cases per year (range 0–13 cases) with a seasonal peak in May and June, driven by the combination of outdoor human contact with an expanded deer mouse (*Peromyscus maniculatus*) population during favorable seasons (Figure 1).[17] The mean age of case patients was 40 y with a male preponderance (99 of 143 cases).[17] All cases were caused by *Sin Nombre* virus, and all cases except 1 occurred in the 4 western-most Canadian provinces of Alberta, British Columbia, Manitoba, and Saskatchewan, with Alberta having more cases than any other province (Figure 4).[17]

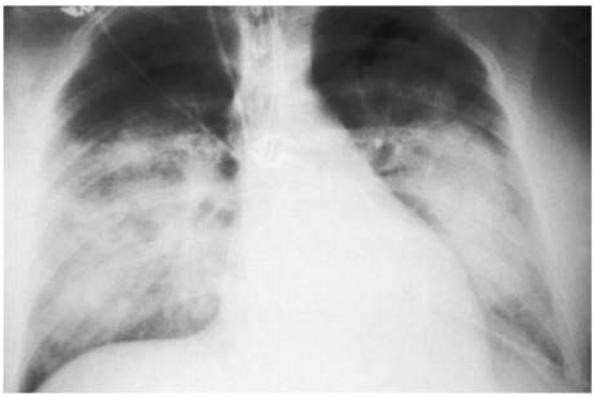

Figure 5. This anterior-posterior portable chest x-ray reveals the mid-staged bilateral pulmonary effusions in a patient with the Hantavirus cardiopulmonary syndrome. Source: United States Centers for Disease Control and Prevention. Public domain. Available at: https://phil.cdc.gov/Details.aspx?pid=6076. Photo credit: D. Loren Ketai, MD.

In summary, active surveillance systems have demonstrated that HCPS cases caused by New World Hantaviruses, primarily the *Sin Nombre* virus, are being reported more frequently today in both the western United States and western Canada, especially in hyper-endemic regions, such as the US Four Corners region and Alberta (Figures 3 and 4). In addition, other New World Hantaviruses with different rodent reservoirs are causing a few cases of HCPS in the eastern United States (Table 3).

Although bites by infected, asymptomatic rodents can transmit Hantaviruses, humans are most commonly infected by inhalation of aerosolized virions from rodent excreta in enclosed spaces, often during sweeping and clean-up of rodent nesting sites.[12,13] Infected mice copiously shed Hantavirus in urine, feces, and saliva, with virions remaining viable and infective for up to 15 d.[15,16]

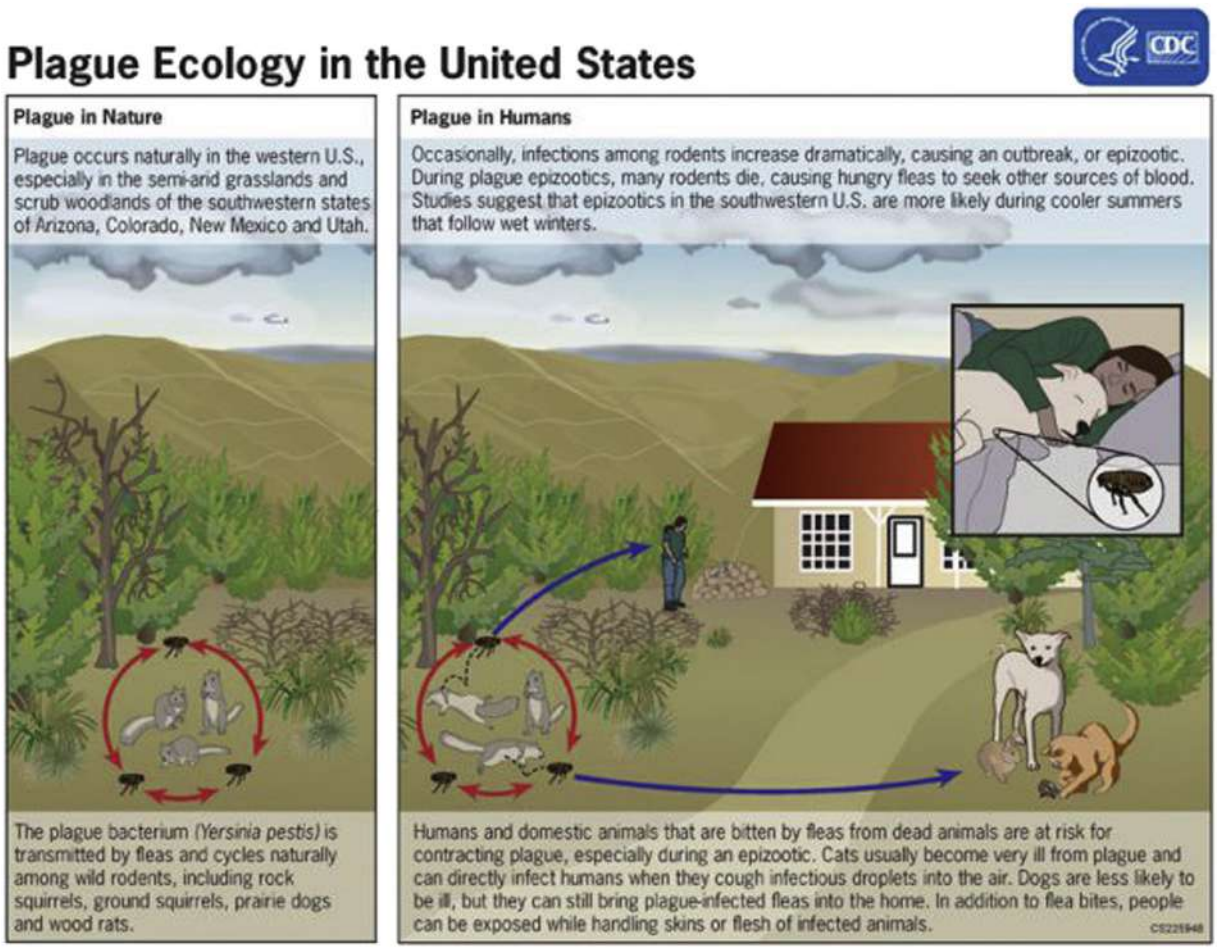

Figure 6. The sylvatic enzootic and epizootic transmission cycles of plague in the western United States. Source: United States Centers for Disease Control and Prevention. Public domain. Available at: https://www.cdc.gov/plague/resources/PlagueEcologyUS.pdf.

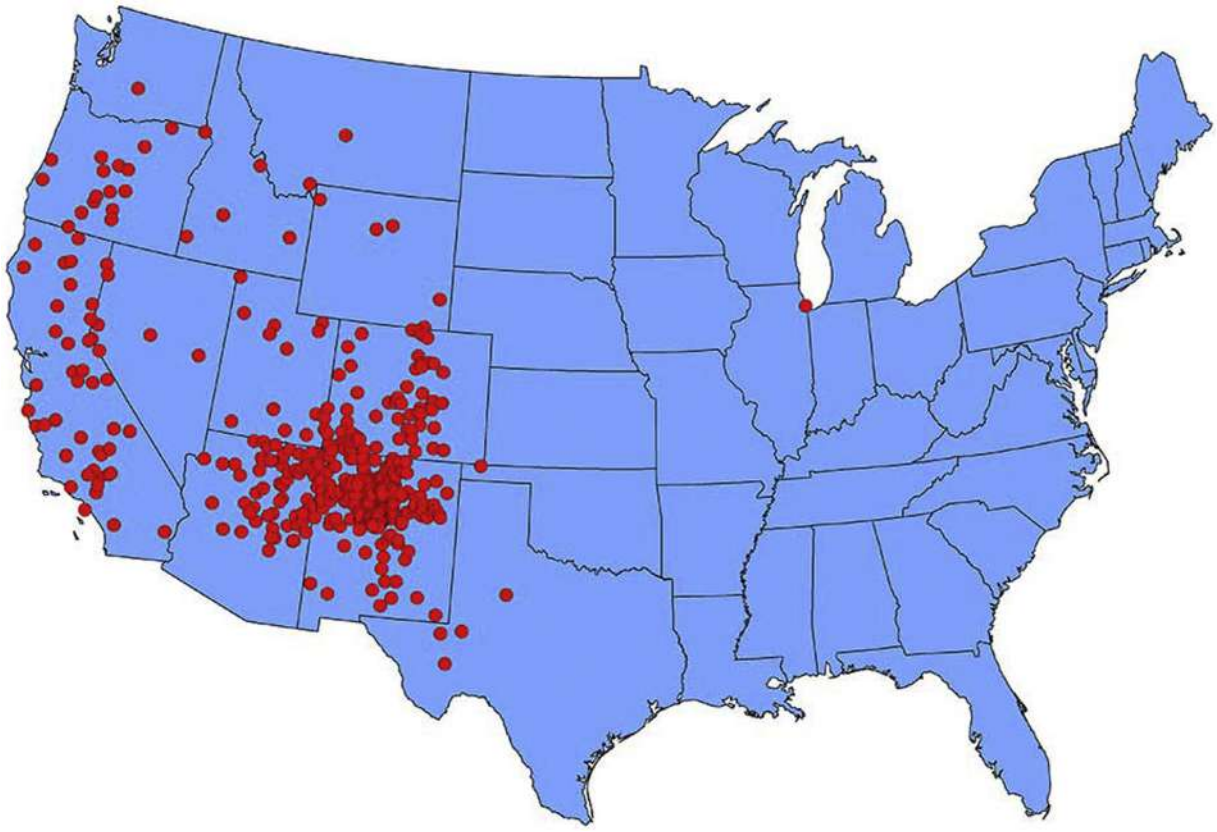

Figure 7. Geographic distribution of cases of human plague by state of reporting, continental United States, 1970–2018. Source: United States Centers for Disease Control and Prevention. Public domain. Available at: https://www.cdc.gov/plague/maps/index.html.

After an incubation period of 9 to 33 d (median 14–17 d), a prodromal febrile phase occurs with chills, headache, myalgias, and vomiting, followed within 3 to 7 d by a cardiopulmonary phase with cough, dyspnea, pulmonary edema and effusions, and respiratory failure requiring mechanical ventilation (Figure 5).

The serologic diagnosis of HCPS may be made, especially in endemic areas, based on the results of a commercial enzyme-linked immunosorbent assay test for antihantavirus immunoglobulins (IgM and/or IgG). Because many serologic tests for the diagnosis of HCPS may cross-react with other New World Hantaviruses endemic in the United States, specific Hantavirus identification by polymerase chain reaction with RNA sequencing of acute specimens collected early in the illness is recommended. Because there is no vaccine or specific antiviral therapy (including ribavirin) for HCPS, only early diagnosis and intensive supportive care, potentially including extracorporeal membrane oxygenation and nitric oxide administration, will reduce the high case fatality rates of HCPS. Wilderness medicine providers should consider a diagnosis of HCPS in persons with febrile illnesses that progress rapidly to respiratory insufficiency after rodent exposure in enclosed spaces, especially in endemic regions experiencing favorable seasonal weather patterns.

LEPTOSPIROSIS

LS is now the most commonly reported rodent-borne infectious disease and the most common zoonotic disease worldwide.[5,21-24] LS has been classified as a reemerging infectious disease by both the CDC and the World Health Organization.[22,23] Fortunately, only about 10% of patients experience severe clinical disease and complications from LS and require hospitalization.[21,22] Between 100 and 200 cases of LS are reported every year in the United States, with most cases reported from Hawaii, where the incidence is increasing during the rainy seasons and on Kauai, the wettest island.[21,22] In a 2011 analysis of LS cases reported to the Hawaii State Department of Health during the period of 1998 to 2008, investigators identified 345 case reports related to in-state exposures, 198 (57%) of which were laboratory confirmed.[22]

Table 4. Rodent reservoirs of plague in the Western United States[27,28]

Rodent reservoirs (common names)	*Rodent reservoirs (Latin names)*	*State distributions (Continental United States)*
Lodgepole chipmunk	*Tamias speciosus*	California
California ground squirrel	*Otospermophilus beecheyi*	California
Golden-mantled ground squirrel	*Callospermophilus lateralis*	California
Wood rats	*Neotoma* spp	Arizona, Colorado, New Mexico, Utah
Rock squirrel	*Spermophilus variegatus*	Arizona, Colorado, New Mexico, Utah
White-tailed antelope squirrel	*Ammospermophilus leucurus*	Arizona, Colorado, New Mexico, Utah
Prairie dogs	*Cynomys* spp	Arizona, Colorado, New Mexico, Utah

In a 2014 analysis of hospital discharge records for 1998 to 2009, investigators reported that the average annual rate of LS-associated hospitalizations was 0.6 hospitalizations per 1,000,000 population.[25] Hospitalization rates were highest for males >20 y of age.[25]

Leptospires are motile spirochetes of the family *Leptospiraceae*, with nearly 300 serotypes divided into human pathogenic strains and saprophytic strains.[22,23] The larger group of pathogenic leptospires comprises the *Leptospira interrogans sensu lato* complex, with over 200 serotypes.[22,23] Although the kidneys of many wild and domestic mammals serve as reservoir hosts for leptospires, rodents, primarily rats and mice, are the most common reservoirs worldwide.[22,23] Like the Hantaviruses, leptospires cause infection without disease in their rodent hosts. Infected rodents excrete leptospires in their urine; these proliferate in freshwater, mud, moist soil, and wet vegetation and remain viable and infectious for months.[22,23] As heavy rains and flooding saturate soil and surface vegetation, leptospires percolate into ground and surface waters, contaminating inland freshwater systems, including lakes and rivers.[22,23]

Human LS infections are transmitted most commonly by direct or indirect contact of mucous membranes, including conjunctivae, or abraded or broken skin with the urine of infected rodents or contaminated surface waters or sediments.[22,24] Less common modes of transmission include rodent bites, ingestion of rodent urine-contaminated water or food, inhalation of infectious aerosols of rodent excreta, congenital transmission, and transmission after breastfeeding, blood transfusions, and organ transplants.[22,23] Person-to-person transmission is possible, but rarely described [22,23]

After an incubation period of 7 d (range 2–29 d), LS displays a wide spectrum of clinical manifestations, ranging from a mildly symptomatic subclinical infection in most cases (80%), to a syndrome of abrupt fever, headache, myalgia, nausea, vomiting, and an occasional maculopapular rash that resolves in a week, to a biphasic illness that starts with fever, myalgia, and conjunctival suffusion in the first week and progression to icteric LS or Weil's disease in 5 to 10% of cases.[5,22,23] Weil's disease is characterized by jaundice, thrombocytopenia, acute renal failure, respiratory distress, and cardiac arrhythmias.[22,23] Weil's disease occurred in 2 out of 74 patients in a triathlon-associated outbreak of LS and had a 1 to 5% case fatality rate that increased with increasing age.[24,26]

The differential diagnosis of LS is broad and includes most febrile infectious diseases, including HCPS and Hantavirus hemorrhagic fever with renal failure syndrome, and relies on a careful exposure history and clinical suspicion supported by serologic testing. The microscopic agglutination test is the most reliable test for LS, but it is time-consuming and only offered by reference laboratories.[22,23] Because IgM antibodies cannot be detected until 5 to 7 d into the illness, acute serologic tests may be negative initially and positive later in the illness and during convalescence. Cultures of leptospires from blood or urine are time-consuming and of limited value in clinical management. Antibiotic therapy with oral doxycycline, ampicillin, amoxicillin, erythromycin, or azithromycin is recommended for mild cases, with intravenous therapy with ceftriaxone or penicillin G recommended for severe cases.[22,23]

Chemoprophylaxis with doxycycline, 200 $mg \cdot wk^{-1}$, has an efficacy rate of 95% and should be considered for soldiers on tropical training maneuvers and for triathletes participating in competitive swimming or whitewater paddling events in tropical, LS-endemic areas.[26] Given the challenges of early diagnosis of LS, empiric treatment with effective oral antibiotics should also be considered in symptomatic patients with high-risk exposures, especially in hyperendemic areas such as Hawaii.

Although vaccines are under development for LS, none are universally available. The best preventive strategies include drinking boiled or bottled water and minimizing exposure to rodent urine-contaminated environments by wearing waterproof boots and clothing. All cuts and abrasions should be covered with waterproof dressings. Triathletes participating in distance swimming events, kayakers, and whitewater rafters should wear

goggles to prevent transconjunctival transmission and avoid submersion in and ingestion of freshwater.[23,26]

Wilderness medicine providers should maintain high levels of suspicion for LS outbreaks after flooding events and freshwater exposure and immersion during outdoor recreational events. Public health officers should immediately promote heightened awareness of LS outbreaks among all flood-affected populations.

PLAGUE

Plague is caused by the aerobic, gram-negative coccobacillus *Yersinia pestis* and is maintained in endemic regions in enzootic, sylvatic cycles among rodents and their fleas (Figure 6). In North America, plague is endemic in California and other western states, especially Arizona, Colorado, New Mexico, and Utah (Figure 7).

As observed by investigators in New Mexico, human plague cases are more frequent during cooler summers that follow above-average precipitation in winter and spring, conditions that result in an abundant food source for an expanded rodent population.[9] As rodent densities increase in new habitats, there is a greater likelihood of flea-transmitted plague in wild animals, such as cougars and rabbits, and in domestic pets, such as cats and dogs (Figure 6).[9,27-29]

Plague is typically transmitted to humans and domestic and wild animals via flea bites, but it may also be transmitted by direct contact with infected body fluids or tissues, inhalation of infectious respiratory droplets, or, rarely, by ingestion of contaminated food or water. Contact with infected pets is a common source of plague in pet owners and veterinarians. Cats are particularly susceptible to plague and are often infected by eating infected rodents.

During the European plague epidemics of the 14th century, the predominant flea vector was the oriental rat flea, *Xenopsylla cheopis*. In the United States, the predominant flea vector of plague is the ground squirrel flea, *Oropsylla montana*.[27] *Yersinia pestis* is amplified in several susceptible rodent reservoir hosts in endemic areas (Table 4).[27,28]

In a 2015 descriptive epidemiologic study of all cases of plague occurring in the United States during 1900 to 2012, investigators described 1006 cases of plague in humans over the 113-y reporting period. Infections were acquired in 18 states, with a male preponderance (65%).[29] Among cases in which the clinical form was documented (n=913), 82% were bubonic, 8% pneumonic, 10% septicemic, 1% pharyngeal, and < 1% gastrointestinal.[29] When race or ethnicity was known, white non-Hispanic persons comprised 55% of cases, Asian and Native Americans 16%, and Hispanics 12%, with the remainder of unknown race or ethnicity.[29] Route of exposure was available in only 30% of cases (n=305), with 106 persons experiencing a known flea bite, 91 handling a sick animal, 64 butchering or skinning a sick animal, and 21 experiencing an animal bite or scratch.[29] Among case-patients with known flea bites, 90% of cases were bubonic and 9% were primary septicemic.[29] Among the bubonic cases, 66% exhibited inguinal or femoral lymphadenopathy.[29] Among persons experiencing an animal bite, scratch, or cough, 76% were exposed to domestic cats.[29]

From 2001 to 2012, investigators described the annual number of plague cases in the United States as ranging from 1 to 17 with a median of 3 cases.[30] However, between April 1, 2015, and August 28, 2015, the CDC's Epidemic Intelligence Service reported 11 cases of plague in residents of 6 states: Arizona (2), California (1), Colorado (4), Georgia (1), New Mexico (2), and Oregon (1).[31] The 2 cases in Georgia and California were linked to exposures near Yosemite National Park.[27,31] Among the 11 case-patients, the median age was 52 y (range 14–79 y), 9 were male, and 3 patients died (ages 16, 52, and 79 y).[31] Investigators did not determine why the number of plague cases in 2015 was higher than usual, but climatic trends and their impact on rodent populations were suspected.[32]

After flea bite, the incubation period for symptoms of bubonic plague, including fever, chills, headaches, nausea, and regional lymphadenopathy, ranges from a few days to a week.[29] With overwhelming infections, hematogenous dissemination may result in secondary pneumonic or septicemic plague. Pneumonic plague may be transmitted from person to person with a short incubation time of 1 h to 2 to 4 d. The bacteremia of septicemic plague can cause disseminated intravascular coagulation with bleeding and ischemic necrosis of digits and limbs.

The diagnosis of plague can be established microscopically, microbiologically, serologically, and molecularly. *Yersinia pestis* can be identified microscopically or in culture. Rapid serologic tests can detect the capsule antigen, and polymerase chain reaction assays can detect both the capsular antigen and the plasminogen activator gene.

With early diagnosis, plague is highly responsive to antibiotic therapy, especially with aminoglycosides, fluoroquinolones, and doxycycline.[31] The mortality rate for untreated plague in the preantibiotic era ranged from 66 to 93%. With early antibiotic therapy, the mortality rate has been reduced to 16%, with the highest case fatality rates found for septicemic plague.[29] Although an older plague vaccine was recommended for laboratory and field personnel working with *Yersinia pestis*

and for troops on maneuvers in endemic areas of Africa and Asia, the vaccine is no longer available in the United States.[33] Newer vaccines are under development.[33]

PREVENTION AND CONTROL OF RODENT-BORNE INFECTIOUS DISEASES

Eradicating all rodent reservoir hosts is both impractical because of the widespread distribution of rodents and undesirable because of the importance of rodents as insectivores and prey for larger predators in the ecosystem. The best and most effective strategies for the control and prevention of rodent-borne infectious diseases include (1) reducing rodent habitat around homes, cabins, and recreational areas by removing brush, rock piles, and firewood stacks; (2) storing all unrefrigerated foods, including pet foods, in thick plastic, glass, or metal containers with tight-fitting lids; (3) limiting contact with all wild and peridomestic rodents; (4) avoiding contact with rodent excreta, if possible, and safely disposing of rodent excreta; (5) wearing gloves when handling, butchering, or skinning a potentially infected animal; (6) modifying the built environment to deter rodents from frequenting and colonizing cabins, campsites, households, and workplaces; (7) using insect repellants topically and on clothing when outdoors; and (8) protecting pets with flea and tick control products and not allowing them to roam freely outdoors or share sleeping space with humans in rodent-borne disease–endemic regions.[34]

Only spring-loaded traps that kill rodents immediately should be deployed; live and sticky traps do not kill rodents, thereby allowing them to bite humans during disposal, transmitting Hantaviruses and creating open wounds for potential LS transmission.[35] While struggling to get free of nonlethal traps, rodents chronically infected with leptospires or Hantaviruses may urinate and emit infectious salivary aerosols, contaminating enclosed spaces.[35] All areas inhabited by rodents should be cleaned with mops wetted with dilute bleach solutions rather than swept or vacuumed because the latter could create infectious aerosols.[35]

Conclusions

Wilderness medicine providers should maintain high levels of suspicion for regional rodent-borne diseases in patients who develop febrile illnesses after exposure to contaminated freshwater after heavy rains or floods and after swimming, rafting, or paddling in endemic areas. Public health educational strategies should encourage limiting human contact with rodents; avoiding contact with or safely disposing of rodent excreta; avoiding contact with contaminated floodwaters, especially contact with open wounds; securely containing outdoor food stores; and modifying wilderness cabins and campsites to deter rodent colonization.

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CLINICAL IMAGE

A Case of Animal Mauling From Nepal

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A 55-y-old male presented to the emergency department with a laceration on the medial aspect of the left thigh (Figure 1).

What animal caused this injury? How should it be treated?

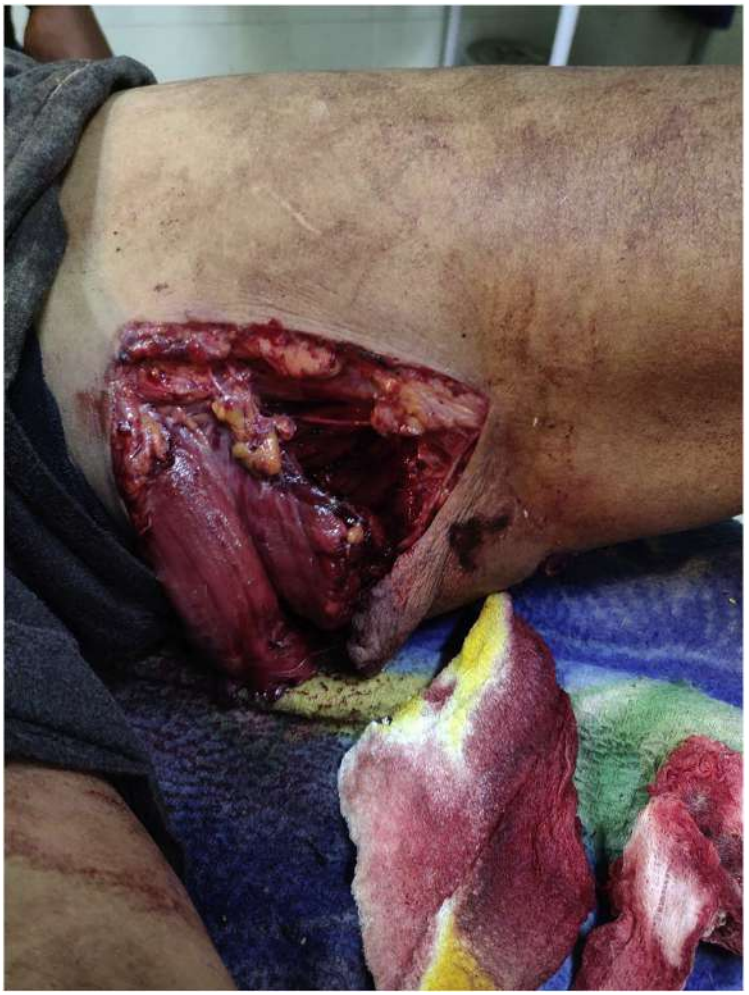

Figure 1. Muscle deep laceration exposing the injured belly of adductor longus and adductor brevis.

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Diagnosis

Mauling by Himalayan Black Bear

Discussion

The patient heard a sudden barking of dogs while he was grazing goats and sheep. The goats and sheep started bleating and running haphazardly in all directions. Suspecting that a predator was nearby, the patient grabbed his shepherd's crook and went toward the goats and sheep. There, he found a large black bear that he described as bigger and stronger than he was. Fearing that the bear would attack and injure his goats, the patient tried to scare the bear with his crook. The bear retaliated by attacking him. When the patient tried to escape, the bear pounded on his back with its claws. The patient stumbled, providing an opportunity for the bear to grab him by the hips and bite him on the left thigh. The patient was rescued by his friends, who scared the bear away.

On examination, the patient was alert and oriented with normal vital signs. The laceration measured 10×10 cm, exposing the injured bellies of the adductor longus and adductor brevis muscles. The contents of Hunter's canal was intact. The patient reported pain of the back and left thigh. There were 3 puncture wounds on his back, with associated contusions. There were also lacerations with contusions on the left lumbar region and right hand. A chest x-ray showed fractures of the left fourth, fifth, and sixth ribs (Figure 2). Arterial and venous Doppler studies of the left leg were normal.

The laceration on the thigh was irrigated and debrided to remove necrotic tissue with the patient under spinal anesthesia. The muscle belly was repaired and the wound was closed (Figure 3). The patient received a dose of tetanus toxoid and a course of broad-spectrum antibiotics.

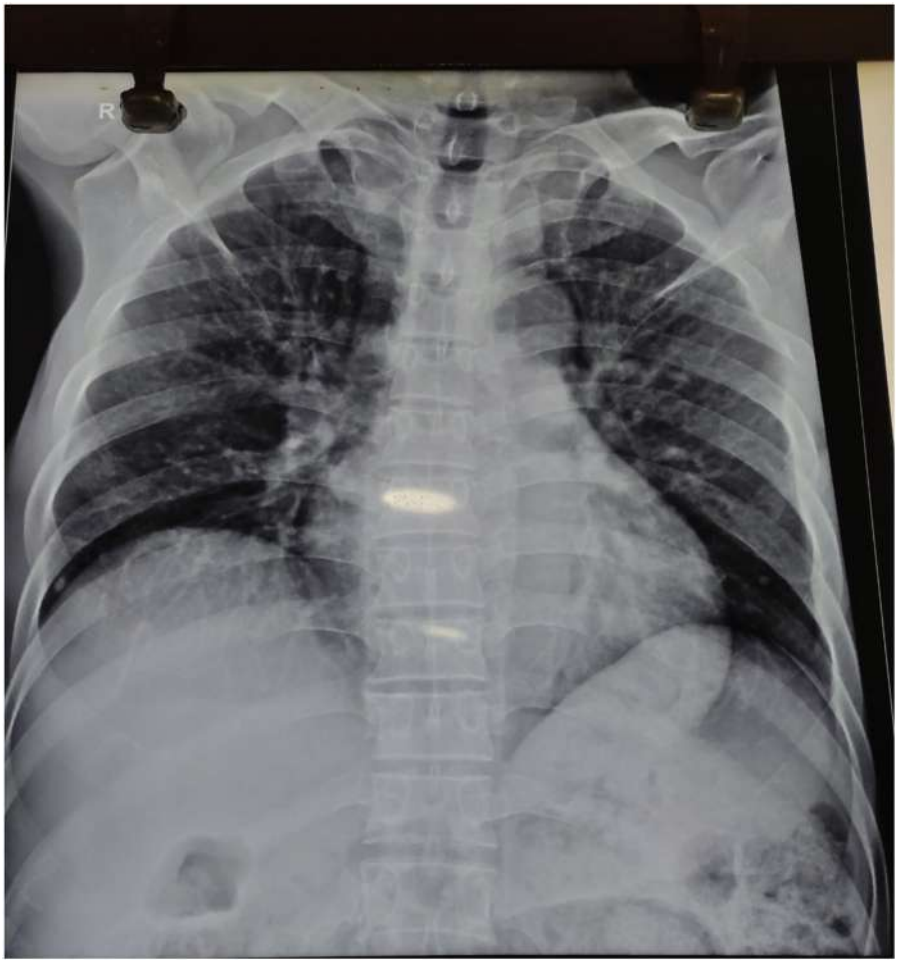

Figure 2. Chest x-ray showing fractures of the left fourth, fifth, and sixth ribs.

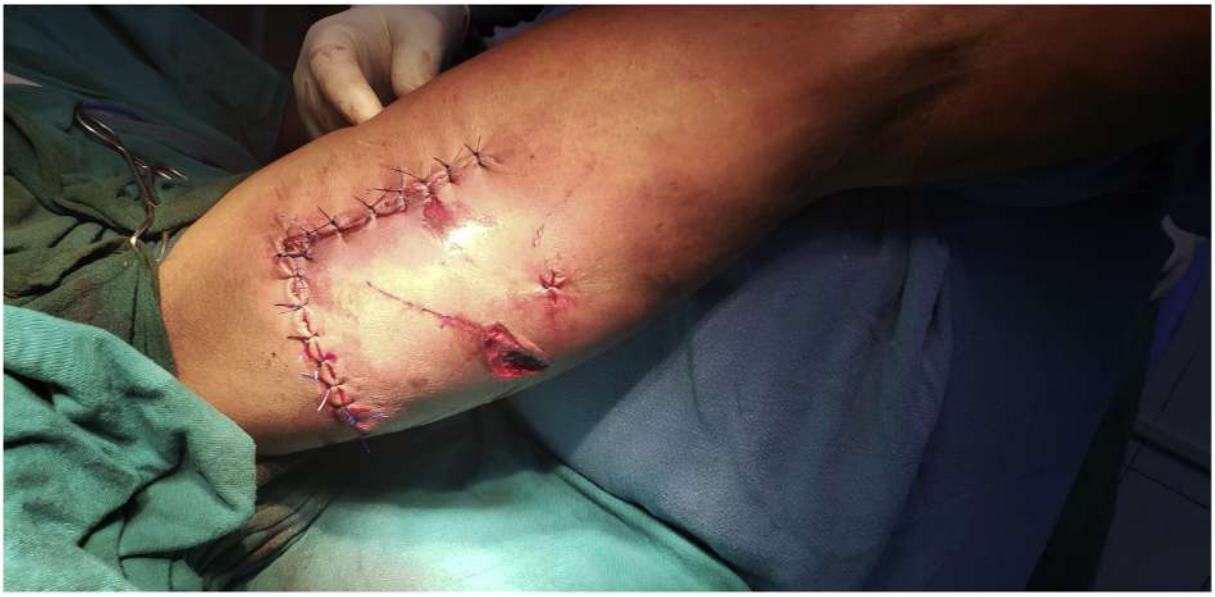

Figure 3. The laceration after repair.

After 2 wk, there was a necrotic wound margin. Sutures were removed and wound margins were debrided. Exploration revealed healthy underlying subcutaneous tissue and the previously sutured muscle. There was no sign of infection. The wound was then reclosed with a tension-free closure. The wound was well healed at 1 mo (Figure 4).

Written informed consent was obtained for the use of images and medical history for educational purposes, including publication.

Discussion

Three bear species are found in Nepal: the sloth bear (*Melursus ursinus*), the Himalayan black bear (*Ursus thibetanus*), and the Himalayan brown bear (*Ursus arctos*). The Himalayan black bear has a mostly black coat with a white or cream-colored chevron on the upper chest. Adult bears are 70 to 100 cm at the shoulder and 120 to 190 cm long. Males weigh an average of 135 kg.[1-3] Himalayan black bears, also known as Asiatic black bears, are found in the middle hills of Nepal from 1500 to 3500 m.[3] The incident occurred in the Palpa district, in the middle hills southwest of Pokhara. Although, bear maulings are common, mortality from bear attacks is rare compared to attacks from other predators.[4] Bears attack humans when they feel threatened or to protect their cubs. Sometimes they may seem to attack suddenly without provocation. Bears often attack the victim's face, necessitating emergency airway management and facial reconstruction.[1,2,4,5] In the absence of facial injuries, bear mauling can be identified by the specific pattern of injuries produced by teeth or claws.[3] Sharp claws and teeth with strong jaws can cause deep wounds. Bear bites can penetrate up to 1.5 cm; claws can penetrate up to 4 cm. Although wounds may appear superficial, careful examination is mandatory to rule out underlying injuries. Prophylactic antibiotics are indicated. Amoxicillin-clavulanate is the first-line agent. Tetanus toxoid should be administered if previous vaccination status is unknown or incomplete.[5] Wounds at high risk for infection, including those with extensive soft tissue injuries or involving bones, joints, or vital structures, should not be closed primarily. Close follow-up is mandatory for all wounds because

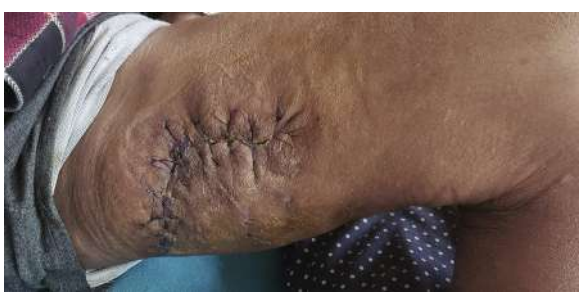

Figure 4. The wound after 1 mo.

the extent of damage may not be obvious, even with careful examination.

Keywords: animal attack; nonfatal injury; thigh laceration

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CLINICAL IMAGE

Worsening Pain After a Snakebite

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Case Report

A 47-y-old man presented to the emergency department 3 h after being bitten by a snake. The patient had been searching in bushes for a golf ball when he was bitten on the left hand by a pit viper (likely *Gloydius spp*). He received the appropriate antivenom (6000 units intravenously) at a local hospital 90 min before being transferred to our referral hospital for further management. On arrival in the emergency department, he reported worsening pain in the left hand. Physical examination revealed 2 fang marks, with swelling and tenderness, over the left second metacarpophalangeal joint (Figure 1).

What is the diagnosis? How would you manage this patient?

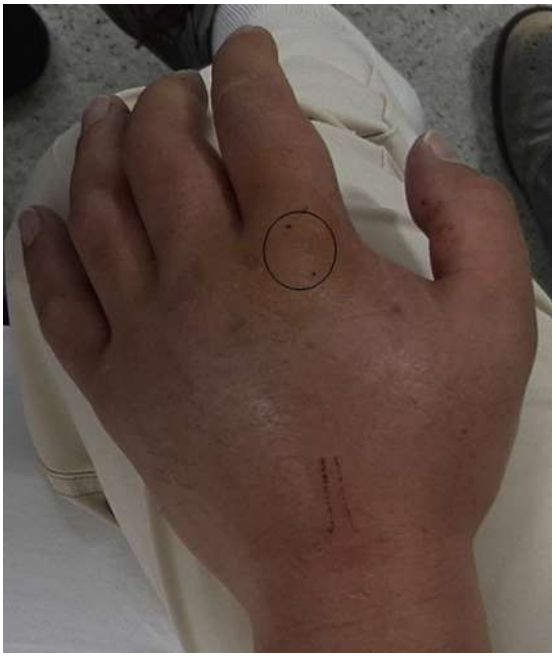

Figure 1. The patient's left hand. Two fang marks are visible in the circled area.

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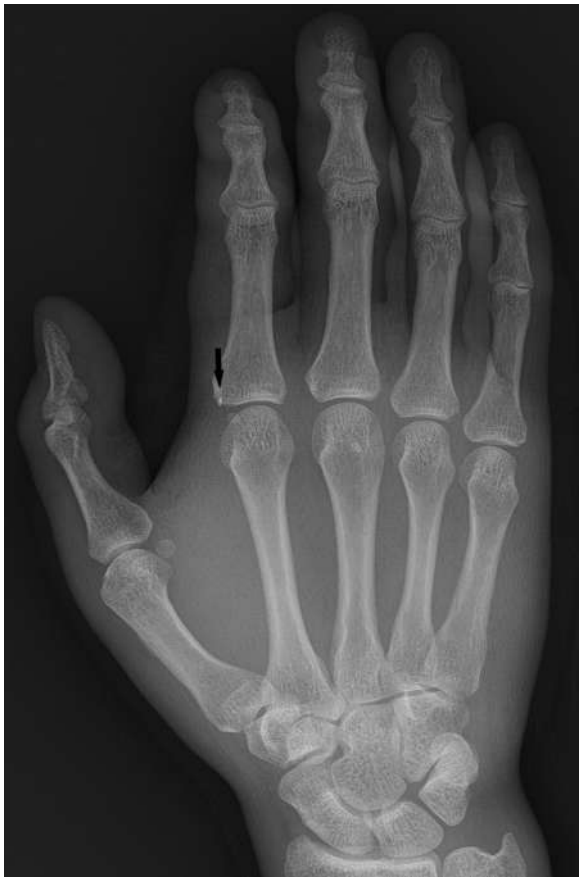

Figure 2. A tiny foreign body (solid arrow) was embedded in the soft tissue near the second metacarpophalangeal joint.

Diagnosis

Retained tooth or tooth fragment.

A plain x-ray of the left hand revealed a tiny foreign body in the soft tissue near the left second metacarpophalangeal joint (Figure 2). A retained tooth or tooth fragment was removed from the wound using fluoroscopy-assisted surgery (Figure 3).

Discussion

X-rays are not necessarily indicated for all snakebites. One indication for obtaining x-rays might be worsening pain and tenderness on delayed presentation.[1] In our patient, worsening of localized pain prompted x-ray evaluation to look for a retained foreign body. Healthcare providers should examine snakebite wounds carefully and obtain x-rays if there is worsening pain or tenderness.

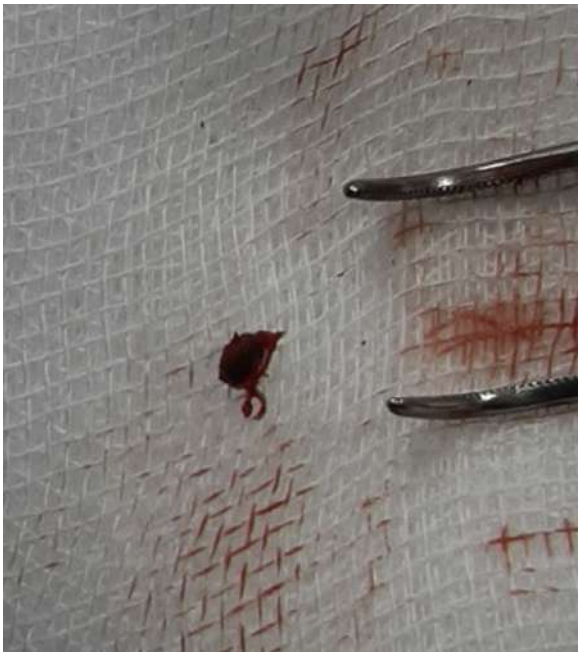

Figure 3. A retained tooth or tooth fragment was surgically removed from the wound.

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