

Venomous Bites, Stings, and Poisoning: An Update



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KEYWORDS

- Snake bite • Lizard bite • Fish sting • Jellyfish sting • Seafood poisoning
- Scorpion sting • Spider bite • Antivenom

KEY POINTS

- Snakebite, largely an occupational disease of impoverished agricultural workers and their families in rural areas of tropical developing countries, causes more than 100,000 deaths each year and, among survivors, great physical and psychological morbidity.
- Serious clinical effects of snakebite envenoming include hemorrhage, shock, acute kidney injury, generalized rhabdomyolysis, descending paralysis, and local tissue damage for which the treatment is antivenom and supportive therapy.
- Invertebrate stings cause fatalities by anaphylaxis, secondary to acquired hypersensitivity (Hymenoptera, such as bees, wasps, and ants, and jellyfish); and by direct envenoming (scorpions, spiders, and jellyfish).
- Simple preventive techniques, such as wearing protective clothing, using a flashlight at night, and excluding venomous animals from sleeping quarters, are of paramount importance to reduce the risk of venomous bites and stings.
- Common and geographically widespread ciguatera, scombroid, and tetrodotoxic fish poisonings and paralytic and amnesic shellfish poisonings, are treated symptomatically and prevented by avoiding eating high-risk species and being aware of danger signals, such as red tides.

VENOMOUS SNAKES

Of the five families of snakes that contain species capable of envenoming humans, the Elapidae and Viperidae are by far the most important from the medical point of view. Elapidae include cobras, kraits, mambas, coral snakes, Austro-Oceanian snakes, and sea snakes (Laticauda and Hydrophiinae). Viperidae comprise old world vipers and adders (Viperinae) and pit vipers (rattlesnakes, moccasins, lance-headed vipers, mamushis, habus, and other Euro-Asian pit vipers). The less important groups are

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Lamprophiidae (Atractaspidinae; African/Middle Eastern burrowing asps) and “Colubridae” (now divided; rear-fanged snakes).¹

In most parts of the globe, except for some islands in the Caribbean, Eastern Mediterranean, and Eastern Pacific, venomous snakes are an environmental and occupational danger.

Importance and Epidemiology

In Brazil, 26,000 snakebites were reported in 2016, with 109 deaths. Well-designed surveys have estimated annual snakebite mortalities of 46,000 in India,² 6000 in Bangladesh,³ and 400 in Sri Lanka.⁴ Community-based studies in selected areas of Africa and Asia revealed incidences of snakebite mortality ranging from 4 to 162 per 100,000 population per year.⁵ Global estimates of almost 3 million bites and up to 140,000 deaths per year have been suggested.⁶ Many survivors suffer long-term physical and psychological sequelae. Most bites are inflicted on the legs or feet of agricultural workers or their families. It is an occupational and environmental disease. In India, where 97% of bites occurred in rural areas, the highest incidence of resulting mortality was among children aged 5 to 14 years old in whom it constituted 3% of all deaths in the country.² Bites by kraits in South Asia, spitting cobras in Africa, and mulga snakes in Australia are inflicted on people sleeping in their homes, especially on the ground.⁷ Snake-bite was accepted by the World Health Organization as a category A neglected tropical disease in 2016, and was discussed at the World Health Assembly in 2018. It may cost more human lives than all other World Health Organization neglected tropical diseases put together. Its neglect has resulted from underestimation of its public health importance. In the rural areas of tropical developing countries in sub-Saharan Africa, Southern Asia, New Guinea, and the Amazon region of South America, access to conventional medical treatment in hospitals is hindered either by difficulties and delays in transporting the victim from remote areas or by a widespread preference for treatment by traditional (herbal) healers.⁷ As a result, many patients die outside health care facilities (77% in India) and, therefore, are not recorded in official health ministry returns. In the United States there are less than seven deaths from snakebites each year and in Australia less than three.⁸ Exotic species kept as pets are an increasing challenge for poisons centers in Western countries.⁹

Prevention

The risk of snakebite is easily reduced by simple common sense measures, such as wearing protective foot ware, using a light and prodding the ground with a stick after dark, sleeping on a raised bed or hammock or under a well tucked-in mosquito net,¹⁰ avoiding notoriously snake-infested habitats, and being especially vigilant at night and after heavy rains and flooding.

Venom and Venom Apparatus

When a viper strikes its prey, the fangs are erected (**Fig. 1**) and compressor muscles squeeze venom from glands situated behind the eyes through venom ducts and venom canals in the fangs.¹¹ Elapid fangs are fixed. Snake venoms are composed of hundreds of proteins, polypeptides, and other compounds. Some of the enzymes are digestive hydrolases and other necrotoxins that cause local tissue damage in human bite victims, others (eg, thrombin-like, prothrombin activators) activate blood coagulation and release or enhance endogenous mediators, lowering blood pressure (kininogens, angiotensin-converting enzyme inhibitors, bradykinin-potentiating peptides). Neurotoxins block neuromuscular transmission presynaptically (eg, phospholipase A₂) or post-synaptically (eg, three-finger polypeptides), causing progressive



Fig. 1. Fangs of white-lipped green pit viper (*Trimeresurus albolabris*) in Thailand showing erectile fangs. (© 2018 David A. Warrell.)

descending paralysis. Phospholipase A_2 myotoxins cause local and generalized rhabdomyolysis.

Clinical Effects

Bite victims may present with symptoms attributable to their understandable anxiety (eg, tachycardia, sweating, dry mouth, hyperventilation leading to light-headedness, paresthesia, and carpopedal spasms), prehospital treatment (eg, effects of tourniquets, local incisions, suction, topical applications of herbs, chemicals), or to envenoming.¹² Depending on the particular species, between 10% and 80% of patients bitten by venomous snakes are not envenomed (dry bites).¹³ Common local symptoms of envenoming include pain, swelling, tenderness and bruising that spread up the bitten limb, bleeding from bite marks, and tender enlargement of draining lymph glands. Systemic envenoming may be announced by nausea, vomiting, and syncope.

Elapid Envenoming

Most elapid bites cause mild or negligible local effects, but venoms of African spitting cobras and Asian cobras, spitting and nonspitting, can induce substantial local swelling, blistering, and necrosis of skin and subcutaneous tissues (**Fig. 2**).^{14,15} Classic neurotoxic effects start as early as 15 minutes or as late as 10 hours after the bite. First evidence is bilateral ptosis and external ophthalmoplegia, progressing to descending paralysis affecting muscles innervated by other cranial nerves and eventually bulbar and respiratory muscles (**Fig. 3**). Australian-Oceanian land snakes can cause paralysis, bleeding/coagulation disturbances, myotoxicity, and acute kidney injury (AKI). Sea snake envenoming results in paralysis and generalized rhabdomyolysis complicated by AKI.

Viper, Adder, and Pit Viper Envenoming

Local effects of viperid venoms are generally more severe than those of elapids. If envenoming has occurred, local swelling is usually evident within 2 hours. Swelling and bruising may spread to affect the whole limb, trunk, and the whole body. Blistering may develop within hours and frank tissue necrosis in days (**Fig. 4**). Hypovolemia, hypotension, and bleeding/coagulation abnormalities are common. Systemic bleeding occurs from gums (**Fig. 5**); nose; gastrointestinal and urogenital tracts; lungs; and into the skin, conjunctivae, and brain. Neuromyotoxicity and AKI are common complications of bites by some species, such as Western Russell's viper (*Daboia russelii*).¹⁶

Laboratory Investigations

A blood count reveals neutrophil leukocytosis, and perhaps thrombocytopenia and anemia. The 20-minute whole-blood clotting test involves placing 2 to 3 mL of freshly drawn venous blood into a new, clean, dry, glass vessel and leaving it undisturbed for 20 minutes. Plastic and detergent-washed vessels do not activate clotting. Failure to clot indicates consumption coagulopathy (plasma fibrinogen concentration <0.5 g/L).¹⁷ Rising serum potassium, creatinine, and urea define AKI. Raised creatine kinase, myoglobin, and potassium levels indicate rhabdomyolysis. Dark red, brown, or black urine may contain erythrocytes, hemoglobin, or myoglobin. Electrocardiogram (EKG) abnormalities include ST-T changes, atrioventricular block, and arrhythmias.



Fig. 2. Areas of superficial necrosis following a bite on the ankle by black-necked spitting cobra (*Naja nigricollis*) bite in Nigeria. (© 2018 David A. Warrell.)



Fig. 3. Bilateral ptosis, external ophthalmoplegia, facial paralysis, inability to open the mouth, and respiratory paralysis in a man bitten by a common krait (*Bungarus caeruleus*) in Sri Lanka. (© 2018 David A. Warrell.)



Fig. 4. Painful inflammation, blepharospasm, and leukorrhea caused by venom spat into the eye by a black-necked spitting cobra (*Naja nigricollis*) in Nigeria. (© 2018 David A. Warrell.)



Fig. 5. Swelling, blistering, and severe local tissue destruction that required amputation 5 days after a bite on the wrist by a Malayan pit viper (*Calloselasma rhodostoma*) in Thailand. The patient presented late after being treated by an herbalist. (© 2018 David A. Warrell.)

Management of Snake Bite

First aid

Most traditional first aid methods have proved useless and harmful. Sound principles are reassurance of the frightened victim, immobilization of the whole patient especially the bitten part, application of a pressure pad over the bite site, and urgent but safe transport to medical care. To delay systemic spread of venom toxins from the site of inoculation, local veins and lymphatics draining the site can be compressed with a pad of material approximately $6 \times 6 \times 3$ cm, tightly bound directly over the bite site with an inelastic bandage. The bitten limb is immobilized by splinting. This is far simpler than the Sutherland compression bandage method and proved effective in a small field trial.¹⁸ In transit to hospital, the patient should, ideally, be placed in the recovery position. Their airway should be guarded and respiration and blood pressure monitored.

Antivenom treatment

Antivenoms (antivenins, antisnakebite sera) are whole or enzyme-digested equine or ovine immunoglobulins that can specifically neutralize the circulating venom toxins against which they were raised. They can correct venom-induced coagulopathies, stop bleeding, and reverse shock and post-synaptic neurotoxicity. Polyspecific (polyvalent) antivenoms cover the venoms of the species of greatest medical importance in a particular geographic area. Monospecific (monovalent) antivenoms are appropriate for areas where only one species exists (eg, adder *Vipera berus* in Scandinavia and parts of Western Europe) or for uncommon bites (eg, boomslang *Dispholidus typus* in Africa and keel-backs *Rhabdophis* sp in South East Asia and Japan). Sadly, these essential drugs are not available in many parts of Africa, Asia, New Guinea, and South America where they are most needed. Indications for antivenom include

1. Evidence of systemic envenoming (hypotension, other signs of cardiovascular toxicity, neurotoxicity, generalized myotoxicity, spontaneous systemic bleeding, uncoagulable blood), supported by peripheral leukocytosis ($>20 \times 10^9/L$), elevated serum enzymes, hemoglobinuria, myoglobinuria, severe anemia/hemoconcentration, uremia, or oliguria.
2. Massive local swelling (more than half of the bitten limb), bites on fingers or toes, and rapidly progressive swelling after bites by species known to cause necrosis.

Intradermal or conjunctival hypersensitivity tests to detect IgE-mediated anaphylaxis do not predict antivenom reactions reliably and should not be used.

Subcutaneous epinephrine (adrenaline; adult dose 2.5 mL of 0.1% solution) given just before starting antivenom treatment reduces frequency and severity of early reactions.¹⁹

Antivenom must be given intravenously because it is poorly bioavailable by subcutaneous or intramuscular routes. Dilution and rate of administration (over 10–60 minutes) seem not to affect the incidence of early reactions.²⁰ Dosage, the same for children as adults, is usually based on rodent assays or judged empirically. The initial dose is repeated if blood coagulability is not restored after about 6 hours or if there is persistence or progression of shock or paralysis after 1 to 2 hours. Ideally, patients should be monitored for 2 to 3 days after antivenom to detect recurrent systemic envenoming resulting from continued absorption of venom from the bite site depot or redistribution of venom toxins.²¹ This has proved to be a particular problem with rapidly cleared Fab fragment antivenoms, such as CroFab, which is used for North American pit viper bites.²²

Antivenom reactions

The risk of early anaphylactic or pyrogenic reactions, occurring within 10 to 180 minutes of administration, is dose-related and is higher with poorly refined antivenoms that contain complement-activating aggregates of IgG fragments or endotoxins acquired during manufacture. Rarely, patients who have been sensitized to equine/ovine proteins through previous exposure (eg, to equine antitetanus serum or rabies immune globulin) may develop IgE-mediated reactions. At the first sign of an early reaction, which may evolve with frightening speed, epinephrine (adrenaline) should be given intramuscularly (adults 0.5–1.0 mL; children 0.01 mL/kg; of 0.1% solution), together with other appropriate resuscitation.

There is also a dose-related risk of late serum-sickness-type reactions. Between 5 and 24 (mean, 7) days after antivenom, patients may develop fever, pruritus, urticaria, arthralgia with periarticular swellings, lymphadenopathy, mononeuritis multiplex, and albuminuria. Mild reactions may respond to oral histamine H₁ blockers (eg, chlorphenamine: adults 2 mg every 6 hours, children 0.25 mg/kg per day in divided doses), but a 5- to 7-day course of oral prednisolone (adults 5 mg every 6 hours, children 0.7 mg/kg per day in divided doses) is often needed to control the distressing symptoms.

Complicating Organ/System Failures: Supportive Treatment

Bulbar and respiratory paralysis

The risk of aspiration pneumonia, airway obstruction, and respiratory failure is prevented by careful monitoring. As soon as there is pooling of secretions in the pharynx or respiratory distress, a cuffed endotracheal tube or supraglottal airway is inserted. Some patients envenomed by snakes whose neurotoxins act post-synaptically (eg, cobras, Australian-Oceanian death adders *Acanthophis*) respond to anticholinesterase drugs, such as neostigmine, given with atropine to block unpleasant muscarinic side effects of acetylcholine.²³ Responsiveness may be tested by the tensilon test using edrophonium²⁴ or, more simply in patients with bilateral ptosis, by the ice-pack test.²⁵

Cardiovascular disturbances

Hypotension and shock are treated with plasma expanders or vasoconstrictors. Hypotension associated with sinus bradycardia may respond to atropine and other dysrhythmias to appropriate antiarrhythmic drugs, such as verapamil, flecainide, or amiodarone.

Acute kidney injury

If conservative management of AKI fails, renal-replacement therapy or hemoperfusion is needed.

Bite wound infections

These occur in less than 5% of cases. The area of the bite may be hot, red, and tender because of inflammatory effects of the venom and so the term “cellulitis” is misleading. A large variety of bacteria (skin commensals, environmental, and from the snake’s mouth) may infect snakebite wounds, but antibiotic prophylaxis is justified only if the wound has been interfered with or there is obvious necrosis. Otherwise, await signs of focal infection, such as an abscess. Aspirate and culture before prescribing. A routine tetanus toxoid booster is justified in all cases of snakebite.

Care of the bitten limb

Nurse the limb in the most comfortable position, avoiding excessive elevation that may increase the risk of intracompartmental ischemia. Blisters and bullae should be left intact to avoid increasing access to infection.

Surgical interventions

Necrotic tissue should be debrided and denuded areas covered with split-skin grafts. Compartment syndrome is grossly overdiagnosed in snakebite victims resulting in many unnecessary, disfiguring, and disabling fasciotomies. Before contemplating any surgery, normal hemostasis must be restored by antivenom and perhaps infusion of clotting factors. Before embarking on fasciotomy, intracompartmental pressure should be measured directly and monitored for at least 1 hour (Fig. 6). Only if pressures are sustained at a level that risks ischemic necrosis should fasciotomy be contemplated and, even in these rare cases, results are disappointing because of the underlying venom-induced necrosis.

Spitting elapid ophthalmia

Spitting cobras and the rinkhals (*Hemachatus haemachatus*) eject streams of venom from their fang tips toward the glittering eyes of perceived assailants.²⁶ Venom causes intensely painful chemical conjunctivitis, edema, and spasms of the eyelids, with profuse purulent secretions (Fig. 7). There is a risk of corneal erosion, hypopyon, anterior uveitis, secondary infections, and blindness. First aid treatment is irrigation of the eyes and affected oral/nasal mucosae with generous volumes of water, milk, urine or any other available bland fluid. Pain is relieved with topical anesthetics, such as tetracaine (with caution), or epinephrine/adrenaline (0.1% eye drops). Corneal abrasions are either excluded by fluorescein staining/slit-lamp examination or prevented with topical antimicrobials (eg, tetracycline, chloramphenicol, or fluoroquinolone).

VENOMOUS LIZARDS

Despite wild claims that the giant Komodo dragon (*Varanus komodoensis*) kills by venom rather than brute force, only two lizards are of proven medical importance, the Gila monster (*Heloderma suspectum*) of the south-western United States and



Fig. 6. Severe spontaneous bleeding from the gingival sulci and into the floor of the mouth in a patient bitten by a saw-scaled or carpet viper (*Echis ocellatus*) in Nigeria. (© 2018 David A. Warrell.)

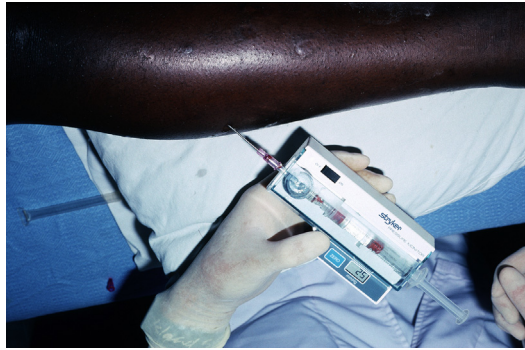


Fig. 7. Direct measurement of pressure in the anterior tibial compartment in a man bitten on the ankle by a puff adder (*Bitis arietans*) in South Africa. Despite the appearances of the tensely swollen, tender, and cold limb, the intracompartmental pressure is only 25 mm Hg. The patient did not require a fasciotomy. (© 2018 David A. Warrell.)

adjacent areas of Mexico and Mexican beaded lizards (*Heloderma horridum*) of western Mexico south to Guatemala.²⁷ Venom from submandibular glands is conducted along grooves in the lower teeth. It contains peptides, such as exendins-3 and -4, which are glucagon-like peptide-1 analogues that have been developed for treatment of type 2 diabetes mellitus.

Clinical Features and Treatment

Bites are rare and never unprovoked. The powerful jaws are difficult to disengage. Severe local pain, tender swelling, and regional lymphadenopathy develop rapidly together with systemic symptoms, such as dizziness and hypotensive collapse, angioedema, sweating, rigors, tinnitus, nausea, and vomiting. Leukocytosis, coagulopathy, electrocardiographic changes, myocardial infarction, and AKI are described, but no fatalities are reliably reported. No antivenom is commercially available. Symptomatic treatment includes powerful analgesia, plasma expanders, and epinephrine (adrenaline) or pressor agents.

VENOMOUS FISH

Dangerous but only rarely fatal stings are inflicted by some marine sharks and dogfish, stingrays and mantas, catfish, weever fish, stargazers or stone-lifters, scorpion fish (**Fig. 8**), stonefish, and lion fish and freshwater stingrays (*Potamotrygon* spp).^{28–30} Their venom glands are embedded in grooves in the spines of fins or gill covers or, in the case of stingrays, beneath an integument covering the long barbed precaudal spines.

Incidence and Epidemiology

Each year, there are reports of weever fish (*Trachynis*) stings around the coasts of Britain and the Adriatic. In the United States there are an estimated 1500 stings by rays and 300 by scorpion fish each year. Stings by freshwater rays are common in the Amazon region. Lion, zebra, tiger, turkey, or red fire fish (*Pterois*, *Dendrochirus* spp) are popular with tropical aquarists whom they sometimes sting. Indo-Pacific *Pterois volitans* and *Pterois miles* have invaded southeastern coastal waters of the United States and Caribbean and the Eastern Mediterranean.

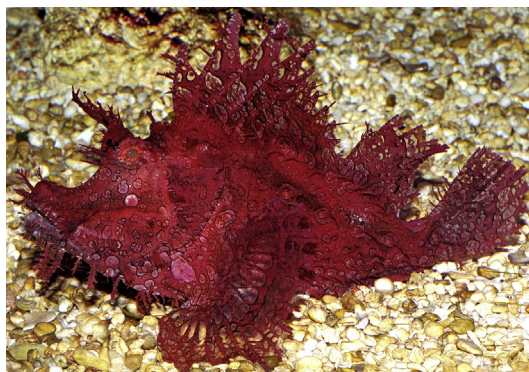


Fig. 8. Weedy scorpionfish (*Rhinopias frondosa*) from the Indian Ocean, capable of inflicting painful stings. (© 2018 David A. Warrell.)

Prevention

The greatest danger is stepping on a stinging fish while wading on the shore or near coral reefs. A shuffling gait, prodding with a stick, and footwear reduce the risk of stings except by stingrays. Divers and fishermen should avoid touching fish unnecessarily.

Venom Composition

Fish venoms contain thermolabile proteins and peptides, enzymes, vasoactive kinins, 5-hydroxytryptamine, histamine, and catecholamines.³¹

Clinical Features

Excruciating pain is associated with tender inflammatory swelling, necrosis, and the risk of secondary infection by marine *Vibrio vulnificus* or freshwater *Aeromonas hydrophila*. Long, barbed stingray spines, up to 30 cm long, lacerate and can penetrate the chest or abdomen, fatally damaging heart, lungs, or viscera as in the case of the famous Australian conservationist, Steve Irwin. Symptoms of systemic envenoming include nausea, vomiting, diarrhea, sweating, hypersalivation, cardiorespiratory disturbances, and generalized convulsions.

Treatment

Rescue the victim from the water, relieve the agonizing pain by immersing the stung part in hot water (<45°C), give supportive care for systemic envenoming, and remove any implanted venomous spines. Australian stonefish (*Synanceja*) antivenom (Seqirus, Melbourne, Australia) covers venoms of some other scorpion fish (Scorpiionidae) including Californian *Scorpaena guttata*. Antibiotic treatment of suspected or proven *Vibrio* and *Aeromonas* infections should include doxycycline or cotrimoxazole.

SEAFOOD (FISH AND SHELLFISH) POISONING

Acute nausea, vomiting, abdominal colic, and diarrhea that develop within minutes or a few hours of eating fish or shellfish is more likely to be caused by marine toxins or allergy than bacterial or viral infections. There are two main clinical syndromes: gastroenteritis with neurotoxic symptoms (ciguatera and tetrodotoxic fish poisoning and neurotoxic and amnesic shellfish poisoning) and histamine-like (scombrototoxic) fish poisoning.

Ciguatera Fish Poisoning

This is the commonest cause of seafood poisoning with an estimated annual global incidence of 50,000 to 500,000 cases (case fatality $\sim 0.1\%$).³² It is underdiagnosed because of ignorance of its distinctive clinical features and lack of a diagnostic test. Climate change and destruction of coral reef systems have expanded its endemic area from tropical oceans (between $\sim 25\text{--}40^\circ\text{N}$ and $30\text{--}25^\circ\text{S}$) to more temperate waters and the increasing appetite for exotic fish in Western countries has led to many sporadic cases. Tropical reef fish, such as groupers, snappers, parrot fish, trigger fish, surgeonfish, mackerel, moray eels, barracudas, and jacks, are most often implicated. Ciguatoxins are polyethers that activate Na^+ or Ca^{2+} channels. Derived ultimately from bacteria in benthic dinoflagellates such as *Gambierdiscus toxicus*, they accumulate in the liver, viscera, and gonads of carnivorous fish at the end of the food chain.

Early symptoms are a burning sensation in the mouth or a metallic taste about 45 minutes after ingestion.³³ Symptoms of acute gastroenteritis follow after about 1 to 6 hours and may persist for a week. After about 24 hours, distinctive neurologic symptoms emerge: generalized pruritus, paresthesia around the mouth and extremities, pain in the teeth, reversed hot-cold sensation (cold allodynia or dysesthesia) especially of the extremities, weakness, ataxia, arthralgia, and myalgia. Neuropsychiatric symptoms may develop within days or weeks. Rarely, cardiovascular disturbances and rashes may occur. Usually, these symptoms last only a few hours, but they may persist for a week, months, or even up to a year as chronic ciguatera in about 5% of cases. Ciguatera-like symptoms after eating turtle flesh (chelonitoxism) are more severe, with higher case-fatality.³⁴

Tetrodotoxic ("Fugu") Fish Poisoning

Scaleless puffer, porcupine (Fig. 9), toad, and sun fish (Tetraodonitiformes) may become highly poisonous at certain times of year. In Japan, puffer fish ("fugu") is particularly relished for its supposed medicinal properties and, despite stringent regulations, there are still about four deaths each year from tetrodotoxic poisoning. Tetrodotoxins are aminoperhydroquinazolines ultimately derived from *Pseudomonas* bacteria. They produce neurotoxic and cardiotoxic effects by blocking voltage-



Fig. 9. Long-spined porcupine fish (*Diodon holacanthusa*), a tetrodotoxic fish (Diodontidae) that is extensively distributed in tropical oceans. (© 2018 David A. Warrell.)

gated Na⁺ channels. They occur in ovaries, viscera, and skin of tetraodontiform fish but also in some amphibians, octopuses, mollusks, xanthid crabs, and other animals.

Clinical features include nausea and gastro-intestinal symptoms, together with neurotoxic symptoms that evolve within 10 to 45 minutes. Paresthesia of the lips, tongue, and throat, altered taste, dizziness, headache, sweating, hypersalivation, and ataxia are associated with ascending flaccid paralysis with fasciculations that lead to respiratory failure. Hypotension, cardiac bradyarrhythmia and tachyarrhythmia, exfoliative dermatitis, and other rashes are also described. Death occurs within 2 to 6 hours of eating the fish.

Neurotoxic and Paralytic Shellfish Poisoning

Thirty minutes after eating contaminated bivalve mollusks (mussels, clams, oysters, cockles, and scallops), patients develop gastroenteritis, chills, sweats, hypotension, arrhythmias, and ciguatera-like paresthesia, including cold allodynia, with myalgia, muscle spasms, vertigo, and ataxia.³⁵ Brevetoxins, derived from *Karenia brevis* dinoflagellates, cause harmful algal blooms, sometimes visible as red tides that kill off marine birds, mammals, and fish. In human beings, they cause neurotoxic shellfish poisoning. Symptoms usually last for a few days; paralysis, seizures, and coma are rare complications. However, tetrahydropurine neurotoxins, such as saxitoxin, and gonyautoxins from dinoflagellates, such as *Alexandrium*, *Pyrodinium*, and *Gymnodinium* spp that also produce red tides, can cause, within 12 hours, the descending paralysis of paralytic shellfish poisoning (fatality ~8% in untreated cases).

Amnesic Shellfish Poisoning

Within 24 hours of ingesting bivalve mollusks (scallops, razor clams) and crustaceans, symptoms of gastroenteritis may develop, but in about half the cases, neurotoxic symptoms, such as severe headache, short-term memory loss, agitation, seizures, and coma, may evolve within 48 hours. Amnesia may be permanent. Outbreaks have been reported from North America, Europe, and elsewhere. The causative toxin, domoic acid, is derived from *Pseudo-nitzschia* diatoms.

Histamine-Like (Scombrototoxic) Fish Poisoning

Bacterial decomposition of the histidine-rich dark flesh of scombroid fish (tuna, mackerel, bonito, skipjack) and canned nonscombroid fish (eg, sardines, pilchard) may be decomposed by bacteria releasing histamine and other toxins.³⁶ First contact of scombrototoxic fish with the lips, tongue, and mouth causes tingling or smarting, a timely warning. Within 20 to 30 minutes of ingestion, histamine-like symptoms may evolve: flushing, burning, sweating, urticaria, pruritis, headache, abdominal colic, nausea, vomiting, diarrhea, bronchial asthma, giddiness, and hypotension.

Treatment of Seafood Poisoning

There are no specific treatments or antidotes. General measures include elimination of gastrointestinal contents, but only if this can be achieved safely within 1 to 2 hours of ingestion, repeated dosing with activated charcoal to bind shellfish toxins to limit their enterohepatic circulation, parenteral fluid replacement, and assisted ventilation where necessary. The value of early mannitol (0.5–1.0 g/kg body weight intravenously over 30–45 minutes within 48–72 hours of exposure) in ciguatera fish poisoning is controversial, but is safe and often recommended.³⁷ For chronic ciguatera poisoning, amitriptyline and several other psychotropic drugs have been used. Scombroid symptoms respond to epinephrine (adrenaline), anti-H₁ histamine blockers, adrenergic β₂ agonist bronchodilators, and fluid replacement.

Prevention

Seafood toxins resist cooking. Avoid all scaleless fish as potentially tetrodotoxic, avoid very large tropical reef fish because they are more likely to be ciguatera-toxic, and eat only fresh fish to avoid scombroid poisoning. Never eat shellfish during dangerous seasons and red tides.

VENOMOUS MARINE INVERTEBRATES

Cnidarians (Coelenterates, Jellyfish, Portuguese Man O' War, Stinging Corals, Sea Anemones)

Cnidarian tentacles are armed with millions of explosive nematocysts (stinging capsules). Triggered by contact, they fire stinging hairs into the dermis to produce strings of painful, irritant weals.^{28–30} Cnidarian venoms contain peptides, vasoactive amines, prostaglandins, kinins, digestive enzymes, and ion channel neurotoxins.³⁸

Epidemiology

North Australian box jellyfish or sea wasps (*Chironex fleckeri*) and other cubomedusoids have been responsible for more than 100 recorded fatalities in the Australo-Indo-Pacific region. Portuguese man o' war (*Physalia* spp) and the Chinese jellyfish *Stomolophus nomurai* stings are rarely fatal. In northern Queensland, Florida, the Caribbean, and Thailand, stings by tiny (10 × 30 mm) cubomedusoids, such as Irukandji (*Carukia barnesi*) can be lethal. Stings by North Atlantic *Chrysaora quinquecirrha*, Pacific (*Chrysaora pacifica*) (Fig. 10), and Mediterranean *Pelagia noctiluca* are common.

Prevention

Avoid bathing or paddling when warning notices are displayed, or keep to “stinger-resistant” enclosures. Lycra, wetsuits, or nylon pantyhose protect against nematocyst stings. Those with a history of anaphylactic symptoms (eg, after *Physalia* stings) should carry self-injectable epinephrine (adrenaline).

Clinical features

Size and shape of weals may be diagnostic. Pain is immediate and severe. Chirodroid (genera *Chironex* and *Chiropsalmus*) envenoming causes rapidly evolving cough, gastrointestinal symptoms, rigors, myalgias, and profuse sweating that may progress to pulmonary edema, generalized convulsions and cardiorespiratory arrest. Irukandji syndrome comprises immediate severe musculoskeletal pain, delayed and persistent trembling, nausea, vomiting, anxiety, generalized sweating, headache, breathlessness, hypertension, raised troponin levels and EKG T-wave inversion, tachycardia,



Fig. 10. Japanese sea nettle (*Chrysaora pacifica*), a common cause of jellyfish stings in the Pacific Ocean. (© 2018 David A. Warrell.)

and cardiac failure. *Physalia* envenoming causes vasospasm, nerve entrapment (eg, carpal tunnel syndrome), intravascular hemolysis, peripheral gangrene, and AKI. Those sensitized by previous stings may suffer anaphylaxis when stung again.

Treatment

Save victims from drowning and give cardiopulmonary resuscitation as required. Commercial vinegar or 3% to 10% aqueous acetic acid solution was believed to inactivate nematocysts of *Chironex fleckeri*, Irukandji, and other cubozoans, but this has been questioned. Shave off adherent tentacles using a razor. Hot water immersion relieves the pain of *Chironex* and *Physalia* stings.³⁹ A slurry of baking soda and water (50% wt/vol) is recommended for stings by *Chrysaora* species. *C fleckeri* antivenom is manufactured in Australia.

Echinodermata (Starfish and Sea Urchins)

Waders can easily impale their feet on echinoderms' long, sharp, venomous spines and grapples, leaving diagnostic blue/black staining at the site of sting. Pain, local swelling, and sometimes syncope, numbness, generalized paralysis, and cardiorespiratory arrest may occur. Penetration of bones and joints leads to secondary infection.

Treatment

Hot water immersion relieves pain. Spines should be removed after softening the skin, usually of the soles of the feet, with 2% salicylic acid ointment or acetone. No antivenoms are available. There is a risk of infection by marine bacteria.

VENOMOUS ARTHROPODS: INSECTS (HYMENOPTERA (BEES, WASPS, YELLOW JACKETS, HORNETS, ANTS))

A single sting by a hymenopteran insect, such as a bee (Apidae), wasp, yellow-jacket, or hornet (Vespidae) (Fig. 11), or ant (Formicidae) can cause rapid death from anaphylaxis in someone previously sensitized to its venom.⁴⁰ Multiple stings are damaging or even fatal through direct effects of large doses of venom even in unsensitized people. This happened during a recent epidemic of African killer bee attacks in the Americas.⁴¹ Hymenopteran venoms contain amines causing pain and larger molecules that are potential allergens, such as phospholipases A, acid phosphomonoesterases, hyaluronidase, and polypeptide neurotoxins (apamin, melittin).

Epidemiology

Fewer than five people die from identified hymenopteran sting anaphylaxis in England and Wales each year, two to three per year in Australia, and 40 to 50 in the United

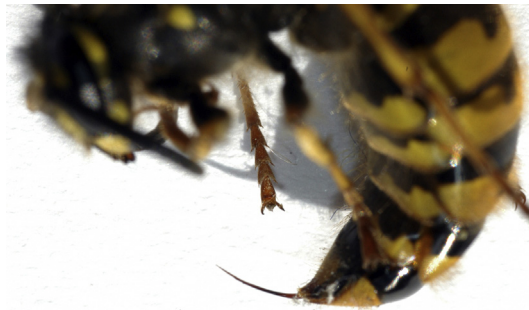


Fig. 11. European wasp (*Vespa germanica*) showing stinger. (© 2018 David A. Warrell.)

States where 4% of the population is susceptible to systemic allergic sting reactions. Beekeepers or their relatives have the highest risk of being sensitized. Imported South American fire ants (*Solenopsis* sp.) are estimated to sting about 2.5 million people each year in the United States, causing systemic allergic reactions in 4 per 100,000 population per year, some of which are fatal. In southern Australia and Tasmania, the prevalence of hypersensitivity to jack jumper ant (*Myrmecia pilosula*) venom is about 2% to 3%. Some reactions are fatal.

Prevention

A history of systemic anaphylaxis following a sting warrants testing for venom-specific IgE in blood (radioallergosorbent test) or by prick skin testing. Those who test positive should be considered for desensitization using purified venoms. After about 2 to 5 years of maintenance desensitization, more than 90% of subjects remain protected against systemic reactions after stopping treatment. Systemic reactions, including anaphylaxis, may complicate desensitization in 5% to 15% of patients. Local reactions are common but usually trivial. Where aggressive hymenopterans (hornets, bees, ants) pose a threat, their nests must be eradicated.

Clinical Features of Hymenopteran Hypersensitivity

Some patients develop purely local symptom each time they are stung. Painful, tender, inflammatory swelling progressing from the site of the sting and may involve the whole limb and persist for up to a week. However, there is a low risk of such people developing systemic (anaphylactic) reactions to subsequent stings. In a separate group of patients, a sting precipitates anaphylaxis: premonitory itching or tingling of scalp, axillae, or groins; flushing; dizziness; syncope; wheezing; abdominal colic (uterine colic in women), diarrhea, incontinence of urine and feces; and tachycardia and visual disturbances that may evolve rapidly within minutes of the sting. Signs include urticaria; angioedema of lips, gums, mouth, and tongue; generalized pruritic erythema with swelling; edema of the glottis; profound hypotension; and loss of consciousness. Deaths have occurred after only 2 minutes. Serum sickness may develop a week or more later. The risk of reactions is increased by β -blockers, ACE inhibitors, and cyclooxygenase-1 and -2 inhibitors.

Diagnosis of Anaphylaxis and Venom Hypersensitivity

Raised plasma mast-cell tryptase concentrations (peak at 0.5–1.5 h, last 6–8 h) confirm anaphylaxis. Detection of venom-specific IgE in serum (radioallergosorbent test) by skin testing or live sting challenge confirms type 1 hypersensitivity. Those who have suffered systemic anaphylaxis, have a 50% to 60% risk of reacting to subsequent stings. Children who have generalized urticaria after a sting have only a 10% chance of reacting when stung again.

Treatment

Barbed bee stings must be removed immediately to prevent injection of more venom. Vespids can sting repeatedly. Ice packs and aspirin are effective in relieving pain. Wasp stings may become infected because some species feed on rotting meat. Massive local reactions may require histamine H_1 blocker, aspirin, nonsteroidal anti-inflammatory agents, and even corticosteroids.

Systemic anaphylaxis demands urgent epinephrine (adrenaline: adults, 0.5–1 mL; children, 0.01 mg/kg of 0.1% [1:1000]) intramuscularly into the anterolateral thigh. Adrenergic β_2 receptor agonists (eg, salbutamol) are given for bronchoconstriction. The roles of histamine H_1 blockers, such as chlorphenamine maleate (adults, 10 mg;

children, 0.2 mg/kg) and corticosteroids is uncertain. People with identified hypersensitivity should wear an identifying tag and must be trained to self-administer 0.1% epinephrine (adrenaline).

SCORPIONS (SCORPIONES: BUTHIDAE, HEMISCORPIIDAE)

Epidemiology

In Brazil in 2016, a total of 91,000 scorpion stings were reported, more than three times the number of snakebites, with 121 deaths, 12 more than from snakebite. Arizona reports 15,000 (mainly *Centruroides exilicauda/sculpturatus*) stings per year, with no fatalities since 1968. Among an estimated 250,000 stings per year by *Centruroides* sp in Mexico, deaths have decreased to 50 per year. In Tunisia, there are about 40,000 stings per year, 1000 hospital admissions, and 100 deaths from *Androctonus*, *Buthus*, and *Leiurus* sp stings. In Iran, *Androctonus* and *Buthus* sp, and especially *Hemiscorpius lepturus*, cause fatalities. In Maharashtra, India, stings by Konkan red scorpions (*Hottentota tamulus*) are common and may prove fatal in adults and children.

Prevention

Exclude scorpions from houses with a row of ceramic tiles at the base of outside walls, making the doorsteps at least 20 cm high, and by using residual insecticides (1% lindane or dieldrin) indoors.

Clinical Features

Many stings are excruciatingly painful. The exception is *H lepturus*, whose stings may be painless. Scorpion venom ion channel toxins release endogenous acetylcholine and catecholamines, producing early cholinergic and later adrenergic effects. Vomiting, profuse sweating, piloerection, alternating bradycardia and tachycardia, abdominal colic, diarrhea, incontinence, and priapism are followed by hypertension, shock, tachyarrhythmia and bradyarrhythmia, EKG evidence of myocarditis, and pulmonary edema. Neurotoxic effects (*Centruroides* sp) include erratic eye movements, fasciculations, muscle spasms that may be misinterpreted as tonic-clonic convulsions, and respiratory embarrassment. Ptosis and dysphagia are reported from *Parabuthus* envenoming (South and East Africa) (Fig. 12), thrombotic strokes from *Nebo hierichonticus* stings in the Middle East, acute pancreatitis from *Tityus trinitatis* in Trinidad, and local necrosis, hemolysis and AKI from *H lepturus*.

Treatment

The most effective analgesia is local anesthetic, administered by digital block in stings on fingers and toes. Antivenom has proved effective in Arizona and India.^{42,43} Cardiovascular symptoms may respond to ancillary vasodilator treatment with prazosin (α_1 -blocker).⁴⁴ Dobutamine is effective for left ventricular failure that evolves despite early prazosin therapy.⁴⁵

SPIDERS (ARANEAE)

The danger of spider bites has been grossly exaggerated. Few species have proved to be of genuine medical importance.⁴⁶

Epidemiology

In Brazil, there were 29,000 spider bites in 2016 with 22 deaths. *Loxosceles* sp (recluse spiders) (Fig. 13) cause frequent bites in Central and Southern America. In the south-central United States, brown recluse spider (*Loxosceles reclusa*) bites caused at least



Fig. 12. Chilean recluse spider (*Loxosceles laeta*) from Brazil. This is the most dangerous species. (© 2018 David A. Warrell.)

six deaths during the last century. Most bites occur in bedrooms while people are asleep or dressing. Black and brown widow spiders (*Latrodectus* sp) are cosmopolitan in distribution. Rare fatalities have been reported in Australia (*Loxosceles hasselti*) and in the United States (*Loxosceles mactans*). Latin American banana spiders (*Phoneutria* sp) cause bites there and in temperate countries in imported bunches of bananas, causing a few bites and deaths. The Sydney funnel web spider (*Atrax robustus*), the most dangerous of all, is restricted to south-eastern Australia and Tasmania an area around Sydney.

Clinical Features

Necrotic araneism

Only *Loxosceles* sp have caused “necrotic araneism.”⁴⁶ Bites are usually painless and pass unnoticed but, over several hours, burning pain evolves at the bite site, with swelling and appearance of the characteristic “red-white-and-blue sign,” with a



Fig. 13. Red-white-and-blue sign appearing 12 hours after a bite by a recluse spider (*Loxosceles gaucho*) in Brazil. (© 2018 David A. Warrell.)



Fig. 14. Armed or wandering spider (*Phoneutria nigriventer*) from Brazil that bit a patient on her middle finger causing severe pain but no systemic symptoms. (© 2018 David A. Warrell.)

penumbra of red vasodilatation, an inner annulus of white vasoconstriction, and a cyanotic, pre necrotic center (Fig. 14). A blackened eschar develops, which sloughs in a few weeks, leaving a full thickness necrotic ulcer that may involve an entire limb or area of the face.

Visceral loxosclism affects

In 10% of cases there is fever, headache, scarlatiniform rash, jaundice, hemoglobinemias, and hemoglobinuria and AKI resulting from intravascular hemolysis and disseminated intravascular coagulation with a case fatality of about 5%.

Neurotoxic araneism

Bites by *Latrodectus*, *Phoneutria* (Fig. 15), and *Atrax* sp cause immediate pain with development of local sweating and piloerection (goose bumps). Painful regional



Fig. 15. Granulated thick-tailed scorpion (*Parabuthus granulatus*) from Southern Africa. (© 2018 David A. Warrell.)

lymphadenopathy, headache, nausea, vomiting, profuse generalized sweating, fever, tachycardia, hypertension, restlessness, irritability, psychosis, priapism, rhabdomyolysis, and diffuse rash may develop. Painful muscle spasms, tremors, and rigidity may affect the face and jaws (producing trismus) and abdominal muscles (simulating acute abdomen).

Treatment

First aid with pressure-immobilization (discussed previously) is recommended for rapidly developing funnel-web spider envenoming. Antivenoms against venoms of *Latrodectus* sp, *Atrax* sp, and *Phoneutria* sp are available.

SUMMARY

This article discusses the epidemiology, prevention, clinical features, and treatment of venomous bites by snakes, lizards, and spiders; stings by fish, jellyfish, echinoderms, insects, and scorpions; and poisoning by ingestion of fish, turtles, and shellfish.

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