CHAPTER 116

Marine Envenomations

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A 28-year-old man was stung on the lateral surface of his right hand by a lionfish when he reached into his tropical fish aquarium to adjust the aerator. Within seconds he experienced severe pain and swelling of his hand. En route to the hospital the patient applied an ice pack. In the emergency department he was awake, alert, and in considerable distress. His vital signs were: blood pressure, 150/90 mm Hg; pulse, 110 beats/min; respiratory rate, 18 breaths/min; oral temperature, 98.6°F (37°C).

Three small linear puncture marks, approximately 8 mm apart, were located on the lateral surface of the patient's right hand. The hand was swollen and erythematous. Neurovascular examination of the hand was normal. (See ILLIONFISH in the Image Library at goldfrankstoxicology.com.)

The hand was immersed in water that had been heated to 110°F (43.3°C). The immersion resulted in pain relief within 5 minutes. However, the pain recurred when the water cooled to room temperature. The patient received a diphtheria-tetanus toxoid vaccination and was discharged 4 hours after arrival to the emergency department. No systemic signs had developed, and his pain was significantly relieved. He was instructed to take ibuprofen 400 mg every 6 hours, for pain and to have his hand examined by his private physician the next day.

Human encounters with venomous marine creatures are commonplace and may result in serious clinical effects. Injuries may arise from direct toxin effects and from mechanical destruction from the stinging apparatus. Significant morbidity and documented deaths have occurred following envenomation with spiny fish, cone snails, octopi, sea snakes, and several species of jellyfish. Despite significant advances in basic science research regarding the biochemical nature of marine toxins and their mechanisms of action, our knowledge of clinical effects in humans, and the optimal therapies for human envenomation, remain limited. Evidence for effective treatment is primarily derived from in vitro and in vivo animal research without the benefit of controlled human trials. However, current research in toxinology (the study of toxic proteins from microbial, plant, and animal origin) coupled with clinical observations provides information that can translate into reduced morbidity and mortality associated with these injuries.

INVERTEBRATES

Cnidaria

The phylum *Cnidaria* (formerly *Coelenterata*) includes more than 9000 species, of which approximately 100 are known to cause injury in humans. They are commonly referred to as *jellyfish;* however, their phylogenetic designations separate "true jellyfish" and other organisms into distinct classes (Table 116–1) (see ILJELLYFISH in the Image Library). All species possess microscopic cnidae (Greek knide = nettle), which are highly specialized organelles consisting of an encapsulated hollow barbed thread bathed in venom. Thousands of these stinging organelles, called *nematocysts* (or *cnidoblasts*), are distributed along tentacles. A trigger mechanism called a *cnidocil* regulates nematocyst discharge. Pressure from contact with a victim's skin, or chemical triggers such as osmotic changes, stimulates discharge of the thread and toxin from its casing. Penetration of flesh leads to hypodermic venom delivery. Nematocysts of most *Cnidaria* are incapable of penetrating human skin, rendering them harmless. *Cnidaria* causing human envenomation, such as the box jellyfish, discharge threads capable of penetrating into the papillary dermis of human skin.[132]

Cubozoa. Members of the class *Cubozoa* are not true jellyfish. Animals in the *Cubomedusae* order have a cube-shaped bell with 4 corners, each of which supports between 1 and 15 tentacles. Species from this order produce the greatest morbidity and mortality of all *Cnidaria*. The order has two main families of toxicologic importance: *Chirodropidae* and *Carybdeidae.*

The *Chirodropidae* family is well known for the box jellyfish *Chironex fleckeri* (Greek cheiro = hand, Latin nex = murderer, is known as "assassin's hand"). The species was named in honor of Dr. Hugo Flecker, a physician from Cairns, Australia.[128] When full grown, its bell measures 25 to 30 cm in diameter, and 15 tentacles are attached at each corner of the bell. These tentacles may extend up to 3 m in length. Another member of this family is *Chiropsalmus quadrigatus,* the sea wasp. Its pale blue color makes detection in water nearly impossible.

The *Carybdeidae* family is most notable for *Carukia barnesi,* the Irukandji jellyfish. It is named in honor of Dr. Jack Barnes, who identified the species as the cause of a severe systemic syndrome following stings among a tribe of Aboriginal people (the Irukandji) in the Cairns region of northern Australia.[59] Its small size, with a bell diameter of 2.5 cm, makes detection in the water difficult.

Hydrozoa. The *Hydrozoa* class, like the *Cubozoa,* are not true jellyfish; however, they are capable of inflicting considerable pain and even death in humans. The order *Siphonophora* (*Physaliidae* family) includes two unusual creatures of toxicologic concern:

TABLE 116–1. Cnidaria

Latin Name	Common Name	Habitat[b]
***Cubozoa* class**		
Chironex fleckeri[a]	Box jellyfish	Tropical Pacific Ocean, Indian Ocean, Gulf of Oman
Carukia barnesi[a]	Irukandji jellyfish	North Australian coast
Chiropsalmus spp[a]	Sea wasp or fire medusa	North Australian coast, Philippines, Japan, Indian Ocean, Gulf of Mexico, Caribbean, and Puerto Rico
C. quadrigatus		
C. quadrumanus		
Carybdea alata	Hawaiian box jelly	Hawaii
Carybdea rastoni	Jimble	Australia
***Hydrozoa* class**		
Physalia physalis[a]	Portuguese man-of-war	Eastern US Coast from Florida to North Carolina, Gulf of Mexico, Australian coastal waters (rare reports)
Physalia utriculus	Bluebottle	Tropical Pacific Ocean, particularly Australia
Millepora alcicornis	Fire coral	Wide spread in tropical waters, including Caribbean
***Scyphozoa* class**		
Chrysaora quinquecirrha	Sea nettle	Chesapeake Bay, widely distributed in temperate and tropical waters
Stomolophus meleagris	Cabbage head or cannonball jelly	Gulf of Mexico, Caribbean
Stomolophus nomurai[a]		Yellow Sea between China and South Korea
Cyanea capillata	Lion's mane or hair jelly	Northwest US coast up to Arctic Sea, Norwegian and British coastlines
Pelagia noctiluca	Mauve stinger or purple-striped jelly	Caribbean
Linuche unguiculata	Thimble jelly	Florida, Mexico, and Caribbean
***Anthozoa*[a] class**		
Anemonia sulcata	European stinging anemone	Eastern Atlantic, Mediterranean, Adriatic Sea
Actinodendron plumosum	Hell's fire anemone	South Pacific
Actinia equina	Beadlet anemone	Great Britain, Ireland

[a]Well-documented human fatalities
[b]Represents most common areas where stings are reported.

Physalia physalis, the Portuguese man-of-war, and its smaller counterpart, *Physalia utriculus,* the bluebottle. They are pelagic (floating) colonial *Hydrozoa,* meaning they exist as a colony of multiple hydroids (*Cnidaria* is a polyp as the dominant life phase) in a formed mass. The easily recognizable blue sail that floats above the surface of the water is filled with nitrogen and carbon monoxide. Tentacles of *P. physalis* may reach lengths in excess of 100 ft and contain more than 750,000 nematocysts in each of its numerous tentacles (up to 40). *Physalia utriculus* has only one tentacle, which measures up to 15 m.

The *Milleporina* order is well known for the sessile *Millepora alcicornis,* fire coral, which also exists as a colony of hydroids. It appears much like true coral and has a white to yellow-green lime carbonate exoskeleton. Small tentacles protrude through minute surface gastropores. The overall structure ranges from 10 cm to 2 m.

Scyphozoa. True jellyfish belong to the class *Scyphozoa* and are extremely diverse in size, shape, and color. Common varieties known to envenomate humans are *Cyanea capillata* (lion's mane or hair jelly), *Chrysaora quinquecirrha* (sea nettle), and *Pelagia noctiluca* (mauve stinger). The mauve stinger is easily recognized; it appears pink in daylight and phosphorescent at night. Larvae of certain *Linuche linguiculata* cause sea bather's eruption (SBE). The larvae are pin-head sized and are seen only when they are grouped in large numbers near the surface of the water.

Anthozoa. The *Anthozoa* class has a diverse membership, including true corals, soft corals, and anemones. Only the anemones are of toxicologic concern. They are common inhabitants of reefs and tide pools and attach themselves to rock or coral. Armed with modified nematocysts known as *sporocysts* located on their tentacles, they can produce stings similar to those of organisms from other *Cnidaria* classes.

History and Epidemiology. Stings from *Cnidaria* represent the overwhelming majority of marine envenomations. In Australia, approximately 10,000 stings per year are recorded from *Physalia* spp alone.[54] Most *Cnidaria* stings occur during the warmer months of the year. Stings occur with greatest frequency on hotter-than-average days with low winds, particularly during times of low precipitation. "Stinger nets" are used in high-risk areas of the Australian coastline; however, one study reported that 63% of stings requiring medical attention occurred within netted waters.[84] Each stinger season, the Royal Darwin Hospital in Australia treats approximately 40 patients with stings.[40] A prospective evaluation of stings presenting to that hospital during a 12-month period from 1999–2000 revealed that 70% resulted from the box jellyfish. The remaining 30% involved other *Cubozoa* such as *C. barnesi*.[103] Although this finding may indicate a predominance of box jellyfish as the cause of stings, it also suggests that stings from box jellyfish are more severe and require medical attention with greater frequently than stings from other *Cubozoa.*

Cases of sea bathers eruption (SBE) a stinging rash from *Cnidaria* larvae, occur in clusters. They display variation in intensity and frequency from year to year, as exemplified by a 25-year hiatus during which no cases were reported in Florida.[138] In 1992, more than 10,000 cases of SBE were seen in south Florida, with similar peaks in the 1940s and 1960s. Cases of SBE also are reported in Cuba, Mexico, the Caribbean, and occasionally in Long Island, New York.

Cnidaria common to the United States include the Portuguese man-of-war and sea nettle. Other species are widely distributed throughout the tropical and temperate waters of the globe (Table 116–1). Locations with documented deaths include the United States (Florida, North Carolina, Texas), Australia, the Indo-Pacific region (Malaysia, Langkawi Islands, Philippines, Solomon Islands, Papua New Guinea), and the coast of China. Since 1884 the estimated number of deaths in Australia attributed to *C. fleckeri* is approximately 70.[54,83] An estimated 2–3 deaths per year occur in Malaysia from an unknown species.[54] Approximately 20–40 deaths are reported yearly in the Philippines from an unidentified species of the *Chirodropidae* family.[54] Three deaths are well documented from *P. physalis* in the United States (Florida, North Carolina).[22,54,131] One death from *Chiropsalmus quadrumanus* occurred along the coast of Texas.[12] Eight fatalities in the Bohai waters of China (Yellow Sea) have been reported from *Stomolophus nomurai*.[54,151] Although *Chirodropidae* are found off the western coast of Africa, no fatalities in that region are documented.

Pathophysiology. *Cnidaria* venoms contain a variety of components that may induce dermanecrosis, myonecrosis, hemolysis, or cardiotoxicity, depending on the particular species. In rats, *C. fleckeri* venom evokes transient blood pressure elevation, followed by hypotension and cardiovascular collapse within minutes.[107,109] Other effects in animals include decreased inotropy, cardiac conduction delay, ventricular tachycardia, and decreased coronary artery flow.[40] However, experiments using the most pure venom extracts without contamination from tentacle material demonstrate cardiovascular collapse without electrocardiographic changes.[109] *Chironex fleckeri* venom also possesses dermanecrotic and hemolytic fractions, although hemolysis in humans is not documented.[9] Two myotoxins from *C. fleckeri* cause powerful sustained muscle contractions in isolated muscle fibers.[44] Isolated heart models using *C. fleckeri* venom suggest its mechanism of action is nonspecific enhancement of cation conductance leading to increased Na^+ and Ca^{2+} entry into cells.[99] Other in vitro work confirms increased Na^+ permeability in cardiac tissue.[61]

Carukia barnesi, the Irukandji jelly, likely induces its dramatic vasopressor effects via catecholamine release. In rats the venom produces a pressor response that is blocked by α_1-adrenoreceptor antagonism.[108] The pressor response is not dose dependent; therefore, catecholamines in the venom would not explain this effect. No electrocardiographic abnormalities occurred in envenomated rats.

Venom from *Physalia* spp blocks neural impulses in isolated frog sciatic nerve[80] and produces ventricular ectopy, cardiovascular collapse, hyperkalemia, and hemolysis in dogs.[70] *Physalia* spp venom inhibits Ca^{2+} entry into the sarcoplasmic reticulum.[80] Similar mechanisms are proposed for *Chrysaora, Chiropsalmus,* and *Stomolophus. Chrysaora quinquecirrha* venom contains a 150-kDa polypeptide that induces atrioventricular block[18] and produces myocardial ischemia, hypertension, dysrhythmias, and nerve conduction block,[23,24] as well as hepatic and renal necrosis.[98] *Chrysaora quinquecirrha*–induced hepatotoxicity is believed to be a direct toxin effect not mediated by pore formation or Ca^{2+} channel effects.[72] Equinatoxin II (EqtII), found in the venom of the anemone *Actinia equina*, induces pore formation in cell membranes, causing hemolysis.[1] This protein belongs to a group of anemone lysins, known as *actinoporins,* which bind to cell membranes and form pores via oligimerization.[88]

Symptoms resulting from stings may be partly immune mediated. Elevated serum anti–sea-nettle immunoglobulin IgM, IgG, and IgE may persist for years in patients with exaggerated reactions to stings compared to controls.[19] A direct correlation between titers against *Chrysaora* and *Physalia* and severity of a visible skin reaction to envenomation, strongly suggests an allergic component.[120] Elevated IgG titers were demonstrated in one death from *P. physalis*.[131] Dermatonecrosis from *C. fleckeri* may involve the release of leukotrienes and other arachidonic acid derivatives and direct cell damage.[41] Postenvenomation syndromes may result from an exaggerated, prolonged, aberrant T-cell response.[25,26] Erythema nodosum has been reported following a sting from *P. physalis,* lending further support to a immunologic component to symptoms.[5] SBE displays a characteristic delay in onset of symptoms and can be effectively treated with steroids, suggesting a primary immune-mediated process for this entity. This is further supported by histopathology which shows the presence of perivascular and interstitial infiltrates with lymphocytes, neutrophils, and eosinophils.[148]

Clinical Manifestations. Most patients with stings are treated beachside and never require hospital treatment. The vast majority of patients with stings who seek medical care have severe pain, but are not systemically poisoned.[40] However, severe systemic manifestations may develop following stings from *C. fleckeri*, *C. barnesi*, *P. physalis*, and a few other *Cnidaria.*

Envenomation by *C. fleckeri* causes the most severe pain and is frequently associated with systemic toxicity. Common symptoms include immediate severe pain, followed by an erythematous whiplike linear rash with a "frosted ladder" appearance. The pain often is excruciating and may require parenteral analgesia. Systemic symptoms include nausea, vomiting, muscle spasms, headache, malaise, fever, and chills. Pain generally abates over several hours, although the rash may persist for days. In a prospective series of *C. fleckeri* stings, 58% manifested delayed hypersensitivity reactions in the form of an itchy maculopapular rash at 7–14 days.[103] Most resolved spontaneously; some were treated with antihistamines and topical corticosteroids.

Some estimates cite a fatality rate following *C. fleckeri* envenomation of 15%–20%.[115] This likely represents a gross overestimation, given the low number of documented fatalities in the context of the extraordinary number of yearly stings. A prospective study of stings from *Cubozoa* over one year in Australia revealed no dysrhythmias, pulmonary edema, or death.[103] No patient received antivenom, and analgesia was the only pharmacotherapy implemented. Hospital admission was not required for any victim. Although most victims suffer only local severe pain, serious systemic toxicity occurs occasionally, and may include vertigo, ataxia, paralysis, delirium, syncope, and respiratory distress. Hypotension, dysrhythmia, pulmonary edema, hemolysis, and acute renal failure characterize the clinical findings. The last 10 reported deaths from *C. fleckeri* occurred in children, suggesting vulnerability due to lower body mass.[40] Fatality is documented following as little as 4 m of tentacle markings.[132] Death, when it occurs, typically is rapid leaving, many victims unable to reach shore. Cardiac arrest and pulmonary edema may develop in young healthy patients without prior cardiopulmonary disease.[76,87,147] Survival is possible with immediate cardiopulmonary resuscitation (CPR).[146] *Chiropsalmus quadrumanus,* a close relative of the box jellyfish, induces symptoms that parallel *C. fleckeri* stings, including pulmonary edema and death.[12]

Irukandji syndrome is a particularly severe form of envenomation following *Cubozoa* stings. The causative species was isolated with brave self-experimentation by Dr. Jack Barnes using the *Cubomedusae* named *Carukia barnesi* in his honor. His conclusion that *C. barnesi* causes Irukandji was confirmed in a retrospective review of 50 cases, 39 of which had skin scrapings consistent with *C. barnesi*.[73] However, one patient who died had nematocysts that could not be identified, suggesting the possible existence of another causative species. This syndrome was thought to be isolated to Australia; however, three recent cases of Irukandjilike syndrome stemming from an unidentified organism were reported in the Florida Keys.[67]

Individuals afflicted with Irukandji syndrome often notice a mild sting while they are in the water; however, skin findings typically are absent. Severe systemic symptoms develop within 30 minutes and mimic a catecholamine surge: tachycardia, palpitations, hyperpnea, headache, pallor, restlessness, apprehension, sweating, and a sense of impending doom. A prominent feature is severe whole-body muscle spasms that come in waves and preferentially affect the back. Spasms are described as unbearable and frequently require parenteral analgesia. Symptoms generally abate over several hours. Admission rates in patients presenting to medical care can exceed 50%.[84] Hypertension is universal and may be severe, with systolic blood pressures well over 200 mm Hg. Two fatalities are described involving severe hypertension (systolic 280/150 mm Hg and 230/90 mm Hg) resulting in intracranial hemorrhage.[50,73] Hypotension frequently follows, requiring vasopressor support. Pulmonary edema results from myocardial dysfunction and is a potentially severe complication that can develop within 2 hours or be delayed several hours. Echocardiograms consistently reveal global ventricular dysfunction,[84,86,90] although focal hypokinesis may be present.[73] Normal cardiac function typically returns after several days.[85] In a retrospective review of 116 cases presenting to Cairns Base Hospital, 22% of patients had elevated troponin I measurements,[73] although some reviews cite a frequency as high as 78%.[86] Nonspecific electrocardiographic changes were frequently noted in those reviews.

Physalia physalis envenomation typically causes severe pain, bullae, and skin necrosis (see ILJELLYFISH in the Image Library). Systemic symptoms include weakness, numbness, anxiety, headache, abdominal and back spasms, lacrimation, nasal discharge, diaphoresis, vertigo, hemolysis, cyanosis, renal failure, shock, and rarely death. Some patients experience local numbness and paralysis of the affected extremity that resolves spontaneously.[74] As with serious *C. fleckeri* stings, cardiovascular collapse and death occur within minutes of envenomation.[22] However, fatalities can be delayed several days following envenomation and may stem from complications such as myocardial infarction and aspiration pneumonia.[131] An unusual presentation is reported of a 4-year-old child who was stung along the North Carolina coast and developed massive hemolysis requiring red blood cell transfusions, followed by renal failure necessitating temporary dialysis.[68] In contrast to *P. physalis, P. utriculus* stings typically are mild and relieved with ice, although systemic toxicity occasionally develops.[56]

Millepora alcicornis (fire coral) is a common cause of stings in southern US and Caribbean waters. Although it belongs to the same phylogenetic class as *P. physalis,* it produces far less significant injuries. It is a nuisance to divers who touch what they perceive to be harmless coral and then suffer moderate burning pain for hours. Untreated pain generally lessens within 90 minutes, with skin wheals flattening at 24 hours and resolving within 1 week. Hyperpigmentation may persist up to 8 weeks.[15] The feather hydroid is the most numerous of the *Hydrozoa* and produces only mild stings.[92]

True jellyfish typically are less harmful to humans than *Cubozoa* or *Hydrozoa*. However, systemic toxicity and occasional deaths are reported from certain species such as *S. nomurai, C. capillata, C. quinquecirrha*, and *P. noctiluca*. *Stomolophus meleagris* is a common cause of stings; however, its weak venom produces only minor injury.[4]

Larvae of *Linuche unguiculata* are the primary cause of a pruritic papular eruption on the skin of sea bathers in Florida, occurring mostly in areas covered by a bathing suit as a result of larvae trapped under the garments. Cases were first noted in 1949 and referred to as SBE.[121] The larvae appear as pin-sized brown to green-brown spheres in the upper 2 inches of the water and typically go unnoticed. In a retrospective review, 50% of people reported a stinging sensation while they were in the water, and 25% reported itching upon exiting the water.[148] The remainder of patients developed symptoms within 11 hours. Skin lesions develop within hours of itching and appear as discrete, closely spaced papules, with pustules, vesicles, and urticaria. Most lesions occur in areas covered by the bathing suit; however, folds of skin such as the axilla, breasts, and neck may be affected. Itching often is severe and prevents sleep. New lesions may continue to develop over 72 hours. The average duration of symptoms is just under 2 weeks, and a small percentage of patients experience a recurrence of lesions several days later. Systemic symptoms such as chills, headache, nausea, vomiting, and malaise may occur. (See ILSEABATHERS in the Image Library.)

Following stings from sea anemones, victims may develop immediate or delayed pain. Skin findings range from mild erythema and itching to ulceration. A review of 55 stings from *Anemonia sulcata* presenting to a hospital in Yugoslavia (Adriatic Sea) revealed that, in addition to the local skin findings, many patients suffered nausea, vomiting, muscle aches, and dizziness.[89] Larvae of the anemone *Edwardsiella lineata* also cause SBE among ocean swimmers in Long Island, New York. The hell's fire anemone *Actinodendron plumosum* is native to the South Pacific and causes significant local pain. One death occurred in the Virgin Islands following envenomation from an unknown species described as a "white anemone with blue tips." The onset of hepatic and renal failure was rapid and required transplantation, after which the patient died.[63] Nonfatal elevation of hepatic enzyme concentrations following anemone sting also is reported.[16]

Diagnostic Testing. Laboratory evaluation may be warranted in patients suffering systemic toxicity following *Cnidaria* envenomation. Serial measurement of serum cardiac markers should be obtained from victims of Irukandji stings or others with consequential cardiovascular toxicity. Following severe stings from a variety of *Cnidaria*, urinalysis, hematocrit, and serum creatinine should be considered to detect the presence of hemolysis and subsequent renal injury. Chest radiography is indicated for complaints of dyspnea or abnormalities in oxygenation. Venom assays are not available, and serum antibody titers are not clinically useful.

Management. Initial interventions after *Cnidaria* envenomation should follow standard management strategies. Secondary measures are directed toward the prevention of further nematocyst discharge, which could intensify pain and enhance toxicity. Many topical agents have been used for this purpose, including

sea water, vinegar, Stingose, methylated spirits, ethanol, isopropyl alcohol, dilute ammonium hydroxide, urine, sodium bicarbonate, papain, shaving cream, and sand.

Vinegar is a common first-line treatment for topical application following *Cnidaria* stings. In vitro trials with *C. fleckeri* tentacles demonstrate complete irreversible inhibition of nematocyst discharge following a 30-second application.[69] Additional study findings include massive nematocyst discharge with application of urine or ethanol, and no effect on discharge with use of sodium bicarbonate. Followup in vivo experiments demonstrate that vinegar is effective for other *Cubozoa,* including Morbakka (large *Cubozoan* in Australia),[49] *Carybdea rastoni,*[52] and *C. barnesi*.[53] Although massive nematocyst discharge occurs when vinegar is applied to *C. capillata* tentacles in vitro clinical exacerbation following this treatment is not reported in humans.[48] Massive discharge also occurs with *C. quinquecirrha.*[28] A smaller degree of discharge (30%) occurs with *P. physalis,*[56] whereas nematocysts of *P. utriculus* are unaffected by application of vinegar.[69]

Stingose is a commercially available product designed to counteract venom of insects, bees, stinging plants, and marine stingers. It is an aqueous solution of 20% aluminum sulfate and 1.1% surfactant. Its proposed mechanism of action is denaturing of proteins and long-chain polysaccharides via interaction with the Al^{3+} ion, as well as osmotic removal of venom. A human volunteer trial involving stings from live tentacles of *C. fleckeri* demonstrated pain relief within 5 seconds of Stingose application.[71] Similar results were achieved following treatment of stings from *C. quinquecirrha*. A field trial that included 17 *C. fleckeri* and 150 *P. utriculus* sting victims who were treated with Stingose immediately following injury was conducted. All victims reported rapid relief. However, placebo or alternative therapies were not used in this case series. The efficacy of treatment with vinegar, Stingose, methylated spirits, and salt water was measured in human volunteers following forearm application of *P. physalis* tentacles.[141] Vinegar demonstrated superior pain control compared to Stingose, whereas methylated spirits increased pain. The study assessed pain relief only and did not investigate the effects of the treatments on nematocyst discharge or systemic toxicity.

In many cases the identity of the "jellyfish" causing injury is unknown. In those cases, therapy must be guided by geographic location. In the United States, where *P. physalis* and *C. quinquecirrha* are of greatest consequence, sea water should be used to aid in tentacle removal given that vinegar enhances nematocyst discharge. In the Indo-Pacific region, where *C. fleckeri* and *C. barnesi* are of greatest concern, vinegar should be the primary agent used. Following a 30-second application, adherent tentacles must be carefully removed. This can be accomplished with a gloved or towel-covered hand, or with sand and gentle scraping with a credit card or other blunt straight-edged tool.

In a nonrandomized trial, ice packs provided rapid effective relief for patients with mild-to-moderate pain from *Cnidaria* stings.[45] Patients with severe pain were less likely to benefit from ice packs. The venom of *C. fleckeri* and *C. quinquecirrha* is heat stable; therefore, hot water is ineffective for venom neutralization and may increase pain.[17]

Pressure immobilization bandaging is a technique that applies sufficient pressure to a wound to impede lymphatic drainage and prevent the entrance of toxin into systemic circulation. It typically has been used for snake bites, and its use following *Cnidaria* stings has sparked controversy. Given the rapid onset of symptoms, the utility of a technique that impedes lymphatic drainage is unlikely to provide benefit. Although the technique would be used only after tentacle removal, some microscopic nematocysts remain adherent to the skin after visible tentacle are removed. In vitro data investigating the effect of pressure on discharged nematocysts demonstrate not only that discharged nematocysts still contain venom, but that applying pressure forces more venom down the hollow tube.[105] This finding is correlated clinically as patients can deteriorate following pressure immobilization bandaging.[55] Given the lack of evidence suggesting benefit, coupled with clear, in vitro, evidence of increased venom delivery with this technique, it should not be used for treatment of *Cnidaria* stings.

Box jellyfish antivenom is sheep-derived whole IgG raised against the "milked" venom of *C. fleckeri.* It has been available in Australia since 1970. Combining *C. fleckeri* venom with box jellyfish antivenom prior to injection into pigs prevents all toxicity.[137] An isolated chick muscle experiment demonstrates that box jellyfish antivenom prevents the neurotoxicity and myotoxicity from *C. fleckeri* following pretreatment; however, there is no "rescue effect."[106] Given that antivenom in humans is always used as a rescue therapy, this research raises concerns regarding efficacy in the clinical setting. Pretreatment of rats with box jellyfish antivenom prevented cardiovascular collapse in 40%, but did not blunt the initial hypertensive effect.[107] In vitro data demonstrate that box jellyfish antivenom neutralizes the dermonecrotic, hemolytic, and lethal fractions of venom from *Chiropsalmus* spp; however, the venom of *P. physalis* and *C. quinquecirrha* were not neutralized.[10] Other in vitro and in vivo data demonstrate incomplete neutralization of *Chiropsalmus* spp venom.[10,106]

There are no controlled studies in humans evaluating the efficacy of box jellyfish antivenom in the treatment of *C. fleckeri* envenomations, nor is there convincing evidence that its use has saved human lives. Despite the frequency of hospital visits for stings from *C. fleckeri* in Australia, the use of box jellyfish antivenom is rare.[40] Evidence for its efficacy stems from case reports suggesting that pain abates rapidly after administration.[14,147] Although box jellyfish antivenom may improve pain control, patients still may require parenteral narcotics for analgesia following antivenom administration.[11] Significant morbidity and mortality still occur despite antivenom use.[39,87,132] Case reports of box jellyfish antivenom use for *C. barnesi* stings demonstrate no apparent benefit.[47]

Many serious stings occur in the Northern Territory of Australia, where stinger nets are not commonly used. Distance from medical care limits the ability to obtain antivenom in a timely fashion.[40] Although box jellyfish antivenom can be administered by paramedics via intramuscular (IM) injection,[55] poor IM absorption and incomplete venom neutralization with antivenoms, as well as delayed peak serum concentrations, limit the utility of this approach.[114] The amount of antivenom required to neutralize twice the lethal dose in humans, is estimated to be 12 vials.[40] The manufacturer recommends treating initially with 1 ampule intravenously (IV) diluted 1:10 with saline or 3 undiluted ampules (1.5–4 mL each) IM at 3 separate sites, if IV access is unavailable. Some authors who have treated multiple patients with antivenom suggest treating coma, dysrhythmia, or respiratory depression with 1 ampule IV, titrating up to 3 ampules with continuation of CPR in patients with refractory dysrhythmia until a total of 6 ampules have been administered.[103] For less serious envenomations, patients can be given 1 ampule if ice packs and parenteral analgesia prove ineffective.[103] Serious adverse events or delayed sequelae following the use of IV antivenom are uncommon, although allergic reactions are a consideration.[133]

Verapamil was considered a treatment for *C. fleckeri* stings based on evidence that calcium entry into cells is an important mechanism of toxicity. One animal model demonstrated synergy with use of verapamil in combination with box jellyfish antivenom,[27] whereas another showed verapamil pretreatment as well as rescue prolonged survival.[20] This is in contrast to other models demonstrating that verapamil negates the benefits of antivenom[107] and increases mortality.[137] Verapamil also has been tested in animals with *C. quinquecirrha* envenomation but demonstrated no benefit.[98] Interestingly, addition of magnesium to antivenom for treatment of *C. fleckeri* envenomation in rats prevented cardiovascular collapse in 100%, suggesting that magnesium may have a role in the treatment of stings from this species.[107] Given that animal data are inconsistent with regard to verapamil and that hypotension may develop with severe envenomation, use of calcium channel blockers is not recommended for treatment of *C. fleckeri* stings.

Treatment for Irukandji syndrome should focus on analgesia and blood pressure control. Several modalities for control of severe hypertension have been suggested and include phentolamine, IV magnesium, and nitroglycerin.[38,51] No single therapy demonstrates superior efficacy, although titratable agents are preferred because hypotension may occur in later stages of toxicity.

Mollusca

The phylum *Mollusca* (Latin mollis = soft) includes the classes *Cephalopoda* (octopus, squid, and cuttlefish) and *Gastropoda* (cone snails). Of the cephalopods, only the blue-ringed octopus *Hapalochlaena maculosa* and the greater blue-ringed octopus *Hapalochlaena lunulata* are of toxicologic concern. Of the 400 species of cone snails that belong to the genus *Conus,* 18 are implicated in human envenomations.

History and Epidemiology. The blue-ringed octopus normally is yellow-brown in color, but it develops iridescent blue rings when it is threatened. It is not aggressive and only causes envenomation in humans when it is handled. A 1983 review of reported octopus envenomations uncovered a total of 14 cases, all of which occurred in Australia.[142] There were 2 deaths[60,130] and 4 serious envenomations. Other reviews suggest up to 7 deaths may have occurred prior to 1969, some outside Australia.[43] The blue-ringed and greater blue-ringed octopus are found in the Indo-Pacific region, primarily in Australian waters. (See ILBLUERING in the Image Library.)

Estimates of reported cone snail envenomations suggest only 15 deaths have occurred worldwide.[46] *Conus geographicus* (fish hunting cone) is the most common species implicated, although *Conus textile* may also cause death in humans. Cone snails are found predominantly in the Indo-Pacific, including all parts of Australia, New Guinea, Solomon Islands, and Philippines. Two deaths from *C. geographicus* occurred in Guam.[82]

Pathophysiology. The octopus salivary gland secretes a toxin that previously was called *maculotoxin.* The structure was later identified as tetrodotoxin.[125] The beak of the octopus creates small punctures in human skin through which venom is introduced. Tetrodotoxin blocks Na^+ conductance in neurons, leading to paralysis. Venom also contains 5-hydroxytryptamine (5-HT), hyaluronidase, tyramine, histamine, tryptamine, octopine, taurine, acetylcholine, and dopamine.[134] Rabbits subjected to bites develop rapid flaccid paralysis without cardiotoxicity and die from asphyxia.[134] Other animal models using venom gland extract demonstrate rapid onset of respiratory muscle paralysis and severe hypotension.[58] Death occurs despite artificial respiration and results from hypotension.

TABLE 116–2. Conus Peptide Targets

Receptor Type	Peptide	Mechanism
Ligand-gated ion channels		
Nicotinic	α-Conotoxin	Competitive antagonism
	M1	neuromuscular junction
	M2	neuronal receptors
5-HT_3	σ-Conotoxin	Noncompetitive antagonism
NMDA	Conantokins	Inhibits conductance
Voltage-gated ion channels		
Ca^{2+}	ω-Conotoxin	Channel blockade
Na^+	μ-Conotoxin	Channel blockade
	δ-Conotoxin	Delayed channel activation
K^+	κ-Conotoxin	Channel blockade
G-protein linked		
Vasopressin receptor	Conopressin-G	Receptor agonism
Neurotensin receptor	Contulakin-G	Receptor agonism

Cone snails have a hollow proboscis that contains a tooth bathed in venom. Envenomation occurs when the shells are handled. The proboscis can extend the length of its shell, thereby envenomating the hand of someone touching the opposite end of the shell. Any *Conus* species contains approximately 100 peptides or *conotoxins* in its venom. Targets include voltage- and ligand-gated ion channels as well as G-protein–linked receptors (Table 116–2).[102] Many of these peptides have been used extensively in laboratory research for their ability to selectively target a variety of specific calcium channel subtypes. *Conus imperialis* (worm hunter) has venom that contains a substantial amount of 5-HT, which is not found in any other *Conus* venom tested thus far.[94] This species also contains a vasopressinlike peptide.[100] *Conus* peptides with antinociceptive properties are being used in human trials of chronic pain. Ziconotide (Prialt, Elan Pharmaceuticals) has completed phase III human trials for control of chronic pain via intrathecal infusion pump.[93] Clinical trials with other peptides for treatment of chronic pain are underway.[136]

Clinical Manifestations. The blue-ringed octopus creates 1 or 2 puncture wounds with its chitinous jaws, causing only a small amount of discomfort. A wheal may develop with erythema, tenderness, and pruritus. Tetrodotoxin exerts a curareform effect that causes paralysis while retains normal mental status. Symptoms include perioral and intraoral paresthesias, diplopia, aphonia, dysphagia, ataxia, weakness, nausea, vomiting, flaccid muscle paralysis, respiratory failure, and death. Detailed case reports demonstrate rapid onset of symptoms.[142] Complete paralysis requiring intubation with findings of fixed and dilated pupils is followed within 24 to 48 hours by near-complete recovery of neuromuscular function.[142] In one reported death, a young man placed the octopus on his shoulder. He subsequently noted a small puncture wound, developed dry mouth, dyspnea, inability to swallow, and became apneic. He developed asystole 30 minutes after arrival at the hospital despite artificial ventilation.[60] Another similar bite resulted in symptom onset at 10 minutes, followed by

death at 90 minutes, despite bystander CPR.[134] With less severe envenomations, cerebellar signs may be present without paralysis. Near-total paralysis with intact mentation resolving over 24 hours is described in humans.[134]

Envenomation from cone snails occurs with careless handling or from rummaging through sand. Cone snails are nocturnal feeders, so they may present more of a hazard to night divers. Symptoms range from a slight sting to excruciating pain. Local symptoms include tissue ischemia, cyanosis, and numbness. Systemic symptoms include weakness, diaphoresis, diplopia, blurred vision, aphonia, dysphagia, generalized muscle paralysis, respiratory failure, cardiovascular collapse, and coma. Death is rapid and occurs within 2 hours. Based on military medical records of more than 30 cases predating 1970, the mortality rate approaches 25%, with *C. geographicus* being the most lethal.[82] Other estimates suggest that, without medical care, mortality may reach 70%.[150] Given the rarity of severe human envenomation from cone snails, it is unclear if death results purely from respiratory insufficiency, or if cardiovascular toxicity plays a significant role.

Diagnostic Testing. Laboratory testing following envenomation from octopi or cone snails should be directed by clinical findings. Coma, respiratory failure, and hypotension merit evaluation of serum metabolic parameters, chest radiography, and electrocardiogram. Tetrodotoxin can be detected in the urine or serum using high-performance liquid chromatography with subsequent fluorescence detection, but this assay is not readily available.[101]

Management. Primary interventions include, maintenance of airway, breathing, and circulation. Some authors recommend hot water (45°–50°C, 113°–122°F) following cone snail stings for pain relief.[82] Unlike *Cnidaria* envenomations, where nematocysts full of venom can persist on the skin and lead to continued venom delivery, stings from the octopus and cone snail mirror those of snake bites, where venom delivery is an immediate and finite event. Therefore, pressure immobilization bandaging may help following octopus or cone stings by decreasing lymphatic spread of toxin without concern for worsening the envenomation.[46] Other measures include local wound care and tetanus prophylaxis. Antivenom is not available for octopus or cone snail venoms.

Echinodermata, Annelida, and Porifera

The *Echinodermata* phylum includes starfish, brittle stars, sea urchins, sand dollars, and sea cucumbers. *Annelida* are segmented worms that include the *Polychaetae* family of bristle worms. Sponges are classified in the *Porifera* phylum. One feature that all three phyla share is the passive envenomation of people who mistakenly handle or step on the animals. Most stings from these creatures are mild.

History and Epidemiology. Echinoderms, annelids, and sponges are ubiquitous ocean inhabitants. The crown-of-thorns starfish *Acanthaster planci* is found in the warmest waters of Polynesia to the Red Sea and is a particularly venomous species because of its sharp spines, which easily puncture human skin. Sea urchins are found in all oceans of the world. Bristle worms such as *Hermodice carunculata* typically are found in tropical waters such as those of Florida and the Caribbean. However, some species live in the frigid waters of Antarctica. The fire sponge *Tedania ignis* is a brilliant yellow-orange sponge found in large numbers in Hawaii and the Florida Keys. Other common American sponges are *Neofibularia nolitangere* (poison-bun sponge or touch-me-not sponge) and *Microciona prolifera* (red sponge). *Neofibularia mordens* (Australian stinging sponge) is a common Southern Australian variety. In the Mediterranean, sponges are often colonized with sea anemones, which may be the cause of severe stings.[15]

Pathophysiology. Sea urchins are covered in spines and pedicellariae. The pedicellariae are pincerlike appendages used for feeding, cleaning, and defense. They generally contain more venom than the spines and are more difficult to remove from wounds. Urchins laden with pedicellariae can evoke more severe stings than urchins with less pedicellariae. Venom contained within the spines consists of steroid glycosides, 5-HT, hemolysin, protease, and acetylcholinelike substances. Some species harbor neurotoxins. The most venomous are species of *Diadema, Echinothrix,* and *Asthenosoma.* Starfish are less noxious because they generally have short, blunt spiny projections. The crown-of-thorns is the exception, with its longer sharp spines containing toxic saponins with hemolytic and anticoagulant effects as well as histaminelike substances.[135] Sea cucumbers excrete holothurin, a sulfated triterpenoid oligoglycoside, from the anus (organs of Cuvier) as a defense. The toxin inhibits neural conduction in fish, leading to paralysis. Some cucumbers eat *Cnidaria* and subsequently secrete their venom.

Bristle worms have many parapodia that have the appearance, but not the function, of legs. Several bristles extend from each parapodium, which gives the family *(Polychaeta)* its name (poly = many, chaetae = bristles). The bristles may penetrate human skin, leading to envenomation with an unknown substance.

Sponges have an elastic skeleton with spicules of silicon dioxide or calcium carbonate. They attach to the sea floor or coral beds. Toxins include halitoxin, odadaic acid, and subcritine, the nature of which is uncertain.[21] Dried sponges are nontoxic; however, on rewetting they may cause toxicity even after several years.[129]

Clinical Manifestations. Most injuries from sea urchins are caused by inadvertently stepping on the spines or attempting to handle the animal. An intense burning with local tissue reaction occurs, including edema and erythema. Rarely, with multiple punctures, light-headedness, numbness, paralysis, bronchospasm, and hypotension may occur, although this is not documented in the medical literature.[3] Reports of death are not substantiated with evidence. The Pacific urchin *Tripneustes* has a neurotoxin with a predilection for cranial nerves.[15] Mild elevations of hepatic enzymes are reported in one patient with foot cellulitis from an urchin sting.[149] Small cuts on the skin from handling starfish may allow venom to penetrate, leading to contact dermatitis. The crown-of-thorns may cause severe pain, nausea, vomiting, and muscular paralysis.[92] Handling sea cucumbers leads to contact dermatitis, intense corneal inflammation, and even blindness. Bristle worms are covered in irritating bristles that can cause a reddened urticarial rash. Symptoms typically are mild and resolve over several hours to days.

Contact with the fire sponge, poison-bun sponge, or red-moss sponge causes erythema, papules, vesicles, and bullae, which generally subside within 3–7 days. Victims may develop fever, chills, and muscle cramps. Skin desquamation occurs at 10 days to 2 months,[4] with chronic skin changes lasting months.[21] Erythema multiforme and anaphylaxis are uncommon complications but may occur with *Neofibularia* spp.[15] Colonization of sponges with

Cnidaria can lead to dermatitis with skin necrosis, referred to as *sponge diver's disease.*

Management. The primary objective following envenomation from sea urchins and crown-of-thorns starfish is analgesia. Submersion of the affected extremity in hot water (105°F–115°F, 40.6°C –46.1°C) is commonly used and administration of oral analgesics generally are sufficient.[46,92] Puncture wounds require radiographic evaluation to locate potential foreign bodies. Spines frequently crumble when extraction is attempted. Intraarticular spines should be surgically removed. Decisions regarding spines in other locations should be influenced by ease of removal, presence of infection, and persistent pain. Tetanus prophylaxis should be addressed. Consideration of antibiotic prophylaxis should be based on degree of injury and patient factors such as diabetes or other immunocompromise. Although most infections likely are secondary to human skin flora, marine flora such as *Mycobacterium marinum* and *Vibrio parahaemolyticus* should be considered potential wound contaminants. Treatment of sponge exposures usually requires only removal of spicules using adhesive tape or the edge of a credit card. Use of antihistamines and topical steroids often provides no relief from stinging sponges.[21]

VERTEBRATES

Snakes

Sea snakes are members of the class *Reptilia* and are divided into 2 subfamilies: *Hydrophiinae* and *Laticaudinae*. They are close relatives of the cobra and krait. They are generally less than 1 m in length, have a flattened tail, and often are brightly colored. Distinction from eels is made by the presence of scales and the absence of fins and gills. There are 52 species of sea snakes, all of which are venomous. At least 6 species are implicated in human fatalities. The most common species cited in human envenomation is *Enhydrina schistosa,* the beaked sea snake. *Pelamis platurus,* the yellow-bellied sea snake, also is frequently implicated.

History and Epidemiology. The true incidence of sea snake envenomation is unknown because many bites go unreported. Worldwide the number of deaths per year may approach 150, with an overall mortality rate estimated at 3%.[46] In a review of 120 documented bites, 51.7% of victims were fisherman handling nets.[111] The remainder of victims were wading or swimming along the coast line. In another review of 101 bites occurring from 1957–1964 in North West Malaysia, more than 50% of bites were from the beaked sea snake, including 7 of the 8 fatal bites in that series, bringing the mortality to 8% prior to the availability of antivenom.[113] However, 31 "dry bites" were excluded, suggesting that the overall mortality is somewhat lower. Of the 20% of patients in that series suffering "serious envenomation," half died despite supportive care.[113] A followup series of patients after the introduction of antivenom described 2 deaths out of 11 "serious envenomations," suggesting a decreased mortality resulting from this intervention. These were all retrospective reviews of published or personally communicated cases, thereby limiting interpretation.

Sea snakes are common to the tropical and temperate Indian and Pacific Oceans, but also are found along the eastern Pacific Coast of Central and South America and the Gulf of California. In this eastern Pacific region, the yellow-bellied sea snake is the only species known. There are no sea snakes in the Atlantic Ocean. The majority of envenomations occur along the coasts of South East Asia, the Persian Gulf, and the Malay Archipelago (Malaysia). Snakes tend to inhabit the turbid coast lines and deeper reefs of these regions.

Pathophysiology. All sea snakes have small front fangs. Their venom is neurotoxic, myotoxic, nephrotoxic, and hemolytic. Known components of the venom include acetylcholinesterase, hyaluronidase, leucine aminopeptidase, 5′-nucleotidase, phosphodiesterase, and phospholipase A. The neurotoxin is a highly stable 6000- to 8000-dalton protein similar to that of the cobra and krait. In mice, beaked sea snake venom is 4–5 times more potent than cobra venom based on a microgram/kilogram ratio; however, cobra venom yield is greater.[31] Venom homology exists across many species.[75] The neurotoxin acts postsynaptically via acetylcholine (ACh) receptor blockade at the neuromuscular junction and presynaptically causes initial release, followed by inhibition of ACh release.[97,116,143] In vitro cell research shows direct nephrotoxicity of crude venom, which may partially account for the nephrotoxicity seen clinically.[124] Renal failure likely is a combination of rhabdomyolysis and direct venom effects on the kidneys.

Clinical Manifestations. Sea snakes generally are docile, except when they are provoked, or during the mating season. Bites typically are painless or inflict minimal discomfort. Between 1 and 4 fang marks are common; however, up to 20 fang marks are possible as a result of multiple bites. The diagnosis can be obscured, because victims may not associate the slight prick following the bite with later onset of ascending paralysis. Symptom onset may occur within minutes, although a delay of up to 6 hours is possible. Although paralysis results from the neurotoxic fraction of the venom, muscle destruction stemming from myotoxic fractions causes painful, stiff muscle movements and myoglobinuria, which are hallmarks of sea snake myotoxicity. Myoglobinuria develops between 30 minutes and 8 hours after the bite. Other classic symptoms include ascending flaccid paralysis, dysphagia, trismus, ptosis, aphonia, nausea, vomiting, fasciculations, and ultimately respiratory insufficiency, seizures, and coma. Morbidity and mortality stem from respiratory paralysis, aspiration, rhabdomyolysis, and renal failure.

Diagnostic Testing. Laboratory diagnostics are directed toward identifying hemolysis, myonecrosis, hyperkalemia, and renal failure. Serum electrolytes, creatinine, and creatine phosphokinase, as well as hematocrit and urinalysis, should be obtained. Elevated concentrations of hepatic enzymes may indicate severe envenomation. Serial measurement of these parameters is recommended.

Management. Prehospital management of sea snake bites mirrors treatment of terrestrial snake bites and includes immobilization of the extremity and consideration of a pressure immobilization bandage to impede lymphatic drainage. Currently no data regarding the efficacy of this technique for sea snake envenomations are available. Tourniquets that impede venous or arterial flow are not recommended and may be detrimental. Airway and respiratory effort should be closely monitored because paralysis can develop rapidly.

The most commonly used antivenoms for sea snakes are equine IgG Fab fragments derived from the beaked sea snake (*E. schistosa*) or terrestrial tiger snake (*Notechis scutatus*) (Table 116–3). In vitro experiments demonstrate that sea snake antivenom is effective for neutralizing all species of sea snakes tested (*Praescutata*

TABLE 116–3. Antivenoms

Organism	Manufacturer	Derivation	Concentration
Box jellyfish			
C. fleckeri	CSL	Ovine, whole IgG	20,000 units/ampule
Sea snake			
E. schistosa (beaked sea snake)	CSL	Equine, IgG Fab	1000 units/ampule
N. scutatus (terrestrial tiger snake)	CSL	Equine, IgG Fab	3000 units/ampule
Stonefish			
S. trachynis	CSL	Equine, IgG Fab	2000 units/ampule

CSL = Commonwealth Serum Laboratories, Melbourne, Australia.

viperina in Thailand, *Pelamis platurus* in Central America, *Laticauda semifasciata* in the Philippines, *Laticauda laticaudata* in Japan, *Hydrophis cyanocinctus*, *Lapemis hardwickii*).[140] Optimal neutralization occurs within the subfamily *Hydrophiinaem,* which contains *E. schistosa*; however, effective neutralization is demonstrated within the subfamily *Laticaudinae*. Terrestrial tiger snake antivenom also can neutralize sea snake venom in vitro. Based on the volume of antivenom required, tiger snake antivenom was more effective for neutralization of all sea snake venoms tested except that of the beaked sea snake, for which sea snake antivenom was more effective.[7] This finding is expected because the beaked sea snake venom is the antigen used for producing sea snake antivenom. Based on units required, sea snake antivenom was more effective for all venoms tested. Another in vitro study comparing tiger snake and sea snake antivenom against venom *E. schistosa* demonstrated tiger snake antivenom was 10 times more effective in terms of milligram of venom neutralized per milliliter antivenom.[96] In the same study, the use of 17 different types of elapid antivenom resulted in poor neutralization of beaked sea snake venom.

In rescue experiments with mice using 11 different sea snake venoms and 4 different antivenoms (*E. schistosa*, *E. schistosa-N. scutatus*, *N. scutatus*, and polyvalent sea snake *Lapemis hardwickii, Laticauda semifasciata, Hydrophis cyanocinctus*), tiger snake antivenom was superior to all others with respect to volume amount required to prevent death.[8] The experiment compared effective dose 50 (ED_{50}) in milliliter amount of antivenom; however, the numbers of stated units per milliliter of antivenoms were not equivalent. One milliliter of tiger snake antivenom used in the experiments contained 380 units, which is 14 times the amount contained per milliliter of monovalent sea snake antivenom (27.3 units/mL). Another finding of the study was improved efficacy with early administration of antivenom.

No controlled human trials have evaluated the efficacy of sea snake antivenom, although case reports suggest improved outcomes and more rapid recovery with its use.[95,113] There are also well-documented cases of successful use of tiger snake antivenom.[2,62] Anecdotal experience in Malaysia using sea snake antivenom suggests slow recovery from myalgias and weakness over 48 hours, compared to resolution over 2 weeks without antivenom (2 cases, 1 control).[112]

Based on in vitro and in vivo research, the optimal antivenom for treatment of sea snake bites is unclear. Both sea snake and tiger snake antivenom are effective in neutralizing a wide variety of sea snake venoms. Therefore, the most readily available antivenom should be used when needed. Commonwealth Serum Laboratories manufactures both monovalent sea snake and tiger snake antivenom for use in Australia. However, limited distribution to aquariums and zoos outside Australia does occur. The manufacturer's guidelines for use of monovalent sea snake antivenom recommend administration of 1 ampule (1,000 units) for systemic symptoms. However, because symptoms may be delayed and early administration is more likely to result in venom neutralization, any evidence of envenomation should prompt the administration of antivenom. The antivenom should be diluted 1:10 with 0.9% sodium chloride solution and administered IV over 30 minutes. A 1:5 dilution can be used for small children. Skin testing is not recommended. Epinephrine and antihistamines should be readily available. No upper limit is suggested for the number of vials to administer, although larger amounts are more likely to result in serum sickness. Patients have received up to 7000 units without adverse effect directly attributable to the antivenom.[95] One ampule (3000 units) of tiger snake antivenom can be used as an alternative, if sea snake antivenom is unavailable. Other treatments should focus on wound care, tetanus prophylaxis, analgesia, and fluid administration to minimize nephrotoxicity from myoglobinuria.

Fish

Stingrays are members of the class *Chondrichthyes* (Order *Rajiformes:* skates and rays). Families include *Dasyatidae* (whip ray or sting ray), *Urolophidae* (round ray), *Myliobatidae* (batfish or eagle ray), *Gymnuridae* (butterfly ray), and *Potamotrygonidae* (river ray, freshwater). The order of toxicity is butterfly ray < eagle ray < stingray, and whip ray < round rays.[4]

The family *Scorpaenidae* is composed of a variety of venomous spiny fish (Table 116–4). Fish in the genus *Pterois* are commonly called *lionfish* (*P. volitans* and *P. lunulata*). Stonefish are grouped under the genus *Synanceja* and include *S. trachynis* (Australian estuarine stonefish), *S. horrida* (Indian stonefish), and *S. verrucosa* (reef stonefish). They are unattractively disguised to blend in with the rocky sea bottom. (See ILSTONEFISH1 and ILSTONEFISH2 in the Image Library.) Scorpionfish have a similar appearance and belong to the genus *Scorpaena* (eg, *S. guttata:* California sculpin). Other *Scorpaenidae* include *Notesthes robusta* (bullrout) and *Gymnapistes marmoratus* (cobbler). The European weeverfish causes toxicity similar to members of *Scorpaenidae* and is classified under the family *Trachinidae*. This includes *Trachinus vipera* (lesser weever) and *T. draco* (greater weever, aka adderpike, stingfish, seacat). These bottom dwellers are smaller and have fewer spines than *Scorpaenidae* and are much less ghoulish in appearance. Another cause of venomous fish stings is catfish. Although most live in freshwater, marine catfish such as *Plotosus lineatus* can cause human envenomation. Other venomous spiny fish include rabbitfish, stargazers, toadfish, ratfish, and even some sharks that have spines on their dorsal fins (Port Jackson shark, dogfish shark).

History and Epidemiology. Some estimates suggest 1500–2000 stingray injuries occur yearly in the United States. Most envenomations occur when the animal is inadvertently stepped on. In a review, a total of 17 fatalities resulting from trunk wounds, hemorrhage, or tetanus, were identified worldwide.[46] In a review of 603 cases of stingray injuries, only 2 deaths occurred, both as a result of intraabdominal trauma.[118] No deaths stemming solely from venom are recorded. There are 11 different species of sting rays in

TABLE 116–4. Spiny Fish

Latin Name	Common Name	Habitat
***Scorpaenidae* family**		
Pterois		
P. volitans	Lionfish (also zebrafish, turkeyfish, or red firefish)	Indo-Pacific region, coast of Florida to North Carolina (nonnative to US coast)
P. lunulata	Lionfish or butterfly cod	
Synanceja		
S. trachynis	Australian estuarine stonefish	Indo-Pacific region
S. horrida	Indian stonefish	
S. verrucosa	Reef stonefish	
Scorpaena		
S. cardinalis	Red rockcod, scorpionfish	Coast of Australia
S. guttata	California sculpin, scorpionfish	Coast of California
Notesthes robusta	Bullrout	Coast of Australia
Gymnapistes marmoratus	Cobbler	
***Trachinidae* family**		
Trachinus		Coasts of Great Britain to Northwest Africa, throughout Mediterranean and Black Seas
T. vipera	Lesser weeverfish	
T. draco	Greater weeverfish (also adderpike, stingfish, or seacat)	

US costal waters (7 in the Atlantic, 4 in the Pacific). In the southeastern United States, *Dasyatis americana* is a common inhabitant. *Urolophus halleri* is the most common species on the western coast of the United States.

Three populations are at highest risk for spiny fish envenomation: fishermen sorting the catch from nets, waders, and aquarium enthusiasts. Only 5 deaths from *Scorpaenidae* have been reported; all resulted from stonefish and are poorly documented.[46] One death in 1915 occurred days after envenomation and likely resulted from infection.[37] No deaths from stonefish are reported in Australia, a country where they are commonly found in coastal waters.[40] The incidence of weeverfish stings is unknown, but they are a common occurrence in the summertime among Italian coastal towns.[30] A review of reported weeverfish stings between 1955 and 1962 identified approximately 12 cases per year resulting in "serious illness."[127] Approximately 10 stings per year are reported in Denmark.[29]

Scorpaenidae are found throughout the tropical and temperate oceans. They exist as far north as the Gulf of Oman and Southern Japan and extend south beyond New Zealand. In the United States, *Scorpaenidae* stings occur in the Florida Keys, the Gulf of Mexico, off the coast of California, and Hawaii. Lionfish (genus *Pterois*) are common to home aquariums and account for most poison center calls involving spiny fish envenomation in the United States. The bullrout inhabits the eastern coast of Australia, along with the cobbler, which is found only in Australia. Weeverfish live in the shallow temperate waters with sandy or muddy bottoms in the eastern Atlantic and Mediterranean, including the European Coast extending to the southern tip of Norway. The marine catfish lives in the tropical Indo-Pacific waters.

Pathophysiology. Stingray tails possess tapered, bilaterally retroserrated spines covered by an integumentary sheath. The ventrolateral groove contains venom glands that saturate the spine with venom and mucus. The venom contains several amino acids, 5-HT, 5′-nucleotidase, and phosphodiesterase.[4] In animal models venom induces local vasoconstriction, bradydysrhythmias, atrioventricular nodal block, subendocardial ischemia, seizures, coma, cardiovascular collapse, and death.[3,118] A rabbit model demonstrates initial vasodilation followed by vasoconstriction and cardiac standstill suggesting a direct cardiac effect.[119] Wound specimens reveal necrotic muscle and neutrophilic infiltrates.[6] Other reports show central hemorrhagic necrosis with surrounding lymphoid and eosinophilic infiltrates indicating an immune-mediated cause of delayed wound healing.[65]

Scorpaenidae have 12–13 dorsal, 2 pelvic, and 3 anal spines that are covered with an integumentary sheath (see ILLIONFISH in the Image Library). Glands at the base contain 5 to 10 mg of venom each. Ornate pectoral fins are not venomous. Venom can remain stable for 24–48 hours after the fish dies.[91] Three main toxins have been isolated from various species of stonefish: stonustoxin (SNTX), verrucotoxin (VTX), and trachynilysin (TLY). SNTX, from *S. horrida,*[66] has 2 subunits, α and β (71,000 and 79,000 daltons, respectively). It induces formation of hydrophilic pores in cell membranes.[32] Toxicity in animals includes hemolysis, local edema, vascular permeability, platelet aggregation, endothelium-dependent vasodilation, and hypotension. Decreased myocardial contractility occurs in rabbits.[122] VTX, isolated from *S. verrucosa,* has homology to SNTX. It blocks cardiac Ca^{2+} channels.[64] TLY, isolated from *S. trachynis,* is a 159-kDa protein that forms pores in cell membranes. It allows Ca^{2+} entry and causes Ca^{2+}-dependent release of ACh from nerve endings at motor endplates and increased catecholamine release.[79,104,123] *Synanceja trachynis* venom causes endothelium-dependent vasodilation and cardiovascular collapse in rats, which appears to be mediated by muscarinic and adrenergic receptors.[33] Hemolysis is demonstrated in animals but does not occur in human erythrocytes.[78] Other venoms of *Scorpaenidae* include hyaluronidase, proteinase, phosphodiesterase, alkaline phosphomonoesterase, arginine esterase, arginine amidinase, 5′-nucleotidase, acetylcholinesterase, and biogenic amines. Crude venom from *G. marmoratus, P. volitans,* and *S. trachynis* leads to increased intracellular Ca^{2+} and muscle contracture in vivo.[36] Toxins from other spiny fish include dracotoxin (*T. draco*), trachinine (*T. vipera*), and nocitoxin (*N. robusta*).[35] Effects mirror those of *Scorpaenidae* toxins.[126]

Clinical Manifestations. Stepping on the body of a stingray causes a reflexive whip of the tail leading to wounds in the lower extremity. Intense pain out of proportion to the appearance of the wound is characteristic. Symptoms peak 30–90 minutes after injury and may persist for 48 hours. Local edema, cyanosis, erythema, and petechiae may follow rapidly and may lead to necrosis and ulceration. Systemic symptoms include weakness, nausea, vomiting, diarrhea, vertigo, headache, syncope, seizures, muscle cramps, fasciculations, hypotension, and dysrhythmias. Chest and abdominal wounds, as well as tetanus, have caused death.[57,110,118]

Stings from stonefish produce immediate severe pain with rapid wound cyanosis and edema that may progress up the injured extremity. Pain reaches a maximum after 30–90 minutes and usually resolves over 6–12 hours, although pain may persist for days. Wound healing may require months. Systemic symptoms following stonefish envenomation may include headache, vomiting, abdominal pain, delirium, seizures, limb paralysis, hypertension, respiratory distress, dysrhythmia, congestive heart failure, and hypotension. In one case report, a healthy male received 6 punctures to the foot and developed rapid pulmonary edema requiring intubation.[81] The patient received 3 ampules of stonefish antivenom and recovered in 24 hours.

A Poison Control Center (PCC) case series from 1979–1988 identified 23 cases of *P. volitans* envenomation.[139] Reported symptoms included pain, swelling, nausea, numbness, joint pain, anxiety, headache, dizziness, and cellulitis. Another PCC series identified 51 *Scorpaenidae* stings (45 *P. pterois*, 6 *S. guttata*).[77] Intense pain was reported in 98%, extension of pain to the limb in 22%, swelling in 58%, and systemic signs (nausea, diaphoresis, dyspnea, chest pain, abdominal pain, weakness, hypotension, and syncope) in 13%. Thirteen percent of patients in the series developed wound infection; one patient's wound healing was delayed several weeks. Stings from weeverfish are similar to *Scorpaenidae* envenomation. One fatal sting occurred on the coast of Spain.[13] The victim developed syncope and cardiopulmonary arrest within 1 hour of envenomation. Autopsy revealed the puncture wound traversed the greater saphenous vein, suggesting direct IV injection of venom. Catfish stings invoke injuries similar to those of other stinging fish.[42]

Management. Wounds caused by stingrays and spiny fish should be carefully examined for imbedded foreign material. Radiographs may uncover occult spines left behind in the wound. Sting ray wounds can be extensive and require surgical attention for vascular or tendonous disruption. Tetanus prophylaxis should be addressed. As discussed for sea urchin stings, treatment with antibiotics may be appropriate for some injuries. Heating stonefish venom to 122°F (50°C) for 5 minutes prevents wound necrosis and hypotensive effects in animal models.[144] In a series of 51 stings from *P. pterois* and *S. guttata,* 80% of patients had complete relief with hot water.[77] Success with using hot water also is reported with weeverfish stings.[117] In a human volunteer study in which subjects received a subcutaneous injection of stingray venom, severe pain developed immediately, and was alleviated with water heated to 122°F (50°C).[118] Pain increased with application of cold water. If relief is not sufficient, local lidocaine injection can alleviate pain.[57] Oral or parenteral analgesia may be required.

Stonefish antivenom is equine-derived IgG Fab fragment and is raised against the venom of *S. trachynis*. Each ampule contains 2000 units and neutralizes 20 mg venom. Between 1965 and 1981, antivenom was used in at least 267 cases.[40] Anecdotal reports suggest it provides effective relief from pain.[40,145] In a review of 26 documented cases in Australia where antivenom was administered IM, no acute adverse effects were identified.[133] Eight patients required 2 ampules. Two of 15 patients who had followup visits suffered serum sickness. Rash may develop several days postinjection.[145] In vitro and in vivo research with the antivenom demonstrates neutralization of venom from *G. marmoratus*[34] and *P. volitans*;[35] however, the application for human therapy is untested.

The manufacturer recommends IM administration, although IV administration may be considered. Administration is indicated for systemic toxicity or pain not controlled with hot water and other analgesics. Dosing is guided by the number of puncture wounds sustained: 1 vial for 1–2 punctures, 2 vials for 3–4 punctures, and 3 vials for 5 or more punctures. Epinephrine and diphenhydramine should be readily available for treatment of anaphylactic reactions.

SUMMARY

Fatalities from marine envenomations are rare. However, significant morbidity may result from bites and stings, including severe pain, retained foreign bodies, infection, respiratory compromise, hypotension, and cardiac dysrhythmias. Interventions should focus on patient comfort and recognition of potential complications. A thorough understanding of the mechanisms of toxicity and expected clinical course following envenomations from marine creatures will provide clinicians with the ability to manage these injuries effectively.

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