

## Envenomation with Skin Manifestations and Treatments

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### Abstract

Jellyfish are smooth-formed animals in the phylum cnidaria, living in around coastal water zones worldwide. Interacting with jellyfish tentacles, even the beached and dying jellyfish, can prompt millions of nematocysts to perforate the skin and infuse the venom through the inverted long spiny tubules, thereby causing toxic manifestations from no effect to extreme pain to death. According to the structure of nematocyst, quantitative toxins are released into body in a short time. Stung by jellyfish possesses a wide spectrum of toxic effects especially on skin and cardiovascular toxicities. However, the mechanism of jellyfish venom is not clear. In this review, we focus on Jellyfish toxins, symptoms and treatment after sting in order to reduce treatment time, improve the survival rate for medical providers and to set a reference for follow-up study.

**Keywords:** Jellyfish; Venom; Cardiovascular; Toxicity; Treatment

### Introduction

Jellyfish are smooth-formed animals in the phylum cnidaria, living in around coastal water zones worldwide. The outbreak of jellyfish state in recent years, which is responsible to harm to fishery supplies, and marine ecosystem, which is linked with ocean climate and other factors related to human intercommunication with the oceans [1-6]. Interacting with jellyfish tentacles, even the beached and dying jellyfish, can prompt millions of nematocysts to perforate the skin and infuse the venom through the inverted long spiny tubules, thereby causing toxic manifestations from no effect to extreme pain to death [7]. Despite their affluence globally, jellyfish are sporadically studied for their toxic properties on humans [8].

### Jellyfish and their Species

Jellyfish are epitomized as free-swimming marine animals subsist of a gelatinous umbrella-frame bell and trailing tentacles. Most jellyfish do not have specially designed digestive, osmo-regulatory, central nervous, respiratory, or circulatory systems. The manubrium is a stalk-like arrangement drooping down from the center of the underside, often enclosed by oral arms, which conjoins with the mouth/anus at the base of the bell. This opens into the gastrovascular cavity, where digestion reports and nutrients are immersed. It is united to the radial canals, which prolong to the margin of the bell, where tentacles are hook up. The bell pulsates for mobility, while stinging tentacles can be used to capture prey as well stinging to human beings [9]. They spectrum from about one millimeter (mm) in bell height and diameter to nearly two meters; the tentacles originating from mouthparts usually broaden apart from this bell dimension. Normally, the

umbrella mass is a gelatinous substantial - the jelly - called mesoglea which is hedged by two layers of covering skin. The top flap is called the epidermis, and the inner flap is known as gastrodermis, which lines the gut [10].

There are four classes (Scyphozoa, Cubozoa, Hydrozoa and Staurozoa) of jellyfish. The true jellyfish or Scyphozoa, also acknowledged as a medusa, is a hollow, transparent creature that looks like an inverted bowl or umbrella. Scyphozoa, the true jellyfish, including *Cyanea capillata*, acknowledged as the lion's mane jellyfish, and *Pelagia noctiluca* [5]. They are found in all the oceans of the world, both swimming in deep waters and floating close to the surface. Scyphozoa have two life stages [11]. In the summer, they are notice floating in the ocean in their medusa form, which may spectrum in size, depending on the species, from two centimeters to two meters across [12]. In the winter, they incline bottom-dwelling polyps, which outturns new medusae in the spring. Medusae have tentacles, which droop down from a central dome and contain nematocysts, the stinging cells that they use to astonish their prey. The stings of some species of jellyfish are lethal to humans [13].

Cubozoa or Box jellyfish, identical in structure to the true jellyfish but more box-like. There are apparently 20 species, which live primarily in tropical and sub-tropical oceans. They are cube-shaped, and have a more refined nervous system than other jellyfish. Discordant other jellyfish, they have true eyes, complete with retinas, corneas and lenses [14]. Their tentacles consist of cnidocytes, which imbue venom into their prey. Two different orders are identified: the large multitentacled chirodropids, which are betwixt the most fatal marine creatures and include *Chironex fleckeri*, noted as the Australian box jellyfish, and the smaller four-tentacled carybdeids, an example of which is *Carukia barnesi* (also known as an Irukandji

jellyfish), which causes Irukandji syndrome [5]. The lethality of venom from Cubozoa, accomplished of killing humans in just a few minutes, has been the center of many studies of jellyfish venoms [15-18].

Hydrozoa, which are not aforesaid as the true jellyfish and include the *Physalia* species, which are siphonophores; the two major *Physalias* are *Physalia physalis*, noted as the Portuguese man-of-war, and *Physalia utriculus*, noted as the Blue bottle [5]. As with all cnidarians, it is the nematocyst, which is subject for the method of envenomation. Contact with the hydrozoans may cause manifestations ranging from mild stinging, erythema, and edema to severely painful vesiculobullous lesions, hemorrhagic lesions, gastrointestinal symptoms, respiratory distress, and death due to contact with *P. physalis* [19,20].

Staurozoa were conventionally contemplated to be an order in the class Scyphozoa, though, novel genetic studies advised they should be related to class of their own. There are about 50 species of stalked jellyfish or Stauromedusae. Unlike most jellyfish, they do not have a free-swimming medusa stage, somewhat; the adult animal is a sessile polyp [21-23].

## Nematocyst and Process of Jellyfish Stings

The word 'jellyfish' point out to the free-floating medusal gelatinous lifecycle stage of members of the phylum cnidaria. An illustrate character of this ancient phylum is the cnidae, an awfully specialized, explosive organelle amplified by the Golgi apparatus and comprised of a collagen-walled capsule containing a rapidly eversible penetrant or non-penetrant tubule. Specialized cnidae generating penetrant 'stinging cells' termed nematoblasts. Each synthesizes a singular nematocyst have a micron-diameter eversible spine-laden tubule of approximately 200~800  $\mu\text{m}$  length [24], allowing the impeachment of capsular filling or 'venom' for the intent of defense and capture of prey [24,25].

In jellyfish, bands or knobs of thousands of densely packed nematocysts line the epithelial surfaces of tentacles. Some jellyfish tentacles reach 40 meters in length, are often cellophane, and pose an important hazard to unwary swimmers [26]. Man-of-war tentacles can each contain as many as 750, 000 stinging nematocysts. A dead man-of-war on the beach or any broken tentacles can possess live nematocysts able to sting for several days. Scyphozoans also have them around the mouth and stomach, and in some species, the medusal bell of the animal. The venom in nematocyst consists of many polypeptides, quaternary ammonium compounds, histamine, 5-HT and catecholamines [26].

Upon physical contact, the capsules of the nematocysts ('spring-loaded syringes') hits a barbed arrow-like tubule within 700 ns of physical contact at high velocity (18.6 m/s) and acceleration ( $5.4 \times 10^6$  g) creating a pressure of 7.7 GPa at the site of impact [27]. Upon contact with human skin or other surface (e.g., cornea), thousands of tubules transporting toxins are accumulates per square centimeter of the epidermis and dermis. The combined physical impalement by barbed tubules and accumulation of potent venom toxins speedily immobilize and kill prey. In humans, toxins are responsible for local and systemic injury and may also incite immunological responses. The length of the penetrant tubules of some species renders possible the direct accumulation of venom toxin into pierced capillaries [28], thus explaining the rapid onset of toxicity in humans.

## Toxicity and Clinical Manifestation

Jellyfish sting is the most frequent injury of marine organism and counter reactions to jellyfish stings vary from the usual non-systemic, localized skin reactions to the rare systemic life-threatening ones, build upon the species of the envenoming organism, the endurance and extent of exposure, the number of nematocysts discharged which affect body area, location and thickness of affected skin, health, weight, age, and backfire of the host to envenomation, and the initial treatment administered [29,30].

### Local symptoms

**Skin symptoms:** Local and immediate skin reaction develops within minutes to hours at the site of the sting and is mainly associated to the toxic effect of venom. Sufferer often howl with the pain and children will often stand in the shallow water where they have been stung, removing at the tentacles, and consequently receiving more stings to their upper limbs. As the keratin of the palms if often too thick for the nematocyst thread tube to penetrate, stings marks will often be confirmed to the backs of the hands only. Contrarily, adults will usually jump back down of the water and run for help, the elevated muscular effort increasing heart rate and consequent venom absorption. Thus the first treatment of jellyfish stinging may be to 'retrieve and restrain', to prevent further envenomation [31].

The lesions are prompt severe pain, and linear weals with a white, ischaemic centre. Larger weals may have a typical 'cross-hatched' or 'frosted-ladder' pattern interrelated to the architecture of the tentacles. Partial or full-thickness skin necrosis may result [32,33]. After some days, the lesions could be vesicular, sometimes hemorrhagic and even necrotic or ulcerative in certain cases, as in *C. fleckeri* stings [33-35]. Regression and constancy of the blisters and pruritus may take as long as 10 days; although, mild hyperchromia and slight roughness in skin pattern may still be noticed for as long as eight months after the sting. Serious envenomations progress surrounding edema and darkening of the skin with vesiculation and partial or full thickness skin death, usually resulting in permanent scarring [31].

In addition to acute skin lesions, which are observed as toxic in features, there may be enduring eruptions at the original sites of cnidarian envenomation, attributed to delayed hypersensitivity [36]. Recurrent skin eruptions covering the sites of the primary lesions may be single or multiple, and may take the form of erythema, urticarial lesions, papules or plaques [30]. These eruptions might be due to the body reacting to the persistent stinging cells as antigen depots that keep on releasing the venom after some chemical or mechanical stimulation [30,37]. A delayed reaction usually progresses days to months after exposure. It is affirm that such a delayed reaction is the result of a type IV immune-pathogenetic mechanism, in adding to the more recurrent type I mechanism, with a central role played by Langerhans cells and T-helper lymphocytes [38].

**Seabather's eruption:** Itchy, erythematous papules and weals develop under swimwear, and lesions are usually potent in tight-fitting areas. The organisms become captured under the bathing costume, and discharge of nematocysts is triggered. It is apparent that an identical clinical frame can be developed by different coelenterates in different waters. In Florida, the Gulf of Mexico and the Caribbean, *Linuche unguiculata* (thimble jellyfish) develop to be responsible, and evidence has recently been noted that all three free-swimming stages of this jellyfish can cause seabather's eruption. Specific IgG antibodies against *L. unguiculata* antigen have been manifested by enzyme-linked

immunosorbent assay (ELISA) in patients with seabather's eruption. Cases in the Long Island region, New York, have been associated to larvae of the sea anemone *Edwardsiella lineata* [36].

**Other local symptoms:** Other non-systemic reactions have been noted such as pigmentary changes, lichenification from persistent rubbing, keloids, granulomas, localized hyperhidrosis and lymphadenopathy, fat atrophy, vasospasm and subsequent limb atrophy, necrosis, gangrene, and contractures [33,39]. Conjunctivitis, eyelid edema, chemosis and corneal ulcerations may occur when tentacles contact eyes. In some cases, eye or corneal stings can lead to severe iritis and increased intraocular pressure or chronic glaucoma, sometimes even years after the sting. Sneezing and rhinorrhea could be associated [40,41]. Severe dyspnea and upper airway obstruction may be caused by stings to the face [42-46].

### Systematic symptoms

**Cardiovascular symptoms:** The cardiac toxicity is characterized by a fast and irregular cardiac rhythm and conduction block. Death may ensue within minutes due to cardiotoxic and neurotoxic agents in the venom that can produce ventricular arrhythmias and cardiac arrest, and respiratory failure, respectively. In a retrospective review of 12 serious cases [47-51], pulmonary edema was a regular feature after an initial phase of mild skin pain followed 30 min after the sting by considerable muscle pain and cramps, tachycardia and hypertension. At a mean time of 14 h (range 1.5~18 h) after the sting pulmonary edema was evident radiologically and in some cases was associated with hypokinetic cardiac dysfunction, reduced cardiac output and raised serum cardiac enzymes. Hypertension [52,53] and hypertension due to catecholamine release [54-57] have been demonstrated in animal models of *C. barnesi* envenomation. However, catecholamine excess has yet to be confirmed in human cases.

**Other systematic symptoms:** Besides the fatal cardiovascular failure, a small proportion of patients develop systemic symptoms such as malaise, arthralgia, headache [33,58,59], and the delayed jellyfish envenomation syndrome (DJES) with systemic multiple organ dysfunction, which generally develops 2 h after jellyfish envenomation, and is particularly important for clinical intervention in contrast to the acute death that occurs between several minutes up to 2 h due to neurotoxicity or cardiotoxicity [60]. The liver and kidney injuries caused by the jellyfish venom are much more serious than cardiopulmonary injuries and might be the leading causes of death with DJES. Moreover, Life-threatening systemic syndromes probably involve different mechanisms depending upon the dose of jellyfish venom.

### Irukandji syndrome

Irukandji syndrome is a fatal systemic reaction lead mainly by a *C. barnesi* sting. It is identified by mild to moderate, tolerable pain followed in 20 to 30 minutes by severe generalized pain and muscle cramping in the abdomen, chest, head, back, and limbs that becomes linked with autonomic characters such as nausea, vomiting, profuse sweating, restlessness and excessive shaking followed by pyrexia, tachyarrhythmias and hypertension. Life-threatening hypertension and hyperkinetic cardiogenic shock, pulmonary edema, or an accident may occur in cases of severe toxicity [61,62]. Myocardial injury with or without pulmonary edema may develop 4 to 18 hours after the sting [51,63].

In a prospective study of victims with jellyfish stings presenting to the Royal Darwin Hospital from 1999 to 2000 [37], 4 of 40 patients had Irukandji syndrome but nematocysts could not be identified from any sting site. The most recent series reported from Darwin [63,64] included 87 victims of whom 65% had severe pain of rapid onset (<30 min) and 63% had visible sting lesions. In this series, systemic features included hypertension and ECG abnormalities among which were atrial and ventricular ectopy, atrioventricular conduction defects, ST-segment elevation, T-wave abnormalities and in one case, ventricular tachycardia associated with cardiomyopathy, acute pulmonary edema and raised troponin levels. Other serious sequelae included renal failure (2 cases) and one case of pancreatitis and ileus.

In another study of 116 patients presenting to Cairns Hospital with Irukandji syndrome over a 12-month period 2001-2002 [65], severe pain and hypertension were common. Of importance was that of 40 victims with the syndrome who had skin scrapings, 39 had nematocysts characteristic of the cnidome of *C. barnesi* while the remaining case had nematocysts of uncertain identity. Although no victim had pulmonary edema, many had raised troponin levels ranging from 1 to 34 µg/L (normal <0.4). Some victims also had ECG abnormalities and echocardiographic abnormalities ranging from mild impairment of systolic function to global myocardial dysfunction which in two victims persisted for 3 and 6 months. One of the victims in this series, a 44-year-old man who had been stung at Opal Reef developed severe hypertension (230/90 mmHg), a high troponin level (34 µg/L) and sustained an intracranial haemorrhage from which he died [65].

## Pathophysiological Mechanisms

### Skin injuries

The accumulation of the complex substance of nematocyst constituents, venom, drifting by jellyfish tubules probably sets off an intricate system of cellular and cytokine interactions analogous to that construed on entry of pathogens or allergens into human skin [66]. However little is noted about the effects of purified venom components in the skin, it is contemplated that the immune response to them is like that to any potential allergen or antigen with keratinocytes, tissue macrophages, dendritic cells (DC) and mast cells being the key cellular mediators. Although keratinocytes are the front line protective defence against physical incursion into the skin, they also have another role which is to release thymic stromal lymphopoietin which activates T-cells to produce cytokines, known to be prominent in allergic dermatitis. Dendritic cells, a heterogeneous population of lymphomyeloid origin critical to the initiation of immune responses, capture and present antigens to T-cells or migrate to regional lymph nodes evoking immune or delayed hypersensitivity allergic reactions. Combinations of pathogen pattern recognition receptors such as mannose-binding lectins and DC-expressed Toll-like receptor heterodimers contribute to innate immune response pathways and may also contribute to the immune responses to jellyfish venoms and associated structural molecules. Given the prominent necrosis induced by the sting of multiple cnidarians species, particularly those of chirodropids, the recently identified DC-activating necrosis receptors, such as CLEC9A (also known as Dendritic cell NK lectin Group Receptor-1 (DNDR-1)) [67,68] may also be contribute to the response to tissue injury.

The pharmacological mechanism elemental the severe pain of jellyfish envenomation remains to be determined. The pain is possibly

due to the effect of exogenous or endogenous mediators such as kinin-like factors on cutaneous nerves. Theories of Irukandji syndrome include ischaemia due to vasoconstriction of arterioles as a result of excess catecholamines, or Na<sup>+</sup> channel-dependent activation of afferent pain pathways [69]. Relevant to this may be the observations that some cnidarian venoms (*C. fleckeri*, *Aiptasia pulchella*, *C. capillata* and *P. physalis*) appear to activate TRPV1, a non-selective cation channel showed in nociceptive neurones [70]. This mechanism is comparable to that of capsaicin and may explain the immediate burning pain victims of these species experience. Whether TRPV1 channels are implicated in Irukandji syndrome is uncertain. Indeed, although Irukandji stings may cause local pain, the characteristic severe muscular pain of delayed onset cannot be explained by the involvement of local nociceptive effects alone. Indeed, compared to the pronounced local, and immediate pain associated with those jellyfish venoms tested [70], Irukandji syndrome pain is very different. Hence a distinct mechanism would be predicted.

### Cardiovascular injuries

Comprehensive studies by Edean of the biological action of nematocyst extract acknowledged that, in envenomated experimental animals, the heart deliberately failed to relax and turned into paralysed in systole [71]. Freeman and Turner revealed that respiratory arrest of apparently central origin was the terminal episodes in all species studied but clear evidence of cardiotoxicity was also achieved [72]. Bradycardia developed, with varying degrees of conduction delay, and terminal atrioventricular block usually occurred. Biphasic blood pressure changes were seen and blood samples, taken before terminal apnoea developed, had varying degrees of haemolysis and raised serum K<sup>+</sup>. Further work by Freeman showed that the cardiovascular picture produced by cardiotoxicity and vasoconstriction might be complicated by baroreceptor stimulation [73,74].

The extreme rapidity of action of the venom and the mechanism of cardiac failure is explained at least in part by intracellular Ca<sup>2+</sup> overload through two possibilities [28]. One putative mechanism is 'stress cardiomyopathy' secondary to hypertension. Although it is curious that a relatively brief period of hypertension (presumably due to release of catecholamines) and in some cases its mediocrity is the sole cause of cardiac failure in Irukandji syndrome victims, a sudden rise in catecholamines may exert toxic effects on human cardiomyocytes resulting in catecholamine-induced 'stress cardiomyopathy' [75]. This phenomenon is also recognised as ventricular apical ballooning or 'Takotsubo cardiomyopathy' [76,77] or otherwise as regional myocardial dysfunction [78]. Moreover, Takotsubo cardiomyopathy has also reported after a sting by another species of jellyfish *Pelagia noctiluca* [79].

A second putative mechanism of cardiac failure is 'membrane poration' [80,81], which may disrupt cell function and allow ingress of lethal toxins and egress of markers of cardiomyocyte damage. In some jellyfish species, e.g. *P. physalis*, Ca<sup>2+</sup> influx appears to be the result of toxin-induced membrane pore formation [81,82]. This may also be the mode of action of *C. fleckeri* venom. Indeed, Bailey et al. [80] observed by electron microscopy, the formation of large numbers of circular lesions in the membranes of rat myocytes after exposure to *C. fleckeri* venom.

### Irukandji syndrome

The Irukandji syndrome has been attributed to certain species of smaller, four-tentacled box jellyfish like *C. barnesi* and *Alatina mordens* [52,53,83-87]. Clinically, some features of Irukandji syndrome resemble that of catecholamine excess, such as that seen in phaeochromocytoma [54]. Accordingly, elevated serum adrenaline and noradrenaline levels have been found in experimentally envenomated animals [52,53,87]. It is notable that some envenomations may also exhibit cardiovascular features similar to this syndrome [88], with catecholamine excess and initial hypertension followed by late hypotension. Animal experiments and human clinical studies have implicated both cytokines (IL-1 $\alpha$ , IL-6, IL8, IFN- $\gamma$ , GM-CSF and TNF- $\alpha$ ) as well as nitric oxide release as an underlying mechanism [88].

Pulmonary edema is a proven complication of Irukandji envenomation [45]. It has not been proven that direct myocardial toxicity can occur, causing hypotension and pulmonary edema. Mechanisms include excessive catecholamine release which has previously been reported as causing myocarditis associated with phaeochromocytoma and exogenous catecholamines, and direct myocardial toxic effects similar to *C. fleckeri* venom and pulmonary edema may result from alteration in the endothelial permeability of the pulmonary vasculature due to a venom effect [89,90].

### Toxic components

Jellyfish venoms are accumulation of toxic and antigenic polypeptides [33,91,92]. Multiple lethal toxins are possibly present in venom or single toxins may have multiple actions. Edean isolated two myotoxins of approximate MWs 150~600 kDa from crude nematocyst venom [93]. The toxins contracted skeletal, smooth and cardiac muscle [93-95]. Although, Bloom et al., working with lyophilised but undestroyed nematocysts achieved by 'beachside' autolysis of tentacles, was not able to establish the existence of the 600 kDa toxin [96] previously determined by Edean [97]. Rather, native polyacrylamide gel electrophoresis of crude venom yielded protein bands of MW 30~200 kDa, which lost activity with freeze-thaw cycles.

The hemolytic component (haemolysin) was started to be studied by Keen and Crone who confirmed it to have a molecular weight of about 70 kDa [98,99]. Crone showed that the haemolysin contained a disulphide bond which was needed for its activity [100]. Hemolysis could be prevented by the presence of either divalent cations or trace amounts of ganglioside but later the interaction of the haemolysin with gangliosides was found to be non-specific in nature [101]. Extracts of nematocyst intracapsular material presented hemolytic activity but had no phospholipase A or proteolytic activity [71]. Further studies of extracts of isolated nematocysts and of tentacles from which nematocysts had been removed confirmed the presence of a haemolytic agent of molecular weight 70 kDa. Recently, two toxin proteins of molecular weight 43 and 45 kDa have been sequenced [102] and share considerable homology with three other known lethal haemolytic proteins from other Chirodromidae *Chironex yamaguchii* (reported as *Chiropsalmus quadrigatus*), as well as the Carybdeidae, *Carybdea arborifera* (reported as *C. rastoni*) and *Alatina moseri* (reported as *C. alata*). Additional larger cytolytic proteins are present in the venom [103] and phospholipase A2 activity is present in tentacles [104]. Some identified protein toxins are antigenic [105]. The venom may act by creating pores in myocytic membranes [80] as has been shown for toxins of *Physalia* [106,107].

## Diagnosis and Differential Diagnosis

### Diagnosis

Diagnosis should be done by the inquires; time of sting, local pain and muscle pain in particular back pain and determines the state of consciousness. The sting itself should be tested and also extent of the sting (important for the difference between 'minor stings' and 'major stings' in *C. fleckri* and *C. quadrigatus* envenoming). Clinical prediction of regional insufficiency and mononeuritis distal to a sting on the extremities should be noticed after the jellyfish sting. Respiratory insufficiency and clinical signs of shock (cardiogenic and anaphylactic shock) should be observed.

In most cases, the individual who have been tingled in water by jellyfish establishes the clinical diagnosis of jellyfish stings. When the clinical picture is unclear, then specific diagnosis is essential. The rapid access to confirm sting envenomation is microscopically which compares to esteemed nematocysts from different jellyfish. A qualified professional should work the microscopic examination. Nematocysts can retrieve by skin scraping or by applying a 4~8 cm long fragment of translucent sticky tape to the tingle site. Skin scraping is more or less painful, but is the superior method for obtaining nematocysts from sting site. The source of nematocysts could be noted by the cross-examination of these scraping although it is hard-won to classified among *C. quadrigatus* and *C. fleckeri*. The nematocysts of these two jellyfish are apparently distinctive from other important jellyfish with the length of 100  $\mu\text{m}$  and width 20  $\mu\text{m}$  [28,108]. The nematocysts of *P. physalis* are circular (diameter of 20  $\mu\text{m}$ ) and *C. capillata* is rod-like (dimensions 25  $\mu\text{m}$   $\times$  5  $\mu\text{m}$ ). Penetrating nematocyst threads are noticed when silver impregnation techniques are used. Edema of the stratum corneum is caused the toxin. Histopathological changes are well construed by Kingston and Southcott [109] and Williamson et al. [31,110,111].

*C. fleckri* causes distinctive lesion; the skin is densely marked with a criss-cross pattern, barred wheels transversely and that may be 8~10 mm wide. These 'frosted ladder arrangement' is similar with the bands of nematocysts on the tentacles. Abrasions yield by the other jellyfish *C. quadrigatus* are precise and milder, and the tentacular area is lesser than that of *C. fleckri* [36].

### Differential diagnosis

The topographical area can be a useful indicator and medical practitioners should be familiar of the jellyfish venomous in their regional area. It can be useful to give attention for physical indication, such as retained jellyfish tentacles and stab spots. A cnidaria often present with severe local pain, whereas other neurological indications such as weakness, gives impression for other neurotoxic organism. A bluebottle tingles (*Physalia* species) are also linked with instant pain and dermal denominating. Systemic symptoms are rare while the pain normally resolves within 1 h. Pain triggered by Irukandji syndrome is normally severe and delayed. Significant dermal denominating is not seen, while decompression sickness can be lead to serious pain and failure shortly after a diver has surfaced [112].

### Decompression sickness

Decompression sickness associates with Irukandji syndrome in a marine diver, which may show a strenuous differential diagnostic complication. Some cases have been reported around the Great Barrier

Reef who have called the DES (Diving Emergency Services) and informed, a marine diver quickly establishes serious low back pain and chest pain (breathing problem). A careful questioning is required while taking medical history. Signs such as minor tingle on the back of the neck and small-scale impression often difficult to see when surfacing the diver. So a careful differentiation symptoms monitoring is needed [113,114].

### Myocardial infarction

Cases with the initial chest pain of the Irukandji syndrome, especially if pulmonary edema (fluid on the lungs) develops, have in the past been misdiagnosed as an acute myocardial infarction with developing heart failure. This may be reinforced by a history of swimming (exertion) especially if the history of a mild sting is not elicited, or is forgotten by the victim. The situation is further confused if blood is taken for cardiac enzymes. In the past enzymes used was the Creatinine phosphokinase (CPK) level that was often raised well above the normal levels. However, when it was differentiated into cardiac and general muscle factions (CK-MB) the cardiac enzyme faction may be normal, whereas the general muscle faction is elevated, often to very high levels--caused by the intense muscle cramps experienced by the hapless victim. However, some severe cases, usually with obvious pulmonary edema, may have a CK-MB well above the normal range (<8), with an abnormal, and significant, ratio (NR<1.6).

### Treatment with envenomation

Proper management plays a significant role in minimizing discomfort and complications after jellyfish envenomation. Although, the evidence behind the currently suggested therapy is relatively weak [5,115]. The best preventive measure is to avoid any contact with seawater during the time jellyfish are invading. Wearing a full-body Lycra stinger suit or equivalent provides good safeguard from stings [14,116]. If stinger nets are used, they should be of less than 0.25 mm mesh size to provide enough preservation against small jellyfish (eg, Irukandji) tentacles [117]. Sufficient application of a topical sting inhibitor such as Safe Sea lotion (a waterproof sunscreen containing octyl methoxycinnamate and zinc oxide that has been expressed to mimic the mucous coating used by clown fish to inhibit sea anemones stings) will also be helpful for swimmers at high risk of exposure to jellyfish as it has been established to significantly decrease the frequency and severity of stings [29,118]. Thick layers of petroleum-based ointment are noticed to be effective as well [61] Moreover, it is most important to avoid touching jellyfishes or their parts on the beaches because they often contain nematocysts that can discharge and sting [119].

### First-aid

In case of jellyfish stings, management subsits of the following steps: (1) Rescue the victim from the water as soon as possible to avoid further contact with jellyfish tentacles and to prevent drowning. The victim should be prevented from rubbing the stung area [26] as that may enhance discharge of nematocysts on the victim's skin. Reassuring the victim helps reduce the skeletal muscle pump activity that panic brings [61]. It is considered that rescuers wear protective clothing and gloves so they can better rescue and treat the victim. (2) As per ARC guidelines, in case of tropical jellyfish (*C. fleckeri* and *C. barnesi*) stings that are life-threatening, the primary objective of the first aid treatment is to preserve life. Shortly after the sting, intravenous (or in field, intramuscular) administration of antivenom available for severe

Australian box jellyfish (*C. fleckeri*) stings may also be required. There are significant concerns, although, regarding the adequacy of the antivenom in reversing the neurotoxic and myotoxic effects of the venom [120]. Magnesium sulfate, which has been noted to improve the potency of the antivenom, may be added for victims of *C. fleckeri* with severe cardiovascular effects who did not respond to advanced life support [14,121]. Magnesium has traditionally been used for the treatment of Irukandji syndrome; although, according to a recent randomized trial, its use needs to be reconsidered until there is good evidence to support it, as it did not demonstrate benefit [122]. Thereafter, the aim of first aid management subsists of deactivation of undischarged nematocysts, inactivation of the toxin, and control of the pain.

### Deactivation of undischarged nematocysts

Most studies suggest that regardless of the stinging species, fresh water should not be applied as first aid as it can induce nematocyst discharge by osmosis [26,121,122]. Seawater can be used to wash tentacles off affected areas. Some of the chemicals traditionally used as home remedies to treat jellyfish stings in humans include acetic acid (vinegar), ethanol (liquor, perfume), ammonia or urea (urine), sodium bicarbonate (baking soda), papain (meat tenderizer), aluminum sulfate, and salt water. Applications up to 15 to 30 minutes have been specified. Although, no evidence on the effectiveness of most of these treatments exists because of unavailability of randomized controlled trials. The type of first aid application used and its effectiveness seem to also vary with the species of jellyfish causing the envenomation.

### Dousing with vinegar

For many years the suggestion of first aid for *C. fleckeri* stings was to pour any form of available alcohol, usually methylated spirits, over the adhering tentacles. The rationale was that the dehydrating effect of the alcohol prevented the movement of fluid into the nematocysts of fluid, which was thought to be the mechanism precipitating their discharge. Although, Hartwick et al. [26] following a chance observation, noticed that the immersion of a piece of living tentacle in methylated spirits caused immediate large-scale nematocyst firing! They produced evidence that the simplest and most economic first-aid procedure was to douse the tentacles with domestic vinegar. Once treated by vinegar, the nematocysts could not be triggered even by exposure to alcohol. Of all the substances tested by Hartwick et al. [26] only vinegar or acetic acid in solutions 3~10% produced rapid and complete inhibition, as tested by later exposure to methylated spirits. A 10% formalin solution produced inhibition but it was slow. The commercial preparation 'Stingose' (Hamilton Labs), which contains 20% aluminium sulphate [123,124], did not inactivate the nematocysts as well as vinegar. Of interest is the observation by Thomas et al. [125,126] that Sting-Aid (an aluminium sulphate solution) was no better than seawater in altering the pain of the Hawaiian 'box jellyfish' *C. alata*. The use of vinegar for jellyfish stings has been long known elsewhere. Light recorded that natives of the Philippines applied a mixture of vinegar and sugar to severe jellyfish stings. Vinegar-treated tentacles may be removed with safety. However, this is not necessary and consumes valuable time. If vinegar is not available, the tentacles may be picked off safely by rescuers since only a harmless pricking may occur on the fingers of the rescuer [31].

### Antivenom and MgSO<sub>4</sub>

Antivenom subsists of concentrated immunoglobulins isolated from the serum of sheep, which have been hyperimmunised with *C. fleckeri* venom. Each ampoule contains sufficient activity to neutralise 20,000 intravenous LD<sub>50</sub> mouse doses. Baxter and Marr [127] showed *in vitro* that the ovine antivenom (raised against 'milked' venom) neutralised the lethal, haemolytic and dermatonecrotic effects of tentacle extract and of 'milked' venom. *C. fleckeri* antivenom is the only jellyfish antivenom manufactured Worldwide and has been in use since 1970 [128].

Antivenom should be injected as soon as first aid is applied. It should be given to a victim of suspected *C. fleckeri* stinging in the following circumstances: Unconsciousness, cardiorespiratory arrest, hypotension, dysrhythmia or hypoventilation [14]. Antivenom should be administered intravenously, preferably by infusion. A dilution of 1 in 10 is advisable. The risk of serum reactions normally precludes the use of antivenom by lay persons but, if an emergency arises remote from medical aid, intramuscular injection by an informed layperson is justifiable. Indeed, several cases of severe envenomation have been treated successfully with intramuscular antivenom administered by trained ambulance personnel on the beach [129,130]. In such circumstances three ampoules should be administered remote from the sites of envenomation or proximal to pressure-immobilisation bandages. The antivenom is considered to be effective in reducing pain and local tissue damage provided it is given early. Williamson et al. reported two cases with remarkably dramatic relief of pain with antivenom [131]. One patient had no relief with pethidine and the other responded neither to topical lignocaine nor iced water. In the latter case the skin lesions were seen to improve within 90 s of the antivenom. Dramatic pain relief in an infant was reported by Boyd [132]. Topical corticosteroid or oral antihistamine or systemic steroids reduces the swelling and itchiness of the skin lesions. Indomethacin and methysergide reduced experimentally induced capillary leakage [133].

Magnesium may be an important adjunctive therapy in envenomation. Prophylactic administration of magnesium alone did not prevent cardiovascular collapse induced by venom in rats but improved the effectiveness of antivenom from 40% to 100%.

### Ca<sup>2+</sup> channel blockade

The use of Ca<sup>2+</sup> channel blocker e.g. verapamil has been advocated in the management of serious *Chironex* envenomations [31,134,135]. *Chironex* envenomation may be acutely life-threatening and in this desperate setting the basis for considering the use of Ca<sup>2+</sup> channel blockade at first appears logical since experimentally causes vasoconstriction [136], decreases coronary blood flow, heart rate and amplitude of contraction in isolated perfused hearts [72]. Moreover, venom preparations caused an influx of Ca<sup>2+</sup> into muscle fibres [71], inhibited uptake of Ca<sup>2+</sup> by the sarcoplasmic reticulum and interfered with electrical events and contraction of myocardial tissue [137]. All these events were assumed to be primarily due to opening of Ca<sup>2+</sup> channels, but the evidence is questionable.

In other studies, although Ca<sup>2+</sup> entry into cardiac myocytes cells has been observed after experimental application of *C. fleckeri* venom, the use of Ca<sup>2+</sup> channel blockade does not prevent Ca<sup>2+</sup> influx [80] and did not prevent acute cardiovascular collapse. Moreover, since Ca<sup>2+</sup> channel blockers cause hypotension and are not used for this reason in treatment of cardiac dysrhythmias in cardiopulmonary resuscitation,

their use is likely to ensure death of a stung victim in the circumstance of acute cardiovascular collapse. If pore formation is indeed the action of toxins in this species as has been observed [80], Ca<sup>2+</sup> channel blockade would not only be harmful but also futile.

### Ice packs or heat

The application of cold packs after the application of vinegar has been shown to provide relief of mild to moderate pain resulting from stings by *Physalia* and a number of species of jellyfish [138-140]. Hot showers appeared to be analgesic for victims of Irukandji syndrome [141] while hot-water immersion of *C. alata* stings was better than applications of vinegar or papain meat tenderiser [142]. A randomized placebo-controlled trial of the analgesic effect of hot and cold packs on stings caused by *C. alata* in Hawaii showed a minimal trend toward pain relief after 10 min of hot pack application. It has long been known that heat inactivates jellyfish venoms, most recently demonstrated with *C. fleckeri* venom by Carrette et al. using temperatures up to 58°C which is impractical for human treatment [143].

### Skin medications

Apart from vinegar no topical agents (anesthetic or steroid preparations) have been considered to be efficacious in case reports. Methylated spirits and ethanol cause nematocyst discharge and should not be used. If vinegar is not available, then Coca cola or old wine (which have similar pH to vinegar) but not urine (a traditional treatment) has been used with moderate beneficial effect, although nowhere near as efficient as vinegar [144,145].

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### References

- Merry C, Barry MG, Ryan M, Tjia JF, Hennessy M, et al. (1999) Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 13: F101-107.
- Kim DH, Seo JN, Yoon WD, Suh YS (2012) Estimating the economic damage caused by jellyfish to fisheries in Korea. *Fisheries Sci* 78: 1147-1152.
- Schrope M (2012) Marine ecology: Attack of the blobs. *Nature* 482: 20-21.
- Burnett JW, Calton GJ, Burnett HW (1986) Jellyfish envenomation syndromes. *J Am Acad Dermatol* 14: 100-106.
- Cegolon L, Heymann WC, Lange JH, Mastrangelo G (2013) Jellyfish stings and their management: A review. *Mar Drugs* 11: 523-550.
- Mebis D (2014) Jellyfish sting injuries. *Hautarzt* 65: 873-878.
- Carrette T, Seymour J (2004) A rapid and repeatable method for venom extraction from cubozoan nematocysts. *Toxicon* 44: 135-139.
- Currie BJ (2003) Marine antivenoms. *J Toxicol Clin Toxicol* 41: 301-308.
- Van Patten P (2004) Sting.
- Kier WM (2012) The diversity of hydrostatic skeletons. *J Exp Biol* 215: 1247-1257.
- Ponce D, Brinkman DL, Potriquet J, Mulvenna J (2016) Tentacle transcriptome and venom proteome of the Pacific sea nettle, *Chrysaora fuscescens* (Cnidaria: Scyphozoa). *Toxins* 8: 102.
- Kramp PL (1961) Synopsis of the medusae of the world. *Journal of the Marine Biological Association of the United Kingdom* 40: 1-469.
- Martellos S, Ukosich L, Avian M (2016) JellyWeb: an interactive information system on Scyphozoa, Cubozoa and Staurozoa. *Zookeys* 554: 1-25.
- Tibballs J (2006) Australian venomous jellyfish, envenomation syndromes, toxins and therapy. *Toxicon* 48: 830-859.
- Ponce D, Brinkman DL, Luna-Ramírez K, Wright CE, Dorantes-Aranda JJ (2015) Comparative study of the toxic effects of *Chrysaora quinquecirrha* (Cnidaria: Scyphozoa) and *Chironex fleckeri* (Cnidaria: Cubozoa) venoms using cell-based assays. *Toxicon* 106: 57-67.
- Brinkman DL, Jia X, Potriquet J, Kumar D, Dash D, et al. (2015) Transcriptome and venom proteome of the box jellyfish *Chironex fleckeri*. *BMC Genomics* 16: 407.
- Chausis S, Smout M, Wilson D, Loukas A, Mulvenna J, et al. (2014) Rapid short term and gradual permanent cardiotoxic effects of vertebrate toxins from *Chironex fleckeri* (Australian box jellyfish) venom. *Toxicon* 80: 17-26.
- McClounan S, Seymour J (2012) Venom and cnidome ontogeny of the cubomedusae *Chironex fleckeri*. *Toxicon* 60: 1335-1341.
- Prieto L, Macías D, Peliz A, Ruiz J (2015) Portuguese Man-of-War (*Physalia physalis*) in the Mediterranean: A permanent invasion or a casual appearance? *Sci Rep* 5: 11545.
- Diaz-García CM, Fuentes-Silva D, Sanchez-Soto C, Domínguez-Pérez D, García-Delgado N, et al. (2012) Toxins from *Physalia physalis* (Cnidaria) raise the intracellular Ca<sup>2+</sup> of beta-cells and promote insulin secretion. *Curr Med Chem* 19: 5414-5423.
- Matus DQ, Pang K, Daly M, Martindale MQ (2007) Expression of pax gene family members in the anthozoan cnidarian, *Nematostella vectensis*. *Evol Develop* 9: 25-38.
- Magie CR, Daly M, Martindale MQ (2007) Gastrulation in the cnidarian *Nematostella vectensis* occurs via invagination not ingression. *Dev Biol* 305: 483-497.
- Scaranelo AM, Marques AF, Smialowski EB, Lederman HM (2004) Evaluation of the rupture of silicone breast implants by mammography, ultrasonography and magnetic resonance imaging in asymptomatic patients: Correlation with surgical findings. *Sao Paulo Med J* 122: 41-47.
- Yanagihara AA, Kuroiwa JM, Oliver LM, Chung JJ, Kunkel DD (2002) Ultrastructure of a novel eurytele nematocyst of *Carybdea alata* Reynaud (Cubozoa, Cnidaria). *Cell Tissue Res* 308: 307-318.
- Fautin DG (2009) Structural diversity, systematics, and evolution of cnidae. *Toxicon* 54: 1054-1064.
- Hartwick R, Callanan V, Williamson J (1980) Disarming the box-jellyfish: nematocyst inhibition in *Chironex fleckeri*. *Med J Aust* 1: 15-20.
- Ozbek S, Balasubramanian PG, Holstein TW (2009) Cnidocyst structure and the biomechanics of discharge. *Toxicon* 54: 1038-1045.
- Rifkin J, Edean R (1983) The structure and function of the nematocysts of *Chironex fleckeri* Southcott, 1956. *Cell Tissue Res* 233: 563-577.
- Boulware DR (2006) A randomized, controlled field trial for the prevention of jellyfish stings with a topical sting inhibitor. *J Travel Med* 13: 166-171.
- Rallis E, Limas C (2007) Recurrent dermatitis after solitary envenomation by jellyfish partially responded to tacrolimus ointment 0.1%. *J Eur Acad Dermatol Venereol* 21: 1287-1288.
- Fenner PJ, Williamson JA (1996) Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 165: 658-661.
- Tamanaha RH, Izumi AK (1996) Persistent cutaneous hypersensitivity reaction after a Hawaiian box jellyfish sting (*Carybdea alata*). *J Am Acad Dermatol* 35: 991-993.
- Burnett JW, Calton GJ, Burnett HW, Mandojana RM (1987) Local and systemic reactions from jellyfish stings. *Clin Dermatol* 5: 14-28.
- Fisher AA (1987) Toxic and allergic cutaneous reactions to jellyfish with special reference to delayed reactions. *Cutis* 40: 303-305.
- Gunn MA (1949) Localized fat atrophy after jellyfish sting. *Br Med J* 2: 687.

36. Tomchik RS, Russell MT, Szmant AM, Black NA (1993) Clinical perspectives on seabather's eruption, also known as 'sea lice'. *JAMA* 269: 1669-1672.
37. O'Reilly GM, Isbister GK, Lawrie PM, Treston GT, Currie BJ (2001) Prospective study of jellyfish stings from tropical Australia, including the major box jellyfish *Chironex fleckeri*. *Med J Aust* 175: 652-655.
38. Veraldi S, Carrera C (2000) Delayed cutaneous reaction to jellyfish. *Int J Dermatol* 39: 28-29.
39. Burnett JW (2009) Treatment of Atlantic cnidarian envenomations. *Toxicol* 54: 1201-1205.
40. Glasser DB, Noell MJ, Burnett JW, Kathuria SS, Rodrigues MM (1992) Ocular jellyfish stings. *Ophthalmology* 99: 1414-1418.
41. Glasser DB, Burnett JW, Kathuria SS, Rodrigues MM (1993) A guinea-pig model of corneal jellyfish envenomations. *Toxicol* 31: 808-812.
42. Armoni M, Ohali M, Hay E (2003) Severe dyspnea due to jellyfish envenomation. *Pediatr Emerg Care* 19: 84-86.
43. Freudenthal AR, Joseph PR (1993) Sea bather's eruption. *The New Eng J Med* 329: 542-544.
44. Clunie GJ, Gough IR, Dury M, Furnival CM, Bolton PM (1980) A trial of imidazole carboxamide and *Corynebacterium parvum* in disseminated melanoma: Clinical and immunologic results. *Cancer* 46: 475-479.
45. Burnett JW, Calton GJ, Fenner PJ, Williamson JA (1988) Serological diagnosis of jellyfish envenomations. *Comp Biochem Physiol Comp Pharmacol Toxicol* 91: 79-83.
46. Németh A, Magyar P, Herceg R, Huszti Z (1987) Potassium-induced histamine release from mast cells and its inhibition by ketotifen. *Agents Actions* 20: 149-152.
47. Martin JC, Audley I (1990) Cardiac failure following irukandji envenomation. *Med J Aust* 153: 164-166.
48. Murphy JM, Mulvihill N, Mulcahy D, Foley B, Smiddy P, et al. (1999) Percutaneous catheter and guidewire fragmentation with local administration of recombinant tissue plasminogen activator as a treatment for massive pulmonary embolism. *Eur Radiol* 9: 959-964.
49. Little M, Mulcahy RF, Wenck DJ (2001) Life-threatening cardiac failure in a healthy young female with irukandji syndrome. *Anaesth Intensive Care* 29: 178-180.
50. Little M, Mulcahy RF (1998) A year's experience of irukandji envenomation in far north Queensland. *Med J Aust* 169: 638-641.
51. Little M, Pereira P, Mulcahy R, Cullen P, Carrette T, et al. (2003) Severe cardiac failure associated with presumed jellyfish sting. Irukandji syndrome? *Anaesth Intensive Care* 31: 642-647.
52. Ramasamy S, Isbister GK, Seymour JE, Hodgson WC (2005) The in vivo cardiovascular effects of an Australasian box jellyfish (*Chirospalmus* sp.) venom in rats. *Toxicol* 45: 321-327.
53. Ramasamy S, Isbister GK, Seymour JE, Hodgson WC (2005) Pharmacologically distinct cardiovascular effects of box jellyfish (*Chironex fleckeri*) venom and a tentacle-only extract in rats. *Toxicol Lett* 155: 219-226.
54. Winkel KD, Tibballs J, Molenaar P, Lambert G, Coles P, et al. (2005) Cardiovascular actions of the venom from the irukandji (*Carukia barnesi*) jellyfish: Effects in human, rat and guinea-pig tissues in vitro and in pigs in vitro. *Clin Exp Pharmacol Physiol* 32: 777-788.
55. Tibballs J, Hawdon G, Winkel K (2001) Mechanism of cardiac failure in irukandji syndrome and first aid treatment for stings. *Anaesth Intensive Care* 29: 552.
56. Fenner PJ, Lewin M (2003) Sublingual glyceryl trinitrate as prehospital treatment for hypertension in irukandji syndrome. *Med J Aust* 179: 655.
57. Pereira LC, Jiménez JA, Medeiros C, da Costa RM (2007) Use and occupation of Olinda littoral (NE, Brazil): Guidelines for an integrated coastal management. *Environ Manage* 40: 210-218.
58. Southcott RV (1989) Injuries from Coleoptera. *Med J Aust* 151: 654-659.
59. Burnett JW, Calton GJ (1987) Jellyfish envenomation syndromes updated. *Ann Emerg Med* 16: 1000-1005.
60. Wang B, Zhang L, Zheng J, Wang Q, Wang T, et al. (2013) Multiple organ dysfunction: A delayed envenomation syndrome caused by tentacle extract from the jellyfish *Cyanea capillata*. *Toxicol* 61: 54-61.
61. Kapamajian MA, Ahmad A, Burnett JW, Burnett HW, Frenkel S (2009) Unilateral orbital inflammation in a child after a jellyfish sting to the lower extremities. *Ophthal Plast Reconstr Surg* 25: 239-241.
62. Tibballs J, Li R, Tibballs HA, Gershwin LA, Winkel KD (2012) Australian carybdeid jellyfish causing "irukandji syndrome". *Toxicol* 59: 617-625.
63. Nickson CP, Waugh EB, Jacups SP, Currie BJ (2009) Irukandji syndrome case series from Australia's Tropical Northern Territory. *Ann Emerg Med* 54: 395-403.
64. Burnett JW, Weinrich D, Williamson JA, Fenner PJ, Lutz LL, et al. (1998) Autonomic neurotoxicity of jellyfish and marine animal venoms. *Clin Auton Res* 8: 125-130.
65. Huynh TT, Seymour J, Pereira P, Mulcahy R, Cullen P, et al. (2003) Severity of irukandji syndrome and nematocyst identification from skin scrapings. *Med J Aust* 178: 38-41.
66. Metz M, Magerl M, Kühl NF, Valeva A, Bhakdi S, et al. (2009) Mast cells determine the magnitude of bacterial toxin-induced skin inflammation. *Exp Dermatol* 18: 160-166.
67. Sancho D, Joffre OP, Keller AM, Rogers NC, Martínez D, et al. (2009) Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. *Nature* 458: 899-903.
68. Tibballs J, Williams D, Sutherland SK (1998) The effects of antivenom and verapamil on the haemodynamic actions of *Chironex fleckeri* (box jellyfish) venom. *Anaesth Intensive Care* 26: 40-45.
69. Corkeron MA (2003) Magnesium infusion to treat irukandji syndrome. *Med J Aust* 178: 411.
70. Cuypers E, Yanagihara A, Karlsson E, Tytgat J (2006) Jellyfish and other cnidarian envenomations cause pain by affecting TRPV1 channels. *FEBS Lett* 580: 5728-5732.
71. Endean R, Henderson L (1969) Further studies of toxic material from nematocysts of the cubomedusan *Chironex fleckeri* Southcott. *Toxicol* 7: 303-314.
72. Freeman SE, Turner RJ (1969) A pharmacological study of the toxin in a cnidarian, *Chironex fleckeri* Southcott. *Br J Pharmacol* 35: 510-520.
73. Freeman SE, Turner RJ (1971) Cardiovascular effects of toxins isolated from the cnidarian *Chironex fleckeri* Southcott. *Br J Pharmacol* 41: 154-166.
74. Freeman SE, Turner RJ (1972) Cardiovascular effects of cnidarian toxins: A comparison of toxins extracted from *Chirospalmus quadrigratus* and *Chironex fleckeri*. *Toxicol* 10: 31-37.
75. Ravingerová T, Adameová A, Kelly T, Antonopoulou E, Pancza D, et al. (2009) Changes in ppar gene expression and myocardial tolerance to ischaemia: Relevance to pleiotropic effects of statins. *Can J Physiol Pharmacol* 87: 1028-1036.
76. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE (2008) Stress (takotsubo) cardiomyopathy--a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med* 5: 22-29.
77. Zeb M, Sambu N, Scott P, Curzen N (2011) Takotsubo cardiomyopathy: A diagnostic challenge. *Postgrad Med J* 87: 51-59.
78. Hurst RT, Askew JW, Reuss CS, Lee RW, Sweeney JP, et al. (2006) Transient midventricular ballooning syndrome: A new variant. *J Am Coll Cardiol* 48: 579-583.
79. Bianchi R, Torella D, Spaccarotella C, Mongiardo A, Indolfi C (2011) Mediterranean jellyfish sting-induced tako-tsubo cardiomyopathy. *Eur Heart J* 32: 18.
80. Bailey PM, Bakker AJ, Seymour JE, Wilce JA (2005) A functional comparison of the venom of three Australian jellyfish--*Chironex fleckeri*, *Chirospalmus* sp., and *Carybdea xaymacana*--on cytosolic Ca<sup>2+</sup>, haemolysis and *Artemia* sp. lethality. *Toxicol* 45: 233-242.
81. Edwards EK Jr, Edwards EK Sr (2000) Immediate, anaphylactic and delayed reactions to jellyfish. *Contact Dermatitis* 43: 244-245.



82. Edwards L, Hessinger DA (2000) Portuguese man-of-war (physalia physalis) venom induces calcium influx into cells by permeabilizing plasma membranes. *Toxicol* 38: 1015-1028.
83. Fenner PJ, Williamson J, Callanan VI, Audley I (1986) Further understanding of, and a new treatment for, "irukandji" (carukia barnesi) stings. *Med J Aust* 569: 572-564.
84. Flecker H (1952) Irukandji sting to north queensland bathers without production of weals but with severe general symptoms. *Med J Aust* 2: 89-91.
85. Fenner PJ, Williamson JA, Burnett JW, Colquhoun DM, Godfrey S, et al. (1988) The "Irukandji syndrome" and acute pulmonary oedema. *J Aust* 149: 150-156.
86. Leggat PA, Harrison SL, Fenner PJ, Durrheim DN, Swinbourne AL (2005) Health advice obtained by tourists travelling to magnetic island: A risk area for 'irukandji' jellyfish in north queensland, australia. *Travel Med Infect Dis* 3: 27-31.
87. Ramasamy S, Isbister GK, Seymour JE, Hodgson WC (2005) The in vivo cardiovascular effects of the irukandji jellyfish (carukia barnesi) nematocyst venom and a tentacle extract in rats. *Toxicol Lett* 155: 135-141.
88. Abdoon NA, Fatani AJ (2009) Correlation between blood pressure, cytokines and nitric oxide in conscious rabbits injected with leirus quinquestriatus quinquestriatus scorpion venom. *Toxicol* 54: 471-480.
89. Corkeron M, Pereira P, Makrocanis C (2004) Early experience with magnesium administration in irukandji syndrome. *Anaesth Intensive Care* 32: 666-669.
90. Tiong K (2009) Irukandji syndrome, catecholamines, and mid-ventricular stress cardiomyopathy. *Eur J Echocardiogr* 10: 334-336.
91. Månsson T, Randle HW, Mandojana RM, Calton GJ, Burnett JW (1985) Recurrent cutaneous jellyfish eruptions without envenomation. *Acta Derm Venereol* 65: 72-75.
92. Noguchi K, Sakanashi M, Matsuzaki T, Nakasone J, Sakanashi M, et al. (2005) Cardiovascular effects and lethality of venom from nematocysts of the box-jellyfish *chiropsalmus quadrigatus* (habu-kurage) in anaesthetized rats. *Toxicol* 45: 519-526.
93. Endean R (1987) Separation of two myotoxins from nematocysts of the box jellyfish (chironex fleckeri). *Toxicol* 25: 483-492.
94. Mayura K, Abdel-Wahhab MA, McKenzie KS, Sarr AB, Edwards JE, et al. (1998) Prevention of maternal and developmental toxicity in rats via dietary inclusion of common aflatoxin sorbents: Potential for hidden risks. *Toxicol Sci* 41: 175-182.
95. Collins SP, Comis A, Marshall M, Hartwick RF, Howden ME (1993) Monoclonal antibodies neutralizing the haemolytic activity of box jellyfish (chironex fleckeri) tentacle extracts. *Comp Biochem Physiol B* 106: 67-70.
96. Bloom DA, Burnett JW, Alderslade P (1998) Partial purification of box jellyfish (chironex fleckeri) nematocyst venom isolated at the beachside. *Toxicol* 36: 1075-1085.
97. Endean R, Monks SA, Cameron AM (1993) Toxins from the box-jellyfish *Chironex fleckeri*. *Toxicol* 31: 397-410.
98. Crone HD, Keen TE (1969) Chromatographic properties of the hemolysin from the cnidarian *chironex fleckeri*. *Toxicol* 7: 79-87.
99. Crone HD, Keen TE (1971) Further studies on the biochemistry of the toxins from the sea wasp *chironex fleckeri*. *Toxicol* 9: 145-151.
100. Crone HD (1976) On the inactivation by gangliosides of the haemolytic protein toxin from the sea wasp (chironex fleckeri). *Toxicol* 14: 494-498.
101. Crone HD, Leake B, Jarvis MW, Freeman SE (1976) On the nature of "maculotoxin", a toxin from the blue-ringed octopus (*hapalochlaena maculosa*). *Toxicol* 14: 423-426.
102. Brinkman DL, Burnell JN (2009) Biochemical and molecular characterisation of cubozoan protein toxins. *Toxicol* 54: 1162-1173.
103. Brinkman D, Burnell J (2008) Partial purification of cytolytic venom proteins from the box jellyfish, *chironex fleckeri*. *Toxicol* 51: 853-863.
104. Nevalainen TJ, Peuravuori HJ, Quinn RJ, Llewellyn LE, Benzie JA, et al. (2004) Phospholipase a2 in cnidaria. *Comp Biochem Physiol B Biochem Mol Biol* 139: 731-735.
105. Brinkman D, Burnell J (2007) Identification, cloning and sequencing of two major venom proteins from the box jellyfish, *chironex fleckeri*. *Toxicol* 50: 850-860.
106. Edwards LP, Whitter E, Hessinger DA (2002) Apparent membrane pore-formation by portuguese man-of-war (physalia physalis) venom in intact cultured cells. *Toxicol* 40: 1299-1305.
107. Williamson JA, Webb RK, Pryor GL (1985) Anaesthesia safety and the "critical incident" technique. *Aust Clin Rev* 17: 57-61.
108. Barnes JH (1960) Observations on jellyfish stings in north queensland. *Med J Aust* 47: 993-999.
109. Kingston CW, Southcott RV (1960) Skin histopathology in fatal jellyfish stinging. *Trans Royal Soc Trop Med and Hyg* 54: 373-384.
110. Winter KL, Isbister GK, McGowan S, Konstantakopoulos N, Seymour JE, et al. (2010) A pharmacological and biochemical examination of the geographical variation of *chironex fleckeri* venom. *Toxicol Lett* 192: 419-424.
111. Meyer PK (1997) Stingray injuries. *Wilder Environ Med* 8: 24-28.
112. Bentlage B, Cartwright P, Yanagihara AA, Lewis C, Richards GS, et al. (2010) Evolution of box jellyfish (cnidaria: Cubozoa), a group of highly toxic invertebrates. *Proc Biol Sci* 277: 493-501.
113. Fenner PJ, Hadok JC (2002) Fatal envenomation by jellyfish causing irukandji syndrome. *Med J Aust* 177: 362-363.
114. Dawson AH (2003) Fatal envenomation by jellyfish causing irukandji syndrome. *Med J Aust* 178: 139-140.
115. Li L, McGee RG, Isbister G, Webster AC (2013) Interventions for the symptoms and signs resulting from jellyfish stings. *Cochrane Database Syst Rev* 12: CD009688.
116. Gershwin L (2006) Jellyfish responsible for Irukandji syndrome. *QJM* 99: 801-802.
117. Cobo ER, Corbeil LB, Gershwin LJ, BonDurant RH (2009) Preputial cellular and antibody responses of bulls vaccinated and/or challenged with *trichomonas foetus*. *Vaccine* 28: 361-370.
118. Kimball AB, Arambula KZ, Stauffer AR, Levy V, Davis VW, et al. (2004) Efficacy of a jellyfish sting inhibitor in preventing jellyfish stings in normal volunteers. *Wilderness Environ Med* 15: 102-108.
119. Auerbach PS (1997) Envenomations from jellyfish and related species. *J Emerg Med* 23: 555-565.
120. Winter KL, Fernando R, Ramasamy S, Seymour JE, Isbister GK, et al. (2007) The in vitro vascular effects of two chirodropid (chironex fleckeri and chiropsella bronzie) venoms. *Toxicol Lett* 168: 13-20.
121. Ramasamy S, Isbister GK, Seymour JE, Hodgson WC (2004) The in vivo cardiovascular effects of box jellyfish *chironex fleckeri* venom in rats: Efficacy of pre-treatment with antivenom, verapamil and magnesium sulphate. *Toxicol* 43: 685-690.
122. McCullagh N, Pereira P, Cullen P, Mulcahy R, Bonin R, et al. (2012) Randomised trial of magnesium in the treatment of irukandji syndrome. *Emerg Med Australas* 24: 560-565.
123. Mariscal RN (1974) Scanning electron microscopy of the sensory surface of the tentacles of sea anemones and corals. *Z Zellforsch Mikrosk Anat* 147: 149-156.
124. Henderson D (1980) Disarming the box-jellyfish. *Med J Aust* 1: 383-384.
125. Thomas CS, Scott SA, Galanis DJ, Goto RS (2001) Box jellyfish (carybdea alata) in waikiki. The analgesic effect of sting-aid, adolph's meat tenderizer and fresh water on their stings: A double-blinded, randomized, placebo-controlled clinical trial. *Hawaii Med J* 60: 205-207.
126. Thomas CS, Scott SA, Galanis DJ, Goto RS (2001) Box jellyfish (carybdea alata) in waikiki: Their influx cycle plus the analgesic effect of hot and cold packs on their stings to swimmers at the beach: A randomized, placebo-controlled, clinical trial. *Hawaii Med J* 60: 100-107.
127. Baxter EH, Marr GM (1974) Sea wasp (*chironex fleckeri*) antivenene: Neutralizing potency against the venom of three other jellyfish species. *Toxicol* 12: 223-229.

128. Nimorakiotakis B, Winkel KD (2003) Marine envenomations. Part 1-- Jellyfish. *Aust Fam Physician* 32: 969-974.
129. Exton DR, Fenner PJ, Williamson JA (1989) Cold packs: Effective topical analgesia in the treatment of painful stings by physalia and other jellyfish. *Med J Aust* 151: 625-626.
130. Beadnell CE, Rider TA, Williamson JA, Fenner PJ (1992) Management of a major box jellyfish (*Chironex fleckeri*) sting. Lessons from the first minutes and hours. *Med J Aust* 156: 655-658.
131. Williamson JA, Le Ray LE, Wohlfahrt M, Fenner PJ (1984) Acute management of serious envenomation by box-jellyfish (*chironex fleckeri*). *Med J Aust* 141: 851-853.
132. Boyd W (1984) Sea-wasp antivenom in a toddler. *Med J Aust* 140: 504.
133. Calton GJ, Burnett JW (1986) Partial purification of *chironex fleckeri* (sea wasp) venom by immunochromatography with antivenom. *Toxicon* 24: 416-420.
134. Burnett JW, Calton GJ (1983) Response of the box-jellyfish (*chironex fleckeri*) cardiotoxin to intravenous administration of verapamil. *Med J Aust* 2: 192-194.
135. Burnett JW, Othman IB, Endean R, Fenner PJ, Callanan VI, et al. (1990) Verapamil potentiation of *chironex* (box-jellyfish) antivenom. *Toxicon* 28: 242-244.
136. Freeman SE, Turner RJ, Silva SR (1974) The venom and venom apparatus of the marine gastropod *conus striatus* linne. *Toxicon* 12: 587-592.
137. Freeman SE (1974) Actions of *chironex fleckeri* toxins on cardiac transmembrane potentials. *Toxicon* 12: 395-404.
138. Currie B (1994) Clinical implications of research on the box-jellyfish *chironex fleckeri*. *Toxicon* 32: 1305-1313.
139. Qas (queensland ambulance service) (1998) Case management guidelines for poisoning, envenomation, cuboidal jellyfish.
140. Taylor JG (2007) Treatment of jellyfish stings. *Med J Aust* 186: 43.
141. Yoshimoto CM, Yanagihara AA (2002) Cnidarian (coelenterate) envenomations in hawai'i improve following heat application. *Trans R Soc Trop Med Hyg* 96: 300-303.
142. Nomura JT, Sato RL, Ahern RM, Snow JL, Kuwaye TT, et al. (2002) A randomized paired comparison trial of cutaneous treatments for acute jellyfish (*carybdea alata*) stings. *Am J Emerg Med* 20: 624-626.
143. Carrette TJ, Cullen P, Little M, Peiera PL, Seymour JE (2002) Temperature effects on box jellyfish venom: A possible treatment for envenomed patients? *Med J Aust* 177: 654-655.
144. Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, et al. (2006) A randomised controlled trial of hot water (45 degrees c) immersion versus ice packs for pain relief in bluebottle stings. *Med J Aust* 184: 329-333.
145. Currie B, Ho S, Alderslade P (1993) Box-jellyfish, Coca-Cola and old wine. *Med J Aust* 158: 868.