Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies

Paul M Bailey, Mark Little, George A Jelinek and Jacqueline A Wilce

Interest in envenoming syndromes caused by Australian jellyfish has been intense since the deaths in early 2002 of two tourists in Queensland, attributed to the Irukandji syndrome. We review current knowledge of these envenoming syndromes, mechanisms of venom action and therapy, focusing on the deadly box jellyfish, Chironex fleckeri*, and the array of jellyfish thought to cause the Irukandji syndrome. Current understanding of jellyfish venom activity is very limited, and many treatments are unproven and based on anecdote.* ***(MJA 2003; 178: 34-37)***

WORLDWIDE MEDIA ATTENTION recently focused on Australia following the first two known human fatalities attributed to the Irukandji syndrome in Queensland in 2002.[1] Jellyfish envenoming represents a major cost to northern Australian communities in terms of public health, leisure and tourism. Management of these syndromes depends on improved understanding of venom action and critical analysis of current therapy.

We review the current state of knowledge of envenoming syndromes caused by Australian jellyfish, the mechanisms of venom action and management. We focus on the deadly box jellyfish, *Chironex fleckeri*, and the array of jellyfish thought to cause the Irukandji syndrome. Information was obtained from a search of MEDLINE, EMBASE and SciFinder Scholar for articles published in English over the period 1966–2002, using the keywords *jellyfish*, *venom*, Chironex fleckeri, *Irukandji*, Carukia barnesi, *antivenom*, *pressure immobilisation bandaging*, *verapamil* and *therapy*.

Chironex fleckeri

The box jellyfish, *C. fleckeri*, is found in tropical waters of Australia's north, from Gladstone in Queensland to Broome in Western Australia (Boxes 1 and 2). It is most prevalent in summer, although stings have been reported year-round.[1] The jellyfish has a transparent box-shaped bell measuring up to 20 cm by 30 cm and weighing up to 6 kg, while the total length of tentacles may exceed 60 m.[3] Skin contact with *C. fleckeri* tentacles can result in dermonecrosis, pain and death, occasionally with alarming speed. Some patients also develop delayed cutaneous hypersensitivity reactions at the sting site.[4]

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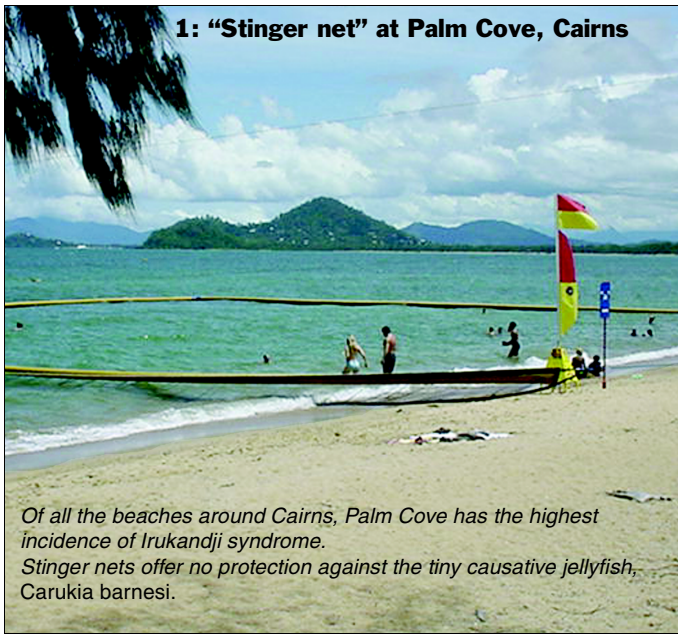


1: "Stinger net" at Palm Cove, Cairns

Of all the beaches around Cairns, Palm Cove has the highest incidence of Irukandji syndrome.
Stinger nets offer no protection against the tiny causative jellyfish, Carukia barnesi.

There have been 67 human deaths attributed to *C. fleckeri*, the most recent a six-year-old boy at Yarrabah, near Cairns in Queensland, in 1999.[1] However, despite this jellyfish's reputation as the "world's most venomous animal",[5] the vast majority of human stings are of little consequence.[4] Most are managed with no analgesia, local ice packs or oral analgesia only, and rarely require hospital admission.

The mechanism of action of *C. fleckeri* venom in severe envenoming remains unclear, but the key events appear to be cardiac or respiratory failure, or both.[6,7] Some patients with severe *C. fleckeri* envenoming have been successfully treated by expired-air resuscitation alone,[8,9] but fatalities have also occurred due to cardiac toxicity in mechanically ventilated patients.[10]

The Irukandji syndrome

A number of jellyfish can cause the Irukandji syndrome,[11] although only *Carukia barnesi* is conclusively known to do

so. *C. barnesi* is a small carybdeid jellyfish with a transparent bell 1.5–2.5 cm in diameter. The infrequency of sightings or capture of *C. barnesi* and other small jellyfish that may cause the Irukandji syndrome makes precise knowledge of its geographic distribution problematic. Cases of Irukandji syndrome have occurred from Rockhampton in Queensland to Broome, although prevalence is greatest in the Cairns region. Recently, an Irukandji-like syndrome was reported in Hawaii.[12]

The Irukandji syndrome most commonly presents with generalised pain, hypertension (often severe), nausea, vomiting, and distress. The similarity of many of these symptoms to decompression sickness can provide a diagnostic challenge in scuba divers. Most patients presenting to emergency departments are treated with opiate analgesia, and about half require admission. A small number require advanced life support, usually because of cardiac failure.[13]

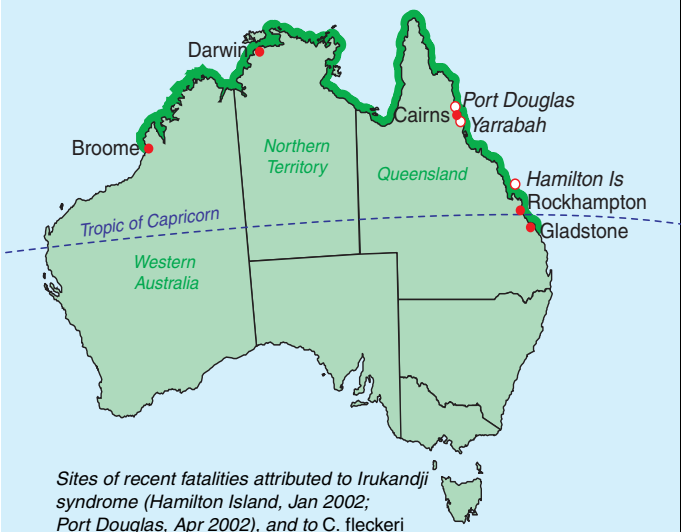
Catecholamine excess has long been proposed as a significant underlying mechanism in severe Irukandji syndrome.[1,3,21] Victims develop symptoms mimicking medical conditions associated with endogenous catecholamine excess, such as phaeochromocytoma. Experiments in ventilated piglets showed a 200-fold increase in serum noradrenalin levels and a 100-fold increase in serum adrenalin levels after injection with crude extract of *C. barnesi*.[22] These experiments quantified for the first time a relationship between experimental envenoming by *C. barnesi* and a hypercatecholaminergic state. However, there is no evidence of further deterioration in patients with cardiac dysfunction associated with severe Irukandji syndrome treated with adrenalin infusions.[11]

The mechanism of the cardiac dysfunction is yet to be elucidated. A review of 11 cases of pulmonary oedema developing in patients with Irukandji syndrome suggested that these patients had features of myocarditis.[23] In a review of 116 patients with Irukandji syndrome presenting to Cairns Base Hospital in the summer of 2001–2002, 25 had raised serum levels of troponin I.[24] Eighteen of these 25 patients had echocardiography, with six showing echocardiographic evidence of cardiac dysfunction. Significantly, no patients developed clinical cardiac failure. It is unclear whether the cardiac dysfunction is caused by a myotoxin or the hypercatecholaminergic state, or a combination.

Venom delivery and action

Jellyfish venom is delivered into prey or victims by millions of microscopic stinging cells, known as nematocysts. Light microscopy examination of nematocysts recovered from victims' skin is used to identify the envenoming jellyfish, particularly in *Chironex* stings. Two techniques are used to harvest nematocysts — scalpel-blade scraping of the sting site, and sticky-tape sampling. These tests generally demonstrate good specificity (ie, positive nematocyst identification correlates well with observed clinical syndromes).[14] Both methods also appear to have similar efficacy in terms of nematocyst retrieval, although, given the low nematocyst identification rates in the Irukandji syndrome, their sensitivity remains unknown.

2: Distribution of *Chironex fleckeri* stings and Irukandji syndrome



Sites of recent fatalities attributed to Irukandji syndrome (Hamilton Island, Jan 2002; Port Douglas, Apr 2002), and to C. fleckeri *envenomation (Yarrabah, 1999).*

The rapid onset of systemic symptoms after major jellyfish envenoming by *C. fleckeri* suggests that venom is "most probably introduced directly into blood vessels".[15] Postmortem evidence from the last *C. fleckeri* fatality demonstrated nematocyst barbs penetrating the vascular dermis.[16]

C. fleckeri venom has haemolytic, lethal, myotoxic and dermonecrotic effects.[17] Current evidence suggests that the venom toxins are proteinaceous and target specific organs. Monoclonal antibodies capable of neutralising *C. fleckeri*-induced haemolysis did not protect against the lethal effects of venom.[18] Several myotoxins, with molecular weights of about 600 kDa and 150 kDa, have been reported in *C fleckeri* venom.[19,20] These toxins showed significant lethality in a mouse model of envenomation and may play a role in human cardiotoxicity.[3] We speculate that these and other, as yet unidentified, proteins cause ion flux and transmitter release through altering cell membrane permeability, either through specific interactions with ion-channels or receptors or through non-specific interactions with cell membranes.

Treatment of jellyfish envenoming

Prevention and first aid

The only reliable preventive measure is to avoid any contact with sea water. Other measures include wearing "stinger suits" or swimming inside "stinger nets" (Box 1), although these do not appear to protect against Irukandji syndrome.[13] First aid measures include retrieval of the patient from the water, activation of the emergency medical system, and cardiopulmonary resuscitation, if appropriate. Acetic acid irreversibly inhibits firing of previously undischarged *C. fleckeri* nematocysts,[25] and has greatest acceptance for beachside treatment of jellyfish stings; large amounts of vinegar are placed in prominent positions along swimming beaches in jellyfish-endemic areas.

3: Characteristics of *Chironex fleckeri* antivenom

Derived from sheep serum

Carries risk of anaphylaxis, although rare

Indications:

- Cardiorespiratory instability
- Cardiac arrest
- Severe pain unrelieved by narcotics

Dose:

- Initial dose is three ampoules, diluted 1 in 10 with normal saline
- If cardiac arrest, give up to six ampoules as an intravenous bolus
- Has been given safely as an intramuscular dose by ambulance staff before reaching hospital

Pressure immobilisation bandaging

Pressure immobilisation bandaging (PIB) is advocated by Queensland[26,27] and national[28] authorities for first aid in jellyfish stings, but not by Northern Territory authorities.[29] It was first proposed because of its effectiveness in treating elapid snakebite,[30] but the link between treatments for snakebite and jellyfish stings is tenuous. Animal models demonstrate that PIB slows entry of snake venom to the circulation by halting lymphatic flow from the venom depot.[31] However, in jellyfish stings, nematocysts may be widely distributed on victims' skin, and there is evidence that venom enters the victim's bloodstream directly rather than via lymphatics.[16] No animal studies have been performed to demonstrate a beneficial effect of PIB in jellyfish stings, and a recent review found no scientific evidence to support the ongoing use of PIB in this setting.[16]

Furthermore, a significant amount of venom may remain in discharged nematocysts adherent to the patient's skin.[32] An in-vitro model of nematocyst discharge showed that pressure equivalent to PIB caused further venom liberation from previously electrically discharged nematocysts from *Chiropsalmus* spp.[32] Similarly, pressure equivalent to PIB caused additional venom release from naturally discharged *C. fleckeri* nematocysts exposed to vinegar, in amount similar to the initial firing.[33]

PIB in jellyfish envenoming thus remains at best unproven, and at worst potentially dangerous. More evidence is required to delineate its role in human jellyfish envenoming. The Australian Resuscitation Council has recently announced a change in advice to a more neutral position.[34]

Treatment of Chironex fleckeri *envenoming*

Antivenom

C. fleckeri antivenom is produced using "milked" venom, obtained by electrical stimulation of *C. fleckeri* tentacles. The antivenom neutralises the lethal, haemolytic, dermonecrotic and pain-inducing effects of milked venom and whole-tentacle extracts in experimental animal models.[3,5,6,35,36] However, it is less effective in neutralising crude nematocyst venom (obtained by mechanical rupture of nematocysts) compared with milked venom in a mouse model,[5] creating doubt as to whether the milked venom used in its production contains all the lethal factors present in native venom.

Evidence supporting the efficacy of *C. fleckeri* antivenom in human envenoming is anecdotal, with several reports of successful use.[9,30,37] However, there is also a report of survival in major envenoming in the absence of antivenom.[8] *C. fleckeri* antivenom appears safe to use. It is widely available in *C. fleckeri*-endemic areas, and is carried routinely by Queensland paramedics. As most patients who are envenomed by *C. fleckeri* have minimal symptoms, we believe that antivenom should be used only in those with cardiorespiratory instability, including cardiac arrest, or severe pain unrelieved by opiate analgesia (Box 3).

Verapamil

Verapamil was initially advocated to treat *C. fleckeri* envenoming on the basis of isolated organ experiments showing that *C. fleckeri* venom causes arterial constriction, reduced coronary blood flow and bradycardia.[38,39] There is experimental evidence that these effects may be due to increased intracellular calcium concentrations in the affected organs.[6,40] Two studies reported that verapamil significantly delayed death in experimental *C. fleckeri* envenoming, perhaps buying time for more definitive therapy.[41,42] However, verapamil was associated with increased morbidity and mortality in a pig model of envenoming.[6]

There are theoretical reasons to be cautious in using verapamil for the potentially unstable patient, as it may potentiate hypotension and induce cardiac dysrhythmias. At best, it can be considered appropriate as experimental treatment for the patient *in extremis*. Clearly, more evidence is required to determine its role.

Treatment of dermonecrosis and delayed cutaneous hypersensitivity reactions

Dermonecrosis is a frequent acute complication of serious *C. fleckeri* stings. While indomethacin and methysergide have been shown to reduce *C. fleckeri*-induced capillary leakage,[43] no animal or human clinical data have identified any agent that reduces long-term scarring. There are case reports of improvement in both acute and long-term cutaneous damage when *C. fleckeri* antivenom is used,[30] but it should be noted that the acute skin changes of *C. fleckeri* envenoming often resolve spontaneously. At present, acute dermonecrosis is treated as a burn, with specific attention to avoiding secondary bacterial infection.[7]

Delayed hypersensitivity reactions are a common late complication of *C. fleckeri* stings, occurring in about 50% of cases, and are usually minor.[4] Corticosteroid cream and oral antihistamines are the mainstay of treatment.

Treatment of Irukandji syndrome

Evidence as to the best treatment for Irukandji syndrome is anecdotal. The relative infrequency of patients with severe illness makes the prospect of high quality evidence unlikely.

Analgesia

Narcotic analgesia is routinely required, but no single agent has met with universal approval. There are several theoretical reasons to avoid pethidine, including potential for norpethidine toxicity and myocardial depression.

Antihypertensive agents

Patients are often hypertensive at presentation, although it is unclear if this is due to pain or catecholamine-like effect. Phentolamine has been used to treat hypertension,[44] but is rarely used in emergency departments and may not be available in some centres. An agent with a shorter half-life may be more advisable given the potential for cardiovascular collapse. Glyceryl trinitrate has been used[15] and may be the first-line agent for hypertension. As cases of echocardiographically proven cardiac dysfunction have occurred, caution should be exercised in avoiding life-threatening hypotension.

Treatment of pulmonary oedema

Pulmonary oedema is treated in the usual manner, with supplemental oxygen, inotropic support with dopamine and adrenalin, and positive-pressure ventilation. The underlying cause appears to be significant cardiac dysfunction which returns to normal within three to four days.

Conclusions

Fundamental knowledge of the biology, venomology and toxidromes of medically important jellyfish is severely lacking. Many therapies currently used for jellyfish envenoming are based on anecdote and may be harmful. Formal understanding of the functional components of jellyfish venom may reveal a mechanism of action that is reversible with currently available pharmaceuticals. Alternatively, novel treatments for envenomed humans may also be developed, based on a more thorough knowledge of the mechanism of action of the venom components.

Competing interests

None identified.

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