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Journal of Toxicology
TOXIN REVIEWS
Vol. 22, No. 1, pp. 115–127, 2003

Jellyfish Antivenoms: Past, Present, and Future

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ABSTRACT

If snake antivenoms are considered orphan drugs, then jellyfish antivenoms are the poorest of the orphans. Despite the diversity, ubiquity and toxicity of the venomous cnidarians, only a single antivenom is available for jellyfish stings worldwide. That antivenom, an ovine whole IgG product, is directed against the 'box' jellyfish, *Chironex fleckeri*, and is manufactured by CSL Limited (Melbourne, Australia). It also neu-

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DOI: 10.1081/TXR-120019024 0731-3837 (Print); 1525-6057 (Online)

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tralises the venom of closely related cubozoans such as *Chiropsalmus quadrigatus*. The recognition of the life-threatening effects of various other jellyfish demonstrates the need for broadening the specificity of the existing product and/or developing additional specific jellyfish antivenoms. These emerging threats include the irukandji syndrome, due to *Carukia barnesi* and other carybdeids, as well as those from scyphozoans such as *Stomolophus* spp. The role of ancillary drug therapy, in addition to, or instead of, antivenoms remains controversial. This review will consider the development of jellyfish antivenoms, their clinical utility and future developments in the field.

Key Words: Jellyfish; Irukandji; Antivenom; Marine stings; *Chironex fleckeri; Carukia barnesi; Chiropsalmus quadrigatus; Stomolophus;* Cnidaria; Envenomation cubozoa; Hydrozoa scyphozoa.

INTRODUCTION

Jellyfish stings are a common summer hazard for sea bathers throughout the world. For example it is estimated that in excess of 10,000 jellyfish stings occur in Australia each year (Fenner and Williamson, 1996). Moreover, in at least some parts of the Pacific, the incidence of envenomation from marine bites and stings appears to be rising due to increasing marine activities by both local and tourist populations (Rual, 1999). In this context new envenomation syndromes and new species of medically significant jellyfish are likely to be encountered. For example, we recently described a severe sting, caused by an unidentified jellyfish, affecting a tourist snorkelling offshore in north Australia (McD Taylor, 2002). Another case, associated with near-fatal cardiac failure, affecting a young marine biologist in a similar unidentified jellyfish sting from the Great Barrier Reef, was also recently reported from the same locality (Little et al., 2001).

The life-threatening effects of such jellyfish argue for the need to broaden the specificity of the existing jellyfish antivenom and/or to develop new antivenoms. These emerging threats include the carybdeid-induced Irukandji syndrome and stings from potentially lethal scyphozoans such as *Stomolophus spp*. This review will commence with an overview of medically significant jellyfish, then will consider the development of jellyfish antivenoms, their clinical utility and future developments in the field.

JELLYFISH BIOLOGY AND TAXONOMY

The generic term ‘jellyfish’ can refer to a multitude of animals in three different classes of the Phylum Cnidaria (see Figure 1). All these groups

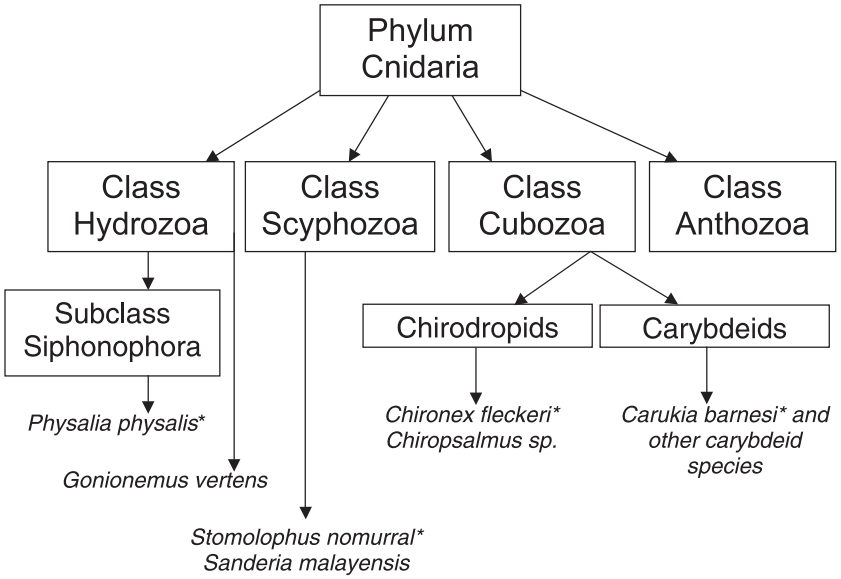

Figure 1. Schematic overview of the taxonomy of medically significant jellyfish. The (*) indicates those species that are definitely or potentially lethal.

have in common a free-floating medusa or jellyfish stage in their lifecycle (Rifkin, 1996). The fourth class of Cnidaria, the anthozoans, includes the corals and sea anemones. Members of this last class lack a medusa stage, and so remain attached to the sea bottom in the polyp form.

The most medically significant jellyfish belong to the class Cubozoa, a group that is entirely marine and, literally, almost invisible in the water. The Cubozoa is divided into two orders, the large multitentacled chirodropids and the smaller, four tentacled, carybdeids. Most famous is the archetype chirodropid 'box' jellyfish, *Chironex fleckeri*. An increasing number of species are represented in the Carybdeidae, best known for the 'Irukandji' jellyfish, *Carukia barnesi* (Southcott, 1967). The results of a recent phylogenetic analysis of cubozoan ribosomal gene sequences is summarised in Figure 2 (Collins, 2002). These results conform to the taxonomic dichotomy dividing the cubozoan species into the Carybdeidae and the Chirodropidae.

Those species found within the class Scyphozoa are the most conspicious due to their large size and colouration, with the medusa stage being dominant in the lifecycle (Rifkin, 1996). The third class of jellyfish, the Hydrozoa, is distinguished by its tendency to form colonies of hydroids that

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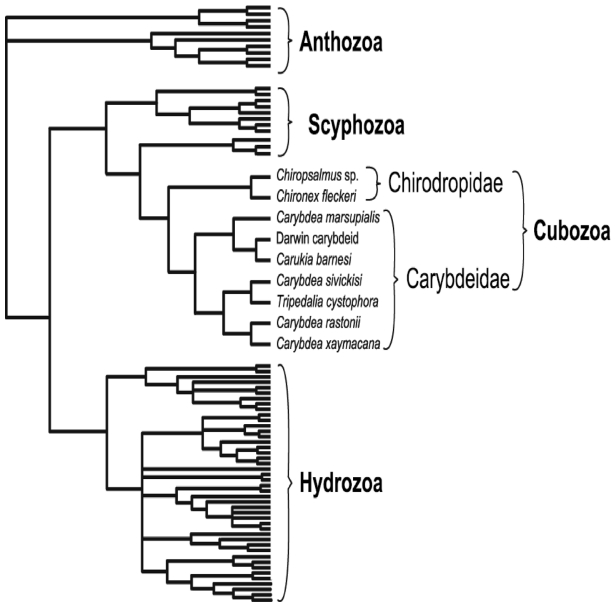

Figure 2. A summary of the most parsimonious tree of the phylogenetic relationships of the Medusozoa plus several anthozoans, focused on the Cubozoa, as determined by ribosomal DNA nucleotide character identity (Collins, 2002).

may be small and inconspicious (Rifkin, 1996). This latter class contains the ubiquitous Portuguese Man-of-War and blue-bottle jellyfish.

JELLYFISH TOXINOLOGY

Whilst fatalities have been attributed to all three Cnidarian classes, the majority are due to chirodropid cubozoans (Fenner and Williamson, 1996). This review will focus on those jellyfish of greatest medical significance in terms of severe morbidity and mortality.

Chirodropoids (Box Jellyfish, *Chironex fleckeri*, and *Chiropsalmus* sp)

The box jellyfish, *C. fleckeri*, is the most dangerous jellyfish and, arguably, the most dangerous venomous creature in the world (Endean,

1988). Its sting may cause death from cardiorespiratory arrest within minutes. In Australia this jellyfish has been responsible for more than 63 deaths over the last century (Williamson et al., 1996). Indeed, continuing chirodropid related fatalities have been recorded through a wide area of the Indo-Pacific region—from Japan and Malaysia to Texas (Bengston et al., 1991; Fenner and Williamson, 1996). The most recent Australian *C. fleckeri* fatality, a young aboriginal child stung whilst wading off a beach south of Cairns, North Queensland, occurred in January 2000 (O'Reilly et al., 2001).

The box jellyfish, and related cubozoan species, are found in coastal tropical waters globally (Burnett et al., 1996), and particularly, but not exclusively, during the summer months (Fenner and Harrison, 2000). *C. fleckeri* is the most important of these species and is a large jellyfish found in the Indo-Pacific. It weighs up to 6 kg and measures about 20–30 cm across the bell. It has 4 bundles of tentacles, which may number up to 60 in total. The tentacles may stretch up to 2 metres. Each tentacle contains many millions of nematocysts, or stinging cells, which discharge on contact.

The mechanism(s) of toxicity are poorly understood, but death is thought to be due to respiratory failure, possibly central in origin, or to direct cardiotoxicity leading to A–V conduction disturbances or to paralysis of the cardiac muscle in systole (Mustafa et al., 1995; Tibballs et al., 1998). Patients may become unconscious before they can leave the water, or run out of the water and collapse on the beach (Burnett et al., 1996). In addition to cardiotoxic and neurotoxic properties, the venom also contains dermatonecrotic and haemolytic components (Baxter and Marr, 1974).

Contact with the tentacles of the box jellyfish results in severe localised pain. Most stings are minor, resulting in only pain and skin changes. When the initial skin vesiculation and weals subside, full thickness dermal necrosis often results in scarring and pigmentation changes. In more severe envenomations, confusion, agitation, unconsciousness, collapse with respiratory failure and/or cardiac arrest may occur. A specific antivenom is available and is discussed in more detail below. The use of ancillary agents, such as verapamil (a calcium channel blocker), is controversial. On the basis of overall information from works published to date, verapamil cannot be recommended as cardiac therapy for the seriously envenomated (Sutherland and Tibballs, 2001).

Chirodropoids *Chiropsalmus* sp

Like the box jellyfish, members of this genus are chirodropoids (box shaped jellyfish with multiple tentacles at each corner). They are smaller

and less dangerous, although still capable of causing severe injuries and even death. *Chiropsalmus quadrigatus* is the most common species in Australian waters and best studied of this genus. The bell measures up to 8 cm, and the number of tentacles on each of the pedalia (fleshy arms) seldom exceeds nine. The tentacles are shorter and finer than those of *C. fleckeri*. Its venom contains lethal, dermatonecrotic and haemolytic properties in approximately the same proportions as *Chironex* venom, but the venom output of *Chiropsalmus* is much less (Freeman and Turner, 1972). No true deaths from the sting of this genus have been reported in Australia, although there have been fatalities elsewhere (Bengston et al., 1991; Fenner and Williamson, 1996). Box jellyfish antivenom has been shown experimentally to neutralise *Chiropsalmus* venom (Baxter and Marr, 1974).

Carybdeids (Irukandji and Others)

Carybdeids are differentiated from chirodropoids by the presence of a single tentacle at each corner of the bell. Carybdeids of medical importance include the 'Irukandji' (*C. barnesi*), the Jimble (*Carybdea rastonii*) and the Morbakka (*Tamoya* sp). The Irukandji syndrome, the most important outcome of carybdeid stings, is defined as a complex of signs and symptoms, mainly seen in northern Australia, attributed to the stings of various jellyfish (Barnes, 1960; Barnes, 1964). The word 'Irukandji' is therefore used here generically applying to all such culprit jellyfish.

This sting is particularly common and troublesome in the northern Australian centres of Cairns-Port Douglas and the Whitsunday islands. For example approximately 160 people from those regions, including many international visitors, were hospitalised with this envenomation during the summer of 2001–02. Unlike *C. fleckeri*, Irukandji stings also occur offshore on the Great Barrier Reef. The significance of this envenomation was underlined by the death of two tourists (one English and one American) who suffered Irukandji envenomation after swimming offshore in central and north Queensland during January and March 2002 respectively. In addition several near-fatalities, affecting Australian children and young adults, were recently described in Rockhampton (Pocock et al., 2001), and Cairns (Little et al., 2001).

This follows the description, more than ten years ago, of the potentially lethal cardiopulmonary decompensation sometimes seen during this envenomation (Fenner et al., 1988). We have also reported a milder illness, termed an 'Irukandji-like' syndrome, from Victoria (Cheng et al., 1999). At

present there is no 'Irukandji' antivenom and the efficacy of the current box jellyfish antivenom (CSL Limited, Parkville), in the treatment of the syndrome, remains uncertain (Fenner et al., 1986). Victims may require hospitalisation for analgesia and sometimes intravenous antihypertensive therapy; alpha-blocking agents such as phentolamine have been used for this purpose (Fenner and Carney, 1999). The role of antihistamines and the optimal use of various types of narcotic analgesic in the management of this illness remains to be determined (Fenner and Carney, 1999; Little and Mulcahy, 1998; Little et al., 2001).

The syndrome has three recognised clinical forms or patterns consisting of 1) acute muscular chest and back pain, 2) catecholamine-like effects notably sweating, anxiety, nausea, vomiting, headache, tachycardia, potentially life-threatening hypertension with supraventricular tachyarrhythmias and, uncommonly, 3) cardio-pulmonary decompensation (Burnett et al., 1996; Fenner and Carney, 1999). Observation of the severity of this latter complication gave rise to the hypothesis that Irukandji venom may be directly cardiotoxic (Fenner et al., 1988). The syndrome usually lasts from hours to days and requires hospitalisation. Also in contrast to that of *C. fleckeri*, the sting itself is only moderately painful, with little associated tissue damage. Rather than linear weals or vesiculation, an area of erythema around 5 cm in diameter may be visible at the site (Burnett et al., 1996).

To date, although others are suspected (Little et al., 2001), only a single species, *Carukia barnesi*, has definitely been shown to be capable of causing the syndrome (Barnes, 1964). The medusa of this species is transparent, measures 1–2 cm and the tentacles are up to 30 cm in length. Whilst little is known of the biology of this jellyfish, it has recently been demonstrated that its venom contains a neuronal sodium channel agonist that stimulates the release of massive quantities of catecholamines in vitro and in vivo (Tibballs et al., 2001). This suggests that the dramatic effects of the Irukandji syndrome are secondary to a hypercatecholaminemic state. Clearly additional research is required to assess the mechanism underlying the various 'Irukandji-like' syndromes (Cheng et al., 1999; Little et al., 2001).

SCYPHOZOAN AND HYDROZOAN JELLYFISH

In China significant morbidity, as well as ongoing mortality, has been reported from the stings of scyphozoan jellyfish such as *Stomolophus nomurai* (Rifkin et al., 1996). Also, at least three fatal envenomations have been attributed to the hydrozoan species known as the Atlantic Portuguese Man-of-War, *Physalia physalis* (Burnett and Gable, 1989).

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BOX JELLYFISH (CHIRONEX FLECKERI) ANTIVENOM—PAST, PRESENT, AND FUTURE

Remarkably, however, despite the diversity, ubiquity and toxicity of the venomous cnidarians, only a single antivenom is available for jellyfish stings worldwide. That antivenom, a purified ovine immunoglobulin (IgG) preparation, is directed against the 'box' jellyfish, *Chironex fleckeri* and was first released for clinical trial in 1970 (Baxter and Marr, 1970, 1974). It is available as vials containing 20,000 Units in 1.5 to 4 mls of aqueous solution. This is sufficient to neutralise 20,000 intravenous lethal dose (50%) [LD_{50}] mouse doses (Sutherland and Tibballs, 2001). In March 1970 the Commonwealth Serum Laboratories, now known as CSL Limited, reported the first use of this product. In these two North Queensland *C. fleckeri* stings the antivenom reportedly had a dramatic effect against the necrotising local tissue reaction (Baxter and Marr, 1970).

However, according to unpublished CSL records, this antivenom was first given for systemic illness to a 9-year-old boy at Four Mile beach, Port Douglas, North Queensland on the 29th of December 1970. This case was reported to CSL by Dr. Jack Barnes (S.K. Sutherland, personal communication). Dr. Barnes noted that, although the culprit jellyfish was not sighted, it was most likely to have been *C. barnesi*. Therefore, the two doses of box jellyfish antivenom were administered for what was, in retrospect, a case of Irukandji syndrome. The first intravenous dose was said to have been ''ineffective'' and, although improvement was seen after the second dose given some 40 minutes later, Barnes felt that this was ''purely coincidental.'' Several subsequent cases of Irukandji syndrome have also been treated with this antivenom to a similarly uncertain outcome (Fenner et al., 1986). In this context it is of interest that box jellyfish antivenom binds to *C. barnesi* and other jellyfish venom components in vitro (Wiltshire et al., 2000).

The first case of the use of the box jellyfish antivenom for systemic envenomation after a *Chironex* sting was a 25-year-old man swimming near East Point in Darwin on 29 March 1971 (S.K. Sutherland, personal communication). The effect of antivenom therapy in this Darwin case was described as 'good' (no further details available). Since these early cases this antivenom has been used in many instance of box jellyfish envenomation (Beadnell et al., 1992; Currie, 1994). Its efficacy for Chirodropidae stings has also been established experimentally by in vitro and in vivo neutralisation studies (summarised in Table 1). No adverse reactions (apart from a single instance of mild generalised rash) have been reported following its use in over 100 cases (Sutherland and Lovering, 1979). It also appears to be safe for use in pregnancy (Williamson et al., 1980).

Table 1. Summary of the experimental and clinical data on the neutralisation of cubozoan, scyphozoan and hydrozoan jellyfish venoms by the box jellyfish (*Chironex fleckeri*) antivenom (CSL Limited).

Jellyfish species	Efficacy of *Chironex fleckeri* antivenom against venom
Chironex fleckeri	In vitro and in vivo experimental efficacy against lethal and dermonecrotic effects as well as in vitro neutralisation of venom haemolytic activity (Baxter and Marr, 1974). Clinical efficacy likely, although the appropriate dose in the context of life-threatening envenomation is difficult to ascertain (Currie, 1994).
Chiropsalmus quadrigatus	In vitro but not in vivo experimental neutralisation of lethal effects, in vitro neutralisation of haemolytic and dermonecrotic effects as well as in vivo efficacy against dermonecrotic effects (Baxter and Marr, 1974). Clinical efficacy likely, although the appropriate dose in the context of life-threatening envenomation is difficult to ascertain (Baxter and Marr, 1970; Currie, 1994).
'Irukandji' jellyfish	No experimental studies yet available using *Carukia barnesi* or other 'Irukandji' venoms. Published and unpublished case reports are inconclusive regarding the efficacy of this antivenom for the Irukandji syndrome (S.K. Sutherland, personal communication; Fenner et al., 1986. It is possible that the variable clinical response to the antivenom in those instances relates to the variation amongst the causative jellyfish species.
Chrysaora quinquecirrha	Ineffective in vitro and in vivo against the experimentally induced lethal, dermonecrotic and haemolytic activities of this venom (Baxter and Marr, 1974).
Physalia physalis	Ineffective in vitro against this venoms lethal and dermonecrotic activities (Baxter and Marr, 1974).

Currently accepted indications for box jellyfish antivenom include cardio-respiratory arrest, or cardiac arrhythmias, difficulty with breathing, speech or swallowing, severe pain, extensive skin lesions, or skin lesions in cosmetically important areas such as face, neck, hands and forearms (Currie, 1994). The usual dose varies with severity between one vial for more moderate stings to three for life-threatening stings (Sutherland and Tibballs, 2001). An examination of the data relating to the cross-neutralising potential of this antivenom leads to the hypothesis that the box jellyfish antivenom will be effective against chirodropid but not carybdeid species (see Table 1).

Our in vitro assessment of the efficacy of the antivenom against the venom of the 'jimble', *Carybdea rastonii*, a carybdeid jellyfish common in South Australia, agrees with this interpretation (unpublished data). Clearly, further research is required to fully assess the potential value of the box jellyfish antivenom in non-chirodropoid stings. It certainly appears to be the case that this antivenom is ineffective at neutralising scyphozoan and hydrozoan jellyfish venoms (Table 1) (Baxter and Marr, 1974). Whether a higher dose will prove effective against carybdeid venoms, notably for the Irukandji syndrome, remains to be determined. It is possible that the effectiveness of this antivenom will vary with the phylogenetic distance of the relevant jellyfish from the immunising species (Figure 1 and Table 1).

The feasibility of an Irukandji antivenom is supported by our initial rabbit immunisation results using carybdeid venom extracts (unpublished data). However one of the greatest challenges to an Irukandji antivenom is the difficulty in obtaining the immunogen. The scarcity of Irukandji jellyfish material may be overcome using a molecular, or DNA based, immunisation strategy. Whilst this technique is not yet in use for commercial antivenom manufacture, it has given promising results when applied experimentally to the neutralisation of snake venoms (Harrison et al., 2000). This technology may also be facilitated by recent developments in the cloning of cubozoan jellyfish genes (J. Wilce, and P. Bailey, personal communication). The time is now ripe for a renewal of interest in jellyfish antivenom research and development.

ACKNOWLEDGMENTS

This work was supported by the Victorian Department of Human Services, the Hermon Slade Foundation, and the Thyne Reid Educational Trust.

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