The Irukandji Syndrome: A Devastating Syndrome caused by a North Australian Jellyfish.

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ABSTRACT

The “Irukandji syndrome” is a group of delayed (10-40 mins, mean 30 mins) severe systemic symptoms occurring after an initial mild skin sting by small carybdeid (box) jellyfish including *Carukia barnesi*, known colloquially as the “Irukandji”. Although the syndrome is well-known in tropical Australia waters, the 1998-99 season in north Queensland was notable for the number of victims with severe toxic heart failure who needed admission to intensive care facilities for more complex investigations and treatment than usual. There have also been other severe and unusual symptoms reported this year, which leads to the conclusion that there may be more than one species of jellyfish causing the Irukandji syndrome, or a seasonal variation in the symptoms and/or severity of symptoms caused by *Carukia*. To date there have been no reported deaths from Irukandji envenomation but there have been a number of patients that were probably only saved by high quality intensive care treatment.

This article describes the updated current state of information on the ecology of jellyfish causing the Irukandji syndrome, introduces the new symptoms, and discusses some treatment regimes that may be effective, as well as problems associated with inappropriate treatment. Research into the cause and treatment of this potentially devastating syndrome is hampered by lack of funding, although there are large costs to the taxpayers for retrieval and medical treatment of victims. These costs are analysed and presented.

THE IRUKANDJI SYNDROME - AN INTRODUCTION

In 1943, whilst serving with troops stationed in the Cairns, north Queensland area, Dr Ron Southcott first described a strange syndrome that occurred in a group of troops who went swimming in the tropical seas. This syndrome presented with a minor skin sting but was followed approximately 30 minutes later by a bizarre set of distressing systemic symptoms. He called these Type “A” stingings to distinguish between another group of jellyfish stings, which caused severe and instant local skin pain (Type “B” stings, later identified as being due to the *Chironex* box jellyfish).[1]

Still unaware of the cause, in 1952 Flecker named this set of delayed systemic symptoms the “Irukandji syndrome”, after a local aboriginal tribe in the Palm Cove, Cairns area, where most of these envenomations occurred.[2] However, it was not until 1966 that Dr Jack Barnes, using some amazing detective work, captured a small (1.5-2.0cm bell diameter) carybdeid (box jellyfish with just one tentacle in each corner). He then stung himself, his son and a volunteer lifesaver to see if it caused the Irukandji syndrome.[3] All three ended up in the Cairns Base Hospital Intensive Care Unit with the typical severe systemic symptoms of the Irukandji syndrome described below (this is not a recommended procedure!). Southcott later named the jellyfish[4] *Carukia barnesi* after its intrepid discoverer.

The “slang” name of Irukandji has previously been reserved for *Carukia barnesi*, but is now increasingly used for any jellyfish causing this bizarre syndrome. **In this article the term “Irukandji” is used for any small carybdeid (small box jellyfish) causing the set of systemic symptoms known as the Irukandji syndrome (described below).** However, it must be remembered that no other small carybdeid jellyfish has even been proven to cause this syndrome, even if it appears it may.

Since this early research, severe systemic symptoms including cases of toxic heart failure have been described.[5 6 7 8] However, this year some 30% of cases reported to the author’s sting database* have had some degree of heart failure, with some cases being severe enough to warrant admission and exhaustive and complex treatment for up to 8 days for severe toxic heart failure, and lung complications. In addition to this there have been further bizarre symptoms reported which are unexplainable at the current time, and which are described below.

A recent 1998 report of 60 Irukandji stings from Cairns[9] did suggest that the Irukandji syndrome was mild and had few severe systemic effects, with the majority of patients being discharged home after several hours monitoring in a specialised “observation ward”, and without the need for admission. A criteria for early discharge was a requirement for less than 2mg/kg of pethidine. However, the authors are aware of two cases where heart failure developed in patients who required less than this amount of pethidine.* It may be more appropriate to use a lower dose of pethidine (such as 1mg/kg) and/or include other criteria such as breathlessness. Also, two of their cases had heart failure and did require admission to a critical care unit. This article included data from the Cairns Region only, where most of the stings occurred inside a “stinger-resistant enclosure”.

Stinger resistant enclosures are nets of small (approximately 20mm diagonally) mesh, suspended from floating pontoons. They provide an area for swimming in the sea that effectively precludes *Chironex* box jellyfish. However, the small mesh nets do allow the entry of smaller jellyfish, including the Irukandji. As the Cairns group describes few cases being admitted to Intensive Care facilities, with the majority of patients sent home, and other regions describe more serious stings and complications, it is possible that a proportion of Cairns Irukandji stings occur from smaller, less mature (and less toxic?) Irukandji, which penetrate the small mesh size of the stinger-resistant nets. Or it may be a different species of carybdeid causing the severe syndrome that has become more common this year in the central Queensland Region. Research is current.

Irukandji sting numbers and intensities do vary considerably each year.* Some seasons there are 100-200 reported cases, whereas in others there may be very few. This may reflect variations in the ecology of species of jellyfish causing the Irukandji syndrome, and/or any unknown environmental factors influencing their ecology.

* Author database containing over 600 case studies of Irukandji envenomation from 1986-99

The Irukandji – Description

Carukia barnesi, the only jellyfish proven to cause this syndrome in tropical Australian waters, has a transparent bell, 1.5-2.5cm in diameter, which makes it almost impossible to see in the water. Reports of it being seen by its victim's are rare.[10] This small carybdeid jellyfish has just 4 tentacles, one in each corner, which are 5-7cm when contracted but may extend to some 60-70cm when the Irukandji is `fishing' for its prey of small fish.[4]

Although the original biological description of the Irukandji was *Carukia barnesi*, there is now mounting evidence to suggest that there may be more than one species of small carybdeid causing the Irukandji syndrome.

The Irukandji – Distribution and ecology

The distribution of Irukandji stings is confirmed from the Rockhampton area in central Queensland, northwards around the north Australian coast, and then as far south as Broome in Western Australia.[11] However, occasionally, some cases of Irukandji syndrome have been reported in Queensland further south to Agnes Water, and even as far south as Moore Park, Bundaberg.* Such reports from southern waters may be confusing, as a large (up to 15cm bell length) carybdeid jellyfish (box-jellyfish with just one tentacle in each corner) also causes a minor "Irukandji-like" syndrome in about 10% of its cases of envenomation.[12] These large carybdeids (*Tamoya spp.)* are commonly reported from the waters of Moreton Bay, where they are known as the "Moreton Bay Carybdeid", "Morbakka", or "Fire jelly".[13] Its milder Irukandji-like syndrome includes several symptoms of the syndrome described below, but they are not as severe, although victims frequently get somewhat distraught with the symptoms. This Irukandji-like syndrome occasionally occurs as far south as Sydney.[11 12]

Although Irukandji stings often occur in deep water, including the offshore Islands of north Queensland and the Outer Barrier Reef, swarms may often be brought to the surface at coastal swimming beaches, by underwater currents. Multiple stings may occur in summer months in these shallow waters off the coastal beaches.[11]

Nothing is currently known of Irukandji life cycle, or life cycles, assuming there is more than one species. However, specimens of a small carybdeid identified as *Carukia barnesi* (PJF) have been caught in October (very early in the season) in Mackay, central Queensland, river outlets, possibly suggesting a coastal factor in the early life cycle. Previously the whole life cycle was believed to be deep ocean water. Work on the biological features of these small carybdeids is currently underway (Seymour 1999, pers. comm., Gershwin 1999 pers. comm.).

Envenomation

Initial sting

The initial envenomation is usually a minor skin sting, which may not even be noticed. However, occasionally it may be more noticeable, causing local pain almost like that of a bee sting. Victims are often seen rubbing or scratching an area of skin, although unaware that they have received a jellyfish sting (Bernstone 1998, pers. comm.). The mark left on the skin with this envenomation is usually the imprint of the small jellyfish bell, making it very difficult, if not almost impossible to see: Less often, tentacle marks may be seen.[6] Within minutes of the usual sting mark caused by the jellyfish bell, the skin may develop a mild blotchy redness and `goose-pimple' effect (pilo-erection), which may last from 30 minutes or more - in some cases this initial sting may be totally missed. The reddish imprint, if visible, may last several days.

After the initial sting there is a characteristic time delay before the onset of the severe systemic symptoms which comprise the Irukandji syndrome.[2] The delay varies between 5 and 50 minutes, but is characteristically 30 minutes after the initial skin envenomation.

Irukandji syndrome

After this characteristic initial time delay, a bizarre set of distressing systemic symptoms occurs. The syndrome has always two recognised clinical sequelae, in some cases the third may also be present: -

1. Pain
2. Catecholamine effects
3. Cardiopulmonary decompensation.

A victim may have any combination of these signs and symptoms, but always has the severe pain:

1. Pain

The syndrome characteristically starts with: -

a) *Low back pain* - a severe `boring' pain in the sacral area;
b) *Muscle pain or `cramps'* - these move rapidly into all four limbs and the abdominal and chest wall muscles. The pain is described as severe, unbearable and coming on in `waves' (similar to labour pains) - although never fading completely;
c) *Chest pain or `tightness'* - usually caused by spasm of the intercostal muscles. There has been no bronchospasm demonstrated. Cardiac muscle pain may also occur, especially in the more severe cases when cardiac specific enzyme levels rise, suggesting cardiac muscle damage. However, chest pains also occur without the enzyme levels rising.

2. Catecholamine excess

Many of the signs and symptoms associated with the Irukandji syndrome resemble those of an adrenal medullary tumour (phaeochromocytoma), funnel-web spider[14] or scorpion envenomation,[15] with excessive release of catecholamines into the bloodstream:-

a) *Sweating* - localised or generalised. In severe envenomation the sweating is usually profuse and drenching. If it is localised it may be at the site of envenomation, or in a body area that is totally unrelated to the sting site.
b) *Piloerection* - localised or generalised. Again, it may be at the original site of envenomation, or an area totally unrelated.

c) *Anxiety and `wretchedness'* - The victim is over-anxious. They feel `absolutely dreadful' and often have “a feeling of impending doom” (a thought often shared by the treating first aider!).
d) *Restlessness* - Victims are restless and move continuously, trying unsuccessfully to get comfortable. This is both part of the general syndrome, and aggravated by the severe muscle pains.
e) *Headache* – may be severe frontal, or global; it may be incapacitating.
f) *Nausea* - often with severe, intractable vomiting.
g) *Increased respiratory rate* - Respiration is often of a `sighing nature', possibly due to the intercostal muscle pains.
h) *Tremor* - A fine tremor, or fasciculation of the small muscles of the limbs.
i) *Pallor, or peripheral cyanosis* - Due to intense peripheral vasoconstriction.
j) *Oliguria* - A reduced urine output probably due to reduced renal perfusion and fluid loss from the sweating and/or vomiting.
k) *Tachycardia* - The heart rate is often fast and may be irregular with ventricular extra-systoles.
l) *Hypertension* - The blood pressure may reach levels as high as 280/150mm Hg in previously normotensive victims.
m) *Cerebral oedema* - A case has recently come to light in which cerebral oedema occurred. This was characterised by unconsciousness and papilloedema followed by arousal after intravenous dexamethasone and mannitol. There has only been one reported case.[8]

The 1998-99 season has produced reports of previously undescribed symptoms and signs.* It was also noted that these symptoms occurred within a few minutes of the initial skin sting, rather than the usual 30 minutes later.:-

n) *Lower leg pains* – Although victims usually get the muscle cramping pain described above, many cases in the 1998-99 season complained of severe burning, neurasthenic and somewhat intractable lower leg pain. This has not been previously reported in the literature.
o) *Priapism* (prolonged erection) – This was reported in two recent cases (Ross 1999, pers. comm.). One case had been treated, prior to helicopter evacuation, with phentolamine, an alpha-adrenergic blocker that could theoretically have caused this. However, the second case did not have any alpha-blocking agents. At this time both cases still had most of the severe symptoms of the Irukandji syndrome, including the severe intractable muscle pains.
p) *“Allergic reaction”* – Reported in two cases in which the victim had periorbital oedema and an expiratory wheeze.
q) *Lassitude / tiredness / depression* – Although no research or follow-up has occurred in this area, in the Author’s experience many victims have a severe lethargy after envenomation. This may last anything from a few days to a few months in rare cases. Further research is necessary.

Later complications:-

3. Cardiopulmonary decompensation

a) *Acute pulmonary oedema* **-** Sudden breathlessness may develop in victims with the Irukandji syndrome, ranging from 8-18 hours post-envenomation (occasionally less). This has proved to be acute pulmonary oedema.[6]

b) *Toxic global dilation of the heart* - Fenner *et al*[6] demonstrated a (toxic) global cardiac dilatation, whereas Martin & Audley felt the oedema may be due to massive alpha-adrenergic stimulation.[7]

Other recent severe cases having echocardiography have also shown marked global cardiac dilatation and/or left ventricular dysfunction (Carney and Fenner 1996-99, unpublished information). Abnormal echocardiograph measurements include left ventricular systolic dimensions of up to 50mm (normal 20-40mm) with diastolic measurements usually around the upper limit of normal (NR 35-55mm) and fractional shortening as low as 9% (NR 25-45%). Blood tests can also be abnormal with increased cardiac enzymes, including the CK-MB ration. No statistical long-term follow up studies have been undertaken but it seems that cardiac function returns to normal fairly rapidly, once the other signs and symptoms have abated. However, the Authors are aware of one case where ECG changes (demonstrated on an exercise stress test as mild ST depression at maximal exertion) persisted for at least 6 months.

Further studies using echocardiography and even Swan-Ganz catheter to measure right atrial, pulmonary artery and pulmonary wedge pressures should provide more information.

Differential diagnosis

1. Myocardial infarction

Cases with the initial chest pain of the Irukandji syndrome, especially if pulmonary oedema develops, have in the past been misdiagnosed as an acute myocardial infarction with developing heart failure.[6] This thought may be reinforced if there is 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 as the creatinine phosphokinase (CPK) level is often raised well above the normal levels. However, when this is differentiated into cardiac (CK-MB) and general muscle fractions the cardiac enzyme fraction may be normal, whereas the general muscle fraction is elevated, often to very high levels – possibly caused by the intense muscle cramps experienced by the hapless victim or a direct myotoxic effect of the venom. However, some severe cases may have a CK-MB well above the normal range (<8), with an abnormal, and significant, ratio (NR <1.6). A number of these cases have significant myocardial toxicity and impaired function and have developed pulmonary oedema,

2. Decompression sickness

The Irukandji syndrome in a diver also resembles decompression sickness, and may present a difficult differential diagnostic problem.[16] There have now been a number of cases where the DES (Diving Emergency Services) have been phoned when, a short time after surfacing, a diver suddenly develops severe low back pain, chest pain (`trouble' breathing) and is distressed and restless.

A high index of suspicion and careful questioning is needed. A history of a minor sting (often on the back of the neck when surfacing), a small mark, often difficult to see, and/or careful differentiation of the symptoms is necessary. Often discussion on this may be conducted over a radiotelephone from a dive boat on the reef to the DES headquarters in Adelaide - no easy task.

First aid treatment

At present there is NO confirmed first aid treatment for Irukandji stings. However, Surf Life Saving Queensland is currently funded by the Australian Rotary Health Fund to conduct a randomised controlled trial testing the following two treatments: -

1. Douse the area with vinegar, remain with the victim, re-assure and encourage rest (muscle activity increases the heart rate and absorption and systemic dissipation of the venom). Or: -
2. Douse the area with vinegar, apply a vinegar soaked pad, a compression bandage, then immobilise the area (if the sting is on a limb).

If symptoms of the Irukandji syndrome occur, the victim is transported to Hospital by ambulance. The ambulance often carry inhaled gases such as Entonox or Penthrane that give some pain relief, but further assessment in hospital is still advisable.

The results of this trial will be published as soon as they become statistically sound.

Medical management

There is no antivenom available. Treatment is symptomatic but vigorous (See flow chart).

<u>1. Pain relief</u>

a) Morphine. 0.025 – 0.05mg/Kg given as an IV dose, and repeated as necessary every five minutes, or as a continuous intravenous infusion. Or: -

b) Pethidine. 0.25 – 0.5 mg/Kg is given as an immediate intra-venous (IV) bolus dose and repeated every 5 minutes, as necessary, or as a continuous infusion with appropriate monitoring.

As respiratory depression may occur, the above regime should only be carried out where respiratory resuscitation skills and facilities are immediately available. Barnes suggested that pethidine was more effective than morphine[3] but there is concern about accumulation of pethidine metabolites when frequent doses are used. There has been no trial comparing the efficacy of these agents in the pain of the Irukandji syndrome, and both have been used effectively. After the severe pain has settled, Barnes advocated aspirin 600mg orally every four hours for adults as the most effective analgesic until the muscle pains had settled.[3]

The neurasthaenic-like pains in the lower legs do not appear to be controlled by the above medication.

Fentanyl (0.5mcgms/kg) has been suggested[9] as an alternate analgesic agent but no clinical trial has been published examining its superiority as an analgesic agent in the Irukandji syndrome. Similarly, promethazine (25-50mg) was suggested to improve the symptoms, but again, no controlled studies have been published to date. Collaborative research is essential between areas where these envenomations occur.

2. Reversal of catecholamine effects

Phentolamine (a short-acting alpha-adrenergic receptor blocking drug) may be given IV as a loading dose of 5mg (adult patient, average weight), followed by 10mg IV repeated when necessary until there is satisfactory control of the blood pressure, sweating, anxiety and tremor.

Note: Verapamil, the calcium channel blocker has been suggested for the treatment of a number of serious jellyfish stings,[17] but in view of the potential problems associated with heart failure using this medication, it is not recommended.

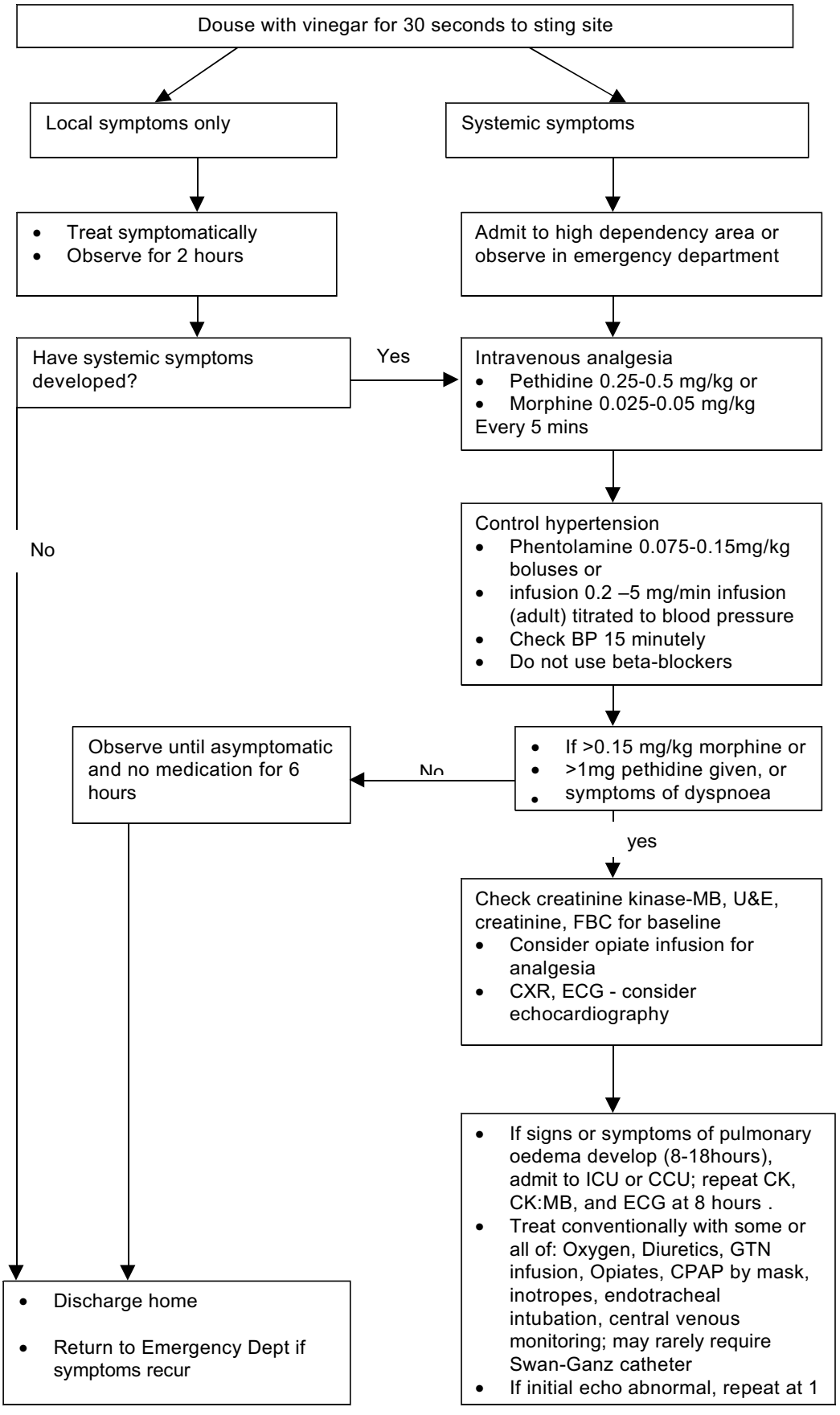
However, Nifedipine, another calcium channel blocker, has been used with some success in scorpion envenomation,[15] which is similar to the Irukandji syndrome, having excess catecholamine release. This may be helpful, however, all risk factors (including any tachycardia) need to be assessed before Nifedipine is used.

The tremor should not be treated with beta-blockers as disastrous hypotension may occur, which has lead to acute renal failure and all its attendant associated risks.*

3. Treatment of pulmonary oedema

a) Monitor with pulse oximetry to measure oxygen saturation. Pulmonary oedema has been treated conventionally with oxygen, diuretics, opiates, and sublingual or intravenous nitrates. A CPAP mask with up to 14l of oxygen with CPAP of 5-10cm H_2O may be required, or even endotracheal intubation: intermittent positive-pressure ventilation may be necessary for continuing, or developing arterial hypoxia.

b) Pulmonary oedema that fails to respond to the above therapy may also need right heart catheterisation and/or inotropic support with agents such as dopamine or dobutamine in a critical care situation.


Douse with vinegar for 30 seconds to sting site
Local symptoms only
Systemic symptoms
Treat symptomatically
Observe for 2 hours
Admit to high dependency area or observe in emergency department
Have systemic symptoms developed?
Yes
Intravenous analgesia
Pethidine 0.25-0.5 mg/kg or
Morphine 0.025-0.05 mg/kg
Every 5 mins
No
Control hypertension
Phentolamine 0.075-0.15mg/kg boluses or
infusion 0.2 –5 mg/min infusion (adult) titrated to blood pressure
Check BP 15 minutely
Do not use beta-blockers
If >0.15 mg/kg morphine or
>1mg pethidine given, or
symptoms of dyspnoea
No
Observe until asymptomatic and no medication for 6 hours
yes
Check creatinine kinase-MB, U&E, creatinine, FBC for baseline
Consider opiate infusion for analgesia
CXR, ECG - consider echocardiography
If signs or symptoms of pulmonary oedema develop (8-18hours), admit to ICU or CCU; repeat CK, CK:MB, and ECG at 8 hours .
Treat conventionally with some or all of: Oxygen, Diuretics, GTN infusion, Opiates, CPAP by mask, inotropes, endotracheal intubation, central venous monitoring; may rarely require Swan-Ganz catheter
If initial echo abnormal, repeat at 1
Discharge home
Return to Emergency Dept if symptoms recur

Costs of the Irukandji syndrome

There is a large cost in the treatment of the Irukandji syndrome to the taxpayer. In the summer season 1998-99 there were some 30 helicopter retrievals of victims from remote locations, including offshore Islands and the Great Barrier Reef. Each journey takes approximately 2 hours return, with costs for the helicopter being $1-2000 per hour. Hospital admission may be a$1000 a day for intensive care treatment and $400 a day for hospital ward treatment. When other costs such as repatriation of domestic or international travellers, time off work and the potentially huge cost of reduced tourism from publicity of such stings is considered, the final costs may rise to be much higher. Funding from State and Australian Governments will assist in research for the development of Irukandji antivenom and should prove cost-effective with comparison to evacuation and hospital stays, and even in the loss of the “tourist dollar”. Trained personnel on Islands and tour boats could administer such antivenom, possibly preventing the need for emergency evacuation and hospital admission.

Approximate costs of severe Irukandji envenomation in remote area:-

Aeromedical retrieval	-	$2000-5000
Intensive care bed (1-8 days maximum)	-	$1000-$8000
Hospital bed (2 days after ICU)	-	$800
Investigations and medical treatments	-	$1000

With a total of up to $15,000 possible for one patient.

Research into Irukandji antivenom

Funding is current from the Australian Rotary Health Fund for surf lifeguards in the Cairns area to try to catch Irukandji in fine mesh nets either pulled slowly through the water by lifeguards in the shallows, or deeper, using a net towed behind an inshore rescue boat (“rubber duck”). Success is limited to date, as finding these small jellyfish in vast tracts of sea water is difficult. Captured Irukandji are placed in small bags without water, and frozen in a domestic freezer until they can be transported (still frozen) to the Australian Venom Research Unit in Melbourne, where work is current analysing the venom, with the aim of producing an antivenom. However, a serious lack of funding is currently delaying many aspects of this project and the development of Irukandji antivenom is expected to take up to 10 years at the current progress.

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