EVIDENCE WORKSHEET for Guideline 8.9.6: Envenomation – Jellyfish stings

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Clinical question:

For victims of jellyfish envenomation in Australia (P), is any intervention (I), better than any other intervention (C) for analgesia, or inhibition of further nematocyst discharge? (O)

Search Strategies:

A. The Cochrane Library (CDSR, CENTRAL, DARE) and Medline (1950 – current)

1. (exp cnidaria) OR (jellyfish.ti,ab) OR (Chironex fleckeri.ti,ab) OR (irukandji.ti,ab) OR (carukia barnesi.ti,ab) OR (physalia.ti,ab) OR (blue?bottle.ti,ab) OR (carybdea alata.ti,ab) OR ("c.alata".ti,ab)
2. (exp emergency treatment) OR (first aid.ti,ab)
3. 1 AND 2
4. Limit 3 to English language

C. EMBASE

1. 'poisonous jellyfish'/exp OR 'poisonous jellyfish' OR 'jellyfish' OR 'coelenterate'/exp
2. 'emergency treatment'/exp OR 'emergency treatment' OR 'first aid'
3. 1 AND 2

Databases / sources searched:

In addition to the electronic databases detailed above, backward and forward searching was undertaken in Scopus, hand-searching of reference lists of relevant articles, text-word based grey literature searches in 'Google Scholar'

Inclusion / exclusion criteria:

Due to the paucity of controlled trials of treatment interventions for jellyfish envenomation, the primary search was highly sensitive in nature. All studies examining the treatment of jellyfish envenomation by species found in Australia waters (case studies, case-series, non-controlled cohorts, controlled studies, systematic reviews) were retrieved for further review. Letters, editorials, papers not available in full or not available in English were excluded.

Search results:

The combined searches outlined above yielded 52 studies, these papers were retrieved and assessed for inclusion as evidence.

Number of papers / studies meeting criteria for further review:

One LOE II trial, one III-2 trial and one LOE IV case series provided clinical evidence for the guideline. A further ten (10) studies not meeting the NHMRC criteria for classification as evidence for an intervention were also used to support the guideline construction.

Level of Evidence	Definitions	Study
I	Evidence obtained from a systematic review of all relevant randomised controlled trials	
II	Evidence obtained from at least one properly designed randomised controlled trial	**Loten et al 2006**
III-1	Evidence obtained from well designed properly pseudo-randomised controlled trials (alternate allocation or other method)	
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group	**Birsa et al 2010**
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group	
IV	Evidence obtained from case series, either post-test or pre-test and post-test	**Exton et al 1989**
Other	Animal, manikin etc	**Currie et al 1993 (epidemiological)** **Hartwick et al 1980 (in vitro)** **Little et al 2003 (epidemiological)** **Fenner & Hadok 2002 (case study)** **Fenner et al 1988 (case study)** **Flecker 1952 (epidemiological)** **Fenner 1991 (review)** **Tibballs 2006 (review)** **Williamson et al 1980 (case study)**

METHODOLOGICAL QUALITY OF STUDIES:

Good	**Fair**	**Poor**
The methodological quality of the study is high with the likelihood of any significant bias being minimal	The methodological quality of the study is reasonable with the potential for significant bias being likely.	The methodological quality of the study is weak possessing considerable and significant biases

A. Methodological quality, levels of evidence & outcomes of studies examining hot water (I) compared with ice (C) for analgesia (O) after *Physalia* (Bluebottle) envenomation.

1. Studies *supportive* for the use of hot water for analgesia after Physalia envenomation:

Good		**Loten 2006 E**					
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

2. Studies *neutral* for the use of hot water for analgesia after Physalia envenomation:

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

2. Studies *negative* for the use of hot water for analgesia after Physalia envenomation:

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

Endpoints:
A: Return of spontaneous circulation
B: Survival of event
C: Survival to hospital discharge
D: Neurologically intact survival
E: Effective analgesia

B. Methodological quality, levels of evidence & outcomes of studies examining vinegar (I) compared with any other treatment, or no treatment (C) for the inhibition of nematocyst discharge (O) after *Chironex fleckeri* (Box jellyfish) envenomation.

1. Studies *supportive* for the use of vinegar for inhibition of nematocyst discharge after analgesia after *Chironex fleckeri* (Box jellyfish) envenomation:

Good							
Fair							**Hartwick 1980 E**
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

2. Studies *neutral* for the use of vinegar for inhibition of nematocyst discharge after analgesia after *Chironex fleckeri* (Box jellyfish) envenomation:

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

3. Studies *negative* for the use of vinegar for inhibition of nematocyst discharge after analgesia after *Chironex fleckeri* (Box jellyfish) envenomation:

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

Endpoints:
A: Return of spontaneous circulation
B: Survival of event
C: Survival to hospital discharge
D: Neurologically intact survival
E: Inhibition of nematocyst discharge

C. Methodological quality, levels of evidence & outcomes of studies examining ice (I) compared with no treatment (C) for analgesia (O) after *Physalia* **(Bluebottle) envenomation.**

1. Studies *supportive* for the use of ice for analgesia after Physalia envenomation

Good							
Fair						Exton 1989 E	
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

2. Studies *neutral* for the use of ice for analgesia after Physalia envenomation:

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

3. Studies *negative* for the use of ice for analgesia after Physalia envenomation

Good							
Fair							
Poor							
	I	**II**	**III-1**	**III-2**	**III-3**	**IV**	**Other**
	NH&MRC level of evidence						

Endpoints:
A: Return of spontaneous circulation
B: Survival of event
C: Survival to hospital discharge
D: Neurologically intact survival
E: Effective analgesia

Class of recommendation:

Class B: Vinegar [acetic acid] should be topically applied to inhibit further nematocyst discharge of *Chironex fleckeri* (Box jellyfish) tentacles on the skin

Class B: Hot water (45^{o}) should be topically applied to provide analgesia for confirmed *Physalia* ('bluebottle') envenomation

Reviewer's final comments and assessment of benefit / risk:

The management of jellyfish envenomation in Australia must be based on the geographical distribution of species known to cause potentially life-threatening envenomation, as it is usually difficult to determine which species has caused a sting. Dangerous species occur primarily in the tropical areas, north of Bundaberg (QLD) and Geraldton (WA) – these are the Box jellyfish (*Chironex fleckeri*) and the approximately 10 small species that cause Irukandji syndrome. One *in vitro* [Hartwick 1980] study showed that 4 – 6% acetic acid (vinegar) inhibited discharge of *C. fleckeri* nematocysts. No studies reported on adverse effects associated with the use of topical acetic acid after Box jellyfish envenomation. Jellyfish envenomation (Blue bottle) in non-tropical Australia is unlikely to be life-threatening, and the primary objective of first-aid should be pain relief. A LOE II randomised trial in Eastern Australia [Loten 2006] showed hot water (45^{o}C) to be superior to ice-packs for the relief of pain after confirmed bluebottle envenomation. One case series (LOE IV) [Exton 1989] reported effective analgesia after the application of ice for mild or moderate pain following bluebottle envenomation - this series had no comparator group. Birsa (2010) conducted an *in vitro* examination of bluebottle nematocyst inhibition and found that 4% lidocaine prevented all nematocyst discharge – this treatment warrants further higher-level studies.

Citation List:

Birsa LM, Verity PG, Lee RF. Evaluation of the effects of various chemicals on discharge of and pain caused by jellyfish nematocysts. Comp Biochem Physiol, Part C 2010; 151: 426-30

Jellyfish tentacles in contact with human skin can produce pain swelling and redness. The pain is due to discharge of jellyfish nematocysts and associated toxins and discharge can be caused by a variety of mechanical and chemical stimuli. A series of tests were carried out with chemicals traditionally used to treat jellyfish stings e.g. acetic acid, ammonia, meat tenderizer, baking soda and urea to determine if these chemicals stimulated or inhibited nematocyst discharge and if they brought relief to testers who were exposed to jellyfish tentacles. *Chrysaora quinquecirrha* (sea nettle) *Chiropsalmus quadrumanus* (sea wasp) and *Physalia physalis* (Portuguese man-of-war) were used in the study. It was found that many of the chemicals traditionally used to treat jellyfish stings stimulated nematocyst discharge and did not relieve the pain. However there was immediate relief when a common anesthetic lidocaine was sprayed on the skin of testers in contact with jellyfish tentacles. Initial exposure of tentacle suspensions to lidocaine prevented the nematocyst discharge by subsequent exposure to acetic acid ethanol ammonia or bromelain. Thus lidocaine in addition to acting as an anesthetic on skin in contact with jellyfish tentacles inhibited

nematocyst discharge possibly by blocking sodium and/or calcium channels of the nematocytes.
LOE III-2 small comparative clinical trial (n=2) with a concurrent, non-randomised, non-blinded control. Fair methodological quality. Also, question of generalisablity to Australian context. The trial tested the analgesic properties of a number of chemicals against envenomation of two human volunteers by two species of jellyfish (Chiropsalmus quadrumanus and Chrysaora quinquecirrha). As neither of these species has been found in Australian waters, the generalisibility of the treatment cannot be assumed. The authors also conducted a non-clinical in vitro study of the inhibitory characteristics of a number of chemicals against nematocyst discharge in the tentacles of three different jellyfish species, including Physalia physalis, finding that lidocaine exhibited the greatest inhibitory effect.

Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK. A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings. Med J Aust 2006; 184: 329-33
To investigate the effectiveness of hot water immersion for the treatment of Physalia sp. (bluebottle or Portuguese Man-of-War) stings. DESIGN: Open-label, randomised comparison trial. Primary analysis was by intention to treat, with secondary analysis of nematocyst-confirmed stings. One halfway interim analysis was planned. SETTING: Surf lifesaving first aid facilities at two beaches in eastern Australia from 30 December 2003 to 5 March 2005. PARTICIPANTS: 96 subjects presenting after swimming in the ocean for treatment of an apparent sting by a bluebottle. INTERVENTIONS: Hot water immersion (45 degrees C) of the affected part versus ice pack application. MAIN OUTCOME MEASURES: The primary outcome was a clinically important reduction in pain as measured by the visual analogue scale (VAS). Secondary outcomes were the development of regional or radiating pain, frequency of systemic symptoms, and proportion with pruritus or rash on follow-up. RESULTS: 49 patients received hot water immersion and 47 received ice packs. The two groups had similar baseline features, except patients treated with hot water had more severe initial pain (VAS [mean +/- SD]: 54 +/- 22 mm versus 42 +/- 22 mm). After 10 minutes, 53% of the hot water group reported less pain versus 32% treated with ice (21%; 95% CI, 1%-39%; P = 0.039). After 20 minutes, 87% of the hot water group reported less pain versus 33% treated with ice (54%; 95% CI, 35%-69%; P = 0.002). The trial was stopped after the halfway interim analysis because hot water immersion was shown to be effective (P = 0.002). Hot water was more effective at 20 minutes in nematocyst-confirmed stings (95% versus 29%; P = 0.002). Radiating pain occurred less with hot water (10% versus 30%; P = 0.039). Systemic effects were uncommon in both groups. CONCLUSIONS: Immersion in water at 45 degrees C for 20 minutes is an effective and practical treatment for pain from bluebottle stings.
LOE II randomised, controlled trial (n= 96) comparing ice packs and hot water for analgesic effect in bluebottle envenomation. Good methodological quality; however participants and assessors not blinded. Primary outcome was decrease in pain level measured with validated instrument (VAS). The trial was halted after 50% enrolment as hot water was shown to be more effective in producing a clinically significant decrease in pain (p=0.002).

Exton DR, Fenner PJ, Williamson JA. Cold packs: effective topical analgesia in the treatment of painful stings by *physalia* and other jellyfish. Med J Aust 1989; 151: 625-6
A study has shown that, when applied to *Physalia* ('bluebottle') jellyfish stings, cold packs are effective as topical analgesia in the relief of mild-to-moderate skin pain. The

application of ice also has been shown to be effective for topical analgesia in a number of other jellyfish stings, including by Cyanea ('hair jellyfish'), Tamoya sp. ('Moreton Bay stinger' or 'fire jelly') and Carybdea rastoni ('jimble') as well as by Physalia. In the current state of knowledge, cold packs or ice are recommended as the first-aid treatment for jellyfish stings with local skin pain.

LOE IV prospective case series of n=143 adult and paediatric victims of confirmed Physalia envenomation. Methodologically fair.

Study intervention consisted of removing adherent tentacles from skin surface, then applying a cloth-covered ice pack for 5-10 minutes; reassessing victim's self-reported pain level and applying a second ice pack for 5-10 minutes if pain persisted. Victims were asked to rate their pain as mild, moderate or severe before treatment. 100% of victims with mild pain, 98% with moderate pain and 75% with severe pain reported complete resolution of pain with ice pack application. Sole outcome was complete resolution of pain.