WORKSHEET to accompany PROPOSED ARC Evidence-Based GUIDELINES

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Guideline applicable: **8.9.6 ENVENOMATION – JELLYFISH STINGS**	**Date submitted to council:** **8 July 2007**

Step 1: State the proposal

ARC Guideline 8.9.6 (February 2005) is titled "ENVENOMATION – JELLYFISH STINGS". For all jellyfish stings, it advises the application of cold packs or wrapped ice for pain relief (Para 2, Page 3). A trial published in 2006 *(1)* has advocated the use of hot water as an effective and practical technique for pain relief after stinging by *Physalia* sp. (bluebottle or Portuguese man-o'-war)[1] stings. Adoption of this conclusion would represent a significant change in this element of the guideline and it was recommended that the evidence base for such a proposal be considered. This review will consider efficacy and safety but the practicalities of the technique, including the delivery of water at the appropriate temperature and the possibility of multiple casualties, would need to be addressed by those choosing to implement the technique if such a change was advocated.

There has been a longstanding belief that all forms of *Physalia* are taxonomically identical *(2)*. Australian observations *(3)* challenged this paradigm. Subsequently fundamental differences in morphology (float, crest and main fishing tentacle) and variable reactivity to vinegar have been identified. These factors suggest the existence of two or more distinct forms, creating a second school postulating two species *(4)*. In particular, if there are forms with differing envenomation patterns, this must be considered and reflected in treatment guidelines.

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in- /out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

Pain relief for stings by jellyfish of the *Physalia* sp. (bluebottle or Portuguese man-o'-war) can be effectively and safely[2] provided by immersion of the affected area in water at 45 degrees Celsius for 20 minutes.

Step 1b: Gather the evidence

Define your search strategy.
(e.g. ((cardiopulmonary-resuscitation*:me or heart-arrest*:me) not (atrial-fibrillation:me of electrophysiology:me)) and hypothermia:ab))

The following terms were recognized as MeSH headings and keywords:

bites and stings, Cnidaria, Cubozoa, cryotherapy, heat, hot water, jellyfish, stings, first aid.

Human, animal model and in vitro studies and "abstract only" studies were accepted. Articles not in English were not pursued.

SALUS (South Australian Health Services Libraries Consortium) or EndNote was used to access OVID.

SALUS was also used to access Evidence Based Medical Reviews .

[1] This reflects the authors' taxonomic belief that *Physalia* is a single species genus. The possibility that it may be "*Physalia* spp." with multiple species significantly complicates the discussion.
[2] As noted above, this proposal does not address the matter of practicality which is an element of the trial conducted by Loten 1. Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK. A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings. Medical Journal of Australia 2006;184(7):329-33.

List electronic databases searched (at least MEDLINE (http://igm.nlm.nih.gov/) Embase, Cochrane database for systematic reviews and Central Register of Controlled Trials (http://www.cochrane.org.au/), and hand searches of journals, review articles, and books.

The primary search was conducted by perusing the following recognized electronic data bases

EBM Reviews - Cochrane Database for Systematic Reviews < 3rd Quarter 2006> (0 results)
EBM Reviews – ACP journal Club < 1991 to September/October 2006 > (0 results)
EBM Reviews – Database of Abstracts of Reviews of Effects < 4th Quarter 2006 > (0 records)
EBM Reviews – Cochrane Central Register of Controlled Trials ,4th Quarter 2006> (7 records)
OVID MEDLINE – 1966 to October Week 4 2006
OVID OLDMEDLINE – 1950 to 1965
EMBASE 1980 to 2006 Week 43 (14 results)

Articles of possible relevance were catalogued in an EndNote 7 library. The references provided by the material retained in this library were scanned and, if relevant articles were found that were not already within the library, they were added to the data base.

• Describe search results; describe best sources for evidence.

A series of searches was performed with various permutations of the MeSH and keywords. A sample search with results is presented below.

#	Search History	Results	Display
1	(Bites and stings).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	8191	DISPLAY
2	Cubozoa/ or Cnidaria/ or jellyfish.mp.	3116	DISPLAY
3	First aid.mp. or First Aid/	6813	DISPLAY
4	1 and 2 and 3[3]	39	DISPLAY
5	Heat/ or hot water.mp.	75417	DISPLAY
6	cryotherapy.mp. or Cryotherapy/	4875	DISPLAY
7	5 and 6	216	DISPLAY
8	5 or 6	80076	DISPLAY
9	4 and 8	2	DISPLAY
10	1 and 2	249	DISPLAY
11	8 and 10	7	DISPLAY
12	1 and 5	45	DISPLAY

Number of articles/sources meeting criteria for further review:

The EndNote library ("bluebottle.enl") ultimately contained (at 13/02/2007) 136 references. These were considered and 94 were thought to justify further attention. Fifty three are documented in the references. Forty six of these have ultimately been incorporated into the work sheet and citation list. The work of Bucherl *(5)*, Burnett *(6)*, Fenner *(7)*, Gershwin *(8)*, Rifkin *(9)*, Strutton *(10)*, Tibballs *(11)* , Totton *(2)* and Turner (*12*) are included for reference. Seven other papers *(47-53)* are included as secondary references of interest

[3] In this particular search, linking the third search ("first aid") to the first two searches with "AND" dramatically reduced the number of results and also allowed a significant number of relevant articles to escape. These were captured in subsequent searches.

Step 2: Determine the Level of Evidence for each study.

For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions	Articles found
Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials	
Level II	Evidence obtained from at least one properly designed randomised controlled trial	Loten *(1)*
Level III-1	Evidence obtained from well designed properly pseudo-randomised controlled trials (alternate allocation or other method)	Bowra *(13)*, Lopez *(14)*, Thomas *(15)*, Nomura *(16)*
Level 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	
Level 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	Peca *(17)*
Level IV (ILCOR5)	Evidence obtained from case series, either post-test or pre-test and post-test	Moritz *(18)*, Exton *(19)*, Yoshimoto (*20*), Taylor (*21*)
Other	Evidence based review (EBR)	Bailey (*22*)
Other	In vitro studies (IVS)	Lane ✳(*23*) ✳(*24*) ⁂ , Endean (*25*), Baxter (*26*), Halstead ✳ (*27*), Endean ⁂*(28)*, Rottini (*29*) , Burnett (*30*)
Other	Mathematical model (MM)	Diller (*31*)
Other (ILCOR6)	Animal model studies (AMS)	Mendelssohn (*32*), Saria (*33*), Exton (*34*), Carrette (35)
Other (ILCOR8)	Rational conjecture and common practices before evidence-based guidelines were required (RCCP)	Burnett (36) (*37*) Fenner ✷(3), Rifkin (38) (4), Holmes (39), Fenner (40) (*41*)
Other	Case report (CR)	Russell (42), Barnes (*43*), Stein ✷(44), Burnett ✷(*45*) ✷*(46)*

✳ ⁂Referring to same work
✷Probably referring to same incident

A significant number of references detailed are listed in the category denoted "Other". Limiting the review to assessing information in Level I-IV studies, as standard in Australian Resuscitation Council recommendations, would prevent consideration of both animal model and in vitro studies. Included in the remaining "Other" subdivisions are a polyglot of references; some expressing personal opinions, some presenting past practices now abandoned and others being of historical interest.

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level I study can be good or poor as a clinical trial, just as a Level II study could be good or poor. Where applicable, please append a code (A to E, as shown below) to categorize the primary endpoint of each study.

Component of Study and Rating	**Good**	**Fair**	**Poor**
Methodology	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.
Articles (use citation marker and code for outcome applicable: e.g. Elam 1998 D)	Lane *(24) (23),* Endean *(25),* Baxter *(26),* Halstead *(27),* Endean *(28)* , Rottini *(29)* , Burnett *(30),* Bowra *(13)* , Carrette *(35),* Loten *(1)* , Diller *(31)*	Mendelssohn *(32),* Moritz *(18),* Exton *(34),* Lopez *(14),* Thomas *(15)* , Nomura *(16),* Bailey *(22)* , Saria *(33)*	Russell *(42)* , Barnes *(43)* Burnett *(36)] (37),* Exton *(19),* Stein *(44),* Fenner *(3),* Holmes *(39),* Rifkin *(38) (4),* Fenner *(40),* Peca *(17),* Fenner *(41),* Burnett *(45),* Yoshimoto *(20),* Burnett *(46),* Taylor *(21)*

Many of the articles provide material, statements or expressions of opinion that do not allow for an assessment of "methodological quality". These have generally been rated as "Poor". The value of such material can be argued but it has been included for the record and to indicate that it has been identified.

Step 2C: Determine the <u>direction</u> of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	**SUPPORT the proposal**	**NEUTRAL**	**OPPOSE the proposal**
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

It is not possible in the context of assessing a small element of a guideline to relate treatment outcomes to the guideline as a whole.

Results have therefore been assessed as simply relating to the proposal presented in Step 1A.

In the context of the proposal, data generated from work on *Physalia* spp. specifically are determined as supportive, neutral or opposing according to the results. Data generated from work on other species is determined as neutral at the best or opposing if deemed so.

One article *(40)* is considered supportive in consideration of heat application but opposing when considering application of fresh water while another *(32)* is considered supportive in terms of heat application but neutral on the matter of venom denaturation.

Step 2D: Cross-tabulate assessed studies by a) *level,* b) *quality* and c) *direction* (ie, supporting or neutral/ opposing)**; combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent, Good,* and *Fair* quality studies by both *Level and Quality of evidence,* and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

In conflict with Australian Resuscitation Council practice, articles deemed "Poor" have not been excluded on the grounds outlined above.

Supporting Evidence

Pain relief for stings by jellyfish of the *Physalia* sp. (bluebottle or Portuguese man-o'-war) can be effectively and safely provided by immersion of the affected area in water at 45 degrees Celsius for 20 minutes.

	I	II	III-1	III-2	III-3	IV	Other
Good		Loten *(1)*					Lane *(23) IVS*, *(24) IVS* , Halstead *(27) IVS*, Diller *(31)MM*
Fair			Bowra *(13)* Lopez *(14)*				Mendelsohn *(32)* AMS, Saria *(33)* AMS, Exton *(34)* AMS
Poor					Exton *(19)*		Burnett *(37)* RCCP, Fenner *(40)* (Heat), *(41)* RCCP

Neutral or Opposing Evidence

Pain relief for stings by jellyfish of the *Physalia* sp. (bluebottle or Portuguese man-o'-war) can be effectively and safely provided by immersion of the affected area in water at 45 degrees Celsius for 20 minutes.

Articles deemed "Opposing" are emboldened in this section.
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		I	II	III-1	III-2	III-3	IV	Other
	Good							Baxter *(26)* IVS, Endean *(25)* IVS, Endean *(28)* IVS, Rottini *(29)* IVS, Burnett *(30)* IVS, Carrette *(35)* AMS
	Fair						Moritz *(18)*	Mendelssohn *(32)* AMS, **Bailey (*22*) EBR,**
	Poor			Thomas *(15)*, Nomura *(16)*			Peca *(17)* Yoshimoto *(20)*	**Russell (*42*) CR, Barnes (*43*) CR,** Burnett (*36*) RCCP, **Stein *(44)* CR, Fenner (*3*) RCCP, Holmes (*39*) RCCP, Rifkin (*38*) RCCP, *(4)* RCCP, Fenner *(40)* (Water), Burnett (*45*) CR, (*46*) CR,** Taylor *(21)*

STEP 3. DETERMINE THE CLASS OF RECOMMENDATION.
Select from these summary definitions.

CLASS	DEFINITION
Class A *Recommended*	Class A treatment recommendations are given to those guidelines which are considered to be beneficial and should be used
Class B: *Acceptable*	Class B treatment recommendations are given to those guidelines which may be beneficial and are acceptable to be used if considered appropriate in that setting

State a Class of Recommendation for the Guideline Proposal.
State either a) the intervention, and then the conditions under which the intervention is either Class A or Class B; or b) the condition, and then whether the intervention is Class A or Class B

Guideline or intervention (Class of recommendation):

Class B

Acceptable

Pain relief for stings by jellyfish of the *Physalia* sp. (bluebottle or Portuguese man-o'-war) can be effectively and safely provided by immersion of the affected area in water at 45 degrees Celsius for 20 minutes.

The safe implementation of this guideline is dependent on

- its use being limited to areas where box jellyfish do not occur;
- the reliable identification of the stinger and
- an effective, well maintained mechanism for ensuring delivery of water at the correct temperature.

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Consider the frequency of adverse events and the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment

Loten and co-workers ***(1)*** have demonstrated that immersion in water at 45 degrees Celsius for 20 minutes may be practically implemented and that it is a safe and effective treatment for *Physalia* sp. in the Newcastle area of New South Wales. Never the less there are a number of significant matters that need consideration before the technique is fully endorsed as an acceptable nation-wide practice.

It is not critical that an effective technique be available for the management of bluebottle stings. These are rarely significant (death has not been recorded in Australian waters) and the pain is usually self limiting and of short duration. However, it is critical that when and where potentially fatal box jellyfish (*Chironex fleckeri*) stings are most likely to be encountered (eg October 1 – June 1 for the Northern Territory , but accepting that they may occur the year around and in a wider geographical distribution), that effective treatment is given and that treatment should incorporate the use of vinegar. There should be no possibility that hot water could be considered the preferred option in that setting.

The following references, addressing the matters of the effect of heat on the pain and the venom of various species have been noted.

Carybdea marsupialis: Rottini ***(29),*** Peca ***(17)***

Carybdea alata: Yoshimoto ***(20),*** Thomas ***(15),*** Nomura ***(16)***.

Carybdea species: Taylor ***(21)***

Chironex fleckeri: Endean ***(25),*** Baxter ***(26),*** Endean ***(28),*** Burnett ***(30),*** Carrette ***(35)***

Chrysaora quinquecirrha: Burnett ***(36)*** ***(30)*** ***(45)***

Physalia spp.:Burnett ***(37)-*** no reference, Lane ***(23),*** Stein ***(44) –*** describing possibly Burnett's experience ***(45)***, Fenner *(3)* - referring to an earlier publication ***(6)***, Carrette ***(35)*** referring to Bucherl ***(5)*** – actually the report of Halstead *(27),* Yoshimoto *(20)*- referring to Lane *(24 Burnett [Burnett, 1977 #32)* ***(46)*** and Loten ***(1)***

Will/can immersion in water at 45 degrees Celsius for 20 minutes cause a superficial burn injury?

The paper by Loten *(1)* indicates that this is not so, at least in subjects older than eight years, and it is claimed that this conclusion is supported by the early work of Moritz ***(18)***. Saria ***(33)***, using an animal model, noted that the threshold temperature which caused noticeable plasma extravasation was 45 degrees Celsius.

An individual's experience describing 15 minutes exposure at 42 degrees Celsius as the extreme of tolerance ***(45)*** has been previously referred to by probably both Stein *(44)* and Fenner ***(3)*** but no other reports have been found of detrimental effect. Old work, referring to older work, stated that "If a limb were immersed in warm water, the tolerance limit was 45-47 degrees Celsius" ***(32).*** Lopez ***(14)*** used immersion water at 43.3 degrees Celsius up to 60 minutes. Neither Yoshimoto ***(20)***, using a "whole-body hot shower" for an unstated time , nor Bowra ***(13),*** using a "hot shower" for a maximum of 10 minutes, indicate the pertinent temperature. Thomas ***(15)*** used chemical hot packs reaching 43.3 degrees Celsius soon after activation with application for 15 minutes without adverse effect. None of these reports documents that heat application could not be tolerated.

Fenner ***(41)***, in discussing the management of stonefish stings, recommends immersing the limb in hot water. Most recent work ***(31)*** indicates that 45 degrees Celsius is lower than a recommended safety standard (116-117 degrees Fahrenheit) aiming to ensure scald protection for children from hot water.

Comment:

Loten's work ***(1)*** has demonstrated that immersion in water at 45 degrees Celsius for 20 minutes is safe and tolerable and no other clinical data is available to the contrary.

Will/can heat applied topically denature venom already remote from the skin surface?

Loten ***(1)*** noted that many marine venoms are heat labile ***(5) –*** perhaps more restrictively could be Halstead ***(27)*** referring to Lane ***(23)*** – *Physalia* spp**.,** Endean ***(48)*** (perhaps ***(25)*** is better), Carrette ***(35)*** and Baxter ***(26)*** – *Chironex fleckeri***.** Work has also been reported on *Carybdea marsupialis* ***(29)***, *Chrysaora quinquecirrha* ***(30)***, and *Physalia* spp. ***(24)*** , ***(37)***- no reference and may be the work of Lane ***(23).*** Further contending that it is feasible that heat penetrates the human dermis to the estimated depth that nematocysts inject toxins, Loten ***(1)*** postulated that topical hot water would be an effective form of treatment by virtue of toxin denaturation. Support was taken from published research and trials of variable quality and uncertain applicability by Carrette ***(35)*** - *Chironex fleckeri*, Nomura ***(16)*** - *Carybdea alata*, Bowra ***(13)*** – *Physalia* spp., Lopez ***(14)*** – unspecified and Thomas ***(15)*** – *Carybdea alata*.

Mendelssohn ***(32),*** reporting earlier work, observed that the subcutaneous temperature was generally significantly lower than that at the surface and it seems unlikely that the temperatures required for venom denaturation will be achieved using Loten's protocol. Lane ***(23)*** notes that the lyophilized toxin of *Physalia* spp. has its activity destroyed in solution after five minutes at 60 degrees C. The hypothesis of denaturation of the venom by heat also assumes that the venom remains within the limb site of envenomation.

Comment:

While Loten's study has shown that immersion in hot water at 45 degrees Celsius for 20 minutes provides significant pain relief, the mechanism remains unproven. This topic requires further investigation but debate on the mechanism does not invalidate the conclusions made by Loten and his co-workers.

Will/can capillary dilatation accelerate venom absorption?

The effect of capillary dilatation associated with the use of hot water, with the potential consequence of facilitating venom absorption, has been noted by Carrette ***(35)*** who highlights the rapid onset of symptoms with *Chironex fleckeri* envenomation associated with its potential fatal outcome and recognizes that the role of hot water in these circumstances is "limited". Bailey ***(22)*** indicates that the venom for *Chironex fleckeri* is "most probably introduced directly into blood vessels" without substantiation. Capillary dilatation may then be more significant and for this reason Rifkin ***(4)*** argues against local application of heat for the treatment of *Physalia physalis*[4] stings but also at the same time states that heat is also ineffective in providing pain relief (relying on unpublished data).

There is a significant amount of literature on the toxinological nature of the venom of *Physalia* spp ***(11)*** ***(30)*** ***(6)*** but the means of its transport after envenomation has occurred is not well defined. It is postulated that venoms with tardier onset are absorbed by lymphatics.

The question of lymphangitis is a feature reported by Stein ***(44)*** , Burnett ***(45)*** and Fenner ***(3)***, all probably referring to a single case, and is of uncertain significance. Yoshimoto ***(20)*** documents several interval references by Burnett in 1989 and 1991.

Comment:

Discussion of this subject remains highly speculative.

Will/can treatment with fresh water cause remaining nematocyst discharge?

Yoshimoto ***(20)*** notes the case report by Barnes ***(43)* -** ?*Chironex fleckeri* - and the proscription of the use of fresh water by Burnett ***(49)*** and Holmes ***(39)*** – for *Chironex fleckeri*. The reports of Exton ***(34)*** and Fenner ***(3)*** suggest that fresh water[5] does not cause discharge of the *Physalia* spp. nematocysts. Yoshimoto ***(20)*** noted that in their series (retrospective with no species identification) "fresh water hot showers were used without clinical evidence of increased envenoming or other adverse effects". It is presumed in that series that the stings resulted from the Hawaiian box jellyfish (*Carybdea alata*) and Portuguese man-o'-war (*Physalia* spp.). Neither Bowra ***(13)*** – *Physalia* & shower – nor Lopez ***(14)* –** no species identification & immersion - indicate whether fresh water was used in their trials.

Exton ***(19)*** – *Physalia* spp. - while focusing on the use of cold packs for pain relief advocate that "if adherent tentacles were present, they first were washed off with water".

Rifkin *(38)* advocates that **"**neither fresh nor sea water should be used to remove tentacles" but also notes "Although initial in vitro studies by the author showed that water did not cause a discharge in *C. fleckeri* or *Physalia* spp. nematocysts, nematocysts within detached tentacles are still very reactive to… contact-chemical stimuli.."

Fenner ***(40)*** states "Recent evidence[6] shows that fresh water will cause discharge of stinging cells, and may make the sting worse; sea water should be used to wash off tentacles and ice wrapped up to keep the area dry."

Laboratory research techniques are based on a recognition that marine nematocysts may be induced to discharge by exposure to fresh water ***(8).***

Comment:

Conflicting and imprecise scientific data make it difficult to be decisive but again Loten's data do not report any adverse clinical effect associated with the use of fresh water for immersion

[4] Reflecting the second school of thought.

[5] Exton does not specify the nature of the water used to challenge the nematocyst.

[6] No references provided

Can the technique be safely used around Australia?

For those experienced in jellyfish stings, including both medical and non-medical personnel, it is recognized that different species have differing geographical distributions ***(7)*** *(22)*. In those areas free of the more dangerous species such as the box jelly fish and those causing the Irukandji syndrome, there may be little understanding by again both medical and non-medical personnel of their potentially lethal sting. It is unlikely that reliable identification of any jellyfish would be forthcoming. The application by such individuals, when they are traveling in unaccustomed regions, of what they believe to be a safe technique (such as hot water immersion) may have a detrimental outcome by delaying appropriate care, possibly causing nematocyst discharge with increased envenomation and could speculatively "enhance movement of the venom into the circulatory system" by virtue of the associated capillary dilatation ***(35)***.

Comment:

At a national level, a direct comparison may be made to the matter of lay personnel performing pulse checks in assessing the need for CPR. It has been demonstrated that it is better to unnecessarily initiate CPR on a patient not in cardiac arrest than it is to refrain from CPR in a patient who needs it. It is arguably better to treat a bluebottle sting (or a sting of unknown origin) with vinegar, wrongly assuming that it was a box jellyfish sting than to wrongly conclude that the sting of a box jellyfish must be that of a bluebottle and treat with hot water immersion.

Conclusion:

Loten et al. have shown that immersion in water at 45 degrees Celsius for 20 minutes hot water is a safe, effective form of treatment, in their hands and environment, for stings by jellyfish of the *Physalia* sp.

There are significant knowledge gaps when considering the management of jellyfish stings. For *Physalia*, these areas specifically include:

- the differences between single and multiple tentacled forms – is it *Physalia* sp. or spp?;
- the manner in which nematocysts respond to stimuli of various types;
- the mechanism of pathogenicity including venom transport after envenomation.

These deficiencies also exist for other species and there is a need for research to address these questions. The results from such research would allow a reasoned approach to the management of jellyfish stings in both pre-hospital and hospital settings.

This lack of knowledge adds to the considerable confusion about the most appropriate first aid treatment. There is a need for an unambiguous, safe, easily applied technique for the first aid treatment of jellyfish stings. Ideally it could be applied with consistency nationally for all cases.

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Dr Lisa-Ann Gershwin of the Australian Marine Stinger Advisory Services has been an unstinting source of information and generous in time providing education, criticism and laboratory exposure to the unexpected. Her research and experience have specifically influenced the usage of sp. or spp. in this worksheet.

Professor Guy Maddern, RP Jepson Professor of Surgery, The Queen Elizabeth Hospital, Woodville, South Australia, provided facilities for information retrieval and Lisa Leopardi skillfully assisted.

Citation List

Citation Marker *(Reference number)*	Full Citation
1. *(22)*	Bailey PM, Little M, Jelinek GA, Wilce JA. Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. Medical Journal of Australia 2003;178(1):34-7. Other EBR; Fair; Opposing Abstract: 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. *In quoting Rifkin (9) on the matter of venom delivery for Chironex fleckeri, states that venom "is most likely introduced directly into blood vessels". This seems to be an erroneous reference.*
2. *(43)*	Barnes JH. Studies on three venomous cubomedusae. Symposia of the Zoological Society of London 1966;16:307-322. Other CR; Poor; Opposing p325 "Fresh water should be seduously avoided until the skin has been treated with a fixative. Thereafter, a shower is not harmful." p329 "In one instance, the collapse was precipitated by application of fresh water, which is absolutely contra-indicated in medusan stings." *Referred to by Yoshimoto (20) as "a report of clinical deterioration following fresh-water application in an apparent Chironex fleckeri sting".*
3. *(26)*	Baxter EH, Marr AG. Sea wasp (Chironex fleckeri) venom: lethal, haemolytic and dermonecrotic properties. Toxicon 1969;7(3):195-210. Other IVS; Good; Neutral or opposing The lethal, haemolytic and dermonecrotic properties of the venom of the sea wasp, *Chironex fleckeri*, were investigated. Variable species susceptibility was evident in the lethal and haemolytic properties. No histamine-releasing action is involved in the dermonecrotic action, which is not reduced by adsorption of the haemolysin on to rbc. Optimum conditions for the haemolytic action were studied and a unit of activity established. The haemolysin is not a phospholipase. The stability of the venom properties to various physical and chemical treatments was studied. Heat, formalin and EDTA reduce all activities. Peptone is useful as a stabilizing additive. Fractionation of the venoms by the use of Sephadex chromatography and adsorption and neutralization studies show that the properties derive from similar, but not the same, compounds. The biologically active molecules causing these activities appear to have a molecular weight of 10,000-30,000. P201 states "When diluted "electrical" venom lots were heated for 10 min at a range of temperatures lethal and haemolytic properties were inactivated at some temperature between 40 and 50 degrees."

	Referred to by Yoshimoto (20) : "This crude venom extract loses its lethal and haemolytic activities after a 10-min treatment at 50 degrees Celsius" Page 202, Table 5
4. *(13)*	Bowra J, Gillett M, Morgan J, Swinburn E. Randomised crossover trial comparing hot showers and icepacks in the treatment of *Physalia* envenomation. Emerg. Med. 2002;13(A22). III-1; Fair; Supportive *Physalia* (`bluebottle') envenomations cause significant morbidity during summer. Consensus is lacking on optimum management, however Surf Life Saving Australia (SLSA) currently advocates ice pack treatment. This study aims to compare hot showers with ice packs for *Physalia* envenomation. Methods: A randomised crossover trial was performed on 54 subjects (age > 6) with *Physalia* envenomation who presented to Manly Life Saving Club between December 2000 and February 2001. Subjects were randomised to a maximum of ten minutes of either ice pack or hot shower. If further analgesia was required, the subject was crossed over into the opposite treatment arm for up to ten minutes. Using a visual analogue scale (VAS) each subject's pain was recorded immediately before treatment, on termination of treatment (if subject elected to cease treatment early), at ten minutes and at twenty minutes after treatment commenced. Unpaired t-tests and Kaplan-Meier survival analysis were used to compare treatments. Results: 27 subjects were randomised into each arm. At the end of treatment, 48% of subjects were pain-free after hot showers versus 29.6% with ice packs. In addition, the percentage pain reduction achieved with hot showers was significantly greater (82.1 + 4.3 versus 65.6 + 6.0%, P < 0.03). Hot showers also resulted in a reduced mean treatment time (11 + 0.95 minutes compared with 14.5 + 1.6 minutes, P < 0.02). There was no significant difference in the numbers that required crossover. Conclusions: For *Physalia* envenomation, hot showers resulted in a significant reduction in pain and treatment duration when compared to ice packs. *Trial December 2000 – February 2001* *No details of temperature of "hot shower".*
5. *(5)*	Bucherl W, Buckley E. Venomous animals and their venom. New York: Academic Press; 1971. *The chapter of particular interest is that by Halstead (27) and references to Bucherl (5) are better seen as the work of Halstead.*
6. *(46)*	Burnett JW. Hot water for treatment of bluebottle stings 24 April 2006. (Personal Communication to Gershwin L) Other CR; Poor: Opposing: "I reviewed the lab book and found the original data from July 2,1987. At that time I took a few drops (0.1-0.2 ml) of purified *Physalia physalis* nematocyst suspension prepared by Renografin density gradient centrifugation and placed it on my volar forearm in a 2-3 cm area. The animal came from East Florida. I rubbed the spot until local pain came and I was sure I was stung then immediately immersed my forearm in a water bath prepared at 42 C (107.8 F). The whole forearm- wrist to elbow- was in the bath for 9 min which is all I could stand. There was significant pain and diaphoresis locally by 30 min and a florid red rash early on which as maximal at 60 min. There were small irregularities on the proximal border but one red line (red lymph channel) extending up several (3-4 cm). I did not like this so I wrote a note to myself-don't do this again. There was no effect on the jellyfish sting pain." *This record is at variance in some details from his description in 2001 (45) – see below.*
7. *(30)*	Burnett JW, Bloom DA, Imafuku S, Houck H, Vanucci S, Aurelian L, et al. Coelenterate venom research 1991-1995: clinical, chemical and immunological aspects. Toxicon 1996;34(11-12):1377-83.

	Other IVS; Good; Neutral p1381 " Heat treatment (60 degrees Celsius/30 min) inactivated the cytolytic factors of both venoms (ie *Chronex fleckeri* and *Chrysaora quinquecirrha*) in both preparations."
8. *(6)*	Burnett JW, Calton GJ. The chemistry and toxicology of some venomous pelagic coelenterates. Toxicon 1977;15(3):177-96. *Referred to by Fenner (3) as stating "The application of heat (up to 41 degrees Celsius) on skin welts from the American Atlantic Physalia physalis has resulted in visibly increased lymphangitis and is thus not recommended for any Physalia sting". I cannot find this text.* *Referred to by Yoshimoto (20) as determining that "some factors are heat stable".*
9. *(36)*	Burnett JW, Calton GJ. Jellyfish envenomation syndromes updated. Ann Emerg Med 1987;16(9):1000-5. Other RCCP; Poor; Neutral Abstract: Jellyfish venoms are mixtures of toxic and/or antigenic polypeptides and enzymes pathogenic to human beings. As newer therapeutic agents become available to treat the various reactions to stings caused by these animals, an accurate diagnosis of the type of reaction the patient experiences and of the offending species will be necessary. Fatal reactions may be caused either by anaphylaxis or by the action of toxins in the venom on the heart, respiratory center, or kidneys. Cutaneous eruptions after envenomation may be local, generalized, exaggerated, recurrent, delayed, persistent, or occur at sites distant from the primary sting. Fat atrophy, pigmentary changes, vasospasm, and contractures with gangrene can occur after jellyfish stings. Identification of the envenoming animal can be made by actual visualization, examination for nematocysts on skin scraping, or serologically. It may also be predicted based on knowledge of location, time, and environmental circumstances of the encounter. First-aid measures designed to prevent additional nematocyst rupture are species-specific. Anaphylaxis should be prevented by the appropriate lifesaving measures. Other syndromes, caused by the toxins of the venom or mediated by humoral or cellular immune mechanisms, should be treated specifically. P1004/121" The application of hot or cold is not beneficial for *Chrysaora* stings."
10. *(37)*	Burnett JW, Calton GJ, Southcott R. The Portuguese Man-of-War. In: Covacevich J, Davie P, Pearn J, editors. Toxic Plants and Animals. Brisbane: Queensland University Press; 1987. p. 86-91. Other RCCP; Poor; Supportive States "The nematocyst toxin is believed to be a highly labile protein complex. It can be denatured by heating to 60 degrees Celsius, or with various organic solvents" *This is possibly referring to the work of Lane (23).)* "Treatment by the applications of water as hot as can be borne has been advocated by some authorities." *This may have been the instigation for the experiment reported in (45) and (46)*
11. *(45)*	Burnett WJ, Williamson JA, Fenner PJ. Box jellyfish in Waikiki.(47). Hawaii Medical Journal 2001;60(11):278. Other CR; Poor; Opposing "We have found that cold packs are of marginal use in sea nettle (*Chrysaora quinquecirrha*) sting and have the disadvantage of giving a small child a "chill". Heat application was unimpressive. On one occasion* one of us (JB) stung his forearm with the Atlantic coast Portuguese man-o'- war tentacles and rapidly immersed that area from wrist to elbow

	in a 42 degrees Celsius constant hot water bath for 15 min. That was all the thermal therapy he could tolerate. Two-minutes after removing the lymphangitic streaks appeared on the upper arm, so this practice was discontinued. Such an event did not appear in the present work probably because less heat was applied" **Referring to a personal experiment in 1987 See (46) but with some variance in details.* *Referred to by Stein (44), Fenner (3) and Yoshimoto (20)* *While it is stated here that "We have found that cold packs are of marginal use in sea nettle (Chrysaora quinquecirrha) sting and have the disadvantage of giving a small child a "chill". Heat application was unimpressive",Burnett (36) states "The application of hot or cold is not beneficial for Chrysaora stings".*
12. *(35)*	Carrette TJ, Cullen P, Little M, Peiera PL, Seymour JE. Temperature effects on box jellyfish venom: a possible treatment for envenomed patients? Med J Aust 2002;177(11-12):654-5. Other AMS: Good; Neutral Abstract: OBJECTIVE: To determine the effect of temperature on lethality of venom from *Chironex fleckeri* (the potentially fatal box jellyfish). DESIGN: Venom extracted from nematocysts of mature *Chironex fleckeri* specimens was exposed to temperatures between 4 degrees C and 58 degrees C for periods of two, five or 20 minutes, and then injected into freshwater crayfish (*Cherax quadricarinatus*) to assess lethality. MAIN OUTCOME MEASURE: Venom lethality, assessed as time to cardiac standstill in crayfish after intramuscular injection. RESULTS: Venom lethality was significantly affected by both temperature (F(7,34) = 21915; P < 0.0001) and time of exposure (F(2,34) = 9907; P < 0.0001). No significant loss of lethality was seen after exposure to temperatures <or= 39 degrees C, even after 20 minutes' exposure. At temperatures >or= 43 degrees C, venom lost its lethality more rapidly the longer the exposure time. Venom was non-lethal after exposure to 48 degrees C for 20 minutes, 53 degrees C for five minutes, and 58 degrees C for two minutes. CONCLUSION: Exposure to heat dramatically reduces the lethality of extracted *C. fleckeri* venom. Although heat application may be of limited use in treating *C. fleckeri* envenoming because of the speed of symptom onset, its use in other box-jellyfish envenomings, such as Irukandji syndrome, requires investigation. *Refers to Bucherl (5) which should be Halstead (27) which mis-states the work of Lane (23)*
13. *(31)*	Diller KR. Adapting adult scald safety standards to children. Journal of Burn Care & Research 2006;27(3):314-22; discussion 323-4. Other MM; Good; Supportive Scald burns by domestic tap water constitute a painful, potentially debilitating, and sometimes-fatal form of thermal injury. In this setting, the very young and older members of the population are particularly susceptible, owing in part to having thinner skin, which renders them more susceptible to thermal insult. Various codes have set forth a safety standard for maximum delivery temperature of domestic tap water at 120 degrees F (48.9 degrees C), based on adult susceptibility to burns. This work addresses the issue of how the current safety standard for tap water temperature could be adjusted to provide a level of protection to children equivalent to that for an adult at 120 degrees F. A well-accepted mathematical model for predicting burn injury as a function of applied surface temperature and time is used to identify these equivalent conditions. Data from the literature of sonographic measurements indicate a representative ratio of child to adult skin thickness of 0.72. The mathematical model shows that the equivalent surface temperature for a threshold scald injury in children is dependent on the depth into the skin at which the injury is identified. For example, the injury produced by a 120 degrees F, 10-second exposure at a depth of 600 microm in an adult is matched in a child at 72% of the depth (432 microm) by an insult of 115.9 degrees F for the same duration. The recommendation is that existing hot water standards be reduced by 3 to 4 degrees F to provide an equivalent level of scald protection to children.

	Supportive of proposal that water at 45 Degrees Celsius is safe even in children. Loten's work (1) *Excluded children under the age of eight years as the tool used for assessing the primary outcome measure had not been validated for that age grouping.*
14. *(28)*	Endean R, Monks SA, Cameron AM. Toxins from the box-jellyfish *Chironex fleckeri*. Toxicon 1993;31(4):397-410. Other IVS; Good; Neutral Abstract: Two myotoxins (T1 and T2) with mol. wts of approximately 600,000 and 150,000, respectively, and a haemolysin (T3) with a mol. wt of approximately 70,000 were isolated from the crude nematocyst venom of C. fleckeri by the use of Sephadex G-200 chromatography. A neurotoxic fraction (T4) and a haemolytic fraction (T5) containing proteins with apparent mol. wts of approximately 150,000 and 70,000, respectively, were also isolated by Sephadex chromatography from crude extracts of tentacular material from which nematocysts had been removed. The three nematocyst toxins and the two toxic fractions from tentacle extracts were lethal to mice on i.v. injection. After SDS-PAGE the myotoxins T1 and T2 yielded similar major bands corresponding with mol. wts different from those yielded by T3 and the toxic tentacle fractions. T1 and T2 appeared to be comprised of aggregations of subunits with mol. wts of approximately 18,000. On HPLC, crude nematocyst venom and the nematocyst toxins T1 and T2 lost their myotoxic properties. The need for thorough removal of extraneous tentacular material from isolated nematocysts, the need for effective rupture of nematocysts, the need to counter the lability of the nematocyst venom and the need to use myotoxicity as a criterion of venom activity if the active components of the venom are to be purified and characterized are emphasized. *Refers to Endean (25) and details "As the myotoxic activity of the crude nematocyst venom...inactivated by heating at 42 degrees Celsius".*
15. *(25)*	Endean R, Henderson L. Further studies of toxic material from nematocysts of the cubomedusan *Chironex fleckeri Southcott*. Toxicon 1969;7(4):303-14. Other IVS; Good; Neutral Abstract-Saline extracts of intracapsular material from the nematocysts of *C. fleckeri* lost their activity against muscle if incubated with protease, heated at *42°,* exposed to strong salt solutions, acid solutions of pH 3 and below, alkaline solutions of pH 10·5 and above, iodine, sodium fluoride, sodium iodoacetate or sodium azide. Their activity against muscle was- unimpaired in the presence of ouabain or by exposure to EDTA for 5 min. Haemolytic activity was exhibited by extracts; the extracts showed no phospholipase A or proteolytic activity. ATPase activity, inhibited by ouabain, was shown by the extracts. Neither the haemolytic activity or the ATPase activity appeared to be directly associated with the activity shown by the extracts against muscle. No evidence for a release of pharmacologically active products from isolated muscle preparations was obtained. The extracts had no action on glycerinated muscle fibres or on muscles exposed to high K. However, *they* elicited activity in `skinned' toad muscle fibres and in barnacle muscle fibres after the action potential had been suppressed by Mn ions. The Ca content of barnacle muscle fibre bundles exposed to dilute toxin extracts for *2* min rose markedly but there was a marked decline in the Ca content of bundles exposed to concentrated extracts for *2* min. *Endean (28) states "As the myotoxic activity of the crude nematocyst venom...inactivated by heating at 42 degrees Celsius".* *Yoshimoto (20) records "Heating at 42 degrees Celsius for 5 min (but not at 40 degrees Celsius for 20 min) abolishes another biological activity, that causing contraction of striated muscle."*

16. *(19)*	Exton DR, Fenner PJ, Williamson JA. Cold packs: effective topical analgesia in the treatment of painful stings by *Physalia* and other jellyfish. Medical Journal of Australia 1989;151(11-12):625-6. III-3; Poor; Supportive Abstract: 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. *While this study is focused on pain relief from the application of cold, the researchers used water to wash off any adherent tentacles apparently without adverse effect. This supports the safety of showering with hot water in the context of Physalia nematocyst discharge.*
17. (34)	Exton DR. Treatment of Physalia physalis envenomation. Medical Journal of Australia 1988;149(1):54. Other AMS; Fair; Supportive *Assessed effect of water (20 tests), methylated spirits (30) and vinegar (34) on Physalia nematocysts. Vinegar and methylated spirits caused nematocysts to discharge. Water did not..* *It is not stated whether the water was "fresh water" or fresh sea-water"* *Testing 1987-8* *Rifkin subsequently explains this anomaly on the basis that they were in fact a Physalia variant with multiple main tentacles described in (3).*
18. *(40)*	Fenner P. Awareness, prevention and treatment of world-wide marine stings and bites. In: International Life Saving Federation Medical/Rescue Conference; 1997; 1997. *Other RCCP; Poor; Supportive (safety of heat application), Opposing(application of fresh water)* **Heat** (for penetrating injuries such as fish spines/spikes etc) eg stonefish, stingray, bullrout, sea urchin envenomation, other spiky fish envenomations. 1. Place the area (usually a limb) in hot water (Note: First, test the temperature of the water yourself to prevent scalding the patient.) 2. Further "top-ups' of hot water may be necessary, but the water must be tested each time to prevent scalding the patient. *If hot water is safe for fish stings, it is arguably safe for "bluebottles".* Other RCCP; Poor; Opposing **Cold Packs** **Note:** "Recent evidence[7] shows that fresh water will cause discharge of stinging cells, and may make the sting worse; sea water should be used to wash off tentacles and ice wrapped up to keep the area dry."
19. *(41)*	Fenner PJ. Marine envenomatiom: An update - a presentation on the current status of marine envenomation first aid and medical treatments. Emerg. Med. 2000;12:295-302. Other RCCP; Poor; Supportive

[7] No references provided

	Fenner p297 actually says that for stonefish " First aid treatment is to place the stung limb in hot water." *Loten understands him, with others, to say treatment of venomous fish stings is "immersion in water 43-45 degrees Celsius for 60-90 minutes".*
20. *(7)*	Fenner PJ, Williamson JA. Worldwide deaths and severe envenomation from jellyfish stings. Medical Journal of Australia 1996;165(11-12):658-61. *While this article describes geographical distribution of various species it does not address the question of this review.*
21. *(3)*	Fenner PJ, Williamson JA, Burnett JW, Rifkin J. First aid treatment of jellyfish stings in Australia. Response to a newly differentiated species.(50). Medical Journal of Australia 1993;158(7):498-501. Other RCCP; Poor; Opposing Vinegar has been shown to inhibit neomatocyst discharge in *Chironex fleckeri*, the deadly north Australian box-jellyfish, and application of vinegar has become accepted first aid, not only for box-jellyfish stings, but also for stings by other Australian jellyfish. However, in a newly differentiated species of *Physalia* in Australian waters, which causes severe envenomation, vinegar was found to cause discharge in up to 30% of neomatocysts. In treating these stings, the use of vinegar is not recommended as it may increase envenomation. Stings from the single-tentacled *Physalia utriculus* (the "bluebottle") are not severe, tentacles with unfired nematocysts rarely adhere to the victim's skin and vinegar dousing is not required. Vinegar treatment is therefore an unnecessary step in the first aid management of any *Physalia* sting but remains an essential first aid treatment for all cubozoan (box) jellyfish tested to date. *In recommending no vinegar the authors continue:* "Cold packs or ice should then be applied for a minimum of 15-20 minutes to reduce skin pain. As ice seems to give only slow relief of skin pain in the severe stings treated to date, early ambulance assistance should be sought." *In considering the application of heat, the authors state* "The application of heat (up to 41 degrees Celsius) on skin welts from the American Atlantic *Physalia physalis* has resulted in visibly increased lymphangitis and is thus not recommended for any *Physalia* sting" *This is similar in description to the report of Burnett (45) which relates to an experience in 1987 but the supporting reference is (6) - this seems to be an error.* *On effect of water on nematocysts:* "In our experience of many experiments over several years, fresh water has not been shown to cause nematocyst discharge"
22. *(8)*	Gershwin L. Nematocysts of the Cubozoa. Zootaxa 2006;1232:1-57. Page 6: Nematocysts can be permanently mounted for study by placing a bit of tentacle, bell snip, or cluster of cirri onto a glass slide, covering with one or two drops of warmed Glycergel (Dako Corp., California), and finishing with a cover slip; gently pressing or tapping with a blunt object will help squash the sample for easier study. For those wishing a cleaner sample, i.e., nematocysts separated from tissue, the simple disintegration isolation method of Bloom et al. (1998) works well. Fresh samples can be made to discharge with the addition of a drop of freshwater, saliva, or ethanol prior to adding the Glycergel; preserved nematocysts cannot be discharged. Since nematocyst identification is ultimately based on the shaft and tubule structures, fresh samples are preferable; however, capsule measurements are best made on undischarged capsules, which are more stable when preserved. Nematocysts are best examined under a compound microscope with a 40x or 100x objective.
23. (*27*)	Halstead B. Venomous coelenterates: Hydroids, jellyfishes, corals and sea anemones. In: Bucherl W, Buckley E, editors. Venomous animals and their venoms. New York: Academic Press, Inc.; 1971. Other IVS; Good; Supportive p410 states "Lane and his co-workers have provided most of the more recent data on the chemical properties of the *Physalia* poison (Lane and Dodge 1958; Lane, 1960, 1961), which is one of the few coelenterate poisons that has been evaluated to any

	extent. The activity of *Physalia* toxin is decreased markedly (sic) by heating to 60 degrees Celsius for 15 minutes (sic)." *Reporting the work of Lane (23) but inaccurately. This is also then perpetuated by Carrette (35) and referenced by Loten (1)*
24. *(39)*	Holmes JL. Marine stingers in far north Queensland. Australas. J. Dermatol. 1996;37 Suppl 1:S23-6. Other RCCP; Poor; Opposing Abstract: Two box jellyfish in particular cause problems in tropical Queensland waters. *Chironex fleckeri* inhabit calm waters close to the shore between November and May. The venom includes three major components: haemolytic dermatonecrotic and myocardial. The dermatonecrotic toxin causes a ladder pattern of whiplash lesions to the skin which ulcerate become necrotic and heal very slowly over months: Neuromuscular paralysis and cardiovascular collapse may be fatal within minutes of envenomation. Emergency treatment comprises inactivation of stinging capsules by vinegar removal of tentacles analgesia, cardiopulmonary resuscitation and the administration of the specific antivenom. *Carukia barnesi* ('Irukandji') are found in both coastal and open waters. A patch of erythema with papules at the sting site is characteristically followed 30 min later by the onset of a catecholamine mediated syndrome. Headache and severe abdominal and back pain are usual and may be followed by hypertension, tachyarrhythmias and cardiogenic shock. pS24 "First Aid (*Chironex fleckeri*): In particular fresh water or alcohol must never be poured onto the affected part."
25. *(23)*	Lane C. The toxin of *Physalia* nematocysts. Ann. N. Y. Acad. Sci. 1960;90:742-50. Other IVS; Good; Supportive p748, Lane states "The toxin is thermolabile in solution, its activity being **completely** (sic) destroyed during **five** minutes (sic) at 60 degrees Celsius". *This is presumably the same work as (24) below*
26. *(24)*	Lane C. The Portuguese man-of-war. Sci. Am. 1960(202):158-168. Other IVS; Good; Supportive p163. "It loses its toxicity when heated to 140 degrees Fahrenheit (60 degrees Celsius), subjected to considerable change in acidity or treated with organic solvents such as alcohol." *Quoted by Yoshimoto (20) but a better source may be Lane (23) See above*
27. *(14)*	Lopez E, Weisman R, Bernstein J. A prospective study of the acute therapy of jellyfish envenomation. J. Toxicol. Clin. Toxicol. 2000;38:512. III-1; Fair; Supportive Abstract: Objectives: Jellyfish envenomations are a frequent occurrence in the warm waters of South Florida. Traditional therapy involves the use of 5% acetic acid (vinegar), applying shaving cream and then scraping the area with the dull-side of a knife to remove adherent tentacles. The envenomated area is then immersed in hot water (110°F), or ice packs are applied for pain relief. There are no studies to determine whether the application of heat or cold is efficacious in relieving pain. We conducted a randomized study to evaluate hot versus cold therapy for the treatment of pain from jellyfish stings.

	Methods: After obtaining verbal informed consent, the patients or health care professionals were instructed to apply 5% acetic acid and to remove adherent tentacles. On odd days, instructions were provided for immersion of the envenomated area in hot water. On even days, instructions were provided for the application of cold packs. Followup calls at I, 4, and 24 hours were made to collect data about the duration and intensity of pain, and the need for rescue analgesics or antihistamines. Results There were a total of 27 patients with jellyfish stings enrolled in the study. Eighteen patients were treated with hot water. Sixteen of these patients reported pain relief within 60 minutes of the initiation of therapy. 2 patients were excluded because of protocol violations. Nine patients were treated with application of ice packs. Five reported pain relief within 60 minutes of the initiation of therapy, 3 patients failed to obtain pain relief with ice packs and experienced pain relief with immersion in hot water. One patient was excluded because of a protocol violation. Conclusion: Immersion of the jellyfish envenomated region in hot water (110°F) was statistically more effective ($p < 0.05$) then the application of ice packs for analgesia. *110 degrees Fahrenheit = 43.3 degrees Celsius* *Same temperature as (15)*
28. *(1)*	Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK. A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings. Medical Journal of Australia 2006;184(7):329-33. II; Good; Supportive OBJECTIVE: 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 : 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 *Dates of trial December 2003 – February 2005* *Refers to Moritz (see below) to claim support for the safety of the temperature used for the shower water.* *If the discussion is to be constrained, the reference to Bucherl (5) should be Halsted (27).* *Reference to Endean (48) probably refers back to Endean (25).*
29. (32)	Mendelssohn K, Rossiter R. Subcutaneous temperatures in moderate temperature burns. Q. J. Exp. Physiol. 1944;32(4):301-308. Other AMS; Fair; Supportive (safety of 45 degrees C), Neutral (denaturation of venom by heat)

	Lewis and Love (51), using a copper-constantan thermocouple, found that, when a heated copper bar was placed on human skin, the limit of tolerance was 47-48.5° C., corresponding to a subcutaneous temperature of 42-43° C. If, on the other hand, a limb were immersed in warm water, the tolerance limit was 45-47° C. (52). At 43-44° C, with a subcutaneous temperature of 37-40° C., there was a flushing of the skin, and 51-52° C: (subcutaneous temperature of 42° C.) produced blistering and wheal formation. Westermark (1927] heated the skin of animals with high frequency currents and recorded the intracutaneous temperature. Rats tolerated 45° C. for 1 1/2 hours and 46° C, for1 hour, but 46° C. for 11/2 hours gave "obvious necrosis." For the pig (? guineapig), 50° C for 4 minutes was without effect, while 50° C. for 8 minutes produced necrosis. Details of these experiments are very meagre. These findings enable us to state to within what limits of temperature the cells of the skin must be subjected, to produce certain of the changes previously observed. This temperature must be intermediate between that of the burning iron and that of the under surface of the skin. Erythema is produced when the cells of the skin are heated to some temperature between 40° and 50°C. Irreversible destruction, characterized- by persistent erythema, flare, slight oedema, scabbing, loss of basophil properties and escape of a pyronin-staining substance from the cytoplasm of the epithelial cells and of nucleoprotein from their nuclei, occurs at temperatures between 45° and 55° C. Massive oedema, separation of the epidermis and coagulation of the epithelium occurs between 50° and 60° C. That irreversible damage is sustained (i.e. cells are killed) between 45° and 50° C. brings skin tissue into line with the observations of other Workers on the ability of living tissues generally to withstand heat (32): An important feature of this study is that it forms a basis for the correlation of "in vitro" enzyme studies, now proceeding, with the conditions actually occurring in the heat-damaged epithelial cell.
30. *(18)*	Moritz AR, Henriques FC. Studies in thermal injury II: the relative importance of time and surface temperature in the causation of cutaneous burns. Am. J. Pathol. 1947;23:695-720. IV; Poor; Neutral *The greater part of this work was done on pigs with some experimentation on humans (pp707-710) with 33 exposures.* *It was noted that, p710, that " '*Discomfort in the form of a stinging sensation occurred between 47.5 and 48.5 degrees Celsius and was felt more intensely by some subjects than by others." *In the porcine model, three experiments were conducted at 46 degrees Celsius for 45, 60 and 90 minutes exposure. The first two produced hyperaemia while the third produced complete epidermal necrosis.* *The tabled results show that three human subjects had small areas exposed on seven occasions to temperatures of 44 (four subjects) and 45 (three subjects) degrees Celsius for between two and six hours. Four events showed epidermal destruction - two at 44 degrees Celsius and two at 45 degrees Celsius.*
31. *(16)*	Nomura JT, Sato RL, Ahern RM, Snow JL, Kuwaye TT, Yamamoto LG. A randomized paired comparison trial of cutaneous treatments for acute jellyfish (*Carybdea alata*) stings. American Journal of Emergency Medicine 2002;20(7):624-6. III-1; Poor; Neutral Abstract: The objective of the study was to compare cutaneous treatments (heat, papain and vinegar) for acute jellyfish (*Carybdea alata*) stings. Healthy adult volunteer subjects received a single-tentacle jellyfish sting on each forearm. One forearm was treated with hot-water immersion (40-41 degrees C). This was compared with the other forearm, which was randomized to a comparison treatment of papain meat tenderizer or vinegar. Pain was measured at 0, 2, 4, 6, 8, 10, 15, and 20 minutes using a 10-cm visual analog scale (VAS). For 25 subject runs, the average VAS scores at t = 0 were 3.6 cm (hot water) and 3.7 cm (comparison treatment). At t = 4 minutes (2 minutes after treatment had started), the

	differences between hot-water and comparison group VAS scores were 2.1 cm versus 3.2 cm, respectively. The mean difference between hot-water and comparison treatments was 1.1 cm (95% confidence interval, 0.6 to 1.6). At t = 20 minutes (the end of the study period), the differences between hot-water and comparison group VAS scores were 0.2 cm versus 1.8 cm, respectively. The mean difference between hot-water and comparison treatments was 1.6 cm (95% confidence interval, 0.9 to 2.3). This study suggests that the most efficacious initial treatment for *C. alata* jellyfish envenomation is hot-water immersion to the afflicted site. *Dates of trial not stated.* *Note temperature 40-41 degrees Celsius* *Limited to Carybdea alata*
32. *(17)*	Peca G, Rafanelli S, Galassi G, Di Bartolo P, Bertini S, Alberani M, et al. Contact reactions to the jellyfish *Carybdea marsupialis*: observation of 40 cases. Contact Dermatitis 1997;36(3):124-6. IV; Poor; Neutral Abstract: Warm salty water, in eight patients, was associated with pain relief in about thirty minutes. A vinegar pack was applied, for 15 minutes, to 20 patients, and resulted in disappearance of symptoms in 20% and improvement in 80%. Alcohol gave similar results. *Dates of trial : July – September 1994* *No indication of water temperature*
33. *(38)*	Rifkin J. Jellyfish mechanisms. In: Williamson J, Fenner P, Burnett J, Rifkin J, editors. Venomous and poisonous marine animals: Medical and biological handbook. First ed. Sydney: University of New South Wales Press; 1996. p. 164-165. Other RCCP; Poor: Opposing The author advocates that "neither fresh nor sea water should be used to remove tentacles" but also notes "Although initial in vitro studies by the author showed that water did not cause a discharge in *C. fleckeri* or *Physalia* nematocysts, nematocysts within detached tentacles are still very reactive to… contact-chemical stimuli..".
34. *(9)*	Rifkin J, Endean R. The structure and function of the nematocysts of *Chironex fleckeri Southcott*, 1956. Cell & Tissue Research 1983;233(3):563-77. Abstract: Microbasic p-mastigophores, euryteles of two size groups, holotrichous isorhizas and atrichous isorhizas, comprise the cnidom of *Chironex fleckeri*, a cubozoan that has been responsible for several human fatalities. In its undischarged state each microbasic mastigophore of *C. fleckeri* consists of a capsule containing matrix and an inverted tube possessing a smooth-walled butt which is loosely coiled helically and which narrows to form a thread that is tightly coiled helically and markedly pleated. Both butt and thread carry three helices of spines and contain a granular matrix. During discharge, the proximal butt spines form initially a piercing stylet. Granular material from the butt and thread is released prior to the release of capsular material. Each eurytele possesses a tube with a butt composed of three bulbs, the middle bulb bearing long spines. Each holotrichous isorhiza possesses a coiled tube bearing small spines along its length. Each atrichous isorhiza exhibits a tube that is devoid of spines and loosely folded in the undischarged condition. The probable role of each type of nematocyst is inferred from its structure and features that enable the ready separation of the nematocysts of *C. fleckeri* from those of scyphozoan jellyfish are discussed. *Referred to by Bailey (22) on the matter of venom delivery for Chironex fleckeri, states that venom "is most likely introduced directly into blood vessels". This seems to be an erroneous reference.*
35. *(4)*	Rifkin J, Williamson J, Fenner P. Anthozoans, hydrozoans and scyphozoans. In: Williamson J, Fenner P, Burnett JW, Rifkin J, editors. Venomous & Poisonous Marine Animals; A medical & biological handbook. Sydney: University of New

	South Wales Press; 1996. p. 180-235. Other RCCP; Poor; Opposing pp198-9 Burnett, J & Fenner, P *Physalia Physalis* (Portuguese man-o'-war) "The local application of heat does not offer pain relief (BURNETT, FENNER, WILLIAMSON 1992, unpublished observations) and carries the possibility of increased venom uptake in the vaso-dliated tissues."
36. *(29)*	Rottini G, Gusmani L, Parovel E, Avian M, Patriarca P. Purification and properties of a cytolytic toxin in venom of the jellyfish *Carybdea marsupialis*. Toxicon 1995;33(3):315-26. Other IVS; Good; Neutral Abstract: A haemolytic toxin was purified by ion-exchange chromatography and FPLC gel filtration from the nematocysts of the jellyfish *Carybdea marsupialis*. Sheep red cells, but not human or rabbit red cells, were susceptible to lysis by the toxin. The toxin is a protein with an apparent molecular mass of about 102-107 kDa, is heat labile, highly unstable in polar media, inactivated by reducing agents, and devoid of phospholipase activity. The experimental data speak in favour of a pore-forming mechanism of toxin action. p319. "The stability of CARTOX (the purified cytolytic toxin from *Carybdea marsupialis*) was temperature dependent, with a half-life ...about 1 min at 60 degrees Celsius)". *Yoshimoto (20) notes that in this trial there was no testing at a temperature suitable for human treatment.*
37. *(42)*	Russell FE. *Physalia* stings: a report of two cases. Toxicon 1966;4(1):65-7. Other CR; Poor; Opposing *Two case reports from Florida of physalia stinging with contrasting treatments including, inter alia, fresh water versus salt water. Refers to Barnes (53) and advocates " Pour ocean water over the injured parts. Do not use fresh water." No evidence.*
38. *(33)*	Saria A. Substance P in sensory nerve fibres contributes to the development of oedema in the rat hind paw after thermal injury. Br. J. Pharmacol. 1984;82(1):217-22. Other AMS; Fair; Supportive Abstract: Immersion of the hind paws of anesthetized rats in hot water for 5 min induced massive plasma protein leakage as indicated by extravasation of Evans blue dye in the skin. The threshold temperature which caused noticeable plasma extravasation was 45 degrees C, a maximal response was obtained between 55 degrees C and 60 degrees C. Pretreatment of rats 2 days after birth with 50 mg kg-1 capsaicin significantly reduced the Evans blue extravasation induced by hot water at 50 degrees C and 60 degrees C, whereas guanethidine pretreatment 24 h before the experiment caused a significantly increased response at 40 degrees C, 45 degrees C and 50 degrees C. When Evans blue was injected between 10 and 120 min after immersion of the paw in hot water, a significant extravasation of the dye was no longer detectable. However, the weight of the paw as well as the weight of the piece of skin taken for Evans blue quantification increased during this period indicating the progressive development of oedema in the skin and underlying tissues. In rats treated with capsaicin as neonates, the increase in paw weight after immersion in water of 50 degrees C for 5 min was significantly delayed during the first hour, but there was no difference after two hours. In rats pretreated with D-Arg1,D-Pro2-,D- Trp7 ,9, Leu11 -substance P, a substance P (SP) antagonist, the Evans blue extravasation was significantly reduced. However, the response, which remained in rats treated with capsaicin as neonates was not blocked by the SP-antagonist.(ABSTRACT TRUNCATED AT 250 WORDS)

39. *(44)*	Stein MR, Marraccini JV, Rothschild NE, Burnett JW. Fatal Portuguese man-o'-war (*Physalia physalis*) envenomation. Ann. Emerg. Med. 1989;18(3):312-5. Other CR; Poor; Opposing Abstract: A fatal case of *Physalia physalis* (Portuguese man-o'-war) envenomation occurred on the Florida Atlantic coast in 1987. Despite appropriate beachside first aid, the patient was conscious only several minutes before having primary respiratory arrest and, later, cardiovascular collapse that resulted in death. Discharged nematocysts were still visible on the injured stratum corneum five days after envenomation. Additional treatment maneuvers suggested by this case include testing the tentacle fragments found on the victim's skin before their removal to ensure that nematocyst firing has been counteracted. We document the first human fatality caused by *P. physalis* envenomation. *P314/133* "Hot compresses are contraindicated because they increase systemic uptake of venom. In one incident, visible erythematous lymphangitic spreading up an extremity was observed after hot compresses. Cold compresses appear to be ineffective." *This presumably also refers to the incident recorded by Burnett (45) (46).*
40. *(10)*	Strutton G, Lumley J. Cutaneous light microscopic and ultrastructural changes in a fatal case of jellyfish envenomation. J. Cutan. Pathol. 1988;15(4):249-55. Abstract: A 5-year-old male suffered fatal envenomation from a jellyfish subsequently identified as *Chironex fleckeri*. Contact with the tentacles of the jellyfish had produced characteristic whiplash-like weals on the skin. At autopsy, skin from these areas was taken and later studied by light microscopy and electron microscopy. Both studies identified numerous nematocysts penetrating the epidermis and papillary dermis in the region of the sting.
41. *(21)*	Taylor J. Treatment of jellyfish stings. Med J Aust 2007;186(1):43. Level IV; Poor; Neutral "An experiment was recently conducted during a morning doctor's seminar at the Busselton Hospital to assess four treatments for jellyfish stings using specimens of *Carybdea* species collected from the nearby waters of Geographe Bay. Two doctors and three medical students consented to participate. The tentacles of the jellyfish were dragged over the moistened forearm, producing two well separated stings on each forearm. After 5 minutes, there were visible red wheals developing at the sting sites. Four different treatment modalities were then tried, one at each sting location: ice, vinegar, aluminium sulfate, and hot water at about 45°C. The participants were asked to assess the degree of pain relief given by the treatment, and the time taken to achieve that pain relief (Box). Hot water was the only successful treatment, relieving 88% of the pain; all participants obtained significant relief in 4–10 minutes. Other treatments were incomplete and temporary. Hot water was later used to treat the other stings." *No details of how hot water applied or how temperature regulated.*
42. *(15)*	Thomas CS, Scott SA, Galanis DJ, Goto RS. 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.(50). Hawaii Medical Journal 2001;60(4):100-7. III-1; Poor; Neutral

	Abstract: The study measured the analgesic effect of hot and cold packs on box jellyfish (*Carybdea alata*) stings to Waikiki swimmers at the beach. Analysis of data showed a minimal trend toward pain relief 10 minutes after the application of hot packs, particularly when the initial pain was mild to moderate. Cold packs showed no clinically significant relief of pain, compared to the control. Data tracking shows that most box jellyfish appear in Waikiki waters on the 9th or 10th day after the full moon. "Because of these results, the authors recommend that all box jellyfish stings be sprayed liberally with vinegar, but that neither hot nor cold packs be applied routinely". *Trial dates 1997-1999 Hot packs at 110 degrees Fahrenheit (43.3 degrees Celsius)* *Limited to Carybdea alata*
43. *(11)*	Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. Toxicon 2006;48(7):830-59. The seas and oceans around Australia harbour numerous venomous jellyfish. *Chironex fleckeri*, the box jellyfish, is the most lethal causing rapid cardiorespiratory depression and although its venom has been characterised, its toxins remain to be identified. A moderately effective antivenom exists which is also partially effective against another chirodropid, *Chiropsalmus* sp. Numerous carybdeids, some unidentified, cause less severe illness, including *Carybdea rastoni* whose toxins CrTX-A and CrTX-B are large proteins. *Carukia barnesi*, another small carybdeid is one cause of the 'Irukandji' syndrome which includes delayed pain from severe muscle cramping, vomiting, anxiety, restlessness, sweating and prostration, and occasionally severe hypertension and acute cardiac failure. The syndrome is in part caused by release of catecholamines but the cause of heart failure is undefined. The venom contains a sodium channel modulator. Two species of *Physalia* are present and although one is potentially lethal, has not caused death in Australian waters. Other significant genera of jellyfish include *Tamoya, Pelagia, Cyanea, Aurelia* and *Chyrosaora*.
44. *(2)*	Totton A. Studies on "*Physalia physalis*" (L). Part 1. Natural history and morphology. Discovery Reports 1960;30:301-368.
45. *(12)*	Turner B, Sullivan P. Disarming the bluebottle: treatment of *Physalia* envenomation. Medical Journal of Australia 1980;2(7):394-5. Compares methylated spirits, vinegar and Stingose in the treatment of *Physalia physalis*. Highlights fact that methylated spirits causes nematocyst discharge.
46. *(20)*	Yoshimoto CM, Yanagihara AA. Cnidarian (coelenterate) envenomations in Hawai'i improve following heat application. Transactions of the Royal Society of Tropical Medicine & Hygiene 2002;96(3):300-3. IV; Poor; Neutral Abstract: A retrospective review of medical records from 113 patients with cnidarian stings in western O'ahu, Hawai'i, was conducted for the 5-year period 1994-98. The most common clinical feature was acute local pain, but cases of anaphylaxis or anaphylactoid syndrome and a persistent or delayed local cutaneous syndrome were also documented. Six cases resembled the Irukandji syndrome described from northern Australia, characterized by severe pain and signs of catecholamine excess, including muscle cramping, elevated blood pressure, diaphoresis, and tremor. Treatment with heat application, usually by means of a whole-body hot shower, appeared to provide better clinical improvement than parenteral analgesics or tranquillizers, particularly in patients with the Irukandji-like syndrome. The heat sensitivity of one or more of the *Carybdea alata* venom components might account for the effect of heat treatment. Prospective, randomized, controlled clinical trials should be performed to assess heat treatment for cnidarian envenomation. *Retrospective review 1 January 1994 – 31 December 1998* *Temperature of hot water unspecified* *No differentiation of jellyfish types although expected to be Carybdea alata or Physalia physalis*

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