Evidence-Based Treatment of Jellyfish Stings in North America and Hawaii

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We performed a systematic review of the evidence supporting various treatments for envenomation by jellyfish (cnidarian) and related organisms in North America and Hawaii. Our review produced 19 pertinent primary articles. Current research demonstrates variable response to treatment, often with conflicting results according to species studied, which contributes to considerable confusion about what treatment is warranted and efficacious. Our review suggests that vinegar causes pain exacerbation or nematocyst discharge in the majority of species. Hot water and topical lidocaine appear more widely beneficial in improving pain symptoms and are preferentially recommended. Unfortunately, they may be difficult to obtain at the site of envenomation, such as the beach or diving sites. In these instances, removing the nematocysts and washing the area with saltwater may be considered. If the envenomation is thought to be due to the bluebottle (*Physalia*), vinegar may be beneficial. [Ann Emerg Med. 2012;xx:xxx.]

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INTRODUCTION

Coastal regions throughout the world report jellyfish stings; only lethal envenomations receive popular-media attention. Although most serious envenomations occur in the waters of the Indo-Pacific region, North American and European waters also provide a habitat for jellyfish, with stings reported.[1-3] In August 2007, San Diego, CA, lifeguards estimated 200 jellyfish stings citywide per day.[4] Even nonfatal jellyfish stings can be extremely painful.[5,6] Occasionally, anaphylaxis and death occur.[3,7]

Proposed treatments for jellyfish envenomation include dilute acetic acid (vinegar), warm urine and ammonia, hot water, sodium bicarbonate (baking soda), and meat tenderizer (papain or bromelain).[8,9] More recently, dilute solutions of local anesthetics (eg, benzocaine, lidocaine) have been recommended as treatment to relieve the pain of jellyfish stings.[10] The rationale for these remedies has been based on the prevention of further envenomation and the inhibition of pain or further tissue destruction. We review and summarize evidence supporting treatment effectiveness for North American and Hawaiian jellyfish stings.

MATERIALS AND METHODS

We considered all English-language studies pertinent to true jellyfish (Cnidaria), box jellyfish, and *Physalia* species commonly found in North American and Hawaiian waters addressing treatment of patient complaints or animal models of nematocyst discharge or extrusion of venom. Previous review articles were reviewed for original research citations. All interventions directed at pain relief, prevention of nematocyst discharge, or extrusion of venom were considered. Outcome measures included resolution of pain or erythema associated with envenomation, discharge of nematocysts, and extrusion of venom.

The following databases were searched: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Reviews, and Google Scholar for relevant trials (published, in press, or in progress) with a methodology consistent with Cochrane Highly Sensitive Search Strategy adapted as needed. No publication-date limit was used. Search terms used were “jellyfish AND envenomation,” “jellyfish AND sting,” “jellyfish AND treatment,” “jellyfish AND nematocyst AND discharge,” and (jellyfish OR cubozoan OR cnidaria OR physalia OR ”Portuguese man-o-war” OR “sea nettle”) AND (pain OR treatment OR vinegar OR ammonia OR heat OR water OR nematocyst). Additional articles were obtained from referenced studies generated by this database search and meeting the inclusion criteria described previously.

Data Collection and Processing

All identified studies were independently reviewed, and consensus was reached by 2 study authors (N.T.W., M.A.D.) about inclusion criteria (Cohen’s ê=0.94). Included studies were assessed independently by the 2 reviewers for adequacy, blinding, randomization, intervention, primary and secondary outcome measures, and bias with a standardized form for data abstraction. Disagreements were discussed and arbitrated to form consensus. Unanimity was reached for all articles included. The following characteristics of included trials were prespecified as potential sources of heterogeneity: species studied, Agency for

Healthcare Research and Quality level of evidence, intervention(s) studied, sample size, patient population, and defined outcome measure. Sources of heterogeneity were explored as explanations for variations in effect between trials and to guide interpretation of the findings.

RESULTS

Initial queries generated 9 published studies that met inclusion criteria of 2,040 potential articles generated by database search. An additional 10 articles were obtained as references, to yield 19 articles meeting inclusion criteria. Results are presented by Agency for Healthcare Research and Quality level of evidence.[11]

One randomized controlled trial and 1 randomized paired comparison trial have been published on *Carybdea* spp (Hawaiian box jellyfish). The results are summarized in Table 1. Two randomized controlled trials and 1 prospective randomized crossover trial have been published addressing the treatment of *Physalia* spp (Portuguese man-o'-war).

Thomas et al[12] measured the analgesic effect of hot and cold packs on Hawaiian box jellyfish (*Carybdea alata*) stings (accidental) in 133 swimmers in Hawaii. Although not known for lethality, *Carybdea alata* sting can cause significant pain, lasting from 20 minutes to 24 hours before resolving spontaneously.[12] Heat reduced pain scores by 5 and 10 minutes after application. There was a significantly higher odds ratio (5.2; 95% confidence interval 1.3 to 22.8) for complete cessation of pain with heat compared with placebo. Poor randomization technique because of practical difficulties, inadequate blinding, altered outcome measures after trial initiation (changed definition of pain cessation), and analysis not based on intention to treat are limitations.

In a follow-up study, Thomas et al[13] measured the analgesic effect of Adolph's (Trumball, CT) meat tenderizer (N=14), freshwater (N=19), seawater (N=16), and aerosolized Sting-Aid (mixture of water, detergent, and aluminum sulfate; N=13) on Hawaiian box jellyfish (*Carybdea alata*) accidental stings in 62 swimmers in Hawaii. Serial pain measurements were recorded with a visual analog scale. No significant differences were found in odds of pain cessation among these 4 treatment groups. Poor randomization technique because of practical difficulties, significant loss to follow-up during a 10-minute period, and lack of identification of jellyfish species causing sting are limitations.

Nomura et al[14] compared hot water immersion with what was considered standard therapy, papain and vinegar, for acute Hawaiian box jellyfish (*Carybdea alata*) stings. Study design included a randomized paired controlled trial of 25 volunteers. Both arms of each volunteer were stung, with one arm treated by hot (40°C to 41°C) water immersion and the other with either vinegar (5% acetic acid) immersion or papain (Adolph's meat tenderizer) in a 4:1 ratio with water. The authors observed that pain scores on a visual analog scale were lower with hot water immersion at 4 and 20 minutes. The study supports the use of hot water immersion; however, the control substances used, papain and vinegar, have had mixed recommendations in previous reviews and are potentially active in promoting further nematocyst discharge. Volunteers were asked to gauge pain scores from 2 simultaneous stings, biasing results by distraction.

Loten et al[15] compared hot water immersion (45°C) or ice pack for pain relief in 96 subjects presenting after swimming in the ocean for treatment of an apparent sting by Pacific Ocean *Physalia*. Primary analysis was by intention to treat, with secondary analysis of nematocyst-confirmed stings. Forty-nine patients received hot water immersion and 47 received ice packs. Less pain at 10 and 20 minutes of treatment was reported in the hot water group ($P \leq .002$). Although the study was concluded early because of significant positive results, selection bias about baseline differences in pain severity and inclusion of only patients primarily with severe stings (as opposed to mild or moderate) may have biased results.

Bowra et al[16] compared hot showers and ice packs for the treatment of Pacific Ocean *Physalia* stings, with a crossover design.[16] Fifty-four adults were randomized to hot shower or cold pack. Twenty-four subjects completed crossover between treatments. No significant difference in pain scores between the 2 treatments in each stage was reported. Combined results from both stages showed that hot showers reduced time to complete relief and greater overall pain reduction at 15 minutes (48% versus 29%; $P<.01$). This study lacked blinding and follow-up.

Turner and Sullivan[17] evaluated the efficacy of various treatments for stings by Pacific Ocean *Physalia physalis*. The forearm of 20 volunteers was divided in 4 quadrants to which a tentacle was applied. Vinegar and aluminum sulfate (Stingose; Hamilton Laboratories) significantly reduced pain 15 minutes after application compared with seawater. Methylated spirits caused a significant increase in pain at application. After 5 minutes, vinegar and Stingose were both more effective at relieving pain compared with seawater by 15 minutes. There was no statistical difference between vinegar and Stingose. The study relied on a subjective assessment of pain. Skin reactions were reported but without a description of the method or the results of this assessment.

The results of level 2 evidence, the experimental paired/crossover study, are summarized in Table 2.

Birsa et al[18] conducted a 2-arm study of the effect of various substances on pain and nematocyst discharge. The authors tested the clinical use of the various treatments on themselves (N=2) after stings from tentacle pieces from the sea wasp (box jellyfish), *Chiropsalmus quadrumanus*, and the Atlantic sea nettle, *Chrysaora quinquecirrha*. The authors noted intense stinging pain, with the intensity greater for *Chrysaora quinquecirrha*, lasting approximately 30 minutes and followed by erythema for up to 24 hours. Pain sensation was based on a perceived change in stinging sensation compared with an untreated arm. Deionized water, meat tenderizer, and urea treatments resulted in no noticeable difference in pain sensation, whereas ammonia, ethanol, and acetic acid increased the perception of pain. Lidocaine hydrochloride concentrations of

Table 1. Level 1 evidence: published randomized controlled trials on the treatment of jellyfish envenomation.

Authors	Type of Study (No. of Subjects)	Group	Intervention	Outcome	Comments
Loten et al[15]	Randomized controlled trial (N=96)	*Physalia* spp	Hot water immersion	Reduced pain perception at 10, 20 min: 53% (*P*=.04), 87% (*P*=.002)	Possible allocation bias
			Ice pack	Reduced pain perception at 10, 20 min: 32%, 33%	
Bowra et al[16]	Prospective randomized crossover trial (N=54)	*Physalia* spp	Hot shower	Pain score reduction: 82.1% (*P*<.05)	No blinding. No controls. Crossover in only 24/54 cases. Lack of follow-up.
			Hot shower	Pain cessation: 48% (*P*<.01)	
			Cold pack	Pain cessation: 29%	
			Hot shower	Total treatment time: 11.0 min (*P*<.05)	
			Cold pack	Total treatment time: 14.6 min	
Nomura et al[14]	Randomized paired trial (N=25; 50 stings)	*Carybdea alata*	Hot water immersion	Pain scores at 0, 4, 20 min: 3.6, 2.1 (*P*<.001), 0.2 (*P*<.001)	Potentially active substances (papain or vinegar) used as controls. No placebo.
			Control	Pain scores at 0, 4, 20 min: 3.7, 3.2, 1.8	
Thomas et al[12]	Randomized controlled trial (N=133)	*Carybdea alata*	Hot pack vs cold pack	Pain scores at 0, 5, 10 min: 42.3, 31.3, 27.5 (*P*<.05) vs 38.3, 32.8 (*P*<.05), 36.2	Poor randomization technique because of practicality. Not analyzed on intention-to-treat basis. Inadequate blinding. Altered outcome measures after starting trial (changed definition of pain cessation).
			Cold pack vs placebo	Pain scores at 0, 5, 10 min: 38.3, 32.8 (*P*<.05), 36.2 vs 38.6, 37.7, 38.2	
			Hot pack vs placebo	Pain scores at 0, 5, 10 min: 42.3, 31.3 (*P*<.05), 27.5 (*P*<.05) vs 38.6, 37.7, 38.2	
				Cessation of pain—odds ratio (95% confidence interval):	
			Hot pack	5.2 (1.3–22.8)	
			Cold pack	0.5 (0.1–2.1)	
			Placebo	1.00	
Thomas et al[13]	Randomized controlled trial (N=62)	*Carybdea alata*	Adolph's meat tenderizer (N=14)	40.7, 36.5, 36.9, 38.6*	Logistic regression model to determine odds of cessation of pain after initial dousing with vinegar. No verification of species of sting. No significant difference in pain relief between interventions. Significant loss to follow-up
			Freshwater (N=19)	44.3, 38.9, 34.5, 40.7*	
			Saltwater (N=16)	42.5, 35.2, 28.1, 35.2*	
			Sting-aid (mixture of water, detergent, and aluminum sulfate; N=13)	46.9, 34.2, 35.3, 32.8*	

Table 1. Continued.

Authors	Type of Study (No. of Subjects)	Group	Intervention	Outcome	Comments
Turner and Sullivan[17]	Prospective controlled clinical trial (N=20)	*Physalia* spp	Vinegar	7/28/1/17†	Subjective assessment, no use of visual analog scale. Did not specify how skin reaction was assessed.
			Stingose (20% aluminum sulfate in detergent)	4/19/6/10†	
			Methylated spirits	27/1/17/2†	
			Saltwater	19/9/12/4†	
			Unsure	3/6/4/7†	

*Data are presented as pain scores at 0, 5, 10, and 15 minutes on visual analog scale.
†Data are presented as number of responses: most painful/most relief/most skin reaction/least skin reaction.

Table 2. Level 2 evidence: nonrandomized controlled trials on the treatment of jellyfish envenomation.

Authors	Type of Study (No. of Subjects)	Species	Intervention	Outcome*	Comments
Birsa et al[18]	Controlled crossover (N=2)			Pain intensity after application of chemical	Small sample, author bias, no blinding. Subjective outcome.
		Chiropsalmus quadrumanus	Control (seawater)	0	
			Control (deionized water)	0	
			Lidocaine (5%)	—	
			Lidocaine (10%)	—	
			Lidocaine (15%)	—	
			Benzocaine (5%)	—	
			Benzocaine (10%)	—	
			Ammonia (20%)	+	
			Acetic acid (5%)	+	
			Ethanol	+	
			Bromelain (meat tenderizer)	0	
		Chrysaora quinquecirrha	Control (seawater)	0	
			Control (deionized water)	0	
			Lidocaine (5%)	—	
			Lidocaine (10%)	—	
			Lidocaine (15%)	—	
			Benzocaine (5%)	N	
			Benzocaine (10%)	N	
			Ammonia (20%)	+	
			Acetic acid (5%)	+	
			Ethanol	+	
			Bromelain (meat tenderizer)	0	

*"0"=No apparent change in sting intensity or duration of pain; "-"=noticeable alleviation of pain intensity and duration of pain; "—"=further reduction in pain intensity; "+"=exacerbation of pain intensity; "N"=no test performed.

10% and 15% produced immediate relief from the stinging sensation. The 4% and 5% solutions of lidocaine produced relief after approximately 1 minute, whereas 1%, 2%, and 3% solutions required 10 to 20 minutes before there was noticeable relief. Benzocaine dissolved in ethanol provided some relief from jellyfish sting, but relief from pain took 10 or more minutes. Redness remained on skin after treatment with benzocaine. Minimal redness was observed after higher lidocaine concentrations (4%, 5%, 10%, and 15%). After treatment with acetic acid or ethanol, more areas of redness were observed than on untreated skin. Correlation between the number of nematocysts discharged and the intensity of the pain felt after a particular chemical treatment was described. This clinical assessment was quasi-experimental and limited by a lack of external validity and statistical analysis. Stings on arms were conducted on the authors, raising questions of author bias. Repeated stings were conducted during a month, which may have resulted in desensitization.

The results of level 3 evidence, cases series, are summarized in Table 3.

A retrospective review of medical records from 113 patients (1994 to 1998) with cnidarian stings in western Oahu, HI, was

Table 3. Level 3 evidence: observational studies with controls, case series on the treatment of jellyfish envenomation.

Author	Type of Study (No. of Subjects)	Group	Intervention	Outcome	Comments
Yoshimoto et al[19]	Retrospective case series	Swimmers with jellyfish stings	Heat application	Pain relief in 23/25 cases (odds ratio 11.5; *P*=.08)	Retrospective. No control group.
	60 (113 reviewed)		Hot shower	Pain relief in 22/23 cases (odds ratio 22.0; *P*=.049)	Significant number of incomplete medical records. Stings most likely caused by *Carybdea alata* and *Carybdea rastoni*. *Carybdea* is the most common species in Hawaii.

conducted.[19] The authors observed that the most common presentation 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 stings from jellyfish of northern Australia, characterized by severe pain and signs of catecholamine excess, including muscle cramping, elevated blood pressure, diaphoresis, and tremor. Treatment with heat application (pain relief in 23/25 cases; odds ratio 11.5; *P*=.08), usually by means of a whole-body hot shower (pain relief in 22/23 cases; odds ratio 22.0; *P*=.049), appeared to provide better clinical improvement than parenteral analgesics or tranquilizers, particularly in patients with the Irukandji-like syndrome. The authors suggested that the heat sensitivity of one or more of the *Carybdea alata* venom components might account for the effect of heat treatment.

The results of level 4 evidence (studies without controls, studies based on physiology and basic science, and expert opinion) are summarized in Table 4.

Exton et al[20] evaluated the effect of ice packs on pain resolution after Pacific *Physalia* envenomation. Results suggest that cold packs are effective in alleviating pain after envenomation. However, no controls and no statistical analysis of results were performed.

Birsa et al[18] described the effect of various substances on nematocyst discharge. Solutions of acetic acid (5%), ethanol (70%), ammonia (20%), and bromelain (meat tenderizer) (10%) added to *Physalia physalis* and *Chrysaora quinquecirrha* tentacle suspensions resulted in the immediate discharge of thousands of nematocysts. Meat tenderizer caused the most discharges (112 nematocysts/mm) from *Physalia physalis* tentacles. Ammonia resulted in the most discharges (80 nematocysts/mm) from *Chrysaora quinquecirrha*. Data were analyzed on orders of magnitude difference between chemical treatments. Little or no nematocyst discharge was observed after the addition of seawater, lidocaine (4%), or sodium bicarbonate solutions. Nematocytes exposed first to lidocaine solutions did not discharge nematocysts after subsequent exposure to acetic acid, ethanol, ammonia, or bromelain. The authors recognized that this was at best semiquantitative.

Pressure immobilization bandages have been demonstrated to increase the release of venom from previously discharged jellyfish nematocysts.[21] In vitro, venom beads released from electrically activated *Chiropsalmus* nematocysts were viewed under direct microscopy before and after application of 40 mm Hg pressure. Saline solution washings of discharged nematocysts before and after application of pressure were tested for toxicity, measured by time to ventricular standstill after injecting into live prawns. Applying pressure caused expression of additional venom from the discharged nematocysts and a return of toxicity.

Anionic solutions were found to provoke discharge of box jellyfish nematocysts, whereas cations inhibited discharge.[22] I^- elicited the highest rate of discharge, whereas Cl^- was less effective. Divalent cations such as Ca^+, Ba^+, and Mg^{2+} failed to induce discharge and when added to iodide solutions blocked discharge. The inhibitory effect of Ca^+ and Ba^+ was higher than that of Mg^{2+}.

Burnett et al[23] tested chemicals for nematocyst discharge from *Chrysaora* and Atlantic Ocean *Physalia* spp. Sodium hypochlorite, sodium hydroxide, acetone, vinegar (5%), and ammonia provoked further nematocyst discharge. Stingose (20% aluminum sulfate in detergent) was effective but caused additional stinging when removed by rinsing. Meat tenderizer and papain were beneficial at high concentrations. Baking soda as a slurry in water or powder was a successful prophylactic preparation against nematocyst rupture unless sodium hypochlorite was used as a triggering mechanism. Vinegar and Stingose best prevented *Physalia* nematocyst discharge.

Taylor[24] assessed 4 treatments on 5 subjects for jellyfish stings, using specimens of *Carybdea* spp. Tentacles were dragged over moistened forearms, producing 2 separate stings on each forearm. After 5 minutes, there were visible red wheals developing at the sting sites. Ice, vinegar, aluminum sulfate, and hot water immersion (45°C) were used. The participants were asked to assess the degree of pain relief and the time taken to achieve relief. Hot water was the only successful treatment, relieving 88% of the pain; all participants obtained significant relief in 4 to 10 minutes. Other treatments relieved pain only incompletely or temporarily.

Table 4. Level 4 evidence: studies without controls, studies based on physiology and basic science, and expert opinion on the treatment of jellyfish envenomation.

Authors	Jellyfish Species (No. of Subjects)	Intervention	Outcome	Comments
Uncontrolled studies				
Exton et al[20]	*Physalia* spp (N=143)	Application of cold packs	Results suggest that cold packs are very effective in the treatment of pain	No controls for treatment with ice packs, no statistical analysis of results
Basic science				
Birsa et al[18]	*Chiropsalmus quadrumanus*		Number of discharged nematocysts (number/mm [SD])	No replication, no blinding
		Ethanol (70%)	66 [14]	
		Ammonia (20%)	80 [16]	
		Bromelain (meat tenderizer) (10%)	29 [10]	
		Acetic acid (5%)	5 [11]	
		Seawater	0	
		Urea (10%)	0	
		Lidocaine (4%)	0	
		Lidocaine (4%) followed by addition of acetic acid	0	
		Lidocaine (4%) followed by addition of ammonia	0	
	Chrysaora quinquecirrha	Ethanol (70%)	53 [26]	
		Ammonia (20%)	80 [5]	
		Meat tenderizer (10%)	112 [16]	
		Acetic acid (5%)	100	
		Seawater	0	
		Urea (10%)	0	
		Lidocaine (4%)	0	
		Lidocaine (4%) followed by addition of acetic acid	0	
		Lidocaine (4%) followed by addition of ammonia	0	
Pereira et al[21]	*Chiropsalmus* spp		Change in bead of venom	
		Application of 40 mm Hg pressure to discharged nematocysts after electrical stimulation	Increased in size	
			Time to ventricular standstill in prawns, s	
		After first washing with 2 mL isotonic saline solution after activation of the nematocysts	60	
		After second washing with 2 mL isotonic saline solution after activation of the nematocysts	540	
		Two washings followed by application of 40 mm Hg pressure	180	

Table 4. Continued.

Authors	Jellyfish Species (No. of Subjects)	Intervention	Outcome	Comments
Salleo et al[22]	*Pelagia noctiluca*		**Percentage of nematocysts discharged by 15 min in ionic solutions at 533 nM (SD) (article also gives results at 266.5, 106.6, and 53.3 nM)**	I^- elicited the highest rate of discharge, whereas Cl^- was less effective. SO^{4-} induced a very slow response. Divalent cations such as Ca^+, Ba^+, and Mg^{2+} not only failed to induce discharge but also, when added to iodide solutions, blocked the discharge effect of the latter. The inhibitory effect of Ca^+ and Ba^+ was higher than that of Mg^{2+}.
		Choline-Cl	24.69 [6.6]	
		KCl	25.79 [8.4]	
		NaCl	26.09 [8.8]	
		LiCl	18.48 [4]	
		CsCl	27.59 [6.6]	
		KI	55.98 [6.6]	
		NaI	50.09 [6.7]	
		K_2SO_4	3.91 [0.8]	
		Na_2SO_4	7.08 [1.6]	
		$(NH_4)_2SO_4$	1.73 [1.3]	
		$CaCl_2$	0	
		$BaCl_2$	0	
		$MgCl_2$	0	
Burnett et al[23]			**Results from addition of test material**	
	Chrysaora quinquecirrha	Acetone	Discharge	
		Sodium hypochlorite	Discharge	
		Acetic acid (5%)	Discharge	
		Household ammonia (diluted <1:15)	Discharge	
			Results from addition of material known to induce discharge, followed rapidly by test material	
		Acetone	Discharge	
		Sodium hypochlorite	Discharge	
		Acetic acid (5%)	Discharge	
		Household ammonia (diluted <1:15)	Discharge	
		Stingose (20% aluminum sulfate in detergent)	Inhibition of discharge	
		Adolph's meat tenderizer	At high concentrations partially digested tentacle and blocked discharges if removed by washing. At lower concentrations did not inhibit.	

Table 4. Continued.

Authors	Jellyfish Species (No. of Subjects)	Intervention	Outcome	Comments
		Papain	At high concentrations partially digested tentacle and blocked discharges if removed by washing. At lower concentrations did not inhibit.	
		MgCl solution	Discharge	
		Baking soda slurry (50% w/v)	Inhibition of discharge. Possible dissolution of tentacle.	
	Physalia physalis	0.1-N NaOH	Discharge	
		Sodium hypochlorite	Discharge	
		Acetic acid (5%)	Inhibition of discharge	
		Baking soda slurry (50% w/v)	Discharge	
		Stingose (20% aluminum sulfate in detergent)	Inhibition of discharge	
Case reports				
Adiga[54]	*Physalia* spp		Case report of brachial artery spasm, which followed a probable second contact with *Physalia*. Intra-arterial injection of reserpine relieved the spasm and a proposed sympathectomy was avoided.	
Gollan[55]	*Physalia* spp		Young man in Western Australia collapsed 15 min after a sting attributed to *Physalia*. Breathing stopped, heart sounds undetectable, pupils dilated and unreactive to light. Responded dramatically to an intravenous injection of antihistamine and recovered. There may have been allergic basis to this severe reaction because 12 years before, the patient had developed facial swelling when swimming in a presumably tidal river.	
Expert opinion/ letter to the editor/description of unpublished study				
Taylor[24]	*Carybdea* spp		Experiment conducted during a morning physician seminar to assess 4 treatments: ice, vinegar, aluminum sulfate, and hot water at about 45°C for stings, using specimens of *Carybdea* spp. Hot water was the only successful treatment, relieving 88% of the pain; other treatments were incomplete or temporary.	

Table 4. Continued.

Authors	Jellyfish Species (No. of Subjects)	Intervention	Outcome	Comments
Burnett et al[5]	*Physalia* spp		Vinegar is an effective agent against Atlantic Coast *Physalia* organelles in the laboratory and is therefore routinely applied in first aid even though benefit may be marginal. *Physalia utriculus*, *Physalia physalis*, and a larger form can be found in the waters of Queensland. Vinegar appears to inhibit discharge in the first 2 but stimulates firing in the latter. Because it is unlikely that swimmers would know what species of *Physalia* stung them, there is not sufficient evidence to support its use clinically.	
			Case of one of the researchers being stung by Atlantic Coast *Physalia*; hot water immersion did not alleviate symptoms and was discontinued.	
	Chrysaora quinquecirrha		Author has found cold packs to be of marginal use. Heat application unimpressive.	
Fenner et al[48]	*Chiropsalmus* spp		Argued that a study by Pereira et al focused on the risk of extruding more venom but did not assess the benefit of likely venom blockade by pressure bandages. Author argued that bandages could block the systemic absorption. Thus, the proximal-to-distal application of bandages on a vinegar-doused arm should be beneficial even if more venom is extruded.	
Tibballs et al[49]	*Chiropsalmus* spp		Argued against a study by Pereira et al because the study made incorrect assumptions: (1) appreciable number of nematocysts remained in human skin; (2) no attempt to validate prawn bioassay; (3) vinegar was assumed not to protect from further discharge, which has been shown to be species dependent; (4) the effect of pressure immobilization in jellyfish stings remains yet to be determined. Local sequestration of venom may enhance toxin inactivation, as appears to be the case for funnel-web spiders.	

Table 4. Continued.

Authors	Jellyfish Species (No. of Subjects)	Intervention	Outcome	Comments
Exton et al[25]	*Physalia* spp		Description of experiment assessing effectiveness of vinegar in *Physalia* stings. Segments of tentacles were observed under the microscope, and solutions of methylated spirits, vinegar, and water were irrigated separately onto the slides. A scale of 1 to 5 was used to measure nematocyst discharge: 30 replications with methylated spirits, 34 with vinegar, and 20 with water. Average scores of methylated spirits (5), vinegar (2), and water (0). Author concluded that application of vinegar seems to further discharge of nematocysts and should therefore be questioned in treatment of *Physalia* stings.	
Fenner and Fitzpatrick[27]	*Cyanea capiillate*		Described an experiment conducted with the methods developed by Hartwick et al, testing vinegar, methylated spirits, and seawater on nematocyst discharge. Vinegar caused discharge, whereas methylated spirits did not cause appreciable discharge. Specific results were not provided.	
Arnold[28]	*Crysaora* spp		Topical papain effective in reducing pain	
	Physalia spp		Topical papain effective in reducing pain	

Table 5. Strength of evidence for inhibition of nematocyst discharge for various treatments of jellyfish stings in North America and Hawaii.

Species	Treatment	Result	Agency for Healthcare Research and Quality Strength of Evidence	Studies
Chiropsalmus quadrumanus	Acetic acid (5%)	Mild discharge	Level 4	Birsa et al[18]
	Ammonia (20%)	Significant discharge	Level 4	Birsa et al[18]
	Bromelain (meat tenderizer) (10%)	Moderate discharge	Level 4	Birsa et al[18]
	Ethanol (70%)	Significant discharge	Level 4	Birsa et al[18]
	Lidocaine (4%)	No discharge	Level 4	Birsa et al[18]
	Lidocaine (4%) followed by addition of acetic acid	Inhibition of discharge	Level 4	Birsa et al[18]
	Lidocaine (4%) followed by addition of ammonia	Inhibition of discharge	Level 4	Birsa et al[18]
	Pressure (44 mm Hg)	Increased extrusion of venom bead	Level 4	Pereira et al[21]
	Seawater	No discharge	Level 4	Birsa et al[18]
	Urea (10%)	No discharge	Level 4	Birsa et al[18]
Chrysaora quinquecirrha	Acetic acid (5%)	Discharge	Level 4	Burnett et al[23]; Birsa et al[18]
	Acetone	Discharge	Level 4	Burnett et al[23]
	Adolph's meat tenderizer	At high concentrations partially digested tentacle and blocked discharge if removed by washing. At lower concentrations did not inhibit.	Level 4	Burnett et al[23]
	Ammonia	Significant discharge	Level 4	Birsa et al[18]
	Baking soda slurry (50% w/v)	Inhibition of discharge. Possible dissolution of tentacle.	Level 4	Burnett et al[23]
	Sodium hypochlorite	Discharge	Level 4	Burnett et al[23]
	Ethanol (70%)	Significant discharge	Level 4	Birsa et al[18]
	Lidocaine (4%)	No discharge	Level 4	Birsa et al[18]
	Lidocaine (4%) followed by addition of acetic acid	Inhibition of discharge	Level 4	Birsa et al[18]
	Lidocaine (4%) followed by addition of ammonia	Inhibition of discharge	Level 4	Birsa et al[18]
	Bromelain (meat tenderizer) (10%)	Significant discharge	Level 4	Birsa et al[18]
	MgCl solution	Discharge	Level 4	Burnett et al[23]
	Papain	At high concentrations partially digested tentacle and blocked discharge if removed by washing. At lower concentrations did not inhibit.	Level 4	Burnett et al[23]
	Seawater	No discharge	Level 4	Birsa et al[18]
	Stingose (20% aluminum sulphate in detergent)	Inhibition of discharge	Level 4	Burnett et al[23]
	Urea (10%)	No discharge	Level 4	Birsa et al[18]
Cyanea capillate	Acetic acid (5%)	Discharge	Level 4	Fenner and Fitzpatrick[27]
	Methylated spirits	No discharge	Level 4	Fenner and Fitzpatrick[27]
Pelagia noctiluca	Choline-Cl	Induced discharge	Level 4	Salleo et al[22]
	KCl	Induced discharge	Level 4	Salleo et al[22]
	NaCl	Induced discharge	Level 4	Salleo et al[22]
	LiCl	Induced discharge	Level 4	Salleo et al[22]
	CsCl	Induced discharge	Level 4	Salleo et al[22]
	KI	Induced discharge	Level 4	Salleo et al[22]
	NaI	Induced discharge	Level 4	Salleo et al[22]
	K_2SO_4	Induced discharge	Level 4	Salleo et al[22]
	Na_2SO_4	Induced discharge	Level 4	Salleo et al[22]
	$(NH_4)_2SO_4$	Induced discharge	Level 4	Salleo et al[22]
	$CaCl_2$	Inhibition of discharge	Level 4	Salleo et al[22]

Table 5. Continued.

Species	Treatment	Result	Agency for Healthcare Research and Quality Strength of Evidence	Studies
	$BaCl_2$	Inhibition of discharge	Level 4	Salleo et al[22]
	$MgCl_2$	Inhibition of discharge	Level 4	Salleo et al[22]
Physalia physalis	0.1-N NaOH	Discharge	Level 4	Burnett et al[23]
	Acetic acid (5%)	Inhibition of discharge	Level 4	Burnett et al[23,35]
		Moderate discharge	Level 4	Exton et al[25]
	Baking soda slurry (50% w/v)	Discharge	Level 4	Burnett et al[23]
	Sodium hypochlorite	Discharge	Level 4	Burnett et al[23]
	Methylated spirits	Significant discharge	Level 4	Exton et al[25]
	Water	No discharge	Level 4	Exton et al[25]

Exton[25] evaluated the use of ice packs in relieving mild, moderate, and severe pain from verified Pacific Ocean *Physalia* stings. A total of 143 patients were enrolled; 16 were regarded as having severe pain, 45 as having moderate pain, and 82 as having mild pain. One hundred percent of patients with mild pain, 77% with moderate pain, and 62.5% with severe pain had resolution of symptoms after the first application of an ice pack. After a second ice pack application, 98% of patients with moderate pain and 75% of those with severe pain reported the complete resolution of pain. There was no control group or statistical analysis of results.

Using the method of Hartwick et al,[26] Fenner and Fitzpatrick[27] tested vinegar, methylated spirits, and seawater on *Cyanea capillate* nematocyst discharge. Vinegar caused discharge, whereas methylated spirits did not cause appreciable discharge. Specific results were not provided. Arnold[28] reported topical papain to be effective in treating stings from *Crysaora* and *Physalia* species.

LIMITATIONS

We sought to include all studies describing therapy in the treatment of jellyfish species commonly found in North America and Hawaii and included both studies generated by database search and reference review to generate studies for inclusion. We included only English-language studies, and there may exist studies in foreign languages that describe different therapies or support or refute the treatments described herein. This systematic review is similarly limited by publication bias, in which other studies not published may have resulted in different findings or may discuss other therapies not previously described. Similarly, this review is limited by the absence of literature on a large number of jellyfish species, particularly those found on the West Coast of the United States, Mexico, and Canada. These species may respond differently to treatment than those previously studied and described by this review.

DISCUSSION

Current recommended treatments of cnidarian stings involve 2 distinct yet ideally simultaneous strategies. One is to reverse the pain and tissue damage from the venom itself. The second is to prevent further discharge of venom-laden nematocysts to allow their eventual removal intact. Some therapies might be successful at the former but fail or worsen effects with regard to the latter. Different effects across different classes or species of jellyfish may occur. The perfect agent would be readily available, cheap, capable of inactivating venom, and applicable across multiple species of jellyfish and would block further release. Our systematic review produced 19 articles pertinent to treatment of envenomation of jellyfish and related organisms found in North America and Hawaii. Thirteen nonsystematic reviews discussing treatment for envenomation by species found in North America and Hawaii were discovered but not included because they were not primary sources.[29-41]

Evidence supporting various treatments, organized by species, on pain (Table 5) and nematocyst discharge (Table 6) is discussed below.

No article generated by this systematic search directly addresses the effects or methods of tentacle removal. A reasonable assumption is that removal of any remaining tentacles would prevent further discharge and would be an important element in the treatment of envenomation. The method of such removal, however, remains ill defined. Attempted removal may itself cause discharge, with further envenomation and potential worsening of symptoms.

Studies by Hartwick et al[26] suggest that vinegar provides relief from jellyfish stings by preventing further nematocyst discharge or through inactivation of the toxin. These experiments were conducted on the Australian box jellyfish *Chironex fleckeri*, which is not found in North America or Hawaii. Two additional studies support prevention of nematocyte discharge with vinegar.[23,42] One of these studies[42] supported vinegar use for *Olindias sambaquiensis*, a species found only in the western South Atlantic and not in North American or Hawaiian waters. One study supports vinegar use in Pacific Ocean *Physalia physalis* to prevent nematocyst discharge.[23] However, vinegar may cause nematocyst discharge in other North American jellyfish, including Atlantic Ocean

Table 6. Strength of evidence for various treatments of jellyfish stings in North America and Hawaii.

Species	Treatment	Result	Agency for Healthcare Research and Quality Strength of Evidence	Studies
Carybdea alata	Acetic acid (5%)	No or incomplete resolution of pain	Level 4	Taylor[24]
	Adolph's meat tenderizer	No difference in resolution of pain compared with Adolph's meat tenderizer, freshwater, or seawater	Level 1	Thomas et al[13]
	Aluminum sulfate	No difference in resolution of pain compared with Adolph's meat tenderizer, freshwater, or seawater	Level 1	Thomas et al[13]
		No or incomplete resolution of pain	Level 4	Taylor[24]
	Cold pack	No statistical change in pain	Level 1	Thomas et al[12]
		No or incomplete resolution of pain	Level 4	Taylor[24]
	Freshwater	No difference in resolution of pain compared with Adolph's meat tenderizer, aluminum sulfate, or seawater	Level 1	Thomas et al[13]
	Hot water	Pain improvement	Level 1	Thomas et al[12]; Nomura et al[14]
		Pain improvement	Level 4	Taylor[24]
	Seawater	No difference in resolution of pain compared with Adolph's meat tenderizer, aluminum sulfate, or freshwater	Level 1	Thomas et al[13]
Chiropsalmus quadrumanus	Acetic acid (5%)	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Ammonia (20%)	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Benzocaine (5%)	Noticeable alleviation of pain	Level 2	Birsa et al[18]
	Benzocaine (10%)	Noticeable alleviation of pain	Level 2	Birsa et al[18]
	Bromelain (meat tenderizer)	No change in pain	Level 2	Birsa et al[18]
	Deionized water	No change in pain	Level 2	Birsa et al[18]
	Ethanol	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Lidocaine (5%)	Noticeable alleviation of pain	Level 2	Birsa et al[18]
	Lidocaine (10%)	Further reduction in pain alleviation	Level 2	Birsa et al[18]
	Lidocaine (15%)	Maximum observed reduction in pain	Level 2	Birsa et al[18]
	Pressure	Expert opinion proximal-to-distal application of pressure immobilization bandage on vinegar-doused arm should be beneficial even if more venom is extruded.	Level 4	Fenner et al[48]
		Expert opinion proximal-to-distal application of pressure immobilization bandage may improve pain and hasten resolution of symptoms.	Level 4	Tibballs et al[49]
	Seawater	No change in pain	Level 2	Birsa et al[18]
Chrysaora quinquecirrha	Acetic acid (5%)	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Ammonia (20%)	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Bromelain (meat tenderizer)	No change in pain	Level 2	Birsa et al[18]
	Cold pack	No or incomplete resolution of pain	Level 4	Burnett et al[35]
	Deionized water	No change in pain	Level 2	Birsa et al[18]
	Ethanol	Exacerbation of pain intensity	Level 2	Birsa et al[18]
	Hot water	No or incomplete resolution of pain	Level 4	Burnett et al[35]
	Lidocaine (5%)	Noticeable alleviation of pain	Level 2	Birsa et al[18]
	Lidocaine (10%)	Further reduction in pain alleviation	Level 2	Birsa et al[18]
	Lidocaine (15%)	Maximum observed reduction in pain	Level 2	Birsa et al[18]
	Papain	Reduction of pain	Level 4	Arnold[28]
	Seawater	No change in pain	Level 2	Birsa et al[18]

Table 6. Continued.

Species	Treatment	Result	Agency for Healthcare Research and Quality Strength of Evidence	Studies
Physalia spp	Acetic acid (5%)	Pain improvement	Level 1	Turner and Sullivan[17]
	Antihistamine	Relieved allergic reaction–like symptoms after sting attributed to *Physalia*	Level 4	Gollan[55]
	Cold pack	Pain improvement	Level 1	Loten et al[15]; Bowra et al, 2006[16]
		Pain improvement	Level 4	Exton et al[20]
	Hot water	Pain improvement	Level 1	Loten et al[15]; Bowra et al, 2006[16]
		No or incomplete resolution of pain	Level 4	Burnett[35]
	Methylated spirits	Exacerbation of pain intensity	Level 1	Turner and Sullivan[17]
	Papain	Improvement of pain and symptoms	Level 4	Arnold[28]
	Reserpine	Intra-arterial injection relieved a case of brachial artery spasm after a sting attributed to *Physalia*	Level 4	Adiga[54]
	Stingose (20% aluminum sulfate in detergent)	Pain improvement	Level 1	Turner and Sullivan[17]

Physalia spp, *Pelagia noctiluca*, *Lytocarpus philippinus*, and *Cyanea capillata*.[25,27,36,43]

Burnett et al[23] recommended a baking soda slurry to decrease further nematocyst release. Alcohol, acids, and urea, however, were found to cause nematocyst discharge in several common species of jellyfish, including the sea nettle (*Chrysaora quinquecirrha*), Atlantic Ocean Portuguese man-o'-war (*Physalia physalis*), hydroid (*L philippinus*), and mauve stinger (*Cyanea capillata*).[10,27,43,44]

Pereira et al[21] evaluated the use of pressure immobilization bandages in the prevention of scyphozoan *Chiropsalmus quadrigatus* nematocyst discharge. Pressure immobilization bandages have been demonstrated to increase the release of venoms.[21,45] *Chiropsalmus quadrigatus* is found in the Pacific Ocean from Australia to the Philippines[46] but not commonly in Caribbean and North American waters.[46,47] A letter to the editor in response to Pereira argued that conclusions focus only on the mechanism of extrusion of venom and did not assess likely benefits.[48] Theoretically, bandages block systemic absorption of toxin and thus may be beneficial even if more venom is extruded. Other concerns include the validity of the prawn bioassay used in the Pereira study, assumptions about the effects of vinegar on discharge, and the presence of remaining nematocysts in skin.[48] Local sequestration of venom may in fact enhance toxin inactivation, as appears to be the case for funnel-web spiders.[49,50]

Evidence supports using aluminum sulfate because it may significantly reduce pain in *Physalia physalis* stings,[17] but no or incomplete resolution of pain was found for *Carybdea alata*.[13,24] It is unclear whether aluminum sulfate mixtures inhibit further envenomation, have direct effects on the venom, or inhibit pain sensation. Observed positive effects may be species dependent. More studies in additional species need to be performed.

The concepts underlying preventing further nematocyst discharge are based on 2 significant assumptions. First, it is assumed that symptoms are due to envenomation. Although likely a valid assumption, this has not been tested methodically in the literature reviewed. Second, there is an assumption about correlation between either the degree of pain or the length of time until pain subsides and the total amount of envenomation, degree of nematocyst release, or both. Although this assumption is likely valid, there are no cited references that prove it. Some authors suggest that in most cases, the effect of inhibition would be modest.[5] Our review did not produce any studies on the utility of simple tentacle removal or the incremental benefit of inhibiting discharge before or after removal.

In their characterization of the venom of *Chironex fleckeri*, Baxter and Marr[51] showed that heat, formalin, and Ethylenediaminetetraacetic acid reduced all activities of the venom. This study provides a theoretical basis for hot water immersion therapy. Experimental evidence for North American and Hawaiian species supports this concept because hot water immersion reduces pain from *Carybdea alata* stings,[12, 14, 24] as well as *Physalia physalis*.[15,16,20] Cold packs, however, likely do not significantly alleviate pain.[12,24] Topical vinegar or acetic acid (5%) has demonstrated inconsistent results in treating pain. Vinegar was ineffective for *Carybdea alata* stings,[24] may cause an increased stinging sensation for *Chiropsalmus quadrumanus* and *Chrysaora quinquecirrha* stings,[18] and reduced pain from *Physalia physalis* stings.[17]

Local anesthetics gain access to their blocking site on the sodium channel by diffusing into or through the cell membrane. These anesthetics block sodium channels and thereby the excitability of all neurons, including sensory neurons.[52] The application of local anesthetics would be expected to reduce the local sensation of pain. Lidocaine treatment may result in immediate relief or at least a reduction in the stinging sensation caused by envenomations from *Chiropsalmus quadrumanus* and *Chrysaora quinquecirrha*.[18] Benzocaine dissolved in ethanol may provide some relief from jellyfish stings but may take 10 minutes or longer to do so.[18]

Deionized water, seawater, meat tenderizer, and urea treatment do not appear to produce any noticeable improvement in pain sensation.[17,18] Ammonia, ethanol, and acetic acid may cause an increased stinging sensation.[18] Weak evidence suggests that topical papain alleviates symptoms from stings.[28] However, this result has been previously questioned.[35]

In conclusion, current treatments for jellyfish envenomation demonstrate variable response, with conflicting results between studies and species. A treatment beneficial for one species may in fact worsen an envenomation from another. This contributes to considerable confusion about what treatment is best for stings whether the species is known or unknown.

Our systematic review was unable to find research evaluating the effects of different methods of tentacle removal. It is reasonable to assume that tentacle removal may limit or prevent further discharge of nematocysts. However, physical removal of tentacles may itself result in discharge from physical stimulation. Removal of tentacles with and without therapies designed to inhibit further discharge should be evaluated more completely by further research.

The American Heart Association–American Red Cross International Consensus on First Aid Science With Treatment Recommendations[53] currently advocates vinegar or baking soda slurry followed by the application of heat (or an ice pack if heat is not available) for all jellyfish stings in North America and Hawaii. Our review, however, suggests that vinegar may not be an ideal agent because it causes pain exacerbation or nematocyst discharge in most species except *Physalia*. Hot water and topical lidocaine appear more universally beneficial in improving pain symptoms and are preferentially recommended. However, these treatments are not always available at beach or diving sites. Removing the nematocysts and washing the area with saltwater may be considered. If the envenomation is thought to be due to *Physalia*, vinegar may be beneficial. Additional studies need to be performed to delineate the best treatment for species not previously examined or evaluated, especially those found in North America.

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