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Treatment of Atlantic cnidarian envenomations

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ABSTRACT

Envenomation syndromes induced by Atlantic cnidaria have been tabulated and their therapy discussed. The pharmacokinetics of the venom has been emphasized. Pain occurs instantly and reaches a zenith rapidly in the surf. The nematocysts have already penetrated the dermis and disease proceeds before help can arrive. This fact plus the relative impermeability of human epidermis hampers the efficacy of topical agents. Oral analgesics, the agents of choice, are seldom offered and systemic administration of these drugs is usually not necessary. The use of hot or cold applications has not been settled. Measures to inactivate nematocysts within tentacles adherent to skin post-sting have been demonstrated *in vitro*, but the clinical significance of these actions has not been shown. Using an abrader (sand, crystalline papain) to counter-irritate nearby skin might provide relief. Antivenoms for Atlantic cnidaria are not available. The instances when verapamil might be employed are very rare. The reasons for the increasing case load of these injuries are discussed and the need to discover more effective therapeutic agents is emphasized.

1. Introduction: the problem

Cnidarian envenomations result from the entry of venom coated nematocyst threads into human integument. Since these venoms are composed of a cocktail of multiple proteinaceous toxins which have different pathogenic actions and target many organs the symptoms of envenomations vary. The time course of these disorders depends upon the nature of the venom and its method of introduction into the skin which controls the transit time to the target (i.e. intradermal, intralymphatic, intravenule, intraarterial, subcutaneous or intramuscular). Other factors determining the symptomatology include the volume of the injection, the time of tentacle–skin contact, the health of the victim and the action of skeletal muscle pumps near the sting site. In general, all cnidarian venoms are similar in content and, with few exceptions most cnidarians appear in the Atlantic. The most obvious difference occurs in the Cubozoa or box jellyfish which are less abundant than in the Indopacific and neither *Carukia barnesi*, *Chironex fleckeri* nor the large rhizostome, *Nemopilema nomurai* have yet to be found in the Western hemisphere.

As time passes more envenomation syndromes are revealed, some disorders are attributed to other animals and newly discovered species, inducing sting-related disorders, are identified. Climate change, alteration in ocean currents pathways and turbulence after violent storms can significantly disturb the distribution of various cnidaria. Therefore the caregiver must be familiar with all syndromes, not just those known today in the Atlantic basin. Newer syndromes continuously will appear.

Table 1 lists all known cnidarian envenomation syndromes. It is beyond the scope of this paper to reference the index cases of entities known prior to 1992 since that information can be retrieved in an earlier publication (Burnett, 2001). Only 11 of the total number of cnidarian induced syndromes have not yet been reported from the Atlantic basin. References for the recent cases are listed at the end of this article.

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Table 1
Cnidarian envenomation syndromes.

Local Reactions	
Toxin-induced to skin, mucosa, and cornea	
Exaggerated local reaction (angioedema)	
Recurrent reactions up to four episodes	
Delayed persistent reactions up to several months	
Distant site reactions (1)	
Local lymphadenopathy	
Seabather's dermatitis	
Tremor distally to sting site	
Muscle cramps up to 2 days	
Tongue paralysis with dysphonia (1)[b]	
Facial swelling (1)	
Hemorrhagic bullae	
Fluctuant mandibular swelling (1)[b]	
Diplopia	
Long-term Reactions	
Telangiectasia (1)	
Keloids	
Pigmentation	
Fat atrophy (1)[a]	
Contractions (>4)	
Gangrene (>4)	
Necrosis (1)	
Ulceration	
Vascular spasm (>6)	
Mononeuritis (7)	
Autonomic nerve paralysis (1)[a]	
Ataxia[a]	
Increased ocular pressure (2)	
Mondor's disease (thrombophlebitis) (1)[a]	
Optic neuroretinitis and optic nerve involvement (1)	
Conjunctival scarring with persistent tearing	
Guillain-Barre syndrome (2)	
Limb bluing	
Deep venous thrombosis (1)[a,b]	
Acquired cold urticaria (1)[a,b]	
Ileus (2)[a,b]	
Myocardial infarction (1)[a,b]	
Bladder atonia (2)[b]	
Biliary dyskinesia (1)[b]	
Post-episode Dermatitis	
Herpes simplex (1)	
Granuloma annulare (1)	
Reactions from Jellyfish Ingestion	
Gastrointestinal symptoms	
Urticaria	
Ciguatera-like symptoms (1)[a,b]	
Stomatitis (1)	
Systemic Reactions	
Toxin-induced	
Irukandji reaction	
Respiratory acidosis, pulmonary edema	
Blurred vision (1)	
Monoarticular arthralgia and reactive arthritis	
Pronounced vomiting	
Psychosis, convulsions, coma, stupor[a]	
Fever	
Muscle spasm	
Renal failure (1–5)	
Fatal Reactions	
Toxin-induced	
Immediate cardiac arrest	*Physalia physalis*
Rapid respiratory arrest	*Carukia barnesi*
Delayed renal failure (>5)	*Chiropsalmus quadrimanus*
	Chiropsalmus quadrigatus
Liver destruction (1)	*Sea anemone*
Cerebral vascular accident[a] in Irukandji syndrome (2)	*Carukia barnesi*
Anaphylaxis (1)	

() Indicates number of reported cases.
[a] Indicates entity not reported in the Atlantic basin.
[b] Index cases included in references. All other can be found in Burnett, 2001.

2. Important general concepts

Topical treatment has been offered to control pain and to inactivate unfired nematocysts adhering to the skin after a sting. Both these goals are hampered by time. The victim is usually stung away from shore and pain is perceived instantly. Therefore the venom immediately after the sting is already in the dermis and millions of nematocysts have fired. The caregiver is playing "catch up ball" from which he never recovers. In the instance of pain relief, the epidermis in a superb barrier which has been refined by evolution to keep topically applied medications out. Today the most potent local steroids or anesthetics need well over 30 min to arrive at therapeutic concentrations in the dermal injury site and that early time arrival requires occluding the ointment or cream with plastic wrap. Inhibiting additional adhering nematocyst discharge implies that further firing will significantly exacerbate the disease which began at the instant of tentacle contact – a finding not as yet demonstrated since maximal pain, and thus considerable disease, has occurred during the first minute. The evidence for nematocyst arrest is reported by 2 techniques: microscopic observation of isolated organelles stimulated then blocked by appropriate solutions or microscopic observation of organelles within tentacle fragments similarly treated. The clinical benefit and applicability of such data have been disputed and never documented.

3. Pathogenesis – allergy or toxicity?

Today there has been only one report of proven anaphylaxis following a cnidarian sting (*Pelagia noctiluca* in the Mediterranean Sea). This case was investigated with *Chrysaora* venom as antigen thereby showing that cnidarian venom cross reactivity is possible. Two other victims who were stung in the Chesapeake Bay by *Chrysaora* were partially proven as suspected anaphylaxis (Hartman et al., 1980). We must clearly define anaphylaxis since cnidarian venoms can produce similar shock via toxic means. Proof of anaphylaxis mostly contains evidence of a rise in antigen specific serum IgE, rupture of the victim's basophils by the specific antigen or a positive passive cutaneous anaphylaxis reaction using the appropriate antigen and antibody.

Millions of cnidarian stings have occurred yet no case of confirmed resistance or hypersensitivity to pain with sequential stings has been reported. People continually swim and get stung, yet no disaster has appeared. One can only conclude that anaphylaxis is extremely rare. My current recommendation to bathers severely stung in the

past, if they swim again, is to be judiciously cognizant of all beach warnings.

4. Specific treatment programs

First aid care focuses on maintenance of cardiopulmonary function. The patient should lie down, kept warm and have an open airway. Pulse rate and blood pressure should be stabilized with closed chest massage (Williamson et al., 1996). Reassurance can be initiated to reduce the skeletal muscle pump activity that panic brings. Control of severe pain can only be achieved by parenteral analgesics or narcotics, if available, to stable victims. In American waters cardiovascular compromise is very rare and severe pain uncommon. Therefore oral analgesics like, ibuprofen, acetaminophen or acetylsalicylic acid, which require at least 40 min to become effective, are drugs of choice. They should be promptly administered. The efficacy and practicability of hot or cold packs if available, are still unsolved. Cold and hot temperatures are usually not tolerated by young children who can be susceptible to hypothermia or burning if they are overexposed on a wide skin area for a long time. Hot applications are currently more accepted yet cold packs are also advocated. Anesthetics, such as lidocaine are ineffective, as mentioned above, unless occluded, in which case 40 min will still be required for relief. Toxicity of this agent can occur if it is applied too widely. Topical corticosteroids are ineffective as they will not penetrate the skin in therapeutic concentrations. The use of papain containing meat tenderizers, which are crystalline, is useless because of non-penetration. Many of the other topical popular pain-relief agents fall into the "wives' tale" category. Placebo effects and the benefit of counterirritation may account for the anecdotal benefit of rubbing sand or crystalline papain on normal skin near the sting site.

Topical preparations to prevent adherent nematocyst rupture or to remove tentacles from the skin may or may not be important as mentioned above. Three solutions have been advocated. Ambient water is always safe, vinegar (5% acetic acid) has been used for box jellyfish and *Physalia* stings but a baking soda slurry (50% baking soda: 50% ambient water) has been recommended for *Cyanea*, *Chrysaora* and most common American Atlantic jellyfish located north of Norfolk, VA. Tentacles can be removed manually, remembering to carefully rinse off the caregiver's fingers immediately afterwards, to prevent secondary stings.

5. Fatal reactions

Only 5 proven fatalities have occurred in the Atlantic region: 2 in Florida, 1 each in North Carolina, Texas and St. Thomas. All occurred in 1980–2000 and the first 3 were a result of *Physalia*, 1 due to a box jellyfish and the other exposure to anemones respectively. In mice, and presumably man, deaths due to cardiac malfunction occur within the first few post-sting hours. Respiratory arrest in humans follows within 3–24 h after the accident. Renal damage requires a few days to be fatal and the solitary liver failure fatality developed more than a week after anemone contact. The first aid protocols outlined above for cardiopulmonary maintenance and pain relief should be followed and the severely stung patient transferred to the intensive care in-patient unit. Specific antivenoms are not available for Atlantic cnidarians.

The only unique drugs which could be employed are verapamil which should be reserved for patients with cardiac dysfunction. Cardiac arrhythmias can occur after cnidarian stings (Dubois et al., 1983). Verapamil has been effective in mice, rats and guinea pigs using several different experimental models with *Physalia*, *Chrysaora* and box jellyfish venoms. Conflicting evidence has appeared and both pros and cons discussed (Burnett and Calton, 2004). However, the "con" supporters have not published results following the same procedures advocated by the "pro" side. In Atlantic waters box jellyfish stings are rare and *Physalia* stings usually not severe enough to alter the heart rhythm, thus restricting the use of this agent. In agonal patients with arrhythmias an infusion would be worth a trial and informal discussion with our government officials has indicated that sufficient, supporting, animal research data exists.

Jellyfish venom induced cardiac damage can target the conducting system, the smooth muscle of the coronary arteries or the myocardium (Dubois et al., 1983). One documented acute myocardial infarction occurred in an envenomated diver who survived with conservative management (Salam et al., 2003). This individual had muscle death but patent coronary arteries by angiography indicating that the event could well have been venom induced giving him an excellent future once he survived the acute episode.

Although less than 200 cases of Irukandji syndrome have been reported in the Key West, northwest Cuba and Guadeloupe, none have presented with pulmonary edema, severe hypertension or a cerebral vascular accident (Pommier et al., 2005). Severe cases should receive intravenous magnesium sulfate or phentolamine (Corkeron, 2003; Williamson et al., 1996). The former agent is currently being evaluated in Queensland. Pulmonary edema and heart failure should be treated according to the usual protocols.

6. Long-term reactions

Some of the dermatological problems can be attacked more specifically. Telangiectasias can be removed with fulguration or laser therapy. Keloids require intradermal corticosteroids. Hyperpigmentation should fade in time or its resolution hastened with topical hydroquinone. Fat atrophy usually spontaneously disappears or can be attenuated cosmetically with injected dermal filters. Joint contractions will require plastic surgical repair and/or physical therapy. Gangrene, necrosis and ulceration need debridement with subsequent grafting. Bed rest, elevation and, if on the limbs, pressure bandages are valuable. Vascular spasm of any extremity has successfully been managed with intraarterial urokinase, compartment pressure release or sympathectomy using the Doppler ultrasound examination or arteriography as helpful diagnostic maneuvers (Abu-Nema et al., 1988).

Mononeuritis, autonomic nerve paralyses, tremors, ataxia, muscle cramps, motor weakness, tongue paralysis with dysphonia, peripheral sensory loss and Guillain-Barre syndrome, should be followed and not treated unless physical therapy is indicated (Burnett, 2006a; Pang and Schwartz, 1993). Bladder atonia may need bladder exercises (Burnett, 2006b). Thrombophlebitis requires local heat, analgesia, limb elevation and may be anticoagulation (Al-Ebrahim et al., 1995; Ingram et al., 1992). Paralytic ileus spontaneously remits within hours.

Optic pain due to nematocyst firing into the cornea may be relieved with topical anesthetic salves and patching. Increased intraocular pressure may necessitate pressure lowering eye drops. Topical corticosteroid ophthalmic preparations are used but evidence for efficacy is lacking. Optic neuroretinitis needs referral to a retinal surgeon. Biliary dyskinesia is difficult to evaluate and requires an abdominal surgical consultation (Burnett, 2006b). Cold urticaria is best treated with oral cyproheptadine and perhaps antihistamines.

7. Local reactions

Pain relief has been discussed. Topical wound care requires daily, adequate cleansing. Hemorrhagic bullae may be punctured but the roof left intact and treated as a local wound. Topical antibiotics are not necessary because secondary infection is rare (Oiso et al., 2004; Mandojana, 1987). Incision and drainage of fluctuant lesions may be necessary (Tahmassebi and O'Sullivan, 1998). Local herpes simplex, if primary, should be treated with systemic acyclovir; but if recurrent, emollients above will be sufficient since antivirals are not effective. Granuloma annulare often remits with occlusive potent topical corticosteroids.

Recurrent or long-term episodes similar to the first sting can only be treated similarly to the initial episode if required. The eruption usually causes pruritus, not pain. A localized granulomatous reaction should respond to intralesional corticosteroids. Local lymphadenopathy is an indication of nearby local damage and not treated.

Seabather's eruption is a frustrating pruritic disorder lasting 10–14 days (Wong et al., 1994). It does not respond to potent corticosteroids even if applied under occlusion. Analgesics, antipuritic menthol-containing lotions and sedating antihistamines may be used alone or in any combination. Systemic corticosteroids are not beneficial. The bathing suit worn at exposure needs to be cleansed before future use. Subsequent episodes of this pesky eruption are treated similarly. Recurrent hives in this disorder can be treated as regular hives with antihistamines.

8. Reactions from ingestion

Withdrawal of the offending preparation is the first maneuver. Fluid replacement may be necessary. Topical lidocaine is effective on mucosa as a mouthwash to treat stomatitis. Careful evaluation of the use of antimotility agents should be made. They may relieve cramping but, on the other hand, increase the retention of toxic compounds.

9. Prevention

Prevention of cnidarian stings begins with obeying beach warning signs installed by lifeguards. Swimwear covering exposed body parts is effective as are thick layers of petroleum-based ointment (Burnett et al., 1968). There is no effective topical barrier ointment that is cosmetically attractive. Several recent attempts to produce such a product have failed because they are applied insufficiently. Since the patient is stung away from the beach and thrashes painfully back through the surf, topical ointments wash away before he returns to shore (Burnett, 2005).

10. Conclusions

We are experiencing more serious cnidarian envenomations. Some result from better case reporting, more animals are regarded as venomous, the same disorder resulting from different animals, more people in the water and possible oceanic changes permitting the wider distribution of venomous species. We have now a better understanding of venom toxinology but we need newer, more effective drugs. The research obstacles are the thermolability of the venoms and their increased adherence to inert structures during chemical isolation. Compounding this are the facts that marine venomous animals are difficult to collect and case reporting is suboptimal. Worldwide research funds that could magnify interest in these compounds are sparse. Finally, the victim rarely is injured directly outside a clinical or research institution where prompt patient care with identification and collection of the culprit animal can be documented.

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Conflict of interest

We have no conflicts of interest with any commercial firms.

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