REVIEW ARTICLE

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Scorpion Envenomation

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Every year, more than 1 million cases of scorpion envenomation are reported worldwide.[1] Although the resultant mortality is lower than that from snake envenomation, there is substantial morbidity and, among children, a risk of death. Almost all systemic scorpion envenomation causes pain at the site of the sting. A mixed autonomic excitation (neuroexcitatory) syndrome that is unique to scorpions follows; the syndrome varies in type and severity according to the type of scorpion.[2-4] In addition, a cytotoxic envenomation syndrome has been reported in areas of Iran in which *Hemiscorpius lepturus* is endemic.[5]

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EPIDEMIOLOGY

Although millions of scorpion stings occur annually,[1] most cases are minor, with localized pain and minimal systemic involvement.[6,7] However, severe envenomation is a major public health problem in certain parts of the world — Central and South America, North Africa, the Middle East, and South Asia. Most scorpions that cause serious medical problems belong to the Buthidae family, which includes scorpions from the genera leiurus in the Near and Middle East, androctonus and buthus in North Africa, tityus in South America, centruroides in North and Central America, mesobuthus in Asia (especially India), and parabuthus in South Africa (for further information on several species in these genera, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[1]

In Mexico, probably hundreds of thousands of stings by centruroides scorpions occur each year. Similar numbers of cases occur in other areas where scorpions are endemic (e.g., in Tunisia[2] and other parts of North Africa and in India[8]).

MECHANISMS OF ENVENOMATION AND PATHOPHYSIOLOGY

Scorpions have a stinger (or telson) in their tail (terminal segment) that contains venom glands. The scorpion hooks the tail over its body, which allows the stinger to penetrate the skin and inject venom. Numerous toxins have been identified in scorpion venoms, most of which are small peptide toxins that target ion channels found in both mammals and insects.[9] The toxins that have the greatest medical consequence are the scorpion α-toxins, which consist of 61 to 76 polypeptides that bind to a specific site on the mammalian voltage-gated sodium channel. Once the toxin binds to a site, it inhibits the inactivation of the channel, which results in prolonged depolarization and, hence, neuronal excitation. Other toxins in scorpion venom act on potassium and calcium channels, but these toxins appear to be less important in human envenomation.[9]

Neuronal excitation stimulates autonomic centers, both sympathetic and parasympathetic, which results in autonomic excitation.[9] In addition, scorpion α-toxins cause massive endogenous release of the catecholamines epinephrine and norepinephrine, as well as other vasoactive peptide hormones, such as neuropeptide Y and endothelin-1.[10] As compared with sympathetic effects, parasympathetic effects are

less severe; when they occur, they are often seen soon after the sting, and they may contribute to respiratory impairment. In contrast, the combination of sympathetic excitation and the release of catecholamine in plasma causes the majority of the severe systemic effects, including myocardial injury, pulmonary edema, and cardiogenic shock (Fig. 1). There is an initial increase in blood pressure and cardiac output, followed by decreasing left ventricular function and hypotension. The mechanisms of cardiac dysfunction and pulmonary edema after scorpion envenomation are complex, but they appear to result from a combination of catecholamine-induced myocarditis and myocardial ischemia (coronary vasoconstriction) and, possibly, a direct effect of toxin on the myocardium.[11]

The direct effects of scorpion toxins on the neuronal sodium channels of the somatic and cranial nervous system cause the classic neuromuscular excitation seen after stings by scorpions in the Americas, such as centruroides species. Central nervous system effects are uncommon and are generally related to the effects of severe envenomation because the toxins cannot cross the blood–brain barrier.

CLINICAL MANIFESTATIONS OF SCORPION STINGS

GENERAL CHARACTERISTICS

Despite the variety of scorpions found worldwide, systemic envenomation is characterized by relatively similar neurotoxic excitation syndromes, irrespective of the species, although some differences do exist. Centruroides and parabuthus scorpions are associated primarily with neuromuscular toxicity,[12] whereas severe envenomation from androctonus, buthus, and mesobuthus scorpions is associated with cardiovascular toxicity, which results from hyperstimulation of autonomic centers and the release of catecholamines (Table S1 in the Supplementary Appendix).[2,8]

Most scorpion stings cause localized pain, whereas only an estimated 10% of stings, even from the most dangerous scorpions, result in severe systemic envenomation. Edema, erythema, paresthesias, muscle fasciculations, and numbness may occur at the site of the sting. It is often difficult to see the sting site or to identify inflammation at the site, despite substantial local pain. Most cases of severe envenomation occur in children. Systemic envenomation is characterized by neuromuscular abnormalities resulting from effects on the somatic and cranial nerves, both cholinergic and adrenergic excitation of the autonomic nervous system, pulmonary edema, and cardiac effects (Fig. 1). Most multiorgan clinical manifestations are caused by neuronal excitation and neurotransmitter release. The clinical effects of stings by various genera of scorpions are reviewed elsewhere.[2,4,8,12-16]

AUTONOMIC EFFECTS

Excitation of the autonomic nervous system is characterized by both parasympathetic and sympathetic responses. Parasympathetic, cholinergic effects may include hypersalivation, profuse diaphoresis, lacrimation, miosis, diarrhea, vomiting, bradycardia, hypotension, increased respiratory secretions, and priapism. Sympathetic, adrenergic effects include tachycardia, hypertension, mydriasis, hyperthermia, hyperglycemia, agitation, and restlessness. Whereas most parasympathetic effects tend to occur early, sympathetic effects persist because of the release of catecholamines and are responsible for severe envenomation.

CARDIOVASCULAR EFFECTS

A range of cardiac conduction abnormalities occur in about one third to one half of patients with systemic envenomation. These effects include atrial tachycardia, ventricular extrasystoles, T-wave inversion, ST-T wave changes, and, less frequently, bundle-branch block.[3,15] Increased autonomic stimulation caused by increased vagal effects on the heart and sympathetic stimulation are the probable causes of these effects (Fig. 1).

Hypertension is common and occurs early in response to sympathetic stimulation. Hypotension is less common, occurs with the development of severe envenomation, and often requires intervention with vasopressors and fluid resuscitation. Many factors are at play in the development of hypotension, with cholinergic stimulation causing vasodilation, fluid loss, and myocardial depression.

Cardiac dysfunction resulting from catecholamine-induced myocarditis and myocardial ischemia complicates severe envenomation from androctonus, buthus, mesobuthus, and tityus scorpions.[8,17] This complication may result in pulmonary edema and cardiogenic shock.[11,15,17]

NEUROLOGIC EFFECTS

Stimulation of the peripheral nervous system results in uncoordinated neuromuscular activity

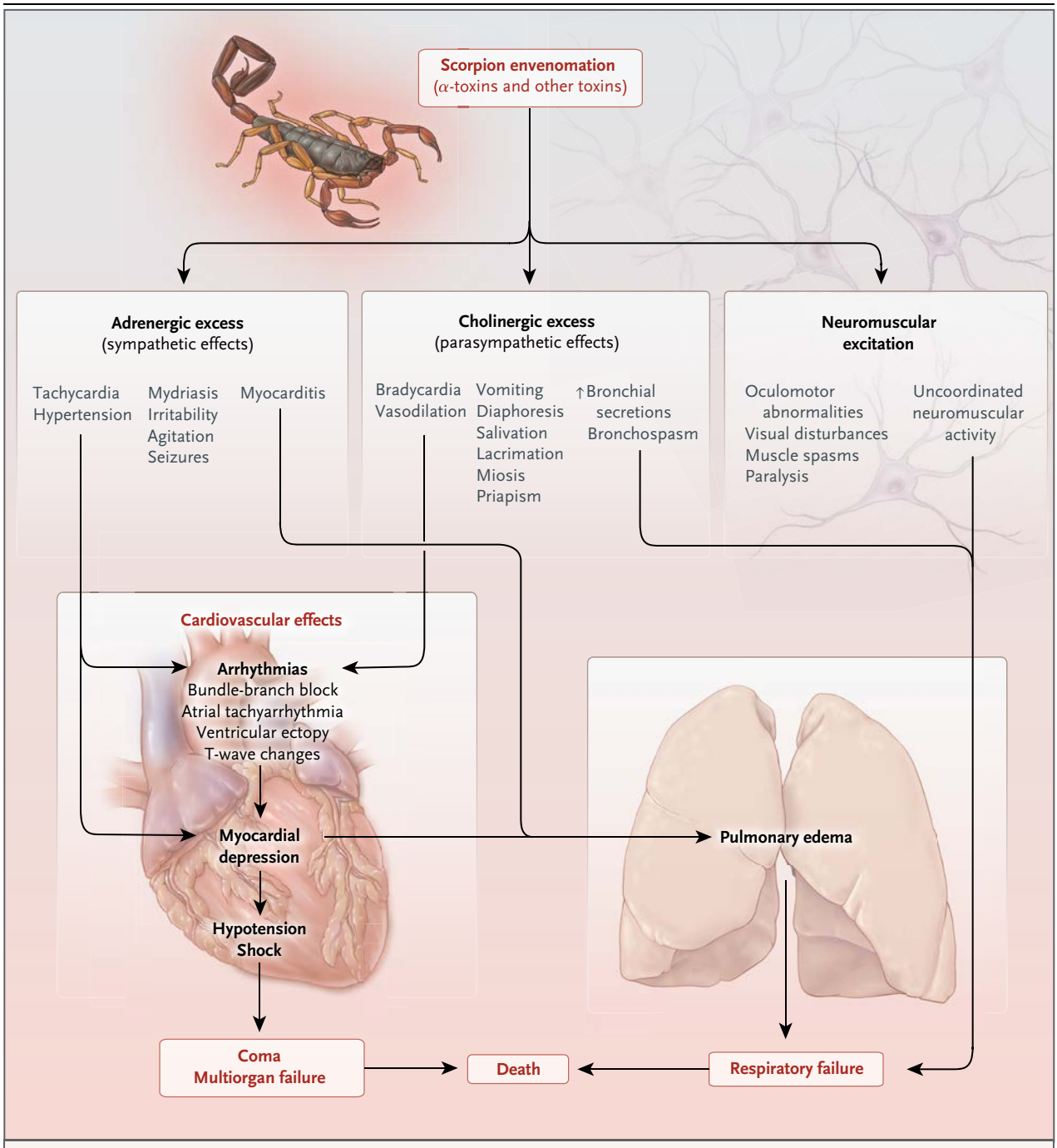

Figure 1. Pathophysiological and Clinical Effects of Systemic Scorpion Envenomation.

The effects of a scorpion sting on autonomic and neuromuscular activity are shown, as are the major effects of severe envenomation, including pulmonary edema, myocardial depression, hypotension, and multiorgan failure. Some scorpion toxins may have direct effects on body tissue, such as cardiac toxic effects.

that is manifested as wild flailing and thrashing of the limbs, abnormal oculomotor movements (e.g., roving eyes), visual disturbances, and muscle fasciculation and spasms of the face and tongue and the arms and legs.[12,18] Uncoordinated neuromuscular activity contributes to respiratory compromise (Fig. 1). Neuromuscular excitation is most commonly reported with envenomation by

centruroides scorpions[12] but may also occur after stings from parabuthus and tityus species.

GASTROINTESTINAL EFFECTS

Vomiting and abdominal pain are common after scorpion stings, and increased gastric motility and diarrhea are also reported. Many of these effects are due to cholinergic stimulation. Acute pancreatitis has been reported with stings from some scorpions, including *Leiurus quinquestriatus* and tityus species.[15,19]

CYTOTOXIC ENVENOMATION

A clinical syndrome that is distinct from typical systemic envenomation occurs with stings from the *H. lepturus* scorpion of Iran. Stings do not cause immediate severe pain. Most cases are characterized by erythema and purpuric and bullous lesions that resolve, but in about 20% of cases there is delayed localized necrosis that develops over hours or days.[5] Systemic features include nausea, vomiting, fever, minor autonomic effects, direct hemolysis with hemoglobinuria, and acute kidney injury that often necessitates dialysis.[5] The syndrome appears to be similar to that associated with bites by loxosceles spiders.[20]

CLINICAL GRADING

Grading systems for scorpion envenomation are available, but they differ from country to country. A recent consensus report defined four classes of scorpion envenomation: local, minor, major, and lethal.[21] However, a large number of signs and symptoms were included in these classes without reference to the pathophysiology of scorpion envenomation, and the report did not focus on treatment. Ideally, clinical grading should direct treatment. A simple approach based on previously reported grading systems and interventions is provided in Table 1.

DIAGNOSTIC INVESTIGATIONS

There are no specific diagnostic investigations recommended for scorpion stings; in the majority of cases, no investigation is required, particularly in the many regions of the world where it is difficult to perform diagnostic tests. Investigations should focus on potential complications of scorpion envenomation; for example, creatinine levels should be measured to assess whether renal failure has occurred, and levels of pancreatic enzymes should be measured to determine whether the sting has induced pancreatitis. Serum scorpion venom levels have been measured in a number of research studies, but such assays are neither generally available nor useful in determining the appropriate treatment. In cases of severe systemic envenomation, an electrocardiogram should be obtained when possible, since electrocardiographic abnormalities are fairly common. Further investigation with echocardiography, assessment of serum markers of cardiac distress, and other investigations of the heart should be guided by the severity of the envenomation and the resources available.

Table 1. Treatment of Scorpion Stings According to Clinical Grade.*

Clinical Grade or Class	Clinical Effects	Treatment
1	Local effects only	Analgesia, local anesthesia
2	Autonomic excitation	Antivenom, prazosin
	Agitation and anxiety	Oral benzodiazepines
3	Pulmonary edema	Admission to intensive care unit, noninvasive or mechanical ventilation, antivenom, vasodilators (e.g., prazosin), in some cases nitroglycerin†‡
	Hypotension and cardiogenic shock	Antivenom, dobutamine infusion†
	Severe neuromuscular excitation (associated with centruroides species)	Antivenom, benzodiazepine infusion†
4	Multiorgan failure, including coma, seizures, and end-organ damage caused by hypotension	Supportive care, mechanical ventilation, inotropes (e.g., dobutamine), benzodiazepine infusion

* These data are based on a number of previously reported grading systems and interventions.[8,11,12,14,21,22]
† The benefit of antivenom is less clear when severe systemic envenomation is well established.[1]
‡ The role of intravenous vasodilators is not well defined; these drugs must be used with caution when administered to patients with established hypotension and when administered in combination with dobutamine.[2]

TREATMENT OF STINGS AND THE ENVENOMATION SYNDROME

Numerous treatments have been recommended for scorpion envenomation, including antivenom, prazosin,[8] inotropic agents,[2] atropine, vasodilators, and benzodiazepines (Tables 1 and 2).[12] However, the evidence for the effectiveness of most treatments is variable, and types of treatment appear to vary according to region.[8] In severe envenomation, the standard intensive care treatment for acute pulmonary edema and cardiogenic shock appears to be appropriate and often includes the use of inotropes and specific vasodilators (Tables 1 and 2). Symptoms related to the site of the sting should be managed with appropriate analgesia

Table 2. Treatments for Scorpion Envenomation, Effects, Indications, and Dosing.*

Treatment	Effect	Indications	Suggested Dosing
Analgesic agent (acetaminophen, ibuprofen)	Provides pain relief and antiinflammatory action; acetaminophen also has antipyretic effect.	Local pain	Follow standard pediatric and adult dosing for pain and fever
Local anesthetic agent	Provides relief from severe local pain	Severe pain that does not respond to analgesia	Follow standard dosing of anesthetic without epinephrine for local wound infiltration, administered at sting site
Antivenom	Binds toxins and prevents them from reaching target site; increases rate of toxin elimination	Systemic envenomation	Follow manufacturer's instructions
Prazosin	Decreases peripheral vascular resistance without affecting cardiac output or heart rate or contributing to elevation of catecholamine levels	Indications of excess catecholamine, hypertension	Administer 0.5 mg prazosin orally every 3 hr (0.25 mg in children)
Dobutamine (or other inotrope)	Treats cardiogenic shock and decreases in cardiac output resulting from elevated catecholamine levels and myocardial injury	Hypotension due to cardiogenic shock	Administer 5–15 μg dobutamine/kg of body weight/min
Nitroglycerin	Acts as vasodilator for treatment of pulmonary edema; decreases preload and afterload through arteriolar dilation and venodilation	Pulmonary edema	Administer 10 μg nitroglycerin/min intravenously in adults, 1–4 μg/kg/hr in children; double rate every 5 min on basis of clinical response, but maintain systolic blood pressure at level >90 mm Hg
Benzodiazepine (e.g., midazolam, diazepam)	Acts as an anticonvulsant and may be effective for treatment of hypertension associated with sympathetic excitation; in cases of severe neuromuscular excitation, used for sedation and symptomatic relief (e.g., midazolam in patients with centruroides stings)	Neuromuscular incoordination, sympathetic agitation and seizures	For neuromuscular incoordination, initially administer midazolam bolus intravenously, 0.05–0.1 mg/kg, then commence infusion at 0.1 mg/kg/hr, adjusting dose to maintain light sleep; for sympathetic agitation and seizures, administer 0.1–0.2 mg diazepam/kg orally or 0.05–0.1 mg diazepam or midazolam/kg intravenously
Atropine	Acts as muscarinic receptor blocker to ameliorate cholinergic effects of sting, including bradycardia, early hypotension, and excessive sweating or salivation; can potentiate sympathetic effects, including hypertension	Severe bradycardia associated with hypotension or cardiac decompensation	Administer 0.5 mg atropine (0.02 mg/kg in children); dose can be repeated if severe bradycardia recurs
Other vasodilator (e.g., hydralazine, captopril, nifedipine, sodium nitroprusside, clonidine)	Decreases peripheral vascular resistance and reduces hypertension, but evidence for use not strong and has potential adverse effects (e.g., sympathetic stimulation, reflex tachycardia)	Not recommended because of potential adverse effects	

* Unless stated otherwise, dosing for adults and children is the same. The data were drawn from a number of sources.[8,11,12,14,21,22]

with acetaminophen and antiinflammatory agents, depending on severity (Table 1).

The use of antivenom for scorpion stings remains controversial, since the results of clinical trials have been both negative and positive. A large study from Tunisia showed no benefit from the routine administration of antivenom.[6] However, that trial did not include many cases of severe or systemic envenomation, in which antivenom would be more likely to have beneficial effects. In contrast, in a small North American clinical trial of centruroides scorpion envenomation (15 patients), neurotoxic effects of envenomation resolved within 4 hours in all 8 patients who received antivenom as compared with only 1 of 7 patients who received placebo.[12] In a randomized, open-label study in India involving 70 patients who had been stung by the red scorpion (*Mesobuthus tamulus*), the patients who received antivenom and prazosin had a more rapid recovery than did those who received prazosin alone.[8] A recent study of red scorpion envenomation in 50 children also compared the use of antivenom and prazosin with prazosin alone and showed that the children who received antivenom plus prazosin had a more rapid recovery (mean between-group difference, 9 hours), were less likely to undergo progression to severe envenomation syndrome, and needed less prazosin than the children who did not receive antivenom.[14]

Although the evidence in favor of antivenom is heterogeneous, given the small size of the trials with positive results and the different scorpion species across studies, the reports, when taken together, suggest that administration of antivenom after a sting is of some benefit — a suggestion that is supported by recent observational studies of antivenom after stings by centruroides species.[23,24] A cost-effectiveness analysis of the use of antivenom for scorpion envenomation in the United States showed that at its current price, antivenom is not cost-effective and that its use should be restricted to cases of severe envenomation.[25] However, once severe envenomation has developed, the administration of antivenom may be less effective, since its primary therapeutic action is to bind toxins; it does not reverse established pathophysiological injury, such as excess levels of catecholamine, pulmonary edema, and cardiogenic shock.[10] (A list of the major scorpion antivenoms manufactured worldwide can be found at http://wikitoxin.toxicology.wikispaces.net/Scorpions.)

SUMMARY

Scorpion stings and envenomation are of clinical importance worldwide, and although most stings cause only local effects, severe envenomation that causes either excessive autonomic activity and cardiovascular toxic effects or neuromuscular toxic effects results in illness and, in the case of children, in death. The specific treatment is the administration of antivenom combined with symptomatic and supportive treatment, including prazosin and dobutamine in patients with cardiovascular toxic effects and benzodiazepines when there is neuromuscular involvement.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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