

WHAT'S NEW IN INTENSIVE CARE



Scorpion envenomation: from a neglected to a helpful disease?

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Scorpion envenomation is a life-threatening accident encountered in tropical and subtropical areas. It remains an under-reported disease but around 1.2 million stings are yearly recorded around the world, ensuing in 3250 deaths as a consequence of acute heart and respiratory failure [1]. The great majority (>90%) of stings by the Old World scorpions (North Africa, India, and the Middle East) are so-called dry stings, resulting in localized discomfort. When systemic envenomation occurs, several systems may be affected, including the gastrointestinal, neurological, inflammatory systems, etc. [2]. Life-threatening presentations with acute heart failure features occur in less than 1% of cases. In what follows, we will strive to show how the little research dedicated to this neglected disease has led to significant scientific advances both through the derived experimental model of the widespread Takotsubo syndrome and by the proliferation of venom-derived drugs.

In 1995, we published a study in *Intensive Care Medicine* which included 9 consecutive young patients admitted to the ICU for pulmonary edema consecutive to severe scorpion envenomation [3]. Early upon ICU admission, all patients were equipped with a pulmonary artery catheter, and had serial echo-doppler examinations in order to assess left ventricular function in comparison to 14 matched controls. This report confirmed the findings of a previous study which was one of the first to unveil the hemodynamic nature of the scorpion envenomation-related pulmonary edema [4]. In addition, the study highlighted two of the peculiar features of scorpion-induced LV dysfunction: the marked and reversible (in days) depression in LV systolic function. The next study has brought together arguments in favor

of the third characteristic of the scorpion-related cardiomyopathy: the right ventricle may also be involved and to the same extent as the LV making unlikely the ischemic hypothesis of scorpion-related cardiomyopathy, especially since the majority of victims are young with healthy coronary circulation [5]. Subsequent studies have tried to unravel the mechanisms involved in scorpion-related cardiomyopathy where a scorpion-specific, ischemic, or catecholaminergic cardiomyopathy were also advocated [6].

Scorpion envenomation as a model of Takotsubo syndrome

The combination of irrefutable arguments linking this cardiomyopathy to the massive discharge of catecholamines reported after severe envenomation eventually led to the argument in favor of a catecholaminergic cardiomyopathy [7]. The Takotsubo syndrome, which typically occurs in stressful or traumatic situations as a consequence of catecholamines discharge, made it possible to reconcile all the observations accumulated around severe envenomation: the severely altered ventricular contractility, most often involving both ventricles, and its rapidly reversible character [8, 9]. Echocardiographic and scintigraphic findings, and ECG abnormalities mimicking ischemia, troponin and BNP release in proportions dissimilar to what is generally measured in acute coronary syndromes, can thus be explained by the Takotsubo syndrome [3, 10–12]. Several studies have recently reported typical Takotsubo syndrome features in severe scorpion envenomation, with reversible circumferential ventricular dysfunction made peculiar by the fact that regional wall motion abnormalities are not limited to

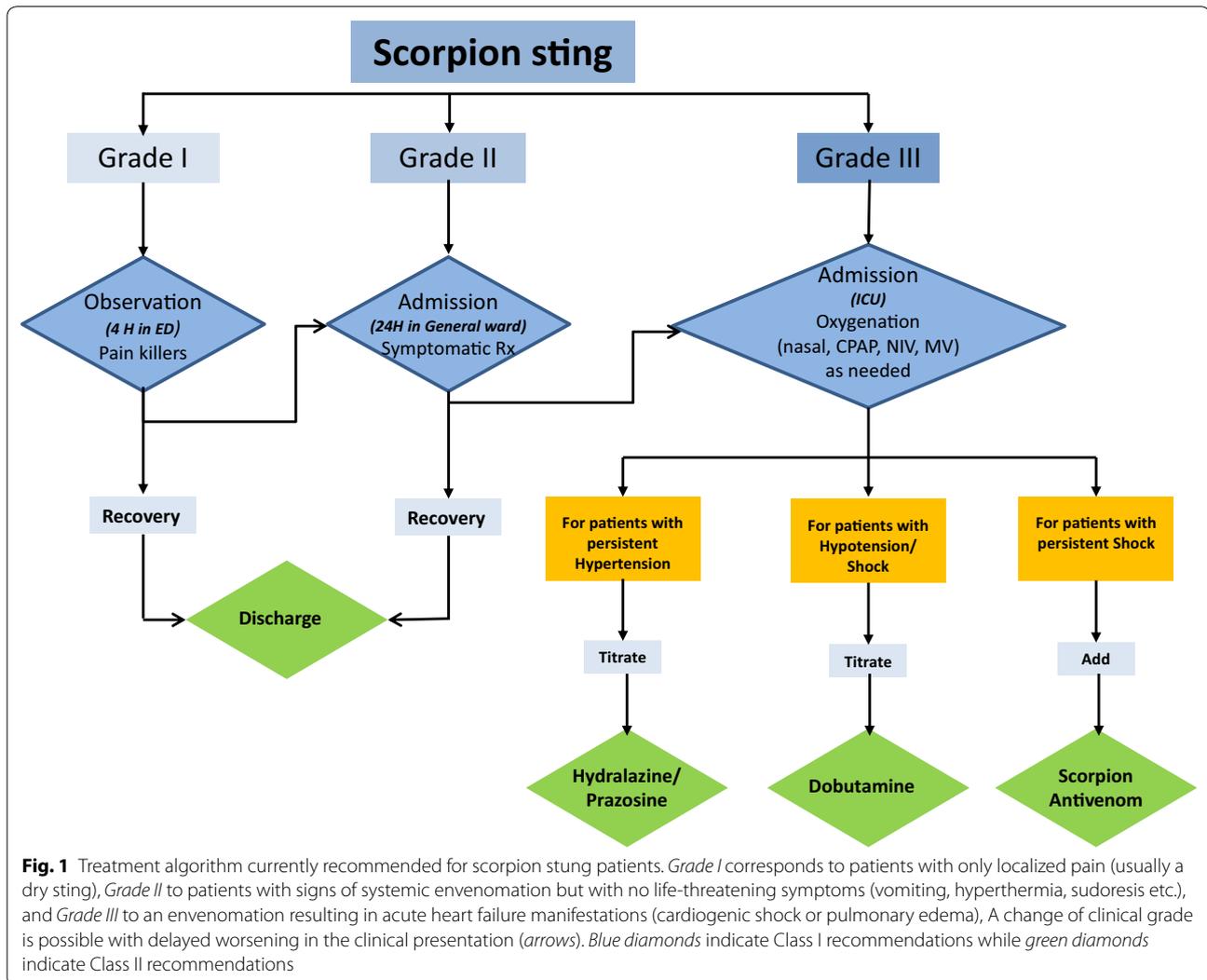
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the distribution of a coronary artery [13–15]. It has been hypothesized that scorpion envenomation can even be considered a model of Takotsubo syndrome [16]. This pathophysiological breakthrough opens new horizons for the management of severe scorpion envenomation where dobutamine, the cornerstone of scorpion-related cardiomyopathy treatment, should probably be considered cautiously in this particular setting. Administration of beta blockers for the secondary prevention after scorpion sting, the overall prognosis, could also be approached differently in the light of these new insights. Figure 1 details the algorithm of current recommendations on the treatment of scorpion envenomation.

Scorpion venom as a valuable source of new therapeutic agents

Despite its confinement to low–middle income countries, scorpion envenomation (and especially scorpion

venom and contained toxin peptides) has succeeded in attracting research laboratories with high potential in basic research. They were first interested by the decryption of the mechanisms of activation/inhibition of cellular channels (principally Na⁺ and K⁺) in order to explain the pathophysiological consequences of human envenomation. It was rapidly obvious that scorpion peptides are potent selective probes of the ion channels with a potential to modulate biological mechanisms involved in the immunological response, the response to infection, and neoplastic diseases, and with a potential for therapeutic applications in human and veterinary medicine [17, 18]. The majority of the pharmaceutical applications of venom peptides originate from snake venoms which are biochemically simple, and target either the neuromuscular or the cardiovascular systems. Venom-based drug discovery began in the 1970s with the development of the antihypertensive drug captopril from an inhibitor of the



angiotensin-converting enzyme isolated from the *Bothrops jararaca* viper [19]. Several venom-derived peptides have proved effective for the treatment of hypertension, diabetes, pain, etc. [20]. Six drugs derived from venom peptides have so far been FDA-approved [18]. In contrast, scorpion venom is more complex, and contains several hundred components with ~100,000 bioactive peptides [17]. Table 1 (supplementary material) provides a short inventory of scorpion peptide toxins with potential application as drug substances in various diseases.

In conclusion: in the last 20 years, scorpion envenomation has evolved from an accident confined to underdeveloped countries with no tradition in research to an experimental and reproducible model of the Takotsubo syndrome, a disease encountered in many stressful and often dramatic circumstances. This disease has yet to fully reveal its physiopathology, for which preventive and curative therapeutic strategies are lacking, and whose potential for recovery is still under investigation. In the same time interval, molecular sequencing techniques, usually resulting in the understanding of the structure/function relationships, have also been used to analyze the many peptides of scorpion venom. The discovery of new pharmacodynamic properties should lead to new drug discoveries whose entry into the international pharmacopoeia could provide new solutions to well-known diseases.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-018-5226-5>) contains supplementary material, which is available to authorized users.

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