Anaphylaxis and insect allergy

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Purpose of review

Anaphylaxis is an acute-onset and potentially life-threatening allergic reaction that can be caused by numerous allergic triggers including stinging insects. This review focuses on recent advances, natural history, risk factors and therapeutic considerations.

Recent findings

Recent work suggests that concerns over insect allergy diagnosis continue to exist. This is especially true with individuals who have a convincing history of a serious life-threatening anaphylactic event, but lack the necessary diagnostic criteria of venom-specific IgE by skin test or in-vitro diagnostic methods to confirm the diagnosis. The role of occult mastocytosis or increased basophile reactivity may play a role in this subset population. Additionally, epinephrine continues to be underutilized as the primary acute intervention for an anaphylactic reaction in the emergent setting.

Summary

The incidence of anaphylaxis continues to rise across all demographic groups, especially those less than 20 years of age. Fortunately, the fatalities related to anaphylaxis appear to have decreased over the past decades. Our understanding of various triggers, associated risk factors, as well as an improved understanding and utilization of biological markers such as serum tryptase have improved. Our ability to treat insect anaphylaxis by venom immunotherapy is highly effective. Unfortunately, anaphylaxis continues to be underappreciated and undertreated especially in regard to insect sting anaphylaxis. This includes the appropriate use of injectable epinephrine as the primary acute management tool. These findings suggest that continued education of the general population, primary care healthcare providers and emergency departments is required.

Keywords

anaphylaxis, epinephrine, hymenoptera, insect, mastocytosis, tryptase

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Introduction

Anaphylaxis is an acute-onset, potentially fatal systemic allergic reaction [1,2]. Anaphylaxis can be triggered in numerous ways, but the three most common triggers are insect stings, foods, and medications [3•,4–6]. Manivannan *et al.* [7] reviewed 208 patients and found that the inciting agents broke down into food (29.6%), medications (22.2%), insects (11.1%), others (7.4%), and unknown (29.6%). However, since large numbers of partially treated episodes often go undiagnosed or unrecognized, it is likely that anaphylaxis is under-reported [8,9]. No one knows the true rates of anaphylaxis in general, although overall global trends indicate increasing rates in all age groups and populations [6,8,10]. The increase is most significant in people living in good socioeconomic conditions and people under the age of 20 [10]. The largest number of anaphylaxis cases typically occurs in children and adolescents; however, fatalities from insect stings are more common in middle-aged and older adults [6,8,9,11].

Epidemiology/natural history of insect sting anaphylaxis

In most regions of the world, Hymenoptera, such as bees, wasps, yellow jackets, and hornets, are the most medically relevant insects, and are responsible for most cases of insect sting-related anaphylaxis, whereas in some geographic regions, *Formicidae* sp. are most common. In the Southeastern US, the imported fire ant-related anaphylaxis (*S. invicta)* is common as well [8,12]. It is important to note that other biting and stinging arthropods, including but not limited to scorpions, beetles, caterpillars, and mosquitoes, have been reported to cause both cutaneous and systemic anaphylaxis [13–17]. Additionally, natural disasters may have an impact on insect sting rates and reactions [18].

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The past two decades have seen more than a two-fold increase in the prevalence of allergic disorders; most of the increase has occurred in industrialized countries [19]. Even though anaphylaxis is on the rise across all demographic groups and regions, patients under the age of 20 appear to be most significantly represented by these trends [6,19]. Population-based studies of emergency department patients offer wide variations in results. They estimate that anaphylaxis resulting from insect stings ranges from 1.5 to 34% [20]. As one might expect, hospitals reporting lower incidence rates are for the most part those located in urban areas where chances of being stung by insects are somewhat lower [20]. In contrast, other areas have reported sharp increases in insect stings. For instance, in Alaska, there has been a 48% state-wide increase in patients seeking care for insect stings over the past decade [21]. During that same period, the first two deaths in Alaska due to insect sting anaphylaxis were reported [22]. The results in Alaska hint, however, at the good news behind this increase: although the incidence of anaphylaxis appears to be on the rise, fatalities associated with insect sting anaphylaxis have decreased within the past decade – by some estimates, up to an 88% decrease [19].

Because we lack reliable data concerning rates of anaphylactic episodes in the US and around the world, the epidemiological trends are difficult to analyze. Figures vary significantly. Current data from population studies estimate the 'incidence of anaphylaxis in western countries to be in the range of 8–50 per 100 000 person-years' [19]. Different data collection methodologies are one cause of this variation. But a more significant cause is that the medical community has not agreed upon a comprehensive definition for anaphylaxis [8,19,20].

Risk factors for sting anaphylaxis

Ruëff *et al.* [23••] identified risk predictors of sting-related anaphylaxis such as patients taking angiotensin-converting enzyme inhibitors (ACEI), patients with vespid allergy, male sex, and interestingly, serum mast cell tryptase levels above 5 ng/l. A European, multicenter study of 962 Hymenoptera venom-sensitive patients looked at predictors of severe systemic anaphylaxis due to Hymenoptera venom allergy [23••]. Of 962 patients, following field sting, 21% had severe anaphylaxis, either grade 3 (anaphylactic shock, loss of consciousness) or grade 4 (cardiac arrest, apnea), using Mueller's criteria [24]. Bonadonna *et al.* [25••] reported a correlation between systemic reaction to Hymenoptera sting and mast cell tryptase. Of 379 patients, 11.6% had serum mast cell tryptase levels exceeding 11.4 ng/ml and of this group the rate of systemic anaphylaxis was 70.5%. Thirty-four of the patients with elevated mast cell tryptase level underwent bone marrow biopsy; of those, 61.7% were diagnosed with systemic mastocytosis [21]. Niedoszytko *et al.* [26] considered mastocytosis regarding the diagnosis, safety and efficacy of venom immunotherapy, whereas others looked at the predictive value of anaphylactic severity with baseline serum tryptase [23••,26].

Clinical features and diagnosis of insect sting anaphylaxis

The diagnosis of Hymenoptera allergy requires both history of a sting event that resulted in a systemic reaction and evidence of venom-specific IgE, either by skin testing or in-vitro testing [27,28].

History

Hymenoptera stings are acutely painful, so most patients are aware that a sting has occurred. When the patient can identify the insect that caused the sting, this can be helpful in diagnosis and treatment. However, patients do not always reliably identify the culprit insect, so the physician may need to use secondary evidence: the presence of the stinger most common with honeybees and the presence of pustule found after imported fire ant stings are reliable indicators.

Local versus systemic

The initial step in the diagnosis of Hymenoptera allergy is to determine whether the patient's reaction was local or systemic (i.e. anaphylaxis), based on a careful history of the sting event.

(1) A local reaction occurs when the symptoms, such as erythema, swelling or pain are confined to tissues contiguous with the sting site. Local reactions may swell to greater than 10 cm and increase in size for 24–48 h and last 5 and 10 days.
(2) In contrast, systemic reactions cause signs and symptoms throughout the body and include a spectrum of manifestations, ranging from mild to life-threatening.
    (a) Mild systemic reactions are often limited to the skin and include flushing, urticaria, and angioedema.
    (b) More severe systemic reactions can be fatal. Upper airway obstruction, including tongue and throat swelling, as well as laryngeal edema, are perhaps the most common cause of fatal anaphylaxis; bronchospasm and hypotension can be fatal as well. Additional signs of anaphylaxis may be gastrointestinal such as nausea, vomiting, diarrhea, and abdominal pain. Neurological manifestations of anaphylaxis can include seizures. Pérez Pimiento *et al.* [29] studied the clinical pattern of insect (*Vespula* sp.) sting reactions in 115 patients in Spain. Of those patients, 90% experienced cutaneous reaction, 54% respiratory, 33% cardiovascular, and 21%

gastrointestinal manifestations. Sixty percent were graded either grade 3 or grade 4 using Mueller's criteria [24].

IgE testing and immunoassays

Once the physician determines that the sting resulted in a systemic or generalized anaphylactic reaction, testing for venom-specific IgE is essential for the diagnosis. Venom-specific IgE may be determined either by skin testing or in-vitro testing (i.e. IgE ImmunoCap assay, Fluorescence Enzyme Immunoassay). In most cases, skin testing by an experienced allergist/immunologist is the preferred initial method, as it is more sensitive and usually less costly. The techniques of venom skin testing and interpretation of results, as well as venom immunotherapy, are outside the scope of this review and may be reviewed elsewhere [30–32]. If skin testing is negative, venom-specific IgE immunoassays should be obtained. It is common practice to postpone testing until 3–6 weeks following the sting event, although it has been demonstrated that in 79% of patients venom allergy can be demonstrated at 1 week [31,33]. From time to time, even though there is convincing history of a systemic reaction to a sting, both skin testing and in-vitro testing are negative. In such cases alternate diagnoses should be considered, including mastocytosis. A serum tryptase should be obtained. If the serum tryptase level is normal, the patient should be re-tested for venom-specific IgE in 3–6 months [34]. Some authors believe there to be role to basophile responsiveness in patients with a history of insect anaphylaxis and negative venom skin tests and venom-specific serum IgE [35].

Once a systemic anaphylactic event from an insect sting has been determined and the presence of venom-specific IgE has been established, the diagnosis can be made and the individual is then a candidate for venom immunotherapy.

Testing in young patients

Insect allergy testing and immunotherapy are generally not necessary in patients 16 years of age and younger who have experienced only mild cutaneous systemic symptoms. Individuals in this age group have only a 10% chance of having a systemic reaction if re-stung. If a subsequent systemic reaction does occur in this age group, it is generally less severe than the initial isolated cutaneous reaction [36,37].

Prevention of insect sting anaphylaxis

In order to adequately prevent insect sting anaphylaxis, we need a more precise system of identifying patients who are at particular risk of experiencing an anaphylactic episode [19]. This would enable physicians to target new therapies or support systems to those who would stand to gain the most benefit [38]. Whereas prior anaphylactic episodes can be an indicator of a person at high risk for subsequent reactions, this is simply not a sufficient or reliable indicator in preventing future anaphylaxis, since it is also not uncommon for anaphylaxis to occur when previous allergic reactions were mild and nonsystemic [39]. In fact, some studies have indicated that as few as 14% of individuals experiencing an anaphylactic episode had a prior history of anaphylactic reactions [39]. Thus, we need improved knowledge within and beyond the medical community of risk factors associated with insect sting anaphylaxis. This is especially vital for asymptomatic sensitized patients [20]. In order to properly screen for individuals at increased risk of anaphylaxis, we also need to properly manage relevant comorbidities, such as underlying respiratory and cardiovascular diseases, as well as need to better identify and avoid anaphylactic triggers.

Management and treatment of anaphylaxis

In addition, for individuals who do have a history of anaphylactic reactions, more serious systemic reactions can be prevented or minimized by physician or self-administered epinephrine through a prescription auto injector such as an Epipen, Adrenaclick or Twinjet [20]. A clear instruction on recognition of anaphylaxis as well as the proper administration technique of epinephrine is critical for the successful acute management of insect anaphylaxis. Unfortunately, in the presence of anaphylaxis, epinephrine continues to be underutilized. Manivannan *et al.* [7] reported that of 208 patients with anaphylaxis, only 104 (50%) received epinephrine, and of those, 27 (13.0%) received repeated doses. Simons *et al.* [40•] reported that of 1885 patients who experienced anaphylaxis, only 27% used epinephrine. The most common cited reasons for nonuse included the use of an antihistamine instead (38%) and lack of prescription for epinephrine (28%). To re-emphasize, the mainstay of immediate anaphylaxis treatment is intramuscular injection of epinephrine [1]. Individuals deemed to be at significant risk of experiencing an anaphylactic reaction are encouraged to carry epinephrine auto-injectors. Current research efforts are working to improve epinephrine formulations and injection quality, as well as to eliminate the risk of needle exposure following injection [1].

Further treatment recommendations

In addition to epinephrine auto-injectors, further anaphylaxis treatment measures include encouraging the patient and medical personnel to have an anaphylaxis emergency plan, achieving prompt and correct medical identification, and improving proper medical education of the patient and healthcare provider [1].

Unfortunately, many healthcare professionals still lack vital knowledge and awareness of anaphylaxis triggers and treatment [1]. Epidemiological studies have shown inadequate responses in patients experiencing venom allergies and extraordinarily low levels of awareness among medical staff of venom immunotherapy methods [20]. It is vital that healthcare providers, especially emergency department staff and primary care providers, have the appropriate knowledge of current triggers and diagnostic criteria to promptly identify anaphylactic patients, individuals at risk for future anaphylaxis, as well as knowledge of appropriate treatments to administer. Furthermore, it is essential that healthcare providers also educate patients and their caretakers of risk factors and appropriate emergency preparedness measures to be taken to minimize risk to anaphylactic patients.

Management of large local reactions

Large local reactions are not generally felt to increase the risk of anaphylaxis with subsequent stings, and therefore venom testing and venom immunotherapy are not typically warranted. In fact, large local reactions may actually decrease the risk of anaphylaxis to 5–10%, compared with the 17% risk seen in patients with asymptomatic sensitization [31,41•]. Testing and immunotherapy in patients with large local reactions may be considered in special circumstances to reduce morbidity. Golden *et al.* [41•] reported a case series of 41 patients with large local reactions following controlled sting challenge. After completion of venom immunotherapy (VIT) for 7–11 weeks, 42% of treated patients had significantly smaller reactions on sting challenge compared with 18% in the untreated control group. Of those that continued VIT for 4 years, 70% experienced significant reduction in large local reaction.

Referral to an allergist/immunologist

Anaphylaxis is a potentially life-threatening condition that is often underappreciated, and therefore, insect anaphylaxis needs special consideration [42]. The allergist/immunologist is uniquely qualified to evaluate anaphylaxis and especially insect anaphylaxis. The 2004 Practice Parameter on stinging insect hypersensitivity cites very clear criteria for when it is appropriate to refer a patient to an allergist/immunologist for evaluation and management of a patient with a history of adverse reaction following an insect sting [31]. On the basis of this guideline, referral is recommended when the patient experienced a systemic reaction to an insect sting; experienced anaphylaxis with an insect sting as a possible cause; needs education regarding stinging insect avoidance or emergency treatment; might be a candidate for venom immunotherapy; has a coexisting medical condition that might complicate treatment of anaphylaxis; or requests an allergy-immunology consultation.

Conclusion

As we have stated, recent studies suggest rising incidence of anaphylaxis, and in some parts of the US this is specifically seen in insect-related events. Anaphylaxis continues to be under-recognized and epinephrine under-utilized. Increased observation of these trends, better understanding of the natural history and risk factors associated with insect-related anaphylaxis, and improved awareness and education are paramount for further reduction in morbidity and mortality of those affected.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 403).

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The incidence rate of anaphylaxis is increasing, particularly during the first two decades of life. Clinical diagnosis is based on patient history, and laboratory tests if available. Long-term risk reduction is important for patients with history of anaphylaxis, and should include management of related comorbidities, avoidance of triggers, immunomodulation, and adoption of emergency treatment plans that often include education of appropriate use of epinephrine auto-injectors and rapid identification of key symptoms.

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