CURRENT OPINION

Insect anaphylaxis: where are we? The stinging facts 2012

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Purpose of review
Insect allergy remains an important cause of morbidity and mortality in the United States. In 2011, the third iteration of the stinging insect hypersensitivity practice parameter was published, the first being published in 1999 and the second in 2004. Since the 2004 edition, our understanding of insect hypersensitivity has continued to expand and has been incorporated into the 2011 edition. This work will review the relevant changes in the management of insect hypersensitivity occurring since 2004 and present our current understanding of the insect hypersensitivity diagnosis and management.

Recent findings
Since the 2004 commissioning by the Joint Task Force (JTF) on Practice Parameters of 'Stinging insect hypersensitivity: a practice parameter update', there have been important contributions to our understanding of insect allergy. These contributions were incorporated into the 2011 iteration. Similar efforts were made by the European Allergy Asthma and Clinical Immunology Interest Group in 2005 and most recently in 2011 by the British Society of Allergy and Clinical Immunology.

Summary
Our understanding of insect allergy, including the natural history, epidemiology, diagnostic testing, and risk factors, has greatly expanded. This evolution of knowledge should provide improved long-term management of stinging insect hypersensitivity. This review will focus primarily on the changes between the 2004 and 2011 stinging insect practice parameter commissioned by the JTF on Practice Parameters, but will, where appropriate, highlight the differences between working groups.

Keywords
anaphylaxis, Hymenoptera, hypersensitivity, insect, tryptase

INTRODUCTION

The adverse health effects of stinging insects remain significant. These effects range from minor skin irritation and pain to severe and potentially lethal anaphylaxis. The United States Centers for Disease Control (CDC) estimates an average annual rate of 90–100 deaths due to venom anaphylaxis (http://www.cdc.gov/niosh/topics/insects/, accessed 23 April 2012). The true rate of insect anaphylaxis may be underestimated, as many episodes are unrecognized or unreported. As with anaphylaxis due to agents such as foods or medications, all ages are affected and with stinging insect allergy, there are also occupational considerations. Furthermore, these concerns are not limited to North America or the United States, but have worldwide implications.

Since the first publication in 1999 of the stinging insect hypersensitivity practice parameter [1], continuing through the 2004 update [2], our understanding of insect hypersensitivity has continued to evolve. In 2011, the third iteration of the stinging insect practice parameter was published by the Joint Task Force (JTF) on Practice Parameters [by the American College of Allergy, Asthma and Immunology (ACAAI) and American Academy of Allergy, Asthma and Immunology (AAAAI)] [3▪]. This exhaustive review summarized the available information using, wherever possible, evidence-based

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KEY POINTS

- Understanding mast cell disease is critical to insect allergy management.
- Improved diagnostic methods hold promise for improved diagnostic accuracy.
- Duration of VIT is 3–5 years for most, but life-long therapy may be necessary.

data and when evidence was lacking, expert opinion. Since the 2004 publishing by the JTF on Practice Parameters of 'Stinging insect hypersensitivity: a practice parameter update', there have been important contributions to our understanding of insect allergy. In 2005, similar efforts were made by the European Allergy Asthma and Clinical Immunology (EAACI) Interest Group on Insect Venom Hypersensitivity [4,5], and most recently in 2011 by the British Society of Allergy and Clinical Immunology (BSACI) [6▪]. Herein, we examine the significant changes between the 2004 and 2011 stinging insect hypersensitivity practice parameters as published by the JTF on Practice Parameters. Where appropriate, we attempt to highlight the important differences between the various working groups. Finally, we will, when able, provide the current insight for issues not necessarily addressed in the various guidelines.

HISTORY

The central elements used to diagnose insect hypersensitivity have not changed over the years. Assessing insect hypersensitivity begins with obtaining a reliable clinical history of a systemic allergic reaction combined with the confirmation of venom-specific IgE by skin testing or in-vitro methods. Although these central elements have not changed, relevant historical diagnostic components have changed as have our approach to testing for venom-specific IgE.

Insects belonging to the order *Hymenoptera* account for the majority insect venom hypersensitivity reactions and fall into three main families: apidae (honeybee and bumblebee), vespidae (hornets, yellow jacket, wasps), and formicidae (fire ants) [7]. There are other stinging and biting insects accounting for hypersensitivity reactions, for the most part not central components of these reviews and are discussed elsewhere [8]. Identification of the culpable insect can be helpful for the diagnosis and treatment of insect allergy [9,10]. Identification is particularly helpful where avoidance education is the primary treatment option. Consequently, it is helpful to know the geographic region in which these insects reside as well as their feeding and nesting habits (Table 1) [11]. In recent years, bumblebees have become an important cause of sting reactions in some settings and may be important in occupational settings. Allergic reactions to bumblebee field stings are rare

Table 1. Hymenoptera biology and habitat

Common names	Taxonomic classification	Nesting habits	Feeding habit	Avoidance strategies
Honeybee[a]	Family Apidae	Commercial hives	Herbivorous. Nectar and pollen flowering trees and plants	Avoid dark or flower-print clothing and wearing floral scents; wear shoes and socks
Yellow jacket	Family Vespidae Vespula species	Multilayered, usually underground (*Vespula vulgaris*); although there is also an aerial yellow jacket (*Dolichovespula arenaria*)[b]	Scavengers, aggressive. Carnivorous	Avoid open food sources, picnic areas, garbage; destroy in-ground nests
Paper Wasp[c]	Family Vespidae Polistes species	Hangs from eaves and porches	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
White-faced Hornet	Family Vespidae Dolichovespula species	Multilayered, open areas	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
Fire ant	Family Formicidae	Earthen mounds in Southern United States	Omnivorous	Avoid mounds; wear shoes, sock and gloves

Source: Self-generated similar to submission in [11].
[a]A subspecies of honeybee exists in South Texas, Central and South America called 'Africanized'. It is more aggressive than local species and is clinically relevant in regions of infestation.
[b]European species include Polistes dominulus, Polistes gallicus, and Polistes nimphus.
[c]Paper wasp is not seen in the United Kingdom.

because of their generally nonaggressive behavior. However, in Europe, systemic allergic reactions have been reported during occupational exposure to greenhouse workers where bumblebees are often used for pollination [12,13]. Bumblebee venom allergy is usually distinct from honeybee venom allergy and requires specific testing [12]. Unfortunately, there is no approved diagnostic venom for skin testing or treatment of bumblebee allergy in the United States.

The clinical presentation of the inciting sting event may have important implications. There is growing evidence that one of the most important predictors of the outcome of a sting is the pattern and severity of previous reactions. This historical feature may play an important role in the recommendation of discontinuing venom immunotherapy (VIT) [14].

DIAGNOSTIC TESTING

Since the 2004 update, there have been significant changes regarding when and how to evaluate for venom-specific IgE. The 2011 JTF parameter provides more guidance on when not to perform diagnostic tests. Although the negative predictive value is very high, the positive predictive value is much lower. There are quality-of-life concerns regarding the impact of positive test results in patients with relatively low risk of reactions. Additionally, venom testing and treatment may not be required in some low-risk patients, but may be warranted for quality-of-life reasons in some individuals. Thus, the change in wording has changed from the 2004 to the 2011 parameter from 'not recommended' to 'not required' for large local reactors and children with cutaneous systemic reactions without other systemic manifestations associated with anaphylaxis.

Skin testing for Hymenoptera venom remains the preferred initial test for the determination of venom-specific IgE [3▪,6▪]. This is most commonly performed using a combination of epicutaneous and intracutaneous methods accompanied by appropriate positive and negative controls. Skin testing usually begins with skin prick testing at 100 μg/ml venom concentrations, and, if negative, intracutaneous testing starting at a venom concentration of between 0.001 and 0.01 μg/ml for most Hymenoptera follows skin prick testing. At intervals of 20–30 min, the skin tests are performed using 10-fold increases in concentration until a positive skin test response occurs or a maximum concentration of 1.0 μg/ml is achieved [15]. A positive skin test reaction at a concentration *or less* 1.0 μg/ml confirms the presence of venom-specific IgE antibodies. Venom concentrations of greater than 1.0 μg/ml have been associated with an increase in irritant skin reactions [16].

Although skin testing for venom-specific IgE remains the cornerstone for the evaluation of insect hypersensitivity, periodically a negative skin test may result, even with a convincing history of a systemic sting reaction. However, in such patients, a negative skin test result for venom-specific IgE should be interpreted with caution, especially when done within the first few weeks following a sting reaction. In such cases, in-vitro testing is indicated [17,18]. Up to 20% of skin-test-positive individuals have undetectable serum levels of venom-specific IgE, whereas 10–20% of patients with negative skin tests may have positive in-vitro results when high-sensitivity assays are included. Consequently, skin testing and in-vitro immunoassays for venom-specific IgE may be considered complementary. Rare occurrences of anaphylaxis have been reported in individuals with negative skin testing in addition to negative in-vitro methods [18,19]. The pathogenesis of these reactions may involve non-IgE mechanisms such as mast cell disorders. Baseline serum tryptase levels to exclude the presence of occult mastocytosis should be considered in these patients [20,21]. These recommendations are consistent in both the 2011 JTF Practice Parameters and the 2011 BSACI guidelines. Our understanding of the role of basophils in the diagnosis and management of insect anaphylaxis continues to evolve. Although not commonly used in the United States, the basophil activation test may eventually play a role in the future in managing individuals with a history of systemic reactions to insect stings but negative venom tests [22–24].

Though not widely available in the United States, newer high sensitivity assays including ImmunoCAP or dialyzed venom may be particularly useful diagnostic tools in the future [25].

As the responsible insect is not always apparent, testing for all relevant insects in the geographical area in question should be done. However, there is considerable cross reactivity between some venoms. This cross-reactivity is often due to cross-reacting carbohydrate determinants between various Hymenoptera, especially honeybee and vespids [26]. If testing reveals a double positive to both honey bee and vespid, further testing via serum IgE may be helpful to distinguish true sensitivity as opposed to cross-reactivity due to cross-reacting carbohydrate determinants. Recent studies have reported the utility of testing to specific serum IgE to recombinant major allergen rApi m1 rVes v5 to discriminate between true allergic sensitivity and cross-reactivity [27].

ACUTE MANAGEMENT

European and North America's recent guidelines stress the importance of recognition and prevention of insect sting-induced anaphylaxis, with early recognition and administration of epinephrine the key to a favorable outcome. Both the EAACI and the U.S. JTF practice parameters agree that epinephrine therapy is underutilized in the emergency setting [28,29,30▪]. Anaphylaxis can be fatal in this patient population and any delay of the administration of epinephrine can increase the risk of death [30▪,31,32]. The JTF parameter also places emphasis on the use of epinephrine with comorbid conditions (i.e. hypertension and cardiac arrhythmias) or concomitant medications [i.e. beta-adrenergic blocking agents and angiotensin-converting enzyme (ACE) inhibitors] as factors that may require special attention in the management of anaphylaxis. However, even in these circumstances, there is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis [30▪,33,34]. Studies [30▪,34] in emergency departments also show the need for better counseling on avoidance, use of epinephrine injectors, and the need for allergy evaluation and treatment. The 2011 U.S. JTF practice parameter also provided additional discussion and guidance on the issues surrounding the prescription of epinephrine injectors and the instructions on when to use or not use them. As in the past, patients who have experienced a systemic reaction to an insect sting should be given a prescription for an injectable epinephrine device, instructed on proper usage, and be advised to carry it with them at all times. Because some patients who experience anaphylaxis might require more than one injection of epinephrine, a prescription for more than one epinephrine injector should be considered [34]. Generally, epinephrine injectors are not required for patients at low risk of a systemic reaction. However, even in patients who have a relatively low risk of a severe anaphylactic reaction from a sting, the decision whether to carry injectable epinephrine can be individualized by discussion between the patient and physician.

LONG-TERM MANAGEMENT

If the central elements of a history of a systemic insect sting reaction and confirmatory presence of venom-specific IgE are established, long-term therapy should be considered. Long-term management of these patients consists of VIT. There are differences on when VIT should be initiated between North American and European guidelines. In the case of severe reactions, both are in agreement that VIT is indicated. In individuals with a systemic reaction of moderate severity, BSACI Guidelines note that VIT is indicated in many patients, whereas North American guidelines suggest offering VIT to all patients with moderately severe systemic reactions. European guidelines generally do not recommend VIT for less severe reaction, without additional risk factors such as an elevated serum tryptase, occupational considerations, or effect on quality of life.

In North America JTF guidelines, VIT is generally not recommended for children aged less than 16 years with only a cutaneous systemic reaction. European guidelines suggest that because children generally have less severe reaction than adults, VIT should be considered in only a small percentage of children with severe systemic reactions.

The 2011 JTF parameters presented new evidence for the application of VIT for individuals with large local reactions [35,36]. Generally, VIT is not recommended for patients with sting with large local reactions, as their risk of future systemic sting reactions is low. However, individuals with limited large local reactions may be considered for skin testing and VIT for quality-of-life reasons and to reduce the morbidity of frequent or unavoidable reactions. The 2011 JTF parameter and BSACI guideline also discuss new evidence, and expert review is presented on the relative risk of beta-adrenergic blocker medications or ACE inhibitors in patients with insect sting allergy or those who are on VIT. Patients with insect allergy who are taking beta-adrenergic blockers may be at greater risk for more serious and difficult-to-treat anaphylaxis. Consequently, patients with insect allergy should avoid these medications unless absolutely necessary [37]. If the individual cannot discontinue the beta-adrenergic-blocking agent, the decision to administer immunotherapy should be made on an individual basis after the analysis of potential risks and benefits. In the past, case reports have suggested an increased risk of systemic reactions in patients using VIT. Recently, a retrospective study [38] conducted over 6 years showed no increased risk for individuals using ACE inhibitors. In either case, those data are limited and determination and the management decision on the use of an ACE inhibitor should be made on a case-by-case basis.

Mast cell disease has become an important component of insect hypersensitivity disease management in both North American and European guidelines [39–41]. The measurement of baseline serum tryptase is recognized as an important predictor of the severity of sting reactions, the frequency of systemic reactions during VIT, the chance of VIT failure, and the risk of relapse if VIT is stopped

[41]. Both North American and European guidelines agree that all patients with venom sensitivity should have a serum tryptase checked. Those with occult mast cell disease may be candidates for lifelong VIT because of the high risk of anaphylaxis in this subset of patients. This patient population is also at risk for anaphylaxis during VIT, though the European guidelines report fewer episodes of anaphylaxis during VIT and therefore recommend its continuation, possibly indefinitely in patients with mast cell disease.

DURATION OF VENOM IMMUNOTHERAPY

Evidence is updated in the 2011 JTF Parameter for the recommendations on discontinuing VIT. Duration of VIT still remains controversial. In general, a 3–5-year treatment period is sufficient and usually recommended. VIT reduces the risk of systemic reactions to stings in adults from 30–60 to 5% [42,43]. As a result, studies have generally concluded that 3–5 years offers sufficient long-term protection. There is more emphasis on the growing evidence that one of the most important predictors of the outcome of a sting is the pattern and severity of previous reactions [43]. In North America, those patients who have had severe life-threatening reactions, lifelong therapy may be warranted as their risk of future reactions appears to be somewhat higher [43,44]. European guidelines do not recommend therapy beyond 3–5 years without additional considerations [5,6▪]. Other circumstances where lifelong therapy is reasonable would be in the setting of mast cell disease those with anaphylaxis to insect sting while on maintenance VIT [45,46]. Lifelong therapy may also be considered in individuals with honeybee allergy and those with occupational exposure to Hymenoptera.

FUTURE EFFORTS

Future therapies and diagnostic strategies for insect allergy hold promise and are under investigation. Currently, studies are exploring the use of CD63 basophil activation tests to monitor the efficacy of VIT [47]. It is also being studied as a tool to decide if VIT can be discontinued in mastocytosis patients [48]. Studies report the development of mucosal immunotherapy for venom allergy similar to what is currently underway in Europe with sublingual immunotherapy [49]. Research in mouse models shows promise for human monoclonal antibody fragment therapy to melittin, a protein found in Africanized bee venom [50]. Human antibody therapy would have less risk of anaphylaxis than the current VIT prescribed. There have also been case reports of omalizumab used as an adjunct to help patients tolerate VIT in those with mast cell disease, who have frequent reactions during buildup phase of the protocol [51]. Finally, a plethora of new venom-specific recombinant in-vitro assays are in development.

CONCLUSION

In summary, the updated guidelines provide additional evidence that we need to continue to be vigilant in recognizing and managing venom hypersensitivity. Management with epinephrine, appropriate counseling on avoidance, and referral to an allergist trained to recognize and manage this potentially lethal condition remain as opportunities for improved care. Once referred, appropriate testing must be conducted. On the basis of history of a systemic allergic reaction and a positive venom-specific test, VIT should be offered. Risk factors for reactions during VIT or future stings, including comorbid conditions or medications, such as beta-adrenergic blockers, ACE inhibitors, or mast cell disease, must be considered. General consensus is to continue VIT for 3–5 years, but certain individuals may benefit from lifelong VIT. Ultimately, the future holds promise with improved diagnostic tools in sorting out the individual with a convincing history of systemic allergic reaction, but remains negative to all currently available diagnostic tools.

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Conflicts of interest

Dr Tracy is a Contributor to UptoDate; Drs. Demain and Khan have no conflicts.

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

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 443).

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