




Diagnosis and Management of Insect Allergy: Barriers and Facilitators in the United States

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Abstract: While guidelines recommend testing and treatment for patients with venom-induced anaphylaxis to prevent morbidity and mortality, significant barriers prevent most patients from receiving the evaluation and treatments that they need. This review examines these barriers in the United States along with the facilitators that can be used to overcome them.

Keywords: insect hypersensitivity, venom, anaphylaxis, immunotherapy, social determinants of health

Introduction

Despite clear guidelines recommending diagnostic testing and desensitization for patients with venom-induced anaphylaxis,¹ barriers prevent many patients from receiving these services. In this review, we examine those barriers and the facilitators that promote access to healthcare within the United States. In cases where barriers and facilitators have not been studied explicitly within the field of venom hypersensitivity, we draw on the data from other areas and describe their potential application to venom allergy.

Barriers to Diagnosis

Patients that experience anaphylaxis from an insect sting should be evaluated by an allergist to confirm the diagnosis and determine appropriate treatment. The diagnosis is made with a combination of history, where the diagnosis of anaphylaxis is confirmed and the probable triggers are determined, and by testing the probable trigger(s) via skin testing and/or blood testing to identify venom-specific IgE.¹

The largest barrier to the diagnosis and management of venom-induced anaphylaxis may be access to appropriately trained specialists. After a period of contraction, the number of practicing allergists has been growing as training positions have expanded.² However, the increase in allergists has not kept up with the needs of the growing population.³ Despite persistent predictions of workforce shortages of allergists,^{2,4} the reform in graduate medical education needed to address the global shortage has not taken place.³

In addition to the need for expanding allergy fellowship training programs, gaps in training within fellowship programs could also be addressed. Fellowship training in Allergy/Immunology includes training in diagnosing and managing venom hypersensitivity,⁵ however there is no specific requirement for the number of patients tested or desensitized (10 immunotherapy prescriptions are required, but not differentiated between aeroallergen and venom immunotherapy).⁶ A survey of 253 allergists in the US confirmed that 100% felt that this was an important skill; however, only 84% felt that they gained this competency during their training.⁷

Immunotherapy is primarily indicated for those with a diagnosis of venom-induced anaphylaxis. An operational consensus definition of anaphylaxis includes the involvement of two or more organ systems after a probable trigger, such as an insect sting.⁸ This definition will work for most patients but may miss those with clonal mast cell disorder, in which hypotension may be the only symptom.⁹ Conversely, this definition may over-diagnose patients with vasovagal,

psychosomatic, and anxiety-related reactions that can include subjective dyspnea, cough, vomiting and hypotension.^{10,11} Thus, the expertise of a well-trained allergist is critical to ensure accuracy in diagnosis. Efforts to cultivate experience with venom allergy across training programs are important as we also strive to increase the number of allergists being trained. A formal assessment of training experiences would be useful in order to determine whether variability in training leads to gaps in competency in this less frequently used skill set.

Beyond having a sufficient number of well-trained allergists, there is generally geographic variability to subspecialty care^{12,13} with evidence that this is also true for allergists.² Subspecialists are more likely to work within population centers, particularly those with training programs. The challenges in accessing care concentrated within urban centers are especially worrisome for patients with venom allergy. Data examining whether stings are more likely in rural areas are not available in the US, however, are supported by studies in the UK,¹⁴ Greece,¹⁵ Spain,¹⁶ and Australia.¹⁷

Telemedicine can address a barrier to care for patients residing in rural communities by promoting access to subspecialty care. Telehealth has been shown to be noninferior to in-person visits for patients with asthma.^{18–21} A systematic review of school-aged children showed promising outcomes for asthma education delivered via telemedicine in terms of improvement in quality of life, symptom management, and symptom burden.²² A meta-analysis of asthma in adults similarly showed that telehealth is effective in improving quality of life and asthma control.²³ The technological advances in digital technology have enhanced access to subspecialists, including allergists.²⁴

While telemedicine holds great promise for the field, a survey of 183 allergists in Turkey found that only 30% of allergists used telemedicine for venom allergy during the COVID epidemic which was lower than those that used telemedicine for other diagnoses.²⁵ The use of skin testing and immunotherapy injections make the use of telemedicine more challenging in a field where procedures are both diagnostic and therapeutic. While telehealth can overcome access to care in a general sense, other mechanisms will be needed to overcome barriers to testing and treatment.

Testing Barriers

The current US stinging insect hypersensitivity practice parameter recommends skin testing as the initial choice in testing¹ based on data suggesting higher sensitivity with skin testing when compared with serum testing.²⁶ It is important to note that there have been significant advances in serum testing compared with the RAST testing used in this study, and a more recent analysis²⁷ noted higher sensitivity using modern ImmunoCAP testing compared with standard intradermal testing. In an accompanying editorial to this paper, Tracy²⁸ notes that access to testing would also be improved using this approach by reducing the potential number of visits needed to make a diagnosis and decreasing the costs associated with intradermal testing incurred by allergists.²⁸ In many areas around the world, serum testing is used in place of skin testing due to barriers accessing venom for testing.²⁹

Skin testing barriers include the venom (cost and access) and the procedure itself, which is time-consuming and less than desirable for patients. Difficulty with access to venom led to notable gaps in access in 2016–2017.³⁰ The cost of the venom itself relative to reimbursement may deter some allergists from routine use of venom skin testing.²⁸ Venom skin testing is time-consuming due to the number of intradermal concentrations being tested. Skin testing for children and others averse to the process of sequential intradermal tests can also be challenging.

Additional barriers to the use of skin testing for venom allergy are the number of antihistaminergic medications that inhibit the wheal-and-flare reaction needed to signify a positive reaction. In addition to first- and second-generation antihistamines, tricyclic antidepressants, sedatives,³¹ and atypical antipsychotics may suppress immediate skin tests.³² Serum testing is not generally affected by the use of medications but may be affected by monoclonal antibodies. Serum testing may be an effective alternative when testing would otherwise be deferred.

The common practice of delaying tests for six weeks following an anaphylactic reaction can become a barrier to testing. This practice is based on data from Goldberg et al,²⁶ which identified a potential refractory phase, resulting in false negative test results within 6 weeks of an anaphylactic event. It is important to note that in the conclusions of this paper the authors do not suggest delaying allergy testing, but rather repeating negative tests if the initial tests were conducted within this time frame.²⁶ The potential for false negatives with earlier testing is only a theoretical barrier, and this common practice warrants additional study to determine whether it causes unnecessary delay in initiation of immunotherapy for patients.

Identification of the Relevant Venom

Based on a single multisite survey of patients,³³ current guidelines recommend not using patient history for identification of the stinging insect triggering an anaphylactic reaction. The results focused on the insects themselves rather than nests that are unique to each genus and excluded other factors that may influence reliability (eg, entomologists and beekeepers may be more reliable in genus determination). In addition, fire ants that produce a pathognomonic sterile pustule due to the activation of neutrophils by the venom alkaloids³⁴ and the presence of these lesions 24 hours after an anaphylactic event is considered diagnostic. In some cases, knowledge of species distribution may be useful in narrowing down the incriminating insect.³⁵ Additional research is warranted to determine the reliability of particular aspects of the history which may reduce the number of extracts used, thereby increasing accessibility for venom immunotherapy.

It can be difficult to identify the offending insect for flying Hymenoptera-induced anaphylaxis based on history alone. As a result, allergists are typically forced to perform venom-specific IgE testing to a range of insects rather than selecting a single type of venom based on history. This often results in more than one positive test result and subsequent choice in selecting the relevant venom extracts to use for desensitization. Without a reliable history, allergists often desensitize patients to all venom types that produce positive test results, increasing cost, time, and potentially risk to patients if clinically irrelevant venoms are used. The current stinging insect hypersensitivity practice parameters¹ recommend skin testing prior to serum testing based on increased sensitivity using older serum testing processes.²⁶ In comparing sensitivity of serum testing versus skin testing, Park et al²⁷ conclude that serum testing is more sensitive. Similar to food-specific IgE, clinically irrelevant sensitization to venom is common in the general population. The presence of venom-specific IgE does not reliably indicate that a patient will have clinical reaction to that venom.³⁶ An alternate interpretation may be that serum testing identifies cross-reactivity of unknown clinical significance, exacerbating the challenge of obtaining venom and desensitizing patients.³⁶

For those with a clinically relevant sensitization to one venom, clinically irrelevant cross-reactivity to other venom types may be the result of cross-reactive epitopes, such as Cross-reactive Carbohydrate Determinants (CCDs)³⁷ rather than unique sensitizations. IgE-inhibition assays can be useful in determining the primary venom in these cases,³⁸ but are not commercially available. Component testing may also be a useful tool in reducing the types of venom selected for immunotherapy in some cases.³⁷ Conversely, component testing for Api m 10 may also be useful in clarifying an allergy to honeybee venom when history is suggestive of honeybee-induced anaphylaxis, but whole venom testing is negative due to the loss of Api m 10 in conventional extracting processes.^{39,40}

Clinically relevant cross-sensitization may be present in patients that react to one species of Vespidae,⁴¹ where treatment with the primary sensitizing insect should result in tolerance to cross-reactive species.⁴² Identifying the insect responsible for the primary sensitization within this family is challenging. Fortunately, *Vespula* and *Dolichovespula* venom can be purchased together as a Mixed Vespid extract. While the cost of this extract is higher than the selection of the individual venom types, the ability to use a single rush-induction phase provides substantial time savings for patients with cross-reactivity among the Vespidae. Of note, *Polistes* are also members of the Vespidae, and therefore do result in cross-reactive positivity but is not included in the Mixed Vespid product.

Identification is even more limited with current commercially available extracts which do not contain many species present in the US. This includes imported species (one species of *Polistes*, three species of *Vespa*) and native species (*Bombus*, *Solenopsis*). Serum testing is available for some, but not all, of these species (Table 1).

Barriers to Auto Injectable Epinephrine

Access, training, and cost, are barriers to epinephrine auto injectors (EAI). Identification by providers of when to prescribe epinephrine is the first step to patient access to an EAI. A study of 208 patients diagnosed with anaphylaxis in the Emergency Room (ER) identified that most patients (36.6%) did not receive an EAI prescription nor an allergist referral (31.3%).⁴³ Inadequate training of EAI by healthcare workers poses another hurdle and was found in a study of 697 patients, where only 31.1% of patients demonstrated correct use of the EAI.⁴⁴

In addition to barriers in access and training, there are barriers in using EAIs by patients. When evaluating patient-driven barriers to prompt epinephrine administration during an event, a study of 66 patients who had been prescribed an EAI at an Allergy and Immunology clinic at a VA medical Center revealed that 92% of patients knew how to use their

Table I Testing Options for Venom-Specific IgE Available in the United States

Order	Family	Genus	Species in North America	HollisterStier Extracts*	Phadia ImmunoCAP
Hymenoptera	Vespidae	<i>Vespa</i>	3	None	<i>V. crabro</i> (imported)
		<i>Vespula</i>	13	Mix of 5 US species	Mix of US species
		<i>Dolichovespula</i>	5	<i>D. arenaria</i>	<i>D. arenaria</i>
				<i>D. maculata</i>	<i>D. maculata</i>
	<i>Polistes</i>	21	Mix of 3 US species	Mix of US species	
			<i>P. dominulus</i> (imported)		
	Apidae	<i>Apis</i>	1	<i>A. mellifera</i>	<i>A. mellifera</i>
		<i>Bombus</i>	46	None	<i>B. terrestris</i> (imported)
	Formicidae	<i>Solenopsis</i>	23	<i>S. invicta</i> (WBE)	<i>S. invicta</i> (imported)
<i>S. richteri</i> (WBE)				<i>S. richteri</i> (imported)	

Notes: *HollisterStier is currently the only supplier of FDA-approved venom extracts in the US. In addition to the venom extracts listed above, a Mixed Vespid extract (containing 100ug of *D. arenaria*, 100ug of *D. maculata*, and 100ug the *Polistes* mixture per milliliter) is available for treatment. This Mixed Vespid extract is not for diagnosis.

Abbreviation: WBE, Whole body extract.

EAI properly but only 58% consistently carried their device.⁴⁵ Cost to the patient may also hinder access. In a survey of 917 patients in the US who had been prescribed an EAI, 89% reported filling prescriptions; however, of the ones who did not, 25% cited that cost as the reason.⁴⁶

Lack of EAI availability and anaphylaxis training is more prevalent in rural and low-income schools. In a survey of school nurses and aides from 1000 schools, 105 rural schools were least likely to have an undesignated EAI available compared to urban and suburban schools and less likely to have a written anaphylaxis plan in the event of a severe allergic reaction (59.4% at rural schools vs 81.7% suburban vs 71.9% urban).⁴⁷ This is important in venom allergy where most of the fatal outcomes in venom anaphylaxis appear to occur with first reactions.⁴⁸ The use of stock epinephrine in schools can increase access to EAIs in resource-limited settings.⁴⁹

The availability of stock epinephrine should be promoted in schools and other public spaces. As with other causes of fatal anaphylaxis, most patients will not have a history of anaphylaxis to draw upon to predict the need for avoidance, auto-injectable epinephrine, or desensitization.^{50,51} The rapidness with which fatal reactions proceed suggests that epinephrine must be immediately available to prevent this outcome.

While the availability of stock epinephrine is important, desensitization substantially decreases the risk of anaphylaxis, making EAIs less critical for patients with known venom allergy. Venom immunotherapy is more effective for *Vespula* (yellow jacket) venom (9% react with subsequent sting challenge) than for honeybee venom (23% react with subsequent sting challenge).⁵² For those with a diagnosis of venom-induced anaphylaxis, venom immunotherapy is a critical intervention. This is especially true for patients without access to autoinjectable epinephrine.

Barriers to Venom Immunotherapy

A study by Patel et al⁵³ described two chart reviews for patients prescribed an EAI and having a diagnosis of venom allergy based on VA medical records from Los Angeles. Time constraints were a common reason for patients not pursuing venom immunotherapy in this study. From 2002 to 2003, 60 patients with reaction to insect venom were identified, of which only 20 were evaluated by an allergist. Review of the allergists' notes verified anaphylaxis in 12 patients of whom none initiated immunotherapy. In their review of cases in 2012–2013, 193 patients with EAI were identified with a diagnosis of venom allergy and only 20 of these were evaluated by an allergist. Fourteen patients seen

by an allergist had a confirmed diagnosis of anaphylaxis. Only one of these patients initiated immunotherapy. The authors noted that time constraints were a motivation for not pursuing immunotherapy in both time periods that were reviewed.

The time investment for patients undergoing venom immunotherapy can be reduced, facilitating initiation. The induction phase of immunotherapy can be reduced from 4 months with conventional build-up dosing to 2 months with modified rush protocols, to 2–3 days with rush protocols and to 4–6 hours using ultrarush induction protocols. Rapid induction immunotherapy protocols appear to be safer than slower induction protocols.⁵⁴ The use of rush-induction protocols increases completion rates reaching maintenance doses for aeroallergen immunotherapy therapy.⁵⁵ However, paradoxically, fewer patients stayed on aeroallergen immunotherapy for three years after rush-induction compared with patients that initiate therapy using conventional weekly build-up schedules⁵⁶ and data suggest that this is also true for fire ant immunotherapy.⁵⁷

Safety comparison between different build-up schedules has been historically difficult as there are different definitions and end points for rush and ultrarush protocols. The best estimates provided by the most recent practice parameters are systemic reaction rates of 5–10% with rush regimens and 0–28% with ultrarush regimens. They concluded that although the risk of a systemic reaction is higher with ultrarush protocols, the risk associated with rush protocols is similar to conventional protocols.¹ Honeybee venom immunotherapy does incur a higher risk (up to 41% with systemic reactions) in comparison to other venoms (up to 25% with yellow jacket venom).⁵²

While the use of pre-medications is common, simplification to the use of H1 blockers as the only premedication, given on the day of flying Hymenoptera immunotherapy, appears sufficiently effective.^{58,59} Thus, it is possible to initiate venom immunotherapy on the day of diagnosis. Ultrarush protocols for fire ant immunotherapy, however, may be safer with more extensive premedication regimens.⁶⁰

As with aeroallergen immunotherapy, a buildup phase is done to reach maintenance dosing which is then continued to sustain unresponsiveness with subsequent exposures to the triggering insect. After reaching the maintenance phase, there are further barriers in adherence with immunotherapy, which is discussed more in the literature with aeroallergen immunotherapy. A systematic review by Park et al of subcutaneous immunotherapy (SCIT) reviewed studies regarding persistence (continuing with immunotherapy) and adherence (persisting with prescribed immunotherapy) with SCIT in the real world. Persistence rates in aeroallergen SCIT were found to be 16–93.7%, and adherence rates were 15.1%–99%. Five of the studies reviewed with a total of 416 patients cited “inconvenience” as the primary reason for discontinuation.⁶¹

Kiel et al⁶² studied levels and predictors of compliance and persistence of aeroallergen SCIT in the Netherlands from 1994 to 2009. Only 23% of patients completed the recommended minimum 3 years of maintenance aeroallergen SCIT in that period. Factors that were associated with an increased rate of persistence included older age, prescription by a general practitioner rather than a specialist, more than one allergen in the immunotherapy, and higher socioeconomic class. The authors considered distance as a likely reason for higher persistence with general practitioners as specialists tend to be about 7 times further in distance.⁶²

A real-life study of adherence for both aeroallergen and venom SCIT in a tertiary care center included 124 patients, 39 of which had venom allergy.⁶³ Their total adherence rate was 56.25%, which increases to 69% when assessing venom SCIT specifically. They evaluated for age, gender, where they lived, type of extract, comorbid disease, induction protocol (clustered vs conventional), frequency of systemic or local reactions, and need for pre-medications. Interestingly, of all the factors considered, the only factor associated with nonadherence was from dose modifications required due to systemic/local reactions or due to missed visits. Depot extracts for venom are available elsewhere but not in the US. These formulations are associated with fewer local reactions in the build-up and maintenance phase of venom immunotherapy and therefore may be more effective at retaining patients on venom immunotherapy when available.⁶⁴

Barriers to adherence to venom and aeroallergen SCIT in the military were evaluated in a study by More et al⁶⁵ 77.4% of 381 patients on SCIT at a single military center were compliant with immunotherapy. Factors resulting in nonadherence included inconvenience (34.5%), precluding medical condition (18.2%), and adverse systemic reaction to immunotherapy (16.4%).⁶⁵ In 2013, a study of 76 patients in a single military center revealed 35% adherence to fire ant immunotherapy at 1-year follow-up.⁶⁶ More recently, Park et al completed a military multi-site study of patients who underwent fire ant SCIT and postulated that lack of adherence could be due to this population’s high relocation rate and

barriers associated with transition of care.⁶¹ More active monitoring and system-level facilitation of venom immunotherapy may be needed.

To facilitate maintenance dose injections, the time between injections can be extended. The FDA-approved package insert for venom extracts recommends maintenance dosing every four weeks. However, intervals of six to eight weeks between injections appear to be safe,⁶⁷ allowing for lower over-all time commitments prospectively, or safely administering doses after missed injections if used retrospectively. After several years of immunotherapy, doses may be spaced to every three months while maintaining safety and effectiveness of the immunotherapy.⁶⁸ While the FDA-approved label is for indefinite use of venom immunotherapy, most patients will have long-lasting protection after three to five years of therapy.⁶⁹ Five years may offer more protection,^{69,70} and indefinite immunotherapy is recommended for those with higher risk factors for subsequent fatal reactions.¹

There is a paucity of information on the role that cost plays in providing access to diagnosis and management of insect hypersensitivity. A study conducted in Portugal examined the consequences of reimbursement cessation for venom immunotherapy; 74% of patients responding to the survey reported stopping VIT due to cost.⁷¹ Additional research to clarify the nature of cost as a barrier to care is needed. Presumably, this barrier would be faced by health insurers that have variable practices and policies, costs directly to the patient, and to physician practices if services are not fully reimbursed.^{72,73} Anecdotally, we know of practices that incur financial losses when providing venom immunotherapy for insured patients. We have also provided extracts to patients that have lacked insurance in our practice; these patients would otherwise have been unable to receive care. Financial barriers faced by physicians could limit their willingness to provide services to patients, adding to the difficulty in accessing physicians with the expertise to diagnose and manage insect hypersensitivity.

Conclusion

Insect hypersensitivity reactions cause significant morbidity and mortality; appropriate diagnosis and management are essential to alleviating them. The primary barrier to diagnosis of insect hypercreativity is difficulty in accessing a trained allergist. Telehealth has the capacity to facilitate access to subspecialists for diagnosis. This does not address the barriers to provision of immunotherapy for patients. Serum testing and component testing may reduce the amount of venom needed for testing and treatment of patients. Use of ultrarush induction protocols for build-up and increasing the spacing interval of maintenance injections may reduce time constraints for those needing immunotherapy while maintaining similar safety profiles as conventional build-up and maintenance dosing. Additional research is needed to better understand the barriers facing those with venom hypersensitivity and how to facilitate the healthcare for these patients.

Disclosure

The authors report no conflicts of interest in this work.

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