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Anaphylaxis (M Sánchez-Borges, Section Editor)

Are Large Local Reactions Useful to Predict Future Anaphylaxis to Hymenoptera Stings?

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Abstract

Purpose of review Unaware of the natural history of large local reactions caused by Hymenoptera stings, patients and clinicians are often concerned when faced with these reactions. These concerns include the difficulty in avoiding stings, the local discomfort, and the fear that the local reaction portends systemic, potentially life-threatening subsequent reactions. This review presents the historical studies that have assessed the natural history of large local reactions caused by Hymenoptera stings and, in doing so, provides rationale for the current consensus guidelines for the management of these reactions.
Recent findings Retrospective and prospective studies in both adult and pediatric populations have provided insight into the natural history of large local reactions caused by Hymenoptera stings dating back to the 1980s. Each of these studies has demonstrated a low risk of future systemic allergic reactions or anaphylaxis in patients with a history of large local reactions.
Summary No clinical biomarker exists to determine the severity of future Hymenoptera sting reactions. Without a reliable clinical biomarker to identify those at risk for systemic allergic reactions or anaphylaxis, recommendations on the management of Hymenoptera sting reactions are derived from retrospective and prospective studies reviewed in this article. These studies provide strong evidence describing a low risk of future systemic allergic reactions or anaphylaxis in patients who have a history of large local reactions. Referral to an allergy specialist can provide reassurance for the referring clinicians and patients with a history of large local reactions. Treatment of large local reactions involves symptom relief with cold compresses, over-the-counter analgesics, oral antihistamines, and occasionally

topical or oral glucocorticoids, usually reserved for very large, protracted reactions. Given the low risk of systemic allergic reactions and anaphylaxis, venom or imported fire ant whole body extract immunotherapy is not recommended for patients with a history of large local reactions. However, there may be some cases where the clinician considers providing an epinephrine autoinjector and/or venom or imported fire ant whole body extract immunotherapy for reasons other than future systemic allergic reactions or anaphylaxis risk. In any case, shared decision-making between the patient and clinician should take place with appropriate documentation of the risks and benefits.

Introduction

Hymenoptera sting reactions can occur at any age and result in a range of allergic and non-allergic clinical responses. Members of the Hymenoptera order causing allergic reactions of clinical importance are of the families Apidae (honeybee, bumblebee, sweat bee), Vespidae (yellow jacket, hornets, paper wasp), and Formicidae (imported fire ant [IFA], jack jumper ant, harvester ant, Chinese needle ant, green-head ant) [1, 2]. These reactions are broadly classified as local or systemic and this distinction is helpful in determining which patients are at risk for systemic allergic reactions (SARs) or life-threatening anaphylaxis from future Hymenoptera stings.

All Hymenoptera stings result in local swelling (2 to 3 cm in diameter), transient pain, and erythema that are contiguous with the sting site. This reaction is due to the toxic effects of the venom. Local reactions can last hours to a few days and typically resolve with simple treatment measures, such as over-the-counter analgesics and cold compresses. Sting reactions can further be classified as large local reactions (LLRs) or SARs of varying degrees, including anaphylaxis. LLRs are a late-phase IgE-mediated inflammatory venom response that results in abnormal inflammation contiguous with the sting site [3, 4]. The initial reaction is usually rapid in onset and mild. However, pain, edema, pruritus, and erythema increase after 6 to 12 h and may progress over 24 to 48 h, crossing joint lines and potentially involving an entire extremity. While there is no universal definition for LLR size, the induration is usually larger than 10 cm in diameter [5•]. LLRs may be associated with lymphangitic streaking within 24 to 48 h, which represents drainage of inflammatory mediators from the sting site rather than infection. Infectious complications of stings generally occur after 72 h. LLRs resolve within 3 to 10 days. The estimated frequency of LLRs ranges from 5 to 25% and are much more common than SARs [6]. SARs, including anaphylaxis, are IgE-mediated and result in signs and symptoms in at least 1 organ system distant from the sting site. Anaphylaxis is a severe, life-threatening SAR resulting in cardiopulmonary collapse or respiratory compromise. Anaphylactic reactions to Hymenoptera stings occur in approximately 0.4 to 0.8% of children with stings and 3% of adults [7, 8]. A conservative estimate is that 40 fatal stings occur annually in the USA, but reliable epidemiologic data are lacking [9].

Allergy testing with appropriate extracts aids with risk assessment and identifies those who are more likely to benefit from venom or imported fire ant whole body extract (IFAWBE) immunotherapy. The presence of specific IgE antibodies to venom constituents increases the likelihood of SARs, but the quantity of specific IgE antibodies does not correlate with severity. Approximately 30 to 60% of patients with a history of a SAR and with specific IgE antibodies (positive skin test or in vitro testing) will experience a SAR when restung [10]. Therefore, identifying patients who are at risk for SARs to Hymenoptera stings is of utmost importance as these patients should be offered venom or IFAWBE immunotherapy [5•]. While LLRs may result in significant morbidity for patients due to prolonged discomfort from induration, compartment syndrome (increased tissue pressure within a closed muscle compartment resulting in muscle and nerve ischemia due to decreased perfusion), or local airway obstruction (if the sting occurs in the oropharynx), the likelihood of

developing a SAR or anaphylaxis upon a repeat sting is low (< 5%) [5•, 11]. Immunotherapy in most cases is not necessary. This article reviews both retrospective and prospective studies on the natural history of LLRs and provides expert opinion on their management.

The natural history of large local reactions

The natural history of LLRs from Hymenoptera stings has been assessed in both retrospective and prospective studies dating back to the 1980s (Table 1). These data provide support for current consensus guidelines for the management of Hymenoptera sting reactions in general and LLRs in particular [5•].

One of the first studies to investigate the natural history of LLRs from flying Hymenoptera stings is a prospective study published by Graft et al. in 1984 [12••]. This study examined the demography, immunology, and significance of LLRs in 54 pediatric patients. Graft et al. reported that 83% of the patients who had a history of LLRs had positive skin test results to one or more venoms and that elevated amounts of venom-specific IgE antibody were usually present. There were a total of 113 repeat stings recorded during the study period and of these repeat stings, only 2% resulted in SARs. Furthermore, the rate of allergic reactions amongst the 54 pediatric patients following a repeat sting was 4%.

The same year Graft et al. published their findings, Mauriello et al. published a prospective and retrospective study following 133 adult patients with a history of LLR from flying Hymenoptera stings over an 8-year period [13••]. Of the 133 patients enrolled in the study, 79 returned for reevaluation, on average 3 years after their LLR. There were a total of 130 repeat stings. One hundred and fourteen of the 130 stings (88%) resulted in repeat LLRs and 1 resulted in a SAR (0.9%). An additional retrospective analysis reviewed the histories of 118 patients with a history of SAR to determine the frequency of preceding LLRs. This analysis determined that five patients with a history of SAR had experienced a preceding LLR. The authors reported that while the prospective analysis did not suggest a risk of SAR, the retrospective analysis did reveal a small number [5•] of patients with a history of LLR who subsequently developed SAR.

Table 1. Systemic allergic reactions (SARs) to Hymenoptera stings in patients with previous history of large local reactions (LLRs)

Author (year)	*n*	Number of stings	% SARs	Remarks
Graft (1984)	54	113	2	Children. LLRs in 83%
Mauriello (1984)	79	130	0.9	Adults
Fernandez (1999)	23	–	0	Children
Golden (2004)	110	44	7	Children
Nguyen (2005)	32	20	0	Children
Pucci (2015)	81	238	0	Adult and children.
	31	59	0	LLRs in 4.2% of patients with SARs

n number of patients with a history of large local reactions to Hymenoptera stings

Fernandez et al. published a prospective study in pediatric patients [14••] in 1999. This analysis focused on the natural history of flying Hymenoptera hypersensitivity over 4 consecutive years in rural Spain. Of the 72 patients in the study, 23 reported a history of LLRs. Subsequent stings in these 23 resulted in 12 patients having similar LLR and 11 a smaller local reaction. None of the patients experienced a SAR after a repeat sting.

Golden et al. reported in 2004 their findings on allergic reactions to flying Hymenoptera stings initially diagnosed in pediatric patients (mean age of 8 years) and then followed for 10 to 20 years prospectively [15••]. Five hundred and twelve of the 1033 patients initially diagnosed with Hymenoptera sting allergy were reevaluated with a mean follow-up of 18 years. One hundred and ten of the patients reported a history of LLRs and 44 of these patients experienced subsequent stings. Amongst these 44 patients, 3 (7%) experienced a SAR. None of these reactions were severe.

The following year, Nguyen et al. published a retrospective study to determine the incidence of SARs in pediatric patients with a history of LLRs and cutaneous systemic reactions to IFA stings [16••]. Thirty-one patients with a history of LLRs and cutaneous systemic allergic reactions were examined. Twenty of the 32 patients (65%) reported that they had not developed more severe allergic reactions with subsequent stings and none of the 20 reported anaphylaxis after subsequent stings.

In 2015, Pucci et al. published a retrospective and prospective study investigating the risk of SAR in patients with a history of LLRs from flying Hymenoptera stings [17••]. A total of 477 patients were included in this study. Three hundred and ninety-six of the patients had a history of SARs to Hymenoptera sting and 81 reported LLRs. Of those with a history of SAR, 17 (4.2%) had a previous LLR as the first manifestation of allergy. Amongst the patients with a history of LLR, all had experienced at least 2 LLRs in their lifetime with a total number of 238 stings without SAR. Fifty-three of these patients were prospectively evaluated over 3 years. Thirty-one (58%) of prospectively evaluated patients experienced a repeat sting with an overall number of 59 repeat stings. These stings resulted in LLRs only.

These studies demonstrate that both pediatric and adult patients with a history of LLRs are far more likely to have a subsequent LLR after a repeat sting than a SAR or anaphylaxis. Based on these results, the risk of SAR or anaphylaxis in a patient with a history of LLR is insufficient to warrant epinephrine autoinjector carriage or venom immunotherapy for management and prevention of a SAR or anaphylaxis. The same can be said for patients with a history of LLRs to IFA stings. These findings have been used to develop the current consensus guidelines for the treatment of patients with a history of LLRs to Hymenoptera stings [5•].

Treatment of large local reaction stings

There are a variety of options in the management of LLRs; however, none are based on evidence.

If a stinger is still present at the sting site, remove it with a scraping motion using a blunt-edged object, such as a tongue depressor or credit card. Avoid attempting to grab the stinger as this may facilitate the release of more venom.

Wash the sting site with soap and water.

Cold compresses, such as a cold, damp washcloth or damp cloth wrapped around an ice pack, can be applied to the reaction site to reduce pain and swelling.

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing inflammation and pain. Common examples of NSAIDs include ibuprofen 200–400 mg orally every 6–8 h as needed (adult dose) and 4–10 mg/kg/dose orally every 6–8 h as needed (pediatric dose) or naproxen 220 mg orally every 8–12 h as needed (adult dose) and 5–10 mg/kg/dose orally every 8–12 h as needed (pediatric dose). The most common adverse effects of NSAIDs include nausea, vomiting, and dyspepsia as they can cause gastric irritation. An alternative to NSAIDs includes acetaminophen (Tylenol). Acetaminophen does not possess the anti-inflammatory properties of NSAIDs, but is an analgesic. Doses of acetaminophen include 325–1000 mg orally every 4–6 h as needed (adult dose) and 10–15 mg/kg orally every 4–6 h as needed (pediatric dose). Total dose over 24 h should not exceed 4 g. Caution should be used in patients with liver disease as acetaminophen is metabolized primarily through the liver.

Antihistamines are useful in the treatment of pruritus and edema. Second-generation antihistamines are less sedating than first generation antihistamines. Second-generation antihistamines include loratadine (Claritin), cetirizine (Zyrtec), and fexofenadine (Allegra). Typical doses include loratadine 10 mg orally daily as needed (adult dose) and 5 mg orally daily as needed (pediatric dose), cetirizine 10 mg orally daily as needed (adult dose) and 2.5–5 mg orally daily as needed (pediatric dose), and fexofenadine 180 mg orally daily as needed (adult dose) and 15–30 mg orally two per day as needed (pediatric dose). A commonly used first-generation antihistamine is diphenhydramine (Benadryl) 25–50 mg orally every 6 h as needed (adult dose) and 6.25–25 mg orally every 4–6 h as needed (pediatric dose).

Low potency topical glucocorticoids such as hydrocortisone 1% cream can be used to treat local erythema and pruritus. This dose can be applied as a thin layer over the reaction site up to four times per day as needed for both adult and pediatric patients. In patients with a known history of protracted LLRs, oral glucocorticoids if started early can hasten recovery. A commonly used oral glucocorticoid is prednisone. Typical doses of prednisone include 40–60 mg orally divided into two or three times a day dosing with a rapid 5-day taper (adult dose) or 1 mg/kg orally divided into twice to four times a day dosing with a rapid 5-day taper (pediatric dose). Common side effects to be aware of with short-course oral prednisone include psychological changes (aggression, agitation), edema of the extremities, hyperglycemia, and tachycardia.

Venom or IFAWBE immunotherapy is usually not necessary as the risk of future SAR or anaphylaxis is low. However, some patients with a history of repeat exposure or recurrent LLRs may benefit from immunotherapy to reduce local reactions and virtually eliminate the chance of future SARs or anaphylaxis. If immunotherapy is started, the maintenance goal should be 100 mcg of purified venom extract of culprit flying Hymenoptera or 0.5 mL of 1:10–1:100 weight/volume of IFAWBE.

Conclusions

Hymenoptera sting reactions range from local, transient responses to life-threatening anaphylaxis. LLRs are delayed IgE-mediated reactions contiguous

with the sting site which can result in significant co-morbidity but are associated with a low risk for future SAR or anaphylaxis (< 5%) [11]. Several retrospective and prospective studies confirm this low risk of both future SARs and anaphylaxis in patients with a history of LLRs. Thus, venom or IFAWBE immunotherapy is not recommended for patients with a history of LLRs. Typically, LLRs can be managed with cold compresses, over-the-counter analgesics, oral antihistamines, and, for severe responses, topical or oral corticosteroids. LLRs resolve in 3 to 10 days. Caveats to this management include LLRs that result in compartment syndrome or local airway obstruction (if the sting occurs in the oropharynx). The patient's quality of life, the frequency of Hymenoptera exposure, and access to medical care influence whether an epinephrine autoinjector is prescribed. After careful discussion with the patient, prescribing an epinephrine autoinjector might be considered in some patients in order to lessen the patient's anxiety about rare, future SARs. Venom or IFAWBE immunotherapy may be warranted in patients with a history of frequent LLRs (more than 1 reaction per year), complicated LLRs, or unavoidable exposure, such as beekeeping, gardening, or landscaping. When venom or IFAWBE immunotherapy is used, the severity of subsequent LLRs is significantly reduced [18•].

Compliance with Ethical Standards

Conflict of Interest

Dr. Kirk V. Shepard II declares that he has no conflict of interest.

Dr. Dennis K. Ledford declares consultancy for AstraZeneca and Genentech; speaker bureau for AstraZeneca, Circassia, Genentech/Roche, Meda, Novartis, Teva; research support paid to institution AstraZeneca, Genentech; legal opinion for drug allergy, asthma death, indoor allergen exposure, metal allergy.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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