Multicenter study of emergency department visits for insect sting allergies

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Background: An earlier study of food-related anaphylaxis in the emergency department (ED) suggested low concordance with national guidelines for anaphylaxis management.

Objective: To extend these findings, we performed a chart review study to describe current ED management of insect sting allergy.

Methods: The Multicenter Airway Research Collaboration performed a chart review study in 15 North American EDs. Investigators reviewed 617 charts of patients with insect sting allergy. Patients were identified by using International Classification of Diseases, 9th Revision, codes 989.5 (toxic effect of venom), 995.0 (other anaphylactic shock), and 995.3 (allergy, unspecified).

Results: The cohort was 42% female and 61% white, with a mean age of 36 ± 19 years. In this cohort, 58% had local reactions, 11% had mild systemic reactions, and 31% had anaphylactic reactions, as defined by multisystem organ involvement or hypotension. Among patients with systemic reactions (mild or anaphylaxis), most (75%) were stung within 6 hours of ED arrival. While in the ED, 69% of systemic reaction patients received antihistamines, 50% systemic corticosteroids, and 12% epinephrine. Almost all systemic reaction patients (95%) were discharged to home. At ED discharge, 27% (95% CI, 22% to 33%) of systemic reaction patients received a prescription for self-injectable epinephrine.

Methods: The Multicenter Airway Research Collaboration performed a chart review study in 15 North American EDs. Investigators reviewed 617 charts of patients with insect sting allergy. Patients were identified by using International Classification of Diseases, 9th Revision, codes 989.5 (toxic effect of venom), 995.0 (other anaphylactic shock), and 995.3 (allergy, unspecified).

Disclosure of potential conflict of interest: A. Long has consulted with AstraZeneca, Schering Plough, and Altana, and is on the speakers’ bureau of Genentech, Novartis, GlaxoSmithKline, Pfizer, Schering Plough, and Sanofi-Aventis. C. Camargo has a consulting arrangement with Dey and Venus and receives grants and research money from Dey. There are no other conflicts of interest to disclose.

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Hymenoptera stings (eg, fire ants, wasps, yellow jackets, and hornets) are thought to have caused anaphylaxis in 0.4% to 5% of the general population.1-4

Other studies report that systemic allergic reactions to Hymenoptera venom occur in 0.4% to 3.3% of individuals.5-8 The potential for a serious adverse outcome is quite real, because 35% to 60% of patients with previous severe systemic reactions will have anaphylaxis if stung again.9 More recent evidence suggests that patients with a history of severe reactions who have negative skin test results may still be at risk for severe reactions despite the negative skin test result.10,11

Although a universal definition of anaphylaxis is not available,2,12,13 there is growing agreement that anaphylaxis represents an acute, severe, multisystem allergic reaction.14,15 The signs and symptoms of an allergic reaction to insect sting can include localized pain, erythema, and swelling that are extreme immediately after the sting but decrease during the subsequent hours. In addition to resulting in acute allergic or anaphylactic reactions, it is important to note that components of venom can lead to direct toxic effects, including hemolysis and seizures, and that these toxic effects can be life-threatening.16

Approximately 40 to 100 Americans die every year as a result of insect stings, but these numbers are thought to be gross underestimates.2-4,9,16 In recent studies, the prevalence of anaphylaxis among all emergency department (ED) visits was estimated to be 0.09% to 1%, or approximately 275,000 visits each year.17,18 Indeed, the ED is the most common medical setting for the diagnosis and management of anaphylaxis,19 a situation that encourages more active collaboration between allergist clinicians and researchers and their counterparts in emergency medicine.

Guidelines recommend treatment of all severe allergic reactions and anaphylaxis with epinephrine, teaching of proper techniques for self-injectable epinephrine, and
referral to an allergist for further testing and probable venom immunotherapy.  Although many patients who develop insect sting anaphylaxis will present to the ED, little is known about the current management of these cases, or of acute allergic reactions in general. Given the spectrum of acute allergic reactions to insect sting, prospective multicenter studies are needed to define better the actual frequency of such visits and to describe their clinical presentations, ED management, and outcomes. In preparation for such a study, we performed a multicenter investigation of 617 patients presenting to the ED with insect sting allergy. Our objective was to describe this patient population and to compare ED management of insect sting allergic reactions, particularly anaphylaxis, with recommended guidelines.

**METHODS**

This retrospective cohort study was performed as part of the Multicenter Airway Research Collaboration, a division of the Emergency Medicine Network. By using a standardized protocol and data abstraction forms, investigators at 15 EDs in 11 US states and 2 Canadian Provinces reviewed ED visits for insect sting allergy. More specifically, sites screened all patients presenting to the ED over a 1-year period with a physician-diagnosed insect sting allergic reaction. They also screened cases coded with a more general allergic reaction code with cause not otherwise specified. All records that suggested a likely insect sting allergic reaction underwent full chart review. Screened charts that revealed allergic reactions caused by exposures other than insect stings did not undergo full chart review. Repeat visits by individual subjects were excluded. Visits during a 1-year period from January 1999 to November 2001 were identified by code from the International Classification of Diseases, 9th Revision. The following codes were used to identify charts for screening: 989.5 (toxic effect of venom), 995.0 (other anaphylactic shock), and 995.3 (allergy, unspecified). The Institutional Review Board at each of the 15 participating hospitals approved the study.

**Data collection**

A structured chart review was performed to assess patients’ demographic characteristics, allergy history, and details of their insect sting allergic reaction. Chart review included past medical history, presentation, and clinical course. Median family income was estimated by using patients’ home zip codes. Symptoms and signs were extracted from all available sources (eg, ambulance sheet, nurse triage note, physician note), and any positive findings were counted. Discharge instructions were recorded for patients sent home from the ED. All data forms were reviewed by site investigators before submission to the Emergency Medicine Network Coordinating Center in Boston, where they underwent further review by trained personnel and then double data entry to avoid data entry errors.

Local reactions were considered to be reactions with skin rash, hives, or swelling confined to or contiguous with the area of the sting. Mild systemic reactions were those that involved some indication of a generalized component but could not be definitively classified as anaphylaxis. Patients with skin rash, hives, or swelling in more than 1 location (and only 1 sting) were considered to have mild systemic reactions. Potentially life-threatening reactions were determined on the basis of patients’ documented symptoms and signs at ED presentation or during the ED course. Our operational definition of anaphylaxis was the involvement of 2 or more organ systems from the following list: skin (eg, hives), respiratory (eg, wheezing), cardiovascular (eg, hypotension), and gastrointestinal (eg, crampy abdominal pain). In this cohort, the presence of hypotension (systolic blood pressure < 100 mm Hg) automatically led to classification as anaphylaxis.

Systemic reactions, including mild and anaphylactic reactions, were further classified into severity of the systemic reaction on the basis of the grading system proposed by Brown. Mild systemic reactions were those involving skin or cutaneous tissue without involvement of other organ systems. Moderate reactions were those classified as anaphylaxis on the basis of the involvement of 2 or more organ systems or hypotension defined as a systolic blood pressure between 90 and 100 mm Hg with no neurologic compromise. Severe reactions were those reactions with a systolic blood pressure < 90 mm Hg or neurologic compromise (eg, confusion, collapse, or loss of consciousness).

**Statistical analysis**

All analyses were performed by using STATA 7.0 (StataCorp, College Station, Tex). Data are presented as proportions (with 95% CIs), means (with SDs), or medians (with interquartile range [IQR]). The association between discharge prescription for self-injectable epinephrine and other factors was examined by using the χ² test, Student t test, and Kruskal-Wallis rank test, as appropriate. Age was included in all multivariate logistic regression models because of its potential clinical significance. Other variables associated with discharge prescription for self-injectable epinephrine (or with the outcome of interest) at P < .10 in univariate analysis or considered to be of potential clinical significance were evaluated for inclusion in multivariate logistic regression models. All factors retained in the final multivariate models were included on the basis of their statistical significance on multivariate analysis or because of their potential clinical significance.

Although individual observations across sites are independent, they may not have been independent within a site. Accordingly, multivariate models were performed by clustering the results on the basis of the site where each patient was enrolled. Results from the clustered and unclustered analyses were nearly identical, so only the clustered analysis results are shown. All odds ratios are presented with 95% CI. The final models were evaluated by using the Hosmer-Lemeshow test. All P values are 2-tailed, with P < .05 considered statistically significant.

**RESULTS**

The screening process produced a cohort of 617 patients for chart review from the 1523 charts identified. Sites contributed an average of 41 patients per site (range, 5-154 cases). Looking at seasonal trends, we found a peak during late summer months (see Fig E1 in the Online Repository in the online version of this article at www.mosby.com/jaci) with most insect sting allergy incidents occurring in July (170, 28%), August (186, 27%), and September (102, 17%). Looking across regions (eg, New England, Mid-Atlantic), there were no differences in this seasonal trend (data not shown).
Patients had an average age of 36 years (range, 1-87 years) and had a slight predominance of males (Table I). Past medical and allergy history also are shown in Table I. Only 32% of patients had a known history of allergic reaction to insect stings. Combining asthma and other known allergic problems, 29% (95% CI, 25% to 33%) of patients had documentation of another, previous allergic problem.

Details of the current insect sting episode are shown in Table II. The median number of stings was 1 (IQR, 1-1). Most patients (87%) were stung on only 1 body part. Among all patients, the hand or arm was the most frequently documented site of the sting. Insect sting allergic reactions in this cohort resulted in signs and symptoms affecting the skin in most patients (86%); generalized skin rash was documented for 6% of patients and generalized swelling for 4%. Respiratory symptoms (22%), gastrointestinal symptoms (10%), and cardiovascular symptoms (6%) also were documented. Seven patients (1%) had documentation of all 4 organ systems being affected.

Categorizing patients into 3 groups on the basis of number of locations on the body affected by rash, hives, or swelling and the severity of the reaction, we determined that 358 (58%) patients had local reactions and 259 (42%) had systemic reactions. Seventy (11%) of the patients with systemic reactions had mild allergic reactions, and 189 (31%) had anaphylaxis (as defined by involvement of 2 or more organ systems or hypotension). Further classifying the systemic reactions by severity grade, 70 (27%) had mild systemic reactions, 143 (55%) had moderate reactions, and 46 (18%) had severe reactions.

Local reactions

Among patients with local reactions, nearly half were treated with antihistamines, and approximately one quarter were treated with systemic steroids. As expected, treatment with respiratory treatments and epinephrine during the ED stay was uncommon in these patients. Nearly all (98%) of patients with documentation of a local reaction were discharged to home. Among patients with local reactions, 6% received antibiotics. Given that large local reactions can resemble cellulitis with extensive erythema, it is possible that these patients treated with antibiotics because of this resemblance.

Mild systemic reactions

Less than 20% of patients with mild systemic reactions were brought to the ED by ambulance. Sixty-five percent of patients with mild systemic reactions arrived to the ED within 6 hours of being stung. Approximately 1/3 of these patients with mild systemic reactions arrived to the ED within 1 hour of symptom onset. Within 3 hours of ED arrival, only 4% (95% CI, 1% to 12%) of patients had documentation of use of intramuscular or subcutaneous epinephrine.

A majority of patients with mild systemic reactions received antihistamines, with 94% of these patients receiving diphenhydramine. Overall, 52% of these patients received systemic steroids. No patients with mild systemic reactions received respiratory treatments (such as inhaled β-agonists or anticholinergics). Only 9% of all patients received epinephrine while in the ED, a finding that did not change when looking only among patients who did not have documentation of intramuscular or subcutaneous epinephrine use during the 3 hours preceding the ED visit. No deaths from insect sting allergic reactions were observed in this group. The vast majority of patients were sent home from the ED (92%), with a median ED length of stay of 115 minutes (IQR, 72-155 minutes).

Anaphylactic reactions

Approximately 1/3 of patients with reactions classified as anaphylaxis were brought to the ED by ambulance. Seventy-nine percent of patients with anaphylactic reactions arrived to the ED within 6 hours of being stung. More than half of these patients arrived to the ED within 1 hour
of symptom onset. Within 3 hours of ED arrival, only 16% (95% CI, 11% to 22%) of patients had documentation of use of intramuscular or subcutaneous epinephrine.

Almost 70% of patients with anaphylaxis received antihistamines. Overall, 49% of these patients received systemic steroids, and 7% received respiratory treatments. Only 13% of all patients received epinephrine while in the ED, a finding that did not change when looking only among patients who did not have documentation of intramuscular or subcutaneous epinephrine use during the 3 hours preceding the ED visit. No deaths from insect sting allergic reactions were observed in patients with anaphylaxis, and most patients were sent home from the ED (97%). Patients with anaphylaxis had a median ED length of stay of 160 minutes (IQR, 98-220 minutes).

Discharge plans

Discharge plans were assessed among patients with systemic reactions (mild or anaphylaxis). These plans varied widely across sites (Fig 1). Overall, 15% of patients with a systemic reaction were given discharge instructions to avoid the offending allergen, with the range extending from 0% to 69%. Only 27% of these patients received a prescription for self-injectable epinephrine at discharge, with a range of 0% to 100%. Among patients who received treatment with epinephrine in the ED, 64% had documentation of self-injectable epinephrine at discharge. Finally, 20% of patients had documentation of referral to an allergist, with a range of 0% to 65%. Only 6 of the 259 patients (2%; 95% CI, 1% to 5%) received all 3 recommended preventive interventions.

Multivariate predictors of a discharge prescription for self-injectable epinephrine among patients with a generalized reaction or anaphylaxis are shown in Table III. The final model had good discrimination with an area under the receiver operator characteristic curve of 0.83. The model also gave a good fit to the data, with a Hosmer-Lemeshow statistic of 6.33 with 10 df ($P = .61$).

DISCUSSION

To our knowledge, we report the largest study of individuals presenting to the ED with insect sting allergic reaction. Among this cohort of 617 patients, 11% had mild systemic allergic reactions and 31% had anaphylaxis, as defined by involvement of 2 or more organ systems or hypotension. Even among the subset of patients with anaphylaxis, concordance with management recommendations was quite low. ED discharge plans also varied widely across participating sites.

Emergency department staff should strive to obtain a thorough medical history in all patients, including those presenting to the ED after an insect sting. Neugut et al2 state that an effective and reliable way to identify individuals at risk of an anaphylactic episode is by their previous allergy history. Estimates state that 35% to 60% of patients with previous severe systemic reactions will have an anaphylactic reaction if stung again.9 Another study suggested, however, that although large local reactions are thought to be IgE-mediated, the risk of anaphylaxis on subsequent sting is small; the authors reported that only 10% of patients with a previous localized reaction went on to have a more severe reaction.16 We found that 32% of patients presenting to the ED with an insect sting reaction had a known history of insect sting allergy; however, detailed information about the nature of the previous reaction (eg, large local or anaphylactic) was not

### Table II. Etiology, presentation, and clinical course of patients presenting to the ED with an insect sting-related allergic reaction, according to type of reaction

<table>
<thead>
<tr>
<th>Current allergic reaction</th>
<th>Overall (n = 617)</th>
<th>Local reaction (n = 358)</th>
<th>Mild systemic reaction (n = 70)</th>
<th>Anaphylaxis* (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of times stung, median (IQR)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Location of sting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand or arm (%)</td>
<td>42</td>
<td>44</td>
<td>51</td>
<td>34</td>
</tr>
<tr>
<td>Foot or leg (%)</td>
<td>20</td>
<td>22</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Head (%)</td>
<td>20</td>
<td>18</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Trunk (%)</td>
<td>9</td>
<td>7</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Neck (%)</td>
<td>7</td>
<td>4</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Other (%)</td>
<td>0.5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Treatments received in ED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamines (%)</td>
<td>57</td>
<td>48</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>Systemic steroids (%)</td>
<td>34</td>
<td>24</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>Respiratory treatments (%)†</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Epinephrine (%)</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Discharged to home (%)</td>
<td>97</td>
<td>98</td>
<td>92</td>
<td>97</td>
</tr>
</tbody>
</table>

*Involvement of 2 or more organ systems, or hypotension alone (see Methods).
†Respiratory treatments include inhaled β-agonists and inhaled anticholinergics.
available in the medical records. Among patients with anaphylaxis, 39% of patients had a known history of insect sting allergy.

Although previous history of insect sting reactions was similar to that in other studies, presentation and ED management varied across studies. Our findings were concordant with those found by Schwartz,1 who found that 163 (50%) of 326 patients presenting to an ED with an insect sting allergic reaction had an insect sting allergic reaction, with 48 (29%) of the insect sting group found to have systemic reactions. The systemic reactions of these 48 patients varied widely, with 45 (94%) having cutaneous symptoms, 21 (44%) having respiratory symptoms, and 10 (21%) having cardiovascular symptoms. Most patients were treated with antihistamines, epinephrine, and corticosteroids, but only 13 (27%) were given a prescription for self-injectable epinephrine, and only 6 (13%) were referred to an allergist. We found similar results regarding reaction severity, organ system involvement, and poor concordance with recommended guidelines.

Signs and symptoms differed between our cohort and a frequently cited 1970 cohort by Brown and Bernton.28 In that study, the most frequent signs and symptoms of allergy to insect stings were local swelling (63%), generalized swelling (56%), generalized itching (55%), itching at sting site (50%), urticaria (49%), dyspnea (43%), weakness (39%), and decreased blood pressure (37%).28 In our study, generalized skin rash was documented for only 6% of patients and generalized swelling for 4%. As expected, signs and symptoms involving skin were most prevalent (86%) among this cohort of insect sting allergic reactions. Only 22% of patients also had respiratory symptoms associated with an insect sting allergic reaction. Even among patients with anaphylaxis, only 15% had documentation of generalized skin rash and only 5% for generalized swelling. Among the anaphylaxis subgroup, however, 60% had documentation of respiratory symptoms.

Data on ED management of anaphylaxis remain sparse, especially in terms of Hymenoptera stings. A retrospective British study by Stewart and Ewan12 screened 1207 charts of ED patients and identified 9 patients with severe anaphylactic reactions and 15 with less severe, generalized reactions, with 3 cases caused by Hymenoptera stings. Another population-based study in Britain found that 28 of 100 anaphylaxis cases were attributable to insect stings or bites. Among these 28 reactions, 3 (11%) were classified as severe reactions.29 Among the ED patients in the current study, we identified 617 patients, of whom 70 (11%) had generalized allergic reactions and 189 (31%) were classified as having anaphylaxis.

An Australian study by Brown et al13 found that 53 (18%) of 304 patients presenting to the ED with acute allergic reactions or anaphylaxis had a reaction caused by insect sting. Among anaphylaxis cases alone, 61% were admitted to the ED observation ward and 6% were admitted to a general medical ward or intensive care unit. By contrast, Stewart and Ewan12 in Britain reported that 12% of their anaphylaxis cases were admitted. In our cohort, only 3% of ED patients were admitted. Even among those ED patients with a potentially life-threatening reaction, 97% were discharged home.

This marked discrepancy could be a result of other causes of allergic reactions besides insect sting being included in the Australian study. Different healthcare systems and treatment patterns also might contribute. However, the most likely explanation is the lack of a universal definition for anaphylaxis, which undoubtedly contributes to practice variation between physicians and institutions.13 Agreement on a clinically useful definition of anaphylaxis is essential to further research and education efforts and should be actively pursued.

For those with anaphylactic reactions, however defined, guidelines recommend use of epinephrine, teaching of proper techniques for self-administration of epinephrine, and referral to an allergist.20 Concordance with these guidelines appears to be very low among these North
American EDs. Among patients with anaphylaxis, only 13% of patients received epinephrine in the ED, 31% had documentation of a discharge prescription for self-injectable epinephrine, and 21% received a referral to an allergist. Thus, these results extend those from our previous study on ED management of food-related allergic reactions and suggest an important opportunity to improve allergy care.

Our results are consistent with earlier data suggesting that few patients receive discharge prescriptions for self-injectable epinephrine. Commonly, the only prescriptions given were refills, an observation that led the authors to conclude that only patients who had a previous prescription for self-injectable epinephrine were given such a prescription on leaving the ED.

Advice on how to prevent future reactions and referral to an allergist has been consistently low throughout the literature. The Australian study found that arrangements to follow-up in an allergy clinic were made for only 23% of patients. The British study reported that 1/6 of patients with less severe reactions were referred to an allergist, whereas surprisingly, no patients with severe anaphylaxis reactions received a referral. A study by McDougale found that only 44% of patients with Hymenoptera anaphylaxis were referred to an allergist for further evaluation. This represents another opportunity to improve allergy care.

A potential limitation of the current study is its retrospective design and sole reliance on the medical record. Is that documentation accurate and complete? Although some of the findings, such as discharge prescriptions for self-injectable epinephrine, may be underestimates, we believe that the large discordance with guideline recommendations across a variety of practice settings cannot be explained by documentation alone.

In addition, differentiation between normal local and large local reactions is important to characterize stings that result from IgE-mediated reactions. Normal local reactions are those with local transient pain with erythema and swelling at the site of the sting; they generally subside within 1 to 2 days. Large local reactions are those reactions with local swelling greater than 5 cm that peak between 24 and 72 hours after the sting. A limitation of the current study is that we were not able to determine the size of reactions (ie, width of skin rash) because this information was not available on medical records. This important issue will require prospective data collection for resolution.

Finally, the participating EDs in this study are academic medical centers, many of which support emergency medicine residency programs. Site investigators were identified through their research interest in allergy and asthma, and this interest may have carried over to other members of their ED staff. Thus, these results may not reflect management patterns among nonacademic or rural EDs.

In summary, this multicenter study demonstrates that concordance with recommended guidelines for the treatment of insect sting allergic reactions is low. Even among the subset with anaphylactic reactions (31% of all patients), concordance was low. At a minimum, there is poor documentation of instructions to avoid future insect stings, discharge prescriptions for self-injectable epinephrine, and referral to an allergist. Because the ED is the most common medical setting for diagnosis and management of anaphylaxis, advances in anaphylaxis management will need the active participation of emergency medicine clinicians and researchers. Our study demonstrates the untapped opportunity for ED staff to guide patients with potentially life-threatening allergies toward better allergy management.

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