



Contents lists available at SciVerse ScienceDirect



Longitudinal study of 954 patients with stinging insect anaphylaxis

Susan A. Rudders, MD^{*}; Sunday Clark, MPH, ScD[†]; Wenhui Wei, PhD, MS, MBA[‡]; and Carlos A. Camargo, Jr, MD, DrPH[§]

^{*} Department of Pediatrics, Division of Asthma and Allergy, Rhode Island Hospital, Alpert School of Medicine at Brown University, Providence, Rhode Island

[†] Department of Emergency Medicine, Weill Cornell Medical College, New York, New York

[‡] Sanofi US, Bridgewater, New Jersey

[§] Department of Emergency Medicine and Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:

Received for publication April 9, 2013.

Received in revised form May 23, 2013.

Accepted for publication June 14, 2013.

ABSTRACT

Background: Stinging insect anaphylaxis (SIA) is a common cause of anaphylaxis and is potentially life-threatening.

Objectives: To examine US patients with an emergency department (ED) visit or hospitalization for SIA to evaluate postdischarge follow-up care.

Methods: We identified all patients with an ED visit or hospitalization for SIA during 2002–2008 in the MarketScan Database using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (index date was the initial ED visit or hospitalization). Patients were required to have continuous full insurance coverage for 1 year or more before and after index. We examined patient factors during the preindex period, characteristics of the index event, and outcomes during the postindex period. Multivariable logistic regression was used to identify independent predictors of receiving preventive anaphylaxis care.

Results: We identified 954 patients with an ED visit or hospitalization for SIA (mean [SD] age, 46 [19] years; 41% female). A total of 85% of patients were discharged directly from the ED. For those hospitalized, the mean hospital stay was 1 day, and 50% spent time in the intensive care unit. Cardiorespiratory failure occurred in 27% of those hospitalized. During the postindex period, 69% filled 1 or more epinephrine autoinjector prescription, but only 14% had 1 or more allergist/immunologist visit. Independent factors associated with receiving preventive anaphylaxis care during the postindex period were higher household income, no ED visit (for any reason) in the preindex period, and no cardiorespiratory arrest or failure during the index event.

Conclusions: Although two-thirds of patients filled a prescription for an epinephrine autoinjector after an ED visit or hospitalization for SIA, only 14% of patients received follow-up care by an allergist/immunologist. This missed opportunity to provide venom immunotherapy, an essentially curative therapy, unnecessarily places patients at risk for recurrent anaphylaxis.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Stinging insect hypersensitivity reactions are one of the most common causes of anaphylaxis.^{1,2} Stinging insect anaphylaxis (SIA) can include a wide range of symptoms, and the most severe forms, involving the respiratory or cardiovascular systems, can be life-threatening.³ Although there are limited recent data on the epidemiology of SIA, earlier studies estimate that potentially life-threatening systemic reactions occur in up to 0.8% of children

and 3% of adults.^{4–6} However, prompt recognition and proper treatment of SIA, including appropriate disposition and long-term allergy management with venom immunotherapy (VIT), can almost completely eliminate the occurrence of future reactions and potential fatalities.⁷

Indeed, all treatment guidelines recommend that patients at risk for SIA should be prescribed an epinephrine autoinjector (EAI) and referred to an allergist/immunologist for diagnostic and therapeutic evaluation.^{8–10} Prior studies have reported that improvement is needed in terms of appropriate disposition of anaphylaxis patients.^{11–14} For example, a study by our group reported that approximately one-third of emergency department (ED) patients did not receive an EAI prescription and even fewer received a referral to an allergist/immunologist on discharge.¹² Despite collective acknowledgment that this area requires further study,

Reprints: Susan A. Rudders, MD, Department of Pediatrics, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903; E-mail: srudders@lifespan.org.

Disclosures: C. A. Camargo, Jr has consultancy arrangements with Dey Pharma/Mylan Inc (Basking Ridge, NJ) and Sanofi Aventis (Bridgewater, NJ). The other authors have no conflicts of interest.

Funding Support: This study was funded by Sanofi US.

our knowledge about the follow-up care received by SIA patients (after they have left the acute care setting) is limited.^{15–18} Therefore, we sought to describe this population using a large administrative database to determine the percentage and characteristics of SIA patients who actually receive preventive allergy care (ie, filling prescriptions for EAI and seeing an allergist/immunologist after their index event). Lastly, we sought to determine the frequency with which these patients present again to any ED or hospital with a recurrent episode of anaphylaxis.

Methods

Data Source

The 2001–2009 Thomson Reuters MarketScan Commercial and Medicare Supplemental Databases were used for this study. These databases provide access to fully adjudicated inpatient and outpatient medical claims, as well as outpatient prescription-drug claims, for approximately 43 million privately insured individuals annually. Individuals are enrolled in approximately 100 health plans, including a variety of fee-for-service and managed care designs. The covered population includes persons with employer-sponsored health insurance for themselves and their dependents and includes individuals 65 years and older with Medicare supplemental insurance. Detailed cost, use, and outcomes data for health care services performed in both inpatient and outpatient settings are available. The medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique enrollee identifiers. The MarketScan Research Databases are fully compliant with the letter and spirit of the Health Insurance Portability and Accountability Act of 1996, and institutional review board review was waived.

Patient Selection

Adults (aged ≥ 18 years) and children (aged < 18 years) were included if they had an ED visit or hospitalization for SIA during the study period (January 1, 2002, to December 31, 2008). The SIA events were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes based on methods 1 and 2 of the Harduar-Morano algorithm.¹⁹ Specifically, in method 1, SIA patients were identified if they had an encounter with a code specific for anaphylactic shock (eg, code 995.0, other anaphylactic shock) in conjunction with a venom-specific code. Venom-specific diagnosis codes included the toxic effect of venom (code 989.5) or a venom-specific Ecode (codes E905, E905.3, E905.5, E905.8, and E905.9). Method 2 identified patients who had codes for the symptoms of anaphylaxis in conjunction with a venom-specific code. The article by Harduar-Morano et al¹⁹ provides additional details of this algorithm.

We required that included patients had continuous medical and prescription coverage for 1 year or more before (preindex) and after (postindex) the date of the index ED visit or hospital discharge. Thus, the index event was the ED visit or hospitalization that served as the anchor for our inclusion criteria, representing the first anaphylaxis event for that patient during the period studied. Patients admitted to the hospital through the ED were captured in the hospitalized cohort. Immunocompromised patients with a diagnosis of AIDS or cancer, patients undergoing organ transplantation during the preindex period, and those with sepsis at index were excluded.

Demographic and Preindex Clinical Characteristics

Demographic characteristics, such as age, sex, and health plan type, were extracted from the claim for the index event. Median household income was estimated by matching the zip code of the patient's residence with that of the 2000 US Census. Clinical

characteristics were collected in the preindex period. The Deyo adaptation of the Charlson Comorbidity Index (CCI) and individual comorbid conditions were based on specific ICD-9-CM codes.²⁰ Preindex prescription fills for EAI were identified by National Drug Code numbers recorded on individual prescription claims, and allergist/immunologist visits were identified by physician specialty, as coded on outpatient medical claims during the preindex period.

Characteristics of the Index Event

Cardiorespiratory failure and subsequent interventions were identified on the index ED claim and hospital facility and professional claims for an inpatient stay using ICD-9-CM, *Current Procedural Terminology*, and *Healthcare Procedure Coding System* codes. Specifically, the cardiorespiratory failure variable was defined using ICD-9-CM codes: 458.xx (hypotension), 427.5 (cardiac arrest), 518.81 (acute respiratory failure), and 799.1 (respiratory arrest). Inpatient measures, including intensive care unit (ICU) stay, length of hospital stay, and discharge destination, were identified on the facility and admission summary claims for the index hospital stay. Costs for the ED and hospital events are represented by the total reimbursed amount for all providers of care associated with the index event, including patient copayment, coinsurance deductibles, coordination of benefits amount, and amount paid by the insurer. All costs were inflated to 2008 US dollars using the medical component of the Consumer Price Index.

Postindex Outcomes

EAI prescription fills and allergist/immunologist visits in the 1-year postindex period were identified as in the preindex period. These data were recorded on individual prescription and medical claims and, therefore, capture care that was sought by the patient and covered by the insurer. In addition, time to first EAI prescription fill and time to first allergist/immunologist visit were determined. Patients with 1 or more subsequent anaphylaxis events and who were treated as an inpatient or in an ED were identified using the same method as that used to identify index events.

Statistical Analyses

All analyses were performed using Stata statistical software, version 12.0 (Stata Corp, College Station, Texas). Data are presented as proportions, means with SDs, and medians with interquartile ranges (IQRs). Unadjusted analyses were performed using the χ^2 test, Fisher exact test, *t* test, and Kruskal-Wallis test, as appropriate. Multivariable logistic regression was used to evaluate independent predictors of receiving appropriate and timely preventive anaphylaxis care, defined as having a prescription fill for an EAI within 30 days after index event or an allergist/immunologist visit within 60 days after the index event during the postindex period. Factors were evaluated for inclusion in the multivariable model if they were found to be associated with the outcome in unadjusted analyses ($P < .20$) or were considered to be potentially clinically significant. Odds ratios are presented with 95% confidence intervals. All *P* values are 2-tailed, with $P < .05$ considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 954 SIA patients were identified during the 7-year study period and were considered eligible to be included in this study based on the patient selection criteria. No deaths occurred. Most of the visits (77%) were during the summer months (June through September) (Fig 1). Demographic and clinical characteristics are listed in Table 1. Patients had a mean age of 46 years, and 41% were female. Most patients had commercial insurance. A Deyo

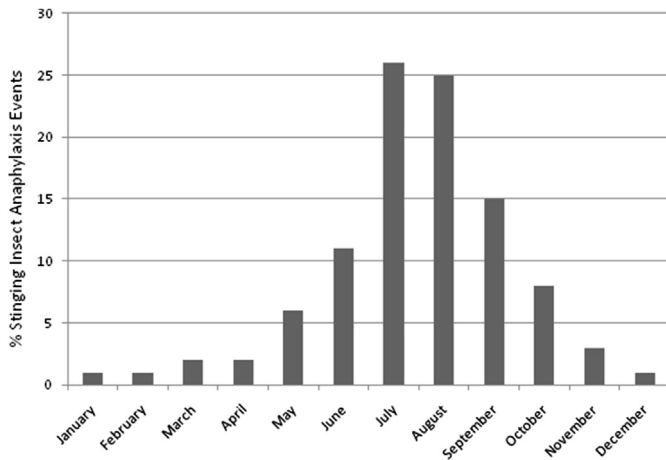


Figure 1. Percentage of stinging insect anaphylaxis visits by month of presentation.

CCI score of 0 was most common (70%), with smaller percentages of patients having a score of 1 (17%) and 2+ (4%), with higher numbers indicating greater levels of comorbidity. In terms of general health care use, 29% had an ED visit, and 9% had a hospitalization for any

Table 1

Demographic and clinical characteristics of patients treated in the emergency department or hospital for stinging insect anaphylaxis

Characteristic	Finding (N = 954)
Demographic	
Age, median (IQR), y	49 (35–58)
Age groups, No. (%)	
0–17 years	122 (13)
18–44 years	278 (29)
45–64 years	427 (45)
≥65 years	127 (13)
Female, No. (%)	393 (41)
Insurance, No. (%)	
Commercial	822 (86)
Medicare	132 (14)
Household income, mean ± SD, US\$	48,847 ± 17,400
Geographic region, US Census region, No. (%)	
Northeast	131 (14)
Midwest	287 (30)
South	415 (44)
West	116 (12)
Other/missing	5 (0.5)
Clinical	
Deyo Charlson Comorbidity Index score, No. (%)	
0	665 (70)
1	158 (17)
≥2	42 (4)
Missing/not available	89 (9)
Comorbidities, No. (%)	
Hypertension	202 (21)
Cardiovascular disease	148 (16)
Asthma	54 (6)
Allergic rhinitis	66 (7)
Personal history of allergy	13 (1)
Mastocytosis	1 (0.1)
Depression	51 (5)
Concomitant medications before index event, No. (%)	
β-Blockers	111 (12)
ACE inhibitors	122 (13)
Antidepressants	186 (20)
Health care use before index event, No. (%)	
Office visit	807 (85)
Laboratory or radiology	728 (76)
ED visit	272 (29)
Hospitalization	89 (9)
Filled EAI prescription before index event, No. (%)	93 (10)
Allergist/immunologist visit before index event, No. (%)	30 (3)

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; EAI, epinephrine autoinjector; ED, emergency department; IQR, interquartile range.

Table 2

Emergency department and hospital clinical presentation and treatment for stinging insect anaphylaxis

Clinical course	Finding (N = 954)
ED course (n = 807)^a	
Cardiorespiratory failure, No. (%)	54 (7)
Hypotension	51 (6)
Cardiac arrest	1 (0.1)
Respiratory arrest	3 (0.4)
Acute respiratory failure	1 (0.1)
Treated with epinephrine	50 (6)
Costs of index ED event in US \$, mean ± SD	1,787 ± 2,353
Hospital course (n = 147)^b	
Cardiorespiratory failure	39 (27)
Hypotension	30 (20)
Cardiac arrest	1 (1)
Respiratory arrest	2 (1)
Acute respiratory failure	7 (5)
Treated with cardiorespiratory interventions	6 (4)
ICU/CCU admission	73 (50)
Hospital length of stay, median (IQR), d	1 (1–3)
Hospital disposition, No. (%)	
Home	132 (90)
Other hospital or acute care	3 (2)
Other	2 (1)
Missing	10 (7)
Costs of index hospitalization, mean ± SD, US\$	11,366 ± 23,856

Abbreviations: CCU, critical care unit; ED, emergency department; ICU, intensive care unit; IQR, interquartile range.

^aTreatment of subset of patients who were treated in the ED only (ie, discharged home directly from the ED).

^bTreatment of patients who were admitted to an inpatient unit from the ED.

reason during the preindex period. The most common preindex comorbidities were hypertension, cardiovascular disease, and psychiatric disease. The most common preindex concomitant medications were antidepressants, angiotensin-converting enzyme inhibitors, and β-blockers. Small percentages of patients had documentation of specific allergic diseases in the preindex period, including 6% with asthma and 7% with allergic rhinitis. Furthermore, 10% of patients filled 1 or more EAI prescription and 3% had 1 or more allergist/immunologist visit in the year leading up to the index event, which supports a low prevalence of preexisting atopy in the study population. Only 1 patient (0.1%) had a comorbid diagnosis of mastocytosis in the preindex period.

Characteristics of the Index Event

ED and hospital treatment for SIA is detailed in Table 2. Most patients (85%) were evaluated and discharged directly from the ED. Cardiorespiratory failure occurred in 7% of patients treated in the ED, with most of these patients specifically experiencing hypotension. Only 6% of patients treated in the ED received epinephrine. Treatment with epinephrine in the ED did not differ between individuals with cardiorespiratory failure and those without cardiorespiratory failure (4% vs 6%; $P = .77$). A total of 15% of SIA patients were hospitalized, and cardiorespiratory failure occurred in a much larger percentage of hospitalized patients (27%). Hospitalized patients had a median length of stay of 1 day (IQR, 1–3 days), and 50% spent time in the ICU. Among the hospitalized patients, the discharge disposition was most frequently home (90%). Mean index event costs (2008 dollars) were \$1,785 ± \$2,352 for ED visits and \$11,366 ± \$23,856 for hospitalization.

Postindex Outcomes

Outcomes and postindex visit health care use is detailed in Table 3. Within 1 year after discharge, 69% of patients with SIA filled 1 or more EAI prescription. The median time to filling the prescription was 1 day (IQR, 0–3 days). By contrast, only 14% of

Table 3

Outcomes of patients treated in the emergency department or hospital for stinging insect anaphylaxis

1-Year outcome	Finding (n = 954)
EAI prescription filled within 1 year, No. (%)	655 (69)
Time to EAI prescription fill, median (IQR), d	1 (0–3)
Allergist/immunologist visit within 1 year, No. (%)	134 (14)
Time to first allergist/immunologist visit, median (IQR), d	34 (13–70)
ED visit or hospitalization for anaphylaxis within 1 year, No. (%)	25 (3)
Time to ED visit or hospitalization, median (IQR), d	5 (1–209)

Abbreviations: EAI, epinephrine autoinjector; ED, emergency department; IQR, interquartile range.

patients with SIA had 1 or more allergist/immunologist visit within 1 year after discharge. The median time to the allergist/immunologist visit was 34 days (IQR, 13–70 days). Lastly, 25 patients (3%) had a subsequent ED visit or hospitalization for anaphylaxis within 1 year of the index visit; almost half (44%) of these recurrent visits occurred within a day of the index event. The overall conclusions regarding postindex outcomes did not materially change based on whether patients were identified by method 1 or method 2 of the case identification algorithm (data not shown).

When specifically looking at the follow-up care of children (n = 122), a similar percentage of children with SIA filled 1 or more EAI prescription within 1 year after discharge (68%) when compared with the population as a whole (69%). The median time to filling the prescription also was 1 day (IQR, 0–2 days). However, a slightly higher percentage of children had 1 or more allergist/immunologist visit in the following year when compared with adults (20% vs 13%, $P = .03$). The median time to the allergist/immunologist visit was 28 days (IQR, 13–52 days). Only 2 children (2%) had an ED visit or hospitalization for anaphylaxis within 1 year of the index visit.

Filling EAI Prescription Within 30 Days of the Index Visit

eTable 1 gives the unadjusted analyses regarding the characteristics of individuals filling 1 or more EAI prescription within 30 days of the index ED visit or hospitalization for SIA vs those who did not. The 2 groups were similar with respect to age, sex, and type of insurance coverage. Those who filled 1 or more EAI prescription had a higher estimated household income. Individuals who filled 1 or more EAI prescription also were more likely to have a lower Deyo CCI score. The 2 groups were similar with respect to most comorbidities, although those filling 1 or more EAI prescription within 30 days were less likely to have a history of cardiovascular disease. Use of concomitant medications during the year before the index event was similar across the 2 groups. Although the 2 groups did not differ with respect to physician office visits (for any reason) before the index event, individuals who filled 1 or more EAI prescription

Table 4

Multivariable predictors of filling eai prescription within 30 days after treatment in emergency department or hospital for stinging insect anaphylaxis

Predictor	OR (95% CI)	P value
Estimated household income (per \$10,000)	1.12 (1.03–1.21)	.007
Deyo Charlson Comorbidity Index score		
0	1.00 (Referent)	
1	0.63 (0.44–0.91)	.01
≥2	0.71 (0.38–1.35)	.30
Missing/not available	0.96 (0.60–1.53)	.85
Cardiorespiratory failure	0.47 (0.30–0.74)	.001

Abbreviations: CI, confidence interval; EAI, epinephrine autoinjector; OR, odds ratio.

Table 5

Multivariable predictors of allergist/immunologist visit within 60 days after treatment in emergency department or hospital for stinging insect anaphylaxis

Predictor	OR (95% CI)	P value
Estimated household income (per \$10,000)	1.17 (1.05–1.32)	.006
Filled EAI prescription before index event	1.97 (1.09–3.57)	.03
Allergist/immunologist visit before index event	3.37 (1.46–7.81)	.005
Office visit for any reason before index event	2.29 (1.03–5.10)	.04

Abbreviations: CI, confidence interval; EAI, epinephrine autoinjector; OR, odds ratio.

within 30 days were less likely to have had ED visits or to be hospitalized before the index event. The 2 groups were equally likely to have filled 1 or more EAI prescription before the index event, but, surprisingly, individuals who filled 1 or more EAI prescription within 30 days were less likely to have an allergist/immunologist visit before the index event. Individuals filling 1 or more EAI prescription also were less likely to experience cardiorespiratory failure during the index event. No statistically significant differences were found in the 2 groups based on their source of care for the index event (ie, discharged home from ED vs hospitalized).

On multivariable analysis, factors independently associated with filling 1 or more EAI prescriptions within 30 days of the index ED visit or hospitalization for anaphylaxis were higher household income, lower Deyo CCI score, and no cardiorespiratory failure during the index event (**Table 4**).

Allergist/Immunologist Visit Within 60 Days of the Index Visit

eTable 2 gives the unadjusted analyses regarding the characteristics of individuals visiting an allergist/immunologist within 60 days of the index ED visit or hospitalization for SIA vs those who did not. The 2 groups were similar with respect to sex and type of insurance coverage. Patients who visited an allergist/immunologist within 60 days of the index visit were younger and had a higher estimated household income. No significant difference was observed for Deyo CCI score or individual comorbidities. Use of concomitant medications during the year before the index event was similar across the 2 groups. The 2 groups were similar with respect to short-term health care utilization as demonstrated by ED visits and hospitalizations for any reason before the index event. However, individuals who visited an allergist/immunologist within 60 days of the index ED visit or hospitalization were more likely to have had a prior office visit for any reason before the index event. It is not surprising that patients visiting an allergist/immunologist within 60 days of the index visit were more likely to have filled 1 or more EAI prescription before the index event and to have an allergist/immunologist visit before the index event. Lastly, there was no difference in whether patients visited an allergist/immunologist within 60 days of the index visit based on cardiorespiratory failure during the index event.

On multivariable analysis, factors independently associated with visiting an allergist/immunologist within 60 days of an index ED visit or hospitalization for anaphylaxis were higher household income, filling 1 or more EAI prescription before the index event, an allergist/immunologist visit before the index event, and an office visit for any reason before the index event. (**Table 5**).

When evaluating patients' receipt of any preventive care (as defined by filling ≥1 EAI prescriptions within 30 days or ≥1 allergist/immunologist visits within 60 days after the index event), the unadjusted associations were similar (data not shown). On multivariable analysis, factors independently associated with receiving

Table 6

Multivariable predictors of receiving preventive anaphylaxis care after treatment in emergency department or hospital for stinging insect anaphylaxis^a

Predictor	OR (95% CI)	P value
Estimated household income (per \$10,000)	1.15 (1.06-1.25)	.001
Deyo Charlson Comorbidity Index score		
0	1.00 (Referent)	
1	0.73 (0.51-1.05)	.09
≥2	0.74 (0.39-1.38)	.36
Missing/not available	0.86 (0.53-1.40)	.53
ED visit before index event	0.61 (0.45-0.83)	.001
Cardiorespiratory failure during event	0.50 (0.32-0.78)	.002

Abbreviations: CI, confidence interval; EAI, epinephrine autoinjector; OR, odds ratio.

^aFilling EAI prescription within 30 days of index event or visiting an allergist/immunologist within 60 days of index event.

any preventive care were higher household income, no ED visit (for any reason) before the index event, and no cardiorespiratory failure during the index event (Table 6).

Discussion

To our knowledge, this is the largest longitudinal study of ED or hospitalized patients with SIA described in recent history. We studied a population of almost 1,000 patients who experienced an acute episode of SIA with at least 1 year of continuous follow-up. A significant number of hospitalized patients had severe reactions as evidenced by our data that 50% spent time in the ICU and 27% experienced cardiorespiratory failure. Only 1 patient had a diagnosis of mastocytosis in the preindex period. We are unable to assess whether additional patients were diagnosed as having mastocytosis after their anaphylaxis event, but it is possible that screening of baseline tryptase levels, a newly described predictor of episodes of severe anaphylaxis due to stinging insects,²¹ could yield further individuals with this diagnosis.

Regarding the short-term management of SIA patients in our study, a lower than expected percentage received epinephrine (the first-line therapy for any form of anaphylaxis) in the ED. We acknowledge that we did not capture patients who received epinephrine before their arrival at the ED, which is likely not an inconsequential number. In a prior study by our group, 26% of patients with SIA received epinephrine before their arrival at the ED.¹² Furthermore, epinephrine treatment data were not available for those patients who were hospitalized. Nevertheless, our study supports previous assertions that stinging insects are a common trigger for anaphylaxis, a potentially life-threatening medical emergency, and that further efforts are required to ensure that the emergency care of these patients is improved.^{7,11–14}

When specifically looking at data on these patients' follow-up care, it is reassuring that most patients filled prescriptions promptly for EAI after their episode of SIA. Still, additional efforts are needed to increase awareness of the value of this potentially life-saving medication because one-third of patients did not fill a prescription for an EAI in the year after an episode of SIA. Furthermore, although most patients filled their prescriptions, we are not able to assess with this database whether the patients actually carried the device with them or were able to use it correctly at time of anaphylaxis event. Numerous studies on stinging insect hypersensitivity and food allergy have clearly pointed toward deficiencies in both of these aspects of "anaphylaxis readiness."^{18,22–24}

Most importantly, our study points toward major deficiencies in SIA patients' receipt of appropriate specialist follow-up consultation. Allergist/immunologist follow-up is important for those at risk for any form of anaphylaxis for proper diagnosis of triggers and to ensure patients receive proper anaphylaxis education (eg,

avoidance measures and EAI training). However, it is especially crucial in the case of SIA because an essentially curative treatment does exist. VIT has been found to be more than 95% effective when indicated.^{25–28} Therefore, after an episode of SIA, follow-up evaluation by an allergist/immunologist is crucial to determine whether the patient is a candidate for this effective and potentially life-saving therapy.

Previous studies from the ED have indicated that patients are often not referred to an allergist/immunologist upon discharge from the ED.^{11,12,14} The limitation of this form of assessment is that many patients might be referred from their primary care physician after the acute event, which is information that would not be captured by review of ED and hospital records. This study examines this question by assessing how many patients actually visited an allergist/immunologist in the period after their episode of SIA. Within our cohort, a disappointingly small percentage (14%) of patients visited an allergist/immunologist after their episode of SIA. These results are consistent with a retrospective study at 2 US centers where 28 of 120 (23%) SIA patients visited an allergist/immunologist¹⁵ and point toward a lack of awareness regarding VIT among both health care professionals and the general population. This finding represents an area where vast improvement is needed, and allergists/immunologists have the potential to be effective advocates for this important practice change.

Our multivariable model may further suggest that improvement in preventive care is especially needed within lower-income patient populations, patients with a greater number of comorbidities, and those with higher use of acute health care settings. Surprisingly, patients with seemingly more severe episodes (as reflected by cardiorespiratory failure) were less likely to have preventive care after the episode of SIA. This finding could be due to competing postdischarge treatment needs; however, it is important that these patients receive additional efforts to ensure that they have an EAI available to them and that they follow up with an allergist/immunologist after discharge. When looking specifically at follow-up, patients were more likely to have an allergist/immunologist visit if they had more nonacute health care use in general before the event and, not surprisingly, if they had specifically visited an allergist/immunologist before the index event. Taken as a whole, this information should guide clinicians in targeting populations of patients who require more explanation or guidance in terms of the benefits of preventive care.

Despite indications of poor follow-up care, a small percentage of patients returned to the ED in the 1-year follow-up period with a recurrent episode of SIA. Furthermore, almost half of repeat visits occurred within 1 day, suggesting that incomplete resolution of symptoms or a relapse (biphasic reaction) were the likely explanations for many of these recurrent visits. Several studies have addressed the natural history of insect hypersensitivity, and it has been described that without VIT as many as 60% of adults and 30% of children with a history of SIA will have a systemic reaction on repeat sting challenge.^{25,27,29,30} On the basis of these data, one would expect that without treatment with VIT, many patients in our population would eventually experience a recurrent episode of SIA. In 1988, Lockey et al³¹ reported survey data on 2,866 adults with a history of a systemic reaction to an insect sting. In this population, almost 30% reported they had experienced 2 or more systemic reactions to insects stings. A more recent study by Cianferoni et al¹⁷ used questionnaire data from 46 ED patients with anaphylaxis (all triggers) within a 7-year follow-up period and also found that 30% reported a recurrent episode. It is likely that a longer follow-up time would also capture further episodes of recurrent episodes of SIA within our population. Unfortunately, the possibility also exists that a considerable number of patients who experience a recurrent episode of SIA would not seek treatment within a medical setting and so would not be captured in a longitudinal database study. In

support of this supposition, only 9 of 46 questionnaire respondents (20%) in the study by Cianferoni et al¹⁷ sought emergency medical treatment for their recurrent episode of anaphylaxis. Furthermore, in 2 separate population surveys, only 24% of British beekeepers¹⁴ and 15% of Israeli schoolchildren³² with a history of a systemic reaction to an insect sting reported that they attended an ED because of their symptoms. The generalization of this trend to the US population would require further study with a prospective study design and a longer period of follow-up.

As described above, the potential limitations of our study include inherent limitations of the administrative database, such as reliance on medical coding to identify cases of SIA and to assess clinical presentations such as cardiorespiratory failure. Because of the retrospective nature of the study design and the case identification method, it is possible that some of the anaphylaxis patients included in the study were patients in whom there was a history of stinging insect allergy in the past, but this was not a clear trigger for the current event. However, the finding that most cases presented during summer months provides supportive information regarding the nature of the trigger. Another potential limitation is that our study population was required to have continuous medical and prescription coverage for 1 or more years before and after the dates of the index ED visit or hospitalization, which limits our ability to generalize these conclusions to underinsured or uninsured populations or comment on overall disease prevalence. Finally, individual medical record reviews were not performed; therefore, we are unable to report specific signs and symptoms of the reactions or comment on the intended disposition of patient from the physician's perspective. On the other hand, our study has several notable advantages. Specifically, we analyzed a very large number of SIA patients from across the country and were able to capture follow-up visits and recurrent episodes regardless of the institution. In addition, we uniquely present data on the actual receipt of preventive care from a patient-centered focus (eg, information about whether the patient actually visited an allergist/immunologist rather than simply receipt of a referral to an allergist/immunologist).

In summary, we report longitudinal data on a population of nearly 1000 US patients who had an ED visit or hospitalization for SIA. Although two-thirds of patients filled a prescription for an EAI in a prompt manner after this acute event, a disappointingly small number of patients received follow-up care by an allergist/immunologist. This lost opportunity to provide diagnostic and therapeutic evaluation for VIT, an essentially curative treatment, places these patients at risk for recurrent potentially life-threatening episodes of anaphylaxis. Further research is needed to determine the barriers (and solutions) to patients' receipt of this preventive care.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.06.020>.

References

- [1] Bilo MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy*. 2009;39:1467–1476.
- [2] Decker WW, Campbell RL, Manivannan V, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol*. 2008;122:1161–1165.
- [3] Golden DB. Insect sting anaphylaxis. *Immunol Allergy Clin N Am*. 2007;27:261–272.
- [4] Golden DBK, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect venom sensitivity. *JAMA*. 1989;262:240–244.
- [5] Settignano GA, Boyd GK. Prevalence of bee sting allergy in 4992 boy scouts. *Act Allergol*. 1970;25:286–291.
- [6] Settignano GA, Newstead GJ, Boyd GK. Frequency of Hymenoptera allergy in an atopic and normal population. *J Allergy*. 1972;50:146–150.
- [7] Clark S, Camargo CA Jr. Emergency treatment and prevention of insect-sting anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2006;6:279–283.
- [8] Golden DB, Moffitt J, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol*. 2011;127:852–4.e1–23.
- [9] Simons FE, Arduzzo LR, Bilò MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2012;12:389–399.
- [10] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–80.e1–42.
- [11] Clark S, Long AA, Gaeta TJ, Camargo CA Jr. Multicenter study of emergency department visits for insect sting allergies. *J Allergy Clin Immunol*. 2005;116:643–649.
- [12] Rudders SA, Banerji A, Katzman DP, Clark S, Camargo CA Jr. Multiple epinephrine doses for stinging insect hypersensitivity reactions treated in the emergency department. *Ann Allergy Asthma Immunol*. 2010;105:85–93.
- [13] Simons FE, Clark S, Camargo CA Jr. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol*. 2009;124:301–306.
- [14] Campbell RL, Luke A, Weaver AL, et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. *Ann Allergy Asthma Immunol*. 2008;101:631–636.
- [15] Johnson T, Dietrich J, Hagan L. Management of stinging insect hypersensitivity: a 5 year retrospective medical record review. *Ann Allergy Asthma Immunol*. 2006;97:223–225.
- [16] Bokanovic D, Aberer W, Griesbacher A, Sturm GJ. Prevalence of Hymenoptera venom allergy and poor adherence to immunotherapy in Austria. *Allergy*. 2011;66:1395–1396.
- [17] Cianferoni A, Novembre E, Pucci N, Lombardi E, Bernardini R, Vierucci A. Anaphylaxis: a 7-year follow-up survey of 46 children. *Ann Allergy Asthma Immunol*. 2004;92:464–468.
- [18] Richter AG, Nightingale P, Huissoon AP, Krishna MT. Risk factors for systemic reactions to bee venom in British beekeepers. *Ann Allergy Asthma Immunol*. 2011;106:159–163.
- [19] Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol*. 2010;126:98–104.
- [20] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
- [21] Rueff F, Przybilla B, Bilò MB, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol*. 2010;126:105–11.e5.
- [22] Kastner M, Harada L, Wasserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. *Allergy*. 2010;65:435–444.
- [23] DeMuth KA, Fitzpatrick AM. Epinephrine autoinjector availability among children with food allergy. *Allergy Asthma Proc*. 2011;32:295–300.
- [24] Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics*. 2000;105:359–362.
- [25] Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med*. 1978;299:157–161.
- [26] Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis. *Clin Ther*. 2000;22:351–358.
- [27] Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med*. 2004;351:668–674.
- [28] Golden DBK. Long term outcome after venom immunotherapy. *Curr Opin Allergy Clin Immunol*. 2010;10:337–341.
- [29] vanderLinden PG, Hack CE, Struyvenberg A, vanderZwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol*. 1994;94:151–159.
- [30] Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol*. 1992;90:335–339.
- [31] Lockett RF, Turkeltaub PC, Baird-Warren IA, et al. The Hymenoptera venom study I, 1979–1982: demographics and history-sting data. *J Allergy Clin Immunol*. 1988;82:370–381.
- [32] Graif Y, Romano-Zelekha O, Livne I, Green MS, Shohat T. Allergic reactions to insect stings: results from a national survey of 10,000 junior high school children in Israel. *J Allergy Clin Immunol*. 2006;117:1435–1439.

eTable 1

Demographic and clinical characteristics of patients treated in the emergency department or hospital for stinging insect anaphylaxis, according to filling EAI prescription within 30 days

Characteristic	Filling EAI prescription within 30 days of index visit		P value
	No (n = 348)	Yes (n = 606)	
Demographic			
Age, median (IQR), y	49 (33–58)	49 (38–58)	.76
Age groups, %			.08
0–17 years	14	12	
18–44 years	30	29	
45–64 years	40	47	
≥65 years	16	12	
Female, %	42	41	.82
Insurance, %			.06
Commercial	83	88	
Medicare	17	12	
Household income, mean ± SD, US\$	46,654 ± 16,385	50,103 ± 17,848	.007
Clinical			
Deyo Charlson Comorbidity Index score, %			.03
0	65	72	
1	21	14	
≥2	5	4	
Missing/not available	9	10	
Comorbidities, %			
Hypertension	23	20	.23
Cardiovascular disease	19	14	.03
Asthma	5	6	.62
Allergic rhinitis	8	6	.30
Personal history of allergy	2	1	.47
Mastocytosis	0.3	0	.19
Depression	7	4	.06
Concomitant medications, %			
β-Blockers	11	12	.92
ACE inhibitors	14	12	.27
Antidepressants	19	20	.89
Health care use before index event, %			
Office visit	84	85	.80
Laboratory or radiology	79	75	.18
ED visit	35	25	.001
Hospitalization	13	7	.004
EAI prescription filled before index event, %	11	9	.49
Allergist/immunologist visit before index event, %	5	2	.02
Cardiorespiratory failure during the event, %	14	7	<.001
Source of treatment for index event, %			.08
ED and discharged home	82	86	
Hospitalized	18	14	

Abbreviations: ACE, angiotensin-converting enzyme; EAI, epinephrine autoinjector; ED, emergency department; IQR, interquartile range.

eTable 2

Demographic and clinical characteristics of patients treated in the emergency department or hospital for stinging insect anaphylaxis, according to allergist/immunologist visit within 60 days after treatment in emergency department or hospital for anaphylaxis

Characteristic	Allergist/immunologist visit within 60 days after index event		P value
	No (n = 858)	Yes (n = 96)	
Demographic			
Age, median (IQR), y	49 (36–58)	47 (34–57)	0.17
Age groups, %			0.02
0–17 years	12	21	
18–44 years	30	21	
45–64 years	44	49	
≥65 years	14	9	
Female, %	41	45	0.45
Insurance, %			0.48
Commercial	86	89	
Medicare	14	11	
Household income, mean ± SD, US\$	48,319 ± 17,079	53,524 ± 19,503	0.009
Clinical			
Deyo Charlson Comorbidity Index score, %			0.17
0	59	76	
1	16	18	
≥2	5	2	
Missing/not available	10	4	
Comorbidities, %			
Hypertension	22	18	0.38
Cardiovascular disease	16	14	0.57
Asthma	6	6	0.79
Allergic rhinitis	7	10	0.15
Personal history of allergy	2	0	0.23
Mastocytosis	0.1	0	0.74
Depression	6	3	0.31
Concomitant medications, %			
β-Blockers	12	10	0.70
ACE inhibitors	13	10	0.46
Antidepressants	19	21	0.73
Health care use before index event, %			
Office visit	84	93	0.02
Laboratory or radiology	76	81	0.23
ED visit	29	27	0.74
Hospitalization	10	4	0.07
EAI prescription filled before index event, %	9	20	<.001
Allergist/immunologist visit before index event, %	2	10	<.001
Cardiorespiratory failure during the event, %	10	11	0.55
Source of treatment for index event, %			0.95
ED and discharged home	85	84	
Hospitalized	15	16	

Abbreviations: ACE, angiotensin-converting enzyme; EAI, epinephrine autoinjector; ED, emergency department; IQR, interquartile range.