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AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions?

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ABSTRACT

Objective: To define the incidence of and clinical practices associated with subcutaneous immunotherapy (SCIT)–related systemic reactions (SRs).

Methods: From 2008–2011, American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma & Immunology members completed an annual survey of SCIT-related SRs of varying severity (with grade 1 indicating mild; grade 2, moderate; and grade 3, severe anaphylaxis). From 2010–2011 (year 3) data were collected regarding SCIT-related procedures, including screening of patients with asthma, dose adjustment during peak pollen seasons, build-up regimens (conventional, cluster, or rush), and premedication.

Results: No fatal reactions were directly or indirectly reported from 2008–2011. The SR rates were similar for all 3 years (0.1% of injection visits; 83% of practices), as were severity grades. On average, for all 3 years, there were 7.1 grade 1, 2.6 grade 2, and 0.4 grade 3 SRs per 10,000 injection visits. Screening for worsening asthma symptoms was highly prevalent (86% always screened). Practices that always reduced doses during peak pollen season were significantly less likely to report grade 2 or 3 SRs (44% vs 65%; $P = .04$). Cluster and rush build-up were associated with significantly more SRs ($P < .001$). Practices that premedicated were significantly more likely to report grade 2 and 3 SRs ($P < .01$).

Conclusion: Fatal reactions to SCIT appear to be declining, possibly related to almost universal screening of asthmatic patients. Adjusting doses during the pollen season may be associated with decreased risk for severe SRs. Cluster and rush immunotherapy were associated with increased risk for SRs. Premedication by practices reporting SRs likely reflects past experience with SRs.

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Introduction

Subcutaneous immunotherapy (SCIT) is highly effective in treating allergic rhinitis, asthma, and stinging insect hypersensitivity. Although serious or life-threatening systemic reactions (SRs) to SCIT are rare, concern over such events may unnecessarily limit its use.^{1–6} On the basis of retrospective surveys of members of the American Academy of Allergy, Asthma & Immunology (AAAAI) conducted before 2002, a fatal anaphylactic reaction to SCIT was

estimated to occur in every 2 million to 2.5 million injections or 3.4 SCIT-related deaths per year. In 2008, a web-based surveillance program was initiated in North America among members of the AAAAI and the American College of Allergy, Asthma & Immunology (ACAAI) to monitor annual incidences of SRs of varying severity related to SCIT and allergen skin testing.^{9,10} This study represents the first national, prospective, longitudinal assessment of adverse SCIT reactions. It is also the first large-scale surveillance study reporting on the incidence and severity of SCIT reactions since initiation of the allergen immunotherapy practice parameters in 2003, which disseminated clinical practice guidelines.^{11–13}

Before initiation of this surveillance program, 6 fatalities were retrospectively reported that transpired between 2001 and 2007.⁹ No new fatal reactions, however, were directly or indirectly reported between July 2008 and July 2010 based on reports from 49% and 37% of AAAAI and ACAAI members who participated in years 1 and 2 of the surveillance program, respectively.^{9,10} On the basis of previous retrospective surveys, the presence of

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uncontrolled asthma and dosing administration during peak pollen seasons were identified as important risk factors for fatal and near-fatal reactions.^{5,7} Despite this, neither physician observation of guidelines regarding preinjection asthma screening nor the effect of dose adjustment during pollen seasons have been well defined.¹⁴ In addition, renewed interest in accelerated build-up regimens (cluster and rush) for aeroallergen SCIT has been tempered by the risk of SRs.^{15,16} Further study regarding the effect of premedication on the risk of accelerated and conventional SCIT is of great interest to practitioners.¹⁶ In year 3 of the national surveillance survey, we therefore sought to assess the effect of these and other clinical practices on the incidence of SCIT reactions. We report results of these year 3 studies and summarize results of the first 3 years of the surveillance project.

Methods

Study Population

Physician members of the ACAAI and AAAAI (3,919 physicians) were surveyed, using previously described methods.^{9,10} A single respondent was identified for multimember practices to report the experience of his or her practice, on an annual basis between July 1, 2008, and August 31, 2011. Potential respondents were contacted by a nonphysician research coordinator and could complete surveys online or by fax. Practice responses were confidential and respondents were deidentified.

Study Design

In all years of the survey, physician respondents were asked to complete previously published questionnaires that described the entire experience of all SCIT providers in their practices.^{9,10} For year 3 (August 1, 2010, through August 31, 2011), participants completed questions regarding clinical practices associated with SCIT administration (eTable 1). All annual surveys queried respondents regarding fatal reactions and SRs to SCIT and skin testing that had occurred in the previous 12 months in their practice. They were also asked if they had knowledge of fatal reactions occurring in other practices in their regional area. In addition, they were asked each year to provide the numbers of mild, moderate, and severe nonfatal allergic SRs in their practices. *Mild reactions* (grade 1) were defined as generalized urticaria or upper respiratory tract symptoms (eg, itching of the palate and throat and sneezing). *Moderate reactions* (grade 2) were defined as asthmatic symptoms accompanied by a reduction in lung function (eg, a peak expiratory flow rate [PEFR] decrease of 20%–40%) with or without generalized urticaria, upper respiratory tract symptoms, or abdominal symptoms (eg, nausea and cramping). *Severe reactions* (grade 3) were defined as life-threatening anaphylaxis with severe airway compromise (eg, PEFR decreases >40%) or upper airway obstruction with stridor or hypotension (with or without loss of consciousness).

Statistical Analyses

SAS statistical software (SAS Institute, Inc, Cary, North Carolina) was used to compute descriptive statistics regarding reaction rates and the number of injection visits.^{9,10} Figures for the number and severity of SRs, number of practices experiencing SRs, and SRs per practice were calculated. Descriptive statistics for clinical practices associated with SCIT (questions 7–13 on eTable 1) were calculated. Because grade 2 and 3 SRs meet the clinical definition of anaphylaxis and are therefore considered more life-threatening than grade 1 SRs, χ^2 tests were used to evaluate the relationship between questions 7 to 13 and having only grade 1 or no SRs vs any grade 2 or 3 SRs. In addition, we determined the mean $\pm$ SD of different severity grades of SRs among practices that only used

a conventional build-up vs cluster or rush build-up methods. The Wilcoxon rank sum test was used to compare these findings.

Results

Participation in the survey peaked at 806 practices (1,922 physicians or 49% of potential respondents) in year 1 and decreased to 513 practices (1,072 physicians or 27% of potential respondents) by year 3. The first 3 years incorporated data from a total of approximately 18.9 million injection visits, or 8.1 million injection visits in year 1, 5.6 million in year 2, and 5.2 million in year 3. Responses were received from all regions of the United States, including 115 practices from the Eastern United States, 102 from the Midwest, 160 from the South, 116 from the West, and 2 from Hawaii, as well as 2 practices from Puerto Rico and 10 from Canada.

Fatal Reactions

No direct reports were made of deaths attributable to SCIT injections or allergen skin testing in the first 3 years of the study (July 1, 2008, through August 31, 2011). No indirectly reported deaths due to skin testing or SCIT injections were reported and confirmed between 2008 and 2011 in community practices outside those of the respondents. As published previously, 6 confirmed fatalities were indirectly reported between 2001 and 2007.⁹

Nonfatal SRs

Respondents reported that 83% of practices annually experienced SRs after SCIT for the first 3 years of the survey (eTable 2).^{9,10} Despite a decrease in the number of SRs reported in year 3 (3,498 total SRs), which corresponded with a decrease in participation, the mean number of SRs per practice was similar for all 3 years (10.5 SRs per practice for year 1, 10.9 for year 2, and 11.6 for year 3). Among practices that provided complete data regarding severity grades, the severity of SRs was also similar across all 3 years. Severe, potentially life-threatening (grade 3) anaphylactic reactions accounted for 3% to 4% of SRs across all 3 years, for an annual mean of 0.4 severe SRs per practice. Similar to the first 2 years of the survey, in year 3, of 300 respondents, 217 (72%) reported at least 1 grade 1, 170 (57%) reported at least 1 grade 2, and 41 (14%) reported at least 1 grade 3 SR.^{9,10} SRs occurred with 0.1% or 1 in every 1,000 injection visits each year.^{9,10} Among practices that provided reaction severity grades and the number of injection visits, the SR rates per 10,000 injection visits were similar across all 3 years (Fig 1). There were 10 SRs per 10,000 injection visits on average, including 7.1 grade 1, 2.6 grade 2, and 0.4 grade 3 SRs per 10,000 injection visits.^{9,10} There were no statistically significant differences in SR rates between different regions of the United States or Canada.

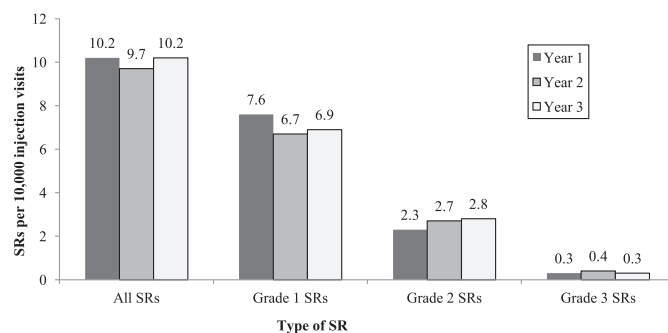


Figure 1. Systemic reactions (SRs) per 10,000 injection visits between July 2008 and August 2011. The number of practices providing complete data on the number of injection visits and the severity of SRs was 626 in year 1, 402 in year 2, and 198 in year 3.

Preinjection Screening of Asthmatic Patients

On the basis of studies indicating that poorly controlled asthma is a risk factor for severe SRs, the allergen immunotherapy practice parameter (third update) recommends that patients be evaluated for asthma symptoms and possibly lung function changes before receiving immunotherapy injections.¹³ On the basis of data from 270 practices, 86% always screened asthmatics for asthma symptoms, and 33% always performed lung function testing (PEFR or forced expiratory volume in 1 second) before administering allergy injections (Fig 2). Another 8% often prescreened and only 2% never prescreened asthmatics for asthma symptoms. No statistically significant relationships were identified between the number or severity of SRs and preinjection screening, possibly because the number of practices that did not screen for asthma was very small.

Dose Adjustment During Peak Pollen Seasons

The immunotherapy practice parameter states that immunotherapy given during periods when the patient is exposed to increased levels of allergens to which they are highly sensitive might be associated with an increased risk of SRs.¹³ We therefore sought to determine whether dose adjustment during peak pollen seasons might modify the risk for severe SRs. Approximately 12% of practices always adjusted doses during peak pollen seasons; dose reduction during peak pollen seasons was less common in the Southern United States, where only 4% of practices always reduced doses ($P = .04$). Practices that always reduced doses during peak pollen seasons were more likely to report *only* mild, grade 1 or no SRs than practices that often, sometimes, or never reduced doses (57% vs 35%; $P = .04$; Fig 3). Similarly, practices that always reduced doses during peak pollen seasons were less likely to report *any* grade 2 or 3 SRs than those that often, sometimes, or never reduced doses (44% vs 65%; $P = .04$).

Severity of SRs Based on Type of Build-up Regimen

It is well known that accelerated build-up schedules (cluster and rush) are associated with an increased frequency of SRs.^{13,16} The severity of SRs reported by practices using these build-up regimens is less well studied, however. We therefore evaluated the risk of more severe SRs among practices using cluster or rush build-up regimens vs those only using a conventional build-up. Among 200 practices using a conventional build-up *only*, there were 5.6 grade 1, 2.0 grade 2, and 0.2 grade 3 SRs per practice (Fig 4). The 60 practices using cluster reported 17.7 grade 1, 8.2 grade 2, and 1.2 grade 3 SRs per practice. Cluster immunotherapy was more commonly used among practices in the Southern United States than in other regions of the United States (32% vs 19% of

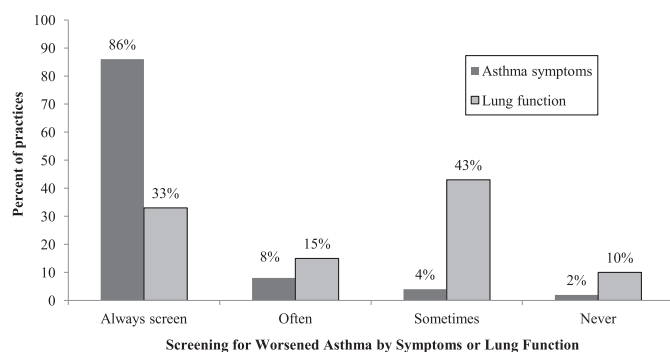


Figure 2. Preinjection methods for screening of asthmatic patients before subcutaneous immunotherapy injections. There were 270 practices providing complete data. No statistically significant relationships were identified between systemic reactions (SRs) and screening for worsened asthma by symptoms or lung function.

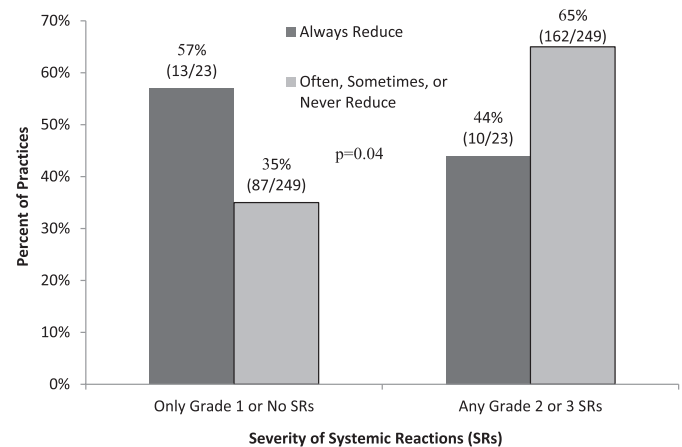


Figure 3. Percentage of practices routinely adjusting doses during the peak pollen seasons and severity of systemic reactions (SRs). There were 272 practices providing complete data. Practices always reducing doses during peak pollen seasons were less likely to experience grade 2 or 3 SRs than practices often, sometimes, or never reducing ($P = .04$).

practices; $P = .04$). Among 32 practices using rush, there were 22.9 grade 1, 12.4 grade 2, and 1.9 grade 3 SRs per practice. Cluster and rush immunotherapy were thus associated with significantly more grade 1 and 2 SRs ($P < .001$); there were too few grade 3 SRs to assess.

Premedication Before SCIT Administration

The immunotherapy practice parameter suggests that premedication might reduce the frequency and severity of SRs caused by conventional and accelerated immunotherapy.¹³ We therefore asked respondents whether patients in their practice are routinely instructed to premedicate with antihistamines or other antiallergic drugs before injections. Of 269 respondents providing complete data, 16% always, 22% often, 46% sometimes, and 15% never premedicated. Among practices reporting grade 2 or 3 SRs, 45% always or often premedicated vs 27% among those reporting only grade 1 SRs (Fig 5). Among practices reporting only grade 1 SRs or no SRs, 25% never premedicated vs 9% among those reporting grade 2 or 3 SRs. Thus, more grade 2 or 3 SRs occurred among practices that always or often premedicated, whereas fewer moderate to severe

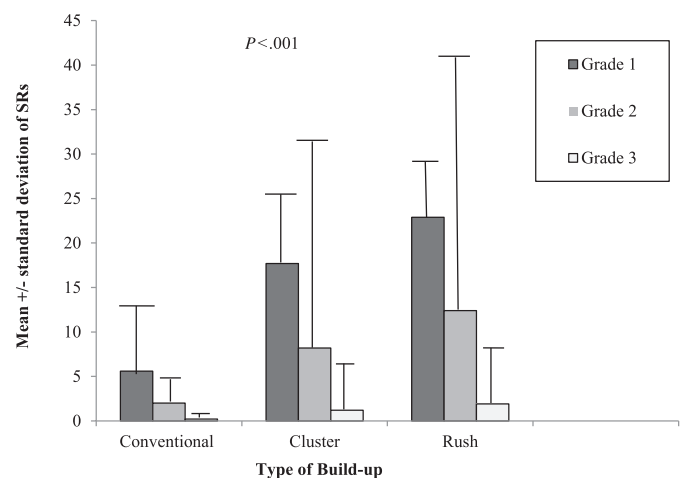


Figure 4. Severity of systemic reactions (SRs) for different types of subcutaneous immunotherapy build-up regimens (conventional, cluster, and rush). There were 266 practices providing complete data. Cluster and rush were associated with significantly more grade 1 and 2 SRs (Wilcoxon rank sum test $P < .001$).

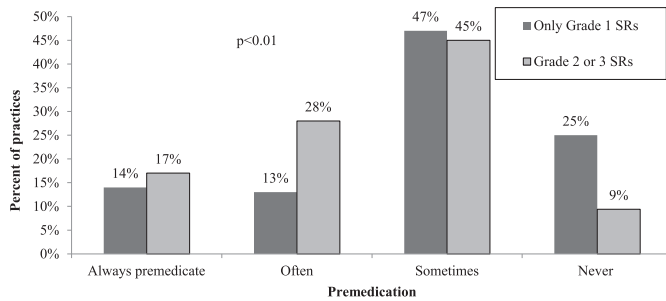


Figure 5. Premedication before subcutaneous immunotherapy and severity of systemic reactions (SRs). There were 269 practices providing complete data. Practices that always or often premedicated were more likely to report grade 2 or 3 SRs than practices that never premedicated ($P < .01$).

SRs occurred among those that never premedicated ($P < .01$). Findings were statistically significant ($P < .01$) for histamine₁ (H₁)-antihistamines only, possibly because fewer practices reported premedicating with other antiallergic drugs (221 with H₁-antihistamines, 14 with H₂-blockers, 24 with antileukotriene antagonists, and 3 with prednisone).

Given the risk of SRs associated with accelerated build-up regimens, we also evaluated the effect of premedication on SR severity specifically among practices using these regimens. Among 60 practices using cluster, 22% always, 32% often, 43% sometimes, and 3% never premedicated. Practices that premedicated for cluster build-up regimens did not have fewer grade 2 or 3 SRs; that is, 28 of 32 practices (88%) that always or often premedicated reported grade 2 or 3 SRs vs 16 of 28 practices (57%) that sometimes or never premedicated ($P = .06$). There was no relationship between the type of premedication used for cluster immunotherapy and the severity of SRs in this small sample; the study was not powered or designed to answer this question. Of 32 practices using rush, 28% always, 25% often, 43% sometimes, and 3% never premedicated before injections. There were no statistically significant findings related to premedication and SR severity for rush, possibly because of a small sample size. Findings regarding the effect of premedication in practices using a conventional build-up only (200 practices) revealed an increased risk for more severe SRs among those always or often using premedication ($P = .03$).

Results for Additional Clinical Procedures Involving SCIT

Controversy remains regarding whether dose adjustments after large local reactions modify the risk of future SRs.^{13,17,18} We therefore evaluated the overall effect of reducing injection doses or repeating the same dose after a large local reaction to aeroallergen SCIT. Among 270 practices, 42% always, 32% often, 25% sometimes, and 2% never adjusted doses after a large local reaction. Dose adjustment after large local reactions did not significantly affect the risk of SRs of any severity grade.

Because most fatal SRs from SCIT occur within 30 minutes after an injection, the immunotherapy practice parameters currently recommend that patients remain in the physician's office for at least 30 minutes after receiving an injection.¹³ On the basis of data from 270 practices, 27% required that patients wait for 20 minutes or less, 15% required 21 to 30 minutes, and 58% required 30 minutes.

β -Blocker therapy is relatively contraindicated in patients receiving aeroallergen SCIT.¹³ On the basis of data from 269 practices, 37% always, 31% often, 23% sometimes, and 9% never excluded patients taking β -blockers from receiving aeroallergen SCIT. There were no statistically significant relationships between SR severity and β -blocker use, possibly because of the small number of practices that prescribed aeroallergen SCIT to patients taking β -blockers.

Given variation related to extract preparation methods, we also asked respondents to describe their method(s) for preparing SCIT aeroallergen extracts (ie, preparation of a maintenance or "patient specific vial" vs a stock vial containing single or multiple allergens of various dilutions, or "shared patient vials"). Of 270 respondents, 82% used patient-specific vials, 17% used shared vials, and 8% used an alternative method. Fewer practices used shared vials in the Southern United States than in other regions of the country (4%; $P < .001$). No statistically significant relationships were found between preparation methods and severity of SRs. We also queried respondents regarding compliance with the updated United States Pharmacopoeia 797 guidelines regarding allergen extract preparation (eTable 1).¹⁹ On the basis of data from 268 practices, 67% reported complied with United States Pharmacopoeia 797.

Discussion

Near-fatal and fatal anaphylactic reactions after SCIT injections are extremely rare.^{7,8} Since 2003, evidence-based practice parameters have highlighted possible contributing factors for life-threatening SRs and have issued clinical recommendations aimed at preventing such events.^{11–13} This annual study initiated in 2008 has generated the largest amount of longitudinal, prospective data regarding SCIT reactions in North America to date.^{9,10} Before 2002, 3 AAAAI-sponsored retrospective surveys confirmed that approximately 3 SCIT-related fatal reactions were occurring each year.^{1,5,7} Although 6 SCIT-related fatal reactions occurred between 2001 and 2007, no fatal reactions were indirectly or directly identified between 2008 and 2011.⁹ These data suggest that fatal reactions to SCIT injections have decreased since 2008. Although impossible to confirm, this trend may be attributable to increased awareness among practicing allergists of contributing risk factors, leading to broad institution of preinjection screening practices in high-risk patients and withholding injections from patients with uncontrolled asthma.

This surveillance study is unique in capturing annual incidence data of SRs of all severity grades. Because of the voluntary nature of the survey, it is not possible to verify how closely the incidence data from this study approximate the true incidence of SRs from SCIT. These data are more likely to reflect the true incidence of SRs among practicing allergists in North America than previous retrospective surveys, however, because of less potential for selection and recall bias because of the prospective design.^{1,7,8} In addition, longitudinal data during the first 3 years are highly consistent from year to year. Despite a decrease in participation in years 2 and 3 that could potentially limit extrapolation of findings from the survey, the similar reaction rates for all 3 years suggests consistency in the experience of participating practices from year to year.

In year 3 of the study, respondents were queried regarding adherence to recommendations to reduce fatal reactions and variations in clinical practice patterns that may affect the risk of SRs. Participating practices reported almost universal screening of asthmatic patients for worsening asthma before administration of injections. We speculate that this may in part explain the decrease in SCIT-related fatalities since 2002. Given that previous retrospective surveys identified dosing during peak pollen season as a strong risk factor for fatal and near-fatal reactions, decreasing injection doses during peak pollen seasons has been suggested in treatment guidelines.¹³ On the basis of data from this study, practices that always reduced doses during peak pollen seasons were less likely to report moderate to severe (grade 2 or 3) SRs. Larger, prospective studies focusing on the effect of dose reduction on SR rates during peak pollen seasons are warranted.

Accelerated build-up regimens have gained popularity in recent years, despite the increased risk of SRs.^{15,16} In this study, we confirmed the increased risk of mild and moderate (grade 1 and 2)

SRs with cluster and rush build-up regimens. No significant differences were identified for grade 3 SRs, possibly because of the overall low frequency of these reactions. Several previous randomized and nonrandomized studies have indicated that premedication may decrease the risk for SRs in patients on accelerated build-up regimens.^{15,20–23} In this study, premedication for cluster build-up was not associated with a decreased risk of grade 2 or 3 SRs. This finding may reflect the lack of randomization in this study and the increased use of premedication among practices previously reporting more severe SRs (ie, reverse causation).

With regard to conventional build-up, premedication also did not reduce the risk of severe SRs, despite evidence from a randomized controlled trial indicating that it might.²⁴ Data from our study indicated an increased risk for severe SRs among practices that premedicated. There are several possible explanations for this finding. Although there are theoretical concerns that premedicating with antihistamines might mask early signs of a SR and thus lead to more severe SRs, it is also plausible that practices with previous experience with severe SRs may have been more likely to institute routine premedication recommendations. It is also possible that practices using higher maintenance doses or other dosing variations may have different premedication patterns. On the basis of data from previous years, patients in practices using higher maintenance doses for house dust-mite and possibly cat and grass were at increased risk of grade 3 SRs.²⁵ We were, however, unable to account for these differences from the dosing data collected in the current study. In the future, continued surveillance and larger, prospective studies focused on the efficacy of premedication regimens may clarify these issues.

In summary, the rates of adverse reactions to SCIT have remained stable for the last 3 years, with no new fatalities to report. Fatalities from SCIT appear to have decreased in the last 10 years, possibly because of almost universal screening of asthma patients before SCIT injections. Adjusting doses during peak pollen seasons may decrease the risk for severe SRs and should be further studied. Cluster and rush immunotherapies are potentially associated with an increased risk for SRs, including at least moderate (grade 2) SRs. Premedication was not associated with a lower risk of SRs in this study, possibly because premedication practices may be shaped by the severity of prior SRs.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2013.01.015>

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eTable 1

Survey questions in year 3 (August 1, 2010, through August 31, 2011)

1. During the past 12 months, have any patients in your entire clinical practice (including patients of your associates) experienced a fatal anaphylactic reaction(s) after an allergen immunotherapy injection?
2. During the past 12 months, have any patients in your entire clinical practice (including patients of your associates) experienced systemic reactions after allergen immunotherapy injections? If yes, how many nonfatal systemic reactions have there been in the entire clinical practice in the past 12 months? According to the severity classification system detailed below, please indicate the number of grades 1, 2, and 3 nonfatal systemic reactions in your entire practice during the past 12 months (including patients of your associates)? Grade 1 → Mild systemic reactions: generalized urticaria or upper respiratory symptoms (itching of the palate and throat, sneezing) Grade 2 → Moderate systemic reactions: asthma (eg, peak expiratory flow rates falls 20%–40%) with or without generalized urticaria, upper respiratory symptoms, or abdominal symptoms (nausea, cramping) Grade 3 → Severe, life-threatening anaphylaxis: severe airway compromise due to severe bronchospasm (eg, peak expiratory flow rate falls >40%), or upper airway obstruction with stridor or hypotension (with or without loss of consciousness)
3. During the past 12 months, are you aware of a fatal anaphylactic reaction(s) associated with an allergen injection in another practice in your community?
4. During the past 12 months, are you aware of a fatal anaphylactic reaction(s) associated with allergen skin testing in your practice? Or in another practice in your community?
5. During the past 12 months, how many subcutaneous allergen injections has your entire practice billed under <i>Current Procedural Terminology</i> codes 95115 and 95117 for single and multiple injections (or other codes)?
6. Please indicate the total number of allergists and nurse practitioners who write orders (or prescribe) immunotherapy in your entire clinical allergy practice. <u>Immunotherapy in your practice</u>
7. Which method best describes the protocol used in your clinical practice for preparing or mixing of commercial aeroallergen extracts for subcutaneous allergen immunotherapy? A maintenance vial or “patient specific vial” is prepared and labeled for each patient by mixing appropriate allergens taken from commercial stock vials. Build-up vials are made for each patient by serial dilution of the starting maintenance vial. Stock vials containing single or multiple allergens of various dilutions are prepared and used to administer single or multiple injections to multiple patients (“shared patient vials”) Other method: please describe.
8. What is the current build-up regimen used in your clinical practice for subcutaneous immunotherapy build-up for aeroallergens (more than one answer can be chosen)? Cluster build-up (multiple injection doses given each visit, on multiple visits to reach maintenance in 2–8 weeks) Conventional slow build-up of incremental doses given 1–2 times per week over months until maintenance doses are achieved Rush immunotherapy using incremental doses of allergen at intervals varying between 15–60 minutes given over 1 to 3 days Other regimen: please describe
9. Please estimate what percentages of patients receiving SCIT for aeroallergens are receiving cluster, conventional, rush, or another build-up method.
10. In your practice, are patients routinely instructed to pre-medicate with antihistamines or anti-allergic drugs prior to each injection? (always, often, sometimes, never) If yes, please indicate which drugs are routinely used to pre-medicate (H ₁ -blockers, H ₂ - blockers, antileukotrienes, and/or prednisone).
11. Prior to receiving allergen injections in your clinic, are patients with asthma pre-screened by asking about recent worsening of asthma symptoms? (always, often, sometimes, never)
12. Prior to receiving allergen injections in your clinic, are patients with asthma prescreened by measurement of lung function (e.g., PEFR or FEV ₁)? (always, often, sometimes, never)
13. In your practice, after a large local reaction to an allergen injection, is the subsequent allergen injection dose reduced or held the same? (always, often, sometimes, never)
14. During the peak of the pollen allergy seasons (e.g., ragweed, grass), are allergen injection doses from maintenance vials reduced in patients with seasonal allergic rhinitis or asthma? (always, often, sometimes, never)
15. Do you routinely exclude patients from receiving immunotherapy if they are taking a β -blocker medication? (always, often, sometimes, never)
16. In your entire clinical practice, what is the waiting period routinely required after allergen injections? (up to and including 20 minutes, 21–30 minutes, 30 minutes, or greater than 30 minutes)
17. Do personnel in your entire allergy practice who prepare allergen extract mixtures comply with United States Pharmacopoeia; USP 797 allergen extract preparation guidelines including the use of aseptic technique during preparation as well as passing annual media fill tests? (yes/no)

eTable 2

Number and type of SRs between July 2008 and 2011

	Year 1 (7/1/2008–7/31/2009)	Year 2 (8/1/2009–7/31/2010)	Year 3 (8/1/2010–8/31/2011)
Total No. of practices ^a	806	630	513
No. of SCIT providers	1,922	1,453	1,072
Practices reporting SRs, %	82	85	82
Total No. of SRs	8,502	5,392	3,498
Total SRs per practice ^b	10.5 ± 26.0 (4.0)	10.9 ± 23.3 (5.0)	11.6 ± 29.5 (3.0)
Grade 1 (mild) SRs			
No. of practices reporting SRs	613	416	217
No. of SRs	6,293	3,720	2,354
SRs per practice ^b	7.8 ± 20.5 (3.0)	7.6 ± 15.5 (3.0)	7.8 ± 16.8 (2.0)
Grade 2 (moderate) SRs			
No. of practices reporting SRs	436	296	170
No. of SRs	1,944	1,476	949
SRs per practice ^b	2.4 ± 6.7 (1.0)	3.0 ± 8.3 (1.0)	3.2 ± 15.1 (1.0)
Grade 3 (severe) SRs			
No. of practices reporting SRs	144	91	41
No. of SRs	265	196	115
SRs per practice ^b	0.3 ± 1.0 (0)	0.4 ± 1.2 (0)	0.4 ± 3.1 (0)

Abbreviations: SCIT, subcutaneous immunotherapy; SR, systemic reaction.

^aThe total number of practices providing complete data regarding SR severity was 804 in year 1, 445 in year 2, and 300 in year 3.^bMean ± SD; values in parentheses represent the median number of SRs per practice.