

AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013-2017): Fatalities, Infections, Delayed Reactions, and Use of Epinephrine Autoinjectors



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What is already known about this topic? Subcutaneous allergen immunotherapy (SCIT) is associated with a significant risk of SRs. There are concerns about potential infections from SCIT.

What does this article add to our knowledge? SCIT-related fatalities increased since 2015, although minimally. SCIT-related infections have not been identified. Patient adherence with prescribed epinephrine autoinjectors for delayed SRs is low.

How does this study impact current management guidelines? Efforts to minimize known risk factors are still needed. Interventions are needed to improve patient adherence with epinephrine for delayed reactions. Procedures used to prepare mixed allergen extract vials in the United States are adequate to prevent injection-related infections.

BACKGROUND: Subcutaneous allergen immunotherapy (SCIT) is highly effective but safety risks exist.

OBJECTIVE: The aims of this study were to: (1) identify clinical practices that could influence fatal and nonfatal systemic allergic reactions (SRs) to SCIT, and (2) identify SCIT-associated infections.

METHODS: From 2008 to 2016, 27% to 51% of American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology members completed an annual survey of SCIT-related SRs of varying severity. Injection-related local cutaneous and systemic infections were queried for 2014-2016. For 2014-2016, respondents were queried about timing of onset of SRs, postinjection waiting times, and prescription/use of epinephrine autoinjectors.

RESULTS: Data were gathered on 54.4 million injection visits (2008-2016). Two confirmed fatalities from SCIT occurred between 2008 and 2014. An additional 5 confirmed fatalities occurred between 2015 and 2017. No infections occurred in 17.3 million injection visits (2014-2016). Among practices monitoring patients for at least 30 minutes, 15% of SRs occurred after 30 minutes. Practices prescribing an epinephrine autoinjector >90% of the time (29% of practices) did not experience lower rates of delayed grade 3/4 SRs. Of patients experiencing grade 3/4 delayed SRs, 26% and 8% used prescribed self-injectable epinephrine devices during 2014-2015 and 2015-2016, respectively.

CONCLUSIONS: There is an unexplained slight increase in SCIT-related fatalities for 2015-2017, although mean annual reported events over 9 years (0.8 fatal reactions per year) have declined. SCIT-related infections were not identified during 2 years of surveillance. The 15% incidence of delayed-onset SRs (>30 minutes) is similar to a prior annual survey. Prescribing epinephrine autoinjectors for SCIT does not appear to improve outcomes, possibly due to low rates of self-administration. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1996-2003)

Key words: Subcutaneous allergen immunotherapy; SCIT; Safety; Fatalities; Asthma; Epinephrine prescription; Cluster immunotherapy; Infection risk

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Subcutaneous allergen immunotherapy (SCIT) is used to treat patients with seasonal and perennial allergic rhinitis, allergic asthma, and stinging insect systemic allergic reactions (SRs), despite the risk of rare fatal reactions (FRs).^{1,2} In 1970, the American Academy of Allergy, Asthma, and Immunology (AAAAI) initiated a series of retrospective surveys conducted

Abbreviations used

AAAAI- American Academy of Allergy, Asthma, and Immunology
ACAAI- American College of Allergy, Asthma, and Immunology
FR- Fatal reaction
SCIT- Subcutaneous allergen immunotherapy
SR- Systemic allergic reaction
WAO- World Allergy Organization

among their members tracking the number of FRs reported between 1945 and 2001.³⁻⁵ In one of the latter surveys conducted between 1990 and 2001, the incidence of a FR was 1 in every 2.5 million injection visits or 3.4 FRs per year.⁵

Prior retrospective surveys also characterized clinical details of FRs, which helped identify possible risk factors contributing to these events. A past or present history of uncontrolled or severe asthma was identified consistently as the most important contributing factor for FRs. Other possible contributing factors include delay in administration of epinephrine, occurrence of the FR during a clinically relevant pollen season, an inadequate postinjection observation period, administration of injections at home or a clinic facility ill-prepared to treat SRs, receiving the first injection from a new vial, and dosing errors.³⁻⁵

The results of these earlier surveys were widely disseminated among the allergy/immunology community. Because FRs continued to occur at a rate of 3 to 4 events per year, in 2008, the AAAAI and the American College of Allergy, Asthma, and Immunology (ACAAI) began sponsoring an annual surveillance study with the primary goal of assessing the annual incidence of SRs of varying severity grades in the clinical practices of their members. Data were also collected regarding specific clinical practices surrounding administration of SCIT that might impact the risk of severe SRs.⁶⁻⁸ Recently, to address the safety of mixing allergen extracts in an outpatient setting, the survey has been expanded to identify annual local or systemic infections associated with SCIT.⁹ Data regarding sublingual allergen immunotherapy were also collected but are not summarized in this article.¹⁰ Results are reported here for SCIT during the sixth, seventh, and eighth years (2014-2016) of the study, and FRs through 2017. Also reported are survey data pertaining to individual clinical practices including postinjection observation periods, delayed onset SRs, and prescription of epinephrine autoinjectors to patients on SCIT.

METHODS

Study population

Physician members of the AAAAI and ACAAI were surveyed using previously described methods.⁶⁻¹¹ The survey coordinator contacted AAAAI and ACAAI members practicing immunotherapy in North America on at least 4 occasions via e-mail or fax. A single respondent was recruited from group practices to report the annual experience of the entire clinical practice from July 1, 2008, through August 31, 2016. Data regarding fatalities reported through August 31, 2018, were also available; other data from 2016 to 2018 are currently being collected and analyzed. Previously described strategies were employed to minimize the chance for duplicate responses, and nonresponders were contacted multiple times via e-mail, fax, and telephone.^{8,10} No patient identifiers were provided by participants, and the identity of participants was removed before data analysis. When possible, participating practices

collected data in “real time” on the date of SRs; data from all practices were provided to the survey team on an annual basis.

Study design

In all years, physician respondents completed questionnaires describing the experience of all SCIT prescribers in their practices.^{6-8,10,11} Participants were queried regarding FRs and SRs to SCIT injections occurring in the previous 12 months in their own practices (direct reports) and any FRs (ie, indirect reports) that occurred in other local practices in their geographic areas. The nonphysician study coordinator vigorously attempted to confirm all reported FRs by contacting physicians reporting these reactions.⁷ Those allergists reporting FRs completed a detailed questionnaire providing specific details of the event, potential contributing factors, and treatment administered.⁵ For events reported during years 1 to 3 (2008-2011; each year includes 12 months of data starting in July), a previously published grading system that included 3 grades of SRs was used.^{6,8,11} For years 4 to 8 (2012-2016), the World Allergy Organization (WAO) grading system was adopted, which includes 4 severity grades for nonfatal SRs (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, very severe).^{7,10,12}

In years 7 and 8 (2014-2016), data regarding local subcutaneous infections and systemic infections associated with SCIT were gathered (see survey questions in Table E1, available in this article's Online Repository at www.jaci-inpractice.org).¹¹ Each year of the survey, new question items were added, including waiting times after SCIT injections (2010-2011 [year 3] and 2013-2016 [years 6-8]), the time of onset of SRs after SCIT injections (2009-2010 [year 2] and 2014-2016 [years 7 and 8]), and the frequency of prescribing epinephrine autoinjectors to patients on SCIT (2013-2016 [years 6-8]). A substudy was conducted in year 7 (2014-2015) asking respondents whether patients prescribed epinephrine autoinjectors used them to treat grade 3 or 4 delayed onset SRs.

Statistical analysis

Descriptive statistics regarding reaction rates and the number of injection visits were calculated using SAS statistical software (Version 9.3, SAS Institute Inc, Cary, NC). The number and severity of SRs, SR rate per number of injection visits and number of treated patients, number of practices experiencing SRs, and SRs per practice were determined. Descriptive statistics regarding waiting times after injections, timing of onset of SRs, and prescription of epinephrine autoinjectors were compiled. χ^2 tests were used to calculate *P* values for differences in SR rates based on waiting times after injections. χ^2 was also used to calculate the *P* value for the relationship between delayed grade 3 or 4 SR rates and prescription of an epinephrine autoinjector >90% of the time.

RESULTS

During year 6 (2013-2014), 1349 physicians prescribing SCIT (39% of 3421 AAAAI and ACAAI members) responded, representing 565 clinical practices; data were collected for 1,383,029 patients and 8.2 million injection visits. During year 7 (2014-2015), 1046 physicians (30% of potential respondents) from 494 practices participated and provided data from 1,360,828 patients and 9.5 million injection visits. In year 8 (2015-2016), 1017 physicians (30% of potential respondents) from 363 practices participated, including data from 535,585 patients and 7.8 million injection visits. Thus, during the first 8 years of this annual retrospective survey (2008-2016), data were gathered on 54.4 million injection visits (based on Current

Procedural Terminology billing codes). Responses were received from all regions of the United States, 2 practices in Puerto Rico, and 10 practices in Canada.

Fatal reactions

Seven known fatalities have occurred under the care of allergists between 2009 and 2017 (Table I). Findings associated with 2 FRs in 2009 and 2014 included in Table I were previously published.^{7,10} Five additional confirmed fatalities from SCIT prescribed by allergists in the United States that occurred between 2015 and 2017 are discussed below.

One FR was reported in a 33-year-old man in 2015. The patient had severe asthma and was prescribed Advair 500/50 mcg 1 puff twice daily. No prior SRs were reported. He had completed an accelerated cluster buildup regimen 2 weeks before the FR, which occurred after the second dose of the maintenance vials (0.1 mL of 1:1 vials). The maintenance vials included tree pollen, grass pollen (equal parts of Timothy, Johnson, Bermuda to a total of 0.6 mL in a 5 mL vial), weed pollen, cat epithelia (0.6 mL in a 5 mL vial), dog epithelia, molds, standardized house dust mite (0.7 mL in a 5 mL vial), and cockroach allergen. Within 30 minutes of receiving injections in the allergist's clinic, he had trouble breathing, wheezing, and then collapsed. He received 5 doses of epinephrine (by an unreported route of administration) and diphenhydramine but could not be resuscitated. He was transferred to the hospital in cardiopulmonary failure and in a comatose state and died 1 to 2 weeks later.

Another FR occurred in 2015 in an adult administered maintenance immunotherapy doses shortly after completing a standard buildup regimen. The patient was obese and had severe asthma with previous hospitalizations and prednisone use; no other clinical details were reported. A third FR occurring during 2016 was reported in an adult male. The patient was receiving SCIT prescribed by an allergist at a local health care clinic at work, supervised by a nurse practitioner. The reporting physician noted that the patient had been vomiting and had diarrhea immediately before the injection, and the clinic staff elected to administer the scheduled SCIT injection. He subsequently experienced systemic symptoms but was not treated by the clinic staff for anaphylaxis because of confusion regarding the etiology of his symptoms. Emergency medical services (EMS) were called when he coded, but it is not clear whether he received epinephrine at that time. Anaphylaxis was confirmed by autopsy.

A fourth FR occurring in 2017 was reported in a 13-year-old boy with asthma of unknown severity. Recent spirometry testing showed that his forced expiratory volume in 1 second was greater than 80%. He received a 0.15 mL dose from maintenance vials (1:1 vials). He waited less than 20 minutes after the injection and left the allergist's office. Approximately 1.5 hours after the injection, a parent arrived home, noted that the patient was wheezing, administered epinephrine, and called 911. He was intubated and transported to the hospital but was pronounced dead on arrival. An autopsy confirmed anaphylaxis as the cause of death. There was 1 additional confirmed FR occurring under the care of an allergist in 2017; however, further details are not available.

Based on the above findings, the rate of FRs occurring from SCIT under the care of allergists between 2008 and 2016 was 6 per 54.4 million injection visits, or 1 fatality in every 9.1 million injection visits. The fatality rate up to 2017 cannot be calculated at this time, given that the total number of injection visits for 2017 are currently pending.

Nonfatal reactions to SCIT

Between 2008 and 2016, on average, SRs occurred in 80% to 85% of practices and during 0.1% of injection visits.^{6-8,10,11} On average for all 8 years, there were 8.7 SRs per 10,000 injection visits annually, including 5.6 grade 1 SRs, 2.7 grade 2 SRs, and 0.35 grade 3 SRs per 10,000 injection visits. One grade 4 SR occurred in every 160,000 injection visits from 2012 to 2016. Data regarding SRs per number of patients treated were not available until 2013. SRs occurred in 0.6% of patients receiving SCIT injections from 2013 to 2016, with grade 4 life-threatening SRs occurring in 0.005% of patients (ie, 1 in 20,000 treated patients).

Consistently similar SR rates (events per 10,000 injection visits) were observed for the first 5 years of the survey for the total number of SRs and for SRs of varying severity (see Figure 1). However, there was a trend suggesting a decline in SR rates in 2013-2016 versus previous annual surveys. As reflected by Figure 1, the fall in the overall SR rate appears to be attributable to a reduction in mild grade 1 SRs. For example, the grade 1 SR rate fell from 7.6 in year 1 to 3.9 events/10,000 injection visits in year 8. Despite a decline in grade 1 SR rates, those for grades 2-4 have remained consistent before and after the annual survey incorporated the WAO severity grading system into the written survey in year 4 (2011-2012). It is noteworthy that the year-to-year rates of the WAO grade 2, 3, and 4 SRs have been remarkably consistent since 2011.

Cutaneous and systemic infections associated with SCIT

In the previous survey conducted and reported for year 7 (2014-2015), physician responders did not identify any local cutaneous or systemic infections associated with SCIT during or after 9.5 million injection visits.⁹ No local or systemic infections were reported during year 8 (2015-2016). Thus, overall from 2014 to 2016, there were no injection-related infections reported in 1.9 million patients and 17.3 million injection visits.

Waiting times after injections

During 2010-2011 (year 3 of the survey), 27% of practices required a postinjection waiting time of 20 minutes or less, 15% required 21 to 30 minutes, and 58% required a waiting period of 30 minutes or more.⁶ Among 435 practices in 2013-2014 (year 6), 66% required an observation time of ≥ 30 minutes. Among 318 practices surveyed in year 7 (2014-2015) and 287 practices in year 8 (2015-2016), 74% required ≥ 30 minutes. Additional data regarding waiting times after injections can be found in Figure 2. We hypothesized that SRs beginning outside the office after a shortened observation period (<30 minutes) could delay timely administration of epinephrine and impact SR severity. We therefore also examined the relationship between waiting times and severity of SRs. There were no statistically significant differences in SR rates overall, or in grade 3 or 4 SRs between practices with waiting times of less than 30 minutes versus those recommending 30 minutes or more ($\chi^2 P = .6$ for total SRs and $P = .9$ for grade 3 or 4 SRs).

Delayed-onset SRs

Previously published data for 2009-2010 (year 2 survey) indicated that 14% of SRs were reportedly delayed in onset (ie, starting at >30 minutes after SCIT injections).¹¹ More recently, all practices participating in surveys from years 7 and 8 (2014-

TABLE I. Fatalities from subcutaneous allergen immunotherapy (SCIT) occurring under the care of allergists from 2009 to 2017

Fatality	Year occurred	Year reported	Direct or indirect report	Age of patient (y)	Sex	Dose/phase of buildup	Asthmatic	Possible contributing factors	Standard treatment for systemic reaction provided in the office of the provider
A ⁷	2009	2013	Direct	43	Male	0.2 mL of 1:10 buildup vial	“Mild-moderate persistent,” on as needed albuterol at the time of reaction, FEV ₁ 69% of predicted	(1) Morbidly obese (BMI 38) (2) Highly allergic to weeds and injection given during weed season (3) Started Lisinopril 1 wk before	Yes
B ¹⁰	2014	2014	Direct	Unknown	Unknown	11th injection from the same vial (unknown if buildup or maintenance)	Unknown	Unknown, no dosing error	Yes
C	2015	2016	Indirect	33	Male	0.1 mL of 1:1 (maintenance) vial; had just finished cluster buildup	Yes, on Advair 500 mcg	Fatal reaction involved asthma symptoms	Yes
D	2015	2017	Indirect	Adult	Unknown	On maintenance dosing after standard buildup	Severe asthma with a history of hospitalizations and prednisone use	Obese	Unknown
E	2016	2017	Direct	Adult	Male	Unknown	Unknown	(1) Shots given at local health care clinic by nurse practitioner who did not recognize anaphylaxis (2) Anaphylaxis confirmed by autopsy	No
F	2017	2017	Indirect	13	Male	0.15 mL of 1:1 (maintenance) vial	Yes, most recent FEV ₁ ≥ 80%	(1) Received SCIT injection and waited less than 20 min in office. He was wheezing when parent arrived home 1.5 h later. Parent administered epinephrine and called EMS. EMT intubated. Pronounced dead on arrival to ED (2) No dosing error (3) Anaphylaxis confirmed by autopsy	No
G	2017	2017	Indirect	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown

BMI, Body mass index; *ED*, emergency department; *EMS*, emergency medical services; *EMT*, emergency medical technician; *FEV₁*, forced expiratory volume in 1 second.

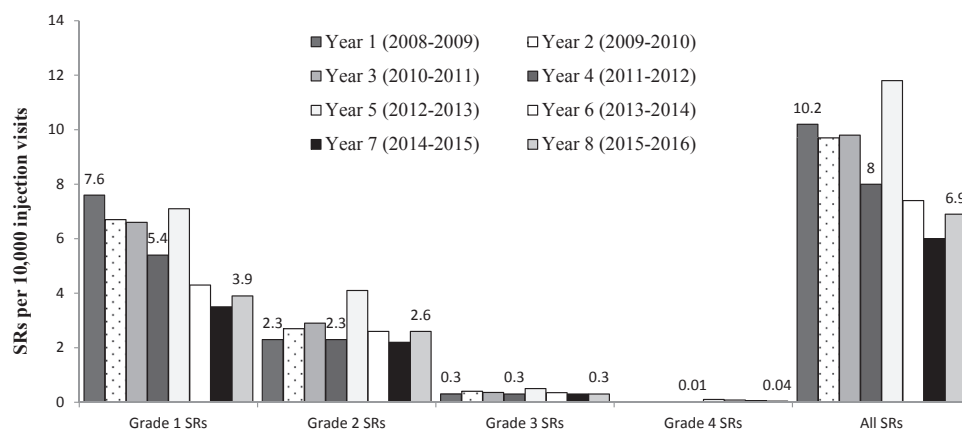


FIGURE 1. Systemic reactions (per 10,000 injection visits) of different severity. Grades for years 1-8 (2008-2016): grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = very severe. Data collection for each year began in the month of July. *SRs*, Systemic allergic reactions.

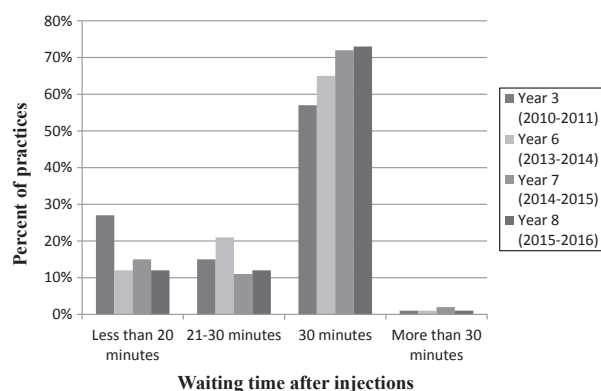


FIGURE 2. Waiting time after injections for year 3 (2010-2011) and years 6-8 (2013-2016). N = 270 practices for year 3, 435 practices for year 6, 318 practices for year 7, and 287 practices for year 8.

2016) reported that for 8692 SRs, 23% began at 10 minutes or less after injections, 31% between 11 and 20 minutes, 27% between 21 and 30 minutes, 19% between 30 and 60 minutes, and 11% reported SRs beginning 60 minutes or more after injections. However, when practices that observed patients for <30 minutes were excluded, only 15% of SRs started after 30 minutes and 0.5% after 60 minutes. Among 3011 delayed-onset (>30 minutes) SRs for which severity data were available for both years, 51% were grade 1, 44% were grade 2, 4.5% were grade 3, and 0.3% were grade 4 SRs. There were no delayed-onset FRs reported for any survey year.

Epinephrine autoinjector prescriptions

Among 436 practices surveyed in year 6 (2013-2014), 20% never prescribed an epinephrine autoinjector for patients on SCIT, 43% sometimes, 14% often, and 24% always prescribed an autoinjector device. Starting in 2014, respondents were queried about the percentage of SCIT patients prescribed autoinjectors. Among 322 practices in 2014-2015 (year 7), 15% never prescribed epinephrine autoinjectors for patients on SCIT,

32% prescribed them <10% of the time, 17% prescribed them 10% to 50% of the time, 7% prescribed them 51% to 90% of the time, and 30% prescribed them >90% of the time. Similar findings were seen for 2015-2016 (year 8) (Figure 3). Because timely administration of epinephrine is known to inhibit the progression of anaphylaxis, we also examined the relationship between prescribing epinephrine autoinjectors and the severity of delayed-onset SRs.¹³ Practices that prescribed epinephrine autoinjectors >90% of the time were not at lesser risk for having a delayed grade 3 or 4 SR ($P = .12$) versus those practices prescribing epinephrine less often (Figure 4).

During year 7 (2014-2015), 14 of 54 of patients (26%) with delayed-onset grade 3 or 4 SRs self-administered epinephrine autoinjectors. During year 8, only 7 of 90 patients (8%) with delayed grade 3 or 4 SRs self-administered epinephrine autoinjectors. Based on a secondary survey of 22 patients with delayed grade 3 or 4 SRs from 2014 to 2015, 21 had been prescribed epinephrine autoinjectors, but only 4 of 21 (19%) self-administered epinephrine. Two patients returned to their allergists' office to receive epinephrine. Three patients were instructed to go to the emergency department; only one of these patients went to the emergency department, and none received epinephrine (Table II).

DISCUSSION

Overall nonfatal SR rates did not increase from 2008 to 2016 and grade 1 (mild) SRs may be declining since 2013, based on data from 54.4 million injection visits in North America, which are the largest amount of such data ever collected. Although FRs remain rare, there was a slight increase in FRs between 2015 and 2017, with 5 new FRs reportedly occurring during that time frame compared with 2 reports from 2009 to 2014. The number of recent FRs may be even higher, given 2 reports of FRs from SCIT reported by media in the last 2 years, which have not yet been confirmed by treating physicians. Nevertheless, considering confirmed FRs during the 9 years of this survey, the annual rate is less than 1 event per year compared with annual rates of 3.4 FRs per year identified in the last AAAAI sponsored retrospective survey spanning 1990-2001.⁵

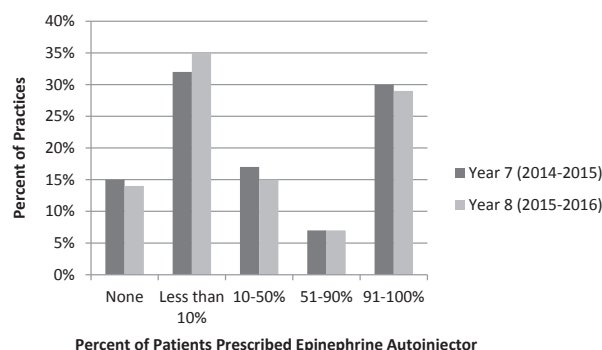


FIGURE 3. Percentage of practices reporting that they prescribe autoinjectors (never, less than 10% of the time, 10% to 50% of the time, 51% to 90% of the time, and 91% to 100% of the time). N = 322 practices in year 7 (2014-2015) and 281 practices in year 8 (2015-2016).

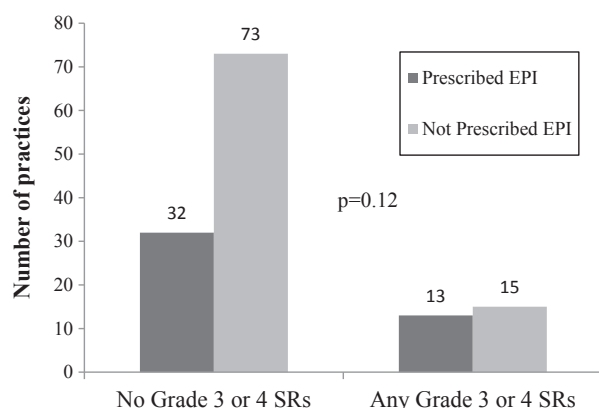


FIGURE 4. Prescribing an epinephrine autoinjector >90% of the time did not decrease the risk of having a delayed grade 3 or 4 SR (χ^2 P = .12). N = 133 practices from 2015-2016 (year 8). EPI, Epinephrine autoinjector; SRs, systemic allergic reactions.

At least 4 FRs since 2009 occurred in patients with asthma, including severe asthma in at least 2 cases. Previous studies found that poorly controlled asthma is a major risk factor for fatal allergic reactions from SCIT.^{5,14,15} The importance of routine preinjection screening either by assessing recent changes in asthma symptoms and/or reduced lung function is highlighted in the Allergen Immunotherapy Practice Parameter.¹

Although respondents in this survey previously indicated a high rate of asthma screening (86%) before injections, more rigorous methods for identifying patients at risk for life-threatening SRs may be needed in asthmatic patients.⁶ Many asthmatic patients benefit greatly from immunotherapy, but care should be taken that asthmatic patients are appropriate candidates for SCIT. For example, avoiding prescription of SCIT for patients whose asthma is not controlled based on Asthma Control Test scores is associated with fewer grade 3 and 4 SRs.¹⁰ Of note, 1 FR occurred in a severe asthmatic who had just reached the maintenance vial after completing a cluster immunotherapy buildup. Although it is not

certain that the FR occurred because of cluster buildup, and this is the first known fatality associated with cluster immunotherapy, accelerated buildup strategies have previously been associated with an increased risk of SRs of all severity grades.¹⁰ Thus, it may not be advisable to recommend accelerated buildup strategies in patients with moderate or severe asthma.

Delay in treatment with epinephrine is another risk factor for FRs identified from previous studies.^{3,5} In one of the aforementioned FRs, lack of timely recognition and treatment of anaphylaxis in a remote health clinic charged with administering injections prescribed by an allergist may have resulted in a meaningful delay in treatment. This experience highlights the need for medical personnel at outside clinic facilities to receive adequate training on safety measures for administering injections, and for recognizing and treating SRs.

Another known risk factor, reactions occurring outside of the allergist's office, was associated with a FR in an asthmatic child receiving SCIT. In this case, the child waited less than 20 minutes in the office. Although an epinephrine autoinjector was available, there was a delay in administration due to the child being home alone when the SR began. Findings from this survey indicate that more practices have required a 30 minute or longer waiting period in recent years (74% for year 8 vs 58% for year 3). Some practitioners have questioned the necessity of 30-minute observation period if epinephrine autoinjectors can be prescribed to all SCIT patients. In this case, prescription of an epinephrine autoinjector was not an effective substitute for an adequate 30 minute post-injection observation period and timely emergency treatment in the physician's office. The latter case resembles a previously documented FR in an asthmatic child administered an allergen injection at home in an inadequate setting to render life-saving treatment.⁵ Both of these events support the Practice Parameter recommendation for an adequate postinjection waiting period after administration of SCIT injections.¹

It is debatable whether prescription of epinephrine autoinjectors leads to improved safety outcomes with SCIT.¹⁶ A theoretical advantage of prescribing an epinephrine device is its availability in the event that a delayed-onset SR (starting at >30 minutes) should occur. Delayed-onset SRs occurred with 14% of injection visits in our previous 2009-2010 survey.¹¹ Initial evaluation of data collected from 2014 to 2016 indicated a much higher delayed SR rate of 30%; however, when we focused on practices that monitor patients for at least 30 minutes, only 15% of SRs began between 31 and 60 minutes and 0.5% after 60 minutes, confirming prior survey data. Interestingly, practices with less than 30-minute observation periods after SCIT injections might explain some prior studies reporting unusually high frequencies of late-onset SRs, because the actual timing of onset of many SRs would not have been observed.^{17,18} It is noteworthy that no FRs were delayed in onset.

Presumably because of concerns about the potential for severe or fatal delayed SRs, 29% of all practices surveyed in years 7 and 8 (2014-2016) prescribed epinephrine autoinjectors for greater than 90% of patients on SCIT in their practices. Although epinephrine may mitigate the progression of SRs when given early, those practices broadly prescribing epinephrine autoinjectors did not appear to have a reduced risk of delayed severe grade 3 or 4 SRs. This may be because only 8% of patients with delayed grade 3 or 4 SRs who were prescribed epinephrine autoinjectors in 2015-2016 actually used

TABLE II. Use of epinephrine in 22 patients from year 7 (2014-2015) with delayed grade 3 or 4 SRs*

	Received epinephrine	Previously prescribed an epinephrine auto-injector	Self-administered epinephrine (if previously prescribed device)	Went to the emergency room (did not receive epinephrine)	Received epinephrine in allergist's office
Number of patients	6/22 (27%)	21/22 (95%)	4/21 (19%)†	1/22 (5%)	2/22 (9%)

*Information from 54 patients with delayed grade 3 or 4 SRs was requested from their physicians and was provided for 22 patients.

†The denominator for this column is 21, which reflects the number of patients who were prescribed epinephrine autoinjectors.

their self-injectable devices. Only 26% of such patients used their epinephrine autoinjectors in the prior year's survey. In the substudy of 22 patients with delayed SRs from 2014 to 2015, almost all patients (21 of 22) reported that they had been prescribed epinephrine by their allergist, but only 4 patients actually used the device during their SRs. This finding highlights the urgent need for better patient education regarding indications for usage of an epinephrine autoinjector. Perhaps, in the future, more convenient devices and formulations can be developed for epinephrine self-administration, especially those strategies that can mitigate patient phobias surrounding self-injection.^{19,20} Currently, it remains unclear whether prescription of an epinephrine autoinjector for patients receiving SCIT is a useful practice, in large part because of poor patient adherence with recommendations for autoinjector use.

Of note, 2 FRs since 2008 occurred in patients who were obese, including one that was morbidly obese. Findings for the latter case were previously published; in that case it was thought that epinephrine needle length may not have been adequate, and that the patient's obesity may have impacted other aspects of treatment.⁷ It is unknown what role, if any, the patient's obesity played in the other FR.

Another important finding from this study is the absence of cutaneous or systemic infections associated with SCIT in 17.3 million injection visits, and 1.9 million patients. There is no evidence to date of a risk of human infections associated with compounding of commercial allergens in outpatient settings under the supervision of practicing allergists in the United States. The absence of reported infections would also indicate that there is no identifiable infection risk associated with subcutaneous injections administered from patient-specific maintenance and diluted buildup vials.

In conclusion, SR rates from SCIT have remained stable, but there has been a disturbing increase in reported fatalities from SCIT in recent years. Several of these FRs have been associated with known risk factors, such as asthma, inadequate waiting time after injections, and delays in treatment with epinephrine. The first FR associated with a cluster buildup regimen has been reported, occurring in a severe asthmatic. Vigilance with regard to procedures that minimize the impact of known risk factors is important. Risk factors have not been identified for some fatalities, which warrants continued investigation. Although delayed-onset SRs are not uncommon, severe delayed SRs are fortunately rare. Routine prescription of epinephrine autoinjector devices has not been shown to decrease risks associated with delayed-onset SRs, in large part because patients rarely use prescribed devices, even for the treatment of severe SRs. Surveillance data over 2 years have not demonstrated any biosafety risk related to infections associated with SCIT as practiced in the United States.¹

REFERENCES

- Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(suppl):S1-S55.
- Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017;118:28-54.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993;92(Pt 1):6-15.
- Bernstein DI, Wanner M, Borish L, Liss GM. Immunotherapy Committee AAoAA, Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110:274-278.e1.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract* 2014;2:161-7.
- Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 2010;104:530-5.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Evaluation of the risk of infection associated with subcutaneous allergen immunotherapy: American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology National Surveillance Study on Allergen Immunotherapy, 2014-2015. *Ann Allergy Asthma Immunol* 2017;118:511-2.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). *Ann Allergy Asthma Immunol* 2016;116:354-359.e2.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: year 2. *Ann Allergy Asthma Immunol* 2011;107:426-431.e1.
- Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol* 2010;125:569-574.e1-574.e7.
- Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J* 2015;8:32.
- Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001;87(suppl 1):47-55.
- Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:169-75.
- Fitzhugh DJ, Bernstein DI. Should epinephrine autoinjectors be prescribed to all patients on subcutaneous immunotherapy? *J Allergy Clin Immunol Pract* 2016;4:862-7.

17. Greenberg MA, Kaufman CR, Gonzalez GE, Trusewycz ZP, Rosenblatt CD, Summers RJ. Late systemic-allergic reactions to inhalant allergen immunotherapy. *J Allergy Clin Immunol* 1988;82:287-90.
18. Cook KA, Ford CM, Leyvas EA, Waalen J, White AA. Half of systemic reactions to allergen immunotherapy are delayed, majority require treatment with epinephrine. *J Allergy Clin Immunol Pract* 2017;5:1415-7.
19. Rachid O, Rawas-Qalaji M, Simons KJ. Epinephrine in anaphylaxis: preclinical study of pharmacokinetics after sublingual administration of taste-masked tablets for potential pediatric use. *Pharmaceutics* 2018;10:24.
20. Rachid O, Rawas-Qalaji MM, Simons FE, Simons KJ. Epinephrine (adrenaline) absorption from new-generation, taste-masked sublingual tablets: a preclinical study. *J Allergy Clin Immunol* 2013;131:236-8.

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TABLE E1. Survey questions in years 6-8 (August 1, 2013, to August 31, 2016). (Some questions were not asked every year, as described in the text)

1. During the past 12 mo, have any patients in your entire clinical practice (including patients of your associates) experienced a fatal anaphylactic reaction(s) after an aeroallergen immunotherapy injection, venom immunotherapy injection, or allergy skin testing?
2. During the past 12 mo, have any patients in your entire clinical practice (including patients of your associates) experienced systemic allergic reactions after aeroallergen immunotherapy injections?
If yes, how many nonfatal systemic reactions have there been in the entire clinical practice in the past 12 mo?
According to the World Allergy Organization severity classification system, please indicate the number of nonfatal systemic reactions in your entire practice during the last 12 mo (including patients of your associates) from aeroallergen immunotherapy that are best described as:
Grade 1→ Symptom(s)/signs of 1 organ system present: generalized urticaria with/without angioedema (NOT laryngeal, tongue, or uvular) or nausea or upper respiratory symptoms (eg, itching of the palate and throat, sneezing) or conjunctival symptoms.
Grade 2→ Asthma RESPONDING to an inhaled bronchodilator and/or GI symptoms including abdominal cramps, vomiting, or diarrhea, or uterine cramps.
Grade 3→ Severe asthma NOT RESPONDING to a bronchodilator or laryngeal, uvular, or tongue edema, with or without stridor.
Grade 4→ Respiratory failure or hypotension with or without loss of consciousness.
3. During the past 12 mo, 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 mo, have any patients in your practice receiving SCIT developed local cutaneous infections including cellulitis or abscess at or near the site of allergen injections from a mixed allergen vial prepared in your office?
5. During the past 12 mo, have you identified any patients in your practice receiving SCIT who developed systemic infections or sepsis associated with the administration of allergen vial prepared in your office?
6. In the past 12 mo, how many systemic reactions began within each of the following time intervals after receiving an allergen injection? 0-10 min__, 11-20 min__, 21-30 min__, 30 min__, 31-60 min__, greater than 60 min__, Onset of reaction unknown__.
7. For nonfatal systemic reactions beginning after 30 min or more after an allergen injection, please indicate the WAO severity grade of reaction.
8. If you reported any grade 3 or 4 (severe or very severe) systemic allergic reactions that began after 30 min or more after an allergen injection, please indicate the number of patients that self-administered an epinephrine autoinjector to treat the reaction.
9. In your entire clinical practice, what is the required waiting period after allergen injections? 0-20 min__, 21-29 min__, 30 min__, greater than 30 min__, other (please describe)__.
10. In your entire clinical practice, what percentage of patients are prescribed an epinephrine autoinjector when starting allergen immunotherapy injections? None__, less than 10%__, 10% to 50%__, 51% to 90%__, 91% to 100%__.
11. During the past 12 mo, how many subcutaneous allergen injections have your entire practice billed under Current Procedural Terminology (CPT) codes 95115 and 95117 for single and multiple injections (or other codes)? How many allergists and nurse practitioners write orders (or prescribe) immunotherapy in your entire clinical allergy practice? What is the total number of patients administered injections in your entire clinical practice (including those of your associates) during the past 12 mo? Were the number of injections and number of patients stated above retrieved from CPT code records in your office computer system?

GI, Gastrointestinal; SCIT, subcutaneous allergen immunotherapy; WAO, World Allergy Organization.

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