

Journal Pre-proof

Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): post-injection monitoring and severe asthma

Tolly G. Epstein MD, MS , Karen Murphy-Berendts BS ,
Gary M. Liss MD, MS , David I. Bernstein MD

PII: S1081-1206(21)00187-3
DOI: <https://doi.org/10.1016/j.anai.2021.03.011>
Reference: ANAI 3533



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 8 February 2021
Revised date: 14 March 2021
Accepted date: 16 March 2021

Please cite this article as: Tolly G. Epstein MD, MS , Karen Murphy-Berendts BS , Gary M. Liss MD, MS , David I. Bernstein MD , Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): post-injection monitoring and severe asthma, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.03.011>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): post-injection monitoring and severe asthma

Tolly G. Epstein, MD, MS^{*†}; Karen Murphy-Berendts, BS[§]; Gary M. Liss, MD, MS[‡];
David I. Bernstein, MD^{*§}

^{*}Division of Immunology, Allergy, and Rheumatology, Department of Medicine,
University of Cincinnati College of Medicine, Cincinnati, Ohio

[†]Allergy Partners of Central Indiana, Indianapolis, Indiana

[§]Bernstein Clinical Research Center, LLC, Cincinnati, Ohio

[‡]University of Toronto, Toronto, Ontario, Canada

Corresponding Author: Tolly Epstein, MD, MS, Division of Immunology, Allergy, and Rheumatology, Department of Medicine, University of Cincinnati College of Medicine, 3255 Eden Ave, Suite 350, ML 0563, Cincinnati, OH 45267; Email: epsteite@uc.edu.

Conflict of Interest: Drs. Epstein, Bernstein, and Liss received funding from the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology for conduct of the study and statistical analysis.

Funding Source: the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology

Key Words: Subcutaneous Allergen Immunotherapy; Systemic Reactions; Asthma; Severe Asthma; Waiting Times; Safety

Abbreviations:

ACAAI=American College of Allergy, Asthma & Immunology

AAAAI=American Academy of Allergy, Asthma & Immunology

SCIT=Subcutaneous allergen immunotherapy

SR=Systemic allergic reaction

FR=Fatal reaction

BMI=Body mass index

ACT=Asthma Control Test

WAO=World Allergy Organization

Word Count: 3,902

Figures: 4

Tables: 1 electronic table

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

Objective: Identify practices that influence systemic allergic reactions (SRs) to SCIT, and SCIT-associated infections.

Methods: ACAAI/AAAAI members completed an annual survey of SCIT-related SRs of varying severity (2008-2018). Injection-related infections were queried (2014-2018). Strategies to enforce post-injection waiting times, and to reduce risks from asthma/severe asthma were queried (2016-2018).

Results: Data were gathered on 64.5 million injection visits. Ten confirmed fatalities occurred since 2008, including 3 new fatalities since 2017. One fatal reaction occurred per 7.2 million injection visits

(2008-2018). No infections occurred. Practices that tracked the time after injections, and required checking out with office personnel, had significantly lower total ($p<0.0001$), Grade 3 (severe) ($p<0.0008$) and Grade 4 (very severe) SRs ($p<0.0001$). Having more asthmatics on SCIT was associated with more Grade 3 SRs ($p<0.02$). Not prescribing SCIT in uncontrolled asthmatics was associated with fewer Grade 3 SRs ($p=0.02$). Having more severe asthmatics on SCIT was associated with more total, Grade 1, and Grade 2 SRs ($p<0.0001$); 50% of Grade 3 and 4 SRs occurred in severe asthmatics.

Conclusion: SCIT- related fatalities have declined since 2008, with a slight increase in recent years. SCIT is not associated with an increased risk of infections. Tracking the time after injections and checking out with office staff confers significantly lower risks of severe SRs. Asthma, and especially severe asthma, are major risk factors for severe and fatal SRs. Strategies that reduce risks for asthmatics, such as not prescribing SCIT to uncontrolled asthmatics, may lower risks.

Introduction

Allergen immunotherapy reduces symptoms and medication requirements in patients with seasonal and perennial allergic rhinitis and IgE dependent asthma.¹ Although subcutaneous allergen immunotherapy (SCIT) injections are administered safely to nearly all patients when given in medically supervised ambulatory settings, near fatal and fatal anaphylactic events rarely occur.^{2,3} Between 1990-2001, it was estimated that one fatal systemic allergic reaction (SR) occurred in every 2.5 million injection visits, or 3.4 fatal systemic reactions per year.² Allergy specialists participating in retrospective surveys identified major contributing factors to fatal reactions (FRs) including: uncontrolled asthma (62%); administration of injections during peak allergy seasons (47%); suboptimal treatment of anaphylaxis (43%); a history of prior SRs to SCIT (53%); dosing errors during administration (35%); and administration in suboptimal settings (21%), such as injections given at home or in clinics where the observation periods were less than 30 minutes.^{2,4,5} In response to concerns over FRs, an annual survey was initiated in 2008 among physician members of the American College of Allergy, Asthma, & Immunology

and American Academy of Allergy, Asthma & Immunology to track the incidence of SRs from SCIT injections.^{6,7} The annual survey has also questioned participants regarding clinical practice patterns that impact the risk of severe SRs. More recently, both local and systemic infections associated with SCIT injections have been assessed.⁷ Seven FRs reported by allergists between 2008-2017 were previously described.⁷ During that time period, Grade 4 anaphylactic SRs were estimated to occur once in every 160,000 injection visits.⁷

The risk of severe uncontrolled asthma contributing to FRs has been well described, providing rationale for recommendations in the Allergen Immunotherapy Practice Parameter to pre-screen all asthma patients on SCIT prior to receiving injections.¹ There is little evidence, however, defining the overall risk of severe SRs among asthmatic patients on SCIT. As mentioned, suboptimal management of anaphylaxis has also been associated with some FRs in which inadequate post-injection observation and/or delay in administration of epinephrine were identified.⁸ Nearly all FRs occur within the first 30 minutes following SCIT injections.¹ According to recent annual survey data, at least 73% of allergy practices observe the 30-minute observation period.⁷

To date, the impact of strict adherence to post-injection monitoring on mitigation of risk of SRs has not been well defined. In addition, there is limited evidence on the relationship between clinical practice patterns related to severe asthmatic patients and the risk of severe SRs. In this report, we present data from participating allergists collected between 2016 and 2018. In addition to reporting FRs and non-fatal SRs of varying severity, we present findings regarding the impact of strategies surrounding post-injection waiting periods as well as relationships between asthma severity, obesity, and the risk of SRs in patients receiving SCIT.

Methods

Study population

Physician members of the AAAAI and ACAAI were recruited to complete the annual survey as previously described.^{6,7,9-11} Briefly, each year the survey coordinator contacted AAAAI and ACAAI members practicing immunotherapy in North America on at least 4 occasions via email or fax. A single respondent was recruited from each practice to report the annual experience of the entire clinical practice from July 1, 2008 through August 31, 2018.⁶ No patient identifiers were provided by participants, and provider participants were deidentified before data analysis. When possible, participating practices collected data in 'real time' on the date of SRs or infections, either by entering these data into their electronic medical records system at the time of occurrence, or by using a standard spreadsheet provided by the study coordinator. Data from all practices were provided to the survey team on an annual basis.

Study design

In all years of the survey, physician respondents completed questionnaires describing the experience of all SCIT prescribers in their practices.¹⁰ Participants were queried regarding confirmed FRs and SRs to SCIT injections occurring in the previous 12 months in their own practices (direct reports) and any FRs that occurred in other local practices in their geographic areas (i.e. indirect reports). Allergists reporting FRs completed a detailed questionnaire providing specific details of the event, contributing factors, and treatment administered.^{6,10} For events reported during years 1 to 3 (2008-2011; each year includes 12 months of data starting in July), a previously described grading system that included 3 grades of SRs was used.^{6,9} For years 4 to 10 (2012-2018), the World Allergy Organization (WAO) grading system was adopted

with four severity grades of nonfatal SRs (Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, very severe).^{7,10,12}

In years 7-10 (2014-2018), respondents were asked to report local cutaneous infections and systemic infections associated with SCIT injections (see survey questions, Table E1).^{7,11} Each year of the survey, novel questions were added to investigate factors contributing to SRs including: waiting times after SCIT injections (2010-2011 [Year 3] and 2013-2017 [years 6-9]); methods used to observe patients after SCIT injections (2016-2017 [year 9]); relationships between SRs and asthma severity, asthma control, asthma prescreening, use of controller therapies for asthma (2016-2018 [years 9 and 10]); and the association between obesity and SRs (2016-2018 [years 9 and 10]).

Statistical analysis

Descriptive statistics regarding reaction rates and the number of injection visits were calculated using SAS statistical software (Version 9.4, 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 were calculated regarding waiting times after injections, methods for post-injection monitoring, number/percent of asthmatics and severe asthmatics per practice, and number of obese (body mass index >40) individuals with SRs of various severity grades. Chi-square tests were used to calculate p values for differences in SR rates for post-injection waiting times, methods for post-injection monitoring, percent of asthmatics and severe asthmatics on SCIT, prescription of SCIT in uncontrolled asthmatics, requirement of controller therapies for asthmatics, and use of peak flow/lung function monitoring prior to SCIT injections. For 2017-

2018, a question regarding the relationship between severe asthma and Grade 3 and 4 SRs was specifically added (Table E1).

Results

Between 2016-2017 (Year 9 of the survey), 945 physicians prescribing SCIT (28% of 3,421 AAAAI and ACAAI members) responded, representing 351 clinical practices. Data was collected for 351,445 patients and 7.2 million injection visits. Between 2017-2018 (Year 10), 658 physicians prescribing SCIT (19%) responded, representing 250 clinical practices. Data was collected for 247,701 patients and 2.9 million injection visits. Participation had declined compared to the 49% of recruited providers participating in Year 1 of the survey (2008-2009). The decline in response rate corresponded with the inability of the survey team to obtain updated AAAAI and ACAAI member lists necessary to recruit non-participating practices and new prescribing allergists. During the first 10 years of the survey (2008-2018), data was gathered on 64.5 million injection visits (based on Current Procedural Terminology billing codes). Responses were received from all regions of the United States, two practices in Puerto Rico, and 10 practices in Canada.

Fatal Reactions

Ten confirmed FRs due to SCIT occurred under the care of allergists from 2008-2019. Details regarding 7 confirmed FRs that occurred up until 2017 have been previously published.⁷ Two FRs occurred in teenagers since 2015, including one already published event.⁷ The previously unpublished, FR in a teenager occurred in 2018; no specific details regarding this FR were available.

The second fatality from 2019 occurred in a 19-year-old female with mild persistent asthma, allergic rhinitis, and atopic dermatitis. When last assessed by her treating physician 5 months prior to the FR, she was taking Flovent 110 mcg 2 puffs twice daily and Montelukast 10 mg daily, Asthma Control Test (ACT) score was 25 (controlled), and she denied recent albuterol use. The responding physician did not indicate whether a peak flow was checked, or if pre-injection asthma symptom screening was performed on the day of the FR. The reaction was not reported to occur during a peak pollen season. No dosing error was reported. On the day of the FR, her injection dose may have been decreased due to previous local reactions. She received either 0.05 ml or 0.1 ml of the 1:1 maintenance vials and waited in the office for less than 10 minutes. On the way home she developed shortness of breath, used albuterol, pulled off the road, and called 911. She reportedly 'coded while Emergency Medical Services were there.' Cardiopulmonary resuscitation was started in the field and continued upon arrival to the Emergency Department (ED). She recovered a heartbeat, and was intubated and placed on an epinephrine drip. No report of the timing of initial epinephrine administration was provided. Upon arrival to the ED she was 'not moving any air,' had pneumomediastinum from bronchospasm, and had poor neurologic responses with a CT scan showing cerebral edema. There was no change in neurologic status in the ICU after warming from therapeutic hypothermia, brain death was considered likely, and she was later pronounced dead.

A third heretofore unreported FR occurred in 2019 in an adult (exact age not reported) with asthma, reported to be controlled at the time of the injection. The responding physician did not indicate if the patient was on a controller therapy, or if a peak flow was checked on the day of the FR, or if the patient had additional co-morbidities. The reaction began within minutes after a SCIT injection and was manifested predominantly by lower airway symptoms. The

patient was immediately treated with multiple doses of intramuscular epinephrine and subsequently transported to a local hospital, remaining intubated for several days before expiring. There was no knowledge of a dosing error. The FR occurred in late summer/early fall but outside of a peak pollen season in the locale where the event occurred.

We recently estimated from this surveillance study an incidence of 1 FR per 9.1 million injection visits between 2008-2016, or less than 1 FR per year.⁷ Due to an increase in FR reports since 2016, the current 10-year average incidence (2008-2018) is estimated at 1 FR per 7.2 million injection visits or less than 1 FR event per year. FRs from 2019 were not included in this estimate given that the total number of injections for 2019-2020 is not available at this time.

Non-fatal SRs to Immunotherapy (2016-2018)

For the first 10 years of the survey, non-fatal SRs occurred in 76-85% of practices, and a mean of 0.1% of all injection visits. Data regarding the number of patients on SCIT were gathered starting in 2013. Since then, SRs were reported to occur in a mean 0.8% (range=0.4-1.5%) of treated patients. During the first 10 years of the survey, a mean of 8.8 SRs occurred per 10,000 injection visits, including 5.5 Grade 1 SRs, 2.9 Grade 2 SRs, and 0.36 Grade 3 SRs per 10,000 injection visits. As described in the methods section, a three-grade severity system was used until 2011, so that what are now defined as Grade 4 (very severe) SRs using WAO criteria, were previously categorized as Grade 3 (severe) SRs.^{13,14} Although SRs of all severity grades showed a downward trend through Year 9 (2016-2017), there was an increase in SRs of all severity grades in Year 10 (2017-2018), including 12.6 total SRs per 10,000 injection visits, 6.8 Grade 1 SRs, 5.0 Grade 2 SRs, and 0.6 Grade 3 SRs per 10,000 injection visits (Figure 1).

Data regarding Grade 4 SRs were gathered since 2011. Between 2011-2018, Grade 4 SRs occurred in approximately 1 in 160,000 injection visits. During Year 10 (2017-2018), the rate of Grade 4 SRs increased to 1 per 100,000 injection visits. Similarly, for 2014-2016, Grade 4 SRs occurred in 0.005% of patients but this increased to 0.01% of patients for 2017-2018.

Cutaneous and systemic infections associated with SCIT

No local or systemic infections from SCIT injections were confirmed for Years 9 and 10 (2016-2018). Thus, no local or systemic infections have been documented in approximately 27.4 million injection visits or in 2.5 million patients receiving SCIT injections, since the addition of relevant survey questions in 2014.^{7,11}

Waiting times after injections and post-injection monitoring strategies

For 2016-2017, 76% (166/215) of practices reported a post-injection waiting period of 30 minutes or greater. No significant differences in rates or severity of non-fatal SRs were found relative to the duration of waiting times after injections. In 2016-2017, we evaluated the impact of different strategies used to *enforce* post-injection waiting times, regardless of duration of required waiting times (see Table E1). Fifty-five percent (117/211) of practices reported that office staff routinely tracked the designated times for monitoring patients after injections and required patients to check out with medical personnel before leaving. In 28% (59/211) of practices, the patient tracked their own time and checked out with medical personnel before leaving, whereas 16% (34/211) of practices relied on patients to track their own time and leave without checking out. Less than 1% of practices did not report any system for tracking post-injection waiting times. As shown in Figure 2, practices that monitored the time after injections

and required patients to check out with medical personnel had significantly lower numbers of total SRs per practice ($p<0.0001$), as well as lower numbers of Grade 3 SRs ($p<0.0008$) and Grade 4 SRs ($p<0.0001$) per practice.

Asthma and SCIT

Asthma is a known risk factor for severe and fatal SCIT reactions.^{2,7,15} In 2016-2017, we asked respondents what percent of their patients on SCIT had asthma of any severity. Potential categories of responses included: none, 0.1-10%, 11-20%, 21-30%, 31-50%, and more than 50%. As shown in Figure 3, and consistent with existing literature, practices with a higher percentage of asthmatics on SCIT had significantly higher rates of Grade 3 SRs ($p<0.02$).¹ Grade 4 SRs occurred more frequently in such practices, although this finding was not statistically significant ($p=0.09$). No significant differences were seen for total SRs, or Grade 1 or 2 SRs related to the percentage of asthmatics on SCIT.

As was seen in previous years of the survey, significantly lower rates of severe SRs were found among practices not prescribing SCIT in patients with uncontrolled asthma ($p=0.02$).¹⁵ That is, for 2016-2017, there were 24 Grade 3 SRs among 124 practices never prescribing SCIT in patients with uncontrolled asthma versus 117 Grade 3 SRs among 93 practices who sometimes, often, or always prescribed SCIT in patients with uncontrolled asthma. There were no significant differences in SR rates based on prescription of controller therapies for asthmatics on SCIT ($p=0.09$). Peak flow or lung function monitoring have previously been suggested for asthmatics prior to receiving SCIT injections. For 2016-2018, practices routinely performing these procedures on asthmatics prior to injections did not report different rates of SRs of any severity than those who did not routinely perform these procedures.

Based on retrospective surveys of FRs to SCIT injections, we hypothesized that severe uncontrolled asthma is a greater risk factor for adverse outcomes with SCIT than asthma in general. For 2016-2017, practices were asked to report the percentages of severe asthma patients receiving SCIT injections in their practice using the following categories: none, more than zero but less than 5%, 5-10%, 11-20%, 21-50%, or more than 50%. To respond to this question, respondents were instructed to refer to the ERS/ATS Task Force (2014) definition of severe asthma (i.e., persistent asthmatic symptoms despite treatment with optimal doses of inhaled corticosteroids, in whom response to treatment is incomplete).¹⁶ Seventy percent (n=149) of practices reported that fewer than 5% of their patients on SCIT had severe asthma. Among the remaining 30% of practices, 45 reported that 5-10% of their patients on SCIT had severe asthma, 22 reported 11-20%, and three practices reported that >20% of patients on SCIT had severe asthma. Practices reporting that >20% of their patients on SCIT had severe asthma had significantly higher rates of total, Grade 1, and Grade 2 SRs ($p<0.0001$ for each comparison). (Figure 4) Findings were not significant for Grade 3 and 4 SRs. For 2017-2018, practices were directly asked the following question: “Of those patients who had WAO Grade 3 or 4 Systemic Reactions in the past year, how many had Severe Asthma?” Respondents indicated that 50% (105/209) of Grade 3 or 4 SRs occurred in severe asthmatics.

Other Risk Factors for SCIT reactions

It was previously hypothesized that obesity may be a risk factor for fatal and severe SRs.^{7,15} For 2016-2017, 3% (6/177) of Grade 3 and 4 SRs occurred in morbidly obese ($\text{BMI}>40 \text{ kg/m}^2$) patients. For 2017-2018, 13% (28/209) of Grade 3 and 4 SRs were in morbidly obese individuals. Due to the limitations of the survey, patient specific data related to the body weight

of all patients on SCIT cannot be gathered. Nevertheless, the age-adjusted US national rate for morbid obesity among adults in 2015-2016 was 7.7% and in 2017-2018 was 9.2%.¹⁷ Thus, combined data from 2016-2018 do not appear to indicate an increased prevalence of morbid obesity among patients with severe SRs from SCIT compared to what would be expected based on rates of morbid obesity in the general population.

Discussion

Fatality rates associated with SCIT injections since 2008 have declined overall compared to a previously reported retrospective study of events from 1990-2001. There has, however, been a slight upward trend in FRs since 2015.² A similar decline in SRs of all severity grades was seen up until 2017, with a small increase in total and severe Grade 3 and 4 SRs since that time. While contributing factors for some FRs have been difficult to elucidate, major risk factors for severe SRs and FRs have remained consistent since they were first identified decades ago.^{4,5} Asthma, and especially severe or poorly controlled asthma, are still the most frequently identified risk factors for severe and fatal reactions. Although there are clear examples where inadequate waiting times have contributed to FRs, optimal strategies for post-injection monitoring have been more controversial.⁷

The third update of the Immunotherapy Practice Parameter recommends a 30 minute post-injection waiting period after SCIT injections.¹ This is based on individual reports of FRs associated with inadequate post-injection monitoring or delays in treatment of anaphylaxis, as seen in several recently published fatalities, and one fatality described in this manuscript.^{4,7,18} Data collected in this survey have not shown a statistically significant relationship between SRs of any severity and the length of the post-injection waiting period. This could be explained by

under-reporting of SRs by those practices not observing patients for longer than 20 minutes.⁷ Significant differences were seen, however, based on the strategy used by individual practices for enforcement of the post-injection waiting period. Practices that tracked the time after injection and required patients to check out with office personnel had significantly lower rates of SRs versus those using other strategies. Practices that allowed patients to track their own time and leave without checking out had very high SR rates, with 3 to 4 fold higher rates of total, Grade 3, and Grade 4 SRs per practice versus those who monitored times and required that patients check out with office personnel. Potential explanations for these differences include: (1) patients may be more likely to remain in the office for the mandatory observation period when directly monitored, and (2) patients may be more likely to inform office personnel of early post-injection symptoms if they are assessed prior to leaving the office, thus enabling treatment of early symptoms prior to progression to severe SRs. We cannot exclude the possibility that other unrelated clinical strategies employed by practices not requiring check out with clinical staff (e.g. inconsistent pre-injection screening of asthmatic patients) could have contributed to greater numbers of reported SRs as well.

Previous data from this surveillance study, as well as two of the new fatalities reported in this manuscript, highlight that asthma is the major risk factor for FRs from SCIT.^{7,15} Data from 2016-2018 show that asthma is also a major risk factor for severe, nonfatal SCIT-related SRs. For 2016-2017, there were significantly higher rates of Grade 3 SRs and possibly higher rates of Grade 4 SRs among practices with a higher percentage of asthmatics on SCIT. As seen in prior years, practices that did not prescribe SCIT for patients with uncontrolled asthma had lower rates of severe SRs for 2016-2017.¹⁵ Checking lung function or peak flow monitoring before SCIT injections did not significantly impact SR rates, however.

Prescription of SCIT for patients with severe asthma has been controversial, given the argument that some severe asthmatics may benefit from SCIT, despite increased risks. For 2016-2017, there were significantly higher rates of total, Grade 1 and 2 SRs among practices with a higher percentage of severe asthmatics on SCIT. Findings were not significant for Grade 3 and 4 SRs for 2016-2017, possibly because of the low number of practices with higher percentages of severe asthmatics on SCIT, and the relative rarity of Grade 3 and 4 SRs overall. For 2017-2018, a very high proportion (50%) of Grade 3 and 4 SRs occurred in severe asthmatics. Based on these findings, any potential benefits from SCIT in severe asthmatics must be balanced against very significant risks for adverse safety events in this population. In the very least, asthma should be well-controlled if starting SCIT, especially for those with a prior history of severe persistent asthma. It has been suggested elsewhere that administration of biologic medications to improve asthma control and lower the risk of SRs from SCIT may be considered.^{19,20} Further study regarding ways to mitigate the safety risks of SCIT in severe asthmatics is needed.

Concerns were raised in recent years regarding the risk of infection from SCIT. To date, no local or systemic infections from SCIT have been reported in 27.4 million injection visits among 2.5 million patients. Thus, there does not appear to be a significant risk of infection from SCIT prepared using standard methods for compounding and administration by Allergist/Immunologists. In addition, although morbid obesity was thought to play a role in at least one recent fatality from SCIT, an increased risk for severe SRs among morbidly obese patients has not been found.¹⁰

Limitations to this survey include that reporting is voluntary, and dependent on accurate recording of events by participating practices. Participants are asked to record data prospectively, in 'real time' if feasible; however, there is the possibility of less accurate reporting

if respondents are not able to do so. In addition, findings regarding ‘uncontrolled asthma’ may be impacted by changes in asthma control that may occur day to day, depending on exposure to exacerbating factors, changes in prescribed medications, and adherence to medications.

Obtaining information regarding the risk domain of asthma control, such as ED visits and oral steroid use may be useful in the future. Findings regarding peak flow and spirometry are also less applicable during the COVID-19 pandemic, due to prohibitions on performance in many settings.

In summary, the overall risk of severe SRs from SCIT remains low. Based on the most recent data, we estimate that 1 FR occurs in 7.2 million SCIT-injection visits, or less than 1 FR per year. Post-injection monitoring that includes keeping track of waiting times and checking out with office personnel before leaving is associated with a significantly lower risk of severe SRs. Asthma, and especially severe asthma, are major risk factors for fatal and severe SRs from SCIT. Strategies that may mitigate risks in asthmatics should be implemented including not prescribing SCIT to severe, uncontrolled asthmatics and considering controller therapies in all mild and moderate asthmatics on SCIT. There is no evidence indicating that SCIT injections pose any risk of local or systemic infections.

References

1. Cox L, Esch RE, Corbett M, Hankin C, Nelson M, Plunkett G. Allergen immunotherapy practice in the United States: guidelines, measures, and outcomes. *Ann Allergy Asthma Immunol* 2011;107(4):289-99; quiz 300. DOI: 10.1016/j.anai.2011.06.018.
2. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *The Journal of allergy and clinical*

immunology 2004;113(6):1129-36. (Research Support, Non-U.S. Gov't) (In eng). DOI: 10.1016/j.jaci.2004.02.006.

3. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. The Journal of allergy and clinical immunology 2006;117(1):169-75. (Research Support, Non-U.S. Gov't) (In eng). DOI: 10.1016/j.jaci.2005.10.010.
4. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79(4):660-77. DOI: 10.1016/s0091-6749(87)80164-1.
5. 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(1 Pt 1):6-15. DOI: 10.1016/0091-6749(93)90030-j.
6. 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. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2010;104(6):530-5. (Randomized Controlled Trial

Research Support, Non-U.S. Gov't) (In eng). DOI: 10.1016/j.anai.2010.04.008.

7. Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013-2017): Fatalities, Infections, Delayed Reactions, and Use of Epinephrine Autoinjectors. J Allergy Clin Immunol Pract 2019;7(6):1996-2003 e1. DOI: 10.1016/j.jaip.2019.01.058.

8. Bernstein DI, Epstein TEG. Safety of allergen immunotherapy in North America from 2008-2017: Lessons learned from the ACAAI/AAAAI National Surveillance Study of adverse reactions to allergen immunotherapy. *Allergy Asthma Proc* 2020;41(2):108-111. DOI: 10.2500/aap.2020.41.200001.
9. 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(4):274-8, 278 e1. DOI: 10.1016/j.anai.2013.01.015.
10. 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(2):161-7. DOI: 10.1016/j.jaip.2014.01.004.
11. 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(4):511-512. DOI: 10.1016/j.anai.2017.01.012.
12. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *The Journal of allergy and clinical immunology* 2010;125(3):569-74, 574 e1-574 e7. (Review) (In eng). DOI: 10.1016/j.jaci.2009.10.060.
13. 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(3):569-74, 574 e1-574 e7. DOI: 10.1016/j.jaci.2009.10.060.
14. 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(6):530-5. DOI: 10.1016/j.anai.2010.04.008.
15. 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). *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2016;116(4):354-359 e2. DOI: 10.1016/j.anai.2016.02.001.
16. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43(2):343-73. DOI: 10.1183/09031936.00202013.
17. Fryer CDC, Margaret D, and Afful, Joseph, Division of Health and Nutrition Examination Surveys. Prevalence of Overweight, Obesity, and Severe Obesity Among Adults Aged 20 and Over: United States, 1960-1962 Through 2017-2018. Centers for Disease Control and Prevention; National Center for Health Statistics, 2020. (<https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm#table1>).
18. 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(6):1129-36. DOI: 10.1016/j.jaci.2004.02.006.

19. Har D, Lee MJ. Systemic reaction rates with omalizumab, subcutaneous immunotherapy, and combination therapy in children with allergic asthma. *Allergy Asthma Proc* 2019;40(1):35-40. DOI: 10.2500/aap.2019.40.4173.
20. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117(1):134-40. DOI: 10.1016/j.jaci.2005.09.036.

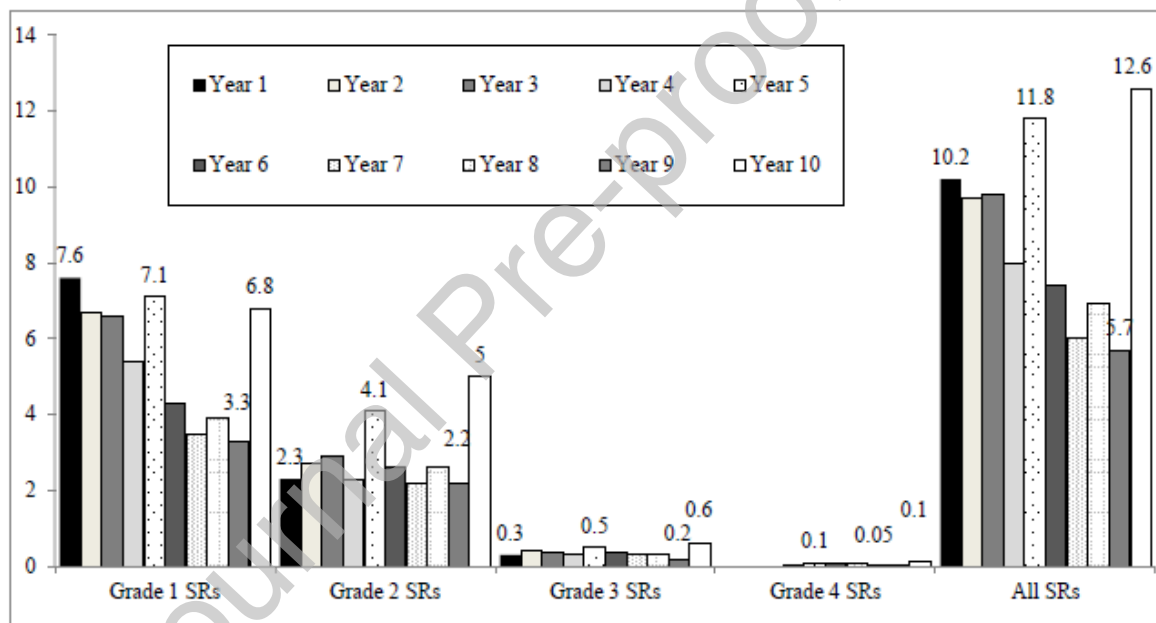


Figure 1: Systemic allergic reactions/10,000 injection visits for 2008-2018 (Years 1-10). Total number of injection visits= 64.5 million reported.

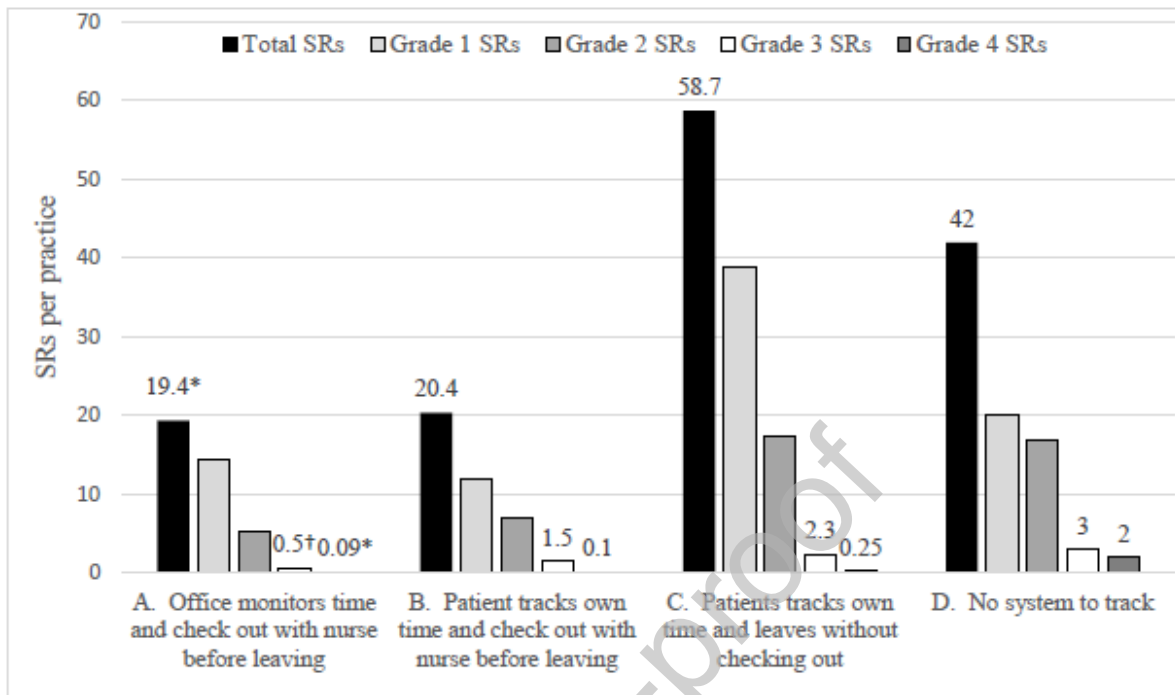


Figure 2: Systemic allergic reactions (SRs) per practice based on strategies for post-injection monitoring. N=211 practices (2016-2017). * $p < 0.0001$ for a lower rate of total SRs and Grade 4 SRs comparing strategy A versus all others. † $p < 0.0008$ for a lower rate of Grade 3 SRs ($p < 0.0008$) comparing strategy A versus all others.

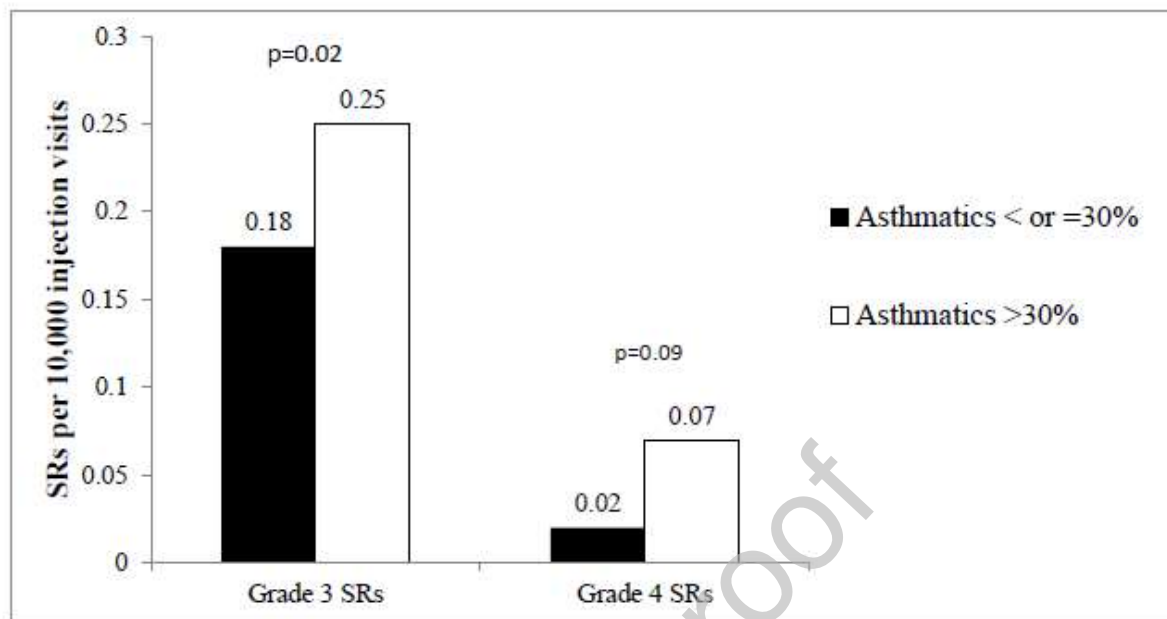


Figure 3: Systemic allergic reactions (SRs) per 10,000 injection visits in 124 practices with less than or equal to 30% of asthmatics on Subcutaneous Allergen Immunotherapy (SCIT), versus 95 practices with greater than 30% asthmatics on SCIT; $p=0.02$ for Grade 3 SRs and $p=0.09$ for Grade 4 SRs

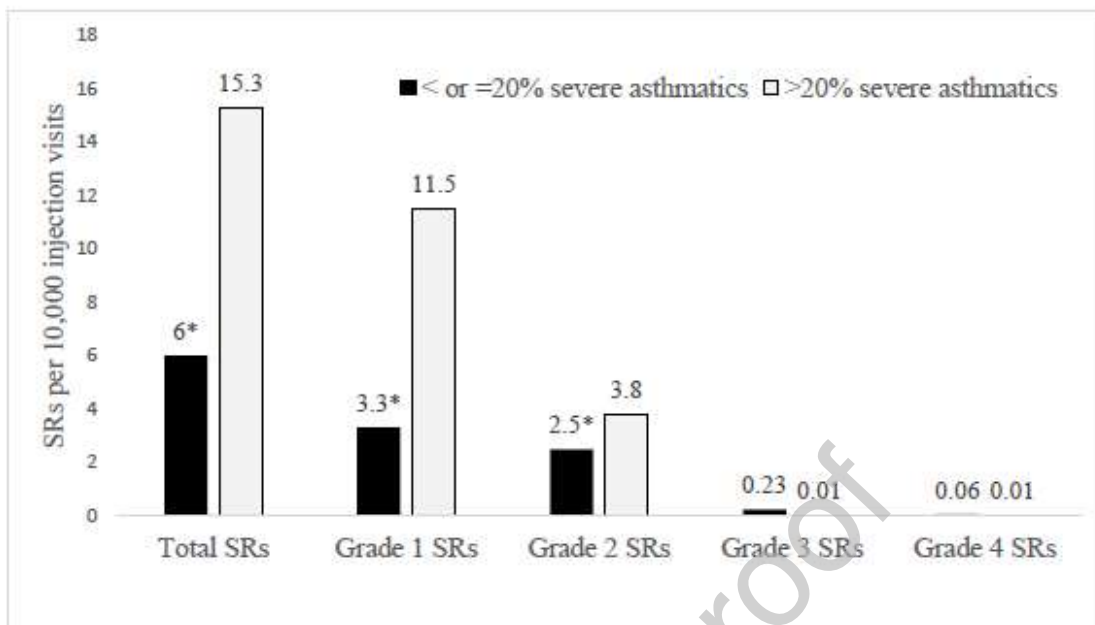


Figure 4: Systemic allergic reactions (SRs) per 10,000 injection visits in practices with less than or equal to 20% severe asthmatics (n=216) versus greater than 20% severe asthmatics (n=3).

*p<0.0001 for lower total, Grade 1, and Grade 2 SRs with less than or equal to 20% versus greater than 20% severe asthmatics

Table E1. Relevant survey questions in years 9-10 (August 1, 2016 through August 31, 2018)

(Some questions were not asked every year, as described in the text)

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 aeroallergen immunotherapy injection, venom immunotherapy injection, or allergy skin testing?
2. During the past 12 months, 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 months?
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 months (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 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, 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 months, have you identified any patients in your practice receiving SCIT who developed systemic infections or sepsis associated with the administration of allergen vials prepared in your office?
6. If you reported any Grade 3 or 4 (severe or very severe) systemic allergic reactions, please indicate the number of patients that were morbidly obese (body mass index >40 kg/m²)?
7. If you reported any Grade 3 or 4 (severe or very severe) systemic allergic reactions, how many occurred in patients with severe asthma [Defined as patients with persistent asthmatic symptoms despite treatment with optimal doses of inhaled corticosteroids, in whom response to treatment of comorbidities is incomplete (*ERS/ATS Task Force Definition 2014*)]?
8. During the past 12 months, how many subcutaneous allergen immunotherapy injections has your entire practice billed under Current Procedural Terminology 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 months?
9. How was data collected from your practice on the number of allergic reactions in the past year: Electronic, continuous 'real-time' reporting system that can be queried for summarized clinical data ____ Chart review ____ Staff or physician memory ____ Other ____?

Immunotherapy in your practice

Asthmatics on SCIT

10. Do you prescribe SCIT in patients with uncontrolled asthma based on Asthma Control Test (ACT) score <20? Always____ Often____ Sometimes____ Never____?
11. What percentage of patients that are on SCIT in your practice have Asthma (of any severity): None____ 0.1 to 10%____ 11-20%____ 21-30%____ 31-50%____ More than 50%____?
12. What percentage of asthma patients that are on SCIT in your practice would be described as having Severe asthma (definition above): None____, Less than 5%____, 5-10%____, 11-20%____, 21-50%____, More than 50%____?
13. Do you routinely check peak expiratory flows or spirometry prior to injections for asthmatics on SCIT: Always____, Often____, Sometimes____, Never____?
14. Does your practice require that persistent asthmatic patients take controller therapies while on SCIT during buildup phase: Always____, Often____, Sometimes____, Never____?
15. Does your practice require that persistent asthmatic patients take controller therapies while on SCIT during maintenance phase: Always____, Often____, Sometimes____, Never____?

Waiting periods after injections

16. In your entire clinical practice, what is the required waiting period after allergen injections: 0-20 minutes____, 21-29 minutes____, 30 minutes____, greater than 30 minutes____, other____?
17. What system do you have in place to monitor whether patients follow the required waiting period after injections: Office monitors time and check out with nurse before leaving____, Patient tracks own time and check out with nurse before leaving____, Patient tracks own time and leaves without checking out____, No system to track____ Other?
18. How often do patients comply with waiting times after injections in your practice: Always____ Often____ Sometimes____ Never____?