

Systemic Allergic Reactions and Anaphylaxis Associated with Allergen Immunotherapy



Yashu Dhamija, MD^{a,*}, Tolly E.G. Epstein, MD, MS^{a,b},
David I. Bernstein, MD^a

KEYWORDS

- Allergen immunotherapy • Subcutaneous immunotherapy
- Sublingual immunotherapy • Systemic reactions • Anaphylaxis

KEY POINTS

- Fatal reactions (FRs) are uncommon but still occur at a rate of 1 in every 7,000,000 injection visits.
- Risk factors for FRs include uncontrolled asthma, a prior systemic reaction (SR), and allergen immunotherapy (AIT) during the peak pollen season.
- Suggested interventions to reduce SR rates in patients undergoing AIT are reviewed.

INTRODUCTION

Subcutaneous allergen immunotherapy (SCIT) is used to treat allergic rhinitis, asthma, atopic dermatitis, and prevent Hymenoptera sting-induced anaphylaxis.^{1,2} The known benefit of SCIT, however, must be considered in each patient relative to the potential risk of a systemic allergic reaction (SR). The lifetime prevalence of anaphylaxis from any cause is estimated to be 0.05% to 2%.³ Limitations, such as recognition, varying definitions, underreporting, miscoding, and attributable causes, may confound population-based estimates. In 1987, known cases of fatalities due to immunotherapy and skin testing dating back to 1945 were reviewed, leading to the first survey of fatal reactions (FRs).^{4,5} Data regarding SRs from allergen immunotherapy (AIT) have been systematically gathered in the North American Immunotherapy Surveillance Study since 2008 and from annual retrospective surveys conducted among members of the American Academy of Allergy, Asthma, & Immunology (AAAAI) and American College of Allergy, Asthma, & Immunology (ACAAI). Although physicians and other health

^a Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML 0563, Medical Science Bldg. (MSB), Rm 7409, Cincinnati, OH 45267-0563, USA; ^b Allergy Partners of Central Indiana, 7430 N Shadeland Ave, Suite 150, Indianapolis, IN 46250, USA

* Corresponding author.

E-mail address: dhamijyu@ucmail.uc.edu

care professionals' participation rates in these surveys vary from year to year, these annual data evaluate millions of injections administered to more than 200,000 patients by hundreds of allergists/immunologists and their associates.⁶ These data result in estimates of the annual incidence of SRs, their severity, and possible risk factors for susceptibility to SRs and anaphylaxis from AIT.⁶ Data, collected between 2013 and 2017, indicate that SRs of varying severity occurred in up to 85% of clinical allergy/immunology practices. A mean of 1 SR per 1000 injection visits (0.1%) is estimated to have occurred between 2008 and 2018.⁶ Life-threatening or near-fatal anaphylactic events, that is, Grade 4, based on World Allergy Organization (WAO) grading criteria for SRs to SCIT, are relatively uncommon and estimated to occur in 0.005% of patients receiving SCIT injections and in 1/160,000 injection visits.⁷ Evidence identifying factors that contribute to SRs and FRs are reviewed in this article. Risk management strategies are proposed to prevent or decrease future SCIT, SRs, anaphylaxis, and FRs.

FATAL REACTIONS AND CONTRIBUTING FACTORS

Fatal anaphylactic reactions from SCIT are rare. Since 1972, 92 confirmed FRs due to SCIT have been reported by physicians in North America.⁴⁻⁶ From 1990 to 2001, 41 FRs were reported, for an estimated rate of 1 in every 2.5 million injections or 3.4 FR per year.⁸ Although the number of reported FRs has decreased, 10 confirmed FR have been reported in the North American Surveillance Study between 2008 and 2019 (1 in every 7.2 million injection visits) in patients receiving care from allergists/immunologists.⁶ This includes 5 new confirmed FRs since 2017. The data from the European surveillance study, prospectively obtained in 3 countries from 2012 to 2014, did not report any FR.⁹ A lack of reports on FR from European studies is likely limited by geographic reporting and brief, periodic data collection.^{9,10}

Details were provided of 273 near-FRs to SCIT injections in the 1990 to 2001 North American Immunotherapy Surveillance Study.^{8,11} This survey identified differences between clinical manifestations during FRs and near-fatal anaphylactic reactions manifested by acute respiratory insufficiency and/or hypotension. As illustrated in Fig. 1, SRs versus near-FRs were characterized by a more frequent occurrence of

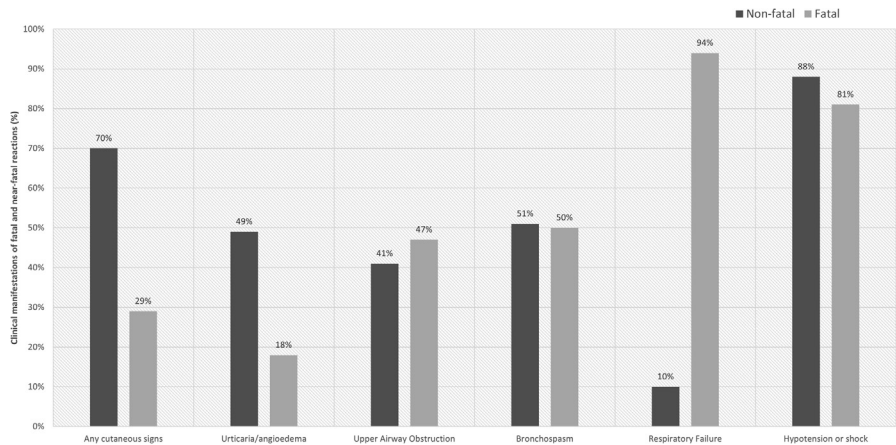


Fig. 1. Fatal reactions: low occurrence of skin manifestations. (*Adapted from Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006 Jan;117(1):169-75.*)

respiratory failure in the absence of cutaneous signs and symptoms. The absence of cutaneous manifestations in these FRs could have delayed recognition and the timely initiation of treatment in some of these cases. **Fig. 2** compares baseline asthma severity characteristics, demonstrating that patients with FRs had higher frequencies of poor asthma control, acute emergency room visits, and hospitalization for asthma, preceding the FR. These data are consistent with other reports, indicating that asthma is a major contributing factor for FRs.

A review of 34 FRs to SCIT from 1985 to 2001 identified contributing risk factors.^{7,8,12} After uncontrolled asthma, prior SRs, administration of injections during the peak pollen seasons, sub-optimal treatment of anaphylaxis, and dosing errors were recognized by treating physicians as possible factors contributing to these FRs in at least 35% of reported cases (**Table 1**). Less frequent factors cited include inadequate postinjection observation periods, administration in a medically unsupervised setting, delayed onset of reactions following the 30-min wait, and coadministration of β -blockers or angiotensin-converting enzyme (ACE) inhibitors.⁸ No contributing factors were reported in 17% of cases.

FATAL REACTIONS SINCE 2008

Details regarding 10 fatalities that have occurred since 2008 are presented in **Table 1**.^{6,13–15} One of the most important findings is that at least 6 of the FRs occurred in patients with asthma; it was unknown whether the other 4 had asthma. At least 2 of the FRs occurred in patients with severe persistent asthma. Another important risk factor in at least 3 FRs was the lack of immediate treatment at the onset of the SRs, in 2 because the patients left the clinic facility before the recommended waiting time, and in the third, because of a lack of recognition of the signs and symptoms of anaphylaxis by health care personnel. At least 2 fatalities occurred in obese individuals. Morbid obesity is suspected to have played a role in lack of response to epinephrine in at least one FR. Two FRs occurred in teenagers and one in a 19-year-old

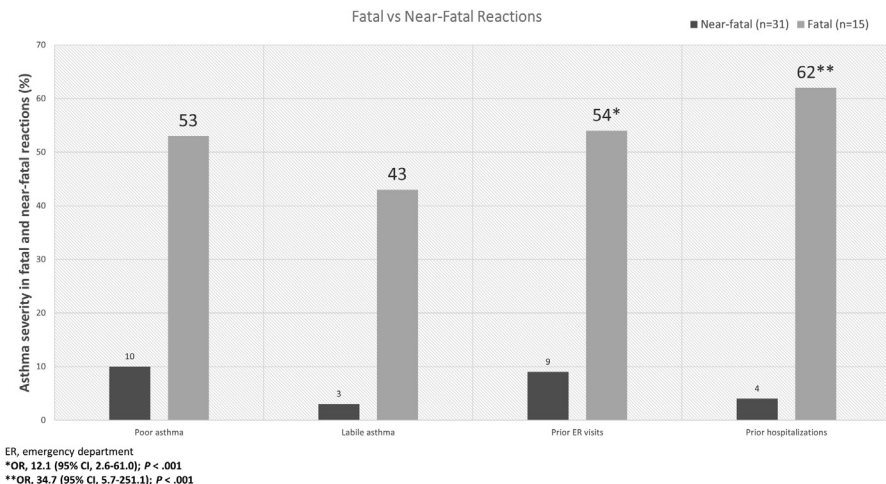


Fig. 2. Comparison of asthma characteristics: fatal versus near-fatal reactions.^aOR, 12.2 (95% CI, 2.6-61.0); $P < .001$. ^bOR, 34.7 (95% CI, 5.7-251.1); $P < .001$. (Adapted from Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol.* 2006 Jan;117(1):169-75.)

Table 1 Risk factors for SCIT fatal systemic reactions	
Risk Factor	Prevalence 1985–2001 (n = 34)
Uncontrolled asthma	62%
Prior systemic reaction	53%
Pollen season	47%
Suboptimal treatment of anaphylaxis (epinephrine)	43%
Dosing error	35%
< 3' observation	12%
Unsupervised setting (home)	9%
Delayed reaction? (onset after 30' observation)	9%
None	17%
β-blocker/ACEI	2%/2%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor.
Data from Refs ^{6,10}

woman. More FRs occurred in men, if the information on gender was provided, although the sample size was too small to know whether these data are significant. FRs occurred in both the buildup and maintenance phase of SCIT. At least one FR was associated with an accelerated cluster schedule, that is, the FR occurred at maintenance dose, 2 weeks after cluster buildup.

SYSTEMIC ALLERGIC REACTIONS ASSOCIATED WITH SUBLINGUAL IMMUNOTHERAPY

Patients commonly experience local oral reactions (80% of all treatment-related adverse events) to FDA-approved sublingual immunotherapy (SLIT) products. Six SRs occurred among 8000 patients treated with SLIT.¹⁶ There are rare case reports of anaphylaxis with SLIT, either as drop as or approved sublingual tablet formulations, and no FRs are documented.^{17–21} In a review of 66 SLIT studies that included safety data, the incidence of SRs from SLIT is about 1 per 384 treatment years (0.056% of doses).²² Severe asthma exacerbations accounted for 14 of the SLIT-related adverse events in this same review. None reported hypotension-associated SRs. In a review of 29 SLIT tablet studies, epinephrine was administered 16 times, with the majority given in the first week, 5 of which were self-administered by patients.²³

CLASSIFYING SEVERITY OF SYSTEMIC ALLERGIC REACTIONS

SRs can vary from mild cutaneous symptoms and signs to life-threatening near-fatal or fatal anaphylaxis.¹ In 2010, a multinational group representing the AAAAI, ACAAI, European Academy of Allergy and Clinical Immunology, and WAO published a consensus grading system for SCIT-related SRs. Although not adapted by regulatory agencies for use in clinical trials, the WAO grading criteria have been used for SCIT reactions in the annual North American Immunotherapy Surveillance Study conducted among practicing allergists/immunologists, since their introduction in 2010. This has enabled the estimation of the annual incidence rate of SCIT-related SRs based on SR severity and identification of factors possibly contributing to Grades 3 and 4 anaphylactic events versus milder Grades 1 and 2. Before the introduction of the

WAO grading system for SCIT-related SRs, the AAAAI/ACAAI North American Immunotherapy Surveillance Study used mild, moderate, and severe reactions to guide responders on grading systemic SRs, retrospectively.^{24,25} Before the implementation of the North American Immunotherapy Surveillance Study, studies evaluating SRs categorized reactions simply as mild or severe.²⁶

CLINICAL AND OTHER FACTORS THAT ENHANCE THE RISK FOR SYSTEMIC ALLERGIC REACTIONS TO SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY

Asthma

Uncontrolled asthma is a risk factor for SCIT-related SRs. The National Immunotherapy Surveillance Study confirms that uncontrolled asthma is a significant risk factor for nonfatal SRs and severe and fatal SRs. Data consistently show practices treating patients with asthma have higher rates of severe and fatal SRs.^{6,14} Two-thirds of all severe Grade 3 or 4 nonfatal SRs occurred in patients with asthma and 50% of Grades 3 and 4 SRs in individuals with severe asthma.^{6,13} Clinical practices that did not prescribe SCIT for individuals with uncontrolled asthma reported fewer severe Grade 3 SRs and those who did prescribe SCIT to such individuals reported significantly more Grades 1 and 2 SRs.⁶ Other studies also show a higher rate of SRs in patients with asthma.^{27–29} Seventy percent of patients with an FEV1 less than 80% predicted versus 12% with an FEV1 $\geq$ 80% of predicted receiving rush SCIT experienced an SR in a prospective trial of 125 patients.³⁰

Therefore, routine clinical screening of patients with asthma and, where necessary, measurement of lung function (peak flow spirometry) is recommended prior to SCIT administration.² Such screening has resulted in significantly fewer Grades 3 and 4 SRs.¹⁴

Clinical trial data from Phase 3 allergic rhinitis studies of grass and ragweed pollen and house dust mite (HDM) SLIT indicate no increased risk of SRs for subjects with concomitant asthma.^{31–33} However, FDA-approved SLIT tablets are not recommended in patients with uncontrolled asthma.³⁴ No SRs were reported in a 2016 placebo-controlled trial evaluating efficacy and safety of HDM SLIT tablet therapy for asthma in 834 adult patients not well controlled by inhaled corticosteroids.³⁵ The safety of commercial therapeutic extract drops used off label for SLIT has not been systematically evaluated in patients with asthma.

Pollen Seasons

Severe and fatal SRs have previously been associated with the administration of SCIT during peak pollen seasons, particularly among highly sensitized individuals.^{4,12,15} North American Immunotherapy Surveillance Study data of 34 FRs before 2005 demonstrate that 47% of cases occurred during the pollen season to which the patient was sensitive.^{8,12} A similar review of 68 near-fatal SRs between 1990 and 2001 found that 46% of cases occurred during peak allergy seasons, the most commonly cited possible contributing factor for these reactions.¹¹ The initiation of SCIT during the pollen season was a risk factor for SRs in a 2020 retrospective study of 12,284 injections in 261 children.³⁶ The results show that most SRs occurred, in decreasing frequency, during the grass, ragweed, and tree pollen seasons.^{14,37}

Data from the National Immunotherapy Surveillance Study indicate that clinical practices that do not increase SCIT doses during pollen seasons were less likely to report Grade 2 (moderate) or 3 (severe) SRs.³⁷ This was most significant for SRs of all severity grades in practices that did not increase SCIT doses in highly sensitized individuals during their peak pollen seasons.¹⁴

No significant differences in SR rates occurred during versus not during the mountain cedar season in a 2017 retrospective study of patients receiving SCIT for mountain cedar.³⁸ However, interpretation of this study was limited by the low number of severe SRs. Albuhaire and colleagues also reviewed SCIT injections in 2 groups of 246 pediatric patients, one in which doses were not increased during peak pollen seasons and the other in which they were increased.³⁹ There was no significant difference in the rate of SRs. In conclusion, because of these differences, more prospective studies are necessary to determine whether and when adjustments of doses during peak pollen seasons are necessary.

Waiting Times, Delayed Systemic Allergic Reactions, Epinephrine Auto-Injectors, and Home Immunotherapy

Most SRs and FRs associated with SCIT occur within the first 30 min of the injection.² Inadequate waiting times following SCIT injections and delays in treatment have also been associated with such reactions.^{4,6,13} Therefore, the third update of the Immunotherapy Practice Parameter recommends a 30-min postinjection waiting period.² Extract manufacturers' product labeling recommend waiting periods of 20 to 30 min.^{40,41} Data from the North American Immunotherapy Surveillance Study do not show a difference in SRs for severity based on a 20- or 30-min postinjection waiting time; however, these data may have been skewed by under-reporting of SRs in clinical practices with shorter observation times.^{6,13} The 2021 North American Immunotherapy Surveillance Study shows a statistically significant difference in total Grades 3 and 4 SRs versus less severe grades based on the enforcement of postinjection waiting periods, that is, monitoring patient waiting times and requiring check-out with office personnel before leaving postinjection.⁶

A 2019 study indicates that around 15% of SRs may begin after 30 min postinjection, although some studies report up to 50% of SCIT-related SRs after 30 min.^{13,42} Most SRs after 30 min are mild or moderate, but severely delayed SRs including anaphylaxis are reported.⁴² Therefore, epinephrine autoinjectors should be considered for patients on SCIT, or at least those who are considered to be at higher risk or have had an SR after 30 min. This recommendation is still debated.⁴³ When last assessed in 2016, almost 30% of practitioners reported that they routinely prescribe epinephrine autoinjectors for all patients on SCIT. However, this did not lower the risk of severe SRs, possibly because of low rates of adherence with the self-administration of autoinjectors among patients experiencing delayed SRs.¹³ In fact, surveillance data show that only 8% to 30% of patients used prescribed autoinjectors for severe Grades 3 or 4 SRs that began after departing the outpatient injection facility.¹³ Based on these data, it is estimated that 8,261 patients would have to be prescribed epinephrine auto-injectors for one delayed SR.⁴⁴

Home administration of SCIT is not recommended due to risks associated with delays in the recognition and administration of epinephrine. These concerns arise from previous rare reports of FRs associated with home administration.^{2,8,36} The only possible exception, whereby the benefit of home administration could outweigh the risk, is for patients with a history of Hymenoptera sting-induced anaphylaxis, with no access to a medical facility, requiring venom immunotherapy (VIT).² Informed consent is necessary and the patient must be educated on recognizing the signs and symptoms of an SR and its treatment.

Accelerated Buildup

Accelerated regimens refer to "cluster" and "rush" buildup protocols for AIT. Cluster AIT involves administering 2 or more SCIT injections per day that are subsequently

increased every 2 to 7 days with the goal of achieving maintenance therapy more rapidly.⁴⁵ Rush schedules are used to increase doses every 15 to 60 min over 1–3 consecutive days until the target dose is achieved.⁴⁶ North American Immunotherapy Surveillance Study data from 270 practices show that 27% use cluster and 12% rush protocols; however, 93% of patients are initiated on standard buildup protocols.¹⁵ Cluster and rush buildups were associated with a higher incidence of SR per injection, than slow buildup, in a 5-year review of a large, multicenter practice. A higher incidence of SRs (11.9%) occurred for cluster versus standard or rush protocols, 2.8% and 2.5, respectively.⁴⁷ The North American Immunotherapy Surveillance Study data show a significant increase in the risk of Grades 1 to 4 SRs in practices using cluster therapy.^{14,37}

Practices that require a lower final cluster dose before transitioning to maintenance had a lower SR rate.^{7,15} This suggests that practices that switch from accelerated buildup to conventional SCIT before reaching maintenance have a lower SR rate (689 SRs) than those which continue an accelerated buildup until maintenance (1,023 SRs).

Doses of Allergen

The National Surveillance Study assessed the relationship between allergen doses and SRs. Practices with Grade 3 versus those with Grade 1 SRs used higher doses of standardized doses of standard HDM allergen products, 1,000 and 1,999 allergy units ($P = .025$). No similar significant dose–response relationship was found with grass pollen or cat allergen products.⁴⁸ SR rates identified in small studies indicate that higher target doses for maintenance are linked with higher rates of SRs.^{49–51}

Previous Systemic Allergic Reactions to Subcutaneous Allergen Immunotherapy

In Year 2 of the North American Immunotherapy Surveillance Study among 630 participating practices, approximately 25% of patients with an SR had a history of a previous SR.⁷ In a review of 177 SRs occurring in a practice of 459 patients receiving 74,183 SCIT injections, a history of SR was not identified as a risk for subsequent SRs.⁵² Smaller studies show approximately one-third to two-thirds of patients with an SR typically had Grade 1 SRs.^{29,53}

It is unclear whether the severity of a subsequent SR is related to the previous SR. For example, among patients in a study from 2010 to 2011 who experienced severe delayed SRs, none had prior SRs.²⁴ There is also no consensus about dose adjustment strategies following SRs; however, stopping SCIT should be considered with repeated SRs.² In summary, prior SRs are considered the second most common risk factor for FRs.

Large Local Reactions

There is conflicting evidence about the risk of SRs following prior large local reactions. This could be due to how such reactions are defined, that is, size and duration.⁵⁴ Two retrospective studies show no difference in the incidence of SRs between dose-adjustments and no-dose-adjustment protocols in patients with large SCIT local reactions. Other retrospective studies found that among patients with SRs, the rate of large local reactions preceding SR events was up to fourfold greater.^{55–58} In summary, large local reactions are poor predictors for future local reactions as well as SRs.^{52,58,59} Also, appropriate intervention for these reactions remains unknown.⁶⁰

Morbid Obesity

Morbid obesity is not a risk factor for severe SRs.¹⁵ North American Immunotherapy Surveillance Study data collected from 2016 to 2018 also did not show an increased rate of severe SRs from SCIT in patients with morbid obesity when adjusting for its prevalence in the general population.⁶ Body mass index was identified as a risk factor in China for local reactions but not SRs in a study of 91 children receiving HDM SCIT.⁶¹

Risks of Concomitant Medications

A theoretic concern about the use of β -blockers in patients on SCIT exists because of the theoretically increased risk of mast cell mediators and inadequate response to injectable epinephrine associated with β -receptor blockade.⁶² However, the use of β -blockers has not been associated with an increased frequency of SRs to SCIT. The AIT Practice Parameter recommends avoiding SCIT in patients requiring β -blockers even though there is little evidence to support this recommendation.² Hepner and colleagues evaluated more than 3,000 patients over 1 year and identified one with an SR who was on a β -blocker.⁶³ Future randomized controlled trials (RCTs) to evaluate the safety of β -blockers in AIT are unlikely due to ethical considerations and the need for large sample sizes.⁶⁴

The use of β -blockers in patients receiving VIT for anaphylaxis to Hymenoptera stings is justified when considering the risk versus the benefit of VIT.⁶² β -blocker use concern arose from a single case report of an FR in a patient receiving VIT while on a β -blocker.⁶⁵ Retrospective studies, however, support the use of β -blockers in patients receiving VIT.⁶⁶

Cases of severe anaphylaxis in patients receiving ACE inhibitors have been anecdotally reported in patients on VIT. However, the assessment of large patient databases did not find an association between their use and SRs to SCIT.^{13,67,68}

MITIGATING RISK FOR SYSTEMIC ALLERGIC REACTIONS: WHAT HAVE WE LEARNED?

There is no precise approach to predict the relative risk of SCIT. It is incumbent on the practicing allergist/immunologist to gauge the risk–benefit for each patient for prescribing SCIT or SLIT. For example, in general, SCIT should not be used in patients with uncontrolled asthma and those with compromised baseline lung function, that is, pretreatment FEV1 $\leq$ 70%. Practices avoiding SCIT in patients with uncontrolled asthma versus those that provide such therapy report 70% fewer life-threatening Grade 4 SRs.¹⁴ Alternative therapies, whereby necessary, should be considered in such patients in lieu of SCIT, for example, biological agents.

Patients with asthma are at highest risk for any SR including severe SRs and strategies to mitigate risk are outlined in **Box 1**. Preinjection asthma screening is recommended, that is, assessing asthma symptoms at the injection visit. This also provides for the opportunity to assess the patient's clinical status and when necessary, treat exacerbations.⁷

General recommendations to improve the safety of SCIT are listed in **Box 2**. It should be administered only in facilities whereby staff members are trained to recognize and treat SRs.⁷ Careful monitoring of SCIT patients for at least 30 min following an injection and requiring checkout with staff members may reduce this risk.¹³

Pharmacotherapy for the Prevention of Systemic Allergic Reactions

Pretreatment can reduce rates of SRs. Treatment with an antihistamine 2 hours before a SCIT injection significantly reduced the rate of severe SRs and shortened the time for

Box 1**Suggested strategies to reduce the risk of anaphylaxis in patients with asthma undergoing AIT.**

1. Preinjection screening for asthma symptoms with or without lung function.
2. Do not initiate SCIT or SLIT in patients with uncontrolled asthma.
3. Withhold SCIT and use alternative treatments in patients with severe, treatment-refractory asthma.
4. Consider potentially safer modalities of AIT (eg, SLIT for patients with controlled asthma).
5. Administer SCIT injections only in adequately equipped clinic facilities with medical staff trained to manage anaphylaxis.
6. Adherence to the 30-min postinjection observation period and check out system.

Abbreviations: AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Adapted from 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 Mar 1;41(2):108-111.

the target dose for cedar pollen and dust mite in an open-label prospective study of 134 patients.⁶⁹ Pretreatment with a combination of H-1 and H-2 antihistamines and prednisone likewise reduced the occurrence of SRs to rush therapy for mixed allergens.⁷⁰ A prospective RCT of omalizumab in patients with persistent asthma showed significantly fewer SRs to SCIT with perennial allergens.⁷¹ Omalizumab also significantly reduced the rate of SRs to rush immunotherapy.^{72,73} However, cost-effectiveness using omalizumab remains a major concern.⁷⁴ Pretreatment with second-generation antihistamines also reduced the rates of SRs and large local reactions for accelerated buildup schedules.^{75,76} However, in spite of this evidence, there is no definitive evidence to support routine pretreatment with antihistamines to prevent SRs with a routine SCIT buildup schedule.

Box 2**General recommendations for improving SCIT tolerability in all treated patients**

1. Modify doses or discontinue SCIT after grade 3 or 4 SRs.
2. Adapt clinic protocols to prevent dosing errors.
3. Administer SCIT injections only in clinics with adequate facilities, and personnel to manage anaphylaxis, and adhere to a 30-min observation period.
4. Modify allergen doses in highly sensitized patients during peak aeroallergen periods.
5. Consider reducing target doses for an accelerated cluster buildup.
6. Prescribe self-injectable epinephrine in SCIT patients at heightened risk for SRs.

Abbreviation: SCIT, subcutaneous immunotherapy.

Adapted from 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 Mar 1;41(2):108-111.

LESSONS LEARNED FROM COVID-19

The COVID-19 pandemic, beginning in 2020, resulted in interruptions in SCIT administration worldwide. Close to 30% of patients who suspend their AIT treatment may not resume it.⁷⁷ This is in spite of the fact that the total number of patients on AIT has increased during the COVID-19 pandemic. Strategies used to mitigate this decrease include deferring initiation, extending the interval between doses, discontinuing patients at an increased risk of complications from COVID-19, and considering SLIT as an alternative treatment.^{78–80} COVID-19-related restrictions also have provided an opportunity to evaluate the impact of lengthening the time interval between doses for aeroallergens and still maintain efficacy and safety. Optimal strategies to restart SCIT following a break are also indicated. Studies designed to help answer these questions are necessary and ongoing.⁸¹

SUMMARY

Although the rates of SRs have declined to an estimated rate of 1 per 1000 injections, FRs still occur. A risk stratification before the initiation of AIT may be of value to better select patients for such treatment. Risk versus benefit is a consideration for any treatment program, including SCIT. Risk factors for FRs include the following: uncontrolled asthma, a history of SR, and injections administered during a peak pollen season. Suggested interventions to reduce AIT SR rates are outlined in **Boxes 1** and **2**. Unmet needs include the safety of SLIT versus SCIT in high-risk populations and safety of modified recombinant allergens. In addition, the impact of COVID-19 on the use of SCIT and SLIT, as well as SRs, is still unclear.

CLINICS CARE POINTS

- Although rates of systemic reactions to SCIT have declined over the years, FRs continue to be reported.
- The most cited potential contributing factors to FRs to SCIT are uncontrolled asthma, a history of prior systemic reaction, administration during pollen season, suboptimal treatment of systemic reactions, and dosing errors.
- A risk–benefit consideration is recommended before initiation for all patients to identify high-risk individuals.
- Suggestions are presented in **Boxes 1** and **2** of the article to reduce rates of systemic and FRs to SCIT.

DISCLOSURE

No external funding for this article. All authors have no financial relationships relevant to this article to disclose. All authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Cox L, Larenas-Linnemann D, Lockey RF, et al. 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.
2. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(1 Suppl):S1–55.
3. Simons FE. Anaphylaxis. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S161–81.

4. Lockey R, Benedict L, Turkeltaub P, et al. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79(4):660–77.
5. Reid M, Lockey R, Turkeltaub P, et al. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol* 1993;92(1):6–15.
6. Epstein TG, Murphy-Berendts K, Liss GM, et al. Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): postinjection monitoring and severe asthma. *Ann Allergy Asthma Immunol* 2021;127(1):64–9.e1.
7. 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):108–11.
8. Bernstein DI, Wanner M, Borish L, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004; 113(6):1129–36 (Research Support, Non-U.S. Gov't) (In eng).
9. Calderón MA, Vidal C, Rodríguez del Río P, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. *Allergy* 2017;72(3):462–72.
10. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, et al. Immunotherapy Committee SEDeAelC. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy* 2004;34(4):527–31.
11. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117(1):169–75.
12. Reid MJ, Lockey RF, Turkeltaub PC, et al. Survey of fatalities from skin testing and immunotherapy 1985-1989 (Research Support, U.S. Gov't, P.H.S.) (In eng). *J Allergy Clin Immunol* 1993;92(1 Pt 1):6–15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8335856>.
13. Epstein TG, Liss GM, Berendts KM, et al. 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.
14. Epstein TG, Liss GM, Murphy-Berendts K, et al. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). *Ann Allergy Asthma Immunol* 2016; 116(4):354–9.e2.
15. Epstein TG, Liss GM, Murphy-Berendts K, et al. 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.e3.
16. Bernstein DI, Bardelas JA Jr, Svanholm Fogh B, et al. A practical guide to the sublingual immunotherapy tablet adverse event profile: implications for clinical practice. *Postgrad Med* 2017;129(6):590–7.
17. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 2008;63(3):374.
18. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009;64(6):963–4.
19. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006;61(10):1236–7.
20. Eifan AO, Keles S, Bahceciler NN, et al. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007;62(5):567–8.

21. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. *J Allergy Clin Immunol* 2009;124(2):378–9.
22. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117(5):1021–35.
23. Nolte H, Casale TB, Lockey RF, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets. *J Allergy Clin Immunol Pract* 2016;5(1):84–9.e3.
24. Epstein TG, Liss GM, Murphy-Berendts K, et al. 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(5):426–431 e1 (Research Support, Non-U.S. Gov't) (In eng).
25. Bernstein DI, Epstein T, Murphy-Berendts K, et al. 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 (Randomized Controlled Trial Research Support, Non-U.S. Gov't) (In eng).
26. Matloff SM, Bailit IW, Parks P, et al. Systemic reactions to immunotherapy (In eng). *Allergy Proc* 1993;14(5):347–50. Available at:<http://www.ncbi.nlm.nih.gov/pubmed/8288117>.
27. Liu JL, Ning WX, Li SX, et al. The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China. *Allergol Immunopathol (Madr)* 2017;45(6):541–8.
28. González-Díaz SN, De La Rosa-López JH, Arias-Cruz A, et al. Reacciones sistémicas relacionadas a la inmunoterapia con alérgenos en Monterrey, México. *Rev Alerg Mex* 2011;58(2):79–86.
29. Erdem SB, Nacaroglu HT, Karaman S, et al. Risk of systemic allergic reactions to allergen immunotherapy in a pediatric allergy clinic in Turkey. *Int J Pediatr Otorhinolaryngol* 2016;84:55–60.
30. Bousquet J, Hejjaoui A, Dhivert H, et al. Immunotherapy with a standardized dermatophagoides pteronyssinus extract: III. Systemic reactions during the rush protocol in patients suffering from asthma. *J Allergy Clin Immunol* 1989;83(4):797–802.
31. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2016;138(6):1631–8.
32. Maloney J, Prenner BM, Bernstein DI, et al. Safety of house dust mite sublingual immunotherapy standardized quality tablet in children allergic to house dust mites. *Ann Allergy Asthma Immunol* 2016;116(1):59–65.
33. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol* 2014;113(1):93–100.e3.
34. Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol* 2017;118(3):276–82.e2.
35. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA* 2016;315(16):1715–25.
36. Gur Cetinkaya P, Kahveci M, Esenboga S, et al. Systemic and large local reactions during subcutaneous grass pollen immunotherapy in children. *Pediatr Allergy Immunol* 2020;31(6):643–50.

37. Epstein TG, Liss GM, Murphy-Berendts K, et al. 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.e1.
38. Wong PH, Quinn JM, Gomez RA, et al. Systemic reactions to immunotherapy during mountain cedar season: implications for seasonal dose adjustment. *J Allergy Clin Immunol Pract* 2017;5(5):1438–9.e1.
39. Albuhairei S, Sare T, Lakin P, et al. Systemic reactions in pediatric patients receiving standardized allergen subcutaneous immunotherapy with and without seasonal dose adjustment. *J Allergy Clin Immunol Pract* (Cambridge, MA) 2018;6(5):1711–6.e4.
40. ALK-Abello, Inc.. Standardized mite, mixed injection, solution [package insert]. U.S. Food and Drug Administration website. 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=4a3539da-7f51-401b-8ac2-101b8a4658f4&type=display>. Accessed August 15, 2021.
41. Nelco Laboratories, Inc.. Allergenic Extract [package insert]. U.S. Food and Drug Administration website. 2009. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ade1e6ce-57e8-4b25-9a07-636f2df69d36&type=display>. Accessed August 15, 2021.
42. Bernstein DI, Epstein T. Systemic reactions to subcutaneous allergen immunotherapy. *Immunol Allergy Clin North Am* 2011;31(2):241–9, viii-ix. (Review) (In eng).
43. Fitzhugh DJ, Bernstein DI. Should epinephrine autoinjectors be prescribed to all patients on subcutaneous immunotherapy? *J Allergy Clin Immunol Pract* 2016;4(5):862–7.
44. Bernstein D, Tankersley M, Russell H. Controversies in allergy: injectable epinephrine should be prescribed to all patients on subcutaneous aeroallergen immunotherapy. *J Allergy Clin Immunol Pract* (Cambridge, MA) 2020;8(4):1211–5.
45. Parmiani S, Fernández Távora L, Moreno C, et al. Clustered schedules in allergen-specific immunotherapy. *Allergologia Immunopathol (Madr)* 2002;30(5):283–91.
46. Smits WL, Giese JK, Letz KL, et al. Safety of rush immunotherapy using a modified schedule: a cumulative experience of 893 patients receiving multiple aeroallergens (In eng). *Allergy Asthma Proc* 2007;28(3):305–12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17619559>.
47. Winslow AW, Turbyville JC, Sublett JW, et al. Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy. *Ann Allergy Asthma Immunol* 2016;117(5):542–5.
48. Liss GM, Murphy-Berendts K, Epstein T, et al. Factors associated with severe versus mild immunotherapy-related systemic reactions: a case-referent study. *J Allergy Clin Immunol* 2011;127(5):1298–300 (Letter Research Support, U.S. Gov't, Non-P.H.S.) (In eng).
49. Moreno V, Alvaríño M, Rodríguez F, et al. Randomized dose-response study of subcutaneous immunotherapy with a *Dermatophagoides pteronyssinus* extract in patients with respiratory allergy. *Immunotherapy* 2016;8(3):265–77 (In English).
50. Holland CL, Samuels KM, Baldwin JL, et al. Systemic reactions to inhalant immunotherapy using 1:1 target dosing. *Ann Allergy Asthma Immunol* 2014;112(5):453–8.
51. Sola J, Da Silva Ferreira JA, Dionicio Elera J, et al. Timothy grass pollen therapeutic vaccine: optimal dose for subcutaneous immunotherapy. *Immunotherapy* 2016;8(3):251–63 (In English).

52. Sani S, Gupta R, Fonacier L, et al. Risk stratification of systemic reactions to subcutaneous immunotherapy: a retrospective study. *Allergy Asthma Proc* 2019; 40(5):338–42.
53. DaVeiga SP, Liu X, Caruso K, et al. Systemic reactions associated with subcutaneous allergen immunotherapy: timing and risk assessment. *Ann Allergy Asthma Immunol* 2011;106(6):533–7.e2.
54. Lieberman P, Tankersley M. Significance of large local reactions that occur during allergen immunotherapy. *J Allergy Clin Immunol Pract* 2015;3(2):310–1.
55. Tankersley MS, Butler KK, Butler WK, et al. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol* 2000;106(5): 840–3.
56. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. *Ann Allergy Asthma Immunol* 2004;92(2):225–7.
57. Roy SR, Sigmon JR, Olivier J, et al. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;99(1):82–6.
58. Calabria CW, Stolfi A, Tankersley MS. The REPEAT study: recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions. *Ann Allergy Asthma Immunol* 2011;106(1):49–53.
59. Calabria CW, Coop CA, Tankersley MS. The LOCAL Study: local reactions do not predict local reactions in allergen immunotherapy. *J Allergy Clin Immunol* 2009; 124(4):739–44 (In eng).
60. Epstein TE, Tankersley MS. Are allergen immunotherapy dose adjustments needed for local reactions, peaks of season, or gaps in treatment? *J Allergy Clin Immunol Pract* (Cambridge, MA) 2017;5(5):1227–33.
61. Yang Y, Ma D, Huang N, et al. Safety of house dust mite subcutaneous immunotherapy in preschool children with respiratory allergic diseases. *Ital J Pediatr* 2021;47(1):101.
62. Nelson HS. Allergy immunotherapy for inhalant allergens: Strategies to minimize adverse reactions. *Allergy Asthma Proc* 2020;41(1):38–44.
63. Hepner MJ, Ownby DR, Anderson JA, et al. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990;86(3 Pt 1):407–11. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1976666.
64. Lang DM. Do β -blockers really enhance the risk of anaphylaxis during immunotherapy? *Curr Allergy Asthma Rep* 2008;8(1):37–44 (In English).
65. Fatal course of *Vesputa* venom immunotherapy: pretreatment withdrawal of the beta blocker may have been involved. *Novartis Found Symp* 2004;257:226–7. Available at: .
66. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol* 2005;115(3):606–10 (Research Support, Non-U.S. Gov't) (In eng).
67. White KMMD, England RWMD. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. *Ann Allergy Asthma Immunol* 2008; 101(4):426–30.
68. Stoevesandt J, Hain J, Stolze I, et al. Angiotensin-converting enzyme inhibitors do not impair the safety of Hymenoptera venom immunotherapy build-up phase. *Clin Exp Allergy* 2014;44(5):747–55.

69. Yoshihiro O, Yoshinori N, Kiyotaka M. Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;96(4):600–5.
70. Portnoy J, Bagstad K, Kanarek H, et al. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy* 1994;73(5):409–18.
71. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125(2):383–9.
72. 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.
73. Casale TB, Kline JN, Busse WW, et al. Omalizumab pretreatment prevents allergic reactions due to rush immunotherapy (RIT). *J Allergy Clin Immunol* 2005;115(2):S65.
74. Rosenberg JL. Lack of pretreatment cost-effectiveness and side effects of omalizumab versus prednisone/montelukast on tolerability of immunotherapy. *J Allergy Clin Immunol* 2011;127(2):548 (In English).
75. Nielsen L, Johnsen CR, Mosbech H, et al. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 1996;97(6):1207–13.
76. Berchtold E, Maibach R, MÜLLER U. Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy* 1992;22(1):59–65.
77. Tsao LR, Villanueva SA, Pines DA, et al. Impact of rapid transition to telemedicine-based delivery on allergy/immunology care during COVID-19. *J Allergy Clin Immunol Pract* 2021;9(7):2672–2679 e2.
78. Shaker MS, Oppenheimer J, Grayson M, et al. COVID-19: Pandemic contingency planning for the allergy and immunology clinic. *J Allergy Clin Immunol Pract* 2020;8(5):1477–88.e5.
79. Searing DA, Dutmer CM, Fleischer DM, et al. A phased approach to resuming suspended allergy/immunology clinical services. *J Allergy Clin Immunol Pract* 2020;8(7):2125–34.
80. Compalati E, Erlewyn-Lajeunesse M, Runa Ali F, et al. Allergen immunotherapy in the era of sars-cov-2. *J Investig Allergol Clin Immunol* 2020;30(6):459–61.
81. Larenas-Linnemann DE, Epstein T, Ponda P, et al. Gaps in allergen immunotherapy administration and subcutaneous allergen immunotherapy dose adjustment schedules: Need for prospective data. *Ann Allergy Asthma Immunol* 2020;125(5):505–6.e2.