

# 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

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## ABSTRACT

*In 2004, it was estimated that one fatal anaphylactic reaction (FR) occurred in every 2.4 million subcutaneous immunotherapy (SCIT) injection visits. Uncontrolled asthma was the most commonly cited factor that contributed to FRs. Results of the annual American College of Allergy, Asthma, and Immunology/American Academy of Allergy, Asthma and Immunology sponsored survey conducted among practicing allergists suggest that one nonfatal systemic reactions (SR) occurred in 0.15% of injection visits and in 0.7% of patients who were treated. Analysis of recent data indicated that FRs are 3.75-fold less frequent. Life-threatening grade 4 anaphylactic reactions are estimated to occur in 0.005% of patients who receive SCIT (or 1/160,000 injection visits). Analysis of data from annual surveys identified the following possible risk factors for SRs: a history of SRs to SCIT, the administration of injections in patients with uncontrolled asthma, use of accelerated buildup regimens, and never adjusting doses during the height of the allergy season. Delayed-onset SRs beginning >30 minutes after injections represented 15% of all SRs in clinics with 30-minute observation periods. The safety profile of sublingual immunotherapy is favorable, with no FRs yet identified for sublingual tablet or liquid formulations. Risk management should focus mainly on patients with uncontrolled asthma by withholding injections in such patients, with recent worsening in asthma symptoms and lung function (e.g., peak expiratory flow rate). Because nearly all FRs and SRs occur within 30 minutes of injections, a 30-minute observation period is recommended. Routinely prescribing epinephrine for all patients did not prevent severe SRs, likely due to poor adherence when SRs occurred. Also, no local or systemic infections were identified in 2.3 million patients attending 24.5 million injection visits, which allayed concerns over infections associated with compounding of allergen extracts by practicing allergists.*

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## WHAT ARE THE RISKS OF SYSTEMIC REACTIONS WITH ALLERGEN IMMUNOTHERAPY?

**I**n a large retrospective survey of North American allergists published in 2004, it was estimated that one fatal anaphylactic reaction (FR) had occurred in every 2.4 million subcutaneous allergen immunotherapy (SCIT) injection visits.<sup>1</sup> In 2008, an annual surveillance study was initiated among practicing allergists in North America to track SCIT-related systemic reactions (SR). Analysis of recent data, since 2008, indicated that confirmed FRs may have decreased to 1 in 9 million injection visits.<sup>2</sup> Based on these data, nonfatal SRs are estimated to occur at a rate of 1/1000 injection visits and

in 0.7% of treated patients. Life-threatening grade 4 anaphylactic reactions were estimated to occur in 0.005% of patients who received SCIT (or 1/160,000 injection visits).<sup>2,3</sup> In this article, we reviewed the clinical evidence, provided insight into risk factors that contributed to severe systemic SCIT reactions, and identified possible approaches to reduce the risk for fatal reactions.

SCIT is effective in treating allergic rhinitis and immunoglobulin E dependent asthma, and in preventing Hymenoptera anaphylaxis.<sup>4</sup> There is a real risk, however, of rare injection-related FRs after SCIT injections. Retrospective surveys conducted in North America (1973–2017) among practicing allergists confirmed a total of 89 fatal events.<sup>1,2,5,6</sup> Uncontrolled or labile asthma has been identified as contributing to at least 60% of reported FRs, with the majority also reporting previous emergency department visits or hospitalization for acute asthma.<sup>1,6</sup> SRs associated with previous injections, delayed administration of epinephrine, allergen dosing errors, and administration during the height of pollen seasons have also been cited as factors that contribute to FRs. Failure to receive injections in a medically supervised setting or leaving the clinic before completing 30 minutes of postinjection observation were cited as contributing to some FRs. In

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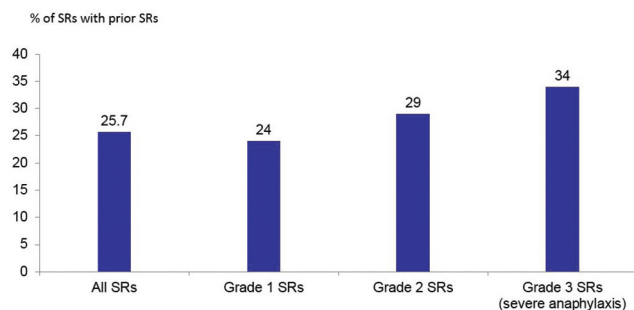


**Figure 1.** Percent of systemic reactions (SR) of varying severity with a history of a previous SR reported by 630 allergy practices participating in year 2 (2009–2010) of the American College of Allergy, Asthma, and Immunology/American Academy of Allergy, Asthma and Immunology Subcutaneous Immunotherapy Surveillance Study. During this year, the SR rate defined as number of events per injection visit was 0.6%.

70% of FRs reported before 2003, no contributing factor was identified; in FRs reported after 2008, 30% did not have a known contributing factor.<sup>1,4,6</sup>

Since 2008, the American College of Allergy, Asthma, and Immunology/American Academy of Allergy, Asthma and Immunology sponsored North American Surveillance Study has been conducted annually among practicing allergists and has confirmed many previously proposed risk factors for nonfatal SRs.<sup>2</sup> For example, two-thirds of all severe grade 3 or 4 nonfatal SRs reportedly occurred in patients with asthma.<sup>2</sup> Previous SRs occurred in 26% of all patients who experienced an SR of any severity (Fig. 1). Accelerated cluster buildup regimens, used by 31% of responding practices, were associated with a greater likelihood of SRs of any severity, regardless of whether premedication was used. Those practices, using a lower final target cluster allergen dose before transitioning to maintenance SCIT, however, were less likely to cause severe SRs.<sup>3</sup> It should be noted that the increased risk for SRs with accelerated cluster buildup regimens seen in the National Surveillance Study has not been found in all studies that investigated this issue.<sup>2,7–9</sup>

In the surveillance study, practices never reducing doses during peak pollen seasons in the buildup or maintenance vials were significantly more likely to report grade 3 or 4 SRs.<sup>3</sup> Of note, this finding has also not been seen in all studies that investigated seasonal patterns for SRs and dose adjustment to minimize reactions during peak pollen seasons.<sup>10–12</sup> In 2 separate years of the annual survey, late-onset SRs beginning >30 minutes after injection administration represented approximately 15% of all SRs, although delay-onset grade 3 or 4 SRs were rare.<sup>2,13</sup> This study and others that reported higher frequencies of delayed-onset SR has prompted a debate with regard to whether all patients receiving SCIT should be prescribed epinephrine autoinjectors.<sup>14</sup>

The U.S. Pharmacopeia recently expressed concerns about a potential risk of local or systemic infections associated with administration of subcutaneous allergen injections from mixed vials compounded in allergy clinics, although such incidents have not been reported. Consistent with this, the annual survey surveyed practicing allergists from 2014 to 2017 with regard to infections. Not a single local or systemic infection was able to be confirmed in 2.3 million patients after 24.5 million injection visits.<sup>2</sup>

The safety profile of sublingual immunotherapy (SLIT) is favorable.<sup>15</sup> To date, fatal anaphylaxis has not been identified with the use of approved SLIT tablet formulations or off-label allergen extracts used for that purpose, although anecdotal cases of nonfatal anaphylaxis have been reported.<sup>16</sup> Single isolated mild SRs have been noted in large double-blind controlled (DBPC) trials of seasonal or perennial allergic rhinitis during clinical development of grass, ragweed, and house-dust mite (HDM) SLIT tablets.<sup>17–19</sup> No SRs were identified in a large double-blind controlled trial that evaluated the efficacy and safety of HDM SLIT tablets in patients with HDM triggered asthma with rhinitis not controlled on inhaled corticosteroids.<sup>20</sup> HDM SLIT tablets also did not increase asthma-related events in patients with mild-moderate asthma who participated in allergic rhinitis clinical trials.<sup>21,22</sup>

## WHAT STRATEGIES MAY REDUCE RISK OF FATAL ANAPHYLAXIS ASSOCIATED WITH SCIT?

Clinical practices designed to reduce severe SRs in asthmatic and all treated patients are listed in Tables 1 and 2 respectively. Analysis of the data clearly defined the risk of uncontrolled asthma in patients receiving SCIT, which indicated that risk management strategies should focus on patients with asthma. Patients with symptomatic asthma at the time of injection are at particularly increased risk. In North America, 86% of allergy practices reported that they routinely performed pre-injection questionnaires for increased symptoms in patients with asthma who received SCIT,<sup>23</sup> but only 33% routinely conducted pre-injection lung function testing (e.g., peak expiratory flow rate). The overall decline in SCIT-related fatalities since 2008 may, in part, be due to implementation of pre-injection screening based on published guidelines.<sup>2,4</sup> Further improvement in fatal and near-fatal SRs may be seen if all practices that administer SCIT universally adopt protocols to assess patients who receive injections for both recent increases in symptoms and reduction in lung function.<sup>1,24</sup>

Although unproven, it is possible that peak flow testing before each injection might capture those patients unwilling to report or unable to perceive recent

**Table 1 Possible strategies to reduce risk of anaphylaxis in patients with asthma**

1. Universal pre-injection screening for asthma symptoms and lung function
2. Do not initiate SCIT in patients with uncontrolled asthma
3. Withhold SCIT in patients with severe treatment refractory asthma for which risks outweigh potential benefits
4. Investigate potentially safer modalities of AIT (*e.g.*, SLIT in patients with mild or moderate controlled asthma, modified therapeutic allergens)
5. Administer SCIT injections only in adequately equipped clinic facilities with medical staff trained to manage anaphylaxis and acute respiratory failure
6. Strict adherence to the 30-min postinjection observation period

SCIT = Subcutaneous immunotherapy; AIT = allergen immunotherapy; SLIT = sublingual immunotherapy.

deterioration in asthma control. In some patients at high risk and with severe persistent asthma, SCIT may not be recommended at all, when considering evidence that suggests that SCIT may be less efficacious in those patients with severe asthma.<sup>25</sup> Further support for a more-selective strategy is provided from data collected in the North American survey; that is, clinics whose practice it was to never initiate SCIT in patients with uncontrolled asthma reported 70% fewer life-threatening grade 4 SRs versus those that sometimes prescribe SCIT in such patients.<sup>26</sup> Although evidence is lacking, the use of SLIT or SCIT with modified allergens could prove to be safer alternatives in patients with severe asthma likely to benefit from allergen immunotherapy.

Because FRs have occurred in facilities ill prepared to optimally manage anaphylaxis and home injections, SCIT must be administered in outpatient facilities staffed with trained personnel adequately prepared to manage anaphylaxis, which may include acute respiratory failure.<sup>4</sup> Because nearly all severe SRs begin within 30 minutes of injections, strict adherence to 30-minute postinjection observation period is recommended.<sup>4</sup> Although analysis of the latest data suggests that 73% of practices observe a 30-minute observation period, universal adherence to this recommendation is likely to enhance management of SRs and subsequent outcomes.<sup>2</sup> Of note, one recent fatality in a child occurred that was associated with inadequate observation time after immunotherapy injections.<sup>2</sup>

Although some practitioners have advocated that epinephrine autoinjectors are an appropriate surrogate for the postinjection waiting period, evidence to

**Table 2 How to improve SCIT tolerability by preventing SRs in all treated patients**

1. Do not recommend SCIT in patients with severe or uncontrolled asthma.
2. Modify doses or discontinue SCIT after grade 3 or 4 SRs
3. Adapt clinic protocols to prevent dosing errors
4. Administer SCIT injections only in clinics with adequate facilities, personnel to manage anaphylaxis, and adhere to a 30-min observation period
5. Consider modifying doses in patients who are highly sensitized during peak aeroallergen periods
6. Consider reducing target doses for an accelerated cluster buildup
7. Targeted prescription and training on use of self-injectable epinephrine in patients at heightened risk for SRs

SCIT = Subcutaneous immunotherapy; SR = systemic reaction.

support this strategy is lacking. Approximately 30% of clinical practices routinely prescribe and train patients on SCIT on the use of self-injectable epinephrine.<sup>2</sup> The surveillance study conducted three annual evaluations of in-field use of epinephrine autoinjectors for SRs and found that only 8–30% of patients used their autoinjectors for grade 3 or 4 SRs that occurred after leaving the clinic. Further analysis revealed that routine prescription of autoinjectors did not prevent delayed-onset grade 3 and 4 SRs.<sup>2</sup> Thus, routinely prescribing epinephrine autoinjectors to patients who do not adhere to 30 minutes of observation does not seem to be an effective strategy. Targeted prescription and intensive training on the use of self-injectable epinephrine in patients at a heightened risk for SRs may prove more effective but is yet to be evaluated systematically. This may be applied to patients with previous SRs (especially delayed), those receiving accelerated buildup (*e.g.*, cluster), and those receiving injections at outside clinics.

## CONCLUSION

Although the risk of fatal SRs seems to be declining overall, continued vigilance is needed to minimize the risk of severe and fatal SRs in patients on SCIT. Special precautions are needed for patients with asthma and who are on SCIT, given the increased risk in this group, including pre-injection screening of symptom control and, possibly, lung function, and not prescribing SCIT for patients with uncontrolled asthma. Additional risk factors include previous SRs, reactions that occur outside of a health-care setting staffed with

trained personnel, delayed administration of epinephrine, and, possibly, peak pollen seasons and accelerated buildup strategies (cluster, rush). Not increasing doses during peak pollen seasons, especially in patients who are highly sensitized, may reduce risks for severe SRs.<sup>3</sup> Premedication with accelerated buildup protocols and changing to conventional buildup in more concentrated vials may reduce risks.<sup>3</sup> There is no evidence to date that routinely prescribing epinephrine autoinjectors to patients on SCIT is an adequate substitute for routine postinjection monitoring of patients on SCIT. No local or systemic infections have been identified from SCIT as routinely prepared in allergist's offices in North America.

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