

Systemic Reactions to Subcutaneous Allergen Immunotherapy

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KEYWORDS

- Subcutaneous immunotherapy • Systemic reactions
- Anaphylaxis

The prevalence of asthma and allergic rhinitis associated with aeroallergen sensitization have increased over the past 40 years, especially in “westernized” developed countries. Thus, much attention has been focused on treatment modalities that may prevent or mitigate clinical expression of severe allergic disorders including asthma.¹ One such therapy, subcutaneous allergen immunotherapy (SCIT), has been practiced for 100 years.² Placebo-controlled trials of seasonal allergic rhinitis (SAR) with single pollen allergens have demonstrated that SCIT is effective in reducing symptoms of SAR and in preventing seasonal allergic asthma in children with SAR.³ Placebo-controlled trials with single allergens (ie, grass pollen, cat, and house dust mite) have also established the efficacy of SCIT in reducing symptoms of asthma due to aeroallergens.⁴ SCIT with purified Hymenoptera venoms is effective in preventing anaphylaxis in patients with previous life-threatening systemic allergic reactions.⁵ However, the clinical benefits of SCIT are tempered by risks of injection-related systemic reactions and life-threatening anaphylaxis.

In 1916, Robert Cooke reported that 3.5% of subcutaneous grass pollen injections were followed by systemic reactions. As early as 1932, 9 fatal reactions (FRs) after SCIT injections were reported in the United States, including one who failed to respond to epinephrine.⁶ A review of fatal reactions to SCIT injections conducted in the United Kingdom identified 26 anaphylactic deaths occurring from 1957 to 1986, all of which occurred among allergic patients with asthma.⁷ This report resulted in the institution of a mandatory 2-hour postinjection waiting period in Great Britain, virtually creating a moratorium on administration of SCIT for many years.

The authors have nothing to disclose.

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Immunol Allergy Clin N Am 31 (2011) 241–249

doi:[10.1016/j.iac.2011.02.007](https://doi.org/10.1016/j.iac.2011.02.007)

immunology.theclinics.com

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In the last 40 years, a series of surveys and descriptive studies have been conducted to define the incidence, prevalence, and factors contributing to injection-related fatal anaphylactic and near-fatal systemic reactions (SRs) in North America. Nearly all such information has been collected from retrospective surveys with the cooperation of practicing allergists in the United States, or reports from individual clinics.^{8–10} Limitations of these retrospective studies include the potential for recall bias, lack of comparator populations, and low participation rates among groups of surveyed physicians. Therefore, data collected in this manner may underestimate the true incidence of fatal and near-fatal injection related to SRs and obviate the ability to define risk factors for severe SRs. Nevertheless, a national reporting program designed to capture adverse events related to SCIT does not exist and, if it did, would rely entirely on non-solicited voluntary reporting of events.

Three retrospective surveys have been performed to identify FRs, and one of these evaluated near-fatal reactions (NFRs) associated with SCIT injections.¹¹ In the first 2 surveys capturing FRs occurring between 1973 and 1989, members of the American Academy of Allergy Asthma and Immunology (AAAAI) were contacted to report FRs occurring after SCIT or skin testing in their practices as well as FRs in other clinical practices in their communities.^{9,10} A third survey was conducted to capture events between 1990 and 2001.⁸ Here, short surveys were sent to all physician members of the AAAAI to inquire about NFRs and FRs associated with either SCIT or skin testing. Physicians were contacted by email, fax, and phone to optimize response rates. Those who reported NFRs ($n = 273$) or FRs ($n = 41$) on the brief survey were contacted again to provide further details about the events in a longer itemized questionnaire. Completed questionnaires were returned for 68 NFRs and 17 FRs.¹¹ Subsequently, a longitudinal annual surveillance study of FRs and all SCIT-related SRs, cosponsored by the AAAAI and American College of Allergy Asthma and Immunology (ACAAI), was initiated in 2008.¹²

In this article, the authors review data derived from the aforementioned retrospective surveys and recently initiated longitudinal surveillance studies of SCIT reactions in clinical allergy practices.

FREQUENCIES OF FATAL SCIT REACTIONS IN NORTH AMERICA

There were 76 direct or indirect reports of FRs after SCIT injections occurring between 1973 and 2001.¹³ In the survey conducted between 1985 and 1989, it was estimated that a FR occurred once in every 2 million injection visits and once in every 2.5 million injection visits from 1990 to 2001.^{8,10} From 1985 to 2001, this averaged to 3 to 3.4 reported deaths per year. Of interest, these incidences were quite similar between surveys despite different methods used for estimating total numbers of injections administered. Subsequently, an additional 6 FRs were identified that had transpired during 2001 to 2007.¹² Based on data collected from the aforementioned longitudinal surveillance study of SRs, no additional FRs related to SCIT occurred between 2008 and 2010.

CLINICAL MANIFESTATIONS OF SCIT-ASSOCIATED FATAL AND NEAR-FATAL ANAPHYLACTIC REACTIONS

Amin and colleagues¹¹ reported results from a long questionnaire regarding details of NFRs and compared these findings with detailed reports of FRs occurring between 1990 and 2001. In this study, one NFR was estimated to occur in every million injections, or 4.7 NFRs per year. Long survey responses were available for 68 of 273 NFRs and 17 of 41 FRs. The clinical manifestations of FRs and NFRs reported in this survey are summarized in **Figs. 1** and **2**. A NFR was defined as respiratory compromise,

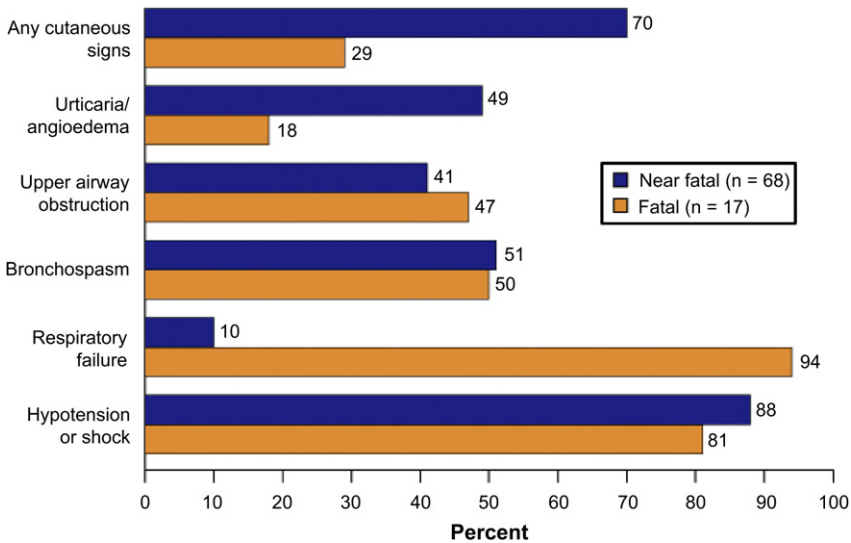


Fig. 1. Comparison of clinical features during FRs and NFRs. "Any cutaneous signs" refers to hives, angioedema, and/or pruritus. "Hypotension" refers to either transient or sustained decrease in blood pressure, and shock refers to cardiovascular collapse. (From Amin HS, Liss GM, Bernstein DI, et al. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117(1):169–75; with permission.)

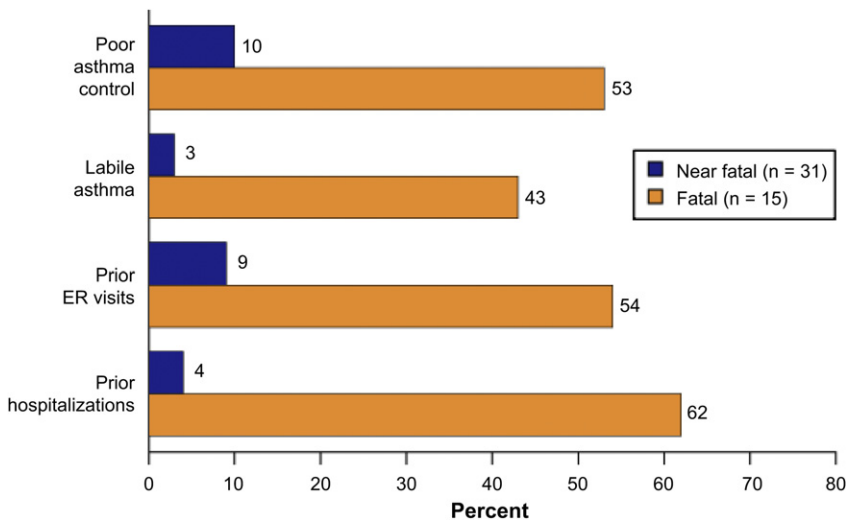


Fig. 2. Comparison of asthma severity in fatal and near-fatal reactions. Odds ratio for prior ER visits = 12.1 (95% confidence interval, 2.6–61.0; $P < .001$); odds ratio for prior hospitalizations = 34.7 (95% confidence interval, 5.7–251.1; $P < .001$). ER, emergency department. (From Amin HS, Liss GM, Bernstein DI, et al. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117(1):169–75; with permission.)

hypotension, or both, requiring emergency epinephrine treatment. Cutaneous manifestations were more frequently noted in patients experiencing NFRs than in patients succumbing to fatal SCIT reactions. It is possible that absence of skin eruptions in these cases delayed recognition and appropriate treatment of anaphylaxis. Hypotension or shock was reported in greater than 80% of FRs and NFRs. Respiratory failure occurred in 94% of FRs but in only 10% of NFRs. Compared with FRs, only a small minority of patients experiencing NFRs had severe or uncontrolled asthma (see [Fig. 2](#)).

FACTORS ASSOCIATED AND POTENTIALLY CONTRIBUTING TO FATAL AND NEAR-FATAL REACTIONS

In a review of 34 FRs from 1985 to 2001, associated and possible contributing factors included: uncontrolled asthma in 62% of cases; a prior history of SRs in 53%; administration of SCIT injections during peak pollen season in 47%; and delay in administration of epinephrine in 43%.^{8,10} In the most recent retrospective survey, Bernstein and colleagues⁸ reported that 15 of 17 fatal reactors had been previously diagnosed with asthma, whereas only 46% of nonfatal reactors had a previous diagnosis of asthma. Epinephrine was not administered to 3 patients with FRs. As shown in [Fig. 1](#), features indicating uncontrolled asthma included a physician's report of labile asthma (43%), poor asthma control (53%), prior emergency department visits for acute asthma (54%), and prior asthma hospitalizations (62%). Other contributing factors identified were failure to observe the recommended postinjection waiting period and administration of injections in suboptimal settings for treatment of severe anaphylaxis (eg, at home). Bernstein and colleagues⁸ reported that the majority of 17 FRs (59%) occurred after injections given from maintenance allergen vials, whereas the majority of FRs reported by Reid and colleagues¹⁰ occurred after injections from buildup vials. Concurrent treatment with β -blockers was observed in 2% of fatal SCIT reactions, although the actual contribution of these drugs to fatal outcomes is unknown. No putative factor contributing to SCIT fatalities could be identified in 17% of the 34 FRs.

In the survey of NFRs occurring between 1990 and 2001, major contributing factors were administration of injections during a peak pollen season in 46% of respondents, and errors in dosing or administration of therapeutic allergens in 25%.¹¹ Other less commonly reported factors associated with NFRs included uncontrolled asthma, prior SRs to SCIT, and delay in administration of epinephrine. In a separate survey evaluating administration errors associated with SCIT, 58% of physicians reported incidents where patients received injections meant for another patient and 74% reported incorrect dosing errors.¹⁴

Recent anecdotal case reports suggest that coadministration of angiotensin-converting enzyme (ACE) inhibitors may enhance the severity of SRs after venom injections.¹⁵ There is no evidence that concomitant ACE inhibitor treatment increases the overall risk for SRs to SCIT, however. Similarly, concomitant treatment with β -adrenergic blockers does not increase the risk for SRs to SCIT.^{16–18} β -Blockade is considered a risk factor for more protracted and difficult-to-treat postinjection anaphylaxis. This concern is based on descriptive studies showing that β -blockade enhances the risk for severe and difficult-to-treat anaphylactoid reactions after intravenous contrast media.¹⁹ In other studies, use of rush immunotherapy or some cluster SCIT schedules are associated with a higher frequency of SRs when compared with a slower buildup protocols.⁴

Uncertainty exists about the potential risk posed by large local reactions. In general, large local reactions have not been shown to predict SRs, nor does adjustment of treatment allergen doses after large local reactions prevent subsequent SRs.²⁰ On

the other hand, in a large retrospective study of patients receiving SCIT, patients experiencing SRs had a threefold greater likelihood of having experienced prior large local reactions when compared with patients without prior SRs.²¹

OVERALL INCIDENCE AND PREVALENCE OF SYSTEMIC REACTIONS AFTER SCIT INJECTIONS

There are reasonably good data defining national incidence and characteristics of fatal and life-threatening reactions with SCIT injections. In a recent review of the published literature, the prevalence of SRs was estimated at 2 in 1000 injections (0.2%) or 5% to 7% of treated patients.⁴ Although initially thought to have a lower risk profile, SRs may be no less frequent with modified polymerized allergen extracts than with standard aqueous allergens.^{22,23} As mentioned, cluster and rush schedules have been reported to result in greater frequencies of systemic reactions compared with slow buildup protocols.^{24,25}

The aforementioned ACAAI/AAAAI Surveillance Study investigated the national annual prevalence of SRs of varying severity among practicing allergists. In a Web-based survey, practitioners administering SCIT were asked to report the numbers of nonfatal SRs in their entire practice during the previous 12 months and to assess severity based on a 3-grade classification system (**Box 1**). In this survey, SRs were categorized as: mild (Grade 1: cutaneous or upper respiratory symptoms); moderate (Grade 2: asthma with reduced lung function); or severe (Grade 3: life-threatening airway compromise or hypotension).

In year 1 of the surveillance program, 806 physicians (representing 1922 SCIT prescribers) reported on their experiences with SRs. SRs were reported in 82% of participating practices, for a total of 8502 SRs, which translated to an overall rate of 10.2 SRs per 10,000 injection visits or 0.1% of all injection visits.¹² By far, the vast majority were mild Grade 1 SRs (74%), whereas 23% were identified as Grade 2 SRs. Only 3% ($n = 265$) of all SRs were serious Grade 3 events. Although Grade 3 reactions occurred in only 3 out of every 100,000 injection visits or 0.003% of injection visits, 18% of practices reported experiencing at least one Grade 3 event between 2008 and 2009. It is remarkable that the relative proportions of Grade 1, 2, and 3 reactions in year 1 of the study were nearly identical to those subsequently reported in year 2 (data unpublished at the time of writing).

Box 1

North American Surveillance Study: classification system of SRs associated with SCIT

Grade 1—Mild systemic reactions: generalized urticaria or upper respiratory symptoms (eg, itching of the palate and throat, sneezing)

Grade 2—Moderate systemic reactions: asthma (eg, peak expiratory flow rate falls 20%–40%) with or without generalized urticaria, upper respiratory symptoms, or abdominal symptoms (nausea, cramping)

Grade 3—Severe, life-threatening anaphylaxis: severe airway compromise due to severe bronchospasm (eg, peak expiratory flow rate falls >40%), or upper airway obstruction with stridor or hypotension (with or without loss of consciousness)

From 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; with permission.

A follow-up Web-based questionnaire survey was conducted in a subset of physician respondents to investigate possible differences in standard SCIT practices between clinics reporting severe Grade 3 reactions and clinics reporting exclusively mild Grade 1 SRs.²⁶ The questionnaire evaluated: criteria for selection of asthmatic patients for SCIT; adjustment of SCIT during peak allergy seasons; adjustment of treatment allergen doses after large local reactions or SRs; customary postinjection observation periods; routine preinjection screening of asthmatics for level of asthma control; use of prediluted patient-specific vials versus sharing of common vials for multiple patients; routine premedication with antihistamines; and routine prescription of self-administered epinephrine in patients on SCIT.

Significant differences in clinical practices related to SCIT between 35 clinics with Grade 3 SRs and 39 clinics reporting only Grade 1 SRs are shown in **Table 1**. Physicians working in clinics experiencing a Grade 3 reaction within the past year were more likely to prescribe patients receiving SCIT epinephrine kits for self-administration, check patient identifiers prior to injection to prevent injection errors via misidentification, and prescribe routine preinjection treatment with H1 blockers. It is probable that practices who had previously experienced severe SRs adopted these strategies to minimize the risk of future severe reactions. In addition, those practices experiencing Grade 3 anaphylactic reactions were more frequently prescribed higher maintenance doses of house dust mite than those clinics reporting Grade 1 SRs.

Table 1 Summary of survey questions showing significant differences in responses (always, often, sometimes, or never) between a subset of allergy practices reporting severe grade 3 SRs and a subset reporting only mild grade 1 SRs after SCIT injections during 2007 and 2008 (n, percentage given in parentheses)						
Question	Severity of Reported SRs	Always	Often	Sometimes	Never	P Value
Are patients asked to provide identifiers prior to immunotherapy?	Grade 1	22 (56.4)	0	2 (5.1)	15 (38.5)	.0094
	Grade 3	22 (62.9)	4 (11.4)	5 (14.3)	4 (11.4)	—
Are asthmatics prescribed epinephrine for self-administration?	Grade 1	5 (12.8)	2 (5.1)	20 (51.3)	12 (30.8)	.0062
	Grade 3	12 (34.3)	1 (2.9)	21 (60)	1 (2.9)	—
Are patients routinely instructed to premedicate with antihistamines and/or antiallergic drugs prior to immunotherapy?	Grade 1	3 (7.7)	5 (12.8)	22 (56.4)	9 (23.1)	.011
	Grade 3	8 (22.9)	10 (28.6)	16 (45.7)	1 (2.9)	—
Are patients on SCIT prescribed epinephrine and instructed on self-administration?	Grade 1	5 (12.8)	2 (5.1)	21 (53.9)	11 (28.2)	.0258
	Grade 3	12 (34.3)	1 (2.9)	20 (57.1)	2 (5.7)	—
Are patients with prior SCIT systemic reactions prescribed epinephrine and instructed on self-administration?	Grade 1	14 (35.9)	8 (20.5)	10 (25.6)	7 (18.0)	.042
	Grade 3	20 (57.1)	6 (17.1)	9 (25.7)	0	—

Data from 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. [Epub ahead of print].

TIME OF ONSET OF SYSTEMIC REACTIONS AND DELAYED-ONSET REACTIONS

Delayed-onset FRs have been documented in the aforementioned retrospective SCIT fatality surveys. Combined data from 58 fatal SCIT reactions from 1983 to 2001, indicate that 10% of FRs began 30 to 60 minutes after administration of SCIT injections.^{8–10} By contrast, only 4% of NFRs were reported to begin later than 30 minutes after injections.¹¹

Previous estimates of delayed-onset injection-related SRs (later than 30 minutes) of all severity grades range between 27–50%,^{18,27–31} and most are described as mild and non-life-threatening. These high estimates of delayed-onset reactions do not match the experience of many practicing allergists. In year 2 of the North American Surveillance Study, time of onset of SRs following injections was assessed, as was administration of epinephrine.³² Of the 35% of respondents providing data regarding the time of onset of reactions, 2117 reported SRs; 71% were mild Grade 1, 25% Grade 2, and only 3% were classified as Grade 3 SRs. Of all reported SRs, 14% began at least 30 minutes after injections. Of note, 13% of severe Grade 3 reactions were delayed-onset SRs. Epinephrine was administered to most (77%) but not all SRs beginning within the recommended 30-minute postinjection waiting period, including 71% of Grade 1, 93% of Grade 2, and 94% of Grade 3 SRs. As expected, epinephrine was not administered for delayed-onset SRs as frequently as for more immediate-onset SRs. For delayed-onset SRs, epinephrine was given for only 60% of all reported delayed-onset SRs (N = 289) including 56% of Grade 1 LRs and 67% of Grade 2 LRs, and in 9 of 9 (100%) Grade 3 LRs.

SUMMARY: LESSONS LEARNED

Despite the descriptive nature of the data collected, much has been learned from the retrospective surveys of fatal and near-fatal SCIT reactions. Recent data from the ACAAI/AAAAI Surveillance Study indicates that the overall incidence of delayed-onset SRs is much less frequent than previously reported (ie, 14%), that most are not severe, and that nearly all anaphylactic reactions occur within the first 30 minutes after injections. Retrospective surveys conducted in the United States have identified consistent risk factors for postinjection anaphylaxis. This information has directly shaped recently published practice guidelines. Such recommendations have been updated in 3 iterations of the Allergen Immunotherapy Practice Parameters, the most recent third update of this document being published in 2011 (following 2003 and 2007).^{33–35} With regard to improving safety of SCIT, these parameters provide specific guidance for:

1. Identifying and monitoring high-risk patients (eg, uncontrolled asthmatics) receiving allergen immunotherapy
2. Considering individual patient risk factors in the decision to recommend allergen immunotherapy
3. Preventing errors in administration
4. Assuring optimal management of anaphylaxis including postinjection observation for at least 30 minutes and epinephrine treatment
5. Considering risk/benefit of concomitant use of β -blockers in patients receiving allergen immunotherapy
6. Managing patients experiencing late-onset SRs and biphasic reactions.

Based on data collected over the previous 2 years from the ACAAI/AAAAI Surveillance Study, no new FRs have been reported. This favorable trend may be attributable in part to heightened awareness of clinical allergists of risk factors for life-threatening

SRs combined with recent implementation of risk management strategies surrounding administration of SCIT.

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