

Systemic Reactions in Pediatric Patients Receiving Standardized Allergen Subcutaneous Immunotherapy with and without Seasonal Dose Adjustment



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What is already known about this topic? Data regarding the safety of standardized subcutaneous immunotherapy (SCIT) in children and the effect of dose adjustment in pollen season are limited.

What does this article add to our knowledge? Standardized SCIT appears to be associated with a systemic reaction rate of 0.429% to 0.364% of visits in pediatric patients. Asthma is a risk factor in younger children. Seasonal dose adjustment did not have a significant effect.

How does this study impact current management guidelines? Pediatric patients might require lower SCIT doses than currently recommended. However, it is not clear that dose adjustment during pollen season is beneficial. Younger asthmatic patients may require more careful monitoring.

BACKGROUND: The 2003 Joint Task Force on Practice Parameters recommended standardizing allergen subcutaneous immunotherapy (SCIT). Data from longitudinal surveillance survey in North America reported a systemic reaction (SR) rate of 0.1% to 0.2% of injection visits. The rate of SR to standardized SCIT in pediatric patients has not been well evaluated.

OBJECTIVE: The objective of this study was to evaluate the rate of SRs to standardized SCIT in pediatric patients aged 5 to 18 years in a single tertiary care center in the United States.

METHODS: A retrospective chart review was conducted in 2 groups: group 1 started SCIT within a period extending from January 2009 to June 2012, whereas group 2 started SCIT within a period extending from January 2013 to June 2016. The protocol was modified in group 2 such that up dosing and

maintenance doses were adjusted in the spring for tree and grass pollen and in the fall for weed pollen.

RESULTS: There were a total of 128 patients in group 1 and 118 patients in group 2. The rate of SR was 0.429% in group 1 and 0.364% in group 2, which was not significant. There was no difference in the severity of SR in the 2 groups with no-fatal or near-fatal SR noted. Asthma was a significant risk factor in the younger age subgroup aged 5 to 11 years.

CONCLUSIONS: Standardized SCIT appears to be associated with an SR rate of 0.429% to 0.364% of visits in pediatric patients. Protocol modification did not lead to a significant drop in SR. Larger multicenter studies are required to further evaluate the rate of SRs from standardized SCIT. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1711-6)

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In 2003, the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology, recommended standardizing allergen subcutaneous immunotherapy (SCIT) and targeting maintenance doses within a specific range for each allergen in an attempt to optimize SCIT practice, reduce unnecessary variation in different practices, and provide guidelines for its safe use.¹ These recommendations were revised in 2007 and 2011.^{2,3}

SCIT is considered overall a safe therapeutic modality.⁴⁻⁸ In a large European retrospective study spanning from 1981 to 2000, the rate of systemic reaction (SR) was 0.01% to 0.06% of injection visits.^{9,10} More recently, data from surveillance in North

Abbreviations used

BCH- Boston Children's Hospital
JTFPP- Joint Task Force on Practice Parameters
SCIT- Subcutaneous immunotherapy
SPT- Skin prick test
SR- Systemic reaction

America reported a rate of SR at 0.1% to 0.2% of injection visits with conventional buildup protocols.⁶ SR rate using a defined standardized SCIT protocol based on the JTFPP recommendations has not been well evaluated.

The 2011 JTFPP reported that SCIT might be associated with a higher risk of SR when patients are exposed to an increased level of allergens though most patients do well without dose adjustments.⁵

In this study, we evaluated the rate of SR to standardized SCIT using a conventional buildup protocol in pediatric patients aged 5 to 18 years with and without seasonal dose adjustments.

METHODS**SCIT extracts and ordering**

The allergens included in SCIT and the vial concentrations are listed in [Supplement E1](#) (available in this article's Online Repository at www.jaci-inpractice.org).

SCIT was ordered using an Excel program in which the extracts were selected. Up to 5 dilutions were prepared. The SCIT protocol in group 1-no-dose-adjustment consisted initially of a buildup period of 28 to 32 weeks starting at 1:1,000 (vol/vol) dilution of the maintenance up to 1:1 (vol/vol), except for a few patients who were started on silver (1:10,000) dilution per provider discretion ([Table E1](#), available in this article's Online Repository at www.jaci-inpractice.org). In group 2-seasonal-dose-adjustment, the buildup period was more prolonged and lasted up to 48 weeks as buildup and maintenance doses were modified from March 15 to June 30 for tree pollen and grass extracts and from August 15 to November 15 for weed extracts. During these 2 periods, the buildup for the pollens was continued up until 0.2 mL of red vial (1:1 vol/vol), after which the pollen dose was kept at 0.2 mL of red until the end of the season and then continued per protocol. The maintenance dose for the corresponding pollens was also dropped to 0.2 mL of red vial during that period.

The Excel program was built to calculate "behind the scenes" the exact volume required for mixing in each vial the ordered extracts, sterile glycerin, and normal saline, so that the final concentration for each specific extract at a specific dilution was the same for all patients, regardless of how many allergens were mixed together.

In addition, after preliminary analysis of the rate of reactions in period 1, the dilution in the red vial for tree pollen mix was decreased from 1:200 to 1:250 per tree pollen. Ragweed content in red vials was also decreased from a mixture of ragweed short and giant (1:100) in group 1 (which was equivalent to approximately 16-24 mcg/mL depending on the concentration of the bulk commercial ragweed extract), to a defined concentration of 16 mcg/mL of short ragweed, or 8 mcg per maintenance dose in group 2. Hence, in group 2, as ragweed allergen comes in variable concentration for each lot number of commercial extracts, the volume of ragweed extract added was calculated every time a new lot number vial was used, with the goal of maintaining a final concentration of 16 mcg/mL in the red vial.

Glycerin is important for preserving the potency of the extracts but is associated with a stinging sensation.¹¹ The maximum glycerin concentration in group 1 was set up to 19% in the red vials with no extra glycerin added to the vials. The updated JTFPP recommends at least 20% glycerin in the vials if they contained <0.25% phenol.³ As we were able to acquire sterile glycerin in period 2, this was added to the vials in an attempt to achieve better potency preservation of the extracts, so that all vials at all dilutions had a fixed glycerin concentration of 25% ([Table E2](#), available in this article's Online Repository at www.jaci-inpractice.org). The program gave a red signal if the glycerin concentration of a specific combination of extracts chosen by the provider exceeded 19% in group 1 and 25% in group 2 as a result of the glycerin content that was already added by the manufacturer in these extracts. The red signal prompted the provider to modify the order and redistribute the extracts in different vials so that a lower glycerin content is achieved by choosing a different combination of extracts ([Figures E1](#) and [E2](#), available in this article's Online Repository at www.jaci-inpractice.org). Only orders with the appropriate glycerin content were accepted and processed by pharmacy. In group 2, sterile glycerin was added to the vials when needed so that regardless of their dilutions, all had 25% glycerin in them, as calculated by pharmacy. Extracts were obtained from 3 companies: Greer (Lenoir, NC), Hollister-Stier (Spokane, Wash), and ALK (Port Washington, NY). Sterile glycerin was obtained from ALK.

Up to 20 attending physicians ordered SCIT for select patients based on their clinical history and positive allergen-specific skin prick test (SPT), intradermal and/or specific-IgE testing to the above allergens. SPT was performed for individual allergens except for a grass mixture, whereas intradermal testing was performed for either individual or mixed allergens (eg, tree pollen mix, mold mix, or dust mite mix). Patients were examined by a nurse or a physician before dose administration and observed for at least 30 minutes before discharge from clinic. Doses were withheld if patients either reported or showed signs of infection or asthma exacerbation.

Chart review

We performed a chart review for all patients aged 5 to 18 years who were initiated on aeroallergen SCIT at Boston Children's Hospital (BCH) and 4 satellite locations (all within 20 miles radius from Boston). The number of injection visits was calculated by retrieving electronically the SCIT visits that were billed under CPT codes 95117 and 95115. Asthma severity was graded by the ordering provider based on published guidelines.¹² Patients receiving venom immunotherapy or omalizumab were excluded. Patients who initiated SCIT before January 1, 2013, were excluded from group 2 to provide a more accurate comparison between the 2 groups. The BCH Institutional Review Board approved this protocol.

Group 1-no-dose-adjustment. The first chart review was performed for patients who were initiated on SCIT between January 1, 2009, and June 30, 2012 (group 1-no-dose adjustment). After a preliminary analysis revealed that the SR rate was elevated in group 1, the protocol was modified as noted above and the changes were implemented in late 2012.

Group 2-seasonal-dose adjustment. Another chart review was conducted for patients who were initiated on SCIT from January 1, 2013, to June 30, 2016 (group 2-seasonal-dose-adjustment).

Age subgroups. In addition, patients in group 1-no-dose-adjustment and group 2-seasonal-dose-adjustment were further subdivided into 2 age subgroups (5-11 years and 12-18 years).

SR grading

All SCIT SRs and decision on dose adjustments after reactions were discussed during the Monthly Quality Forum meeting at BCH attended by Allergy faculty. A review of the minutes as well as of the charts of patients who reacted was performed, to collect information on the type of reaction, timing, extract, dose injected, and rescue therapy administered. We used the 5-level grading system developed by World Allergy Organization to assess the severity of SR (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).¹³ SRs were classified either as immediate (occurring within 30 minutes) or as delayed (occurring more than 30 minutes after IT administration). SRs were treated with antihistamines, epinephrine, and/or albuterol based on reaction severity and systems involved at the discretion of the supervising attending physician.

Statistical analysis

We characterized patients across group 1-no-dose-adjustment and group 2-seasonal-dose-adjustment using descriptive statistics. Medians (with interquartile and minimum-maximum ranges) and counts (percentages) are exhibited to summarize continuous and categorical variables, respectively. Associations between patient group and categorical variables were assessed using the χ^2 test. The association between patient group and age was assessed using the Wilcoxon 2-sample test. For all modeling of SR rate and association testing for any SR in a patient, we dichotomized levels of asthma severity into a binary variable where asthma of any severity was considered positive for asthma, and no asthma was considered negative. We tested for association of any SR in a patient, to the covariates of patient group, atopic dermatitis, age group, dichotomous asthma, gender, food allergy, and conjunctivitis. We also calculated stratified odds ratios for the remaining covariates while holding either dichotomous asthma or age group constant. We tested a null hypothesis of no association using a χ^2 test or Fisher's exact test where appropriate. SR rates per visit were modeled as a binomial outcome with a multiplicative overdispersion parameter, using a generalized linear mixed regression on the covariates of patient group, atopic dermatitis, age group, dichotomous asthma, gender, food allergy, conjunctivitis, and interaction terms of binary asthma with all other covariates. All estimates of main effects and interactions are partial in the sense of being adjusted for all other effects present in the model. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). All tests were 2-tailed, and a nominal $P < .05$ was used to define the threshold of significance.

RESULTS

Demographics

In group 1-no-dose-adjustment, 128 pediatric patients had a total of 4,194 injection visits, whereas in group 2, 118 pediatric patients had a total of 4,393 injection visits. All patients had allergic rhinitis. There was no significant difference in demographics between group 1 and group 2, including gender (63.3% male in group 1, 61% male in group 2), asthma (67% vs 62%, respectively), allergic conjunctivitis, atopic dermatitis and food allergies, or mean age at SCIT initiation (11.4 vs 12.28 years) (Table I).

Group 1-no-dose-adjustment SRs

In group 1-no-dose-adjustment, there were a total of 18 SRs in 14 patients or 11% of subjects (Table IB). Four patients (28.6%) experienced 2 SRs each. The rate of SR was 0.429% of injection visits. Three (16.7%) of these SRs were grade 1, 13

TABLE I. Demographic data

	5-11 years old	12-18 years old	Total
(A) All patients			
Patients, n (%)	122 (49.6)	124 (50.4)	246 (100)
Age, y (mean $\pm$ SD)	8.56 $\pm$ 1.89	14.51 $\pm$ 2.08	11.56 $\pm$ 3.58
Gender (M), n (%)	84 (68.9)	69 (55.6)	153 (62.2)
Conjunctivitis, n (%)	73 (59.8)	59 (47.6)	130 (52.8)
Asthma, n (%)*	86 (70.5)	73 (58.9)	159 (64.6)
Mild intermittent	56 (65.1)	38 (52)	94 (58.5)
Mild persistent	12 (14)	19 (26)	31 (19.5)
Moderate persistent	15 (17.4)	12 (16.4)	27 (16.9)
Severe persistent	3 (3.5)	4 (5.5)	7 (4.4)
Food allergy, n (%)	54 (44.2)	44 (35.5)	98 (39.8)
Atopic dermatitis, n (%)	45 (36.9)	31 (25)	76 (30.1)
(B) Group 1-no-dose-adjustment			
Patients, n (%)	67 (52)	61 (48)	128 (100)
Age, y (mean $\pm$ SD)	8.5 $\pm$ 1.90	14.5 $\pm$ 2.15	11.4 $\pm$ 43.64
Gender (M), n (%)	45 (67.2)	36 (59)	81 (63.3)
Conjunctivitis, n (%)	34 (51)	24 (39)	58 (45)
Asthma, n (%)	48 (72)	38 (62.3)	86 (67)
Mild intermittent	33 (68.7)	20 (52.6)	53 (61.6)
Mild persistent	6 (12.5)	9 (23.7)	15 (17.4)
Moderate persistent	6 (12.5)	6 (15.8)	12 (14)
Severe persistent	3 (6.3)	3 (7.9)	6 (7)
Food allergy, n (%)	28 (41.8)	20 (32.8)	48 (37.5)
Atopic dermatitis, n (%)	23 (34.3)	16 (26.2)	39 (34.4)
(C) Group 2-seasonal-dose-adjustment			
Patients, n (%)	55 (46.6)	63 (53.4)	118 (100)
Age, y (mean $\pm$ SD)	8.72 $\pm$ 1.82	14.52 $\pm$ 2.03	12.28 $\pm$ 3.53
Gender (M), n (%)	39 (71)	33 (52.3)	72 (61)
Conjunctivitis, n (%)	37 (67.2)	35 (55.6)	72 (61)
Asthma, n (%)	38 (69)	35 (55.5)	73 (62)
Mild intermittent	23 (60.5)	18 (51.4)	41 (56.2)
Mild persistent	6 (15.8)	10 (28.6)	16 (22)
Moderate persistent	9 (23.7)	6 (17)	15 (20.5)
Severe persistent	0 (0)	1 (3)	1 (1.3)
Food allergy, n (%)	26 (47.2)	24 (38)	50 (42.4)
Atopic dermatitis, n (%)	22 (40)	15 (23.8)	37 (31.4)

SD, Standard deviation; SR, systemic reaction.

*Asthma was found to be a risk factor for SR in the 5- to 11-year age group (P value = .0009). All other demographic factors were not significant.

(72.2%) were grade 2, and 2 (11.1%) were grade 3. There was no grade 4 or grade 5 SR (Figure 1). The majority of SRs (15 SR, 83.3%) occurred within 30 minutes, whereas 3 reactions (16.7%) were delayed (Figure 2). Thirteen SRs (72.2%) were treated with epinephrine and antihistamines, whereas the rest received antihistamines and/or albuterol.

The vast majority of SRs (83.3%) occurred in the buildup phase of the protocol. One reaction occurred in the green, 1 in the blue, 3 in the yellow, and 10 (55.6%) in the red phase of the buildup (Figure 3). Three SRs (16.7%) occurred during the maintenance phase. Asthma were more frequent among the 14 subjects who developed SR compared with the whole group 1 population (93% vs 67%, respectively), but this did not reach statistical significance ($P = .09$). Interestingly, asthma was present in all younger patients who developed SR though this was not statistically significant ($P = .094$).

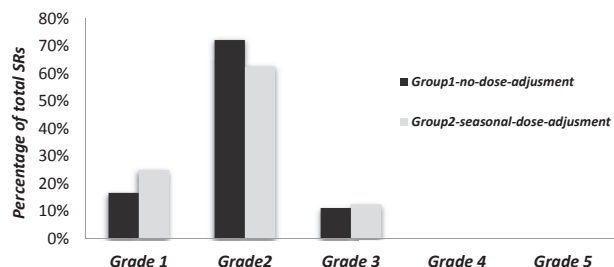


FIGURE 1. The percentage of total SRs for each group, stratified by severity based on WAO criteria. The majority of SRs were grade 2 for both groups. *SR*, Systemic reaction; *WAO*, World Allergy Organization.

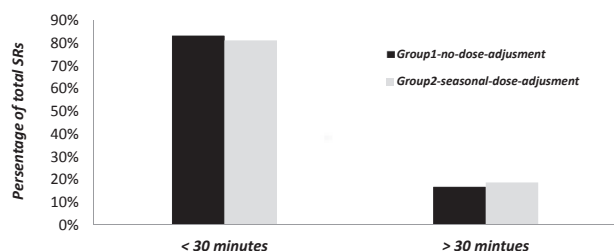


FIGURE 2. Timing of SRs in group 1-no-dose-adjustment and group 2-seasonal-dose-adjustment. Most of SRs occurred in less than 30 minutes after SCIT injection in both groups. *SCIT*, Subcutaneous immunotherapy; *SR*, systemic reaction.

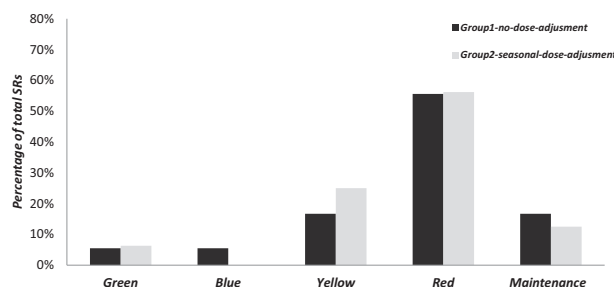


FIGURE 3. Percentage of total SRs within each group, occurring during each phase of the SCIT protocol. The majority of reactions occurred during the buildup phase (green, yellow, blue, and red concentration) for both groups. A total of 55.6% and 56.3% of SRs occurred in the red phase of buildup for group 1 and group 2, respectively. *SCIT*, Subcutaneous immunotherapy; *SR*, systemic reaction.

In addition, the rate of SR was even higher in the 5- to 11-year age subgroup, at 0.52% injection visits compared with 0.340% in the 12- to 18-year subgroup, but this difference did not reach clinical significance ($P = .52$). There was no statistically significant association within a specific age subgroup between SR risk and gender or other atopic conditions.

Group 2-seasonal-dose-adjustment SRs

Thirteen patients (11%) experienced a total of 16 SRs, with a reaction rate of 0.364% of 4,393 injection visits (Table IC).

Three patients (23%) experienced 2 reactions each. Four SRs (25%) were grade 1, 10 (62.5%) were grade 2, and 2 reactions (12.5%) grade 3. Similar to group 1, there were no grade 4 or 5 reactions (Figure 1).

As seen in group 1-no-dose-adjustment, the majority of reactions (81.3%) occurred within 30 minutes, whereas 3 SRs (18.8%) were delayed, occurring more than 30 minutes after SCIT administration (Figure 2). Ten reactions (62.5%) were treated with epinephrine and antihistamines, whereas antihistamines and/or albuterol were administered for the rest.

As seen in group 1, the majority of reactions occurred during buildup. One reaction was observed in green, 4 in the yellow, and 9 reactions (56.3%) occurred during the red buildup phase (Figure 3). Two SRs (12.5%) occurred during the maintenance phase. Atopic conditions including asthma (or asthma severity) were not associated with a statistically increased risk of SR. Similar to group 1, asthma was present in all 5 patients who reacted in the younger age group, though this was not statistically significant ($P = .6034$). On the other hand, only 37.5% of patients who reacted in the 12- to 18-year age group had asthma ($P = .271$). There was also no increased association within a specific age subgroup between risk of SR and atopic conditions.

Comparison between group 1-no-dose-adjustment and group2-seasonal-dose-adjustment

After protocol modification, the rate of SR decreased from 0.429% of injection visits in group 1 to 0.364% of injection visits in group 2. This change however did not achieve statistical significance ($P = .638$). No significant difference in SR timing or severity or in the percentage of patients who reacted was noted between the 2 groups. When combining the 2 groups together, 10.9% of 246 patients reacted and the rate of SR was 0.39% of injection visits. A total of 82.3% occurred within 30 minutes and 20% were delayed. A total of 28 reactions (82%) occurred during buildup, 19 (56%) of which occurred at the highest concentration. There were 6 (18%) maintenance reactions. No specific demographic risk factor, such as gender ($P = .362$), age ($P = .878$), and asthma ($P = .461$), could be associated with the increased risk of reaction. However, when combining patients aged 5 to 11 years from group 1 and group 2, asthma was found to be a significant risk factor for SR ($P = .0009$), unlike in older patients ($P = .889$). All other demographic variables were not significant in the combined age subgroups.

DISCUSSION

The literature is very scarce about the safety of SCIT in the pediatric population. To our knowledge, this is the largest and possibly the first study to evaluate the rate of SR in pediatric patients who are receiving SCIT using a standardized conventional protocol based on the JTFPP. Our study provided some unique aspects, including the use of an Excel program that facilitates dose calculation for allergen mixture and glycerin volumes in pharmacy. This allowed for the option of minimizing the number of injections whenever possible or desired, while abiding with a defined dose for each allergen based on JTFPP recommendations for all patients, regardless of the combination of extracts chosen by the provider. In addition, in group 2, we have standardized all vials regardless of their dilutions so that the glycerin concentration was always 25%, in an attempt to preserve the potency of the vials better and hence minimize variability in

dosing that could occur from potency loss. We also calculated ragweed volume in group 2, so that the final concentration was always 16 mcg/mL in the red vial. Finally, it has a quality improvement aspect that evaluated the effect of seasonal dose adjustments, over similar periods of time of 3½ years each. We found that the rate of SR was higher (0.364% to 0.429% of visits) in our patient population compared with other US studies. In addition, a greater proportion of patients had SR (10.9%), compared with 2% to 5% of patients in most studies and surveys.¹⁴ For example, a large retrospective study on nonfatal SCIT performed over a 20-year period (1981-2000) before JTFPP has shown that the rate of SR was low at 0.06% of 435,854 injections in 5.2% of 4,000 patients for the first 10 years, and 0.01% of injections in 1.08% of patients in the second decade. Data from surveillance in North America reported relatively low rate of SRs at 0.1% to 0.2% of injection visits with a conventional buildup protocol.⁶ Although the survey provides important data related to a very large number of injections in numerous practices in the United States, some of the limitations included voluntary reporting and lack of information on specific allergen used, maintenance doses, updosing protocol, and glycerin content.

More recently, an interesting report by Lim et al¹⁵ showed an SR rate of 0.32% of injections in 120 pediatric patients aged 5 to 17 years compared with 0.17% in 150 adults, in a study that spanned 2 decades from 1995 to 2015 and included a total of 56,457 injections. We have not evaluated the rate of SR using our standardized SCIT protocol in adults. We also cannot exclude that this higher SR rate might have been secondary to the homogeneously standardized doses among all patients that while compliant with JTFPP recommendations may have been more concentrated than commonly used in other practices, even though possibly more reflective of the effect of these recommended doses on SR. Limitations of comparison between studies include the significant variability of SCIT protocols between different practices or academic sites in dose adjustments, extract selection, maintenance doses, and glycerin content in addition to geographic location.¹⁶

Prior studies have suggested that dose adjustment during allergy season may decrease the rate of SR¹⁷ though 2 large studies did not show an increase in SR during the pollen season.^{18,19} In our study, with seasonal dose adjustment, the rate of SR was still higher than what was reported in the United States, and though it decreased compared with group 1, that change was not significantly different. The severity of SR was similar between the 2 groups. The majority of SRs were grade 2 followed by grade 1 in both groups, with no grade 4 or 5 noted. These findings are consistent with prior studies.^{5,6,15} However, as a consequence of dose adjustment and withholding updosing beyond 0.2 cc of reds during these seasons, the duration of updosing was prolonged from 28 to 32 weeks to up to 48 weeks. It is possible that statistical significance could have been reached with a much higher number of patients or injection visits. However, dose adjustment of a specific pollen vial during a corresponding season may also lead to dosing errors, in addition to delays in reaching maintenance dosing and greater number of injection visits to the office. It is not clear based on our results and others that dose adjustment is warranted at all in the general population or more specifically in pediatric patients, or whether it should be restricted to patients who react during the pollen season.²⁰ Larger multisite trials will be required to carefully evaluate such approach.

As for the timing of SR, we found that 82.3% of reactions occurred within 30 minutes of SCIT administration, which is very consistent with findings reported by Bernstein et al⁵ that 86% of reactions were found to be immediate.

Severe persistent asthma was found to be a predictor of increased risk for SR from SCIT.²¹ As seen in the study by Lim et al,¹⁵ the majority of our pediatric patient population was asthmatic (67% in group 1 and 62% in group 2). In our study, asthma was found to be a significant risk factor for SR in the younger age group. Although the rate of SR dropped in this subgroup after protocol modification, this however did not reach statistical significance. Unlike findings by Lim et al that patients aged 5 to 12 years were more likely to have reactions than the teenagers aged 13 to 17 years, there were no significant differences in SR rate between the younger group and the older one in our patient population. Although we evaluated a higher number of patients, Lim et al reported on a much larger number of injections. While we did not find a significant association between severity of asthma, or other atopic conditions and risk of SR, this might have been secondary to an overall small number of reactions. No dose response SCIT studies have been published in the pediatric age group.²² Large safety and efficacy trials with possibly different arms of allergen dosing are needed to evaluate whether pediatric patients in different age subgroups may benefit from lower SCIT dosing compared with adults or even older children.

One limitation of our study is that we could not evaluate the potential effect of compliance on the rate of SR. Another limitation is that patients were receiving allergens mixes, including those who did not undergo formal standardization yet (such as tree pollens, molds, dog, and cockroach).³

In addition, we found that most of the SRs occurred in the last phase of the buildup (red vials). Given the low number of SRs, we could not evaluate well whether coseasonal initiation of SCIT may lead to higher SR rate. A recent systemic review has suggested however that this may not be of significant concern.²³

In conclusion, the current standardized allergen SCIT protocol adopted at BCH appears to be associated with an SR rate of 0.429% to 0.364% of visits in pediatric patients. No significant difference in the rate of SR was found after protocol modification and dose adjustment during pollen seasons. In the younger age group, asthma was a significant risk factor for SR. Larger multicenter studies are required to further evaluate the safety and efficacy of standardized SCIT, the impact of dose adjustment during pollen season, and the presence of demographic risk factors in the pediatric age group. These multicenter studies will require strong scientific designs and careful allergen vial preparations, aiming at minimization of dose variability in between patients, defined glycerin content, strict criteria for reaction severity rating, and careful assessment of compliance, new extract use, uses of mixes versus individual extracts and association of risk factors including asthma and its severity, as well as other atopic conditions.

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ONLINE REPOSITORY

SUPPLEMENT E1: THE ALLERGENS INCLUDED IN SUBCUTANEOUS IMMUNOTHERAPY (SCIT) AND THE VIAL CONCENTRATIONS

Nine tree pollen mix (White Ash, Birch Mix, Maple Mix [Boxelder, Sugar Maple, Red Maple], Mountain Cedar, Eastern Cottonwood, American Elm, Hickory Shagbark, Mulberry mix [Red and White] and Oak mix [Eastern Oak: black, red, white]), 4 grass mix (Kentucky Blue/June, Orchard, Redtop, Timothy), 4 molds mix (*Alternaria*, *Aspergillus niger*, *Cladosporium sphaerospermum*, and *Penicillium chrysogenum*), cat hair, dog, mites mix (DF and DP), 3 weed pollen (Sagebrush, Plantain, and Ragweed), and cockroach. Tree

pollen and weed selection was based on the National Allergy Bureau Count in 2008 in New England. All vials were prepared under the hood in the intravenous sterile preparation area in the Boston Children's Hospital pharmacy. When ordered, molds and cockroach were mixed together in a separate vial, per Joint Task Force on Practice Parameters, because of their protease effect. The other extracts could be mixed in up to 3 different vials. In the text, the silver color refers to the vials with the 1:10,000 vol/vol dilution of maintenance, green to 1:1,000, blue to 1:100, yellow to 1:10, and red to 1:1. In each cohort, when new vials were prepared by pharmacy, the next administered SCIT dose was reduced to 50% of the last dose, followed by a buildup.

Patient First Name

Template

Patient Last Name

Sample

Medical Record Number

Dr. SCIT

Physician Name

Date Ordered

8/9/2017

Children's Hospital Boston Immunotherapy

To Undo any entry, press
CTRL + Z together

Prepare Dilutions:

☒ 1:1 Red

☒ 1:10 Yellow

☒ 1:100 Blue

☒ 1:1,000 Green

☐ 1:10,000 Silver

Vial 1 - Low Proteolytic	Prescribing Detail				Compounding Detail					
	Total Volume (ml)		10		DO NOT MODIFY THIS AREA					
	Maximum Glycerin Concentration (%)		25.0%							
	Antigen Number				Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot	
	1	Cat Hair	BAU/ml	3,000	10,000	3.00	50%	1.5	GTY092834567	
	2	Grass Mix #4	BAU/ml	2,000	10,000	2.00	50%	1.0	C07090904	
	3		-	-	-	0.00	0%	0.0		
	4		-	-	-	0.00	0%	0.0		
	Sub Total Volume (ml)					5.00		2.5		
	Diluent saline (ml)			OK		5.00				
Additional Glycerin	DO NOT USE					0.00	50%	0.0		
Additive contributed Glycerin %			OK			25.0%				
Total Glycerin %				25%		25.0%		2.5		
Vial 2 - Low Proteolytic	Prescribing Detail				Compounding Detail					
	Total Volume (ml)		10		DO NOT MODIFY THIS AREA					
	Concentration (%)		25.0%							
	Antigen Number				Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot	
	1		-	-	-	0.00	0%	0.0		
	2		-	-	-	0.00	0%	0.0		
	3		-	-	-	0.00	0%	0.0		
	4		-	-	-	0.00	0%	0.0		
	Sub Total Volume (ml)					0.00		0.0		
	Diluent saline (ml)			OK		5.00				
Additional Glycerin	DO NOT USE					5.00	50%	2.5		
Additive contributed Glycerin %			OK			0.0%				
Total Glycerin %				25%		25.0%		2.5		
Vial 3 - Low Proteolytic	Prescribing Detail				Compounding Detail					
	Total Volume (ml)		10		DO NOT MODIFY THIS AREA					
	Concentration (%)		25.0%							
	Antigen Number				Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot	
	1		-	-	-	0.00	0%	0.0		
	2		-	-	-	0.00	0%	0.0		
	3		-	-	-	0.00	0%	0.0		
	4		-	-	-	0.00	0%	0.0		
	Sub Total Volume (ml)					0.00		0.0		
	Diluent saline (ml)			OK		5.00				
Additional Glycerin	DO NOT USE					5.00	50%	2.5		
Additive contributed Glycerin %			OK			0.0%				
Total Glycerin %				25%		25.0%		2.5		
Vial - High Proteolytic	Prescribing Detail				Compounding Detail					
	Total Volume (ml)		10		DO NOT MODIFY THIS AREA					
	Concentration (%)		25.0%							
	Antigen Number				Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot	
	1		-	-	-	0.00	0%	0.0		
	2		-	-	-	0.00	0%	0.0		
	Sub Total Volume (ml)					0.00		0.0		
	Diluent saline (ml)			OK		5.00				
	Additional Glycerin	DO NOT USE					5.00	50%	2.5	
	Additive contributed Glycerin %			OK			0.0%			
Total Glycerin %				25%		25.0%		2.5		

Prescriber Signature

Attending Signature

Phone / Pager

/

Date

-

0

-

FIGURE E1. Example of ordering resulting in a glycerin concentration >25%, leading to red signal error.

Patient First Name **Template**

Patient Last Name **Sample**

Medical Record Number **0**

Physician Name **Dr. SCIT**

Date Ordered **8/9/2017**

Children's Hospital Boston Immunotherapy

**To Undo any entry, press
CTRL + Z together**

Prepare Dilutions:

☒ 1:1 Red
 ☐ 1:10 Yellow
 ☒ 1:100 Blue
 ☒ 1:1,000 Green
 ☐ 1:10,000 Silver

Prescribing Detail					Compounding Detail					
Vial 1 - Low Proteolytic	Total Volume (ml)	10				DO NOT MODIFY THIS AREA				
	Maximum Glycerin Concentration (%)	25.0%								
	Antigen Number					Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
	1	Cat Hair	BAU/ml		3,000	10,000	3.00	50%	1.5	GTY092834567
	2	Dog Hair	1:X		100	10	1.00	0%	0.0	C07090903
	3	Mites DF/DP "MIX"	AU/ml		1,000	15,000	0.67	50%	0.3	C07090904
	4		-		-	-	0.00	0%	0.0	
	Sub Total Volume (ml)					4.67		1.8		
	Diluent saline (ml)				OK	4.00				
	Additional Glycerin	DO NOT USE				1.33	50%	0.7		
Additive contributed Glycerin %	OK									
Total Glycerin %				25%	18.3%					
					25.0%			2.5		
Vial 2 - Low Proteolytic	Total Volume (ml)	10				DO NOT MODIFY THIS AREA				
	Concentration (%)	25.0%								
	Antigen Number					Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
	1	Tree Mix #9	1:X		250	130	5.20	23%	1.2	LOT2349876
	2	Grass Mix #4	BAU/ml		2,000	10,000	2.00	50%	1.0	C07090904
	3		-		-	-	0.00	0%	0.0	
	4		-		-	-	0.00	0%	0.0	
	Sub Total Volume (ml)					7.20		2.2		
	Diluent saline (ml)				OK	2.19				
	Additional Glycerin	DO NOT USE				0.61	50%	0.3		
Additive contributed Glycerin %	OK									
Total Glycerin %				25%	22.0%					
					25.0%			2.5		
Vial 3 - Low Proteolytic	Total Volume (ml)	10				DO NOT MODIFY THIS AREA				
	Concentration (%)	25.0%								
	Antigen Number					Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
	1	Sagebrush	1:X		100	10	1.00	0%	0.0	C07090902
	2	Ragweed Short	AU/ml		16	300	0.53	50%	0.3	C07090908
	3		-		-	-	0.00	0%	0.0	
	4		-		-	-	0.00	0%	0.0	
	Sub Total Volume (ml)					1.53		0.3		
	Diluent saline (ml)				OK	4.00				
	Additional Glycerin	DO NOT USE				4.47	50%	2.2		
Additive contributed Glycerin %	OK									
Total Glycerin %				25%	2.7%					
					25.0%			2.5		
Vial - High Proteolytic	Total Volume (ml)	10				DO NOT MODIFY THIS AREA				
	Concentration (%)	25.0%								
	Antigen Number					Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
	1		-		-	-	0.00	0%	0.0	
	2		-		-	-	0.00	0%	0.0	
	Sub Total Volume (ml)					0.00		0.0		
	Diluent saline (ml)				OK	5.00				
	Additional Glycerin	DO NOT USE				5.00	50%	2.5		
	Additive contributed Glycerin %				OK					
	Total Glycerin %				25%	0.0%				
					25.0%			2.5		

Prescriber Signature _____

Attending Signature _____

Phone / Pager _____

Date _____

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FIGURE E2. Example of extracts ordered allowing for glycerin concentration of 25%. Program shows examples of calculated volumes of bulk extracts, normal saline, and glycerin added in red vial.

TABLE E1. Conventional buildup protocol schedule

Silver 1:10,00	Green 1:1,000	Blue 1:100	Yellow 1:10	Red 1:1
0.1	0.1	0.1	0.05	0.05
0.2	0.2	0.2	0.1	0.07
0.4	0.4	0.3	0.2	0.1
0.5	0.5	0.4	0.25	0.15
		0.5	0.3	0.2
			0.35	0.25
			0.4	0.3
			0.45	0.35
			0.5	0.4
				0.45
				0.5

TABLE E2. IT extract and glycerin concentration in group 1 and group 2

	Standardized IT red vial concentration or dilution in group 1	Standardized IT red vial concentration or dilution in group 2
Dust mite mix*	2,000 AU/mL	2,000 AU/mL
Cat hair	3,000 BAU/mL	3,000 BAU/mL
Dog	1:100	1:100
Cockroach	1:100	1:100
Grass†	2,000 BAU/mL	2,000 BAU/mL
Ragweed‡	1:100 (final dose variable 12-24 mcg/mL)	16 mcg/mL
Plantain weed	1:100	1:100
Sagebrush weed	1:100	1:100
Molds mix§	1:150	1:150
Tree pollens	1:200	1:250
Glycerin¶	Up to 19%	25%

*Dust mite mix DF and DP (1000 AU/mL for each extract).

†Grass mix#4 (Kentucky Blue/June, Orchard, Redtop, Timothy; 500 BAU/mL for each extract).

‡Ragweed short and giant in group 1; Ragweed short in group 2.

§Mold mix 1:150 dilution for each mold.

||Tree pollen mix: White Ash, Birch Mix, Maple Mix (Boxelder, Sugar Maple, Red Maple), Mountain Cedar, Eastern Cottonwood, American Elm, Hickory Shagbark, Mulberry mix (Red and White) and Oak mix (Eastern Oak: black, red, white); 1:200 dilution for each pollen in group 1, and 1:250 dilution for each pollen in group 2.

¶Glycerin content: up to 19% in red vials in group 1, 25% of all vials at any dilution in group 2.

TABLE E3. World Allergy Organization (WAO) grading of systemic reaction severity

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
Grade 2	Asthma responding to an inhaled bronchodilator and/or gastrointestinal symptoms, including abdominal cramps, vomiting, or diarrhea, or uterine
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
Grade 5	Fatal reaction

Patient First Name
Patient Last Name
Medical Record Number
Physician Name
Date Ordered

Template
Sample
0
Dr. SCIT
8/9/2017

Children's Hospital Boston Immunotherapy
To Undo any entry, press
CTRL + Z together

Prepare Dilutions:

☒ 1:1 Red ☒ 1:10 Yellow ☒ 1:100 Blue ☒ 1:1,000 Green ☐ 1:10,000 Silver

Prescribing Detail				
Total Volume (ml)	10			
Maximum Glycerin Concentration (%)	25.0%			
Antigen Number				
1	Cat Hair	BAU/ml	3,000	
2	Dog Hair	1:X	100	
3	Mites DF/DP "MIX"	AU/ml	1,000	
4		-	-	
Sub Total Volume (ml)				
Diluent saline (ml)				OK
Additional Glycerin	DO NOT USE			
Additive contributed Glycerin %				OK
Total Glycerin %			25%	

Vial 1 - Low Proteolytic

Compounding Detail				
DO NOT MODIFY THIS AREA				
Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
10,000	3.00	50%	1.5	GTY092834567
10	1.00	0%	0.0	C07090903
15,000	0.67	50%	0.3	C07090904
-	0.00	0%	0.0	
	4.67		1.8	
	4.00			
	1.33	50%	0.7	
	18.3%			
	25.0%		2.5	

Total Volume (ml)	10			
Concentration (%)	25.0%			
Antigen Number				
1	Tree Mix #9	1:X	250	
2	Grass Mix #4	BAU/ml	2,000	
3		-	-	
4		-	-	
Sub Total Volume (ml)				
Diluent saline (ml)				OK
Additional Glycerin	DO NOT USE			
Additive contributed Glycerin %				OK
Total Glycerin %			25%	

Vial 2 - Low Proteolytic

DO NOT MODIFY THIS AREA				
Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
130	5.20	23%	1.2	LOT2349876
10,000	2.00	50%	1.0	C07090904
-	0.00	0%	0.0	
-	0.00	0%	0.0	
-	7.20		2.2	
	2.19			
	0.61	50%	0.3	
	22.0%			
	25.0%		2.5	

Total Volume (ml)	10			
Concentration (%)	25.0%			
Antigen Number				
1	Sagebrush	1:X	100	
2	Ragweed Short	AU/ml	16	
3		-	-	
4		-	-	
Sub Total Volume (ml)				
Diluent saline (ml)				OK
Additional Glycerin	DO NOT USE			
Additive contributed Glycerin %				OK
Total Glycerin %			25%	

Vial 3 - Low Proteolytic

DO NOT MODIFY THIS AREA				
Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
10	1.00	0%	0.0	C07090902
300	0.53	50%	0.3	C07090908
-	0.00	0%	0.0	
-	0.00	0%	0.0	
	1.53		0.3	
	4.00			
	4.47	50%	2.2	
	2.7%			
	25.0%		2.5	

Total Volume (ml)	10			
Concentration (%)	25.0%			
Antigen Number				
1		-	-	
2		-	-	
Sub Total Volume (ml)				
Diluent saline (ml)				OK
Additional Glycerin	DO NOT USE			
Additive contributed Glycerin %				OK
Total Glycerin %			25%	

Vial - High Proteolytic

DO NOT MODIFY THIS AREA				
Manufacturer Concentration (AU / ML or BAU / ml or Ratio - X)	Additive Volume (ml)	Glycerin	Contributed glycerin volume	Manufacturer Lot
-	0.00	0%	0.0	
-	0.00	0%	0.0	
	5.00		0.0	
	5.00	50%	2.5	
	0.0%			
	25.0%		2.5	

Prescriber Signature _____

Attending Signature _____

Phone / Pager _____

Date _____

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