

Pro/Con Review

Are Allergen Immunotherapy Dose Adjustments Needed for Local Reactions, Peaks of Season, or Gaps in Treatment?

Tolly E. Epstein, MD, MS^{a,b}, and Mike S. Tankersley, MD^c *Cincinnati, Ohio; Indianapolis, Ind; and Memphis, Tenn*

INTRODUCTION

We have been asked to debate the merits of dose adjustments for local reactions (LRs), pollen seasons, and gaps in therapy for subcutaneous allergen immunotherapy (SCIT). As allergists are aware, SCIT is a highly effective therapy for allergic rhinitis, asthma, atopic dermatitis, and stinging insect hypersensitivity. Severe and life-threatening events due to SCIT appear to be declining and are relatively rare, but they do occur.¹⁻⁵ Since 1973, at least 84 fatalities from SCIT in the United States and Canada have been reported.¹⁻⁸ There have been at least 4 confirmed fatalities since 2008, with 2 of these occurring under the care of allergists.^{4,5} Based on data from the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology (AAAAI/ACAAI) national surveillance study, systemic reactions (SRs) occur in 0.1% of injection visits, and there were at least 63 World Allergy Organization grade 4 SCIT reactions between 2012 and 2013.⁵ Given that the significant benefits of SCIT are coupled with very real risks of adverse outcomes, allergists must evaluate strategies that will balance both sides of this equation.

ALLERGEN IMMUNOTHERAPY DOSE ADJUSTMENTS ARE NEEDED FOR LRs

Pro position

Disclosure: This is not necessarily my own opinion.

Given the risk of severe and potentially life-threatening reactions from SCIT, prescribers should take a conservative approach to minimize risks. This includes lowering doses and/or slowing down the build-up after LRs, and especially with large local reactions (LLRs) to SCIT. The immunotherapy practice parameters state that “Published studies indicate that individual local reactions do not appear to be predictive of subsequent

systemic reactions”; however, they also admit that “some patients with a greater frequency of large local reactions might be at an increased risk of future systemic reactions.”⁹

More than 90% of allergists adjust doses after LRs. Reasons for adjustment that are commonly cited include concern that LRs cause discomfort that lead to patient noncompliance (88.9%), concern that LRs are predictive of future LRs (45.7%), and concern that LRs are predictive of future SRs (29.2%).¹⁰ One of the difficulties in interpreting the literature for LRs is that definitions for LRs versus LLRs vary. Small LRs have recently been defined as erythema and/or swelling of more than 5 mm and less than or equal to the size of the patient’s palm at 30 minutes, or just any reaction that is smaller than the palm of the hand.^{11,12} LLRs have variably been defined as more than 25 mm induration for at least 12 hours, more than 20 mm for at least 24 hours, more than 40 mm, or larger than the patient’s palm.^{13,14} In a survey of 249 patients who were active-duty or retired military personnel and their spouses and children, the authors reported that 71% experienced LRs, but that 96% would not stop SCIT because of LRs; however, only 20.3% of these reactions were larger than the palm of the hand. Even with the majority of reactions not meeting the definition for LLRs in this study, 13.6% of patients found reactions moderately bothersome and 5.1% found them extremely bothersome.¹²

Tankersley may attempt to dissuade practitioners from concerns regarding LRs based on data from retrospective studies that include LRs of various sizes. Regarding whether LRs predict future LRs, Tankersley may argue that only 27% of LRs (of all sizes) are followed by another LR, and 6% of LLRs are followed by another LLR.¹¹ However, in that same publication, Calabria et al¹¹ admit that “future studies measuring the ability of local reactions of a specific size (i.e., 50 mm and so forth) to predict local reactions would further add to the local reaction and immunotherapy literature.” Tankersley may also present data indicating that LRs do not predict SRs with the next injection; however, in a retrospective review of a large multicenter allergy practice that adjusts doses for LLRs (defined as >25 mm, the size of a quarter), patients with SRs experienced LLRs in 35.2% of visits versus 8.9% of visits in a group matched for age, sex, and allergen sensitivity ($P < .001$).¹⁵ In that study, although 33% of the SRs were immediately preceded by an LLR, individual LLRs were not predictive of future SRs with the next dose, but LLRs preceded SRs in approximately one-third of cases. In another retrospective 1-year, single-site study involving 360 patients, those experiencing SRs were also more likely to have experienced LLRs, defined as larger than the patient’s palm. In that study, of those patients who experienced an LLR, 41.7% also experienced an SR, whereas only 10.7% of non-LLR patients had an SR.¹⁶ Tankersley may also argue that studies have found that

^aDivision of Immunology, Allergy, and Rheumatology, Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

^bAllergy Partners of Central Indiana, Indianapolis, Ind

^cDivision of Allergy and Immunology, Department of Pediatrics, Le Bonheur Children’s Medical Center, University of Tennessee Health Science Center, Memphis, Tenn

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication November 22, 2016; revised April 10, 2017; accepted for publication April 13, 2017.

Available online ■■

Corresponding author: Mike S. Tankersley, MD, Division of Allergy and Immunology, Le Bonheur Children’s Medical Center, University of Tennessee Health Science Center, 51 North Dunlap, Ste 400, Memphis, TN 38105. E-mail: mtankers6@uthsc.edu.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.04.022>

Abbreviations used

AAAAI/ACAAI- American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology

LR- Local reaction

LLR- Large local reaction

SCIT- Subcutaneous immunotherapy

SR- Systemic reaction

reducing doses with LLRs does not decrease SR rates; however, the practice parameters acknowledge insufficient data in this area and state that “Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy modification on them are needed.”⁹

In conclusion, we should adjust doses for LR, and especially for LLRs, to SCIT, given that (1) we do not have extensive prospective, multicenter data from which to draw firm conclusions; (2) various cutoff points used to define LR and LLRs confound interpretation of existing literature; and (3) there is a potential link between increased rates of LLRs and SRs for some patients. If more than 90% of allergists adjust doses after LR, could all these allergists be wrong? See Table I for a summary of the Pro position.

Con position

Disclosure: I have not routinely dose adjusted for LR since 1998.

I agree with Epstein that, as allergists, we should implement conservative measures to minimize SR risks for our patients. However, any measure undertaken should be evidence-based so that in an effort to provide benefit we do not actually create harm to those we serve. Over the last 2 decades a significant amount of literature has accumulated that clearly lays out 4 reasons that allergists should not routinely dose adjust for LR.

First, LR are not predictive of SRs. Allergists have historically considered an LR to be a flashing yellow traffic light warning us to yield and “do something” to avoid an impending SR with a future SCIT injection. In the 1990s, we found among our SCIT population at Wilford Hall in San Antonio, Texas, that we had several patients who could never attain a maintenance dose because of our dose adjustment protocol for LR. Thus, we designed a protocol to prospectively evaluate over a 9-month period whether a no-dose adjustment schedule for LR impacted SR rates compared with the previous 9 months before the initiation of this study.¹⁷ In this prospective study, SR rates were not significantly different, with a rate of 0.8% under the dose adjustment schedule (65 SRs/8076 injections) and 1.1% under the no-dose adjustment schedule (49 SRs/4850 injections) ($P = .24$). See Figure 1. This study was significant because it was the first to specifically evaluate what happens at the injection visit immediately following an LR. The sensitivity of an LR predicting an SR was only 15% and the positive predictive value of an LR predicting an SR was also poor at 17%. The inability of an LR to predict an SR has also been supported in another prospective study,¹⁸ and 2 additional studies have had the same conclusions.^{19,20} Finally, the above referenced REPEAT study by Calabria was notable for 3 reasons: (1) a no-dose adjustment protocol was followed for LLRs, (2) it was only in a subpopulation of patients with LLR that an increased SR rate was seen (58.3% of patients who had an LLR never had an SR), and (3)

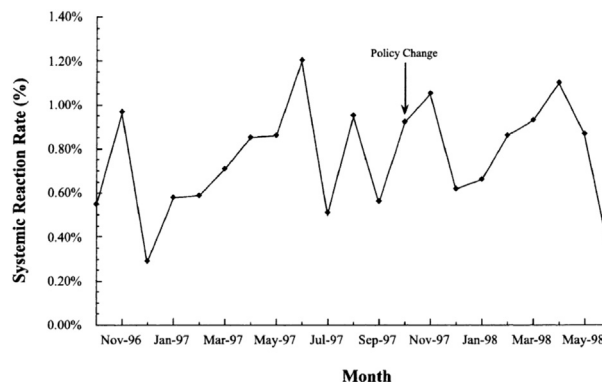


FIGURE 1. Monthly rates of systemic reactions after allergen injections.¹⁷ Dose adjustment for LR was discontinued on October 1, 1997.

patients with 1 or more LLR did not have an increased SR risk.¹⁶ Thus, the LLR-SR association is seen among a subpopulation of patients with LLR regardless of whether you adjust the dose or not, so why dose adjust?

Second, LR are not predictive of LR.⁹ Some allergists justify a dose adjustment due to concerns that an LR predicts a subsequent, potentially larger, LR, and so adjust doses to prevent a subsequent LR.¹⁰ In the LOCAL study, both sensitivity (26.2%) and positive predictive value (27.2%) for an LR predicting a subsequent LR were poor.¹¹ It was actually the specificity of the absence of an LR predicting the absence of a subsequent LR that was more reliable (85.5%). Again, though well intended by the allergist, dose adjusting for an LR should not be used to prevent an LR at the next injection.

Third, LR are not bothersome to patients. Although almost 90% of allergists reported dose adjusting for LR due to a concern that patient discomfort would lead to noncompliance,¹⁰ when we asked 249 patients on SCIT at our clinic (100% response rate) the overwhelming majority (81.9%) deemed their LR not bothersome at all or only slightly bothersome.¹² Because dose adjustments increase patient visits and costs, a dose adjustment protocol may more likely result in an unintended decrease in compliance. Unnecessarily increasing visits and costs is bothersome to patients.

Fourth, LR are an uncommon reason that patients discontinue SCIT. Again, although noncompliance is a concern for allergists,¹⁰ 96% of patients stated they would not stop SCIT because of LR.¹² In addition, when 381 active SCIT charts from a military medical center were analyzed under a no-dose adjustment protocol for LR and noncompliant patients were contacted, inconvenience (34.5%) was the single most important reason for discontinuation.²¹ LR were an uncommon reason for discontinuation and reported as a reason in only 5.5% of those who stopped SCIT. Of interest, there was a high compliance rate (77.4%) under this no-dose adjustment for LR protocol. These military data are applicable to all practice types.²²

In light of this extensive literature, why would allergists continue to dose adjust for LR? The evidence supports that SCIT dose adjustments are not needed for LR. Dose adjustments for LR delay achievement of a therapeutic dose, increase costs, introduce additional visits, create inconvenience, decrease compliance, and put the patient at increased risk of

TABLE I. Allergen immunotherapy dose adjustments are needed for LRs

Pro
• Lack of prospective, multicenter data to dispute the perceived impact of LRs^{9,11} • Various cutoff points used to define LRs and LLRs confound interpretation of literature¹¹⁻¹⁴ • Potential link between increased rates of LLRs and SR^{9,15,16}
Con
• LRs are not predictive of SRs¹⁶⁻²⁰ • LRs are not predictive of LRs^{9,11} • LRs are not bothersome to patients¹² • LRs are an uncommon reason that patients discontinue immunotherapy^{12,21}

administration errors.¹⁰⁻¹⁴ Proper education of both office staff and patients on LRs results in an increased comfort level by all with a standing no-dose adjustment protocol within the clinic.^{11,12} See Table I for a summary of the Con position.

ALLERGEN IMMUNOTHERAPY DOSE ADJUSTMENTS ARE NEEDED FOR PEAKS OF SEASON

Pro position

Disclosure: I have worked in practices that do not adjust doses for peak seasons, practices that adjust only in the most sensitive patients, and practices that adjust for all patients who are sensitive to a particular allergen.

In a survey of 1201 AAAAI members in 2012, it was found that 40% of practices routinely adjusted doses during pollen seasons.²³ Practitioners with more than 10 years in practice were more likely to adjust doses (43% vs 28%; $P = .001$), suggesting that more experienced practitioners had found value in adjusting doses for pollen seasons in their practice. Nonacademic practices and practices with more than 100 SCIT patients were more likely to adjust doses ($P = .001$). Among 513 practices surveyed between 2012 and 2013 by the AAAAI/ACAAI national surveillance study, 12% of practices always adjusted doses during peak pollen seasons, with fewer practices in the South US (4%) adjusting doses ($P = .04$).³

Tankersley may argue that there is no increased risk for SRs during peak pollen seasons. However, there are limitations with all studies that have been conducted regarding the occurrence of SRs during pollen seasons. Smaller, single-site studies may be too small to find significant differences, and may not be applicable to other parts of the country. Larger, national studies combine data from geographic locations with different types and lengths of pollen seasons, which may dilute findings. In addition, both smaller and larger studies have been confounded by existing dose adjustment patterns (ie, practitioners already reducing doses during peak seasons).

I would argue that we should be most concerned about the data for severe and fatal reactions. Based on retrospective surveys summarizing 34 fatal SCIT reactions that occurred before 2005, 47% of fatalities occurred during a pollen season to which the patient was sensitized.^{7,8} See Table II. A similar survey regarding 68 near-fatal reactions found that 46% of reactions occurred at the height of the allergy season (ie, when a particular allergen was pollenating based on practitioners' reporting).²⁴ Peak pollen

TABLE II. Factors implicated in fatal SCIT reactions ($n = 34$)^{7,8}

1. Uncontrolled asthma	62%
2. Prior SR	53%
3. Pollen season	47%
4. Epinephrine delay, not given	43%
5. Dosing/administration errors	35%
6. None reported	17%
7. Inadequate waiting period	12%
8. Reaction began after 30 min	9%
9. Home administration	9%
10. Beta-blockers/ACE inhibitors	2%/2%

ACE, Angiotensin-converting enzyme.

TABLE III. Factors implicated in near-fatal SCIT reactions ($n = 68$)²⁴

1. Height of allergy season	46%
2. Dosing/administration errors	25% (3 intramuscular)
3. Uncontrolled asthma	10%
4. Prior SR	9%
5. Epinephrine delay/not given	6%
6. Inadequate wait after shot given	3%
7. Beta-blockers/ACE inhibitors	3%
8. Late-onset reactions, >30 min	4%

ACE, Angiotensin-converting enzyme.

TABLE IV. Allergen immunotherapy dose adjustments are needed for peaks of season

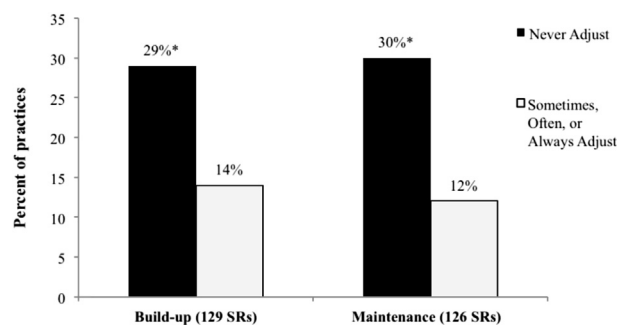
Pro
• Most studies have not found differences in SR rates during particular pollen seasons, but confounded by limitations of study design^{9,25-27} • Pollen seasons are a major risk factor for fatal and near-fatal reactions^{4,7,8,24} • Surveillance data indicate a reduced risk for severe SRs among practices that reduce or do not increase doses during peak pollen seasons, particularly among highly sensitive patients³⁻⁵
Con
• SRs are not increased during the pollen season^{9,25-27} • Administration of therapeutic doses during the pollen season is not a risk factor for severe reactions^{9,25-27} • Seasonal dose adjustments delay achievement of therapeutic doses^{11,13,17} • Seasonal dose adjustments diminish therapeutic efficacy of all allergens^{11,13,17}

season was the single biggest risk factor for near-fatal SCIT reactions in that study.²⁴ See Table III. A recent fatality reported in 2014 also occurred during weed pollen season in an individual who was highly sensitized to weeds.⁴

Data from the AAAAI/ACAAI national surveillance study indicate that lowering or not increasing doses during peak pollen seasons may lower the risk of severe SRs. This study asks practitioners to prospectively gather data regarding SRs in their practice annually, then compiles data from each practice at the end of every year. The study found that among 272 practices (5.2 million injection visits) between 2010 and 2011, practices

TABLE V. Allergen immunotherapy dose adjustments are needed for gaps in treatment

Pro	- Supported by solid theoretical rational given understanding of the process of induction of tolerance^{9,29-32} - Almost universally accepted because of clinical experience, despite lack of studies due to ethical concerns^{9,28}
Con	- Dose adjustments prolong the time to a therapeutic maintenance dose^{13,17} - Dose adjustments create a logistical burden to patient^{13,33} - Dose adjustments result in an economic burden to patient^{13,17} - Dose adjustments result in decreased patient compliance^{13,33}

**FIGURE 2.** The percentage of practices that experienced at least 1 grade 3 or 4 SR based on whether they dose adjusted during peak pollen seasons (2011-2012). Complete data were available for 268 practices.⁴ * $P < .001$ for the percentage of practices that experienced at least 1 grade 3 or 4 SR (WAO system) in those that never adjusted doses versus those that sometimes, often, or always adjusted doses. WAO, World Allergy Organization.

that always reduced or leveled off doses (did not increase doses) during peak pollen seasons were significantly less likely to report any grade 2 or 3 (moderate or severe) SRs (44% vs 65% that often, sometimes, or never reduced doses; $P < .05$).³ This finding was reproduced in 2011-2012 in 235 practices (4.3 million injection visits), with significantly increased rates of grade 3 or 4 (severe or very severe) SRs seen among practices that never reduced or leveled off doses during peak pollens seasons ($P < .001$).⁴ A similar effect was seen for both build-up and maintenance vials in that study. See Figure 2.

One of the questions that often arise is whether we need to adjust doses during peak seasons in all patients who are sensitized to a particular pollen, or whether there are certain patient characteristics that should guide us in this regard. Based on data from the national surveillance study in 2012-2013 involving 392 practices (5.6 million injection visits), 63% of practices leveled off doses for patients who had experienced SRs during a particular pollen season in the past, 27% leveled off doses in patients who had highly positive skin test results that corresponded to a particular pollen season, and 10% leveled off doses regardless of sensitization pattern, vial contents, or history of SRs.⁵ The study found that leveling off doses in patients with highly positive skin test results corresponding with a particular pollen season was the only strategy that was significantly associated with a decrease in SRs, and it impacted SRs of all severity grades ($P < .05$).⁵

Tankersley may argue that data in favor of dose adjustment should be disregarded because they are “survey data,” and that other practice patterns could have affected results. Nevertheless, I would argue that these data are representative of what is being done in the “real” world by a broad-spectrum of practices across the United States, and are less prone to recall bias than other retrospective studies given that participants are requested to gather data at the time SRs occur, and data are compiled annually by study staff. In addition, there is no evidence that practices that do not increase doses during pollen seasons are prescribing lower maintenance doses of standard allergens overall. Tankersley may also raise concerns that reducing or holding doses during pollen seasons will negatively impact therapeutic efficacy. Although slower build-up may prolong achievement of maintenance dosing for the price of increased safety, patients do still achieve maintenance.

In conclusion, it is true that most studies have not found differences in SR rates during particular pollen seasons, but multiple confounding factors may have impacted results. Peak pollen seasons, particular in highly sensitive patients, have been shown to be a significant risk factor for fatal and near-fatal reactions. The national AAAAI/ACAAI survey also repeatedly found that not increasing doses during pollen seasons was associated with lower severe SRs, particularly among highly sensitive patients. Practitioners must therefore balance safety concerns with convenience factors and the rate at which therapeutic efficacy can be achieved. See Table IV for a summary of the Pro position.

Con position

Disclosure: I have never dose adjusted for peaks of season, not even once in 20 years of practice.

Given the inherent limitations with surveys, I would like to share the prospective studies that serve as the basis for my position. As stated in the practice parameter, “several published studies have not found an association between pollen seasons and systemic reactions,”⁹ SCIT dose adjustments are not needed for peaks of season.

In a prospective study within the Atlanta Allergy Clinic with 9 allergists at 9 locations, 4578 patients with 162,436 injection visits and 346,251 injections were evaluated. The results of this SCIT cohort showed no direct correlation between pollen counts and the occurrence of SRs. The authors stated that there was no correlation between SRs and pollen seasons. Rather, more SRs occurred when the pollen counts were relatively low.²⁵ A second prospective study from 1976 to 1989 investigated 4810 patients who received 513,368 injections.²⁶ The 3 most important factors associated with SRs were type of allergen, rate of increase, and patient sensitivity. No increased incidence of SRs was seen during grass or ragweed season. The authors concluded there was no evidence of an association with increased SRs during pollen seasons in their study. Finally, in a third prospective study with 423 patients and 17,526 SCIT doses, there was a 0.3% SR rate over a 13-month period during 1996-1997.²⁷ The authors reported that a higher ratio of SRs was not found during pollen seasons although allergen concentrations in vials had significantly increased during these periods. Of note, build-up doses were left unchanged and only maintenance doses were cut 50% during pollen seasons. Interestingly, 40% of SRs could have been prevented if SCIT had been stopped after a patient had their third SR (“three strikes and yer out”).

TABLE VI. Sample SCIT build-up dose adjustment protocol

- 1-14 d—increase according to schedule
- 15-28 d—repeat last dose
- 29-35 d—decrease by 1 dose
- 36-42 d—decrease by 2 doses
- 43-49 d—decrease by 3 doses
- 50-56 d—decrease by 4 doses
- 57-84 d—decrease by 1 vial, same volume
- 85-112 d—decrease by 2 vials, same volume
- >112 d—start all over (eg, 0.05 mL 1:1000 v/v, green vial)

As seen in these 3 separate prospective studies, SRs are not increased during pollen seasons and the administration of therapeutic doses during pollen seasons is not a risk factor for SRs. Seasonal dose adjustments delay achievement of therapeutic doses, may diminish therapeutic efficacy of all allergens, and are unnecessary. See [Table IV](#) for a summary of the Con position.

ALLERGEN IMMUNOTHERAPY DOSE ADJUSTMENTS ARE NEEDED FOR GAPS IN TREATMENT

Pro position

Disclosure: I have always adjusted doses for gaps in therapy.

The practice parameters state, “There is no retrospective or prospective published evidence to support modification of doses of allergen immunotherapy because of treatment gaps during the build-up or maintenance phases. However, it is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged.”⁹ An example from the parameters is given for missed doses during build-up on weekly or biweekly injections as follows: if a patient has missed 8 to 13 days, then they receive the same dose as previous; for 14 to 21 days, the dose is reduced by 25%; and for 21 to 28 days, the dose is reduced by 50%, etc. The main reason for a lack of evidence supporting this strategy is that the need for adjustment is almost universally accepted and most practitioners would consider it unethical to put patients at risk for SRs by not reducing doses after gaps in therapy.

An interesting study worth mentioning is Vervloet et al’s²⁸ 1980 article where 64 physicians were, in their words, “interrogated” regarding their 19,739 patients who had received 151,997 injections. The SR rate among this group was 0.1% (155 SRs), with 50% of the SRs resulting from “errors” such as a change of vials (old to new) in 27%, errors in vial or dosage in 10%, and an interval between injections that was either too short (defined as <5 days) or too long (>3 months) in 4%. There were no fatalities in this study. This study highlights the need for dose adjustments for vial changes (old to new) and potentially gaps in therapy.

Anecdotally on the basis of my own clinical experience, I see more LLRs and SRs after a gap in therapy with both build-up and maintenance vials; this risk appears to go down when doses are decreased then built back up. The theoretical reasoning behind dose adjustment for gaps in therapy is sound. Given that the process to achieve tolerance requires prolonged, stepwise, increasing exposure to an antigen, it is logical that if a patient is not exposed to an antigen for a sufficient period of time during the build-up phase they may not achieve or lose tolerance to that

TABLE VII. Sample SCIT maintenance dose adjustment protocol

- 1-42 d—repeat maintenance dose
- 43-49 d—decrease by 1 dose
- 50-56 d—decrease by 2 doses
- 57-63 d—decrease by 3 doses
- 64-70 d—decrease by 4 doses
- 71-84 d—decrease by 1 vial, same volume
- 85-112 d—decrease by 2 vials, same volume
- >112 d—start all over (eg, 0.05 mL 1:1000 v/v, green vial)

particular dose of the antigen. We know that T-cell tolerance with induction of regulatory T-cell responses does not happen in a matter of weeks of exposure, but after months to years.²⁹ This implies that brief exposure to an antigen is not enough to induce long-term tolerance, and that longer term, regular exposure is required. We also know from clinical studies that it takes at least 3 years on SCIT before long-term tolerance to aeroallergens is achieved.³⁰⁻³² Patients whose treatment is interrupted before they have achieved long-term tolerance (<3 years) are therefore at risk for a relapse in symptoms and increased risk of SRs. See [Table V](#) for a summary of the Pro position.

Con position

Disclosure: I routinely dose adjust for gaps in treatment so will suggest a less conservative dose adjustment.

Although SCIT dose adjustments are needed for gaps in treatment, Epstein has rightly stated from the practice parameters that there have never been any published studies comparing different dose adjustment schedules for these gaps. In my own practice for the last 2 decades, I have used a separate dose adjustment schedule for build-up ([Table VI](#)) and maintenance ([Table VII](#)) SCIT dosing. The advantage of protocols such as these 2 is that the nursing staff have a road map for dose adjustments. I suspect that all allergists have similar clinic protocols that their SCIT staff use given the regularity of noncompliance with SCIT. Anecdotal experience shapes our practice with these protocols and, as Epstein has shared from her own anecdotal experience, allergists then form opinions on the basis of their experience. However, anecdotal experience does not equate to evidence-based medicine, so this specific area of dose adjustments is ripe for study.

Two allergists using the same protocols in [Tables VI](#) and [VII](#) may actually be executing very different plans if their schedules ([Table VIII](#)) are different (eg, an A schedule would move a patient through a vial in 4 injections, whereas an E schedule would do it in 10 injections). If this patient was on schedule E for their 1:1 v/v red maintenance vial and it had been 50 to 56 days since they received their last injection of 0.4 mL, they would have their dose decreased 4 doses per [Table VI](#) to 0.2 mL. However, if the patient was on a B schedule, their dose would be decreased 4 doses to 0.05 mL. Some allergists, on the basis of reference from the practice parameter, might choose to use a percentage decrease (eg, 25%); however, this method can be time consuming and result in varying dose adjustments by the nursing staff given the higher math involved with some doses. Thus, one can see how both the build-up schedule and the dose adjustment schedule pair together to produce variability in the dose that goes into the patient’s arm at the visit after the break in therapy.

Regarding new vials, the practice parameters make several comments: “The dose generally is the same with each injection,

TABLE VIII. Sample SCIT build-up schedules

Schedule A	Schedule B	Schedule C	Schedule D	Schedule E
0.05 mL	0.05 mL	0.05 mL	0.05 mL	0.05 mL
0.15 mL	0.10 mL	0.07 mL	0.07 mL	0.07 mL
0.25 mL	0.20 mL	0.10 mL	0.10 mL	0.10 mL
0.50 mL	0.30 mL	0.20 mL	0.15 mL	0.15 mL
	0.40 mL	0.30 mL	0.20 mL	0.20 mL
	0.50 mL	0.40 mL	0.25 mL	0.25 mL
		0.50 mL	0.30 mL	0.30 mL
			0.40 mL	0.35 mL
			0.50 mL	0.40 mL
				0.45 mL
				0.50 mL

although modifications can be made based on several variables (i.e., new vials); risk factors for immunotherapy that have been identified include...injections from new vials; instructions on adjustments that might be necessary under the following circumstances: when providing patients with new vials” and “recognize that dosage adjustments downward are usually necessary with a newly prepared allergen immunotherapy extract.”⁹ We agree on a need to dose adjust but just do not have current data to demonstrate one dose adjustment protocol to be superior over another. Although a traditional dose adjustment may be a 50% decrease in the dose, this creates patient disadvantages such as delivery of a subtherapeutic dose and a logistical and economic burden on the patient to build back up to the maintenance dose, which could take up to 5 visits (eg, using an E schedule in Table VIII). Waibel et al³³ have reported an alternative to this traditional dose adjustment in the form of a cluster schedule. Two cluster doses of 0.25 mL with the new vial were given 30 minutes apart. This 2-step, cluster method was well tolerated with high satisfaction by both pediatric and adult patients on aeroallergen SCIT. This regimen provided a therapeutic dose at the visit, created a minimal logistical burden (an extra 30 minutes), and a resulted in a decreased economic burden to the patient.

Another paradigm to consider as a model for dose adjusting for gaps in therapy would be the pregnant patient on SCIT. The practice parameter supports continuation of SCIT during the build-up phase at a dose that is likely to be therapeutic, but the dose is usually not increased. I typically have these patients then go to once monthly injections at their current dose until they deliver. Allergists might consider using this same paradigm for all patients in the build-up phase but at doses likely to be therapeutic. Thus, a break in therapy would default to a less conservative adjustment like Table VII rather than the more conservative adjustment used during build-up in Table VI. This would result in a patient coming in 36 days from their last 1:1 v/v red vial 0.2 mL dose receiving the same 0.2 mL dose rather than dropping back 2 doses.

Finally, allergists should consider the venom SCIT paradigm of spreading maintenance injections out to every 8 weeks after 2 years of therapy. Although not recommending this spacing for routine therapeutic dosing, a patient who has been on an aeroallergen SCIT maintenance dose for 18 to 24 months who has an 8-week gap in therapy would just have the maintenance dose repeated rather than decreasing it by 2 doses as recommended by

the example in Table VII. See Table V for a summary of the Con position.

SUMMARY AND CONCLUSIONS

There is universal agreement on the following: (1) allergists currently perform dose adjustments whether it be for LR, pollen seasons, or gaps in treatment; (2) allergists differ in which clinical situations they dose adjust; (3) allergists differ in strategies for and how much they dose adjust; and (4) there is no published evidence to support modification of doses because of treatment gaps during build-up or maintenance phases of SCIT. Because the ultimate goal of SCIT is to achieve a therapeutic maintenance dose in a safe and timely manner, it is imperative that our community continue to encourage evidence-based practices. Large practices with uniform SCIT dosing may be good settings to conduct safety studies comparing not only dose adjustment schedules but also build-up schedules; however, national data from multiple centers that account for geographic variability and provide adequate numbers of patients and severe SRs from which to draw conclusions are also needed. Allergists need look no further than our own history of administering whole-body extract with flying Hymenoptera venom, which was ultimately found to be no more effective than placebo, to realize that just because everyone is doing it does not make it right.³⁴ Because the ultimate goal of SCIT is to achieve a therapeutic maintenance dose in a safe and timely manner, it is imperative that our community continue to investigate and encourage evidence-based practices.

REFERENCES

- Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 2010;104:530-5.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy: year 2. *Ann Allergy Asthma Immunol* 2011;107:426-431.e1.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110:274-278.e1.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract* 2014;2:161-7.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: national surveillance study on allergen immunotherapy (2008-2013). *Ann Allergy Asthma Immunol* 2016;116:354-359.e2.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993;92:6-15.
- Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
- Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127:S1-55.
- Coop CA, Tankersley MS. Dose adjustment practices among allergists for local reactions to immunotherapy. *Ann Allergy Asthma Immunol* 2007;99:77-81.
- Calabria CW, Coop CA, Tankersley MS. The LOCAL study: local reactions do not predict local reactions in allergen immunotherapy. *J Allergy Clin Immunol* 2009;124:739-44.

12. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. *Ann Allergy Asthma Immunol* 2008;101:96-100.
13. Tankersley MS. How should allergists deal with local reactions to allergen immunotherapy? *Curr Allergy Asthma Rep* 2011;11:115-21.
14. Lieberman P, Tankersley M. Significance of large local reactions that occur during allergen immunotherapy. *J Allergy Clin Immunol Pract* 2015;3:310-1.
15. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;99:82-6.
16. 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;106:49-53.
17. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol* 2000;106:840-3.
18. Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. *Ann Allergy* 1986;56:331-4.
19. 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;92:225-7.
20. Tankersley MS. Dose adjustments are unnecessary for local reactions occurring at immunotherapy satellite clinics. *J Allergy Clin Immunol* 2004;113:S111.
21. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol* 2002;88:391-4.
22. Tankersley MS. I'm not strange, I'm just like you. *Ann Allergy Asthma Immunol* 2013;110:131-2.
23. Ponda P, Mithani S, Kopyltsova Y, Sison C, Gupta P, Larenas D, et al. Allergen immunotherapy practice patterns: a worldwide survey. *Ann Allergy Asthma Immunol* 2012;108:454-459.e7.
24. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:169-75.
25. Tinkelman DG, Cole WQ III, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995;95:8-14.
26. Lin MS, Tanner E, Lynn J, Friday GA Jr. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. *Ann Allergy* 1993;71:557-62.
27. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy* 2004;34:527-31.
28. Vervloet D, Khairallah E, Arnaud A, Charpin J. A prospective national study of the safety of immunotherapy. *Clin Allergy* 1980;10:59-64.
29. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2011;127:18-27.
30. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
31. Des Roches A, Paradis L, Knani J, Hejjoui A, Dhivert H, Chanez P, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, V: duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;51:430-3.
32. Naclerio RM, Proud D, Moylan B, Balcer S, Freidhoff L, Kagey-Sobotka A, et al. A double-blind study of the discontinuation of ragweed immunotherapy. *J Allergy Clin Immunol* 1997;100:293-300.
33. Waibel KH, Owens TJ, Crisp HC, Gomez RA. Clinical and immunologic assessment of a cluster method during allergen immunotherapy refill dosing. *J Allergy Clin Immunol Pract* 2014;2:793-4.
34. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.