

# Efficacy of epinephrine and diphenhydramine rinses in decreasing local reactions to subcutaneous aeroallergen immunotherapy

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## ABSTRACT

**Background:** Although local reactions (LR) to subcutaneous immunotherapy (SCIT) occur in 26–86% of patients, there are no well-studied strategies to manage LRs.

**Objective:** To complete a prospective, randomized, single-blind, controlled trial that compared pre-rinsing SCIT syringes with diphenhydramine, epinephrine, or placebo in patients who were receiving aeroallergen SCIT and experiencing LRs despite pretreatment with an antihistamine.

**Methods:** Patients ages  $\geq 5$  years who were receiving aeroallergen SCIT per a conventional dosing schedule and who were experiencing LRs despite premedicating with an oral antihistamine were randomized to diphenhydramine, epinephrine, or placebo rinse, and were followed up for three subsequent visits. At each visit, the patients were asked (yes or no) if LRs improved.

**Results:** A total of 490 patients were enrolled in the study. Seventy-four of the 490 patients (15.1%) experienced an LR despite pretreatment with an oral antihistamine and were randomized into an intervention group. At visit 1, an epinephrine rinse was strongly associated with decreasing LR compared with both diphenhydramine rinse and placebo ( $p < 0.001$ ). There was no difference among the intervention groups at visits 2 and 3. In patients who reported a consistent outcome at all three visits, the epinephrine rinse was significantly associated with a decrease in LR compared with both diphenhydramine rinse and placebo rinse ( $p = 0.05$ ).

**Conclusion:** In patients who received aeroallergen SCIT per a conventional dosing schedule, an epinephrine rinse significantly decreased LR at the first visit, and also within a population that reported a consistent outcome at all three study visits. In patients already premedicating with an oral antihistamine, adding an epinephrine rinse is a safe and effective strategy to decrease LRs to aeroallergen SCIT.

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Subcutaneous immunotherapy (SCIT) to aeroallergens, introduced >100 years ago by Freeman and Noon,<sup>1</sup> is an important and distinguishing therapeutic option in the practice of allergy-immunology. SCIT is an effective, disease-modifying therapy for allergic rhinitis, allergic conjunctivitis, allergic asthma, and, in some cases, atopic dermatitis.<sup>2</sup> SCIT has been shown to improve symptoms, have a medication-

sparing effect for allergic rhinitis and asthma,<sup>3,4</sup> and to potentially improve symptoms in patients with atopic dermatitis triggered by aeroallergens.<sup>5,6</sup> SCIT induces a state of tolerance to aeroallergen(s) by causing a shift from a T-helper type 2 to a T-helper type 1 immune response.<sup>7</sup> Patients who completed a course of SCIT have improved quality of life<sup>8,9</sup> and decreased health-care costs for the care of their atopic conditions.<sup>10,11</sup>

The benefits of SCIT come with the risk of both systemic reactions (SR) and local reactions (LR).<sup>2</sup> Although SRs are a more serious clinical scenario and are the reason for monitoring patients with SCIT in a medical setting after SCIT administration, LRs more commonly impact patients. LRs, depending on the cited study, affect 26–86% of patients who receive SCIT.<sup>12–15</sup> LRs can result in pain, pruritus, erythema, warmth, and edema at the injection site.<sup>16</sup> It is our experience that LRs may be a source of concern for patients and are a common reason that they contact the office for treatment advice. It is generally accepted that LRs do not predict SRs,<sup>17</sup> but an increased rate of SRs has been shown in patients who experience LRs.<sup>18</sup> A survey of 249 patients undergoing immunotherapy found that,

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although many patients experienced LR, most would not stop immunotherapy due to these LR.<sup>12</sup>

Even if patients continue SCIT despite LR, LR occur frequently and can lead to bothersome symptoms, which raises the question of how to best address them. Antihistamines have been shown to be effective in decreasing LR in cluster immunotherapy<sup>19</sup> and in venom immunotherapy<sup>20–22</sup> but have not been evaluated in aeroallergen immunotherapy administered with a conventional dosing protocol. A study of 15 patients on the use of leukotriene modifiers for preventing LR in Venom immunotherapy (VIT) showed modest efficacy.<sup>23</sup> Downward dose adjustment for LR is also a management strategy, but this has been largely examined in the context of preventing SRs, as discussed above.<sup>24</sup>

Other strategies for addressing LR include the use of a dry needle, alternating injection sites, split dosing, stretching the skin before injection, cold compresses at the injection site, nonsteroidal anti-inflammatory drug treatment, and reformulating allergen immunotherapy (AIT) concentration, although robust data for these strategies are lacking.<sup>12</sup> Another less commonly used strategy for decreasing LR is to pre-rinse the AIT syringe with either diphenhydramine or epinephrine. Although there are no controlled studies to our knowledge that support this practice, this strategy has been used by a small number of allergy practices.<sup>2</sup> We sought to assess the efficacy of pre-rinsing AIT syringes with either diphenhydramine or epinephrine in reducing LR to aeroallergen SCIT through a prospective, randomized, single-blind, placebo controlled trial in patients ages  $\geq 5$  years who received SCIT with a conventional dosing protocol.

## METHODS

The study was conducted at the Rochester Regional Health outpatient allergy practice in Rochester, New York, from August 2016 through January 2019, and was approved by the Rochester Regional Health's local institutional review board (approval CIC 1662-B-16 Ramsey). There were four full-time and two part-time allergists in the practice who saw patients in three office locations. Three of the six physicians participated in this study. SCIT was administered in recommended doses from the American Academy of Allergy, Asthma, and Immunology (AAAAI) practice parameters.<sup>2</sup> Extracts for immunotherapy were supplied by Greer (Lenoir, NC). The standardized office build-up protocol consisted of 21 steps (Table 1), with patients coming every 2–14 days for build-up dosing and every 28 days for maintenance dosing, up to a maximum interval of 35 days. After 35 days, dosing was adjusted to account for lateness.

All the patients ages  $\geq 5$  years who started SCIT were offered enrollment in the study. Patients receiving venom immunotherapy or SCIT per the cluster dosing

Table 1 Subcutaneous immunotherapy build-up protocol

1:1000, mL	1:100, mL	1:10, mL	1:1, mL
0.05			
0.1	0.1	0.1	0.1
0.2	0.2	0.2	0.2
0.3	0.3	0.3	0.3
0.4	0.4	0.4	0.4
0.5	0.5	0.5	0.5*

\*The usual maintenance dose is 0.5 mL of 1:1 concentration; build-up dosing was administered every 2–14 days.

schedule and pregnant patients were excluded. Once enrolled, the patients were instructed to premedicate with a second-generation antihistamine (loratadine, cetirizine, fexofenadine, levocetirizine, desloratadine) if they experienced an LR to SCIT after their previous visit. An LR to SCIT was defined as any bothersome symptoms, according to the patients, at the injection site, including pruritus, erythema, and/or swelling.

If a subject reported an LR despite premedication with an antihistamine, he or she was randomized per Microsoft Excel software (Microsoft Corp., Redmond, WA) to receive a diphenhydramine, epinephrine, or placebo rinse with his or her next three injections. The patients, but not the study staff, were blinded to the intervention. The subjects were then asked at their subsequent three visits if symptoms of LR were adequately improved (yes or no) with the addition of the rinse. Doses of SCIT were not adjusted downward for LR. Information collected from the enrolled patients included age, gender, type and number of aeroallergen groups included in immunotherapy extracts, number of injections, dose at which the subject experienced the LR, and the presence or absence of asthma. Aeroallergen groups were defined as the following: cat, dog, dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*), roach, trees, grasses, weeds, and molds.

The technique for administering SCIT with a rinse was as follows: 1 mL of diphenhydramine, epinephrine, or placebo (sterile water) was drawn up into a 27-gauge, one-half-inch-long syringe used to administer SCIT. Once the syringe was coated in the rinse, the rinse was discarded. The coated syringe was then used to draw up the desired dose of the allergy extracts. The extracts were then injected into the subcutaneous tissue of the upper arm per usual technique.<sup>2</sup> All the patients were monitored for 30 minutes per standard recommendations<sup>2</sup> and were asked to self-monitor for ensuing LR.

## Statistical Analysis

Statistical analysis was performed by using STATA software (StataCorp LLC, College Station, TX). At

baseline, the Kruskal-Wallis test was used to compare the baseline median age. The  $\chi^2$  test was used to compare the frequencies of the baseline variables among the intervention groups. The  $\chi^2$  test was also used to identify associations between outcomes and intervention groups (diphenhydramine, epinephrine and placebo).

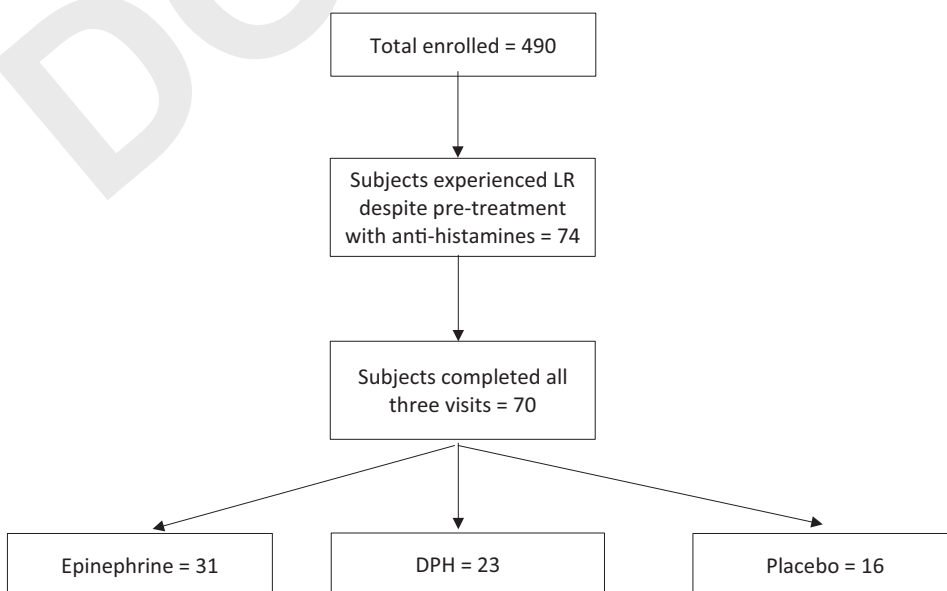
## RESULTS

Over a 29-month period from August 2016 to January 2019, 490 patients were consented for the study. Of these 490 patients, 74 (15.1%) experienced an LR despite pretreatment with an oral antihistamine and were randomized into one of three intervention groups (diphenhydramine, epinephrine, placebo) (Fig. 1). Seventy of the 74 patients (94.6%) completed all three study visits and were included in the statistical analysis. The four patients who were not included in the analysis did not continue with SCIT. Baseline characteristics are presented in Table 2. The mean age of the patients was  $30.6 \pm 16.3$  years, with a range from 7 to 69 years. Of the 70 patients, 46 (65.7%) were females. Twenty-seven patients (34.3%) had asthma. The mean (SD) number of aeroallergens per group was  $4.7 \pm 1.6$ . The median dose at which the subjects experienced an LR despite pretreatment with an oral antihistamine was dose 16 (1:10, 0.5 mL) (IQ: dose 11 [1:100, 0.5 mL] to dose 19 [1:1, 0.3 mL]). The median (IQ) numbers of injections per visit were 2.0 (1–2), with 21 patients who received one injection, 40 received two injections, and 9 received three injections. With the exception of an unequal distribution of patients who received SCIT to weeds, there were no statistically significant differences among the three groups. Trees were the most commonly included aeroallergen group, included in 59 of 70 (84.3%) of SCIT extracts. In order of decreasing

frequency, the other aeroallergen groups included in SCIT extracts were weeds in 5 of 70 (81.4%), dust mites in 53 of 70 (75.7%), grasses in 52 of 70 (74.3%), cat in 42 of 70 (60.0%), molds in 29 of 70 (41.4%), dog in 27 of 70 (38.6%), and roach in 5 of 70 (7.1%).

At visit 1, 32 of 35 subjects in the epinephrine group (91.4%) reported an improvement in LRs compared with 16 of 25 subjects (64%) in the diphenhydramine group, and 5 of 18 subjects (27.8%) in the placebo group. The epinephrine rinse, therefore, was strongly associated with decreasing LRs compared with both the diphenhydramine rinse and placebo ( $p < 0.001$ ) (Fig. 2). At visits 2 and 3, although there was not a statistically significant difference among the intervention groups, there was a nonsignificant trend toward improvement, which was most notable in the epinephrine group.

Of the 70 subjects, 41 reported a consistent outcome at all three study visits (*i.e.*, the intervention helped at all three visits or the intervention did not help at any of the three visits). Twenty-two of 31 subjects (71.0%) in the epinephrine group reported a consistent outcome at all three visits compared with 14 of 23 (60.9%) who reported a consistent outcome in the diphenhydramine group compared with only 5 of 16 subjects (31.3%) in the placebo group who reported a consistent outcome. When only evaluating subjects with a consistent outcome, 21 of 22 subjects (95.5%) in the epinephrine group reported an improvement in LRs compared with 9 of 14 subjects (64.3%) in the diphenhydramine group and with 1 of 5 subjects (20%) in the placebo group. The epinephrine rinse, therefore, was strongly associated with a decrease in LRs compared with both the diphenhydramine rinse and placebo rinse throughout the duration of the three study visits ( $p = 0.001$ ) (Fig. 3). No difference was detected between the diphenhydramine rinse and the placebo rinse. None



**Figure 1.** Study enrollment and group assignments. DPH = diphenhydramine.

Table 2 Demographics of the study population

	Placebo	Epinephrine	Diphenhydramine	Total
Number of subjects	16	31	23	70
Age, $\pm$ SD, y	28.1 $\pm$ 14.3	30.4 $\pm$ 15.6	32.6 $\pm$ 18.6	30.6 $\pm$ 16.3
Female subjects, no. (%)	12 (75.0)	19 (61.3)	15 (65.%)	46 (65.7)
Asthma, no. (%)	8 (50)	7 (22.6)	12 (52.2)	27 (34.3)
No. injections (mean number of injections $\pm$ SD)	1.6 $\pm$ 0.5	1.9 $\pm$ 0.7	1.9 $\pm$ 0.6	1.8 $\pm$ 0.6
Dose at intervention (1:10), mL	0.3	0.4	0.4	0.4
No. allergenic groups, no. (%)	4.2 $\pm$ 1.5	4.7 $\pm$ 1.4	4.9 $\pm$ 1.8	4.7 $\pm$ 1.6
Cat	9 (56.3)	18 (58.1)	15 (65.2)	42 (60.0)
Dog	5 (31.3)	11 (35.5)	11 (47.8)	27 (38.6)
Mites	12 (75)	22 (71.0)	19 (82.6)	53 (75.7)
Roach	1 (6.3)	4 (12.9)	0 (0)	5 (7.1)
Trees	13 (81.3)	26 (83.9)	20 (87.0)	59 (84.3)
Grasses	12 (75)	23 (74.2)	17 (73.9)	52 (74.3)
Weeds*	9 (56.3)	29 (93.5)	19 (82.6)	57 (81.4)
Molds	6 (37.5)	12 (38.7)	11 (47.8)	29 (41.4)

SD = Standard deviation.

\*Unequal distribution of weeds among the groups,  $p < 0.05$ .

of the 70 subjects reported any adverse effects in any of the three intervention groups. There were no SRs to SCIT in the study cohort.

## DISCUSSION

To our knowledge, this was the first prospective, randomized controlled study to evaluate the efficacy of either the diphenhydramine or epinephrine rinse to decrease LR to conventional aeroallergen SCIT in

patients already premedicating with antihistamines. Analysis of our data showed that the epinephrine rinse was associated with a decrease in LR compared with diphenhydramine and placebo at the first visit after implementation. The epinephrine rinse was also superior to the diphenhydramine and placebo rinses in individuals who reported a consistent outcome at all three study visits.

LRs have been estimated to occur in 26–82% of patients who receive SCIT.<sup>12</sup> Although it is unclear

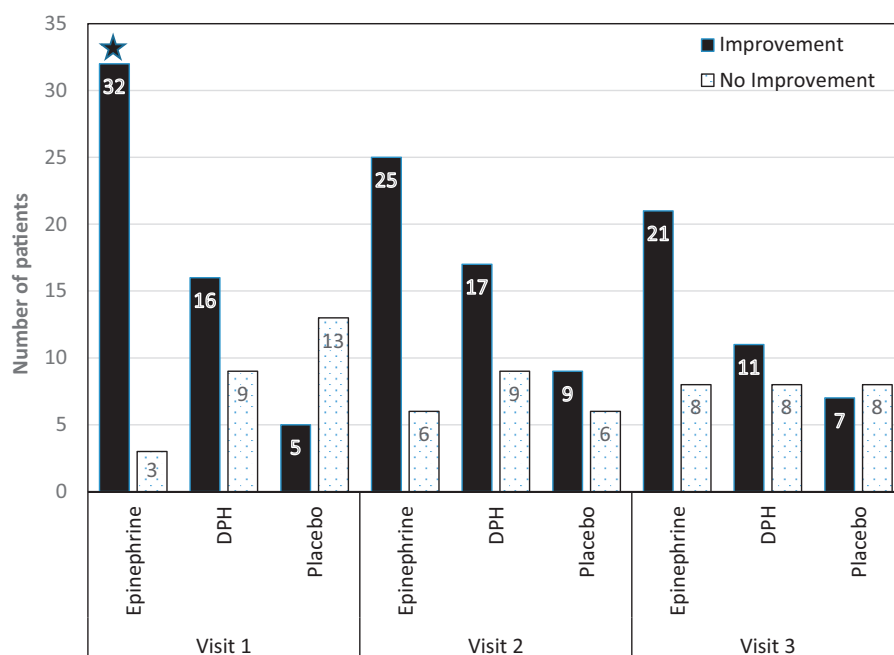
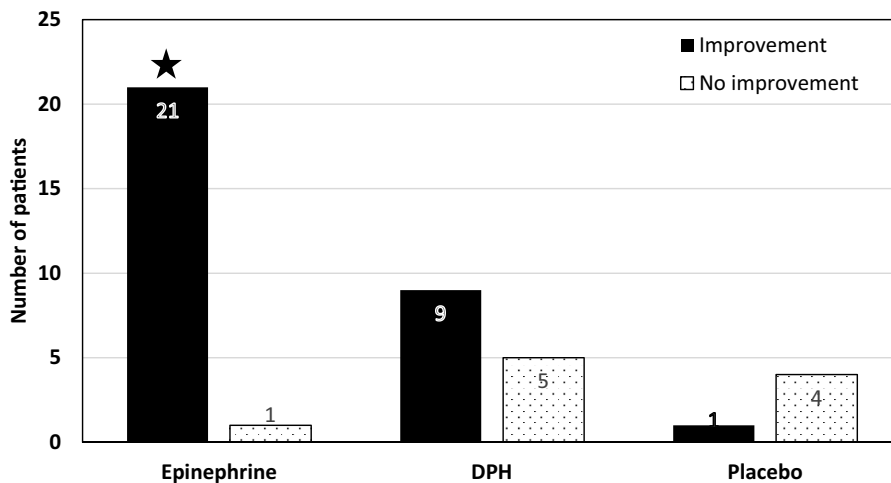


Figure 2. Outcomes of the study population stratified by visit and group assignment. ★ $p < 0.001$ ,  $\chi^2$  test. DPH = diphenhydramine.





**Figure 3.** Outcomes for consistent responders in study stratified by assignment group. ★ $p=0.001$ ,  $\chi^2$  test. DPH = diphenhydramine.

why there is a wide range of reported LRs, it is likely related to the heterogeneous manner in which LRs are defined,<sup>12</sup> type of dosing schedule used, or type of immunotherapy administered. In our study, the rate of LRs not responsive to premedication with an antihistamine was 15.1%. We suspected that this rate of LRs was lower than those previously reported because patients who responded to antihistamines were not randomized. We hypothesized that premedication with an antihistamine was an effective initial intervention in many patients who experience an LR, which has been demonstrated in venom immunotherapy.<sup>22</sup>

In our study, the epinephrine rinse was statistically superior to both diphenhydramine and placebo at visit 1, with a trend toward improvement at visits 2 and 3. This finding was similar to studies that evaluated the efficacy of premedication with systemic antihistamines for LRs to venom immunotherapy, which demonstrated an early benefit in treating erythema, edema, and pruritus, without this effect persisting.<sup>22</sup> There is a retrospective analysis that examined the addition of epinephrine rinses for SCIT in 72 patients that demonstrated a significant reduction in the frequency of LRs, consistent with our findings.<sup>25</sup> However, this uncontrolled study only included patients on maintenance SCIT, whereas the majority of LRs occurred during the build-up phase of SCIT in our study.

There is a paucity of data that looked at other techniques to diminish LRs, including dose splitting, stretching the skin, cold compresses, alternating injection sites, premedication with nonsteroidal anti-inflammatory drugs, and the “dry needle” technique, and these techniques are largely anecdotal in nature.<sup>26</sup> Premedication with acetaminophen or ibuprofen may decrease local swelling and/or redness with childhood vaccination<sup>27</sup> but has not been evaluated with SCIT. The dry needle technique involves discarding the needle used to draw up extracts and then

using a new needle to administer SCIT. A single study of survey-only data that evaluated this technique demonstrated a reduction in LR size. However, there was no comparison from one visit to the next, no control group, and only a reported perception of utility.<sup>28</sup>

The efficacy of an epinephrine rinse may be related to its local vasoconstrictive properties through alpha-1 receptor agonism, which thus decreases local swelling, and possibly results in slower allergen absorption. Our study may underestimate the beneficial effect of epinephrine rinses because the majority of the patients were enrolled in the build-up phase, and the patients received increased doses of SCIT without dose adjustment for LRs. A sustained effect of an epinephrine rinse may have occurred if only the maintenance phase of SCIT was studied. The lack of efficacy of a diphenhydramine rinse may be due to masking the potential benefit of the rinse due to concurrent premedication with a systemic antihistamine.

Previous studies showed that LRs have a varying effect on patients’ impression of SCIT.<sup>12,29</sup> One study<sup>29</sup> revealed that 81.4% of patients found LRs slightly or not bothersome; however, most of these LRs were small, so this may have impacted findings. Ninety-six percent of these patients reported that they would continue immunotherapy despite LRs.<sup>12</sup> Similarly, another study reported that LRs led to nonadherence with SCIT in 5.5% of patients.<sup>29</sup> Our intervention was a well-tolerated, low-risk intervention that addressed a consideration that patients may have in discontinuing SCIT. Downward dose adjustment is a strategy used to decrease LRs, despite an absence of supporting literature. The epinephrine rinse offers the benefit of addressing a bothersome LR without cutting back on the dose of immunotherapy, when a dose adjustment would increase the number of required visits and thus possibly increase patient burden.<sup>25</sup> A previous study

reported that copayments were the reason that 40% of patients were nonadherent with SCIT.<sup>30</sup> Minimizing patient visits for SCIT, therefore, may play an important role in patient satisfaction and adherence.

We believe that our study had several strengths, including that it was the first study to evaluate treatments for LR with a conventional dosing schedule of SCIT with a placebo controlled, single-blind design in which the patients were followed up over three consecutive visits. Our study was performed in a real-world setting and included a heterogeneous group of patients who received SCIT for both allergic rhinoconjunctivitis and allergic asthma. Our study design evaluated the efficacy of syringe rinses only after LR persisted despite pretreatment with a systemic antihistamine, which is a commonly accepted first-line treatment for LR.<sup>16–18</sup>

Despite these strengths, we also acknowledge limitations to the study. Our data would be stronger with a larger sample size. Enrollment was slower than expected because pretreatment with antihistamines obviated the need for a rinse, and, therefore, our randomization was geared toward 200 patients, so this explained the inequality among our groups in the randomization. Our study was also limited in that our staff was not blinded to the treatment effect. We attempted to mitigate this shortcoming by asking standardized questions at each study visit. Our study did not have a strict definition for LR and left this up to patient interpretation.

Although this may have led to variable interpretations of LR by the patients, we believed that these LR were still clinically relevant in the real-world setting, along with the fact that there is significant heterogeneity with previous definitions of LR in the literature. An additional limitation was that the patients reported effectiveness of the study intervention at the next SCIT visit, which could be up to 35 days after the intervention. This lengthy interval period could lead to recall bias with regard to previous symptoms of an LR. Also, our data may not be generalizable to other practice populations given the significant variation in SCIT dosing and content among other allergy practices.

## CONCLUSION

To our knowledge, this was the first prospective, placebo controlled study to evaluate an intervention to improve LR during a conventional dosing schedule of SCIT. We evaluated the efficacy of using an epinephrine or diphenhydramine rinse to decrease an LR that persisted despite pretreatment with a systemic antihistamine. We demonstrated benefit with an epinephrine rinse at the first visit as well as with patients who reported a consistent outcome at all three study visits. The epinephrine rinse was well tolerated, with no

reported adverse effects. Analysis of our study data provides allergists with an efficacious and safe strategy to decrease LR to SCIT.

## REFERENCES

- Freeman J, Noon L. Further observations of the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet*. 1911; II:814–817.
- 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(Suppl):S1–S55.
- Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection therapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007; (1):CD00936.
- Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010; (4): CD001186.
- Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J Allergy Clin Immunol*. 2006; 118:1292–1298.
- Werfel T, Breuer K, Rüeff F, Przybilla B, Worm M, Grewe M, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy*. 2006; 61:202–205.
- Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. *J Allergy Clin Immunol*. 2004; 113:1025–1034.
- Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017; 72:1825–1848.
- Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol*. 2011; 128:791–799.e6.
- Brüggenjürgen B, Reinhold T, Brehler R, Laake E, Wiese G, Machate U, et al. Cost-effectiveness of specific subcutaneous immunotherapy in patients with allergic rhinitis and allergic asthma. *Ann Allergy Asthma Immunol*. 2008; 101:316–324.
- Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess*. 2013; 17: vi, xi–xiv, 1–322.
- Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. *Ann Allergy Asthma Immunol*. 2008; 101:96–100.
- Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. *Ann Allergy*. 1986; 56:331–334.
- Prigal SJ. A ten-year study of repository injections of allergens: local reactions and their management. *Ann Allergy*. 1972; 30:529–535.
- Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. *J Allergy Clin Immunol*. 2000; 106:840–843.
- James C, Bernstein D. Allergen immunotherapy: an updated review of safety. *Curr Opin Allergy Clin Immunol*. 2017; 17:55–59.
- Calabria CW, Coop CA, Tankersley MS. The LOCAL Study: local reactions do not predict local reactions in allergen immunotherapy. *J Allergy Clin Immunol*. 2009; 124:739–744.
- 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; 99:82–86.

19. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol.* 1996; 97:1207–1213.
20. Berchtold E, Maibach R, Müller U. Reduction of side effects from rush immunotherapy with honey bee venom by pretreatment with terfenadine. *Clin Exp Allergy.* 1992; 22:59–65.
21. Reimers A, Hari Y, Müller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. *Allergy.* 2000; 55:484–488.
22. Brockow K, Kiehn M, Riethmüller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 1997; 100:458–463.
23. Wohrl S, Gamper S, Hemmer W, Heinze G, Stingl G, Kinaciyan T. Premedication with montelukast reduces local reactions of allergen immunotherapy. *Int Arch Allergy Immunol.* 2007; 144:137–142.
24. 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.
25. Casselman K, Kim Y, Peppers B, Hostofer R, Tcheurekdjian H. Effectiveness of epinephrine rinses in decreasing local reactions in subcutaneous immunotherapy. *Ann Allergy Asthma Immunol.* 2016; 117:S22eS124 P072.
26. Coop CA. Local reactions from subcutaneous allergen immunotherapy. *Immunotherapy.* 2013; 5:1339–1345.
27. Das RR, Panigrahi I, Naik SS. The effect of prophylactic antipyretic administration on post-vaccination adverse reactions and antibody response in children: a systematic review. *PLoS One.* 2014; 9:e106629.
28. Coop C, Yip S, Tankersley M. The dry needle technique. *Ann Allergy Asthma Immunol.* 2014; 113:120–121.
29. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. *Ann Allergy Asthma Immunol.* 2002; 88:391–394.
30. Vaswani R, Garg A, Parikh L, Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. *Ann Allergy Asthma Immunol.* 2015; 115:241–243. □

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