

A 10-year experience of a novel and safe modified environmental rush immunotherapy protocol

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ABSTRACT

Background: Allergen immunotherapy (AIT) is an effective treatment option for allergic rhinitis. Although conventional AIT takes 6 months to reach maintenance dosing, rush AIT accelerates the build-up period and reaches the maintenance dose months earlier. However, accelerated schedules of AIT carry an increased risk of systemic reactions (SR).

Objective: We aimed to describe a novel 1-day, eight-step modified environmental rush immunotherapy (MERIT) protocol, characteristics of the patients who underwent this therapy, and the safety of this procedure. We also compared distinguishing features of those patients with SRs.

Methods: We retrospectively analyzed demographic and clinical data of 362 adult patients seen in an outpatient university allergy clinic, from January 2005 to January 2015, and who underwent MERIT protocol treatment for allergic rhinitis.

Results: In a univariate analysis, the factors significantly associated with SR were lower body mass index (BMI); younger age; a higher number of allergens in the extracts; and the presence of cat, dust mite, and certain weed pollens. In a multivariate analysis, cat, dust mite, and mugwort were significantly associated with SRs. Over the 10-year period, 50 patients experienced SRs (13.81%), with a total number of 68 SRs. Only 4.7% of the SRs occurred on the MERIT day. Most SRs occurred >30 minutes and were mild. Our MERIT protocol continuation rate for all the patients was 49.2% and did not seem to be influenced by having an SR versus no SR.

Conclusion: We present a modified rush AIT protocol that seems to be effective and safe. Most patients tolerated therapy, and only a minority of patients developed SRs, which generally were mild. We identified novel risk factors for SRs that may help determine optimal dosing to decrease the risk of SRs. Ultimately, future studies will be needed to compare the safety of our MERIT protocol with traditional AIT.

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Allergen immunotherapy (AIT) is recognized as an effective treatment option for allergic rhinitis.^{1,2} AIT involves administering allergens in gradually increasing doses over time. With conventional AIT, it takes ~3 to 6 months to reach maintenance dosing, depending on the type of protocol.³ In 1930, Freeman⁴ first introduced rush AIT. Rush AIT is a form of accelerated immunotherapy in which patients receive multiple increasing doses of allergen extract every 15–60 minutes and reach maintenance concentration over one to several days.³ The proposed benefits of rush AIT include reaching maintenance dosing months earlier, more rapid symptomatic improvement, increased pa-

tient compliance, and reduced dosing errors by using fewer vials of differing concentrations.^{5–8}

Despite these advantages, rush AIT schedules have been shown to carry an increased risk of systemic reactions (SR), especially in the protocols that reach the full maintenance dose over a short period of time.^{2,6,8–12} Therefore, to improve safety, practitioners have published a variety of modified rush AIT protocols, with an initial rapid build-up that reaches a lower concentration, followed by a gradual titration to the full maintenance dose.^{2,5–9,11–13} Despite these modifications, risk factors for an SR in modified rush AIT include a history of asthma,^{7,13} strong aeroallergen sensitization,^{6,9} and higher rush AIT target doses.^{6,8,9,12} However, pretreatment before rush immunotherapy with systemic corticosteroids, antihistamines, and leukotriene modifiers has been shown to reduce adverse reactions.^{6,7,14}

We present a novel 1-day, eight-step outpatient modified environmental rush immunotherapy (MERIT) protocol for seasonal and perennial aeroallergens with the use of a systemic premedication regimen. This MERIT protocol consisted of a 1-day rush protocol, followed by gradual build-up to the full maintenance dose. This protocol decreased the duration of the

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Table 1 MERIT protocol

Time	Vial Dilution, vol/vol*	Dose, mL
9:00 A.M.	Silver vial, 1:10,000	0.1
10:00 A.M.	Silver vial, 1:10,000	0.3
11:00 A.M.	Green vial, 1:1000	0.1
12:00 P.M.	Green vial, 1:1000	0.3
1:00 P.M.	Blue vial, 1:100	0.1
2:00 P.M.	Blue vial, 1:100	0.2
3:00 P.M.	Blue vial, 1:100	0.3
4:00 P.M.#	Blue vial, 1:100	0.4

MERIT = Modified environmental rush immunotherapy.

*All dilutions are expressed as vol/vol from the maintenance concentration.

#The patients were monitored for 1 hour after the last dose.

build-up phase by 50%, which resulted in fewer visits and less time before the maintenance dose was reached. We aim to describe patient characteristics, protocol safety, and identify distinguishing features of patients who experienced SRs compared with no SRs (NSR).

METHODS

Study Design

This was a retrospective analysis of demographic and clinical data from adult patients with allergic rhinitis seen in an outpatient university allergy clinic over a 10-year period (January 2005 to January 2015) who underwent the MERIT protocol (Table 1). A total of 362 patients were identified by The International Classification of Diseases, Ninth Revision procedure code for rapid desensitization (code 95180).¹⁵ This study received an expedited approval by the institutional review board at the University of Pittsburgh (PRO15040559).

Allergy Skin Testing and Extracts

Aeroallergen sensitization was determined by either percutaneous skin testing ($n = 325$) with Quin-tip (Jubilant HollisterStier LLC, Spokane, WA) by using glycerinated allergen extracts (Greer Laboratories, Inc., Lenoir, NC) or serum-specific immunoglobulin E (IgE) measurement ($n = 37$) by using ImmunoCAP (Quest Diagnostics, Inc., Madison, NJ). Although percutaneous skin testing was preferred, serum-specific IgE testing was performed if the patients elected serum measurement or had systemic antihistamine use and were unable to withhold use of antihistamines for skin testing. A small subset of patients ($n = 36$) with a negative percutaneous skin testing result but a strong clinical suspicion of an allergic trigger underwent further evaluation with intra-

dermal testing at 1:100 dilution. A positive percutaneous skin testing result was determined as a wheal of ≥ 3 mm than the size of the diluent control 20 minutes after placement.¹⁶

For serologic testing, the presence of allergen-specific IgE antibodies of >0.35 kU/L was interpreted as a positive result. Results of testing were interpreted in the context of clinical presentation. Allergen extract content and concentrations were chosen in compliance with recommendations from the Allergen Immunotherapy Practice Parameter,³ and vials were created to avoid proteolytic degradation (Table 2). Both standardized and nonstandardized allergen extracts were obtained from commercial suppliers (Greer Laboratories). We used all individual allergens for our allergen extract preparation, with the exception of Eastern 8-Tree Mix (American elm, American beech, eastern cottonwood, red oak, birch, hickory, white ash, maple) and 7-Grass Mix (Kentucky blue/June, meadow fescue, orchard, perennial ryegrass, redtop, sweet vernal, timothy).

MERIT Treatment Course

The MERIT protocol was a 1-day, eight-step outpatient protocol that involved escalating doses of AIT, given hourly, beginning with 0.1 mL of 1:10,000 dilution and ending with 0.4 mL of 1:100 dilution (Table 1). Before starting therapy, the risks and benefits, including the risk of SRs, were discussed with all the patients who signed informed consent. Pretreatment medications were prescribed the day before and day of protocol as follows: Prednisone 40 mg, montelukast 10 mg, a nonsedating H₁ and H₂ antihistamine. As a safety precaution, all the patients were prescribed autoinjectable epinephrine. For patients with asthma, a baseline forced expiratory volume in 1 second was measured before initiation of therapy. Before MERIT and all subsequent AIT injections, peak expiratory flow measurements were completed in all patients with asthma.

In addition, if the patients developed respiratory symptoms during the protocol, repeated peak flow measurements were obtained. After completing the MERIT protocol, the patients were observed for 1 hour. Subsequently, the patients returned the following week and started gradual build-up therapy, beginning with 1:10 dilution through 1:1 (maintenance) concentration (Table 3). During the gradual build-up phase, the patients were pretreated with a nonsedating H₁ antihistamine on the day of injections. The patients received injections one to two times weekly until reaching maintenance therapy, after which injections were administered monthly. During the build-up and maintenance phases, the patients were observed in the clinic for 20–30 minutes after an injection for monitoring of reactions.^{3,17} SR severity was graded by using

Table 2 Allergen extract stock solutions and maintenance dosing

Allergen Extract*	Stock Concentration	Maintenance Concentration
Molds		
<i>Alternaria, Epicoccum, Penicillium, Cladosporium, Helminthosporium</i>	1:10 wt/vol	1:100 wt/vol
<i>Aspergillus</i>	1:20 wt/vol	1:100 wt/vol
Weed pollen		
English plantain, pigweed	1:10 wt/vol	1:100 wt/vol
Cocklebur, lamb's quarter, mugwort	1:20 wt/vol	1:100 wt/vol
Ragweed	1:20 wt/vol	1:200 wt/vol
Grass pollen mix#	100,000 AU/mL	2000 AU/mL
Tree pollen		
Birch, hickory, maple, oak, sycamore	1:10 wt/vol	1:100 wt/vol
Tree mix, ash, elm, mulberry, pine, walnut§	1:20 wt/vol	1:100 wt/vol
Cat	10,000 BAU/mL	2000 BAU/mL
Dog	1:10 wt/vol	1:100 wt/vol
Cockroach	1:10 wt/vol	1:250 wt/vol
Dust mite		
<i>Dermatophagoides farinae, Dermatophagoides pteronyssinus</i>	10,000 AU/mL	1000 AU/mL

AU = Allergy unit; BAU = bioequivalent allergy unit.

*All extracts were obtained from Greer Laboratories.

#Includes Kentucky blue/june, meadow fescue, orchard, perennial ryegrass, redtop, sweet vernal, timothy.

§Includes white ash, white oak, birch, red maple, beech, cottonwood, elm, hickory.

Table 3 Build-up allergen immunotherapy protocol after MERIT day*

Dose No.	Vial, vol/vol#	Dose, mL
1	Gold vial, 1:10	0.05
2	Gold vial, 1:10	0.10
3	Gold vial, 1:10	0.20
4	Gold vial, 1:10	0.30
5	Gold vial, 1:10	0.40
6	Gold vial, 1:10	0.50
7	Red vial, 1:1	0.05
8	Red vial, 1:1	0.10
9	Red vial, 1:1	0.15
10	Red vial, 1:1	0.20
11	Red vial, 1:1	0.25
12	Red vial, 1:1	0.30
13	Red vial, 1:1	0.35
14	Red vial, 1:1	0.40
15	Red vial, 1:1	0.45
16	Red vial, 1:1	0.50

MERIT = Modified environmental rush immunotherapy.

*Doses may be given one or two times weekly, depending on patient preference.

#All dilutions are expressed as vol/vol from the maintenance concentration.

the World Health Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.¹⁸

Statistical Analysis

Data were analyzed by using the JMP software program (JMP Statistical discovery, Cary, NC). The χ^2 analysis was used for categorical variables. The continuous data were analyzed nonparametrically with Kruskal-Wallis testing. The results were reported as ratios and percentages of the entire cohort. A p value of <0.05 was considered statistically significant. Univariate analysis was initially used to evaluate the relationship between variables and the presence of SR, and those variables with $p < 0.1$ were then subjected to multiple linear regression analysis. Potential predictors included demographic factors (age, body mass index [BMI]), comorbidities (urticaria and/or angioedema), and allergen extract data (the number of allergens in the extract and the presence of individual allergens in the extract, such as cat, dust mite, ragweed, cocklebur, and mugwort).

RESULTS

Patient Characteristics

A total of 362 patients were identified who completed the MERIT protocol. The majority were female

Table 4 Patient demographics

Characteristic	MERIT Population (N = 362)	SR (n = 50)	NSR (n = 312)	p Value, SR vs NSR*#	p Value, SR vs NSR*§
Male/female	132/230	18/32	114/198	0.94	
Race: white/black/other, no.	292/34/18	42/3/3	250/31/15	0.64	
Age, median (IQR), y	33.0 (26.0–43.0)	29.5 (25.0–36.0)	33.0 (2.1–43.8)	0.06	0.08
BMI, median (IQR), kg/m ²	26.2 (23.0–30.7)	25.0 (22.6–28.5)	26.6 (23.1–31.0)	0.04	0.52
Angioedema, no. (%)	5 (1.4)	2 (4.0)	3 (1.0)	0.09	0.18
Anaphylaxis history, no. (%)	27 (7.5)	4 (8.0)	23 (7.4)	0.88	
Asthma, no. (%)	173 (47.8)	24 (48.0)	149 (41.2)	0.97	
Eczema, no. (%)	41 (11.3)	9 (18.0)	32 (10.3)	0.11	
Food allergy, no. (%)	73 (20.2)	13 (26.0)	60 (19.2)	0.28	
Pet ownership, no. (%)	246 (68.0)	30 (60.0)	216 (69.2)	0.19	
Urticaria, no. (%)	39 (12.5)	9 (18.0)	30 (9.6)	0.08	0.11

MERIT = Modified environmental rush immunotherapy; SR = systemic reaction; NSR = no systemic reaction; IQR = interquartile range; BMI = body mass index.

*A *p* value of <0.05 was considered statistically significant.

#Results of a univariate analysis.

§Results of a multivariate analysis.

patients (63.5%) (Table 4). In our population, 50 patients experienced SRs (13.8%) at any time during AIT therapy, with 4.7% occurring on the MERIT day. When comparing those who had an SR versus those with NSR, there was no sex association. In univariate analysis, a lower BMI was associated with SR ($p = 0.04$) and there was a trend toward younger age ($p = 0.06$) and a history of urticaria and angioedema in those who developed an SR versus NSR ($p = 0.08$ and 0.09 , respectively). There was no association between the occurrence of an SR and patient history of asthma or anaphylaxis. In multivariate analysis, only age tended to be associated with the occurrence of SRs ($p = 0.08$) (Table 4).

Allergen Extract Content and SRs

The patients in our study received AIT to single or multiple allergens. The median number of allergens in the extracts for the entire population was 6, with a minimum of 1 ($n = 9$) and a maximum of 16 allergens ($n = 2$). Each allergen included in the extract was recorded as a single allergen, including Eastern 8-Tree Mix and 7-Grass Mix. Of the 362 patients who underwent the MERIT protocol, the majority (71%) had both seasonal and perennial allergens in their extract, whereas 22% had perennial allergens and 7% had seasonal allergens only. Overall, the most commonly included allergens were dust mite (75%), cat (66%), any weed pollen (65%), and grass mix pollen (61%).

In univariate analysis, the patients who developed an SR had a significantly higher number of individual extracts in their allergen extract compared with those

with NSR (median, 8 versus 6; $p = 0.003$). However, in multivariate analysis, the number of allergens in the extract was not statistically significant ($p = 0.13$). When comparing extracts of patients with SRs and patients with NSRs, in univariate analysis, significantly more patients with SRs had allergen extracts that contained cat, dust mite (*Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*), ragweed, cocklebur, and mugwort (all p values of <0.05) (Fig. 1). Allergens that maintained an association with the occurrence of SRs in multivariate analysis were cat ($p = 0.0075$), dust mites ($p = 0.017$), and mugwort ($p = 0.021$).

SR Timing and Severity

In our population, 50 patients experienced 68 total SRs (33 patients had 1 SR, 16 patients had 2 SRs and 1 patient had 3 SRs). The majority of SRs occurred during the post-MERIT protocol build-up period (37 reactions [54.4% of the total SRs]), followed by the MERIT day (17 reactions [25% of the total SRs]), and then during the maintenance phase (14 reactions [20.6% of the total SRs]). During the build-up, SRs occurred almost twice as commonly during 1:1 vial administration ($n = 24$) than during earlier build-up doses ($n = 13$). On the MERIT day, the dose that most commonly caused an SR was the final dose, of 0.4 mL of 1:100 dilution ($n = 8$), followed by the second-to-last dose, of 0.3 mL of 1:100 dilution ($n = 4$). However, one patient did develop isolated pruritus 30 minutes after the 0.1-mL dose of 1:10,000 dilution. Of the 68 total SRs, 35 (51%) were grade 1, 31 (46%) were grade 2, and 2 (3%) were grade 3 (Fig. 2 *a*). There were no grade 4 or 5

Figure 1. Aeroallergen extract content in those with systemic reactions (SR) versus no SRs (NSR); percentages were determined by dividing the total number of SRs or NSR to a particular extract over the total SRs or NSRs in the population. *The *p* value of <0.05 by univariate and multivariate analyses.

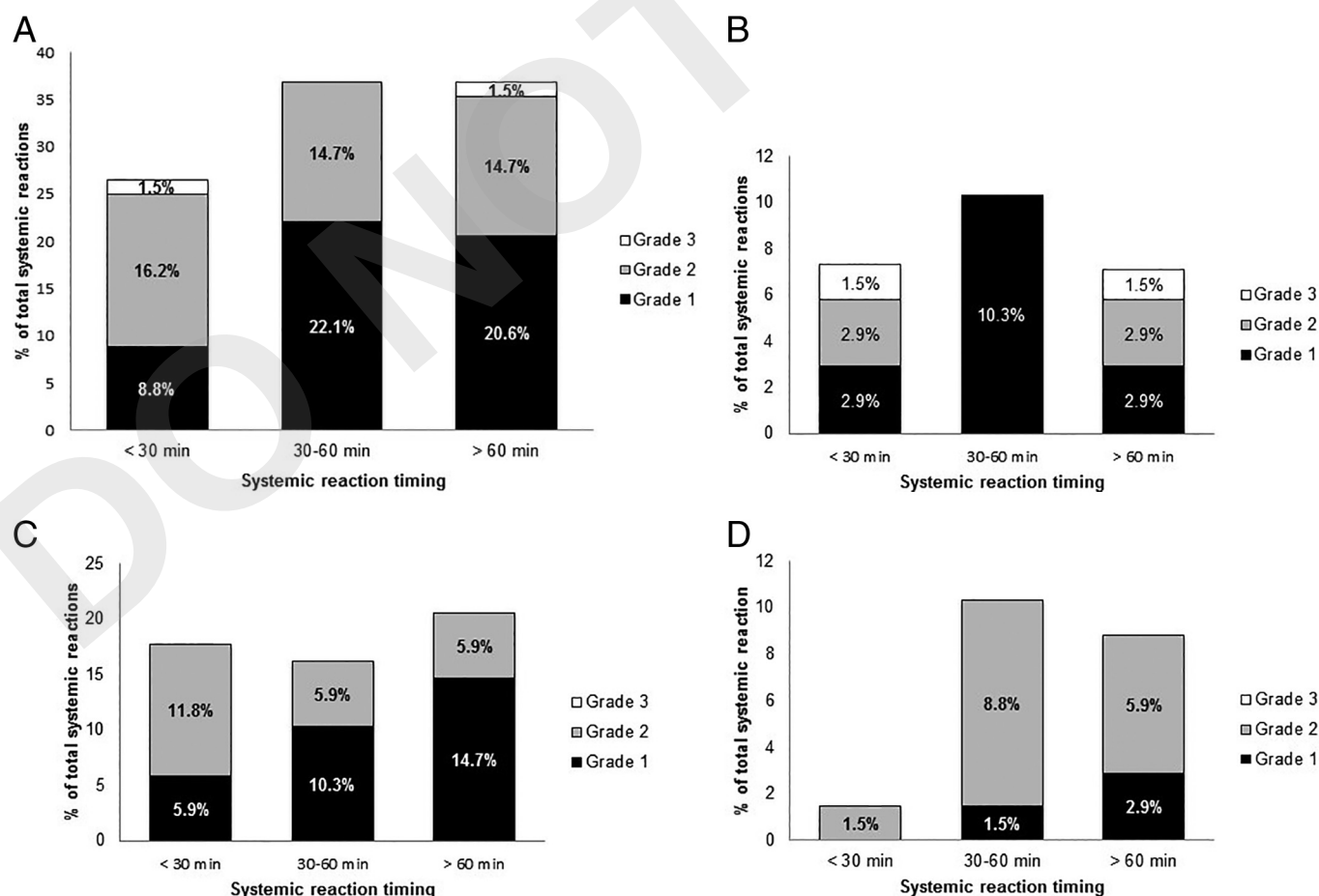
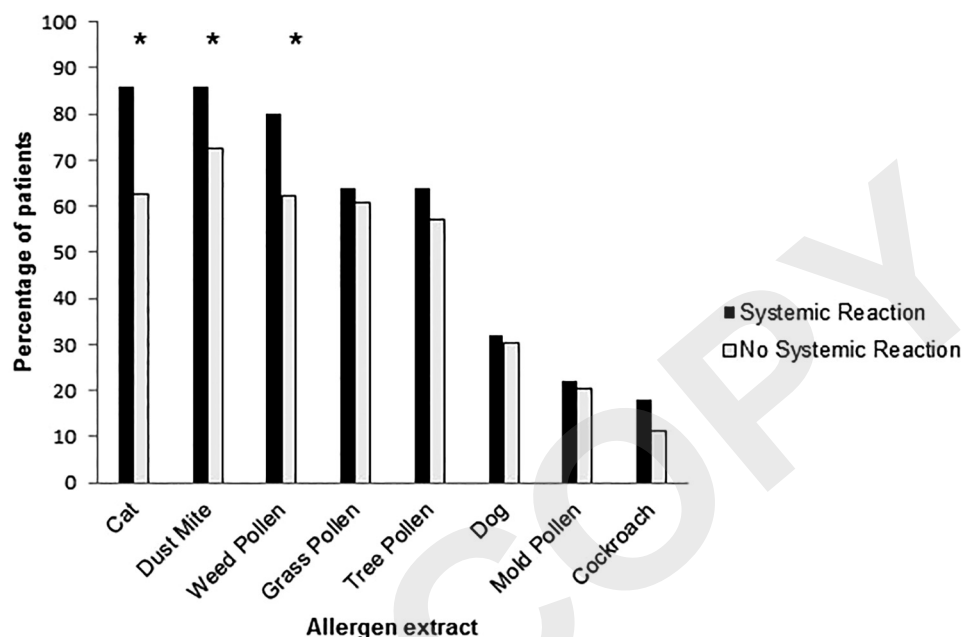


Figure 2. The timing and severity of reactions. (a) The timing and severity of all reactions during any time of therapy (*n* = 68) (modified rush immunotherapy [MERIT] protocol day through maintenance); (b) MERIT day timing and severity of systemic reaction (SR) (*n* = 68); (c) build-up therapy timing and severity of SR (*n* = 68); and (d) maintenance therapy timing and severity of SR (*n* = 68).

reactions. Both grade 3 reactions occurred on the MERIT day.

One grade 3 SR occurred within 20 minutes of the 0.1-mL dose of 1:100 dilution, when the patient developed lower lip swelling, which prompted administration of intramuscular (IM) diphenhydramine. Subsequently, the patient developed cough and globus sensation, therefore IM epinephrine was administered. The patient was observed for 20 minutes, with partial improvement in throat discomfort. At that point, flexible laryngoscopy revealed paradoxical movement of the vocal cords without laryngeal edema. The patient was observed for another hour and was discharged home from the clinic, with resolution of symptoms. This patient continued AIT and successfully reached the maintenance dose, without additional SR. The other grade 3 reaction was delayed by several hours after completion of the MERIT protocol. While at home, the patient developed mild tongue swelling, fatigue, and difficulty breathing. After self-administering IM epinephrine, the patient was taken to a local emergency department where the patient's vital signs were normal and no swelling was noted. The tryptase level, drawn within 3 hours of the onset of symptoms, was normal (2 ng/mL). The patient was observed overnight in the hospital and discharged the following day. The patient decided not to continue AIT.

Overall, 50 SRs (73.5%) were delayed by >30 minutes, half of which were delayed by >60 minutes (Fig. 2 *a-d*). Furthermore, delayed SRs tended to be more frequently grade 1, whereas early SR tended to be more frequently be grade 2 (Fig. 2 *a*). Of note, the majority of reactions on the MERIT day occurred within 60 minutes and were grade 1 (Fig. 2 *b*). All SRs were treated according to the standard of care and in compliance with recommendations from the Allergen Immunotherapy Practice Parameter.³ AIT was prematurely discontinued (before completing maintenance dosing of a minimum 3 years) in 184 of 362 (50.8%), and, of those patients, 20 of 184 (11%) experienced an SR. Interestingly, the occurrence of an SR did not impact the AIT premature discontinuation rate ($p = 0.10$).

DISCUSSION

We present a novel modified AIT rush protocol for multiple aeroallergens in an outpatient setting. Over the past 10 years, 362 adult patients underwent the MERIT regimen. The majority of patients completed the protocol without any systemic complications. On the MERIT day, our goal was to reach a meaningful therapeutic dose while decreasing the risk of an SR. To accomplish this, we elected to use initial and target doses in the middle range of previously published protocols.^{6-9,12} We started with 0.1 mL of the 1:10,000 dilution and finished with 0.4 mL of the 1:100 dilution.

Smits *et al.*⁸ used 0.025 mL of 1:1,000,000 dilution and Portnoy *et al.*⁶ began with 0.3 mL of 1:100,000 dilution as initial doses, whereas Temino *et al.*¹² and Harvey *et al.*⁹ began their rush protocols at the same dilution level as ours (1:10,000) but with higher volumes, 0.5 mL and 0.3 mL, respectively. Smits *et al.*⁸ and Sharkey and Portnoy⁷ ended their rush protocols at lower doses than ours, at 0.1 mL of 1:1,000 dilution and 0.2 mL of 1:100 dilution, respectively, whereas Temino *et al.*¹² and Harvey *et al.*⁹ reached higher doses, at 0.2 mL of 1:10 dilution and 0.05 mL of 1:1 concentration, respectively.

On the MERIT day, we administered each dose hourly to allow sufficient observation for SRs. This was a longer interval than other reported studies. Smits *et al.*⁸ maintained a 15-minute dosing interval throughout. Several other investigators began their protocols with 15–30-minute interdose intervals and progressed to 1-hour intervals as the doses escalated.^{6,7,9,12} After completion of our MERIT protocol, the patients were monitored in the clinic for 1 hour before discharge, similar to Temino *et al.*¹² and Sharkey and Portnoy.⁷ In contrast, Smits *et al.*⁸ observed patients for 30 minutes after the last injection, whereas Harvey *et al.*⁹ monitored patients for 2 hours after the final dose. It is noteworthy that Morias-Almeida *et al.*¹¹ and Cardona *et al.*¹³ used an ultrarush AIT protocol administered with an allergoid extract (depigmented polymerized dust mite allergen) that consisted of only two doses. Because the clinical efficacy of depigmented polymerized extract compared with the extracts used in traditional AIT is unknown, a direct comparison with these studies was not possible.

Based on previous studies that demonstrated a decrease in SRs with pretreatment before rush protocols, we also elected to use pretreatment before the MERIT day.⁶ Our protocol included taking prednisone, a second-generation H₁ antihistamine, an H₂ antihistamine, and a leukotriene modifier the day before and the day of MERIT. Harvey *et al.*⁹ had a similar pretreatment protocol. Smits *et al.*,⁸ Portnoy *et al.*,⁶ and Sharkey and Portnoy⁷ used a 3-day pretreatment protocol of antihistamines and prednisone. In addition, at the end of the MERIT day, all of our patients were discharged from the clinic with their previously prescribed epinephrine autoinjector.

By using univariate analysis, our study identified several novel risk factors for having an SR in the setting of modified rush immunotherapy, including a lower BMI. We also reported that there was a trend toward SRs in younger patients and in patients with a history of urticaria and/or angioedema. Unlike Smits *et al.*,⁸ who found a female predominance in patients who developed SR, we found no sex predominance, which was consistent with the findings of Harvey *et al.*⁹ Although Sharkey and Portnoy⁷ and Smits *et al.*⁸ reported

that subjects who experienced SR were more likely to carry an asthma diagnosis, our study, as well as those by Harvey *et al.*⁹ and Temino *et al.*,¹² did not confirm this association. We also found no association between SRs and food allergy, atopic dermatitis, or a history of anaphylaxis.

In addition to the demographic features identified, univariate analysis revealed a significantly higher number of allergen extracts in those patients who experienced SRs versus NSRs, which differed from previous univariate studies, which found no difference between the groups.^{6,9} In addition, we found that cat, cocklebur, and mugwort were associated with a risk of SR in rush AIT. Some of our findings were similar to other studies that reported that ragweed and dust mite allergens were associated with SR.⁷⁻⁹ Furthermore, unlike other rush protocols, we did not find that dog or mold was seen more often in SRs, which may be due to potency variability among different extracts.

Previously published studies on rush immunotherapy used only univariate statistical analysis when analyzing risk factors for SRs. In our multivariate analysis, the presence of dust mite, cat, and mugwort in allergen extract was significantly associated with SR. Younger age tended to be associated with SRs ($p = 0.08$). This may necessitate further study. We can speculate that patients with these risk factors for SRs should have their final dose on the rush day or the maintenance dose adjusted to decrease the risk of SRs. Overall, our protocol's risk of SRs was 13.8% per patient population (50 patients with SR per 362 total patients) during the entire duration of AIT (MERIT day, build-up, and maintenance). Only 4.7% of all the patients had an SR on the MERIT day. Previous comparable studies demonstrated wide ranges of SRs on the rush AIT day, which varied from 23 to 38% per population when using a variety of rush schedules.^{6-8,12} Although Smits *et al.*⁸ reported an SR rate of 2%, their target dose on the rush day was significantly lower (0.1 mL of 1:1000 dilution) than our MERIT target dose (0.4 mL of 1:100 dilution).

Unlike some rush protocols in which SRs were seen at lower doses,^{6,8} we had only one questionable SR after the first dose of the MERIT protocol (0.1 mL of 1:10,000 dilution) and no SRs with injections from the 1:1000 dilution vial. On the rush MERIT day, SRs seemed to occur with higher doses of allergen extract (1:100 dilution). In other rush protocols, the majority of reactions occurred with various doses that ranged from 1:1,000 dilution to maintenance concentration.^{6,7,9} Our protocol was designed with the intent to decrease the risk of SR while at the same time completing >50% of build-up dosing in one day. Analysis of our data supported a decision not to advance extract dosing to 1:10 dilution on the rush day and to keep interval doses 1 hour apart. It is noteworthy that our SR percentage was reported per total number of patients and not per total

number of injections, which would have made the percentage of SRs much lower.

In our study, on the MERIT day, 12 of 17 total SRs occurred within 60 minutes, which validated the safety of 1 hour of observation after the last dose. During all phases of our protocol (MERIT day, build-up, and maintenance), SRs most commonly developed >30 minutes after an injection, with greater than one third of SRs being delayed for >1 hour and some beyond several hours. Other studies reported that SRs occurred most commonly after 30 minutes,^{7,9} with a minority of SRs delayed by ≥ 2 hours.^{9,12} The current recommended observation period after an allergen injection during the build-up or maintenance phase is 30 minutes, and the recommended treatment for all the grades of SRs is IM epinephrine.³ Most SRs in our study, albeit mild, occurred outside of the 30-minute observation window. This justified our decision to prescribe an epinephrine autoinjector to all the patients who underwent AIT should SRs occur once they left the office.

Although one of the theoretical advantages of rush AIT is increased adherence, little has been published in this area. Temino *et al.*¹² compared patient adherence between patients who completed rush therapy versus a conventional build-up and reported that 61% of patients on rush AIT continued therapy to the end of the study versus 46% of those on conventional AIT. Unfortunately, their study was not powered to detect a statistically significant difference, although results indicated greater adherence in those who completed rush AIT.¹² Our MERIT protocol adherence rate for all the patients was 49.2% and, importantly, did not seem to be influenced by having an SR versus NSR.

There were several limitations in this study. Due to its retrospective nature, descriptions and severity of reactions could have been underreported because of recall bias. However, we believed that this was unlikely because recovered documentation was very detailed. Because our clinic uses multiple allergen extracts specific to our region, our data may be less generalizable to other populations in other regions. Although undergoing AIT during the pollen season is an established risk factor for SRs,¹⁹ we elected not to modify our MERIT protocol based on the pollen season because the majority of the patients were polysensitized to seasonal and perennial allergens. In addition, there were other factors, such as the presence of a pet in the home, climate and geographic differences, and allergy extract potency variability, that may have influenced these observations. Ultimately, larger prospective studies would be beneficial to further determine the safety and adherence to rush protocols. Also, the risk factors identified here should be verified in a large and demographically diverse population.

CONCLUSION

We present a modified rush AIT protocol that seems to be effective and safe. Most of the patients tolerated the therapy, and only a minority of the patients developed SRs, which generally were mild. We identified novel risk factors for SRs in the setting of MERIT protocol that may help determine optimal dosing to decrease the risk of SRs in these patients at higher risk. Ultimately, future studies will be needed to compare the safety of our MERIT protocol with traditional AIT.

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