

Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice

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Background: Subcutaneous allergen-specific immunotherapy is a proven, highly effective treatment for immunoglobulin E-mediated diseases. Despite its proven benefits, only a small percentage of patients with allergic disease use immunotherapy, in part because of the inconvenience associated with treatment. Cluster allergen immunotherapy may offer patients a more convenient treatment option but is prescribed infrequently because of the perception that accelerated immunotherapy buildup leads a higher rate of systemic reactions.

Objective: To examine the safety of cluster immunotherapy and identify risk factors for systemic reactions during cluster buildup.

Methods: A retrospective, observational review in a large, multicenter allergy practice group was conducted for patients receiving cluster immunotherapy between May 2008 and October 2010.

Results: Data from 441 patients receiving cluster immunotherapy were collected. Forty-eight patients (10.9%) experienced systemic reactions. Based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System, 18 grade 1 reactions (38.3%), 23 grade 2 reactions (48.9%), 5 grade 3 reactions (10.6%), 1 grade 4 reaction (2.1%), and no grade 5 reactions were seen. Risk factors for a systemic reaction included: female sex, physician diagnosis of asthma, age 21 to 40 years, and inclusion of certain allergens in the immunotherapy vaccine.

Conclusions: Cluster immunotherapy allows patients to reach their immunotherapy maintenance dose more rapidly and may lead to more rapid symptomatic improvement. However, the cluster buildup may lead to a higher rate of systemic reactions. Identifying risk factors for systemic reactions will help improve the safety of cluster immunotherapy.

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INTRODUCTION

Subcutaneous allergen-specific immunotherapy (SCIT) is a highly effective, immune-modifying treatment for allergic rhinitis and allergic asthma.¹⁻⁴ By altering the immune response to environmental allergens, SCIT not only improves disease control but may affect the natural history of allergic sensitization. Among sensitized children, some studies have demonstrated that SCIT has the potential of reducing the incidence of new allergic sensitization and decreasing the risk of progression to asthma.⁵⁻⁷ Despite these benefits, only a small percentage of patients with allergic disease use immunotherapy as a treatment option, and many patients discontinue treatment before completing the recommended protocol.⁸

Although many factors play a role in the relatively infrequent use of immunotherapy, the inconvenience associated with conventional buildup is a frequently cited concern.^{9,10} Conventional buildup involves once- or twice-weekly injections

over the course of several months to reach the maintenance dose, requiring frequent visits to a physician's office and possibly time missed from school or work. Accelerated buildup SCIT has been an accepted treatment option since the early 20th century, when Freeman described his experience with rush immunotherapy, which involves a very rapid buildup with numerous doses delivered in a single day.¹¹ In contrast, cluster immunotherapy typically involves a slower buildup, with 2 or 3 sequential injections per day. By administering injections 1 or 2 times per week on nonconsecutive days, many cluster protocols allow patients to reach the maintenance dose within a month. The accelerated buildup is more convenient for patients, leads to more rapid symptomatic improvement, and may induce immune changes more rapidly than conventional immunotherapy.¹² Consequently, patients who present near the beginning of the pollen season may be able to reach their maintenance dose and experience clinical benefit during that season. Furthermore, the reduction in office visits and number of injections associated with accelerated schedules may reduce the overall cost of immunotherapy.¹³

Despite the proven efficacy and convenience of cluster immunotherapy, it is prescribed for only a small percentage of immunotherapy patients. This may be attributable to the perception that cluster immunotherapy leads to a higher rate of systemic reactions, which are the primary risk associated with SCIT. The incidence of systemic reactions with conventional buildup protocols varies widely. One review reported

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incidence figures ranging from 0.84% to 28.6%, with the exception of 1 study involving patients highly sensitized to ragweed that found a higher rate of reactions.¹⁴ Although the risk of severe anaphylaxis is a concern with immunotherapy, most reactions are mild, and fatalities occur approximately once in every 2 million injections. Although some studies have reported a higher incidence of reactions during accelerated buildup, others have found no significant difference.^{15–25} By identifying risk factors for systemic reactions, appropriate patient selection and cluster immunotherapy protocols can be enhanced to potentially improve patient safety.

This retrospective database review was performed to determine the rate of systemic reactions with cluster immunotherapy in our practice and to identify risk factors associated with systemic reactions. Recognizing patient characteristics or aspects of clinical protocols associated with reactions may help improve patient safety with cluster immunotherapy.

METHODS

Patients

A retrospective review was conducted at a large, multicenter, single-specialty, private allergy practice (Allergy Partners, Pennsylvania). Data were collected on all patients receiving cluster immunotherapy between May 2008 and October 2010. A total of 441 patients received cluster allergen-specific immunotherapy at Allergy Partners locations during this time, and all patients were included in this review. Patients were determined to be candidates for immunotherapy by their allergist, and the practice does not use specific inclusion or exclusion criteria for patients to receive cluster immunotherapy. Patients who were deemed appropriate for cluster immunotherapy by their treating physician were given the option of conventional or cluster buildup. The risks and benefits of cluster immunotherapy were discussed, including a possible higher rate of systemic reactions compared with conventional buildup. Signed consent for cluster immunotherapy administration was obtained.

Allergen Extracts

All allergen extracts are obtained from Greer Laboratories (Lenoir, North Carolina). Immunotherapy extracts are mixed and distributed by Allergy Partners for all practice locations from a central laboratory located in Asheville, North Carolina. The allergen vaccine content and maintenance dose are determined by the treating physician. Allergy Partners uses default allergen concentrations designed to provide a maintenance dose in compliance with the Allergen Immunotherapy Practice Parameter.²³ The treating physician may adjust the extract concentration and maintenance dose as deemed appropriate for individual patients. Approximately 95% of immunotherapy extracts prepared by the practice use the default concentrations.

Data Collection

During allergen immunotherapy, all reactions, including local and systemic, are recorded for every patient at the respective

office. Mandatory reporting of data for all patients receiving cluster immunotherapy is made to the central extract laboratory for quality control, safety, and regulatory purposes. Details of all systemic reactions, including demographics, allergen mix(es), patient symptoms, treatment received, time until onset of symptoms, dose-eliciting reaction, and outcomes, are reported by the individual offices and entered into a database at the central laboratory. For spirometry the most recent data in the patient's chart was used, and spirometry was not performed at the first cluster visit.

Cluster Immunotherapy Protocol

All cluster immunotherapy doses are administered in an Allergy Partners practice facility. A physician, nurse practitioner, or physician assistant is present during immunotherapy administration and during the observation period. Patients are observed for 30 minutes between doses and after the final dose of the day. The cluster immunotherapy protocol consists of 8 office visits. During the first 3 visits, patients receive 3 immunotherapy doses per visit. During visits 4 through 7, patients receive 2 doses per visit, and patients reach maintenance with a single dose at visit 8 (Table 1). Patients typically receive cluster doses either once or twice per week. Patients are premedicated at the discretion of the treating physician.

Grading of Systemic Reactions

All systemic reactions were independently reviewed by the same 2 physicians and graded according to The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System²⁶ (Table 2). If the grades assigned by the 2 physicians did not agree, the record was then reviewed by a third physician.

Table 1. Cluster Immunotherapy Protocol

Visit no.	Injection no.	Concentration (volume:volume)	Volume mL
1	1	1:1,000	0.1
	2		0.4
	3		0.1
2	4	1:100	0.2
	5		0.4
	6		0.07
3	7	1:10	0.1
	8		0.15
	9		0.25
4	10	1:1	0.35
	11		0.5
5	12	1:1	0.07
	13		0.1
6	14		0.15
	15		0.2
7	16		0.3
	17		0.4
8	18		0.5

Table 2. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System²⁶

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms (s)/sign(s) of 1 organ system present Cutaneous Generalized pruritus, urticaria, flushing, or sensation of heat or warmth or Angioedema (not laryngeal, tongue, or uvular) or Upper Respiratory Rhinitis—(eg, sneezing, rhinorrhea, nasal pruritus, or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or Conjunctival Erythema, pruritus, or tearing Other Nausea, metallic taste, or headache	Symptom(s)/sign(s) of more than 1 organ system presents or Lower Respiratory Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV ₁ drop, responding to an inhaled bronchodilator) or Gastrointestinal Abdominal cramps, vomiting, or diarrhea or Other Uterine cramps	Lower respiratory Asthma (eg, 40% PEF or FEV ₁ drop NOT responding to an inhaled bronchodilator) or Upper respiratory Laryngeal, uvula, or tongue edema with or without stridor	Lower or upper respiratory Respiratory failure with or without loss of consciousness or Cardiovascular Hypotension with or without loss of consciousness	Death

Statistical Analysis

Association between potential risk factors for all subjects and incidence of a systemic reaction was examined using a likelihood ratio χ^2 test on each risk factor individually.

RESULTS

Demographics

Four hundred forty-one patients started cluster immunotherapy buildup (Table 3). Patients had a mean age of 38.1 years (standard deviation [SD], 16.7 years) and ranged from 6 to 81 years of age. Of the 441 patients, 40.1% were male, and 59.9% were female. All patients had been diagnosed with allergic rhinitis, allergic conjunctivitis, or allergic asthma by an allergist. One hundred twenty-seven (28.8%) of the patients had a physician diagnosis of asthma. Patients with asthma had a mean forced expiratory volume in 1 second (FEV₁) of 93.7% predicted, with a range of 64 to 118% predicted. Dust mite was the most common allergen included in immunotherapy vaccines; 87.3% of patients received dust mite extract, 68.3% grass pollen, 65.3% tree pollen, 63.7% weed pollen, 52.2% cat, 47.8% dog, 42.6% mold, and 17.0% cockroach. Three hundred fifty-three (80.0%) patients reached the maintenance immunotherapy dose (Fig 1). One hundred ninety-two (43.5%) completed the cluster buildup

protocol to the maintenance dose. One hundred sixty-one (36.5%) changed to conventional dosing at some point and continued to the maintenance dose. Of the 249 patients who discontinued cluster buildup, 91 (36.5%) stopped because of large local reactions, 47 (18.9%) because of scheduling conflicts, 44 (17.7%) because of systemic reactions, and 62 (24.9%) either listed another reason or no reason was listed.

Systemic Reactions

Of the 441 patients who received cluster immunotherapy, 48 patients (10.9%) had a systemic reaction during the buildup phase (Table 4). Forty-four of the 48 patients experiencing a systemic reaction discontinued the cluster buildup. Overall, 36 (75%) of the patients having a systemic reaction reached the maintenance dose. Four successfully completed the cluster buildup to the maintenance dose after their systemic reaction, and 32 switched to a conventional buildup protocol and reached the maintenance dose.

Twenty-six of the systemic reactions involved a single organ system, and 21 involved 2 or more systems. For 1 reaction, symptoms were inadvertently not recorded. Based on the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System,²⁶ 18 of the systemic reactions were a grade 1. This constituted 4.1% of all

Table 3. Demographic Data

Demographics	Finding
Total no. of patients	441
Age, mean (range), yrs	38.1 (6–81)
Sex, no. (%) of patients	
Male	177 (40.1)
Female	264 (59.9)
Diagnosis of asthma, no. (%) of patients	
Yes	127 (28.8)
No	314 (71.2)
Allergen contained in extract, no. (%) of patients	
Dust mites	385 (87.3)
Grasses	301 (68.3)
Trees	288 (65.3)
Weeds	281 (63.7)
Cat	230 (52.2)
Dog	211 (47.8)
Mold	188 (42.6)
Cockroach	75 (17.0)
Premedication before immunotherapy, no. (%) of patients	
Yes	407 (92.3)
No	34 (7.7)

patients and 38.3% of systemic reactions. Twenty-three were grade 2 (5.2% of patients, 48.9% of reactions), 5 were grade 3 (1.1% of patients, 10.6% of reactions), and 1 was grade 4 (0.2% of patients and 2.1% of reactions) (Table 5). The only grade 4 reaction consisted of brief loss of consciousness because of hypotension. No fatalities occurred during cluster

Table 4. Percent of Patients Experiencing a Systemic Reaction

Patients	Percent of patients experiencing a systemic reaction (no. of reactions)
All patients	10.9% (48)
Patients diagnosed with asthma	19.7% (25)
Patients without asthma	7.3% (23)
Patients <21 yrs of age	13.1% (10)
Patients age 21–40	17.8% (30)
Patients >40 yrs of age	4.3% (8)
Women	14.4% (38)
Men	5.6% (10)

immunotherapy. Of the 47 systemic reactions for which symptoms were recorded, 30 (63.8%) included cutaneous symptoms, 20 (42.6%) lower respiratory symptoms, 13 (27.7%) upper respiratory symptoms, 4 (8.5%) conjunctival symptoms, 3 (6.4%) gastrointestinal symptoms, and 1 (2.1%) cardiovascular symptoms.

One hundred twenty-seven (28.8%) of the 441 patients had a physician diagnosis of asthma. Patients with asthma had a significantly higher incidence of systemic reactions (19.7 vs 7.3%, $P = .0005$) (Table 6). Lung function was not a risk factor among patients with asthma. When FEV₁ was divided into 3 categories (<80% predicted, 80–90%, and >90%), no significant correlation was found with risk of systemic reaction ($P = .9389$). Likewise, when FEV₁ percent predicted was treated as a continuous variable, no significant correlation was found ($P = .6487$). For this analysis, the most recent

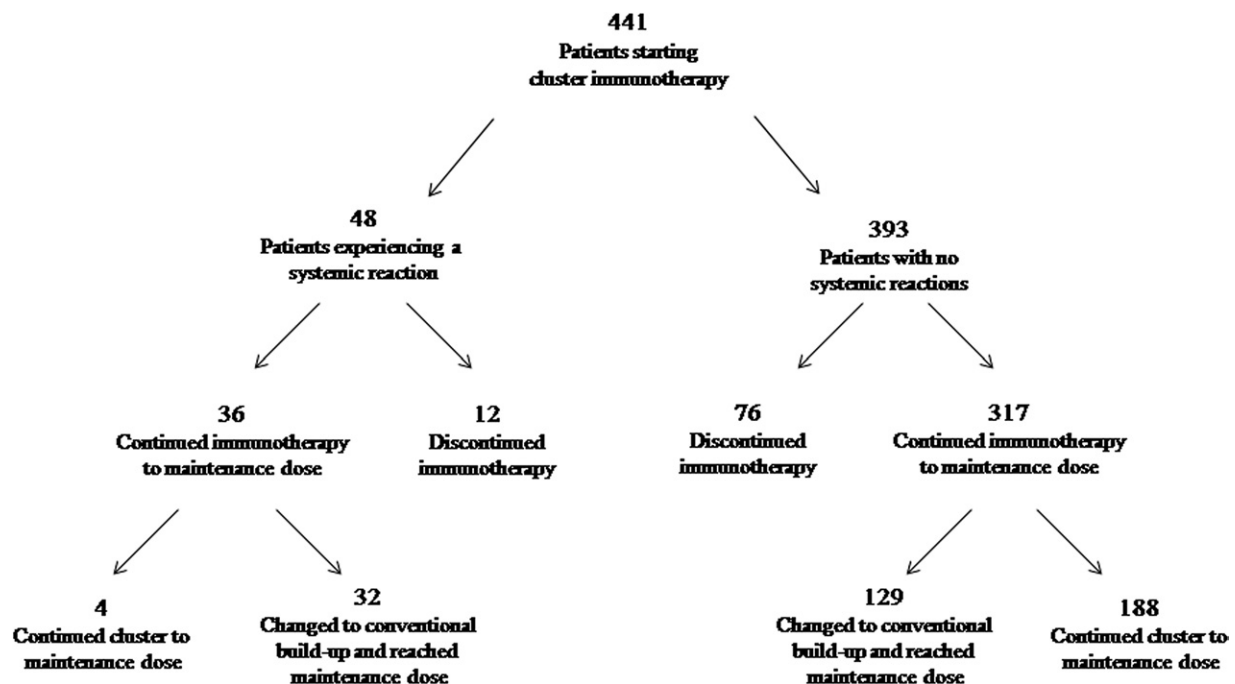


Figure 1. Patient flow.

Table 5. Systemic Reactions Occurring during Cluster Build-up

Systemic reactions	No. of reactions (% of systemic reactions)	Percent of total patients
WAO grade		
Grade 1	18 (38.3)	4.1
Grade 2	23 (48.9)	5.2
Grade 3	5 (10.6)	1.1
Grade 4	1 (2.1)	0.2
Grade 5	0 (0)	0
Organ systems involved in reaction		
Cutaneous	30 (63.8)	6.8
Lower respiratory	20 (42.6)	4.5
Upper respiratory	13 (27.7)	2.9
Conjunctival	4 (8.5)	0.9
Gastrointestinal	3 (6.4)	0.7
Cardiovascular	1 (2.1)	0.2
Reactions involving a single organ system	26 (55.3)	5.9
Reactions involving 2 or more organ systems	21 (44.5)	4.8

spirometry recorded in the patient's chart was used, and spirometry was not obtained at the first cluster dose. Of the 48 patients with systemic reactions, 25 had a diagnosis of asthma. Thirteen of these 25 patients experienced lower respiratory symptoms.

For analyses, patients were divided into 3 age groups: younger than 21 years of age, 21 to 40, and older than 40. Patients aged 21 to 40 years were significantly more likely to have a systemic reaction (17.8%) compared with patients younger than 21 years (13.1%) and older than 40 years (4.3%) ($P = .0001$).

Women were more likely to have a systemic reaction than men ($P = .0027$). Thirty-eight of the 48 (79.2%) systemic reactions occurred in women, and 59.9% of participants in the study were women.

No systemic reactions occurred with injections from the 1:1,000 (vol/vol) vial of extract. Of the 48 systemic reactions, 6 (12.5%) occurred in the 1:100 (vol/vol) vial, 25 (52.1%) in the 1:10 (vol/vol) vial, and 17 (35.4%) in the 1:1 (vol/vol) vial. Ten (20.8%) reactions occurred with the 0.25-mL dose in the 1:10 (vol/vol) vial (Table 7).

Time elapsed from eliciting injection until onset of symptoms was divided into 4 categories: less than 15 minutes, 15

Table 6. Risk Factors Associated with Systemic Reactions

Risk factor	P-value
Physician diagnosis of asthma	.0005
Grasses in immunotherapy vaccine	.0040
Weeds in immunotherapy vaccine	.0143
Cat in immunotherapy vaccine	.0018
Dog in immunotherapy vaccine	.0135
Age 21–40 years	.0001
Female sex	.0027

Table 7. Concentration of Immunotherapy Extract Leading to Systemic Reactions

Concentration of extract (vol:vol)	No. of patients (%)
1:1,000	0 (0)
1:100	6 (12.5)
1:10	25 (52.1)
1:1	17 (35.4)

to 30 minutes, 31 to 60 minutes, and longer than 60 minutes. The time between injection and onset of symptoms was not recorded for 3 reactions. Among the 45 reactions for which a time to onset was recorded, 6 (13.3%) reactions occurred less than 15 minutes after the eliciting injection was given. Fourteen (31.1%) reactions occurred after 15 to 30 minutes, 12 (26.7%) after 31 to 60 minutes, and 13 (28.8%) more than 60 minutes after the immunotherapy dose (Table 8).

Of the 441 patients, 407 patients (92.3%) routinely premedicated before their cluster immunotherapy injections. Two hundred twenty-seven patients (55.8%) premedicated with an oral antihistamine alone, 14 (3.4%) with montelukast alone, and 166 (40.8%) with a combination of medications. Among patients who experienced a systemic reaction, 46 of the 48 had premedicated before the reaction. Patients who premedicated with a combination of medications were more likely to have a systemic reaction ($P = .0488$). Of patients who did not premedicate, 5.9% had a systemic reaction. Of those premedicating, 7.9% premedicating with an oral antihistamine alone, 7.1% premedicating with montelukast alone, and 16.3% premedicating with a combination of medications had a systemic reaction.

Inclusion of certain allergens in the immunotherapy extract was significantly related to the rate of systemic reactions. Patients with grass pollen ($P = .0040$), weed pollen ($P = .0143$), cat ($P = .0019$), and dog ($P = 0.0135$) in their extract were more likely to have a systemic reaction.

One hundred five (23.8%) patients routinely received cluster doses twice per week. Three hundred one (68.3%) received them once per week, and 35 (7.9%) received them at irregular intervals. The frequency of cluster doses was not related to the rate of systemic reactions ($P = .6120$).

DISCUSSION

For nearly 100 years, accelerated rate buildup for allergen immunotherapy has offered patients a more convenient treatment option. Utilization of cluster and other accelerated protocols has been limited, in part because of concerns of im-

Table 8. Time from Eliciting Injection until Onset of Reaction

Time until onset of reaction (minutes)	No. patients (%)
<15	6 (13.3)
15–30	14 (31.1)
31–60	12 (26.7)
>60	13 (28.8)

munotherapy-induced systemic reactions. We observed that 10.9% of patients receiving cluster immunotherapy in our practice experienced a systemic reaction during buildup, an incidence exceeding our experience with conventional buildup. We previously reported a 2-year retrospective database review, which included patients receiving immunotherapy to environmental allergens and hymenoptera venom immunotherapy.²⁷ The previous study included patients on maintenance dose and in the buildup phase of treatment. Two hundred eighty-three systemic reactions were noted during the previous database review, giving a systemic reaction incidence of 0.043% of immunotherapy visits. An estimated 12,963 patients were receiving immunotherapy during the time covered by the previous retrospective study, giving an estimated incidence of 2.2 systemic reactions per 100 patients treated. Because of study design differences, it is difficult to make a direct comparison between our current review and the previous report. As expected, the current review found a higher incidence of systemic reactions, because it includes only patients in the buildup phase of immunotherapy. However, the nearly 5-fold increase in incidence may be attributable in part to the more aggressive buildup protocol.

Premedication has been reported to decrease the risk of systemic reactions with immunotherapy.^{28–30} In our experience, patients who premedicated with a combination of medications, usually an oral antihistamine and montelukast, had a higher rate of systemic reactions. Several aspects of study design complicate the interpretation of these data. First, 92% of patients premedicated in this review, making it difficult to determine a significant difference. Second, the choice of medications used for premedication was left to the discretion of the treating physician and may have led to a selection bias. Physicians may premedicate more aggressively those patients deemed a higher risk of a systemic reaction. In future studies, a standardized premedication routine could help clarify this issue.

The Allergen Immunotherapy Practice Parameter recommends a minimum 30-minute wait period after administration of immunotherapy, because most severe systemic reactions occur within 30 minutes with conventional buildup.²³ We found that only 44.4% of systemic reactions during cluster buildup occurred within 30 minutes, and 28.8% of reactions occurred more than an hour after the eliciting injection. This is similar to another cluster immunotherapy study, during which 23.8% of systemic reactions occurred within the typical 30-minute wait period.³¹ Some other accelerated buildup immunotherapy studies have noted similar findings, including 1 rush immunotherapy study, which had a mean time to onset of symptoms of 50 minutes.^{32–34} Based on these findings, providers need to make patients aware of possible delayed reactions after cluster immunotherapy visits. If future studies corroborate these findings, we may need to recommend a longer observation period with cluster immunotherapy.

Most reactions (52.1%) occurred in the 1:10 (vol/vol) vial of extract. Most patients who experienced a systemic reaction did not continue with cluster buildup and therefore selected

out patients at higher risk for a systemic reaction. Furthermore, only 43.5% of patients completed the cluster protocol to the maintenance dose. Patients who discontinued the cluster buildup did not receive all of the injections and, therefore, were not at risk of having reactions to higher concentrations of extract. If all patients had completed cluster buildup, we would have likely seen more reactions to the 1:1 vial of extract. Ten (20.8%) systemic reactions were attributed to the 0.25-mL dose in the 1:10 (vol/vol) vial. This was the 3rd dose on the 3rd cluster visit. Subsequent cluster visits included only 2 doses. By adjusting our protocol and limiting the 3rd visit to only 2 doses of extract, we may increase safety and significantly lower the rate of systemic reactions.

In our experience, patients with a physician diagnosis of asthma had a significantly higher incidence of systemic reactions, a finding supported by other studies.^{18,35} In contrast to our experience, one recent study found a similar incidence of reactions for patients with and without asthma during cluster buildup. The study by Serrano et al³¹ carefully excluded patients with uncontrolled asthma. In our review, no specific inclusion or exclusion criteria were found for patients with asthma. The decision to prescribe cluster immunotherapy for a patient was left to the discretion of the treating physician. More strict criteria relating to asthma control may decrease the risk of systemic reactions in the future. Interestingly, we found that lung function, reported as FEV₁ percent predicted, did not correlate with the incidence of systemic reactions among patients with asthma. Our protocol did not require spirometry at the time cluster buildup was started. For this review, we simply used the most recent FEV₁ recorded in the patient's chart. Therefore, the FEV₁ recorded may not have accurately reflected the patient's asthma control at the time of cluster immunotherapy. In the future, obtaining spirometry during the first cluster visit may more accurately predict the risk of reactions.

Patients aged 21 to 40 years were more likely to have a systemic reaction than both younger and older patients. Whether this is a true effect of age or artifact of selection bias is unclear. The treating physician may be more conservative when starting both younger and older patients on cluster immunotherapy and choose only patients they believe are at low risk of having a systemic reaction. Standardized criteria for patient selection could help clarify age as a risk factor.

The review's lack of specific inclusion and exclusion criteria makes analyses of risk factors more difficult. However, this review provides valuable real-world experience with accelerated immunotherapy buildup. Most clinical allergy practices do not use strict, predetermined criteria for prescribing cluster immunotherapy and leave this decision to the discretion of the treating physician. By carefully selecting patients appropriate for cluster immunotherapy based on risk factors found in our experience and the findings of others, we can offer patients the numerous benefits of cluster immunotherapy while minimizing the risk of anaphylaxis.

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