

Safety of Rapid Allergen Vaccination in Children Utilizing a 2.5-Hour Protocol

WILLIAM SMITS, M.D.,^{1,2} JEANNIE GIESE, N.P.,¹ KEVIN LETZ, N.D.,^{1,3,4}
and AUSTIN SCHLIE, B.A.¹

ABSTRACT

Immunotherapy is an accepted mode of treatment for children suffering from allergic rhinitis and allergic asthma. This study demonstrates that rapid allergen vaccination (RAV) can be as safe and effective as conventional allergen vaccination (CAV). RAV may also improve patient adherence. A total of 148 patients diagnosed with allergic rhinitis and mild to severe asthma underwent RAV over a 2.5-h period in an office-based setting. Patients were monitored for reactions during the procedure and continued on a CAV schedule. Adherence was reviewed subsequently. During the procedure, eight patients (5.4%) experienced systemic reaction, and none experienced true anaphylaxis. Typically, 6 months of build-up period was saved. Patients reached efficacious dosages almost immediately. Adherence rates were 95.3%, 90.5%, and 79.7% at 3, 6, and 12 months, respectively. Effective doses of allergen vaccine can be safely and successfully achieved using a 2.5-h protocol for children. Advantages of RAV over CAV include improved adherence with almost immediate clinical efficacy, and decreased cost for the patient. (*Pediatr Asthma Allergy Immunol* 2005; 18[3]:131–139.)

INTRODUCTION

ALLERGEN VACCINATION, otherwise known as immunotherapy, is effective in the treatment of allergic rhinitis,^{1–4} allergic asthma,^{5–11} and hymenoptera allergy.^{12,13} Conventional allergen vaccination (CAV) utilizes a protocol of weekly, gradually increasing dosages of vaccination serum until a maintenance dose is reached. Subsequently, the maintenance dose administration frequency is reduced to biweekly or monthly for a 3–5-year duration. It is the goal that upon completion of the therapy, immunity is induced and remission of the disease is achieved. Effectiveness of the CAV at altering the immune system is supported by measurable levels of IgG4 immunoglobulin.¹ CAV's mechanism of action occurs via decrease of T-helper-type-2 cells and an increase of T-helper type-1 cells that leads to decreased expression of allergic disease.

CAV has demonstrated effectiveness in the treatment of a number of allergic conditions; however, its effectiveness is usually limited because of patient adherence. Low adherence rate presents the most impos-

¹The Allergy and Asthma Center, Fort Wayne, Indiana.

²Indiana University School of Medicine, Fort Wayne Center, Fort Wayne, Indiana.

³University of Phoenix Online, Phoenix, Arizona.

⁴Indiana Wesleyan University, Fort Wayne, Indiana.

ing barrier to the effectiveness of CAV, because the therapy requires long-term commitment and discipline. Adherence rates at 1 year for CAV above 60% are very unusual.^{14,15}

Rapid allergen vaccination (RAV), otherwise known as rapid desensitization or rush immunotherapy, may improve adherence by providing the patient with quicker efficacy than CAV schedules and thus reducing morbidity from the allergic disease. Moreover, RAV can eliminate up to 6 months of weekly and costly build-up injections, resulting in cost savings for both the physician and patient (in terms of time and material).

An immunizing dosage is achieved much more quickly with RAV than with CAV. Through a series of increasing doses of allergen serum, a patient may reach an effective "maintenance dose" in a period of 1–7 days.^{10,16,17} The major controversy surrounding this procedure is its safety; more specifically, its potentially increased risk of systemic reactions resulting in anaphylaxis or death.^{18,19} Systemic reactions have been reported to be greater than 15% in previous studies.^{17,20–23} Recently, Sharkey and Portnoy²⁴ reported a systemic reaction rate of 23%. Their report described these rates as comparable to CAV,²³ with reported rates of 0.8–46.7%. Such high rates of reaction are unacceptable for utilization of the procedure in the office setting. Most practicing allergists would agree that these rates are much higher than those occurring in their offices.

Encouraged by the preliminary findings of Inglefield in a 1996 abstract at the annual meeting of the American College of Allergy, Asthma, and Immunology, an effort was initiated to improve this procedure to assure optimal safety. Subsequent research demonstrated that with careful patient selection, premedication, and a lower targeted endpoint dose, RAV could be performed safely and effectively in the private clinical setting.²⁵ However, the publication also indicated that age, notably children (especially those of pediatric age), was an important risk factor for systemic reactions from RAV, prompting further investigation of this hypothesis.²⁵ The purpose of this study is to investigate, through a retrospective chart analysis of pediatric patients, whether the procedure of RAV is both safe and effective in the office-based setting of the practicing allergist. This study looks at the systemic reaction rate and adherence of patients 1–18 years old.

MATERIALS AND METHODS

Selection of patients

The demographics and age distribution of the RAV patients can be found in Table 1. There were 148 patients involved in this study. The age of the patients was 1–18 years. All were selected from an office-based allergy setting. All patients were diagnosed with one or more of the following conditions: allergic rhinitis, allergic asthma and chronic sinusitis; each exhibited IgE positivity by percutaneous testing and exhibited a history consistent with allergic mediated disease. All patients were given the choice between CAV and RAV. Informed consent, outlining the potentially greater risks for the RAV procedure, including the potential greater risk of anaphylaxis, was obtained from all patients who underwent the procedure.

Exclusion criteria included the following:

1. A history of anaphylaxis
2. A FEV₁ of <70% predicted by pulmonary function testing
3. A history of cardiovascular disease
4. Current beta-blocker therapy

TABLE 1. NUMBER OF RAV PATIENTS OF EACH SEX AND EXEMPLIFYING SPECIFIC DIAGNOSES

<i>Males</i>	<i>Females</i>	<i>Allergic rhinitis</i>	<i>Chronic sinusitis</i>	<i>Asthma</i>
88	60	143	23	118

RAV, rapid allergen vaccination.

PEDIATRIC RAPID ALLERGEN VACCINATION

The study also received institutional review and approval by Parkview Institutional Review Board, Fort Wayne, Indiana.

Percutaneous allergy testing

Commercial allergy testing extracts used included 1:10 (wt/vol) standardized glycerinated extracts from Greer Laboratories (Lenoir, NC). Epicutaneous technique was performed with the DermaPick (Greer Laboratories, Lenoir, NC). Intradermal tests were placed with the same allergen extract using a 1:2,000 dilution with 25-gauge syringes. Tests were read 20 min after placement. Skin sensitivity was measured as millimeters of wheal and flare. Those who tested negative to percutaneous testing underwent further intradermal testing to confirm IgE sensitivity. Intradermal tests were considered positive when either the wheal or flare was ≥ 5 mm than the negative diluent control.

Allergen vaccination extract

Vaccine extracts were prepared using stock formulations from Greer Laboratories. Both aqueous and glycerinated extracts were used to achieve a concentrate of 1:100 wt/vol of the mixed extract. Serial 10-fold dilutions of this concentrate were prepared identically to that used for CAV. Targeted final dose during the RAV procedure was that of a 1:1,000 dilution to minimize systemic reactions. Separate vials were used for pollen and mold extract to reduce proteolytic degradation. All extracts were stored at approximately 4°C. Serum varied with each individual patient. A combination of 2–32 allergens were mixed together to achieve the final dilution of 1:100, which was approximated. Most patients' serum included a variety of aero-allergens, including a combination of mold, tree, grass, weed, mite, dust, cat, and dog. Standardized extracts for ragweed, cat, dust mite, and grass were used. The final dosage concentrations for these allergen extracts are listed in Table 2.

Procedure for rapid allergen vaccination

All patients presenting to the clinic who were thought to benefit from immunotherapy were given the option to begin this therapy. Patients who were considered acceptable candidates for this procedure as outlined above were given the option to participate in the RAV procedure as an alternative to CAV. Once candidates were identified, the procedure was scheduled 1–2 weeks later. A 3-day premedication regimen of prednisone and antihistamine was prescribed as follows: for patients aged 1–12 years, prednisone or prednisolone, 20 mg BID; and for ages 12 and over, prednisone, 30 mg BID. The antihistamine used included cetirizine, fexofenadine, and loratidine at the age-appropriate dosage. Previous use, side effects, insurance, age, form (e.g., syrup, pill, chewable) were all factors considered in choosing the appropriate antihistamine for individual patients. It was not investigated whether or not the specific antihistamine had an effect on likelihood of systemic reaction. Generally, the usual antihistamine that the patient had success with previously or was currently using was chosen for the purpose of premedication. An informed consent, approved by an institutional review board, was explained by a registered nurse and then obtained with a written consent form signed by the patient if 18 years of age or the parent/guardian if the patient was younger than 18 years of age.

TABLE 2. FINAL DOSAGE CONCENTRATIONS OF UNSTANDARDIZED ALLERGEN EXTRACTS

<i>Allergens</i>	<i>Concentration</i>
Grasses	4000 BAU in 0.4 cc of 1:10 concentration
Dust mite	200 BAU in 0.4 cc of 1:10 concentration
Cat	400 BAU in 0.4 cc of 1:10 concentration
Ragweed	4.76 U/mL in 0.4 cc of 1:10 concentration

On the day of the procedure, patients were reassessed with a history, physical examination, and spirometry. Any documented clinical worsening (e.g., upper respiratory infection [URI] or decreased spirometry) resulted in rescheduling of the procedure.

The dosing schedule is outlined in Table 3. The administration schedule was developed by reviewing the literature and assessing the reasons other researchers (specifically Portnoy et al.) were experiencing relatively high reaction rates.^{22,24} Given high systemic reaction rate in the most concentrated vials, the resulting schedule appeared to best minimize reaction risk. The premedication schedule resembled that of previous studies cited in the bibliography.^{22,24} If patients received two injections (e.g., separated pollen and fungal allergens), one was administered in each arm using the same schedule. We did not alternate arms for injections. Patients were observed for 30 min after their last injection and discharged if stable. After the RAV procedure, patients resumed a CAV schedule.

Data analysis

The purpose of this study is to investigate, through a retrospective chart analysis, whether the procedure of RAV is both safe and effective in the office-based setting of the practicing allergist. The study investigated a group of patients ranging in age from 1 to 18 years having undergone the RAV at least 1 year prior to the study at The Allergy and Asthma Center, P.C. Thus, the patients included in this study have undergone the RAV procedure between the years of 1998 and 2002.

A database that was previously designed for the purpose of organizing the data pertaining to all patients that have undergone the RAV procedure was queried, and the information relating to the particular study was sequestered. Variables that are considered and recorded for the purpose of the study include the following:

1. Age
2. History and prior diagnoses of rhinitis, sinusitis, conjunctivitis, and asthma
3. Local reactions, systemic reactions, anaphylaxis
4. Adherence at 3, 6, and 12 months following the completion of the procedure

The variables of age, rhinitis, sinusitis, conjunctivitis, and asthma have been selected for analysis in order to provide an idea of the respiratory medical background of the patients in this age group that have undergone RAV, as well as give indication of the application and extension of these results to similar cohorts. The variables of local reactions, systemic reactions, and anaphylaxis resulting during the RAV procedure were chosen as indicators of the safety of the RAV procedure. Adherence of the patients at 3, 6, and 12 months upon resuming a CAV schedule after the completion of the RAV is used to compare the adherence with RAV to adherence rates in the literature for those undergoing purely CAV.

The results of this study are reported as ratios and standard percentages of the entire cohort. Systemic and local reaction rates, anaphylaxis rates, and adherence at 3, 6, and 12 months for the patients undergo-

TABLE 3. DOSING SCHEDULE FOR PATIENTS RECEIVING A 2–3 h RAV PROCEDURE

<i>Time (min)</i>	<i>Volume (cc)</i>	<i>Dilution</i>
0	0.025	1:1,000,000
15	0.25	1:1,000,000
30	0.025	1:100,000
45	0.25	1:100,000
60	0.025	1:10,000
75	0.25	1:10,000
90	0.025	1:1,000
105	0.1	1:1,000

RAV, rapid allergen vaccination.

PEDIATRIC RAPID ALLERGEN VACCINATION

ing RAV in this study are then compared to the reaction rates of conventional allergen vaccination published in the literature. Subsequently, these results provide the grounds for the drawing of appropriate conclusions for the study.

RESULTS

A total of 148 patients underwent rapid desensitization utilizing a 105-min protocol (Table 3). They ranged from 1 to 18 years of age. Of the 148 patients, 88 of them were male (59.5%), and 60 of them were female (40.5%); 143 (96.6%) of the patients had allergic rhinitis, 118 (79.7%) had asthma, and 23 (15.5%) had chronic sinusitis (Table 1).

Systemic reactions to RAV

Systemic reactions occurred in eight of the 148 patients (5.4%) between the second and final dose of the procedure, and none of the patients experienced anaphylactic shock. A detailed description of each systemic reaction can be found in Tables 4 and 5. All eight patients who suffered a systemic reaction were patients with asthma on inhaled corticosteroids, three of the eight patients were male (37.5%), and five of the eight were female (62.5%). All of the patients were treated and sent home the same day. Each patient was monitored one-on-one by a trained physician or nurse for at least 60 min following an adverse event. All of the patients continued with a CAV regimen following the rapid protocol. Every systemic reaction occurred within 15 min of the injection. Treatment usually included one or a combination of the following: nebu-

TABLE 4. DESCRIPTION AND TREATMENT OF SYSTEMIC REACTIONS TO RAV

<i>Patient no.</i>	<i>Age/sex</i>	<i>Reaction</i>	<i>Time to reaction</i>	<i>Reaction dose</i>	<i>Treatment</i>	<i>Late reaction</i>
28	13/M	Difficulty breathing	5 min	0.025 mL of 1:1,000	Nebulized albuterol	No
56	15/F	Chest tightness	5 min	0.1 mL of 1:1,000	Nebulized albuterol	No
64	13/F	Chest tightness, shortness of breath, inflammation of neck and back	15 min	0.25 mL of 1:100,000	25 mg Benedryl (finished RAV schedule)	No
88	8/M	Coughing, Chest congestion	15 min	0.25 mL of 1:10,000	Prednisone 30 mg twice daily	No
93	18/F	Chest tightness	15 min	1.0 mL of 1:1,000	Nebulized Xopenex	No
113	7/M	Throat tightness	15 min	0.025 mL of 1:1,000	None (self-limited)	No
119	7/F	Chest tightness	15 min	0.1 mL of 1:1,000	None (self-limited)	No
140	10/F	Chest and throat tightness, shortness of breath, minimal cough	15 min	0.25 mL of 1:100,000	Maxair 2 puffs, Astelin 2 × each nare, nebulized albuterol	Yes

RAV, rapid allergen vaccination.

TABLE 5. CHARACTERISTICS OF PATIENTS WHO EXPERIENCED SYSTEMIC REACTIONS TO RAV

Patient no.	Age	Sex	Rhinitis	Asthma	Mold	Tree	Grass	Weed	Mite	Dust	Cat	Dog
28	13	M	X	X	X	X	X	X	X	X		X
56	15	F	X	X	X	X	X	X	X	X	X	X
64	13	F	X	X	X	X	X	X	X	X		X
88	8	M	X	X	X	X	X	X	X	X	X	X
93	18	F		X	X	X	X	X	X	X		
113	7	M	X	X	X	X	X	X	X	X		X
119	7	F	X	X	X	X	X	X	X	X	X	
140	10	F	X	X	X				X	X		

RAV, rapid allergen vaccination.

lized breathing treatment with albuterol, two sprays in each nostril of azelastine, and diphenhydramine taken orally or intramuscularly. Every patient that was treated was discharged within several hours, and no one required treatment with subcutaneous epinephrine or hospitalization. The patients who reacted were not given epinephrine because the reactions are better characterized as moderate hypersensitivity reactions rather than anaphylactic shock according to a recent study by Brown published in the *Journal of Allergy and Clinical Immunology*.²⁶ Indeed, mild rhinorrhea is considered a systemic reaction; however, the use of epinephrine in such a case would constitute over-treatment. Epinephrine was available and prepared for these patients in case the initial therapy failed. The extract composition of those patients who had a systemic reaction included mold (100%), tree (87.5%), weed (87.5%), and grass (87.5%).

Build-up period

After the RAV procedure, patients typically required ≥ 2 more months of build-up to achieve their targeted maintenance dose.

Adherence

The adherence rate for patients undergoing the RAV procedure can be found in Table 6. The adherence rate at 3 months was found to be 95.3%, at 6 months 90.5%, and after 12 months 79.7%.

DISCUSSION

CAV is an effective and safe procedure that has been shown to significantly improve symptoms associated with allergic disease.¹⁻¹³ CAV is often viewed by patients and referring physicians as an inconvenient procedure^{14,15} that can take as much as a year or longer to reach efficacy. As a result, a strategy that enhances efficacy and retains the safety associated with CAV would be a welcome treatment option. RAV is an alternative procedure that shows great promise to enhance adherence and thus improve efficacy over CAV.

TABLE 6. ADHERENCE WITH RAV AT 3, 6, AND 12 MONTHS

Months after RAV procedure	Total number of patients	Adherence (%)
3	141	95.3
6	134	90.5
12	118	79.7

RAV, rapid allergen vaccination.

PEDIATRIC RAPID ALLERGEN VACCINATION

In a previous study of all ages, we investigated the safety and efficacy of RAV in 137 patients. It was found that the systemic reaction rates for RAV compared favorably to the reaction rates of CAV as well as the reaction rates of earlier RAV studies.²⁵ Moreover, those patients who underwent RAV exhibited a high adherence rate compared to reported CAV rates.²⁵ (Because this was a retrospective study, a corresponding CAV cohort was not available.)

A corollary finding of the before-mentioned study was that the pediatric age group may be associated with increased risk of systemic reaction. Four of the six patients experiencing a systemic reaction were 13 years of age or younger, accounting for 66.7% of the systemic reactions. Only 36 patients of the entire patient cohort of 137 patients fell in this age group, representing 26.3% of their study population. Thus, the associated systemic reaction rate of the group of patients 13 years of age and younger is 11.1%.

In previous studies, high rates of systemic reactions have limited the utilization of RAV by practitioners.^{17,19,21–23} In this study we have found that RAV is just as safe in patients 18 years of age and younger as in adults. Systemic reaction rates for this study were comparable to those found in our earlier study of patients of all ages, and compared favorably to those of Portnoy et al.^{22–25} We have found that through careful patient selection and routine premedication, the risk of systemic reactions is greatly reduced.^{27,28}

The main reason for the reduced systemic reactions compared to previous reports relates primarily to our lower targeted endpoint vaccination dosage for the RAV procedure. In previous studies, the higher dosages that were administered led to a high rate of systemic reactions.²⁴ By reducing the dosage, a significant drop in systemic reactions was observed. Our targeted endpoint dosage represents a 10-fold reduction in dosage compared to that of Portnoy et al.^{24,25} In fact, had we utilized a 100-fold reduction in dosage, our systemic reactions may have decreased another 37.5% because patients 56, 113, and 119 reacted to the most concentrated dose (1:1,000 dilution).

With the rising costs in the last ten years for the treatment of asthma and allergic diseases, the cost effectiveness of treatments has become a major concern for patients and insurance companies alike.²⁹ The latest immune therapy, Omalizumab, can exceed \$20,000 annually. Because of the rising cost of allergy and asthma treatments, cost-effective healthcare for allergic patients has become a priority for allergists. Patients who undergo RAV can save up to 6 months of a build-up period, reducing the cost of therapy by as much as 50% in the first year of immunotherapy (calculated by eliminating 24 weekly vaccinations). The simplification of treatment and reduction of personal economic cost appears to have increased patient adherence.

Inconvenience is cited in previous studies as being the number one reason for patients discontinuing allergen vaccinations.^{14,15,30} Thus, the rate of allergen vaccination drop out is high. In contrast to CAV, RAV has reduced the time period for allergen vaccination by several months, achieved effective doses within weeks, and as a result has substantially increased efficacy and adherence to therapy. Our adherence rate at 12 months was 79.7%, which is significantly higher than the previously reported adherence rates of Lower et al.¹⁵ and Cohn and Pizzi's¹⁴ of 56% and 50%, respectively, for patients undergoing CAV. Other possible advantages of RAV include quicker accruing of immunotherapy benefits than with CAV, resulting in less morbidity, decreased medication, decreased symptoms, decreased emergency room visits and fewer hospitalizations.

The purpose of this study was to investigate, through a retrospective chart analysis of pediatric patients, whether the procedure of RAV utilizing a modified 105-min protocol is both safe and effective in the office-based setting of the practicing allergist. RAV can be utilized in the treatment of a variety of patients that are typically seen in an allergist's office. The authors were motivated to pursue this study of RAV in pediatric patients because of this age group's previously reported higher risk of systemic reaction for reasons that were unclear.²⁵ It was the desire of the authors to better understand this apparent risk factor. By performing the RAV procedure in our office with proper monitoring, medical equipment, and trained personnel, the maintenance dosage was accomplished in a safe and controlled environment for pediatric patients.

CONCLUSION

RAV using a 2.5-h protocol with premedication is a safe and effective procedure for allergic rhinitis and allergic asthma. Patients undergoing this procedure are able to reach a maintenance dosage in a shorter time

than with CAV. Caution and clinical judgment should be exercised when using this procedure. It is emphasized that allergists must use their best judgment and experience to select patients for this procedure, just as they would in the careful selection of patients for traditional immunotherapy, because anaphylaxis can occur. We found that systemic reactions occur less frequently with this procedure when using lower targeted endpoint vaccination doses than previously reported and patients may continue on CAV schedules to achieve the ultimate targeted maintenance vaccine dosage.

ACKNOWLEDGMENT

This research was previously presented as an abstract at the 2004 Annual Meeting of the American College of Allergy, Asthma & Immunology, Boston.

REFERENCES

1. Creticos PS. Immunotherapy with allergens. *JAMA* 1992; 268:2834–2839.
2. McHugh SM, Lavelle B, Kemeny DM, et al. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssinus* in allergic rhinitis, comparing clinical outcome with changes in antigen specific IgE, IgG, and IgG subclasses. *J Allergy Clin Immunol* 1990; 86:521–531.
3. Norman P, Van Metre TE. The safety of allergenic immunotherapy. *J Allergy Clin Immunol* 1990; 85:522–525.
4. Ross R, Nelson H, Finefold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin Ther* 2000; 22:342–350.
5. Bousquet J, Michel FB. Specific immunotherapy in asthma: is it effective? *J Allergy Clin Immunol* 1994; 94:1–11.
6. Cantani A, Businco E, Benincori N, et al. A three-year controlled study in children with pollinosis treated with immunotherapy. *Ann Allergy* 1984; 53:79–84.
7. Cantani A, Arcese G, Lucenti P, et al. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. *J Investig Allergol Clin Immunol* 1997; 7:90–97.
8. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. *J Allergy Clin Immunol* 1993; 91:709–722.
9. Malling HJ. Allergen-specific immune therapy in the treatment of asthma. *Ugeskr Laeger* 2000; 162:477–479.
10. Nagata M, Yamamoto H, Tabe K, et al. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: changes in in vivo and in vitro responses to HDM. *Intern Med* 1993; 32:702–709.
11. Ross R, Nelson H, Finefold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther* 2000; 22:329–341.
12. Bernstein DI, Mittman RJ, Kagen SL, et al. Clinical and immunologic studies of rapid venom immunotherapy in *Hymenoptera*-sensitive patients. *J Allergy Clin Immunol* 1989; 84:951–959.
13. Ross R, Nelson H, Finefold I. Effectiveness of specific immunotherapy in the treatment of *Hymenoptera* venom hypersensitivity: a meta-analysis. *Clin Ther* 2000; 22:351–358.
14. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993; 91:734–737.
15. Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. *Ann Allergy* 1993; 70:480–482.
16. Bousquet J, Calvayrac P, Guerin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. *In vivo* and *in vitro* parameters after a short course of treatment. *J Allergy Clin Immunol* 1985; 76:734–744.
17. Hejjaoui A, Ferrando R, Dhivert H, et al. Systemic reactions occurring during immunotherapy with standardized pollen extracts. *J Allergy Clin Immunol* 1992; 89:925–933.
18. Bousquet J, Guerin B, Dotte A, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. *Clin Allergy* 1985; 15:179–192.

PEDIATRIC RAPID ALLERGEN VACCINATION

19. Sundin B, Lilja G, Graff-Lonnevig V, et al. Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. *J Allergy Clin Immunol* 1986; 77:478–487.
20. Bousquet J, Hejjaoui A, Dhivert H, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol with patients suffering from asthma. *J Allergy Clin Immunol* 1989; 83:797–802.
21. Hejjaoui A, Dhivert H, Michel FB, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol* 1990; 85:473–479.
22. Portnoy J, King K, Kanarek H, et al. Incidence of systemic reactions during rush immunotherapy. *Ann Allergy* 1992; 68:493–498.
23. Stewart GE II, Lockey RF. Systemic reactions from allergen immunotherapy. *J Allergy Clin Immunol* 1992; 90:567–578.
24. Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. *Ann Allergy Asthma Immunol* 1996; 76:175–180.
25. Smits W, Inglefield JT, Letz K, et al. Improved immunotherapy with a rapid allergen vaccination schedule: a study of 137 patients. *Ear Nose Throat J* 2003; 82:881–887.
26. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004; 114:371–376.
27. Nielson L, Johnsen CR, Mosbech H, et al. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 1996; 97:1207–1213.
28. Portnoy J, Bagstad K, Kanarek H, et al. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy* 1994; 73:409–418.
29. Allergen immunotherapy: therapeutic vaccines for allergic diseases. 1998; *Allergy* 44(Suppl):1–42.
30. Rudd S. Immunotherapy compliance—a shot in the dark. *Ann Allergy Asthma Immunol* 1995; 74:195–198.

Address reprint requests to:

W.L. Smits, M.D.

The Allergy and Asthma Center

7230 Engle Road, Suite 300

Fort Wayne, IN 46804

E-mail: wlsmits@allergyasthmacenter.com