



Allergen immunotherapy practice patterns: a worldwide survey

Punita Ponda, MD ^{*}; Sima Mithani, MD ^{*}; Yelena Kopyltsova, MD ^{*}; Cristina Sison, PhD [†]; Payel Gupta, MD [‡]; Désirée Larenas, MD [§]; and Vincent R. Bonagura, MD ^{*}

^{*} North Shore-Long Island Jewish Health System, Great Neck, New York

[†] Feinstein Institute for Medical Research, Manhasset, New York

[‡] SUNY Downstate Medical Center-Long Island College Hospital, Brooklyn, New York

[§] Hospital Medica Sur, Mexico City, Mexico

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ABSTRACT

Background: Allergists around the world have different practice styles when administering subcutaneous aeroallergen immunotherapy (IT) in peak pollen seasons, especially when changing doses or frequency of IT. The Immunotherapy practice parameters do not specifically address this issue.

Objectives: Given the paucity of good data about adjustment of allergen immunotherapy during the pollen seasons, we examined whether a significant difference is present in the way allergists administer immunotherapy during allergy seasons.

Methods: To quantify the practice styles of allergists who are members of the American Academy of Allergy, Asthma and Immunology (AAAAI), a self-reported electronic survey was disseminated in September 2010 with the help of the AAAAI Needs Assessment Committee. The responses were tallied and analyzed according to demographic information.

Results: A total of 1,201 allergists in the AAAAI responded to the survey. Most responders practice in an urban or suburban nonacademic practice in the United States and have been in practice for more than 10 years. The size of their practice was variable. Those in practice for more than 10 years were more likely to adjust the dose and frequency of immunotherapy in pollen seasons.

Conclusion: This survey highlights the differences in the practice styles of AAAAI member allergists, and these differences may be associated with their demographic characteristics. Given the wide variability in how allergists adjust dose and frequency of immunotherapy during pollen seasons, establishing guidelines regarding this routine dilemma might help standardize the delivery of treatment to patients.

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Introduction

Allergen-specific immunotherapy has been used for at least a century as a desensitizing treatment for allergic diseases in children and adults. Since the original observation by Noon that treatment with whole grass pollen extract reduced symptoms from hay fever, we continue to use mainly whole allergen extracts as the primary mode of administration of subcutaneous allergen immunotherapy (SCIT).¹ However, since that time our understanding of the mechanisms of immunotherapy, and the immunological changes conferred by its administration has increased dramatically.² Currently, the clinical efficacy of SCIT in the treatment of allergic rhinitis, allergic conjunctivitis, asthma, and stinging insect hypersensitivity is well established.^{3,4}

Allergists have attempted to develop immunotherapy dosing protocols since the early 1900s, with the first documented rush protocol being developed in 1928.⁵ In 1996, the full immunotherapy practice parameters were published with specific guidelines for the dosing and the frequency of immunotherapy. Recommendations for major allergen content for optimal efficacy were published in the World Health Organization position paper in 1998.⁶ Advances in the past have depended on understanding the mechanism involved and the characterization and standardization of allergen extracts.⁷

More recently, the Joint Task Force on Practice Parameters developed an updated practice parameter for allergen immunotherapy, which was released in January 2011 in the *Journal of Allergy and Clinical Immunology*. The parameters establish guidelines for providing safe and effective allergen immunotherapy and, in turn, were expected to reduce variations in practice styles.

However, allergists around the world employ a variety of practice styles that may not be fully consistent with recommendations. For example, self-reported surveys administered to AAAAI allergists in 2004 and 2006 confirmed significant variability in the AAAAI member practices.⁸ Also, over the last several decades no

Reprints: Punita Ponda, MD, Department of Allergy & Immunology, North Shore-Long Island Jewish Health System, 865 Northern Boulevard, Suite 101, Great Neck, NY 11021; E-mail: pponda@nshs.edu.

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consistent consensus has been reached on the appropriate frequency of administration of immunotherapy during pollen season.^{9–11} Subsequent to the 2006 survey, two updates of the Immunotherapy Practice Parameters have been made. However, whether the practice parameters and other methods of communicating suggested practice guidelines have led to more uniformity is unclear.

In practice, knowledge of the methods employed by allergists regarding specific routine decisions about dosing and frequency of immunotherapy would be useful to determine the extent of variability in the day-to-day administration of immunotherapy worldwide. In this study, we attempted to objectively quantify the variability in administration of immunotherapy and correlate the extent of variability with suggested guidelines or, in some cases, the lack of guidelines.

Methods

Study design and setting

To quantify the practice styles of allergists who are members of the AAAAI, an electronic survey was disseminated in September 2010 via Survey Monkey with the help of the AAAAI Immunotherapy Committee and with the approval of the AAAAI Needs Assessment Committee. The link to the voluntary survey was distributed via e-mail in the fall of 2010, and the data obtained was collected anonymously through this survey site. Potential participants were informed in detail about the study goals and the survey procedures. The survey questions inquired about demographics and background information of each respondent, practice styles for dose and frequency changes during pollen seasons, contingencies for gaps in immunotherapy treatment, and overall duration of immunotherapy. Participants consented by answering question 1 on the survey, which required a yes or no response to the statement “I agree to participate in this survey and understand that it is anonymous and data will be reported in aggregate form only.” Questions 2 through 28 inquired about demographics and extract dosing information. Questions 29 through 41 approached issues regarding practice styles for dose and frequency changes during the pollen season. Questions 42 through 60 concerned gaps in immunotherapy treatment. Questions 61 through 66 elicited information regarding the duration of immunotherapy. Results for questions 42 through 66 will be discussed further in a separate publication. Please see the eAppendix for the complete questionnaire.

Statistical analysis

The objective of the study was to describe the basic demographic characteristics of allergists and immunologists with respect to area (urban/suburban) and type of practice (academic/nonacademic), years in practice and size of practice, and to correlate the variety of practice styles (dose and frequency adjustments) when administering subcutaneous immunotherapy during peak pollen seasons with the demographic characteristics.

The statistical approach used to analyze the questionnaire was primarily descriptive in nature. Formal statistical methods (eg, contingency tables, odds ratios, *t* tests, Fisher's exact tests) were carried out to investigate possible associations between demographic characteristics and various practice styles and beliefs.

No statistical analysis was done of the questionnaire items with open-ended responses; these responses were descriptively listed and interpreted by the clinical investigators.

Results

A total of 1,201 AAAAI worldwide members responded to the survey (25% response rate). Among these, 93% (*n* = 1,119) reported currently prescribing subcutaneous immunotherapy.

Table 1

Demographics of survey respondents based on county of practice, years in practice, practice area, practice setting, and number of SCIT patients seen in practice per month

Characteristics	Responders
Country of practice (<i>N</i> = 1,056)	
USA	912 (86%)
Europe	35 (3%)
Canada	37 (4%)
Other	72 (7%)
Years in practice (<i>N</i> = 1,057)	
< 10 years	376 (36%)
> 10 years	681 (64%)
Practice area (<i>N</i> = 1,061)	
Urban	451 (42%)
Suburban	558 (53%)
Rural	52 (5%)
Practice setting (<i>N</i> = 1,052)	
Academic	322 (31%)
Nonacademic	730 (69%)
Number of SCIT patients (<i>N</i> = 1,078)	
<100	376 (35%)
100–400	406 (38%)
>400	296 (27%)

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy.

Demographic results

The respondents were diverse in practice location, practice type, years of practice, and the size of the practice (Table 1 and eFig 2). However, most respondents were from the United States, practicing in a suburban area in a nonacademic setting with more than 10 years of experience.

Unit of measurement for allergens

We tabulated the responses for the unit of measurement most commonly used for dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, grass pollen, and tree pollen.

For *D. farinae* (*D.f.*) given together with *D. pteronyssinus* (*D.p.*), most allergists use allergy unit (AU) as the unit of measure for the extract. The allergists' choice of AU as a unit of measure was not significantly associated with any of the demographic characteristics.

Similarly for *D. farinae* or *D. pteronyssinus* given without the other, AU was the most likely unit of measure, although approximately 15% of the respondents did not use this measure. Again, no significant difference was seen between allergists who used AU as the unit of measure and those who do not with respect to any of the demographic characteristics. Those who did not use AU as a unit of measurement reported using the following units instead: micrograms, protein nitrogen unit (PNU), bioequivalent allergy unit (BAU), therapeutic units (TU), index of reactivity (IR), SQ-units/mL, and mass units.

For cat IT, approximately 90% of responders used BAU (standardized extract) as recommended by the 2011 practice guidelines.¹⁰ Similarly, no significant association was seen with demographic characteristics and the likelihood of using units of measure other than BAU. These other units of measurement were micrograms, PNU, TU, IR, weight/volume (wt/vol), and SQ-units/mL.

For grass pollen, approximately 90% of the responders use units of BAU, PNU, or wt/vol. No European practitioners used measures other than BAU, PNU, or wt/vol. The other units of measurement used were micrograms, TU, IR, and SQ-units/mL.

When asked about tree pollens, more than 13% of responders stated that they use extracts with units of measure other than BAU, PNU or wt/vol. European practitioners did not use any other measures than the ones listed above. However, 25% of Canadian allergists, and 12% of those in the remainder of the world used units

Table 2
Practitioners who dose adjust during pollen season

Characteristics	Proportion who dose adjusted during pollen season	P
Country of practice		
USA (N = 508)	199 (39%)	.001
Europe (N = 16)	13 (81%)	
Canada (N = 21)	13 (62%)	
Other (N = 40)	15 (6%)	
Years in practice		
<10 years (N = 193)	66 (34%)	.02
>10 years (N = 391)	175 (45%)	
Practice area		
Urban (N = 232)	109 (47%)	NS
Suburban (N = 320)	121 (38%)	
Rural (N = 35)	12 (34%)	
Practice setting		
Academic (N = 167)	72 (43%)	NS
Non-academic (N = 416)	167 (40%)	
Number of SCIT patients		
<100 (N = 156)	65 (42%)	NS
100–400 (N = 234)	91 (39%)	
>400 (N = 174)	82 (47%)	

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy; NS, non-statistically significant with $P > .05$.

Data are based on county of practice, years in practice, practice area, practice setting, and number of SCIT patients seen in practice per month. Responses are tabulated based on percentage answering affirmatively to dose adjustment during pollen season.

other than BAU, PNU, or wt/vol for tree pollen such as TU, IR, micrograms, or SQ-units/mL.

The diversity of responses for target maintenance dose for dust mites, cat, grass, and tree pollens showed a poor understanding of the intended question. Thus, none of these responses was used in further statistical analysis or interpretation.

Dose adjustment during peak pollen season

When other factors such as peak pollen season influence decisions about immunotherapy, approximately 11% of responders change doses of immunotherapy for all of their patients, 31% change doses for select patients, and the remainder do not dose adjust ($P < .02$; Table 2). Of the practitioners who dose adjust during peak pollen season, European and Canadian allergists were more likely to adjust doses during peak pollen season than allergists in any other country (81% and 62% versus approximately 40%; $P < .002$). Thirty-four percent of allergists in practice for less than 10 years and 45% of allergists in practice for more than 10 years tend to dose-adjust during the peak pollen season. Of the practitioners who did adjust doses, approximately one fourth changed doses during the buildup phase of IT, one fourth changed during maintenance, and half changed during both buildup and maintenance. Practitioners in practice for more than 10 years were significantly more likely to dose adjust during buildup and maintenance ($P < .03$). In contrast, 48% of allergists in practice for less than 10 years dose adjust during the buildup phase only. The remainder of the demographic characteristics were not significantly associated with patterns of dose adjustment. In addition, of the responders who did dose adjust during pollen season, most adjust by decreasing the dose by a certain percentage of the original dose. (See Fig 1 and eFig 3).

Dose adjustment based on symptoms and skin test reactivity

Most practitioners (58%) did adjust IT doses for upper airway allergic symptoms (eFig 1 and eTable 1). However, the practitioner demographics did not significantly affect their decision to dose adjust. Most responders were also likely to adjust the dose for asthma symptoms. Those allergists in practice for less than 10 years (100%) always reduced doses in comparison with those allergists in

practice for 10 years or more (87%) to reduce the dose for patients with asthma symptoms ($P < .02$). Unlike European allergists, most allergists in the United States and other countries were significantly more likely to reduce the SCIT dose for a high rate of skin test reactivity ($P < .001$). Allergists in practice for 10 years or more reduce doses for the high rate of skin reactivity more often than allergists in practice for less than 10 years (63% vs 42%; $P < .004$).

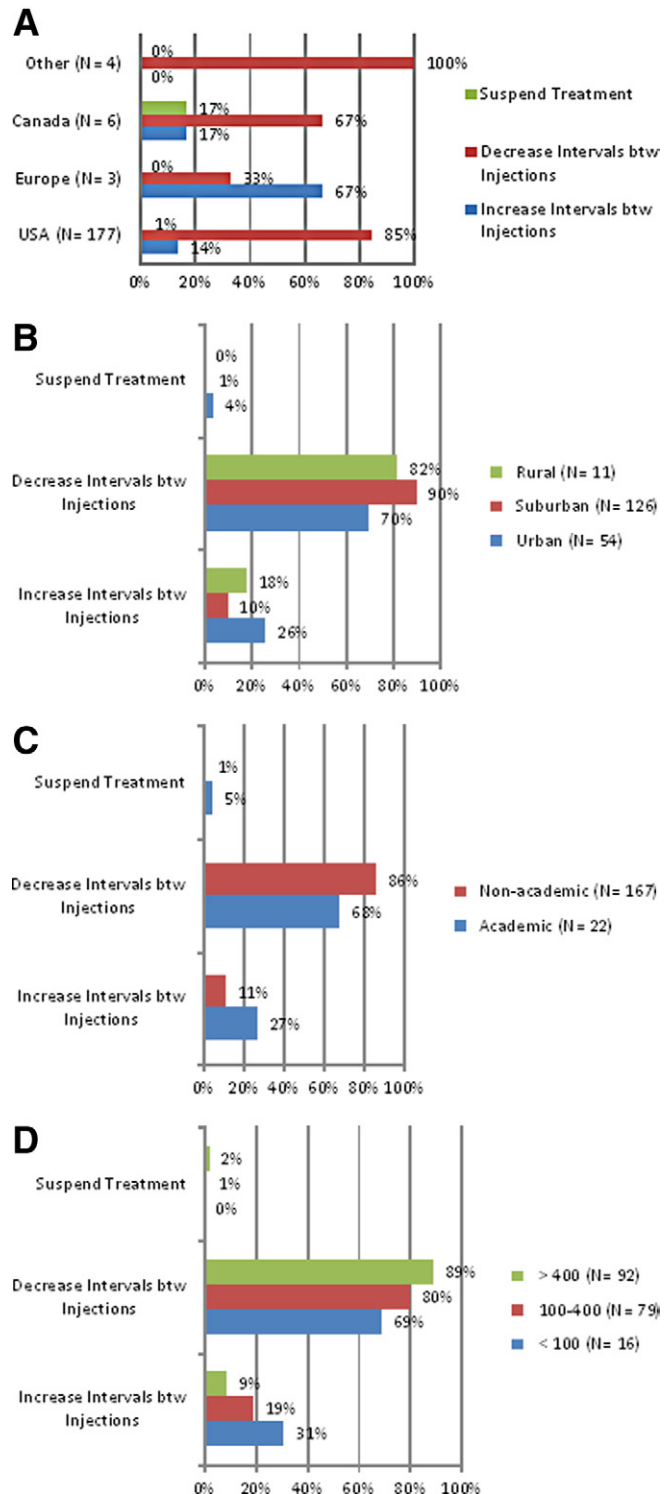


Fig 1. Interval changes made for symptoms during the pollen season based on demographic characteristics. (A) Interval changes (suspend, decrease intervals, increase intervals) by country of practice, $P < .001$; (B) by practice area, $P < .05$; (C) practice setting, $P < .001$; (D) number of SCIT patients per month, $P < .005$.

Table 3
Practitioners adjusting frequency during the pollen season

Characteristics	Proportion routinely changing SCIT frequency during the pollen season	P
Country of practice		
USA (N = 504)	201 (40%)	.05
Europe (N = 16)	5 (31%)	
Canada (N = 21)	9 (43%)	
Other (N = 39)	7 (18%)	
Years in practice		
< 10 years (N = 191)	53 (28%)	.001
> 10 years (N = 388)	168 (43%)	
Practice area		
Urban (N = 229)	69 (30%)	.004
Suburban (N = 318)	140 (44%)	
Rural (N = 35)	14 (40%)	
Practice setting		
Academic (N = 166)	33 (20%)	.001
Non-academic (N = 412)	188 (46%)	
Number of SCIT patients		
<100 (N = 155)	24 (15%)	.001
100–400 (N = 232)	93 (40%)	
>400 (N = 172)	100 (58%)	

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy; NS, non-statistically significant with $P > .05$.

Data are based on county of practice, years in practice, practice area, practice setting, and number of SCIT patients seen in practice per month. Responses are tabulated based on percentage answering affirmatively to changing SCIT frequency during the pollen season.

Significantly fewer practitioners in academic institutions reduced doses for patients with a high rate of skin test reactivity than did those in nonacademic settings (41% vs 64%; $P < .002$).

Frequency adjustment during pollen season

Most allergists (85%) follow the current practice parameter guidelines and give SCIT every 2 to 4 weeks during the maintenance phase regardless of the demographic characteristics. However, allergists in practice for more than 10 years were significantly more likely to have “other” intervals of treatment (18% vs 8%; $P \leq .001$), as were practitioners in a nonacademic setting (17% vs 10%; $P < .04$). Although most adhere to the 2- to 4-week frequency (interval between IT injections) overall, the larger the size of the practice, the more likely a practitioner was to have maintenance IT at other intervals ($P < .001$).

The survey results also show that although most allergists worldwide do not routinely change the frequency of immunotherapy during any part of the pollen season, a significant 40% do (Table 3).

The US and Canadian practitioners, those in practice for more than 10 years (76% vs 24%), those in nonacademic practice (46% vs 20%), in a large practice (58%), or in a suburban setting (44%) are more likely to change the interval between injections ($P < .001$). Of those who do, most practitioners change frequency during the maintenance phase only (not significant).

Frequency adjustment based on symptoms

Of the allergists who change frequency, most (90%) change the frequency of IT for rhinitis or conjunctivitis symptoms during the peak pollen season (eTable 2 and Fig 1). If a practitioner changed the frequency of shots, he or she was more likely in a large ($P < .05$) or a nonacademic practice ($P \leq .002$) (Table 4). Also, most practitioners who change the frequency of IT during the pollen season for rhinitis or conjunctivitis symptoms were more likely to be practicing in the United States (94%; $P \leq .001$).

Of the responders who change the frequency of maintenance SCIT intervals based on rhinitis or conjunctivitis symptoms during the pollen season, most tend to decrease the interval between injections (75%). Most allergists in practice in a non- European

Table 4
Frequency adjustment based on symptoms during pollen season

Characteristics	Proportion changing frequency for rhinitis/ conjunctivitis during pollen season	P
Country of practice		
USA (N = 193)	182 (94%)	.001
Europe (N = 5)	3 (60%)	
Canada (N = 9)	6 (67%)	
Other (N = 7)	4 (57%)	
Years in practice		
<10 years (N = 52)	45 (87%)	NS
>10 years (N = 161)	149 (93%)	
Practice area		
Urban (N = 65)	57 (88%)	NS
Suburban (N = 137)	127 (93%)	
Rural (N = 13)	12 (92%)	
Practice setting		
Academic (N = 31)	23 (74%)	.002
Nonacademic (N = 182)	171 (94%)	
Number of SCIT patients		
<100 (N = 23)	17 (74%)	.05
100–400 (N = 91)	84 (92%)	
>400 (N = 97)	91 (94%)	

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy; NS, non-statistically significant, with $P > .05$.

Data based on symptoms during pollen season based on county of practice, years in practice, practice area, practice setting and number of SCIT patients seen in practice per month. Responses are tabulated based on percentage who answered affirmatively to changing frequency for rhinitis/conjunctivitis symptoms during pollen season.

country decrease the interval between injections. Furthermore, practice area in a suburban environment and nonacademic setting were associated with a higher likelihood of decreasing the interval. Similarly, the larger the practice, the more likely the practitioner was to decrease the interval between injections.

Discussion

The use of immunotherapy as an effective treatment modality for allergic rhinitis and allergic conjunctivitis is well established.³ Since the origin of immunotherapy in the early 20th century, we have learned a great deal about the mechanism of desensitization and the role of the immune system in this process.² However, the details of how immunotherapy is practiced in the clinician's office have not changed as much since allergists first began this method of desensitization.¹² Similarly, the risks associated with immunotherapy and the rate of fatalities has not significantly improved in the last decade.¹³ A recent review by Casale¹⁴ suggested that this may be attributable to clinicians' nonadherence to the published practice guidelines.¹⁴ Analysis of the data obtained in this study also identifies some other possible reasons for the inconsistency in allergists' practice style.

In our survey, we found wide variability in practice styles of allergists worldwide. When questions were directed at issues specifically or clearly addressed in the Immunotherapy Practice Parameters such as dose reduction for asthma symptoms (Summary Statement 32),⁸ practitioners were very uniform in their response, with only 6% of practitioners worldwide stating that they do not reduce the dose. For other well-defined recommendations such as the type of extracts used for dust mite, cat, and grass pollen (Summary Statement 76),¹¹ although differences have been found in the availability and formulation of allergen extracts in different parts of the world,¹⁵ much uniformity also was found, and the demographic characteristics of the responders did not significantly change their practice style. Of note, however, was a sizeable minority (10–15%) who did not adhere to the recommended target doses or the standardized extracts. This is consistent with a similar self-reported survey done by Coifman and Cox⁸ published in 2006. This study noted that 16% of the responders did not adhere to specific recommendations in the practice guidelines by

allowing home immunotherapy.⁸ Another study that highlights a similar rate of nonadherence to specific recommendations was published by Karpel¹⁶; in which approximately 10% of physician responders continued to prescribe long-acting beta agonists despite the Food and Drug Administration black box warning.¹⁶ Thus, approximately 10% may possibly be the natural prevalence of practitioners who do not adhere to the recommendations even when strongly and clearly stated in formal guidelines.

Not surprisingly, when some decisions made routinely in the administration of immunotherapy are not fully addressed in the current practice guidelines, the variability is amplified. For example, summary statement 50 in the 2011 Immunotherapy guidelines states, "Immunotherapy given during periods when the patient is exposed to increased levels of allergens to which they are highly sensitive might be associated with an increased risk of a systemic reaction. However, although survey data have noted this to be a risk factor for severe reactions, several published studies have not found an association between pollen seasons and systemic reaction. . . most patients do well without dose adjustment."¹⁰ Hence, there was no clear recommendation in the practice parameters regarding whether to dose adjust or not during pollen seasons.

Also, regarding the frequency of IT, a report published by Fortner⁹ in 1982 suggested that weekly IT was associated with increased symptom control when compared with monthly IT.⁹ Similarly, Hakansson et al¹⁰ in 1997 found that immunotherapy during pollen season was able to prevent eosinophil priming in patients with asthma who were allergic to birch pollen.¹⁰ However, current practice recommendations suggest an interval of 2 to 4 weeks regardless of season.¹¹ Therefore, when the survey questions addressed routine issues such as adjustment of doses based on pollen season, increased skin test reactivity, or the adjustment of the frequency of IT based on rhino-conjunctivitis symptoms in pollen season, the practice styles were much more diverse. The responders' decisions seemed to be influenced much more by their personal demographic characteristics in these cases.

Specifically, we observed that allergists in practice for 10 years or more were more likely to dose adjust during the peak pollen season, more likely to change frequency of IT during pollen season, more likely to change doses in both buildup and maintenance phases, and more likely to change doses because of higher skin test reactivity than those in practice for less than 10 years. Given the lack of convincing data regarding appropriate dosing and frequency changes in the literature, a practitioner's own experience with SCIT may guide individual decisions. Possibly allergists who are closer to their formal fellowship training are likely to more closely follow current recommended doses and intervals regardless of the season. Practitioners with more experience also might be more comfortable adjusting the doses and frequency based on their own clinical judgment. This is consistent with other studies in which prescribing habits were associated with the length of time since medical school graduation.¹⁷ However, an alternative explanation for this is a cohort phenomenon, in which practitioners adhere to the style most practiced during their initial training. Therefore, practitioners who trained within a few years of each other might practice the same way. This may also account for the differences in patterns of practice we observed in association with proximity to formal training.

Similarly, the practice setting was associated with significant differences in practice style as has been found in prior studies.¹⁸ In our study, those in an academic practice (defined as "academic, within a medical school, hospital or other multispecialty academic program.") were less likely to routinely change the frequency of SCIT in pollen seasons or for rhino-conjunctivitis symptoms. They were also less likely to reduce doses for a high rate of skin test reactivity. One can theorize that those in an academic practice in which trainees may question the reasons for various decisions may

be more likely to adhere to established guidelines and less likely to base decisions on individual practitioner experiences.

However, the exact reasons for specific differences between practitioners' styles cannot be fully addressed by the current study. There are other inherent limitations of the study as well. Although a 25% response rate is higher than many other reported surveys of allergists (16–17%) and physicians (10%) in the past, an even higher response rate would have likely made statistical analysis more robust for all parameters studied.^{7,12,19} The fact that this was a self-reported survey also introduces an inherent bias that responses maybe tainted by the practitioner's self-perception. However, given the large number of responses received, statistical power was not restrictive, and self-perception may be just as important as objective measures when discussing physician styles of practice.

In summary, we have observed much variability in the practice styles of allergists worldwide and correlated several demographic characteristics that might have influenced practitioner decisions when addressing issues that deviate from the normal or expected dosing and frequency of SCIT. Whether the lack of published data regarding these issues drives these inconsistencies, or whether the inherent practitioner differences are paramount to explain the variability, is unclear. No matter what the cause of the differences, prior studies have noted that when guidelines make specific recommendations regarding a specific practice concern, there is an increase in uniformity, although one may not achieve 100% adherence. One such study that reviewed specific prescribing patterns noted that after changes in the prescribing recommendations for cat immunotherapy in 2007, there was a measurable improvement from 18% of prescriptions written in the recommended range in 2003 to 83% in 2007.²⁰ Therefore, future studies need to address dosing and frequency of immunotherapy to lead us toward uniform guidelines in treating SCIT patients during seasons with high pollen counts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [10.1016/j.anai.2012.04.002](https://doi.org/10.1016/j.anai.2012.04.002).

eAppendix**Practice Patterns: Subcutaneous Immunotherapy (SCIT) Adjustments during the Pollen Season****Consent**

1. I agree to participate in this survey and understand that it is anonymous and data will be reported in aggregate form only.

- ☐ Yes
☐ No

Demographics

2. Do you currently prescribe subcutaneous immunotherapy?

- ☐ Yes
☐ No (end of survey)

3. Where do you practice?

United States

International

Location

- ☐
☐
 Other (please specify) ☐

4. How many years have you been in practice as an allergist?

☐

5. Are you still a fellow-in-training?

- ☐ Yes
☐ No

6. Is your practice in a(n) _____ area?

(IN CASE OF MULTIPLE OFFICES: FILL IN HOW YOU SHOULD BEST CHARACTERIZE YOUR PRACTICE)

- ☐ Rural
☐ Urban
☐ Sub-urban

7. Is your practice in a(n) _____ setting?

- ☐ Academic, within a medical school, hospital, or other multispecialty academic program
☐ Other

8. How many patients do you treat with immunotherapy at this moment in your clinic/office (shots can be given in your clinic/office or elsewhere but under your management)?

☐

9. What is your target maintenance dose for:

Dermatophagoides farinae if given together with *D. pteronyssinus*?

- ☐ _____ AU;
☐ _____ not applicable
☐ _____ other

Dermatophagoides farinae if given without *D. pteronyssinus*?

- ☐ _____ AU;
☐ _____ not applicable
☐ _____ other

Dermatophagoides pteronyssinus if given together with *D. farinae*?

- ☐ _____ AU;
☐ _____ not applicable
☐ _____ other

Dermatophagoides pteronyssinus if given without *D. farinae*?

- ☐ _____ AU;
☐ _____ not applicable
☐ _____ other

Cat?

- ☐ _____ BAU
☐ _____ not applicable
☐ _____ other

Grass pollens?

- ☐ _____ BAU
☐ _____ PNU
☐ _____ wt/volume
☐ _____ not applicable
☐ _____ other

Tree pollens?

- ☐ _____ BAU
☐ _____ PNU
☐ _____ wt/volume
☐ _____ not applicable
☐ _____ other

10. For immunotherapy patients (SCIT), do you routinely dose-adjust during peak pollen season?

- ☐ Yes, routinely in all patients
☐ No
☐ Yes, in selected patients

11. If you do dose-adjust for patients during peak pollen season, when do you dose adjust?

- ☐ during the build-up phase
☐ during the maintenance phase
☐ during both

12. If you dose adjust, how much do you normally reduce the maintenance dose during (peak) pollen season (IF YOU DON'T DOSE- REDUCE, PLEASE FILL IN 0%)

A: for all patients by: ☐% or _____ mL or _____ doses
☐% or _____ mL or _____ doses

13. For patients whom you selectively dose-adjust during peak pollen season, do you REDUCE the dose for patients with active upper airway allergy symptoms (rhinitis/conjunctivitis)?

- ☐ Yes
☐ No
☐ not applicable ☐

14. For patients whom you selectively dose-adjust during peak pollen season, do you REDUCE the dose for patients with asthma symptoms?

- ☐ Yes
☐ No
☐ Not applicable (do not give IT with asthma symptoms or don't dose adjust)
☐

15. For patients whom you selectively dose-adjust during peak pollen season, do you REDUCE the dose for patients with a high rate of skin test reactivity?

- ☐ Yes
☐ No
☐ Not applicable
☐

16. What is the usual frequency (interval between shots) of subcutaneous immunotherapy (SCIT) during the maintenance phase in your practice?

- ☐ Every 3 weeks
☐ Every 4 weeks
☐ Every 5 weeks
☐ Other: _____

17. For subcutaneous immunotherapy (SCIT) patients, do you routinely change the frequency (interval between shots) during any part of the pollen season?

- ☐ Yes, always
☐ No
☐ Yes, in selected patients

18. If you do change the frequency (interval between shots) for patients during the pollen season, in which phase do you change the frequency?

- ☐ during the build-up phase
☐ during the maintenance phase
☐ during both
☐ Not applicable—don't change frequency

19. If you change the frequency (interval between shots) during the build-up phase in pollen season, how often do you give immunotherapy (SCIT)?

- ☐ _____ days apart
☐ Not applicable—don't change frequency

20. If you change the frequency (interval between shots) during maintenance in pollen season, how often do you give SCIT?

- ☐ _____ weeks apart
☐ Not applicable—don't change frequency

21. Do you change the frequency of immunotherapy intervals if a patient has increased symptoms (rhinitis/conjunctivitis) during the pollen season?

- ☐ Yes, always
☐ No
☐ Yes, selectively

22. If you do change the frequency of maintenance immunotherapy intervals based on symptoms (rhinitis/conjunctivitis) during the pollen season, what do you do?

- ☐ Increase the interval between injections
☐ Decrease the interval between injections
☐ Suspend treatment
☐ Not applicable—don't change frequency

Dose adjustment schedules for missed doses (unplanned gaps) in immunotherapy administration

In the following section, two methods of dose-adjustment after unplanned gaps in IT administration are mentioned:

- I. Based on the time elapsed since the last given dose (eg, last applied dose was 10th of July, now it is 25th of August = 48 days)
- II. Based on the time elapsed since the last scheduled dose (eg, patient was scheduled for administration 10th of August but didn't come. Now he comes in on the 25th = 15 days late). In all questions these two options are repeated: please mark the one that applies to your clinic/office and fill in the specific data that are asked for.

23. In your office, how do you adjust the administration of IT if a patient misses a dose?

- ☐ Based on the time elapsed since the last given dose
☐ Based on the time elapsed since the last scheduled dose
☐ Other _____
☐ We have no routine dose adjustment plan for patients that miss dose(s)

24. During the build-up phase: If a patient comes in late for the next IT administration . . .

when do you decide to make a dose-adjustment?

(PLEASE MARK THE RIGHT OPTION AND FILL IN THE DAYS)

- ☐ Based on time since the last dose was given: if more than _____ days have passed

- ☐ Based on time since last scheduled dose: if patient comes in _____ days late.
☐ We have no routine dose adjustment plan for patients that miss dose(s) during the build-up phase.

25. During the build-up phase of IT: If a patient comes in late for his or her next IT dose, which of the options below best describes the dose-adjustment you practice?

(MARK AND FILL IN IF NEEDED)

For the first missed dose:

- ☐ Repeat last dose
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

For the second missed dose:

- ☐ Reduce to prior dose (2 doses back)
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

For the third missed dose:

- ☐ Reduce to prior dose (3 doses back)
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

When do you decide to completely restart immunotherapy?

After interruption of the build-up phase for more than _____ days.

26. During the maintenance phase of IT: If a patient comes in late for the next IT administration when do you decide to make a dose-adjustment?

(PLEASE MARK THE RIGHT OPTION AND FILL IN THE WEEKS)

- ☐ Based on time since the last dose was given: if more than _____ weeks have passed
☐ Based on time since last scheduled dose: if patient comes in _____ weeks late.
☐ We have no routine dose adjustment plan for patients that miss dose(s) during the maintenance phase of IT.

27. During the maintenance phase of IT: If a patient comes in late for his or her next IT dose, which of the options below best describes the dose-adjustment you practice?

(MARK AND FILL IN IF NEEDED)

For the first missed dose:

- ☐ Repeat last dose
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

For the second missed dose:

- ☐ Reduce to prior dose (2 doses back)
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

For the third missed dose:

- ☐ Reduce to prior dose (3 doses back)
☐ Lower by _____ percent
☐ Reduce volume by _____ mL.
☐ Other _____
☐ No dose adjustment
☐ No plan for dose adjustment

When do you decide to completely restart immunotherapy?
 After interruption of the maintenance phase for more than _____ weeks.

Compliance and Long-Term Immunotherapy: Beyond the 5 Years

28. On average, for how long do you prescribe subcutaneous aeroallergen immunotherapy (SCIT)?

- ☐ Indefinitely
☐ On average for _____ years

Please fill in: ☐ years

29. Do you have any patients on subcutaneous aeroallergen immunotherapy (SCIT) beyond 5 years?

- ☐ None
☐ Very few
☐ Few
☐ Quite some

Please give us an estimated percentage in regards to the following:

Of all patients you start on SCIT:

What percentage of patients stop IT...

30. after 1 year:

Please fill in: ☐%

31. after 2 years:

Please fill in: ☐%

32. after 3 years:

Please fill in: ☐%

33. after 4–5 years:

Please fill in: ☐%

34. after more than 5 years:

Please fill in: ☐%

35. What are the possible reason(s) for premature discontinuation of immunotherapy (SCIT)?

(Based on a scale FROM 1 TO 5 (1 = most probable cause; and 5 = least probable cause))

- ☐ Patient abandons treatment because of ☐ repeatedly large local reactions
☐ Physician decides to suspend treatment because of ☐ repeatedly large local reactions
☐ Patient abandons treatment because of systemic adverse event
☐ Physician decides to suspend treatment because of systemic adverse event
☐ Patient abandons treatment because of high costs
☐ Patient abandons treatment because of change in reimbursement
☐ Patient abandons treatment because of scheduling problems
☐ Patient abandons treatment because of lack of improvement
☐ Other: Please fill in: ☐

36. What would be the reason(s) for continuing immunotherapy (SCIT) beyond 5 years? (PLEASE SELECT ALL THAT APPLY)

- ☐ The patient has only improved partially and might improve more.
☐ The patient has improved very well and does not want to relapse.
☐ After stopping the patient felt symptoms came back and was reinitiated.
☐ I do not stop when the patient is on venom immunotherapy.
☐ I do not continue beyond 5 years of therapy.

Other (please specify) ☐

eTable 1
Dose adjustment based on symptoms and skin test reactivity

Characteristics	Proportion who dose-reduce for upper airway allergy symptoms	P-value	Proportion who dose-reduce for asthma symptoms	P-value	Proportion who reduce dose for high rate of skin test reactivity	P-value
Country of practice						
USA	106/182 (58%)	NS	104/115 (90%)	NS	113/186 (61%)	0.007
Europe	9/12 (75%)		7/8 (88%)		2/13 (15%)	
Canada	6/11 (55%)		8/10 (80%)		6/13 (46%)	
Other	7/13 (54%)		12/12 (100%)		10/14 (71%)	
Years in practice						
< 10 years	31/58 (54%)	NS	37/37 (100%)	0.02	25/60 (42%)	0.004
> 10 years	97/161 (60%)		95/109 (87%)		106/167 (63%)	
Practice area						
Urban	58/96 (60%)	NS	65/72 (90%)	NS	54/102 (53%)	NS
Suburban	63/111 (57%)		60/66 (91%)		71/113 (63%)	
Rural	8/13 (62%)		8/9 (89%)		7/13 (54%)	
Practice setting						
Academic	38/62 (61%)	NS	44/47 (94%)	NS	27/66 (41%)	0.002
Non-academic	89/155 (57%)		86/97 (89%)		102/159 (64%)	
Number of SCIT patients						
< 100	33/57 (58%)	0.05	33/37 (89%)	NS	29/62 (47%)	NS
100–400	57/85 (67%)		56/60 (93%)		54/87 (62%)	
> 400	36/75 (48%)		41/47 (87%)		46/76 (61%)	

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy; NS, non–statistically significant with $P > .05$.

Data are based on symptoms and initial skin test reactivity. Responses were grouped by country of practice, years in practice, practice area, practice setting and number of SCIT patients seen in practice per month. Responses were tabulated based on the following categories: dose reduction for upper airway symptoms (rhinoconjunctivitis), dose reduction for asthma symptoms, dose reduction for initial skin test reactivity.

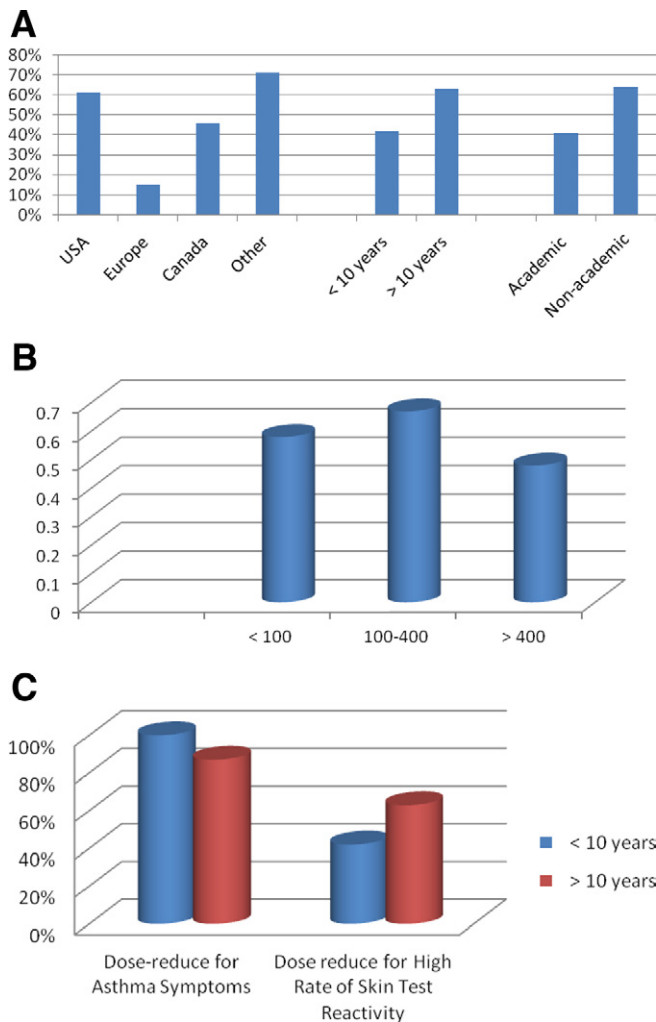
eTable 2

Interval changes made for symptoms during the pollen season

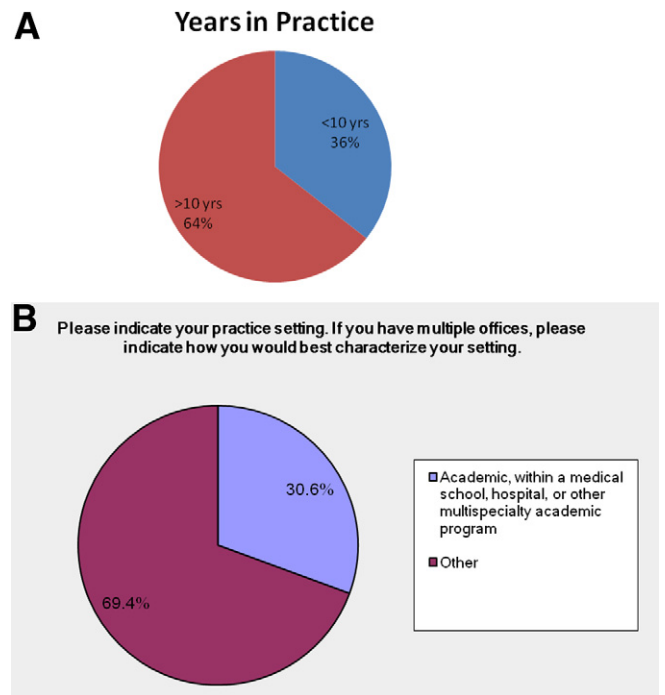
Characteristics	Proportion who increase intervals between injections	Proportion who decrease intervals between injections	Proportion who suspend treatment
Country of practice	.001		
USA (<i>N</i> = 177)	25 (14%)	150 (85%)	2 (1%)
Europe (<i>N</i> = 3)	2 (67%)	1 (33%)	0 (0%)
Canada (<i>N</i> = 6)	1 (17%)	4 (67%)	1 (17%)
Other (<i>N</i> = 4)	0 (0%)	4 (100%)	0 (0%)
Years in practice	NS		
< 10 years (<i>N</i> = 42)	8 (19%)	34 (81%)	0 (0%)
> 10 years (<i>N</i> = 147)	20 (14%)	124 (84%)	3 (2%)
Practice area	.05		
Urban (<i>N</i> = 54)	14 (26%)	38 (70%)	2 (4%)
Suburban (<i>N</i> = 126)	12 (10%)	113 (90%)	1 (1%)
Rural (<i>N</i> = 11)	2 (18%)	9 (82%)	0 (0%)
Practice setting	.001		
Academic (<i>N</i> = 22)	6 (27%)	15 (68%)	1 (5%)
Nonacademic (<i>N</i> = 167)	21 (11%)	144 (86%)	2 (1%)
Number of SCIT patients	.005		
<100 (<i>N</i> = 16)	5 (31%)	11 (69%)	0 (0%)
100–400 (<i>N</i> = 79)	15 (19%)	63 (80%)	1 (1%)
> 400 (<i>N</i> = 92)	8 (9%)	82 (89%)	2 (2%)

Abbreviations: N, number of responders; SCIT, subcutaneous immunotherapy; NS, non statistically significant with *P* value > .05.

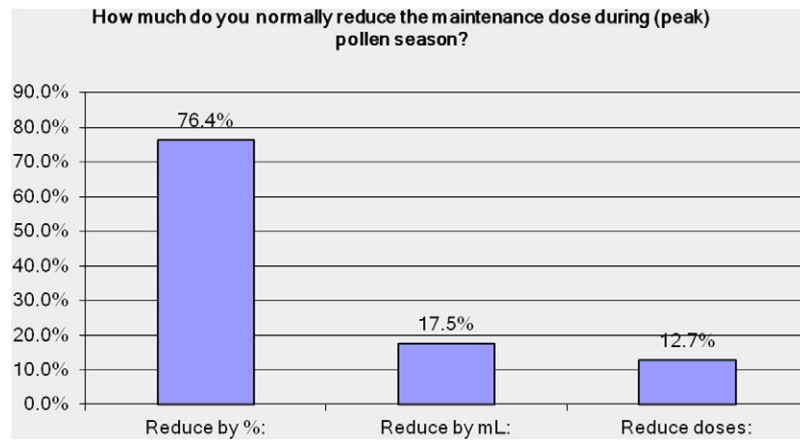
Interval changes made for symptoms during the pollen season based on county of practice, years in practice, practice area, practice setting and number of SCIT patients seen per months. The responses were tabulated based on percentage of responders who either increase, decrease or suspect treatment.



eFig 1. (A) Dose reduction for high rate of skin test reactivity based on demographic characteristics by county, years in practice, and practice setting subgroups. All subgroups reached a P -value $< .05$. Please refer to supplement for additional data. (B) Dose reduction for upper airway allergy symptoms based on number of patients in practice. Small (<100 SCIT patients per month), medium-sized (100–400 SCIT patients per month), and large practices (>400 SCIT patients per month). $P < .05$. (C) Dose adjustment based on symptoms of asthma or high rate of skin test reactivity compared with number of years in practice. Dose reduction for asthma symptoms group; $P < .02$, dose reduce for high rate of skin test reactivity group, $P < .05$.



eFig 2. (A) Years in practice: <10 years or >10 years. (B) Practice setting: academic or nonacademic.



eFig 3. Percent reduction of the maintenance dose during peak pollen season: reduction by percent, milliliters (mL), or other (reduce dose).