

Sublingual immunotherapy in children with allergic polysensitization

Giorgio Ciprandi, M.D.,¹ G. Cadario, ■■,² G.M. Di Gioacchino, ■■,³ S. Gangemi, ■■,⁴ A. Gasparini, ■■,⁵ S. Isola, ■■,⁴ F. Marengo, ■■,² S.M. Minelli, ■■,⁶ L. Ricciardi, ■■,³ E. Ridolo, ■■,⁷ V. Pravettoni, ■■,⁸ C. Valle, ■■,⁹ M. Verini, ■■,¹⁰ M. Zambito, ■■,¹¹ C. Incorvaia, ■■,¹² P. Puccinelli, ■■,¹³ S. Scurati, ■■,¹³ and F. Frati ■■¹³

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ABSTRACT

Polysensitization is quite frequent in allergic children and may cause difficulties for the allergist in prescribing allergen-specific immunotherapy. This study aimed at evaluating the clinical effectiveness of 1 year of sublingual immunotherapy (SLIT) in a cohort of Italian allergic children with polysensitization. This open study was performed on 51 polysensitized children (34 boys; mean age, 11.8 years; range, 5.2–17.7 years) with allergic rhinitis and/or mild to moderate asthma. All of them were treated with SLIT for 1 year. The kind and the number of prescribed allergen extracts, the type of diagnosis, the severity of symptoms, and the use of drugs were evaluated at baseline and after 1 year. The adverse events to SLIT were also evaluated. Forty-two children were treated with a single extract, four with two different extracts and three with a mix of allergens. SLIT treatment induced a significant reduction in the number of sensitizations ($p = 0.018$); significant improvement of allergic rhinitis classification and severity; significant reduction of ocular, nasal, and bronchial symptoms ($p < 0.01$ for all); and drugs use ($p < 0.01$ for all drugs). No systemic reactions to SLIT were observed. This open study provides evidence that polysensitization is not an obstacle for prescribing SLIT in polysensitized children. Indeed, SLIT efficacy on clinical parameters is significant after 1 year and the therapy is safe.

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Key words: Allergic rhinitis, asthma, children, classification and severity, sublingual immunotherapy

Allergic rhinitis (AR) has a steadily increasing prevalence in children^{1,2} and causes substantial social and economic costs. In fact, school performance and absences (including parents' work absences), daily activities and plays, and quality of sleep are significantly affected in children with AR.³ AR classification has been revised in the Allergic Rhinitis and Its Impact on Asthma (ARIA) document.² This classification is based on frequency and duration of the symptoms: intermittent AR (IAR), symptoms occurring for <4 days/week or <4 consecutive weeks, and persistent AR (PER),

symptoms occurring for >4 days/week and >4 consecutive weeks. Recently, a study provided the first evidence concerning the use of ARIA classification in children.⁴

Moreover, it is well known that AR is frequently associated with asthma.^{5,6} Asthma is classified in the Global Initiative for Asthma (GINA) guidelines based on severity and duration of symptoms as intermittent or persistent and may include a mild, moderate, or severe type.⁷ On the other hand, the phenomenon of polysensitization, *i.e.*, the trend to become sensitized to more allergens over time, is quite frequent in allergic children and starts very early in childhood⁸ and concurs with the burden of AR.

AR management includes patient education, allergen avoidance, drug therapy, and, when appropriate, allergen-specific immunotherapy.⁹ Allergen-specific immunotherapy is the practice of administering gradually increasing doses of the causal allergen extract to reduce allergic symptoms by achieving clinical tolerance toward the causal allergen.¹⁰ Sublingual immunotherapy (SLIT) has been developed and is presently the most prescribed way in many European countries.⁹ The rationale of SLIT is that oral administration of high-dose allergen may reduce and prevent IgE responses. Methodologically, the extract is kept under the tongue for a few minutes and then swallowed. SLIT efficacy has

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From the ¹Dipartimento Medicina Interna, Az. Osp. Universitaria San Martino, Genoa, Italy, ²S.C. Allergologia e Immunologia Clinica, A.O. San Giovanni Battista (Molinette), Turin, Italy, ³Dipartimento di Medicina e Scienze dell'Invecchiamento, Immunologia e Medicina del lavoro, Università G. d'Annunzio, Chieti, Italy, ⁴S.U.O. Complessa Allergologia, Policlinico, Messina, Italy, ⁵Ambulatorio di allergologia–Az. Osp. Melegnano–Presidio Osp. Cernusco sul Naviglio, Milan, Italy, ⁶Ambulatorio di Allergologia, U.O. Medicina Generale, Ospedale Campi Salentina, Lecce, Italy, ⁷Dipartimento di Scienze Cliniche, Università di Parma, Italy, ⁸U.O. Complessa di Allergologia e Immunologia Clinica, Fondazione IRCCS Ospedale Maggiore Policlinico Mangiagalli Regina Elena, Milan, Italy, ⁹Unità di Allergologia, Ospedale S. Paolo, Milan, Italy, ¹⁰U.O. Allergologia e Fisiopatologia Respiratoria, Clinica Pediatrica, Ospedale Clinico, Chieti, Italy, ¹¹U.O. Specialista di Allergologia AUSL 6, Palermo, Italy, ¹²Allergy/Pulmonary rehabilitation, ICP, Milano, Italy, and ¹³Scientific Department, Stallergenes, Milan, Italy

Address correspondence and reprint requests to Giorgio Ciprandi, M.D., Semeiotica e Metodologia Medica I, DIMI, Viale Benedetto XV 6, 16132 Genoa, Italy

E-mail address: gio.cip@libero.it

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been evaluated in the European Academy of Allergy and Clinical Immunology/ESPACI document,¹¹ in the ARIA document,² and evidenced by two meta-analyses on patients with AR and asthma.^{12,13}

Polysensitization has been well documented both in a general population survey and in an asthma population-based study.^{14,15} Therefore, polysensitization is a common feature in AR patients and may cause some doubts in choosing the allergen extract for SLIT. In this regard, the evaluation of SLIT efficacy in polysensitized patients still represents an unanswered question and there is no study on this issue conducted in pediatric populations. Therefore, the aim of this open study was to evaluate the clinical effects of SLIT in a group of AR polysensitized children, assessing ARIA classification, the GINA classification, symptoms severity, and drug use.

MATERIALS AND METHODS

Study Design

The study was conducted in 11 allergy centers homogeneously distributed in Italy. The study was approved by the Review Board of each participating center and an informed consent was obtained from the parents of each patient. The study started during the fall of 2005 and lasted 1 year.

Subjects

Fifty-one polysensitized children (34 boys and 17 girls; mean age, 11.8 years; range, 5.2–17.7 years) with AR were consecutively and prospectively evaluated. A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study based on polysensitization, clinical history of nasal and/or bronchial symptoms since at least 2 years, and clear relationship between exposure to sensitizing allergen and symptom occurrence.

Skin-prick test were performed and assessed as stated by the European Academy of Allergy and Clinical Immunology.¹⁶ The panel consisted of house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, *Parietaria officinalis* (wall pellitory), birch, hazel, olive tree, ragweed, mugwort, *Artemisia absinthium*, *Alternaria tenuis*, *Cladosporium*, and *Aspergillus* mix (Stallergenes, Milan, Italy). Polysensitization was defined based on two or more positive skin-prick tests.

The diagnosis of IAR or PAR and its severity was made based on ARIA criteria.² The diagnosis of asthma and the severity evaluation were made according to GINA criteria.⁹

All children were treated with 1-year SLIT and were evaluated at baseline (V1) and after 1 year (V2). The product used for SLIT therapy was produced by Stal-

lergenes: Staloral 300 I.R. Allergen extract references have been previously defined in a comprehensive review.¹⁷ It was administered according to the manufacturer's schedule. The allergen selection was based on the clear demonstration of the cause-effect relationship between exposure to sensitizing allergen and symptom occurrence. For this reason, one or more allergens were chosen for SLIT.

Children gave a subjective judgment of both the severity of their symptoms and the use of drugs by a visual analog scale (VAS) according to validated criteria.¹⁸ For symptoms, VAS must assess a global evaluation including all symptoms (for eyes, itching, tearing and redness; for nose, itching, rhinorrhea, and obstruction; for bronchial symptoms, cough, wheezing, and dyspnea); VAS score ranged from 0 (absence of symptom) to 10 (very severe symptom). For drug use, VAS score ranged from 0 (no drug use) to 10 (maximal drug use).

Adherence to treatment was assessed by a diary card compiled by parents and reporting the number of doses and date of assumption. Adverse events to SLIT were recorded in diary cards.

Statistical Analysis

Continuous and/or discrete parameters are reported as mean, SD, third quartile, and frequency. Categorical parameters are reported in contingency tables.

Homogeneity of data was been evaluated by χ^2 -Fisher's test. The significance of the values concerning the relationship coefficient has been calculated by Student's *t*-test. The *p* value concerning the statistical significance was considered equal to 0.05. Statistical analysis has been performed by statistical package BMDP Dynamic produced by BMDP Statistical Software, Inc. (Los Angeles, CA).

RESULTS

The most relevant allergens in the polysensitized children were grass pollen, giving positive SPT in 45 (88.2%) children, followed by *Dermatophagoides*, positive in 21 (41.2%) patients and wall pellitory, positive in 16 (31.4%) patients (Table 1).

SLIT was performed in 42 children using one allergen extract (26 children were treated with grass extract, and 16 were treated with *Dermatophagoides* extract), in 4 children using two allergen extracts (2 children were treated with grasses and mites extracts, and 2 children were treated with wall pellitory and mites extracts), and in 3 children using more than two allergen extracts (grasses, wall pellitory, and mites extracts). The number of sensitizations significantly diminished after 1 year of SLIT (*p* = 0.0186), as reported in Fig. 1.

Concerning the classification and the severity of AR at baseline, 11 children had IAR (3 of them with mild

Table 1 Allergens distribution (and percentages) to skin-prick test

Allergen	n	%
<i>Dermatophagoides</i>	21	41.2
Grasses	45	88.2
Wall pellitory	16	31.4
Olive	16	31.4
Birch, hazelnut, and alder	20	39.2
Cypress	9	17.6
<i>Artemisia absinthium</i>	10	19.6
Ragweed	8	15.7
<i>Alternaria</i>	7	13.7
Cat	17	33.3
Dog	7	13.7
Other	9	17.6

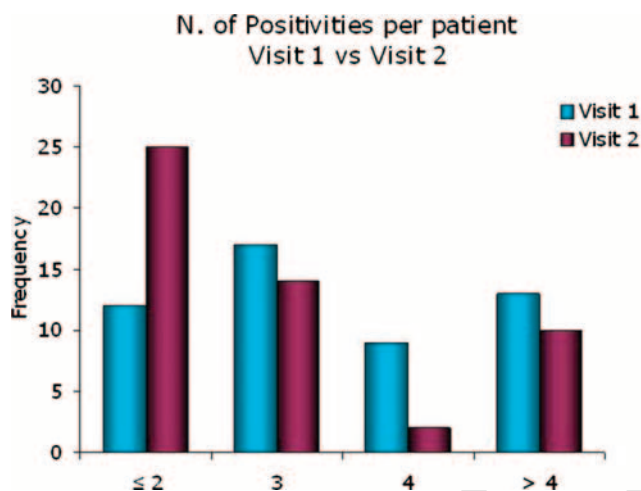


Figure 1. Mean number of sensitizations for children before and after 1 year of sublingual immunotherapy (SLIT).

symptoms and 8 with moderate-severe symptoms); 38 children had PER (9 with mild and 29 with moderate-severe symptoms; Fig. 2). After 1 year of SLIT treatment, 20 patients had IAR (12 with mild and 8 with moderate-severe symptoms); 29 patients had PER (16 with mild and 13 with moderate-severe symptoms). There was an improvement of AR grade and the difference was statistically significant to McNemar test (0.0103).

Concerning the asthma diagnosis and severity at baseline, 21 children had AR associated with asthma and 2 had asthma alone; at V2, however, 3 children did not present asthma symptoms, the number of children with moderate persistent asthma changed from 7 to 5, and the single child with severe persistent asthma at baseline passed to a moderate one after 1 year, as reported in Fig. 3.

Figure 4 shows the mean (+SD) of conjunctival, nasal, and bronchial symptoms assessed by VAS at base-

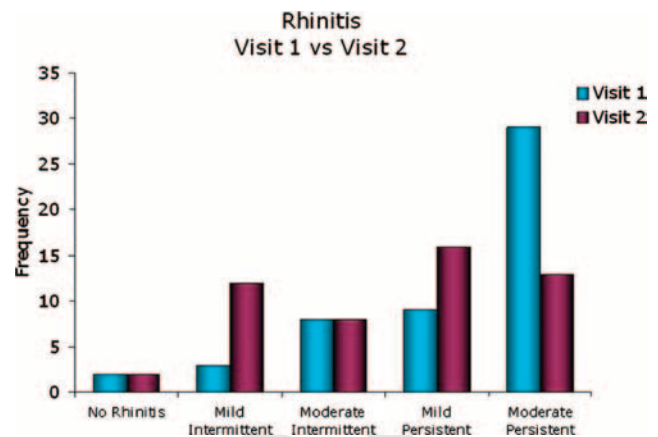


Figure 2. Type and severity of rhinitis before and after 1 year of sublingual immunotherapy (SLIT).

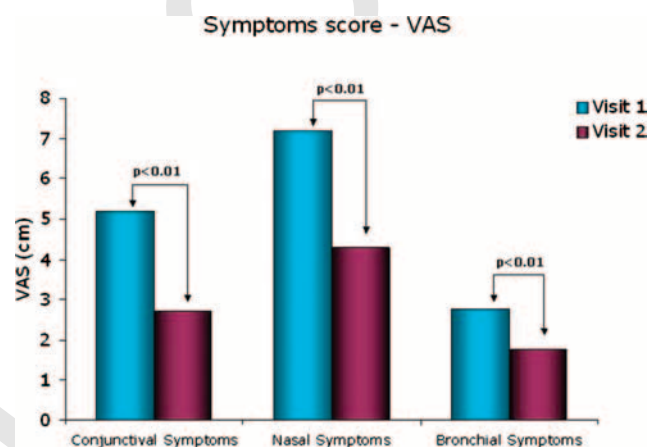


Figure 3. Type and severity of asthma before and after 1 year of sublingual immunotherapy (SLIT).

line and after 1 year. A significant decrease was found in ocular ($p < 0.01$), nasal ($p < 0.01$), and bronchial symptoms ($p < 0.01$). Likewise, the use of drugs significantly diminished after 1 year of SLIT treatment concerning intranasal corticosteroids, antihistamines, inhaled corticosteroids, and short- and long-acting B2-agonists ($p < 0.01$ for all).

Concerning the adherence to the treatment, 31 children had a complete adherence with no interruption of the schedule, 10 patients had only one interruption, and 3 patients had two interruptions. No systemic reactions were observed. The reported adverse reactions were 18 local reactions, all mild and self-resolving, and 5 gastrointestinal reactions, also mild and self-resolving; no organ (respiratory) reaction has been reported.

DISCUSSION

Polysensitization is an immunologic phenomenon that is clinically significant and relevant from an epidemiological point of view, as reported in recent surveys.^{8,19,20} The increasing number of sensitizations

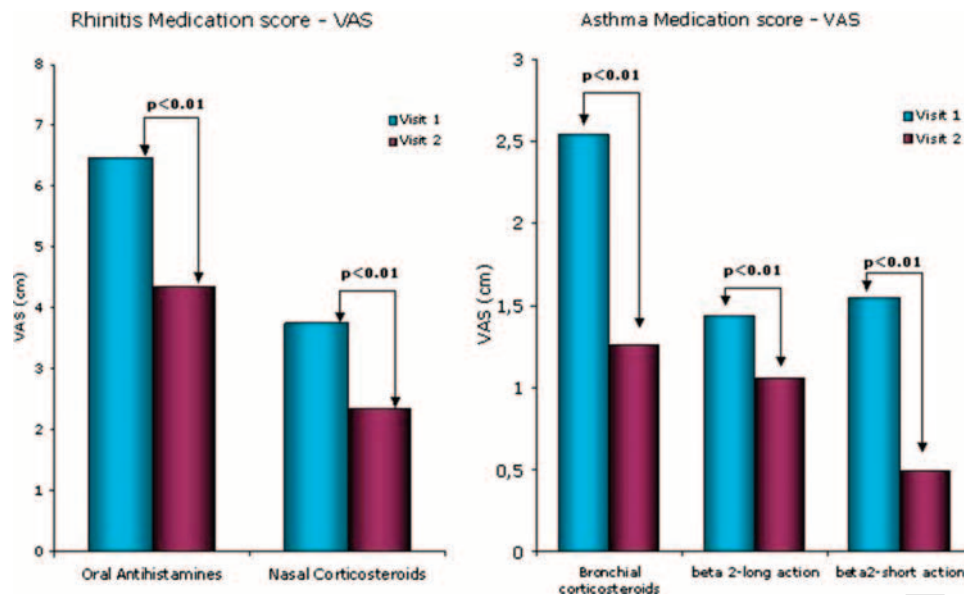


Figure 4. Symptoms severity assessed by visual analog (VAS) scale before and after 1 year of sublingual immunotherapy (SLIT).

seems to characterize the natural history of the allergic patient and may represent a typical evolution of allergy. Polysensitization may be associated with a different clinical picture in respect to monosensitized patients, and especially with a more impaired quality of life.²¹

This open study aimed at evaluating the 1-year clinical effectiveness of SLIT in a cohort of polysensitized children. The analysis of the basal characteristics of children showed that the majority of them (>80%) have the PER type and the moderate-severe form. This finding may be partially explained by the relevant number of sensitizations per patient in our cohort and may depend on the type of studied populations, offering confirmations to previous studies.^{19,20,22} Second, about one-half of patients with AR had also asthma, which thus represents an important comorbidity for AR, as stated in the ARIA document.² About asthma severity, most patients had the intermittent form, whereas almost all patients with persistent asthma had mild-moderate severity of symptoms.

The present study, based on real-life clinical practice, provides some interesting observations on this issue. First, grass pollen was the most relevant allergen followed by house-dust mites; this finding confirms previous studies conducted in Italy.²³ Although the mean number of sensitizations is 3.65, a single extract was chosen in about two-thirds of patients, and few allergens were used in the remaining patients. This model indicates that polysensitization should not constitute an impediment to SLIT prescription if only few allergens are chosen. On the other hand, this choice seems to be correct because SLIT efficacy is confirmed in this cohort also limiting the number of used allergens. In particular, the suitability of the allergen choice is confirmed by SLIT effectiveness on the improvement of

AR and asthma classifications. Indeed, asthma becomes less frequent after treatment as well as IAR becomes more frequent; thus, the severity of symptoms significantly decreases after SLIT treatment. A further confirmation of the validity of such strategy is the perception of symptom severity and of the drug use assessed by patients. Probably, these findings also result from both a close adherence to the schedule and an optimal safety profile of SLIT. A few studies investigated the effects of immunotherapy with multiple allergens.^{24,25} Adkinson *et al.* conducted a controlled trial of subcutaneous immunotherapy (SCIT) in children with allergic asthma using several (up to seven) allergens and found no discernible benefit.²³ By contrast, Alvarez-Cuesta *et al.* showed in a placebo-controlled study that SCIT with both grass and olive pollen was able to significantly improve the quality of life in patients with seasonal AR due to double sensitization.²⁵ A recent open study used SLIT to evaluate the respective efficacy of treatment with grass pollen, birch pollen, or both, in patients with double sensitization to such pollens²⁶; SLIT with only grass pollen achieved some improvement in the season of birch pollen, and *vice versa*; the authors attributed this outcome to possible cross-reactivity of the two pollen allergens or to induction by the first SLIT treatment of production of interleukin-10, which exerts a partially nonspecific immunologic regulatory effect. However, SLIT with both pollens provided the best clinical outcome.

Our results indicate that SLIT with one or two allergen extracts significantly improved the AR classification and severity and reduced both symptom severity perception and drug use, confirming a previous study conducted on polysensitized adults.²¹ However, a clear limitation of this study is that it has been conducted as an open study; thus, it is not possible to exclude that

results might also depend on natural history and/or placebo effect. In addition, VAS evaluation could have produced some recall bias.

On the other hand, there are several unanswered/not completely answered questions concerning the SLIT and SCIT efficacy in polysensitized patients and the efficacy of multiallergen immunotherapy.^{27–30} In this regard, this open study may represent a real-life setting and may suggest some considerations: polysensitization is a relevant aspect in allergic children and must be carefully evaluated, mainly, if immunotherapy is considered for treatment, but it should not represent a counter-indication for prescribing such treatment.

This preliminary study reported that the choice limited to one to two allergen extracts could be sufficient and effective in improving allergic symptoms in polysensitized children. However, further controlled studies to fully confirm these findings are warranted.

REFERENCES

1. Asher I. ISAAC International Study of Asthma and Allergies in Childhood. *Pediatr Pulmonol* 42:100, 2007.
2. Bousquet J, Khaltav N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
3. Crystal-Peters J, Crown WH, Goetzel RZ, and Schutt DC. The cost of productivity losses associated with allergic rhinitis. *Am J Manag Care* 6:373–378, 2000.
4. Ciprandi G, Cadario G, Di Gioacchino M, et al. Intermittent and persistent allergic rhinitis and association with asthma in children. *Eur J Inflamm* 6:123–128, 2008.
5. Pederson PA, and Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy* 38:25–29, 1983.
6. Bugiani M, Carosso A, Migliore E, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 60:165–170, 2005.
7. National Heart, Lung, and Blood Institute (NHBL). Global Initiative for Asthma. Pocket guide for asthma management and prevention. NHBL, National Institutes of Health (NIH), NIH Publication No. 96-3659B, Bethesda, MD, 1997.
8. Fasce L, Tosca MA, Baroffio M, et al. Atopic infants with wheezing start always with monosensitization. *Allergy Asthma Proc* 28:449–453, 2007.
9. Passalacqua G, and Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 119:881–891, 2007.
10. Frew AJ. Immunotherapy of allergic disease. *J Allergy Clin Immunol* 111:S712–S719, 2003.
11. Malling HJ, Abreo-Nogueira J, Alvarez-Cuesta E, et al. Local immunotherapy. *Allergy* 53:933–948, 1998.
12. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: A meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 97:141–148, 2006.
13. Penagos M, Passalacqua G, Compalati E, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of

allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 133:599–609, 2008.

14. Arbes SJ Jr, Gergen PJ, Elliott L, and Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: Results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 116:377–383, 2005.
15. Craig TJ, King TS, Lemanske RF Jr, et al. Aeroallergen sensitization correlates with PC(20) and exhaled nitric oxide in subjects with mild-to-moderate asthma. *J Allergy Clin Immunol* 121:671–677, 2008.
16. Dreborg S (Ed). EAACI Subcommittee on Skin Tests. Skin tests used in type I allergy testing. *Allergy* 44 (suppl 10):22–31, 1989.
17. Larenas-Linnemann D, and Cox LS. European allergen extract units and potency: Review of available information. *Ann Allergy Asthma Immunol* 100:137–145, 2008.
18. Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 62:367–372, 2007.
19. Antonicelli L, Micucci C, Voltolini S, et al. Allergic rhinitis and asthma comorbidity: ARIA classification of rhinitis does not correlate with the prevalence of asthma. *Clin Exp Allergy* 37: 954–960, 2007.
20. Wallace DV, Dykewicz MS, Bernstein DI, et al.; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122(suppl 2):S1–S84, 2008.
21. Ciprandi G, Alesina R, Ariano R, et al. Characteristics of patients with allergic polysensitization: The POLISMAIL study. *Eur Ann Allergy Clin Immunol* 40:77–83, 2008.
22. Bousquet J, Annesi-Maesano I, Carat F, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. *Clin Exp Allergy* 35:728–732, 2005.
23. Ciprandi G, Cirillo I, Vizzaccaro A, et al. Seasonal and perennial allergic rhinitis: Is this classification adherent to real life? A population based study. *Allergy* 60:882–887, 2005.
24. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 336:324–331, 1997.
25. Alvarez-Cuesta E, Aragonese-Gilsanz E, Martin-Garcia C, et al. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: Changes in quality of life. *Clin Exp Allergy* 35: 572–578, 2005.
26. Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol* 98:274–280, 2007.
27. Cox L. Allergen immunotherapy and asthma: Efficacy, safety, and other considerations. *Allergy Asthma Proc* 29:580–589, 2008.
28. Finegold I. Immunotherapy: When to initiate treatment in children. *Allergy Asthma Proc* 28:698–705, 2007. (PubMed PMID: 18201435.)
29. Larenas-Linnemann DE. Sublingual immunotherapy: Dosing in relation to clinical and immunological efficacy. *Allergy Asthma Proc* 29:130–139, 2008.
30. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: A practice parameter second update. *J Allergy Clin Immunol* 120(suppl 3):S25–S85, 2007.

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