

ORIGINAL ARTICLE

Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain

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Keywords

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Abstract

Background: Allergic rhinitis (AR) is the most common chronic disease in children. The main objective of this study was to analyze the comorbidities and therapeutic approaches for AR in a Spanish pediatric population.

Methods: Children aged 6 to 12 years with AR were included in an observational, cross-sectional, multicenter study.

Results: 1,275 children were recruited from 271 centers. AR was intermittent in 59.5% of cases, persistent in 40.5%, seasonal in 60.7%, and perennial in 39.3% of patients. The most frequent comorbidities were conjunctivitis (53.6%), asthma (49.5%), atopic dermatitis (40%), rhinosinusitis (26.1%), otitis media (23.8%), and adenoid hypertrophy (17.3%). Overall, patients with persistent, moderate or severe, AR were more likely to present comorbidities, except for food allergy and urticaria. The most common drugs used for treatment of AR were oral antihistamines (76%), nasal corticosteroids (49%) and a combination of both (45%). Antihistamines and nasal corticosteroids were used on demand (<18 days) in 38 and 41% of patients, respectively; for 18–30 days in 22 and 27%; for 1–3 months in 31 and 29%; and for more than 3 months in 8 and 3%, respectively. Eye drops were used in 32% and specific immunotherapy in 21% of patients.

Conclusion: Comorbidities are frequent in children with AR, supporting the notion of allergy as a systemic disease. Severity and duration of AR were significantly associated with presence of most of comorbidities. The most common drugs used for AR treatment were oral antihistamines, followed by nasal corticosteroids and a combination of both used on demand.

Although probably under-diagnosed, allergic rhinitis (AR) is the most common chronic disease in childhood, with a prevalence of up to 40% (1). AR has been proven to have a significant impact on children's cognitive performance and quality of life (2–5). Comorbidities are common in children with AR and can also significantly impact a child's health. Many associated diseases affect other related systems or organs or are associated with other atopic diseases. Few prospective series have been published, which have searched for the presence of all types of comorbidities in AR in children (6),

although some publications have analyzed specific entities associated with AR in different populations (7–11).

For treatment of children with AR, a proper stepwise approach is crucial to optimize the risk/benefit ratio of any therapeutic intervention and also to treat comorbidities (12, 13). Issues of compliance and convenience also are important considerations (14). First-line therapy consists of second-generation antihistamines and intranasal corticosteroids, which are the preferred agents for children with persistent symptoms. Allergen immunotherapy can also be a valuable

intervention. However, some of these therapeutic approaches have a low quality of evidence accordingly, as revealed in a recent ARIA guidelines update (14).

The main objective of this study was to analyze the comorbidities and therapeutic approach of allergic rhinitis in the Spanish pediatric population through a real-life study. As another novelty, in this study, we used two validated tools to classify AR severity in children—the original (o-ARIA) (15) and the modified (m-ARIA) ARIA classification (16, 17).

Study design and patients

The patients and methods used in this study have been described previously (15). In brief, an epidemiological, multi-center, cross-sectional study of current clinical practice for AR was conducted in almost all the provinces of Spain. This breadth of scope may justify its being considered a real-life study. A total of 271 centers and 334 investigators from allergy, otorhinolaryngology (ENT), and pediatrics departments participated. Patients were included if they fulfilled the following criteria: (i) 6–12 years of age, (ii) previous diagnosis of AR made by an allergist, and (iii) written parental informed consent. Patients were considered to suffer from AR if they had: (i) symptoms suggestive of rhinitis over the 2 or more years prior to the study and (ii) at least one positive skin prick test and/or serum-specific IgE to a clinically relevant aeroallergen. The children were enrolled within a 3-month period between May and July 2008 and were recruited from all regions of Spain to avoid any geographic bias. The study was approved by the Ethics Committee of Hospital Clínic de Barcelona, Spain.

Study outcomes

Demographic data (age, gender, height, and weight), place of residence, and allergen sensitization profile were obtained. The presence of comorbidities and the therapeutic approach adopted were also evaluated. Duration of AR was classified according to the ARIA guidelines as persistent (symptoms lasting more than 4 days a week and over more than 4 wks) or intermittent (symptoms lasting up to 4 days a week or up to 4 wks). AR severity was assessed according to the four ARIA items (sleep, daily activities/sport/leisure, academic performance, and troublesome symptoms) and classified according to different severity levels as mild (no affected items) or moderate/severe (one or more affected items) based on the o-ARIA classification (15); additionally, a distinction was made between moderate (one to three affected items) and severe (all four items affected) AR using the m-ARIA classification (16, 17).

Conjunctivitis symptoms were assessed using the total ocular symptom score (TOSS) by calculating the sum of scores for ocular itching, tearing, and redness. Each ocular symptom was scored on a scale from 0 to 3 (0, no symptoms; 1, mild; 2, moderate; 3, severe) resulting in a TOSS ranging from 0 to 9.

Statistical methods

A descriptive analysis of the study population was performed. Patients were compared according to their different severity

levels based on the two ARIA classifications. The analysis was carried out using the Statistical Analysis System (SAS Institute Inc. NC, USA) program, version 9.1.3. All variables were described for the total sample. The number of valid cases (N) was used in all tables, figures, and graphics and when calculating percentages or any other statistical consideration. Continuous variables were summarized based on the number of valid cases (N), mean, standard deviation, median, and extreme values; categorical variables were described by means of number of valid cases (N) and percentages in every category, while variables with an asymmetric frequency distribution were described using the medians and their 25th to 75th percentiles. Odds ratios (OR) and 95% confidence intervals (CI) for association between AR and comorbidities were calculated using logistic regression analysis. Other appropriate tests (chi-squared, Mann–Whitney, or Kruskal–Wallis) were used in each case for other comparisons. Statistical significance was set at a p value of < 0.05.

Results

Children aged 6–12 yrs were included (N = 1275). Most of the clinical characteristics of this sample have been previously described (15). The median age was 9.0 yrs (p25–p75: 7.0–11.0), and 745 (58.7%) were males. Average body mass index (BMI) was 17.4: 12 children were overweight Grade I, three were overweight Grade II, and 98.1% had normal weight. The mean duration of AR was 2.5 ± 2.4 yrs.

Geographic distribution

Most of the children lived in urban locations (67%), followed by those living in suburban (18%), and rural (14%) areas.

Cause of rhinitis

The most frequent allergen involved was pollen (53.5%), followed by house dust mites (43.5%), animal dander (14%), and molds (7%).

Characteristics of rhinitis

AR was intermittent in 59.5% of cases, persistent in 40.5%, seasonal in 60.7%, and perennial in 39.3% of patients. Using the o-ARIA classification, 10% of the patients had mild, while 90% had moderate/severe AR; on the other hand, using the m-ARIA criteria, moderate disease accounted for 60% of cases, severe for 30%, and 10% mild. The most frequent forms of AR using o-ARIA were moderate/severe intermittent (52%) followed by moderate/severe persistent (38%), mild intermittent (7%), and mild persistent (3%) rhinitis. According to the m-ARIA criteria, the most prevalent were moderate intermittent (35%), moderate persistent (24%), severe intermittent (16%), severe persistent (15%), mild intermittent (7%), and mild persistent (3%) forms.

Comorbidities

76.5% of patients had any concomitant disease. The most frequent were conjunctivitis (53.6%), asthma (49.5%), atopic

dermatitis (40%), followed by rhinosinusitis (26.1%), otitis media (23.8%), and adenoid hypertrophy (17.3%). Figs 1 and 2 depict the frequency of total and different comorbidities according to the duration and severity of AR based on the m-ARIA classification. Table 1 shows logistic regression odds ratios for associations with different comorbidities according to the duration and severity of AR based on the m-ARIA classification.

Ocular symptoms

More than a half of the children (53.6%) complained of ocular symptoms accompanying their rhinitis. ORs for association between conjunctivitis and AR were all positive and significant considering duration and severity according to the m-ARIA classification. The highest OR was found between severe or moderate vs. mild AR (Table 1). Table 2 shows the frequency and severity of ocular symptoms in patients suffering from AR. In intermittent AR, a significantly higher ocular itching score was obtained when comparing moderate/severe with mild AR ($p = 0.0005$) as well as tearing ($p = 0.0013$) and redness ($p = 0.0041$). In persistent AR, ocular itching, tearing, and redness scores were also higher in moderate/severe than in mild AR ($p = 0.012$, $p = 0.022$, and $p = 0.0016$, respectively). In mild intermittent or persistent AR, tearing was absent in 50% and 45% of patients, respectively; ocular itching was absent in 36% and 25%, respectively; and redness was absent in 46% and 40%, respectively. Using the m-ARIA classification, severity of ocular symptoms was associated with severity of intermittent or persistent rhinitis (Fig. 3) and higher scores in TOSS were also associated with severity of AR ($p = 0.0001$).

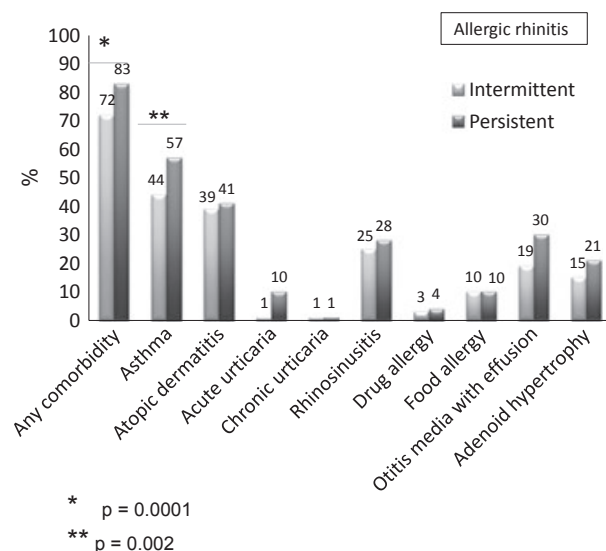


Figure 1 Frequency of comorbidities according to the duration of allergic rhinitis.

Asthma and other comorbidities

The likelihood (OR) of presenting AR and other comorbidities is shown in Table 1. Most comorbidities had positive and significant ORs considering intensity and severity according to the m-ARIA classification, except for acute urticaria and drug and food allergy. Considering association, ORs with asthma were not significant between moderate vs. mild and severe vs. moderate AR, but ORs were significantly associated with persistent vs. intermittent and severe vs. mild AR. In atopic dermatitis and rhinosinusitis, ORs were not significant between intermittent and persistent AR. Interestingly, in patients with otitis media and adenoid hypertrophy, ORs for the association with more severe AR were the highest obtained in this study.

Treatments

Eight hundred sixty-three children were under pharmacologic treatment at the time of the study.

Antihistamines were given to 655 (76%) of the patients receiving treatment. Topical nasal administration was employed in only nine patients and the rest received antihistamines orally. Antihistamines were used on demand (<18 days) in 38% of patients, for 18–30 days in 22%, for 1–3 months in 31%, and for more than 3 months in 8%.

Regarding corticosteroids, 427 (33.5%) of patients were treated with nasal topical corticosteroids, and only one patient reported having received intramuscular corticosteroids and three oral corticosteroids. Corticosteroids were used on demand (<18 days) in 41% of patients, for 18–30 days in 27%, for 1–3 months in 29%, and for more than 3 months in 3%. Combined treatment of antihistamines and corticosteroids was given to 30.8% (393) of patients. Leukotriene modifiers were given to only 17 (2%) patients.

No significant difference was found considering drugs used for treatment and severity of the disease when using the o-ARIA or m-ARIA classifications; however, when perennial or seasonal classification was used, nasal steroids were significantly more commonly prescribed in perennial rhinitis ($p = 0.04$).

Eye drops of antihistamines or mast cell stabilizers were used in 267 (21.7%) patients. These were used on demand (<18 days) in 73% of patients, for 18–30 days in 15%, for 1–3 months in 10%, and for more than 3 months in 2%. Specific immunotherapy was indicated in 21% of patients. In these cases, sublingual immunotherapy was prescribed in 30.5% of patients and subcutaneous immunotherapy in 69.5%.

Discussion

Allergic rhinitis is the most common chronic disease in childhood in many countries (1). In a study performed in Spain, AR was found to be the most frequently diagnosed allergic disease (44.9%) in patients under the age of 14 yrs consulting for the first time (18, 19). We offer here an initial approach to the comorbidities and patient management of AR based on a real-life study in 1275 Spanish children aged 6–12 yrs having a median age of 9 yrs. This is the age when AR

Table 1 Presence of comorbidities and odds ratios of association with duration and severity of allergic rhinitis according to modified ARIA

Disease	Comparison	OR [95% Conf interval]			p value
Any comorbidity	Persistent vs. intermittent	1.80	1.38	2.36	0.0000
	Moderate vs. mild	1.94	1.31	2.87	0.0009
	Severe vs. mild	2.07	1.35	3.19	0.0008
	Severe vs. moderate	1.07	0.80	1.44	0.6457
Conjunctivitis	Persistent vs. intermittent	1.31	1.05	1.65	0.0179
	Moderate vs. mild	2.38	1.60	3.54	0.0000
	Severe vs. mild	3.82	2.49	5.84	0.0000
	Severe vs. moderate	1.60	1.24	2.07	0.0003
Asthma	Persistent vs. intermittent	1.73	1.38	2.17	0.0000
	Moderate vs. mild	1.28	0.87	1.89	0.2054
	Severe vs. mild	1.55	1.03	2.33	0.0365
	Severe vs. moderate	1.21	0.94	1.55	0.1393
Atopic dermatitis	Persistent vs. intermittent	1.06	0.83	1.34	0.6589
	Moderate vs. mild	1.69	1.09	2.62	0.0170
	Severe vs. mild	1.79	1.13	2.84	0.0121
	Severe vs. moderate	1.06	0.82	1.37	0.6648
Acute urticaria	Persistent vs. intermittent	0.70	0.47	1.05	0.0868
	Moderate vs. mild	1.70	0.80	3.61	0.1651
	Severe vs. mild	1.34	0.60	3.00	0.4744
	Severe vs. moderate	0.79	0.51	1.22	0.2902
Rhinosinusitis	Persistent vs. intermittent	1.21	0.92	1.60	0.1717
	Moderate vs. mild	1.91	1.08	3.36	0.0239
	Severe vs. mild	2.60	1.45	4.67	0.0010
	Severe vs. moderate	1.36	1.02	1.83	0.0369
Drug allergy	Persistent vs. intermittent	1.29	0.63	2.67	0.4876
	Moderate vs. mild	0.86	0.25	3.03	0.8198
	Severe vs. mild	1.13	0.31	4.18	0.8521
	Severe vs. moderate	1.31	0.58	2.94	0.5125
Food allergy	Persistent vs. intermittent	1.06	0.70	1.61	0.7821
	Moderate vs. mild	0.76	0.38	1.50	0.4215
	Severe vs. mild	1.02	0.50	2.08	0.9622
	Severe vs. moderate	1.34	0.85	2.13	0.2052
Otitis media	Persistent vs. intermittent	1.81	1.36	2.39	0.0000
	Moderate vs. mild	3.29	1.63	6.63	0.0005
	Severe vs. mild	3.84	1.87	7.87	0.0001
	Severe vs. moderate	1.17	0.86	1.58	0.3170
Adenoid hypertrophy	Persistent vs. intermittent	1.46	1.06	2.02	0.0217
	Moderate vs. mild	2.41	1.14	5.07	0.0176
	Severe vs. mild	4.62	2.17	9.82	0.0000
	Severe vs. moderate	1.92	1.40	2.64	0.0000

presence is highest among children in Spain as well as other parts of the world (1, 2, 18–20).

In this study, male gender was more prevalent (58.7%) than female, as has been described in previous studies (18, 19, 21–23). This fact has no clear explanation, although it may be explained by the higher prevalence of atopy in male children (21).

According to the o-ARIA classification (15), 52% had moderate/severe intermittent and 38% exhibited a moderate/severe persistent form. According to the m-ARIA criteria (17), moderate intermittent was the most frequent classification (35%), followed by moderate persistent (24%). The higher prevalence of moderate/severe patients may be the result of selection bias, as patients were recruited mostly from tertiary

centers. Data concerning allergen sensitization were similar to previous studies conducted in Spain (18–20) in which pollen, followed by mites and pet dander, were the most frequent allergens involved in the population studied.

Mostly of the patients (76.5%) had any comorbidities associated with AR, ORs were positive and significant for conjunctivitis, asthma, atopic dermatitis, rhinosinusitis, otitis media, and adenoid hypertrophy; these findings were similar to those of previous studies (6, 13–19). Overall, patients with persistent, moderate or severe, AR was more likely to present subsequent comorbidities. In our study, 53.6% of the children complained of ocular symptoms, mostly mild to moderate, accompanying their rhinitis. Of note, an association between severity and duration of AR and conjunctivitis symptoms was

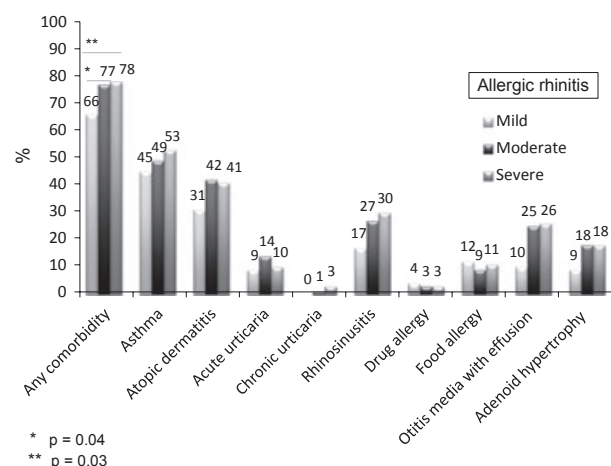


Figure 2 Frequency of comorbidities according to severity classification using the modified ARIA.

Table 2 Frequency and severity of ocular symptoms in patients suffering from allergic rhinitis

	Itching		Tearing		Redness	
	N	Percentage	N	Percentage	N	Percentage
Absent	71	10.6	171	25.8	138	20.8
Mild	297	44.4	280	42.2	267	40.2
Moderate	226	33.8	180	27.1	202	30.4
Severe	75	11.2	33	5	57	8.6

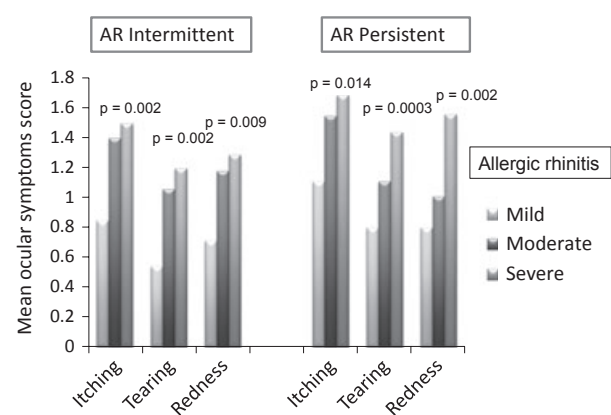


Figure 3 Association of severity of ocular symptoms with severity of allergic rhinitis using modified ARIA.

demonstrated. In intermittent AR, ocular symptoms were more significantly associated with moderate/severe than with mild AR. In patients with persistent AR, ocular itching, tearing, and redness were also more significantly associated with moderate/severe versus mild AR.

Using the m-ARIA classification, severity of ocular symptoms was also significantly associated with severity of intermittent or persistent rhinitis, as well as higher scores in total ocular symptoms score. Duration and severity of AR had positive and significant ORs (varying from 3.82 to 1.31) with conjunctivitis diagnosis.

The association between asthma and rhinitis in this study was 49.5%, similar to a previous study conducted in Spain (45%), (19) although higher than that described in Western Europe in phase III of the ISAAC study, which included Spain (23). This study showed that in children aged 6–14 yrs, this association accounted for 30–35% of patients. This difference in the association between rhinitis and asthma can be attributed in our study to the fact that the diagnosis was made by specialists using specific tests. The likelihood of asthma diagnosis in patients with AR was clearly related to duration and severity of AR. Several studies have demonstrated that patients with perennial AR have increased risk of developing asthma (24).

Atopic dermatitis was common among patients with AR (40%), indeed, to an extent that is higher than that reported in a previous study performed in Spain (18). Atopic dermatitis has been described as a risk factor for development of AR and even more severe form of AR (25, 26). In this study, the diagnosis of atopic dermatitis was associated with more severe AR when using m-ARIA classification.

The other more frequent comorbidities were associated with diseases related to the area of the upper airways, such as rhinosinusitis and otitis media with effusion, which confirms the hypothesis that inflammation of contiguous structures of the nose is a common finding. The presence of these diseases was associated again with severe AR (27–29), and ORs for association were the highest obtained in this study.

These interrelations support the notion of allergy as a systemic disease and, consequently, demonstrate the need for an integral diagnosis and therapeutic approach.

One of most interesting results of our study is its depiction of how AR is treated. Similar to those of a previous study in a Spanish population (19, 20), a very high proportion of patients studied was treated with oral antihistamines (76%), although 49% received nasal corticosteroids, and 45% were receiving a combination of both drugs. This contrasts with the lack of evidence for the benefit of antihistamine add-on therapy with topical nasal steroids for children with intermittent or persistent allergic rhinitis (30). This frequent use of nasal corticosteroids may be due to the high number of patients with moderate or severe AR included in this study and likely based on the higher efficacy of intranasal glucocorticosteroids, although the evidence is of low quality (14). However, there was no significant difference between type of drug used and severity of the disease when applying the m-ARIA or o-ARIA classifications. Nevertheless, when perennial–seasonal classification was considered, nasal corticosteroids were significantly more prescribed in perennial AR. Interestingly, although recommended in guidelines (14, 24), nasal antihistamines and leukotriene modifiers were barely used, and antiallergic eye drops were used in only 21.7% of the patients. Of note, in spite of the high frequency of asthma

in this population, leukotriene modifiers were not a drug of choice of Spanish doctors.

Specific immunotherapy was used in one in five (21%) included patients. Of these, 30.5% were receiving sublingual immunotherapy, and 69.5% subcutaneous immunotherapy. These figures are in agreement with previous reports of type of immunotherapy used for AR in Spain (19) but do not fit with recent recommendations (31) and also contrasts with higher use of sublingual immunotherapy in other countries such as France or Italy. The low number of patients treated with specific immunotherapy may be explained by the fact that many specialists prefer to wait and see the evolution of the disease before initiating immunotherapy treatment (32) or because ENT specialists do not tend to prescribe immunotherapy.

The frequent presence of comorbidities in children with AR makes it essential to optimize symptomatic and etiologic treatments to improve both AR itself and its associated diseases, and even alter the natural history of AR using immunotherapy. When deciding drug therapy and mode of administration, the patient's preference must also be kept in mind.

The main limitations of the study are that it is not a population-based study and that patients were recruited from secondary and tertiary centers. However, the main strengths are that it is a prospective study to look for association of many comorbidities in a high number of patients, the fact that diagnosis was performed during a visit to specialists and that the therapeutic approach to this entity can be considered as a real-life study in which doctors administer therapy with no predefined scheme.

In summary, this real-life large-scale prospective study conducted in Spanish children diagnosed with AR confirms the presence of such common comorbidities as conjunctivitis,

asthma, and atopic dermatitis. Severity of AR was significantly associated with presence of comorbidities that involve inflammation of contiguous structures of the nose. Overall, children were treated according to the ARIA guidelines, although almost half of the patients received a combination of oral antihistamines and nasal glucocorticoids, while nasal antihistamines and leukotriene modifiers were scarcely used.

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Conflicts of interest

María Dolores Ibáñez reports having served as a consultant to ALK-Abello and Novartis, having been paid lecture fees by MSD and ALK-Abelló, and having received grant support from ALK-Abelló.

Javier Montoro has served as consultant for FAES, MSD and GSK.

Joaquín Sastre reports having served as a consultant to Thermofisher, MSD, FAES Farma, MEDA, Roche, Sanofi, Novartis, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, FAES FARMA; and having received grant support from Thermofisher, GSK, and ALK-Abelló.

Joaquim Mullol has been member of national and international scientific advisory Boards (consulting), received fees for lectures or grants for research projects from: Boehringer-Ingelheim, Esteve, FAES, GSK, Hartington Pharmaceuticals, Johnson & Johnson, MEDA, MSD, Novartis, Pierre Fabre, Sanofi, Schering Plough, UCB, Uriach Group, and Zambon.

Other authors declare no conflict of interests.

References

1. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D; the ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008; **19**: 110–24.
2. Meltzer EO, Blaiss MS, Derebery J, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 2009; **124**: S43–70.
3. Passalacqua G, Canonica GW, Baiardini I. Rhinitis, rhinosinusitis and quality of life in children. *Pediatr Allergy Immunol* 2007; **18** (Suppl. 18): 40–5.
4. Jáuregui I, Mullol J, Dávila I, et al. Allergic rhinitis and school performance. *J Invest Allergol Clin Immunol* 2009; **19** (Suppl. 1): 32–9.
5. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin* 2004; **20**: 1937–52.
6. Westman M, Stjärne P, Asarnoj A, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol* 2012; **129**: 403–8.
7. Knight LC, Eccles R, Morris S. Seasonal allergic rhinitis and its effects on eustachian tube function and middle ear pressure. *Clin Otolaryngol Allied Sci* 1992; **17**: 308–12.
8. Pinto JM, Baroody FM. Chronic sinusitis and allergic rhinitis: at the nexus of sinonasal inflammatory disease. *J Otolaryngol* 2002; **31** (Suppl. 1): S10–7.
9. Slavin RG. Complications of allergic rhinitis: implications for sinusitis and asthma. *J Allergy Clin Immunol* 1998; **101**: S357–60.
10. Craig TJ, Sherkat A, Safaei S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep* 2010; **10**: 113–21.
11. Mullol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. *J Invest Allergol Clin Immunol* 2008; **18**: 415–9.
12. Meltzer EO. Allergic rhinitis: managing the pediatric spectrum. *Allergy Asthma Proc* 2006; **27**: 2–8.
13. Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. *Pediatr Allergy Immunol* 2010; **21**: e107–13.
14. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; **126**: 466–76.
15. Jáuregui I, Dávila I, Sastre J, et al. Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study. *Pediatr Allergy Immunol* 2011; **22**: 388–92.
16. Valero A, Ferrer M, Sastre J, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol* 2007; **120**: 359–65.

17. Montoro J, Del Cuvillo A, Mullol J, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. *Allergy* 2012; **67**: 1437–42.
18. Ibáñez MD, Garde JM. Allergy in patients under fourteen years of age in Alergológica 2005. *J Investig Allergol Clin Immunol* 2009; **19** (Suppl. 2): 61–8.
19. Ibáñez MD, Navarro A, Sánchez MC, et al. Rhinitis and its association with asthma in patients under 14 years of age treated in allergy departments in Spain. *J Investig Allergol Clin Immunol* 2010; **20**: 402–6.
20. Navarro A, Colás C, Antón E, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: alergológica-2005. *J Investig Allergol Clin Immunol* 2009; **19** (Suppl. 2): 7–13.
21. Arnedo-Pena A, García-Marcos L, García Hernández G, et al. Time trends and geographical variations in the prevalence of symptoms of allergic rhinitis in 6-7-year-old children from eight areas of Spain according to the ISAAC. *An Pediatr (Barc)* 2005; **62**: 229–36.
22. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997; **8**: 161–76.
23. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Monteford S, Shah J, the ISAAC Phase Three Study Group. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009; **64**: 123–48.
24. Bousquet J, Kaltaev N, Cruz AA, ARIA Workshop Group; World Health Organization. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen. *Allergy* 2008; **63** (Suppl. 86): 8–160.
25. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis—a prospective follow-up to 7 years of age. *Allergy* 2000; **55**: 240–5.
26. Batlles Garrido J, Torres-Borrego J, Bonillo Perales A, et al. Prevalence and factors linked to atopic eczema in 10- and 11-year-old schoolchildren. Isaac 2 in Almeria, Spain. *Allergol Immunopathol (Madr)* 2010; **38**: 174–80.
27. Higuchi O, Adachi Y, Itazawa T, et al. Relationship between rhinitis and nocturnal cough in school children. *Pediatr Allergy Immunol* 2012; **23**: 562–6.
28. Di Berardino F, Romagnoli M. Adenoidal hypertrophy and allergic rhinitis. *Pediatr Allergy Immunol* 2011; **22**: 646.
29. Lack G, Caulfield H, Penagos M. The link between otitis media with effusion and allergy: a potential role for intranasal corticosteroids. *Pediatr Allergy Immunol* 2011; **22**: 258–66.
30. Nasser M, Fedorowicz Z, Aljufairi H, McKerrow W. Antihistamines used in addition to topical nasal steroids for intermittent and persistent allergic rhinitis in children. *Cochrane Database Syst Rev* 2010; **7**: CD006989.
31. Calderon MA, Gerth van Wijk R, Eichler I, et al. Perspectives on allergen specific immunotherapy in Childhood: an EAACI position statement. *Pediatr Allergy Immunol* 2012; **23**: 300–6.
32. Ibero M, Justicia JL, Alvaro M, et al. Diagnosis and treatment of allergic rhinitis in children: results of the PETRA study. *Allergol Immunopathol* 2012; **40**: 138–43.